Review

Historical perspective

A brief history of human brain mapping

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Human functional brain mapping as we presently know it began when the experimental strategies of cognitive psychology were combined with modern brain-imaging techniques (first positron emission tomography and then functional magnetic resonance imaging) to examine how brain function supports mental activities. This marriage of disciplines and techniques galvanized the field of cognitive neuroscience, which has rapidly expanded to include a broad range of the social sciences in addition to basic scientists interested in the neurophysiology, cell biology and genetics of the imaging signals. Although much of this work has transpired over the past couple of decades, its roots can be traced back more than a century.

Introduction

Over the past 30 years the field of cognitive neuroscience has emerged as an important growth area in neuroscience. Cognitive neuroscience combines the experimental strategies of cognitive psychology with various techniques to actually examine how brain function supports mental activities. Leading this research in normal humans are the techniques of functional brain imaging: positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) along with electroencephalography (EEG), electrocorticography (ECoG), magnetoencephalography (MEG) and, most recently, optical imaging with near-infrared spectroscopy (NIRS).

It is easy to conclude that much of the work leading to the emergence of functional brain imaging in particular and cognitive neuroscience in general has transpired over the past decade or so because of much recent prominence at scientific meetings and in the scientific literature. Additionally, it has received substantial media attention probably related to the human fascination with brain-mind questions. In truth, crucial work has been occurring for more than a century.

To place current work in perspective, I present a brief historical overview (Figure 1) of some of the concepts, events and personalities that have shaped functional brain imaging as we know it today. I call upon not only published accounts of many events and discoveries but also recollections shared with me by those who have lived through the remarkable events of the past several decades. Such views serve to not only breathe life into the science but also carry the caveat that they are necessarily colored by one's own involvement.

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I focus on human brain imaging with PET and fMRI recognizing that other techniques, particularly electrical (e.g. EEG, MEG and ECoG), also have and will continue to have an important role. I begin with a discussion of the physiology of brain imaging with PET and fMRI.

Physiology

The signals obtained with PET and fMRI are based on changes in blood flow, oxygen consumption and glucose utilization that relate in a surprisingly precise way to the cellular activity of the brain, including astrocytes and neurons. The details of these relationships are presented, discussed and debated elsewhere [1–6]. Here, some basic facts necessary to understand the history of functional brain imaging are briefly presented.

Blood flow

The majority of functional brain imaging with PET and MRI, in addition to earlier non-tomographic techniques, is made possible because blood flow changes locally in the brain in relation to changes in cellular activity [1]. The idea that local blood flow within the brain is intimately related to brain function is surprisingly old. Angelo Mosso, a prominent Italian physiologist of the 19th century, had ingeniously monitored the pulsations of the brain in adults through neurosurgically created bony defects in the skulls of patients. He noted that when his subjects engaged tasks such as mathematical calculations the pulsations of the brain increased locally. Such observations led him to conclude, presciently, that blood flow to the brain followed function [7]. The actual physiological relationship between brain function and blood flow was first explored in 1890 by Charles Roy and Charles Sherrington [8].

Despite this promising beginning, interest in the relationship between brain function and brain blood flow almost ceased during the first quarter of the 20th century. Undoubtedly, this was owing, in part, to a lack of tools sufficiently sophisticated to pursue this line of research. In addition, the work of Leonard Hill, Hunterian Professor of the Royal College of Surgeons in England, was probably influential [9]. His eminence as a physiologist overshadowed the inadequacy of his own experiments that wrongly led him to conclude no relationship existed between brain function and brain circulation.

There was no serious challenge to Leonard Hill's views until a remarkable clinical study of a patient Walter K. was reported by John Fulton in the 1928 issue of the journal *Brain* [10]. During the course of his evaluation and treatment for a vascular malformation lying over his visual cortex, Walter K. remarked to his physicians that a noise

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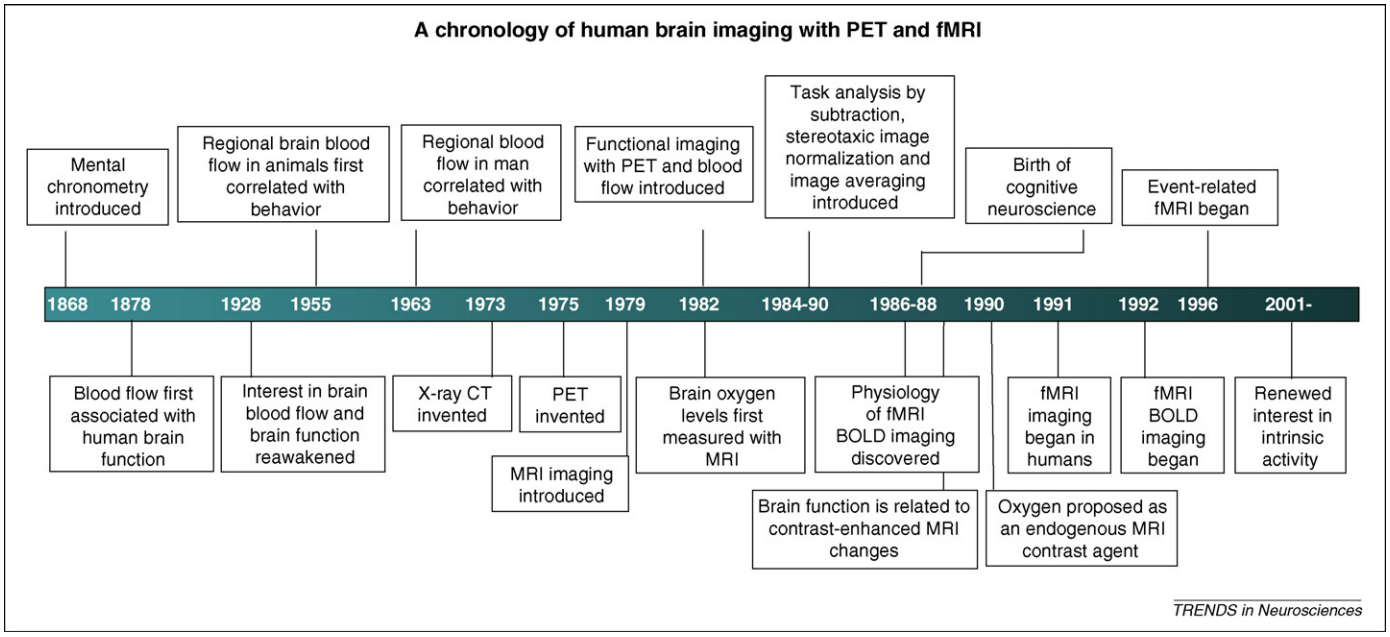

Figure 1. A chronology of major events associated with the development of human brain imaging with PET and fMRI.

(i.e. bruit) that he perceived in the back of his head increased in intensity when he was using his eyes. He said that he had often noticed this during the proceeding several years but had 'never thought much of it'. As Fulton commented, 'It was not difficult to convince ourselves that when the patient suddenly began to use his eyes after a prolonged period of rest in a dark room, there was a prompt and noticeable increase in the intensity of his bruit. Activity of his other sense organs, moreover, had no effect upon his bruit.' The conclusion drawn from this remarkable case was that blood flow to visual cortices was sensitive to the attention paid to objects in the environment.

It was not until the close of World War II that Seymour Kety and his colleagues (University of Pennsylvania and National Institutes of Health) opened the next chapter in studies of brain circulation and metabolism. Kety developed the first quantitative method for measuring whole-brain blood flow and metabolism in humans [11]. Because their measurements were confined to the whole brain they were not suitable for 'brain mapping'. However, their introduction of an *in vivo* tissue autoradiographic measurement of regional blood flow in laboratory animals [12,13] provided the first glimpse of quantitative regional changes in blood flow in the brain related directly to brain function. Derivatives of this technique many years later became important for the measurement of blood flow in humans when PET provided a means of quantifying the spatial distribution of radiotracers in tissue without the need for invasive autoradiography (see later).

Following on the heels of the work by Kety and colleagues, David Ingvar (University of Lund, Sweden), Neils Lassen (University of Copenhagen, Denmark) and their Scandinavian colleagues introduced methods applicable to humans that permitted regional blood-flow measurements to be made using scintillation detectors arrayed like a helmet over the head. They demonstrated conclusively that brain blood flow changed regionally in normal human subjects during task performance (for a summary of their early work see Ref. [14]).

Metabolism

Until 1986 it was thought that behaviorally induced increases in local blood flow were the direct consequence of an increase in the brain's need for oxygen to metabolize glucose to carbon dioxide and water for the production of energy [15]. Based on this hypothesis, functionally induced increases in blood flow should be accompanied by quantitatively similar changes in oxygen consumption with no change in the ratio of oxy- to deoxyhemoglobin. Although widely held, this hypothesis was based on rather scanty data [16]. Furthermore, it ignored much earlier work by Ray Cooper and colleagues (Burden Neurological Institute, Stapelton, Bristol, UK) [17]. Cooper recorded oxygen availability in the human cortex in patients undergoing evaluation for epilepsy while their subjects performed various cognitive and motor tasks. They clearly showed task-induced focal increases in oxygen availability signifying that blood flow had increased more than oxygen consumption (recordings by Cooper are hard to distinguish from today's task-induced fMRI blood oxygen-level-dependent [BOLD] time–activity curves [17]).

Conventional wisdom was seriously challenged by much more substantial quantitative data from PET [18,19]. These data (Figure 2a), derided at the time by the established figures in the field as untrue because they violated conventional wisdom, demonstrated conclusively that functionally induced increases in blood flow in normal humans were not accompanied by changes of similar magnitude in oxygen consumption. The increase in glucose utilization also increased significantly more than would have been predicted by the increase in oxygen consumption. Although the degree to which oxygen consumption increases has varied across experiments [18–22], it has always been significantly less than that predicted by the

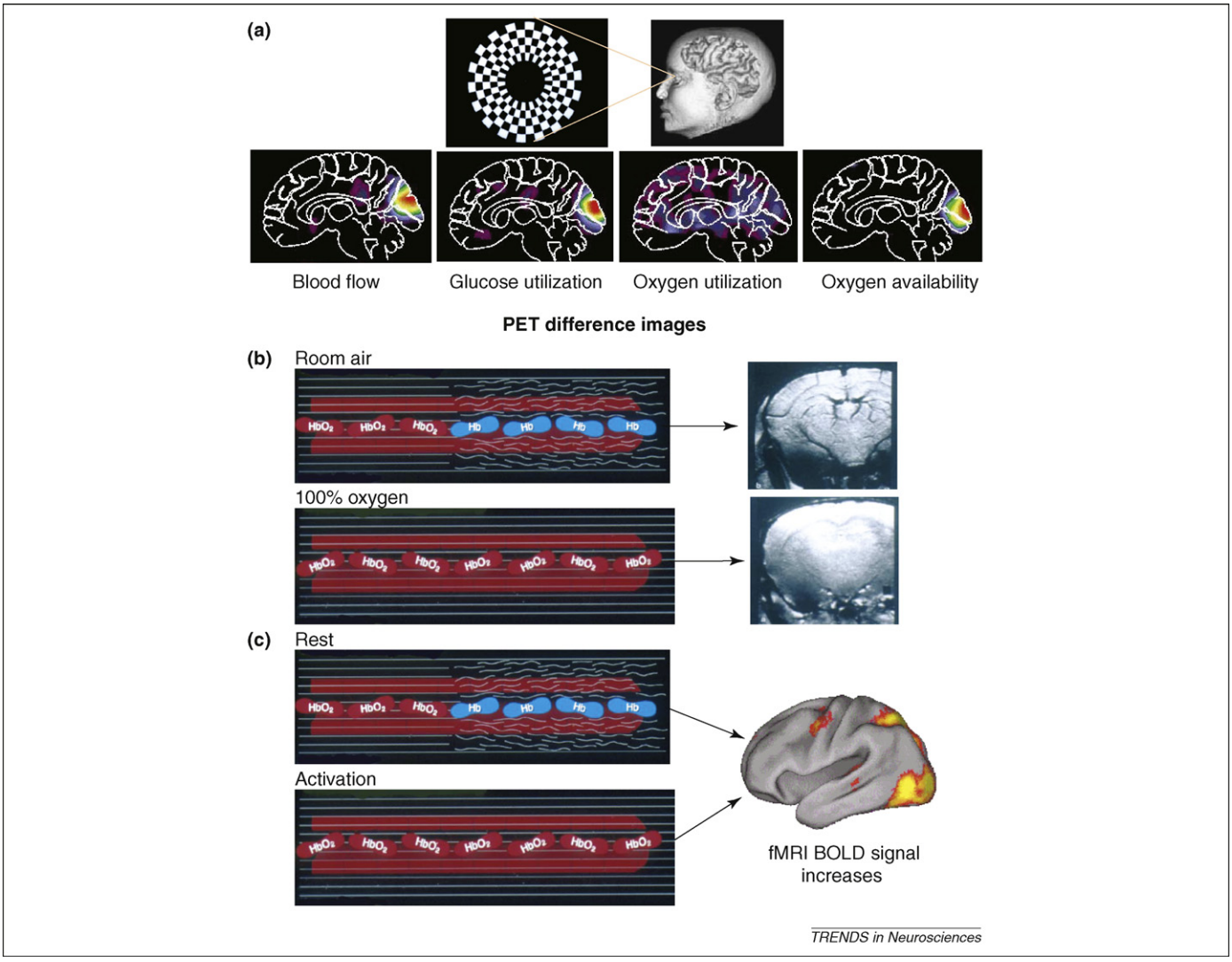

Figure 2. Functional brain imaging with PET or fMRI is based on changes in brain circulation and metabolism that are associated with activity changes in both neurons and astrocytes. The profile of these changes was first detailed by PET **(a)**, which showed that activity increases, in this case evoked by stimulation of the visual cortex by a reversing annular checkerboard, consist of increases in blood flow (49%) and glucose utilization (21%) that far exceed that of oxygen utilization (5%) (images adapted from Ref. [19]). As a result, the amount of oxygen available in the brain increases (supply increases relative to demand) causing the relative percentage of deoxyhemoglobin (a paramagnetic substance; Box 1) to decrease. The fMRI signal arises because of this change in the relative amount of deoxyhemoglobin (Hb). As shown in part **(b)**, veins containing Hb (dark areas on the upper image) disappear when the animal is breathed on 100% oxygen (lower image) (original experimental data from Ogawa and colleagues [43]). In the human fMRI experiment **(c)**, Hb is decreased because blood flow increases more than oxygen consumption as in part (a) leading to an enhanced signal portrayed here as a localized increase in the fMRI BOLD signal.

increase in either the blood flow or the glucose utilization when these variables are measured reliably by validated methods. The resulting fall in deoxyhemoglobin, which was known from much earlier work to be paramagnetic [23] (Box 1), was to have clear implications for the interpretation of fMRI based on deoxyhemoglobin as an *in vivo* MRI contrast agent (see later).

Instrumentation

X-ray computed tomography

In 1971 Godfrey Hounsfield introduced X-ray computed tomography (or CT as it is now called) at Atkinson Morley's Hospital in London. In creating CT, Hounsfield had arrived at a practical solution to the problem of creating three-dimensional transaxial tomographic images of an intact object from data obtained by passing highly focused X-ray beams through the object and recording their attenuation. Hounsfield's invention received enormous attention and quite literally changed the way in which we looked at the human brain. Gone, also, were difficult to interpret, unpleasant and sometimes dangerous clinical techniques such as pneumoencephalography (Box 2). CT was, however, an anatomical tool. Function was to be the province of PET and MRI.

Box 1. Deoxygenated hemoglobin

Deoxygenated hemoglobin as found in veins disrupts a magnetic field whereas oxygenated hemoglobin as found in arteries does not. This results from the fact that deoxygenated hemoglobin behaves like a little magnet when in a magnet field owing to the presence of exposed iron in the hemoglobin molecule. The presence of oxygen 'neutralizes' the effect of the iron such that oxygenated blood can be present in a magnetic field without disrupting it. Because of this property, deoxyhemoglobin is referred to as paramagnetic. Its presence in larges veins in the resting state make the veins stand out as dark lines (i.e. signal dropout; Figure 2b).

Box 2. Pneumoencephalography

A technique used by neurologists and neurosurgeons until the advent of X-ray CT to localize mass lesions such as tumors and blood clots in an around the brain. The technique consisted of removing spinal fluid and replacing it with air, which would rise in the remaining spinal fluid like air bubbles in water into the brain ventricles and over its surface when the patient was in an upright position. The patient was then manipulated in space while strapped into a specially mounted chair facilitating the movement of the air bubbles. X-rays were taken in various positions enabling clinicians to 'outline' the contours of the brain. Great skill was required to interpret these X-rays and, for the patient, this was most unpleasant because of the attendant severe headaches.

Box 3. Tissue autoradiography

This involves the systemic administration of a radiolabeled compound of interest. When the compound has reached the organ of interest the animal is sacrificed and the organ is removed, sliced and placed on X-ray film enabling researchers to assess the distribution of the radiolabeled compound. In the case of C^{14}-deoxyglucose (DG), an analog of the primary fuel of the brain, glucose, it enters the brain where it is taken up by cells in proportion to their metabolism. On entry into the cell it is phosphorylated. Once this has occurred the DG is trapped in the cell because its further metabolism is blocked because of its structure and exit from the cell is blocked because it is phosphorylated. Exquisite maps of brain metabolism in animals resulted from the extensive use of this technique in neuroscience research. This technique was extended to PET using deoxyglucose labeled with fluorine [18] rather than carbon [14].

Positron emission tomography

PET derives its name and its fundamental properties from a group of radionuclides (^{15}O, ^{11}C, ^{18}F and ^{13}N), whose properties include short half-lives (^{15}O = 2 min, ^{13}N = 10 min, ^{11}C = 20 min and ^{18}F = 110 min), a unique decay scheme involving the emission of positrons and chemical properties whose relevance to studies in biology and medicine arises from the fact that carbon, nitrogen and oxygen are the building blocks of most biological molecules and fluorine can be substituted for hydrogen in some molecules (for a review of PET fundamentals see Ref. [24]).

The use of radiopharmaceuticals labeled with positron-emitting radionuclides for biomedical research and clinical application had been the objective of several research groups. The first medical cyclotron was installed in the Hammersmith Hospital in London in 1955 and was followed by installations at the Massachusetts General Hospital and Washington University's Mallinckrodt Institute of Radiology in 1965. By 1974 there were 15 such installations worldwide [25]. Work among these groups provided much important background knowledge for the introduction of PET (for reviews, see Refs [26–28]).

A group of investigators at Washington University's Mallinckrodt Institute of Radiology were inspired by the introduction of X-ray CT. They were working with radiopharmaceuticals labeled with positron-emitting radionuclides with a focus on studies of the brain. They realized that if an image of the density of a transverse section of the body could be reconstructed from the measured attenuation of highly-focused X-ray beams projected through the section (i.e. the basis of X-ray CT), then the distribution of a radionuclide within the section (especially ones that decayed by positron emission) could be accurately and quantitatively reconstructed from its emissions (interestingly, this idea was first suggested, but not implemented, in 1951 [29]). A flurry of activity ensued resulting in the design and construction of a positron emission tomograph christened PETT (positron emission transaxial tomography) [30,31]. The term 'transaxial' was later dropped to make it simply PET as we know it today.

Metabolism versus blood flow

Work on the neural correlates of human behaviors with PET began with studies of brain glucose metabolism and the tracer ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG). This was an extension of the autoradiographic deoxyglucose technique (Box 3) developed by Sokoloff and his colleagues (National Institutes of Health) for studies in laboratory animals [32]. Sokoloff had demonstrated the sensitivity of this technique to functional changes in neuronal activity in a wide-ranging group of animal experiments (for an excellent early summary see Ref. [33]).

With FDG PET, 30–40 min was used typically for image acquisition. Because of this long data-acquisition time, functional brain mapping as we know it today would not have developed. Needed were speed of data acquisition and measurement repeatability to assess brain function. Because of this, blood flow became the technique of choice with PET because it could be measured quickly (<1 min) using an easily produced radiopharmaceutical ($H_2{}^{15}O$) whose short half life (123 s) enabled repeat (up to 12) measurements in the same subject.

Magnet resonance imaging

Finally, another technology emerged contemporaneously with PET and CT. This was MRI. MRI is based upon yet another set of physical principles associated with the behavior of atoms in water (often described by their nuclei or protons) in a magnetic field. When placed in a strong magnet field, these protons behave like tiny bar magnets by lining up in parallel with the magnet field. When these protons are disturbed from their equilibrium state by radio frequency pulses, a voltage is induced in a receiver coil that can be characterized by its change in magnitude over time. Because these time-dependent changes in voltage are a function of the local environment of the protons, many important deductions can be made about the tissue being examined.

The physical principles associated with MRI were discovered independently by Felix Bloch (Harvard University) and Edward Purcell (Stanford University) and his colleagues in 1946 (for detailed early reviews of this work see Refs [34,35]). Many years of research followed, in which the technique was used for basic research in chemistry. During this time it was known as nuclear magnetic resonance (NMR).

In 1973, Paul Lauterbur [36] came up with a strategy in which the NMR signals could be used to create cross-sectional images in much the same manner as CT (for a review, see Ref. [37]). Interest was immediate not only because the technique was free of any ionizing radiation but also because it produced superb images of the human

body with much greater detail and variety than CT because of its sensitivity to soft tissues. Although imaging with this technique initially retained the name nuclear magnetic resonance or NMR, it was changed after a short time to magnetic resonance imaging or MRI to eliminate the term 'nuclear', which some thought might detract from its clinical acceptance.

Although clinical imaging with MRI flourished after its introduction, there also existed in the scientific community the knowledge that MRI could also tell us much about tissue chemistry, perfusion and metabolism. This view was the result of many years of basic NMR research indicating that intrinsic signals from tissue in addition to signals from exogenously administered MRI contrast agents could be used to extract such information. Functional brain imaging with MRI was able to tap this knowledge base with remarkable results. It was an interesting convergence of research in MRI techniques, studies of the magnetic properties of deoxyhemoglobin and research on circulatory and metabolic correlates of changes in brain activity (see earlier) that led to the development of this approach.

The emergence of functional MRI

A important first step in the development of fMRI was the work of group of researchers at the Massachusetts General Hospital working on the use of exogenously administered MRI contrast agents designed to produce transient changes in the MRI image as the agent passed through the brain after its intravenous administration. Work in rodents [38] and dogs [39] using contrast agents confined to the vascular compartment and novel rapid data acquisition strategies demonstrated for the first time with MRI that it was possible to measure changes in brain blood volume produced by physiological manipulations of brain blood flow. This approach was extended to normal human volunteers for task activation brain mapping by the same group in 1991 [40] in a much heralded study demonstrating for the first time that MRI was to be a serious player in the functional mapping of the human brain.

This study caused much excitement, especially in the MRI community, which was anxious to join the rapidly expanding cognitive neuroscience revolution. What this study demonstrated clearly was that, within one imaging modality, superb anatomical images and physiology relevant to brain function could be combined. The primary limitation of the approach was the need to administer a contrast agent, which is something that could only be done a limited number of times. However, physiology (Figure 2a) and the ingenuity of the MRI researchers came to the rescue. The answer came from the property of deoxyhemoglobin in a magnetic field.

It was Michael Faraday who first studied the magnetic properties of hemoglobin. In experiments on the 8 November 1845 he noted (to his surprise because hemoglobin contains iron) that dried blood was not magnetic, writing 'Must try fluid blood' [41]. Remarkably, 91 years later his obscure laboratory note somehow caught the attention of Linus Pauling and Charles Coryell [23] who found that the magnetic susceptibilities (i.e. the ability to interact with a magnetic field) of oxygenated and deoxygenated hemoglobin differed significantly. Deoxyhemoglobin was paramagnetic and, hence, equivalent to an MRI contrast agent, whereas oxyhemoglobin was not (Box 1). Of course, the role of this observation in the development of fMRI did not occur to Pauling and Coryell.

In 1982, Keith Thulborn took the story one step further while seeking to exploit the difference in magnetic susceptibility of oxy- and deoxyhemoglobin for the measurement of brain oxygen consumption with MRI [42]. In this often overlooked work he clearly demonstrated the feasibility of measuring the state of oxygenation of blood *in vivo* with MRI, another crucial step on the road to fMRI BOLD imaging as we know it.

Experiments performed by Sieji Ogawa and colleagues (AT&T Bell Laboratories) were a crucial next step in establishing the basis of fMRI BOLD imaging. In their experiments, the concentration of deoxygenated blood in the brains of living rodents was manipulated by alternately breathing his animals on room air and 100% oxygen. On room air, detailed anatomy of venules and veins were easily visible throughout the rat brain as dark structures (Figure 2b). This was owing to the loss of MRI signal in the presence of deoxyhemoglobin (Box 1). On 100% oxygen, the venous structures disappeared. Ogawa labeled his finding 'blood oxygen level dependent contrast' or BOLD contrast [43] and noted that 'BOLD contrast adds an additional feature to magnetic resonance imaging and complements other techniques that are attempting to provide positron emission tomography-like measurements related to regional neural activity' [43].

The potential of BOLD fMRI was soon realized (Figure 2c) with publications from three groups in 1992 [44–46]. The events leading up to these publications (particularly from the group at the Massachusetts General Hospital led by Ken Kwong [44] and the group that represented the combined resources Sieji Ogawa and David Tank from the AT&T Bell Laboratories and Kamil Ugirbil, Ravi Menon and their colleagues at the University of Minnesota [46]) provide insight into how the research actually unfolded. Space here does not permit a detailed recounting of these fascinating events. Interested readers might wish to read a more detailed account, based on my interviews with the key participants [47].

Since the introduction of fMRI BOLD imaging, the growth of functional brain imaging has been nothing short of spectacular. Although MRI also offers additional approaches to the measurement of brain function [44,48], it is BOLD imaging that has dominated the research agenda thus far.

However, the success of the human brain imaging was the product not only of relevant physiology that could be imaged and the scanning devices that could accomplish this but also of the behavioral paradigms that approached human behavior in a principled and quantitative manner while accommodating the constraints of the imaging environment and strategies to process the resulting data. I turn to these important issues next.

Image processing

Stereotaxy

As PET images of task-induced changes in regional blood flow started to accumulate, an old problem resurfaced.

How do you objectively relate functional imaging data to brain anatomy? This problem was neither new to functional brain imaging with PET nor previously unexplored.

The solution came in the form of a technique called 'stereotaxy', which was first developed by Horsley and Clarke for animal research in 1908 and much later applied by to humans by neurosurgeons (for additional details see Ref. [47]). Stereotaxy in humans is usually based on the assumption that all points in the cerebral hemispheres of an individual have a predictable relationship to a horizontal plane running through the anterior and posterior commissures. Acquiring specific measurements of an individual brain, obtained from a skull X-ray [49], CT, MRI or even a PET blood-flow image [50], permits an exact relationship to be established with a 'standard' brain in one of the stereotaxic brain atlases.

Although continuing to be modified and refined, this strategy has remained a central feature of all functional brain imaging in humans. Interesting recent advances have included the development of a probabilistic brain atlas by an international consortium of researchers [51] and surface-based coordinate systems of the human cerebral cortex [52].

Image averaging

The initial use of stereotaxy in PET functional brain imaging was to determine the location of activity changes. This approach worked nicely for robust responses that could be appreciated in individual difference images (Figure 2a). However, other early experiments yielded data in which the responses were not robust, were varied from subject to subject in location and were easily confused by what was being termed image 'noise'. These data were proving to be problematic and generated much concern. Most worrisome was the observation that, after conversion of a response focus from an individual difference image into stereotaxic space, there remained considerable variability in the location of the responses across individuals.

In response to these problems and concerns, an effort was mounted at Washington University to obtain averages of difference images across subjects in a standard stereotaxic space. The wisdom of this effort was not universally embraced by members of the laboratory. The skeptics maintained that individual variability was simply too great to accommodate averaging. The skeptics predicted that averaged images would be just 'mush'.

When the first set of averaged blood-flow images from a group of five subjects receiving somatosensory stimulation of one hand came up on the monitor, it was obvious to everyone present that they were neither unrecognizable nor 'mush'. Noise was dramatically reduced and responses were crisp and clear [53]. Skepticism vanished instantly. The processing of functional brain images had taken an important step forward. From PET on to fMRI, averaging in one form or another both across and within individuals, is a key element in the processing of functional image data.

Statistical analysis

With the aforementioned strategies in hand (i.e. stereotaxic normalization, image averaging), investigators using PET were suddenly confronted with yet another challenge: images containing enormous amounts of data. The specter of unacceptably high false discovery rates loomed large without an obvious remedy. One obvious approach would have been to place independently determined regions of interest within difference images to test specific hypotheses about how the task under investigation was instantiated in the brain (i.e. traditional hypothesis testing). One important drawback to this approach was that it assumed the very knowledge that was being sought, namely, how the brain is organized. What was needed was a hypothesis-generating approach.

Many of the details of how these uniquely challenging statistical questions were addressed are now of historical interest only (for more details see Ref. [47]). Statisticians, statistically minded neuroscientists and others quickly found the problems inherent in the analysis of functional brain images from PET and MRI stimulating and challenging (for a review, see Ref. [47]). From these important beginnings the approaches have become increasingly sophisticated, varied and powerful.

The behavioral agenda

The study of human cognition with PET was aided greatly by the involvement of cognitive psychologists in the 1980s whose experimental designs for dissecting human behaviors using information-processing theories fit extremely well with emerging functional brain-imaging strategies [54]. It might have been the combination of cognitive psychology and systems neuroscience with brain imaging that lifted this work from a state of indifference and obscurity in the neuroscience community in the 1970s to its current role of prominence.

This strategy was based on a concept introduced by the Dutch physiologist Franciscus C. Donders in 1868 (reprinted in Ref. [55]). Donders proposed a general method to measure thought processes based on a simple logic. He subtracted the time needed to respond to a light (say, by pressing a key) from the time needed to respond to a particular color of light. He found that discriminating color required ~50 ms. In this way, Donders isolated and measured a mental process for the first time by subtracting a control state (i.e. responding to a light) from a task state (i.e. discriminating the color of the light). This strategy was first fully implemented in an early series of papers on single-word processing [56,57] (Figure 3). Since then, it has been exploited with exponentially increasing sophistication in the functional imaging world.

Although much that is currently being done with fMRI can be viewed as a logical extension of work with PET, one addition to the fMRI armamentarium represented a truly unique and important advance in the way in which functional brain imaging was done. This was the introduction of single-trial or event-related fMRI [58–61]. When the cognitive subtraction strategy was implemented, cognitive psychologists had to abandon their traditional mixed-trial design in which the properties of stimuli were varied within a single trial. PET imaging even with blood flow was too slow to measure responses to individual stimuli with any accuracy. fMRI, however, was quite capable of doing so. As with other aspects of imaging, single-trial fMRI has advanced rapidly in terms of sophistication.

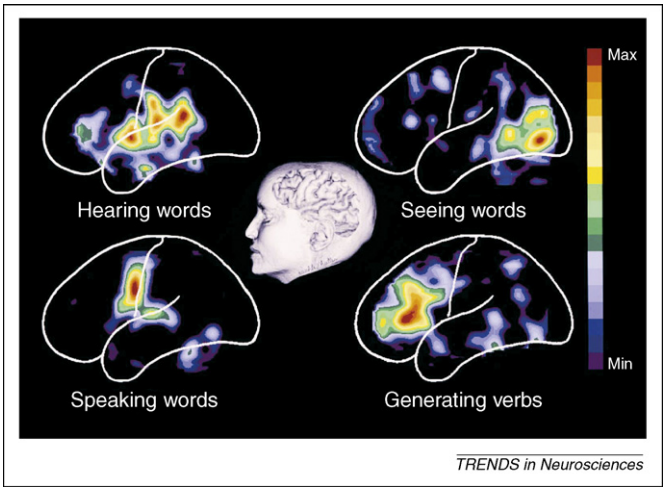

Figure 3. Iconic PET blood-flow-difference images obtained from an early study of the processing of single words [57], in this case common English nouns. This was one of the first studies to combine a hierarchical task design (visual fixation – hearing or seeing nouns – speaking nouns – generating verbs) with image subtraction, cross-subject image registration and averaging. It established a basic paradigm for this type of work that has persisted to the present.

The present

It is easy to be optimistic about the human brain-mapping agenda. Its growth, particularly since the advent of fMRI BOLD imaging, has been dramatic. However, challenges do arise because of the immense diversity of this agenda.

Neuroscientists interested in brain function from a cellular and molecular perspective now are obliged to understand not only the concepts and strategies of cognitive psychology but also a wide array of behavioral disciplines covered under the rubric of social neuroscience [62,63]. At the same time, behavioral scientists interested in relating their work to the brain are confronted by a rapidly increasing body of knowledge concerning the biological correlates of functional neuroimaging signals. Understanding this work depends on complex concepts not only from neurophysiology [2,6] but also from theoretical neuroscience [64,65], cell biology [1] and even genetics [66]. The complexity of all of this increases when issues related to disease are introduced as they are with increasing frequency. It is easy to understand, then, how researchers at all levels occasionally feel a sense of unease in dealing comprehensively with this agenda. Under such circumstances, it is tempting to retreat into the narrow confines of one's own area of expertise; a pathway, however, that will ultimately limit the potential of one's work.

The future

As we look to the future, changes clearly appear on the horizon. It might be too strong to suggest that we are facing a paradigm shift [67], but certainly some reorientation is taking place in terms of how we understand brain function. Although this reorientation has received substantial

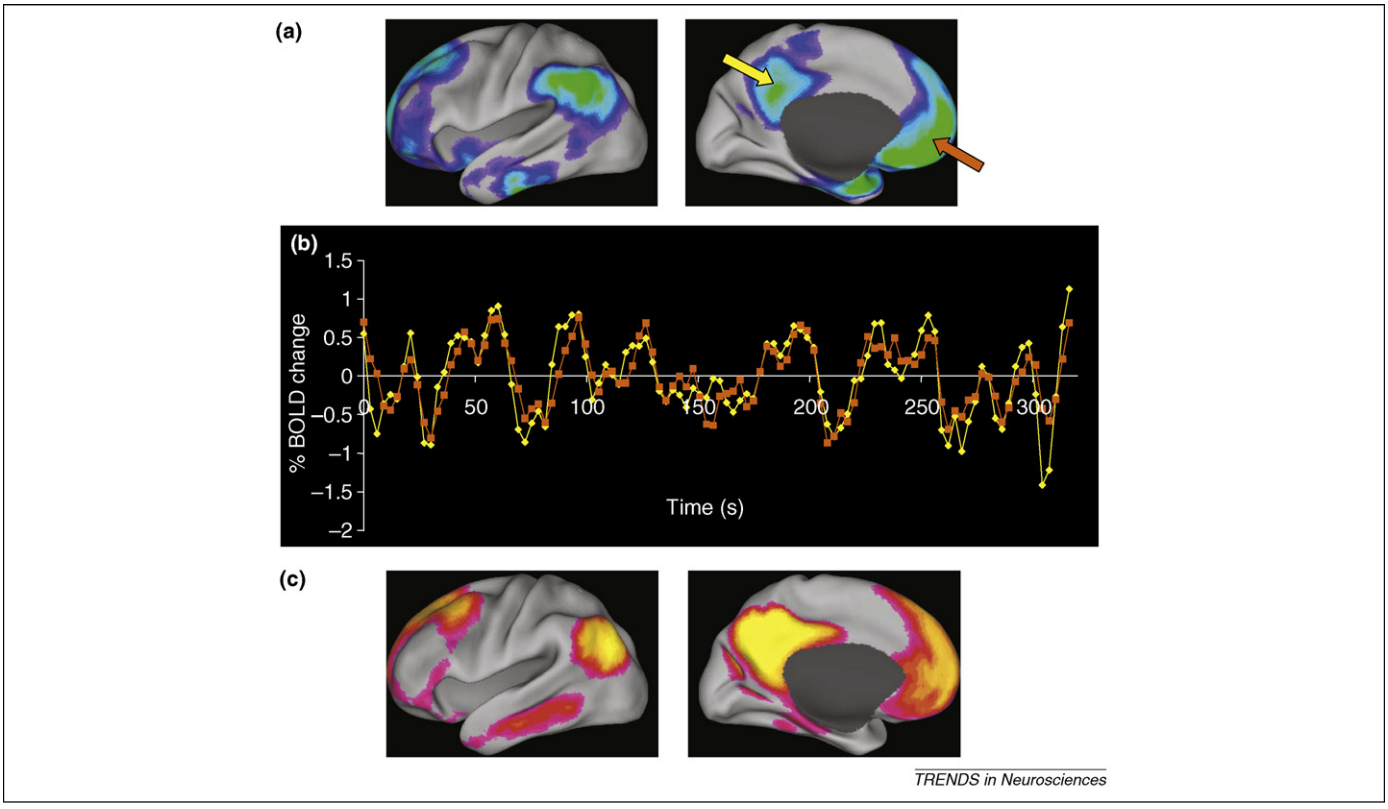

Figure 4. A comparison of activity decreases during the performance of goal directed tasks **(a)** in the default network [77] and coherent activity within the same network in the resting state derived from spontaneous fluctuations in the fMRI BOLD signal (see Ref. [73] for further details). Performance of a wide variety of tasks has called attention to a group of brain areas (a) that decrease their activity during task performance (data adapted from Ref. [78]). This particular group of brain areas has come to be known as the 'default network' and serves as an exemplar of all areas of the cerebral cortex that exhibit a systems level organization in the resting (default) state [73]. If the spontaneous fMRI BOLD signal activity in these areas is recorded [arrows in part (a)] in the resting state, what emerges is a remarkable correlation in the spontaneous fluctuations of the fMRI BOLD signals obtained from the two areas **(b)**. Using these fluctuations to analyze the network as a whole [73] reveals a level of functional organization **(c)** that parallels that seen in the task-related activity decreases (a). These data provide a dramatic demonstration of the intrinsic organization of the human brain, which is likely to provide a crucial context for all human behavior in health and disease. These data were adapted from our earlier published work [79].

stimulation from imaging work with PET and fMRI, it has its roots in more than a century of discussions on the nature of brain functions.

Since the 19th century, and possibly longer, two perspectives on brain functions have existed (an excellent introduction is to be found in chapter 1 of Ref. [68]). One view posits that the brain is primarily driven by external inputs; the other holds that the brain operates on its own, intrinsically, with sensory information interacting with rather than determining its operation. Although neither view is today dominant, the former clearly has motivated the majority of research at all levels of neuroscience including that in cognitive neuroscience. This is not entirely surprising given the enormous success of experiments measuring brain responses to controlled stimuli.

From a cost-based perspective, however, intrinsic activity seems to be far more important than evoked activity in terms of overall brain function. Studies of the actual changes in energy consumption associated with evoked changes in brain activity have revealed that the additional energy required for such brain responses represents an extremely small percent (~1.0%) of the ongoing energy consumption (for a review, see Ref. [1]). Furthermore, converging data indicate that 60–80% of the ongoing energy consumption reflects work associated with the input and output of neurons (for a review, see Ref. [1]). From this perspective it seems fair to conclude that a large fraction of the functional activity of the brain is unaccounted for [69]. What do we know about the organization of this activity from an imaging perspective?

PET provided an initial clue in the form of highly organized activity decreases during the performance of most goal-directed behaviors. This led to the concept of an organized default mode of intrinsic brain function [70] and the identification of a unique network of brain areas that typified this organization (i.e. the default mode network of the brain; Figure 4a; for a recent review of its functional importance see Ref. [71]). More recently, it was discovered by Biswal and colleagues [72] that the 'noise' in the fMRI BOLD signal in the frequency range below 0.1 Hz reflects spontaneous fluctuating neuronal activity (for a recent review, see Ref. [73]). This activity exhibits striking patterns of coherence within known brain networks in the absence of observable behaviors (Figure 4c). Future work in functional brain imaging using this approach is most exciting to anticipate.

Finally, a too often overlooked feature of brain-imaging signals is the presence of aerobic glycolysis (Figure 2a). Aerobic glycolysis is present in the resting state [74,75] and, when looked for, is observed to increase locally with increases in activity [19,22,76] (Figure 2a). The many unique contributions of glycolysis to such things as protein phosphorylation; membrane, DNA and RNA synthesis; and the brain's redox state are routinely overlooked when its importance is assessed solely on the basis of the amount of energy it provides (only 2 ATP versus 30 ATP for oxidative phosphorylation). As we seek to enrich our understanding of brain-imaging signals in the context of such important processes as learning, memory and development, understanding the role of glycolysis independent of its role in oxidative phosphorylation probably will be most informative.

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