Brain Work and Brain Imaging

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Abstract

Functional brain imaging with positron emission tomography and magnetic resonance imaging has been used extensively to map regional changes in brain activity. The signal used by both techniques is based on changes in local circulation and metabolism (brain work). Our understanding of the cell biology of these changes has progressed greatly in the past decade. New insights have emerged on the role of astrocytes in signal transduction as has an appreciation of the unique contribution of aerobic glycolysis to brain energy metabolism. Likewise our understanding of the neurophysiologic processes responsible for imaging signals has progressed from an assumption that spiking activity (output) of neurons is most relevant to one focused on their input. Finally, neuroimaging, with its unique metabolic perspective, has alerted us to the ongoing and costly intrinsic activity within brain systems that most likely represents the largest fraction of the brain's functional activity.

Contents

[P]hysiology and psychology, instead of prosecuting their studies, as some now recommend, more strictly apart one from another than at present, will find it serviceable for each to give to the results achieved by the other even closer heed than has been customary hitherto.
(Sherrington 1906)

PET: positron emission tomography

MRI: magnetic resonance imaging

fMRI: functional magnetic resonance imaging

INTRODUCTION

Over 30 years have now passed since the introduction of X-ray computed tomography (Hounsfield 1973). This event created a revolution in medical diagnosis and catalyzed the development of other imaging techniques, particularly position emission tomography (PET) and magnetic resonance imaging (MRI) (for historical reviews see Kevles 1997, Raichle 2003b, Webb 1990). The introduction of PET and MRI presented researchers with an unprecedented opportunity to examine the neurobiological correlates of human behaviors. This opportunity was seized by researchers worldwide, first with PET and later with functional MRI (fMRI) (for an historical review see Raichle 2000). The result was the creation of a new scientific discipline known as cognitive neuroscience (Gazzaniga 2004) and, more recently, social neuroscience (Cacioppo et al. 2002, 2005), with a combined agenda that now encompasses virtually all aspects of human behavior in health and disease (Illes et al. 2003).

Equally remarkable has been the worldwide movement to establish research-imaging centers in which expensive imaging equipment (primarily MRI), along with teams of investigators, is devoted exclusively to research (Raichle 2003a). This development breaks a longstanding tradition in which research on humans and laboratory animals uses clinical equipment, part time, in a hospital setting, usually after hours. We know of no recent compilation of the budget for this new agenda, but there is no doubt it is substantial.

Neuroimaging with PET and MRI has received considerable attention from the scientific community and the general public. This relates not only to the potential scientific and clinical importance of the work but also to the fact that cognitive and social neuroscience touches on subjects of importance to everyone. In addition, the imaging data produced by researchers are often quite intriguing: Observing the brain at work seems to fascinate scientists and nonscientists alike.

Despite these successes, some researchers have questioned the ability of this approach to provide analyses of brain function that are sufficiently refined to truly enlighten us about the relationship between behavior and brain function (Nichols & Newsome 1999). One of the keys to evaluating such concerns is to relate neuroimaging work to that which parallels it

in other areas of neuroscience as so presciently noted by Sherrington (1906) a century ago. Among the most important questions in this regard is how to relate neuroimaging measurements to the biology and neurophysiology of brain cells and their microvasculature. Importantly, there has been a burst of interest in the neurobiology of the signals generated by PET and MRI. This has ranged from neurophysiology (Lauritzen 2001, 2005; Logothetis et al. 2001; Mukamel et al. 2005; Thompson et al. 2004) to studies of brain circulation and metabolism (Buxton et al. 2004, Mintun et al. 2001, Offenhauser et al. 2005, Powers et al. 1996, Shulman et al. 2004), cell biology (Kasischke et al. 2004, Magistretti & Chatton 2005), and genetics (Fan et al. 2003, Pezawas et al. 2005).

Although knowledge is expanding rapidly, it is incomplete. As a result we recognize that some of the points we make in this review are speculative and, in some instances, controversial. Nonetheless, we hope they serve to identify important elements of the biology of neuroimaging that can usefully stimulate future discussion and research.

Finally, we would like our readers to appreciate that evaluating the results of neuroimaging research not only involves understanding what causes the evoked responses, the increases ("activations") and decreases ("deactivations") in neuroimaging signals, but also the context in which these changes are taking place. This involves defining a physiologic baseline level of activity in the brain and the intrinsic functional activity this baseline instantiates. In this review we address all these aspects of neuroimaging.

EVOKED FUNCTIONAL ACTIVITY

Blood Flow Follows Changes in Cellular Activity

Behaviorally evoked changes in blood flow are at the heart of functional brain imaging signals (**Figure 1**), whether they come from PET or fMRI. Italian physiologist Mosso (1881) first described what he correctly surmised to be a functional change in regional brain circulation evoked by the performance of a mental

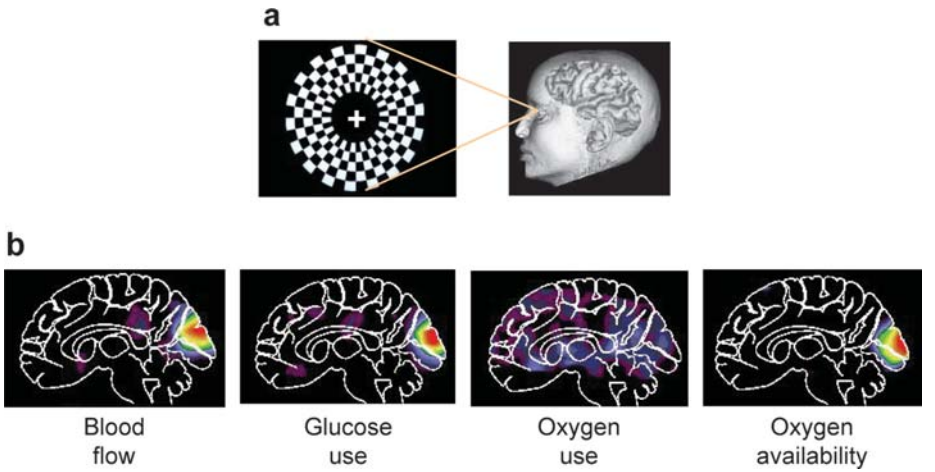

Figure 1

Stimulation of the human visual cortex with a reversing annular checkerboard when compared with a simple fixation crosshair (*a*) produces dramatic increases in blood flow and glucose use in the visual cortex that are unaccompanied by similar increases in oxygen use (*b*). The result is an increase in the local oxygen availability (*b*) because the increased supply of oxygen by flowing blood exceeds the increased local demand for oxygen. Data adapted from Fox et al. 1988.

BOLD: blood oxygen level dependent

Local field potentials (LFPs): the electrical fields recorded from microelectrodes in the brain thought to reflect the weighted average of input signals on the dendrites and cell bodies of neurons in the vicinity of the electrode

arithmetic task. Measuring continuous brain pulsations over the right prefrontal cortex of a subject with a bony defect in the skull, he noted that both when his subject commenced the calculation and later reported the result, brain pulsations rose over the right prefrontal cortex. We know from Mosso's records that this remarkable experiment was performed on Monday, September 23, 1878. In the intervening 128 years, experiments too numerous to count have amply confirmed and extended this observation (for reviews, see Lassen et al. 1978; Raichle 1987, 2000). In the modern era of neuroimaging, its derivatives are undoubtedly performed hundreds if not thousands of times a day.

Despite the centrality of blood-flow changes to the imaging signals we observe with PET and fMRI, the complexity of the relationship of blood flow and metabolism to the underlying cellular events has only recently become more fully appreciated. One of the unresolved issues is just why blood flow changes with the brain activity. The intuitively appealing notion that blood-flow changes merely serve to adjust glucose and oxygen delivery to the variable energy demands of the brain now appears oversimplified if not factually incorrect (Mintun et al. 2001, Powers et al. 1996). We hope our reasons for making such an assertion will become clear as we review work here that has shaped our opinions. We begin with an examination of the neurophysiologic correlates of this blood-flow change.

Neurophysiology of Neuroimaging

It is logical to ask what it is in the behavior of neurons that accounts for the blood-flow changes we observe in neuroimaging. For many the answer generally has been the spiking activity or output of neurons. This view likely reflects the success achieved in recording single- and multiunit activity mainly in large, active principal neurons and the important insights these studies have provided. This perspective has begun to change as the result of recent work, but uncertainty lingers in the minds of many.

In highly influential work on the issue, Logothetis and colleagues (2001) used sophisticated and technically demanding methodology to combine electrophysiological and fMRI blood oxygen level—dependent (BOLD) measurements in the same experimental animal. In studies of the visual cortex of the anesthetized monkey where simultaneous measurements were made of single- and multiunit activity along with local field potentials (LFPs) and BOLD contrast, they were able to show experimentally that the BOLD signal best correlated with the LFPs and not the unit activity. They concluded that fMRI BOLD signals are a reflection of changes in LFPs and not spikes (Logothetis 2003, Logothetis & Wandell 2004, Logothetis et al. 2001).

Examination of Logothetis et al.'s (2001) modeling data, however, has caused some to question this conclusion. These doubts have arisen from a comparison of the r^2 values obtained from correlations between LFPs and BOLD ($r^2 = 0.521$) with those obtained from correlations between BOLD and multiunit activity ($r^2 = 0.445$). Although significantly different statistically (i.e., LFPs > multiunit activity), these theoretical correlations have suggested to some that an exclusive relationship between BOLD and LFPs and the physiology LFPs represent may not exist.

Another recent paper appears to support these concerns (Mukamel et al. 2005). In this study, Mukamel et al. (2005) compared single-unit activity and LFPs with changes in fMRI BOLD in two groups of awake humans exposed to the same stimulus paradigm. The electrophysiology was done in one group of two individuals with epilepsy and implanted electrodes, and the BOLD imaging was done in another group of 11 normal subjects. The spikes and LFPs from the first group were used in a regression analysis of the BOLD contrast data from the second group. The investigators found equally good correlations between LFPs and BOLD contrast as those

between spikes and BOLD contrast. They concluded that "fMRI signals can provide a reliable measure of the firing rate of human cortical neurons."

How are we to distinguish causality from correlation in such experiments? Is it the input to neurons as reflected in LFPs that primarily drives the generation of functional brain imaging signals or is it the output of neurons as manifested by their spiking activity? If it is the former, how do we explain results that suggest spiking activity and LFPs are nearly equivalent in their ability to predict the imaging signals (Mukamel et al. 2005)? These are questions that confront anyone hoping to better understand the relationship between functional imaging signals and the underlying cellular events. We believe the evidence favors a dominant role for the input to neurons as reflected in the LFPs for the following reasons.

Early experimental work by Schwartz and colleagues (1979) provides critical supporting evidence. In their experiments they measured regional brain–glucose metabolism in rats using the then newly introduced 2-deoxyglucose tissue autoradiographic technique for the measurement of regional brain–glucose metabolism in laboratory animals (Sokoloff et al. 1977). In their experiments they subjected rats to an osmotic load sufficient to stimulate cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. Important for the results they obtained, the axon terminals of these cells reside in the posterior pituitary gland, at a significant distance from the cell bodies. This made it possible to unambiguously compare the metabolic activity in the two locations.

The result was dramatic (**Figure 2**); metabolism increased significantly in the area of the axon terminals in the posterior pituitary gland and not measurably in the cell bodies residing in the hypothalamus. This result was not only supported by other work (Lightman et al. 1982, Mata et al. 1980, Sharp 1976, Wong-Riley 1989), but also was consistent with the known correlation between the cost of maintaining ionic gradients and the

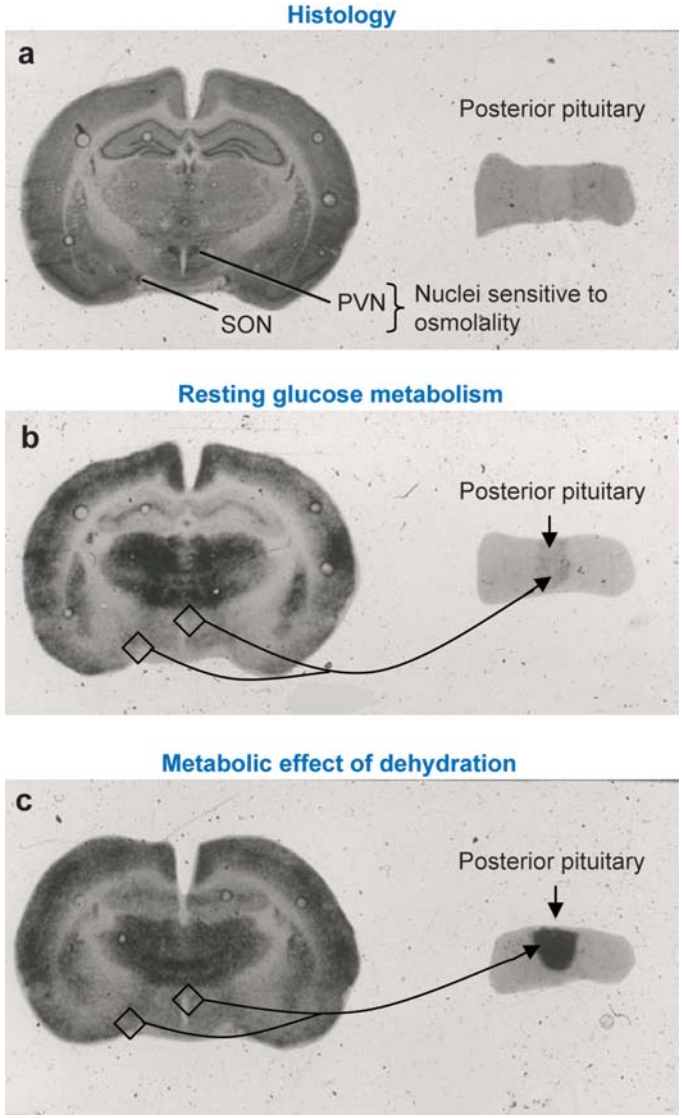

Figure 2

(*a*) A coronal histological section of the rat brain (Nissl stain) at the level of the hypothalamus (*left*) and the pituitary gland (toluidine blue stain; *right*). (*b*) Resting glucose metabolism measured autoradiographically with (^{14}C)-2-deoxyglucose (Sokoloff et al. 1977). (*c*) Glucose metabolism during osmotic stimulation. Osmotic stimulation of the supraoptic and paraventricular nuclei of the hypothalamus of the rat by increasing the osmolality of its drinking water causes minimal if any change in the metabolism of the cell bodies in the hypothalamus but dramatic increases in the metabolism of axon terminals in the posterior pituitary. Figure adapted from Schwartz et al. 1979 with permission.

surface-to-volume ratio of the involved cellular elements (Cohen & De Weer 1977, Ritchie 1967).

Consistent with these early results have been more recent studies showing clearly that local tissue blood flow can be dissociated dramatically and convincingly from the spiking activity of neurons, whereas blood flow measured in the same experiments is consistently correlated with the LFPs (Lauritzen 2001, Thomsen et al. 2004). To our knowledge, experiments in which blood flow and LFPs change in parallel and are anticorrelated with spiking have no convincing experimental counterpart in which blood flow and spiking activity change in parallel and are anticorrelated with the LFPs.

How then do we understand experimental results that show equivalent correlations of the imaging signals with LFPs and the spiking activity of neurons (Mukamel et al. 2005)? The answer probably lies in the manner in which the cerebral cortex is organized intrinsically, important features of which are invisible to imaging techniques such as fMRI and PET. Quite simply, the vast majority of the excitatory and inhibitory nerve terminals in the cerebral cortex come from cells in the immediate vicinity of the synapse (Binzegger et al. 2004, Sillito & Jones 2002, Stettler et al. 2002). It is actually quite surprising how few cortical synapses are associated with cells outside of the cerebral cortex. For example, only approximately 5% of the synapses in V1 come from cells in the lateral geniculate nucleus in the cat (Peters & Payne 1993), and comparable numbers have been found in the monkey (Peters et al. 1994). Therefore it should come as no surprise that similar correlations might well be observed between functional imaging signals and both LFPs and spikes. It is when a discrepancy is encountered that it becomes important to understand the true basis of the imaging signals. A particularly telling example occurred when attentionally mediated changes in activity were observed in V1 with imaging but not with traditional single-unit recording (Pessoa et al. 2003).

Thus, in our view, it is incorrect to propose using functional neuroimaging signals as simple surrogate measures of the spiking activity of neurons. Rather, these results provide complementary information related to the input into a neuronal assembly, which may (Mukamel et al. 2005), or may not (Lauritzen 2001, Thomsen et al. 2004), correlate with the output. It all depends upon the particular circumstances. Adopting this perspective greatly increases the probability of properly interpreting extant and future research, especially when electrophysiological recordings and brain imaging results are compared, as they should be.

As research on the neurophysiologic correlates of the functional brain imaging signals has moved forward, it has become increasingly apparent that astrocytes also play a critical role. This view has emerged as the result of a new appreciation of the complex manner in which the energy necessary for brain function is generated. We turn to these important issues below.

Unique Features of Brain Metabolism

Standard teaching in most textbooks is that the energy needed for brain function is produced entirely by the oxidation of glucose to carbon dioxide and water (Siesjo 1978). Because the brain tissue itself contains relatively little dissolved oxygen (most unused oxygen in the brain remains bound to hemoglobin in red blood cells), it logically follows that the brain must be dependent for its moment-to-moment functions on a continuous supply of oxygen via flowing blood. Consistent with this observation is the fact that consciousness is lost in approximately 15 s when blood flow suddenly ceases owing to a failure in the cardiovascular system (e.g., cardiac arrest or vasodepressor syncope). On the basis of this rather straightforward reasoning, it was, for many years, nearly universally believed that blood-flow increases associated with cellular-activity increases must be related

to the need for additional oxygen, notwithstanding a number of early observations suggesting blood flow might increase in excess of the increase in oxygen consumption (e.g., see Brodersen et al. 1973, Cooper & Crow 1975, Howse et al. 1973, Plum & Duffy 1975, Plum et al. 1968). Some reluctance to accept an alternative explanation suggested by these early studies likely relates to the fact that most, but not all, of the observations were made in the setting of experimentally induced epileptic seizures, a condition involving highly abnormal increases in brain activity often accompanied by profound cardiovascular changes (i.e., increases in blood pressure and cardiac output).

Because of the belief that the brain is dependent for its moment-to-moment function on the oxidation of glucose, it came as a great surprise to most when it was first quantitatively demonstrated in the normal human brain with PET that activity-induced increases in blood flow are not accompanied by proportionate increases in oxygen consumption (Blomqvist et al. 1994, Fox et al. 1988, Madsen et al. 1995) (**Figure 1**). Although oxygen consumption does increase, this increase is much less than the increase in blood flow and glucose consumption. Two important results of this discovery led to the birth of fMRI (see The Origins of Functional Magnetic Resonance Imaging) and a re-examination of brain energy metabolism. We now examine the latter in some detail.

THE ORIGINS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING

Pauling & Coryell (1936) demonstrated that deoxygenated hemoglobin disrupts a magnetic field, whereas oxygenated hemoglobin does not. For this reason MRI images, which are obtained using an intense magnetic field, can exhibit darkening of the image in areas of draining veins owing to the loss of signal. If blood flow increases suddenly in the face of an increase in cellular activity and this increase is not accompanied by an increase in oxygen consumption of comparable magnitude (Fox & Raichle 1986, Fox et al. 1988), oxygenation in capillaries and veins is increased (i.e., supply increases more than demand) (**Figure 1**). Ogawa and colleagues (1990) demonstrated this would lead to an enhancement of the MRI signal that could be detected. They termed this enhancement the BOLD contrast. Beginning remarkably soon after the first demonstrations in humans (Bandettini et al. 1992, Kwong et al. 1992, Ogawa et al. 1992), BOLD contrast fMRI has come to dominate the functional neuroimaging field.

BLOOD FLOW AND OXIDATIVE PHOSPHORYLATION

One especially well-articulated and thoughtful line of research has focused specifically on the relationship between blood flow and oxygen consumption. Work pioneered by Buxton and colleagues (2004) is exemplary in this regard. They have examined in various ways the possibility that the discrepancy between the blood flow and oxygen consumption changes could result from the well-known fact that oxygen is poorly diffusible in brain tissue. According to this view, blood flow necessarily must increase more than oxygen consumption when cellular activity increases to maintain the tissue-oxygen gradients necessary for adequate delivery of oxygen to the tissue. In our view this hypothesis, intuitively appealing as it might seem, has been challenged successfully by two observations.

First, experimentally decreasing oxygen availability in circulating blood by having normal subjects breath air with a reduced oxygen content fails to cause a compensatory blood-flow response when brain cellular activity is stimulated (Mintun et al. 2000). This is consistent with an important earlier observation that graded hypoxia does not stimulate resting brain–blood flow in normal subjects until a critical threshold is reached (Shimojyo et al. 1968), a threshold much lower than that posited to occur in functional brain imaging experiments (Mintun et al. 2000).

Second, sustained visual stimulation (i.e., 25 min) is associated with an initial increase in blood flow far in excess of oxygen consumption. But over time, oxygen consumption

Aerobic glycolysis: glycolysis occurring in the presence of oxygen but in excess of that required for the production of the pyruvate needed for oxidative phosphorylation

Glycolysis: the energy-generating biochemical process whereby intracellular glucose is converted to pyruvate and lactate with the net production of two ATP molecules

Oxidative phosphorylation: the energy-generating biochemical process whereby intracellular pyruvate, produced by glycolysis, is oxidized to carbon dioxide and water with the production of 30 ATP molecules of ATP. This process requires oxygen.

ATP: adenosine triphosphate

begins to increase as blood flow falls (Mintun et al. 2002). This is further evidence that the increase in blood flow associated with an increase in cellular activity is not invariably driven by an increased demand for oxygen.

If the brain were to rely on a timely increase in oxygen delivery every time neuronal activity suddenly increased, a change in blood flow would not be the answer. The blood-flow response to a sudden change in neuronal activity is remarkably slow relative to the events that provoke it (Boynton et al. 1996). It usually begins several seconds after the onset of a change and does not reach its maximum for 4–6 s. This is hardly the type of response needed to cope with a sudden increase in the requirement for oxygen occurring over milliseconds, although it might well accommodate more slowly varying, spontaneous activity, a subject we discuss below.

Thus, instead of depending on a timely increase in blood flow to supply an increased need for oxygen, it would be far more efficient for the brain simply to extract more oxygen from that available in the circulating blood. On average approximately 40% of available oxygen is removed from blood passing through the brain, leaving a substantial reserve to cope with sudden increases in demand. Such an intuitively appealing mechanism has been posited to occur on the basis of research with optical imaging (Vanzetta & Grinvald 1999) and other techniques capable of measurements of tissue oxygenation at a temporal resolution approximating that of the changing cellular events (Kasischke et al. 2004; Offenhauser et al. 2005; Thompson et al. 2003, 2004). In these studies researchers have observed a sudden local decrease in oxygenated hemoglobin that is reversed seconds later when blood flow increases in excess of the oxygen demands of the tissue. This initial transient decrease in oxygenated hemoglobin has been termed the "initial dip" and interpreted as evidence for a sudden increase in oxygen consumption in advance of an increase in blood flow. Despite these results, this intuitively appealing concept has remained controversial because the initial dip is not always found (Buxton 2001, Kim et al. 2000, Logothetis 2000, Thompson et al. 2004).

One of the most important but often overlooked observations in discussions of the genesis of functional imaging signals is the increase in glucose consumption that invariably accompanies the increase in blood flow (Blomqvist et al. 1994, Fox et al. 1988, Madsen et al. 1995) (**Figure 1**). Because this occurrs in the presence of adequate tissue oxygenation it is referred to as aerobic glycolysis. We turn to a discussion of this observation and its implications for our understanding of the cell biology of brain imaging signals below.

Aerobic Glycolysis

As discussed above in detail, the vast majority of the energy consumed by the brain is provided by the metabolism of glucose to carbon dioxide and water, a process that begins with glycolysis and ends with oxidative phosphorylation. It is easy to think of the two processes as inextricably linked in the normal brain. That is likely not strictly the case (**Figure 3**).

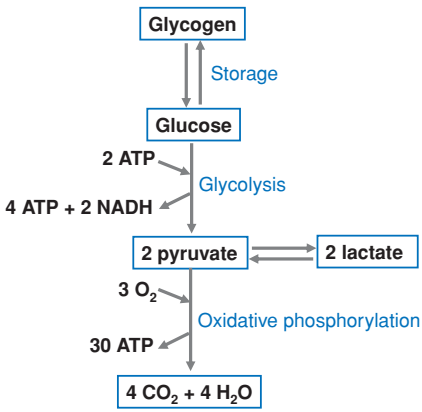

Figure 3

A schematic representation of the metabolism of glucose from glycolysis to oxidative phosphorylation. Energy for brain work is produced in the form of adenosine triphosphate (ATP). Glucose is available from flowing blood as well as glycogen stored in astrocytes. When pyruvate is produced in excess of that needed for oxidative phosphorylation, it is converted to lactate.

Both glycolysis and oxidative phosphorylation produce energy in the form of adenosine triphosphate (ATP) but by far the largest amount is produced by oxidative phosphorylation (~30 ATP molecules per molecule of glucose compared with a net of 2 for glycolysis). Oxidative phosphorylation is obviously a much more efficient process than glycolysis in terms of the amount of glucose needed for the energy produced. As such, oxidative phosphorylation is the source of most of the energy needed for neuronal signaling in the brain. However, it need not be the only source, especially during rapid increases in neuronal activity. An important advantage that glycolysis has over oxidative phosphorylation, other than it can operate without oxygen, is that it is much faster (McGilvery & Goldstein 1983). Because glycolysis is able to make pyruvate much faster than it can be oxidized, ATP can be made nearly twice as fast by converting glucose to lactate, which accumulates in the presence of excess pyruvate (**Figure 3**), as it can by oxidizing glucose completely. This speed by which glycolysis can deliver energy beginning with either glycogen or glucose may offer one explanation for a role in brain cellular function independent of oxidative phosphorylation when a sudden change in activity must be accommodated. Although the contribution of glycolysis alone to brain energy production may be small in relation to that produced by oxidative phosphorylation, that contribution may be, nevertheless, of strategic importance.

The Role of the Astrocyte

The suggestion that glycolysis has a special role in brain energy production stimulated an important series of investigations focused on astrocytes (Kasischke et al. 2004, Magistretti et al. 1999, Pellerin & Magistretti 2004). From this work has emerged the concept that the observed increase in glycolysis results from the uptake of glutamate into astrocytes from excitatory synapses along with Na^+ (**Figure 4**). The intracellular glutamate is converted to glutamine and the resulting rise in intracellular sodium increases the activity of membrane-bound Na^+/K^+-ATPase. Both processes result in the hydrolysis of ATP (Erecinska & Silver 1994, Magistretti & Chatton 2005, Silver et al. 1997). The synthesis of new ATP appears to be done by glycolysis alone, at least in the astrocyte.

The general idea that glycolysis might supply ATP for membrane-bound Na^+/K^+-ATPase is neither new nor restricted to the brain. Data from human red cell membranes (Mercer & Dunham 1981), skeletal muscle (Okamoto et al. 2001), vascular smooth muscle (Campbell & Paul 1992), and neurons (Wu et al. 1997) all provide independent evidence in support of such a possibility. Several other lines of research provide additional support directly related to astrocytes.

Glycolytically linked modulation of blood flow. Recent work in laboratory animals (Ido et al. 2001, 2004) and humans (Mintun et al. 2004, Vlassenko et al. 2006) has demonstrated that the blood-flow response to an increase in the cellular activity is modified by changes in the plasma lactate/pyruvate ratio: Blood flow is augmented when the lactate/pyruvate is raised and attenuated when it is lowered. On the basis of the near equilibrium between the ratios of lactate/pyruvate and cytosolic free $NADH/NAD^+$ (which reflects the intracellular redox state), these results suggest NADH is an important sensor of the circulatory needs of the cell linked to its glycolytic activity. The latter cannot proceed to generate ATP without the continuing replenishment of NAD^+. That such a blood flow–sensing mechanism might be housed within astrocytes as suggested by Kasischke and colleagues (2004) adds to the potential importance of this cell in the ongoing functional activity of the brain and highlights its role in mediating the blood-flow responses so critical to the genesis of the neuroimaging signals (Mulligan & MacVicar 2004, Takano et al. 2006, Zonta et al. 2003).

Astrocyte glycogen. The critical role for astrocyte glycolysis in glutamate cycling

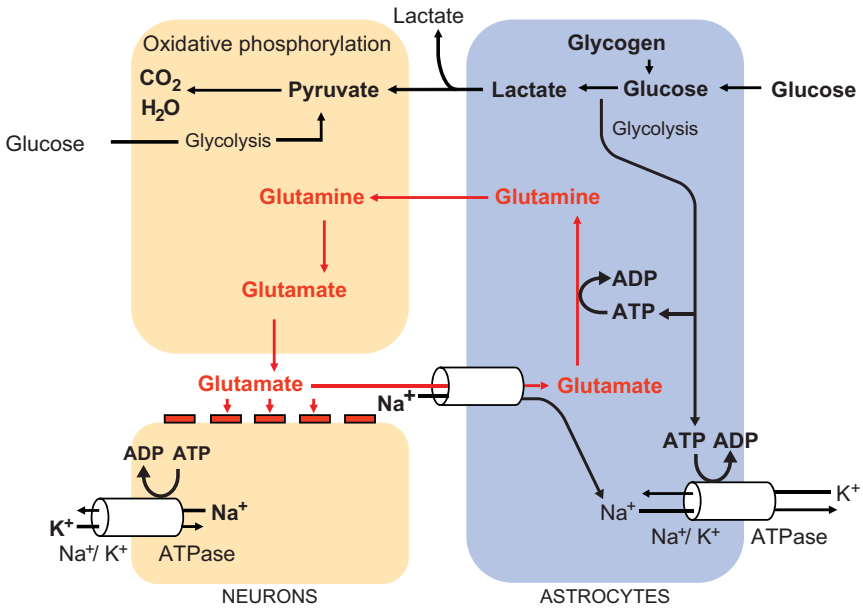

Figure 4

A schematic representation of the cellular metabolic events associated with the cycling of glutamate. Of particular importance is the role played by aerobic glycolysis in astrocytes in supplying the energy used by Na^+/K^+-ATPase to extrude the Na^+ taken up along with glutamate from the synapse and the conversion of glutamate to glutamine. The excess lactate produced can either be "shuttled" to the adjacent neurons where it is converted to pyruvate and further metabolized by oxidative phosphorylation to CO_2 and H_2O or removed from the brain as lactate in flowing blood. As illustrated, Na^+/K^+-ATPase also plays a critical role in neurons as well. It remains to be determined whether the glycolysis associated with Na^+/K^+-ATPase at neuronal sites also contributes to the genesis of brain imaging signals.

provides a convenient explanation for the well-known observation that astrocytes are the sole repository of glycogen in the brain (Brown 2004). Glycogen can be broken down to glucose in milliseconds in a process known as glycogenolysis, providing a readily available energy substrate for moment-to-moment changes in brain function (Swanson et al. 1992) that is not immediately dependent on flowing blood (**Figure 3**).

Furthermore, glycogenolysis appears, in part, to be orchestrated by a complex, multiplicative process involving the central noradrenergic system (Harik et al. 1979, 1982; Magistretti et al. 1995; Stone & Ariano 1989), which is, broadly, concerned with performance optimization (i.e., arousal) across wide areas of the cerebral cortex (Aston-Jones & Cohen 2005), and vasoactive intestinal polypeptide (VIP), which acts locally to amplify this norepinephrine-induced performance optimization in task-relevant areas of cortex (Magistretti et al. 1981). That such complex processes elegantly embodying the integration of high-level behaviors also include the orchestration of glycogenolysis in astrocytes (Magistretti et al. 1981, 1995) lends credence to the hypothesis that astrocytes and the glycolytic machinery they house are uniquely involved in the coordination of the metabolic and circulatory requirements associated with changes in brain function.

Glycogenolysis: the metabolic breakdown of glycogen to glucose

Activity-induced alkalinization of the astrocyte. Finally, increased neuronal activity results in alkalinization within the astrocyte, despite an increased production of lactate owing to glycolysis (Chesler & Kraig 1987). An important consequence of this change in intracellular pH is the stimulation of

glycolysis, a result of the high sensitivity of phosphofructokinase, a critical enzyme in the regulation of glycolysis to changes in intracellular pH (Triveda & Danforth 1966, Ui 1966, Williamson 1970).

Glycolysis and Oxidative Phosphorylation

One might ask whether oxidative phosphorylation, a much more efficient source of energy than glycolysis, becomes more important when a state change becomes fixed. In this regard, it has been well documented in other systems (e.g., muscle) that whereas sudden increases in activity are accommodated by increases in aerobic glycolysis, a new, higher level of oxidative phosphorylation follows if increased activity persists (Weibel 1984). In the brain, levels of cytochrome oxidase, a mitochondrial enzyme critical for oxidative phosphorylation, appears to reflect ongoing activity levels within and among neurons and adjusts its levels to activity changes when these occur over hours to days (Wong-Riley 1989). Despite these observations, the information to date from quantative imaging studies is inconclusive regarding the possibility that a sustained increase in neuronal activity might cause a new baseline level of oxidative phosphorylation.

In our initial report (Fox & Raichle 1986) we noted no such effect for stimulation periods as long as 5 min. Several conflicting reports have followed. One suggests rapid increases in oxygen consumption re-establishes the resting relationship between blood flow and metabolism over a few minutes (Frahm et al. 1996); in another study of continuous stimulation for 30 min, no adaptation occurred (Bandettini et al. 1997). Finally, in our more recent study (Mintun et al. 2002), continuous passive visual stimulation with a vertical visual grating provoked an initial increase in blood flow of 39% above control (visual fixation) in visual cortex. Oxygen consumption initially increased to 6%. By 25 min of continuous stimulation, oxygen consumption had increased to 14% from an initial value of 6% above control, and blood flow had declined to 24% from an initial value of 39% above control. Following the termination of stimulation, all measurements returned to their control levels (M.A. Mintun, personal communication).

The role of glycolysis was not assessed in any of the above studies. This makes the study by Madsen and colleagues (1995) interesting. They measured whole brain–blood flow, oxygen consumption, and glucose utilization using well-accepted, quantitative techniques while subjects performed the cognitively demanding Wisconsin Card Sorting Task. During the task performance that lasted 20 min, blood flow and glucose utilization rose immediately and remained elevated in parallel along with an increased production of lactate, whereas oxygen consumption did not appear to change. Of particular interest was that the increased glycolysis associated with task performance persisted for more than 1 h after termination of task performance (Madsen et al. 1995) even though blood flow had returned to control levels. These results not only confirmed the increased aerobic glycolysis during task performance others had observed (Blomqvist et al. 1994, Fox et al. 1988), but also demonstrated its persistence during a 40-min period of continuing measurements following the cessation of task performance.

The above observations offer seemingly conflicting views of the complex metabolic and circulatory responses to task performance that remain to be fully understood. Presently we do not know whether a persistent increase in activity leads to a new baseline level of blood flow and metabolism in which increased oxidative phosphorylation meets increased energy demands. Variables such as task difficulty and novelty clearly need to be considered carefully in future work attempting to answer this question. Likewise, we need to understand the more general biological question of why the energy demands of membrane-bound Na^+/K^+-ATPase seem to be preferentially served by glycolysis and

whether the exclusive role of glycolysis in this situation is ever relinquished to oxidative phosphorylation.

GABA: gamma-aminobutyric acid

The Lactate Shuttle

One area of controversy persists concerning the glycolysis associated with glutamate cycling by astrocytes. This concerns the fate of the lactate produced by aerobic glycolysis in the astrocyte. It has been suggested that a significant proportion of the lactate produced in the astrocyte is "shuttled" to the neuron where it is further metabolized by oxidative phosphorylation (Magistretti et al. 1999) (**Figure 4**). The controversy has centered on the degree to which this occurs and the relative dependency of neurons on lactate as an energy substrate (e.g., see Aubert et al. 2005, Chih & Roberts 2003, Pellerin & Magistretti 2003). A resolution of this controversy is not presently at hand. It is sufficient to say that some fraction of the lactate produced in the course of normal brain activity is left to find its way out of the brain where it has been detected in brain venous blood for many years in humans as well as laboratory animals (Gibbs et al. 1942, Raichle et al. 1970, Siesjo 1978).

An important question to be answered is what fraction of the lactate produced by glycolysis in astrocytes is represented in lactate leaving the brain in venous blood. Relevant to this issue are intriguing new data (Porras et al. 2004) suggesting an increase in glutamatergic neurotransmission (i.e., activation) may redistribute glucose away from neurons and into astrocytes by rapidly inhibiting glucose transport into neurons. One important implication of this observation is that under such circumstances, neurons would rely more heavily on astrocyte-produced lactate as a precursor for oxidative phosphorylation (**Figure 3**). If that were to happen, an increased fraction of the astrocyte glycolysis would be "masked" by neuronal oxidative phosphorylation attenuating changes likely to be observed in the fMRI BOLD signal.

Other Neurotransmitters

One could ask whether other neurotransmitters also contribute to neuroimaging signals in a manner similar to glutamate. Here the evidence is much less complete. We do know from the work of Magistretti and colleagues (Chatton et al. 2003) that, in contrast to glutamate, the exposure of astrocytes to gamma-aminobutyric acid (GABA) does not elicit a burst of glycolysis. From this we might surmise that a BOLD-based fMRI signal would not be associated with a change in GABA-mediated inhibition. Yet extant data, albeit limited, do suggest that GABA-mediated increases in inhibitory neurotransmission produce an increase in glucose consumption measured with tissue autoradiography in laboratory animals (Ackerman et al. 1984, Batini et al. 1984, Biral et al. 1984, McCasland & Hibbard 1997) and blood flow measured in humans with PET (Hershey et al. 2003). How might we understand such observations in the context of fMRI using BOLD contrast? Two issues come to mind.

First, one must consider the information provided by various neuroimaging techniques in relation to the question being posed. The interpretation of blood flow and glucose metabolism data with regard to oxidative phosphorylation, glycolysis, and GABAergic neurotransmission is ambiguous. The mistake is to assume that a change in glucose consumption or blood flow necessarily reflects a change in oxidative phosphorylation. Neither can distinguish a change in aerobic glycolysis from a change in oxidative phosphorylation. As discussed above, the brain may employ glycolysis independently or in combination with oxidative phosphorylation. Measurements of blood flow and glucose consumption, separately or together, do not provide the critical information to distinguish the two. Only by adding a measurement of oxygen consumption will the needed information be obtained. Hence, we need studies employing paradigms that produce changes clearly attributable to an increase in GABAergic

neurotransmission coupled with well-validated, quantitative measurement of the relevant variables (CBF, $CMRO_2$, and CMRGlu).

Second, one must consider what we know about metabolic compartmentalization (i.e., the segregation of glycolytic enzymes) at sites other than the astrocyte that might be related to GABAergic neurotransmission. Several observations suggest that metabolic compartmentalization might occur in neurons as well. In this regard an interesting example is the discovery several years ago by Siekevitz and colleagues (Wu et al. 1997) of glycolytic enzymes localized in a structure called the postsynaptic density at the postsynaptic membrane of the synapse, an area with few if any mitochondria. They presented evidence that the compartmentalization of glycolytic enzymes could supply the energy needs of nerve signal transduction. Most directly relevant to GABAergic neurotransmission has been the recently presented evidence that a key enzyme in the regulation of glycolysis (GAPDH) can perform a dual role as a receptor kinase and a glycolytic enzyme, effectively linking glycolysis to neuronal inhibition (Laschet et al. 2004).

What we do not know is how a change in glycolysis in excess of that needed locally for oxidative phosphorylation in any of these circumstances might affect measurements of brain hemodynamics and metabolism. Is glycolytically produced lactate in the postsynaptic density shuttled to the mitochondria (Aubert et al. 2005) where oxidative phosphorylation takes place in sync with the changes in glycolysis, making such metabolic changes undetectable by current functional imaging techniques? Or does an increase in glycolysis in areas such as the postsynaptic density of dendrites sometimes exceed the requirements of oxidative phosphorylation, thereby contributing to the fMRI BOLD signal we observe? Finally, should we not be asking such questions about the energy metabolism of Na^+/K^+-ATPase at every site at which it operates in the brain (**Figure 4**)?

Above we focus entirely on evoked increases in brain activity. For most researchers this is the primary focus of functional imaging studies and, more generally, electrophysiological recording as well. However, as we argue below, it likely represents only a small fraction of the true functional activity of the brain. The departure this perspective represents from the standard view was initiated by three observations made in imaging research: (*a*) activity decreases during task performance, (*b*) the functional significance of spontaneous activity ("noise") in the fMRI BOLD signal, and (*c*) the disparity in energy cost between evoked activity and that we refer to as intrinsic activity. We turn to these issues below.

ACTIVITY DECREASES (DEACTIVATIONS)

Historically, brain imaging work with PET and fMRI has emphasized task-induced increases in regional brain activity associated with the execution of a wide variety of tasks. More recently, however, researchers have become aware of the presence of task-induced decreases in regional brain activity in their data. Whereas the location of task-induced activity increases generally are task-specific, regional task-induced activity decreases can either be quite task specific (e.g., decreases within particular elements of a sensory system not directly involved in the processing of a stimulus (Amedi et al. 2005, Drevets et al. 1995, Ghatan et al. 1998, Kawashima et al. 1995, Shmuel et al. 2002, Smith et al. 2002, Somers et al. 1999) or largely independent of the task content (Andreasen et al. 1995, Binder et al. 1999, Mazoyer et al. 2001, Shulman et al. 1997) (**Figure 5**).

One of the challenges in interpreting activity decreases in functional imaging experiments is establishing a proper reference upon which to base a decision regarding the true valence of these activity changes. Skeptics have worried that functional activity decreases merely represent activations in an unconstrained resting state (Martin 1999, Stark &

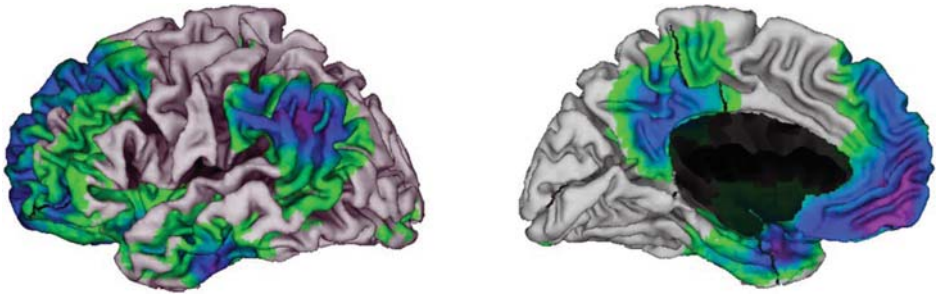

Figure 5

Regional activity decreases commonly associated with the performance of a wide variety of goal-directed tasks are observed with both PET and fMRI. These data (a meta-analysis of nine PET studies involving 134 normal subjects) were adapted from an earlier study of ours (Shulman et al. 1997) and are shown here on surface maps of the cerebral cortex (Van Essen et al. 2001). We have referred to these areas of the brain as representing a "default mode" of brain function (Raichle et al. 2001).

OEF: oxygen extraction fraction

Squire 2001). We have approached this challenge by defining a physiologic baseline in terms of quantitative regional brain–blood flow and oxygen consumption measured with PET relative to which control conditions and other task states could be compared (Gusnard & Raichle 2001, Raichle et al. 2001). We believe that reviewing our approach in some detail is critical to an understanding of the significance to be attached to functional activation and deactivation responses in particular and to the intrinsic functional activity of the brain implied by their presence.

Defining a Baseline Level of Activity

Provoked by the dilemma of interpreting activity decreases in imaging data and the hypothesis put forward that they merely represented unaccounted for activations in control conditions, we decided to test the validity of this hypothesis in a quantifiable manner using PET (Raichle et al. 2001). Critical to the test we performed was the use of an agreed-upon definition of activation and the ability to measure it quantitatively with PET.

Fortunately, there is general agreement in the imaging-research community on the definition of activation that we review above in detail. Briefly summarized here, when neuronal activity locally increases in the brain, regional blood flow increases more than oxygen consumption (**Figure 1**). Hence, the amount of oxygen remaining in the blood leaving the activated region increases. That is, the increased supply of oxygen exceeds the increased demand (Fox & Raichle 1986, Fox et al. 1988).

One additional feature of the relationship between brain blood flow and oxygen consumption was important for our test. This was the long standing observation that the ratio of oxygen consumed by the brain to that delivered in flowing blood is, on average, remarkably constant across the brain (for an introduction to this literature, see Raichle et al. 2001). Thus, whereas oxygen consumption in white matter is approximately one-fourth that of gray matter, the ratio of oxygen consumed to that delivered is the same as in gray matter. This ratio is formally known as the oxygen extraction fraction (OEF). How did the acknowledgment of this ratio's uniformity serve our purpose? It allowed us to posit that if areas were truly activated in the resting state condition, then they should exhibit a significant regional decrease in OEF when compared with other areas of the brain in that condition (Raichle et al. 2001).

Armed with the above definition of activation and the ability of PET to quantitatively assess the presence of activation as a

significant regional decrease in the OEF, we examined two groups of normal subjects in the resting state and initially confined our analysis to those areas of the brain frequently exhibiting the aforementioned imaging signal decreases (**Figure 5**). In this analysis we found no evidence that these areas were activated in the resting state; that is, the average OEF in these areas did not differ from any other areas of the brain. We concluded these regional decreases, observed commonly during task performance, represented the presence of functionality that was ongoing in the resting state and attenuated only when resources were temporarily reallocated during goal-directed behaviors, hence our original designation of them as default functions (Gusnard & Raichle 2001, Raichle et al. 2001).

After performing the above analysis (Raichle et al. 2001) on the aforementioned areas (**Figure 5**), we searched our data for any other areas that might exhibit evidence of activation in the resting state and found none (Raichle et al. 2001). This observation is important in suggesting that aspects of the brain's intrinsic functionality are not confined to those areas we designated as a "default system" (**Figure 5**) and is consistent with the observation that activity decreases do occur in other areas of the brain in a more task-specific manner (see above).

We make four important comments in summary. First, the importance of using PET rather than fMRI to define a physiologic baseline state of the brain needs to be emphasized. Our work was critically dependent on the ability of PET to provide absolute, quantitative, and reproducible measurements of regional blood flow and oxygen consumption in the human brain. PET is uniquely suited to do so, operating as it does with tracer techniques that have been validated against objective standards (Martin et al. 1987, Mintun et al. 1984, Raichle et al. 1983). fMRI as it is conventionally practiced using BOLD imaging does not offer a similar absolute reference (Aguirre et al. 2002, Detre & Wang 2002), and hence estimated changes in parameters such as oxygen consumption must be viewed with caution until further work is done to determine their validity (e.g., see Kim et al. 1999).

Second, in functional imaging studies using fMRI BOLD contrast, comparisons are always made between two states closely spaced in time because background BOLD activity, for reasons currently not understood, does not remain constant. Limiting their considerations to fMRI, some have concluded, therefore, that a functional imaging baseline cannot be defined. We appreciate the potential for confusion, particularly when terms such as control state, control condition, and baseline are used interchangeably, which occurs frequently in the imaging literature. Although the term physiologic baseline as we have defined it is not appropriately applied to fMRI data directly, the terms control state and control condition may be applied equally well to both PET and fMRI imaging techniques. Importantly, when low-level control states such as eyes-closed rest or visual fixation are used, the results from both imaging techniques are virtually identical (Raichle 1998, Simpson et al. 2000).

Third, the baseline as we have defined it refers to a physiologic, functionally significant state of the brain, and acknowledging it provides a means by which we can differentiate intrinsic brain activity from that evoked during task performance. Fourth, the particular control condition or state to which a task of interest is compared can significantly affect the results and their interpretation (Gusnard & Raichle 2001). We argue that inclusion of a control condition referable to a physiological baseline, among those control conditions employed in any functional imaging study, puts one in the best position to correctly understand imaging data. This claim is made notwithstanding expressed concerns that low-level control conditions fail to establish a "zero-activity" condition. We argue that brains are never at a zero-activity level and that such a view often encourages loose and misleading use of the term activation.

We are under no illusions, however, that this well-established term will be replaced any time soon.

Oxygen-glucose index (OGI): the molar ratio of oxygen consumption to glucose utilization used in the production of energy

Understanding Deactivations in Metabolic Terms

An important conceptual feature of deactivations as we define them above is that they are observed in both PET blood flow and fMRI BOLD images (e.g., see figure 1 in Simpson et al. 2000 for a direct comparison). Why is this important?

Recall that the reason we can monitor activity increases (activations) with fMRI BOLD contrast is that blood flow increases more than oxygen consumption, thereby creating a local increase in the amount of oxygenated hemoglobin (**Figures 1** and **6**). Furthermore, this increase in blood flow is accompanied by an increase in aerobic glycolysis. As discussed above, this means that during a period of increased activity, aerobic glycolysis operates at a rate in excess of that needed for oxidative phosphorylation.

It should be recalled that when glycolysis and oxidative phosphorylation are perfectly matched, it takes 6 mol of oxygen to convert 1 mol of glucose to carbon dioxide and water. This molar ratio of oxygen consumption to glucose utilization is often referred to as the oxygen-glucose index (OGI) and is used to assess the relationship between glycolysis and oxidative phosphorylation. Importantly, whereas the OGI can fall below six when glycolysis increases more than oxidative phosphorylation, the OGI theoretically cannot increase above six because that would imply that the substrate required for oxidative phosphorylation (pyruvate) is consumed faster than it is supplied. Thus, where glycolysis operates at a rate greater than needed for oxidative

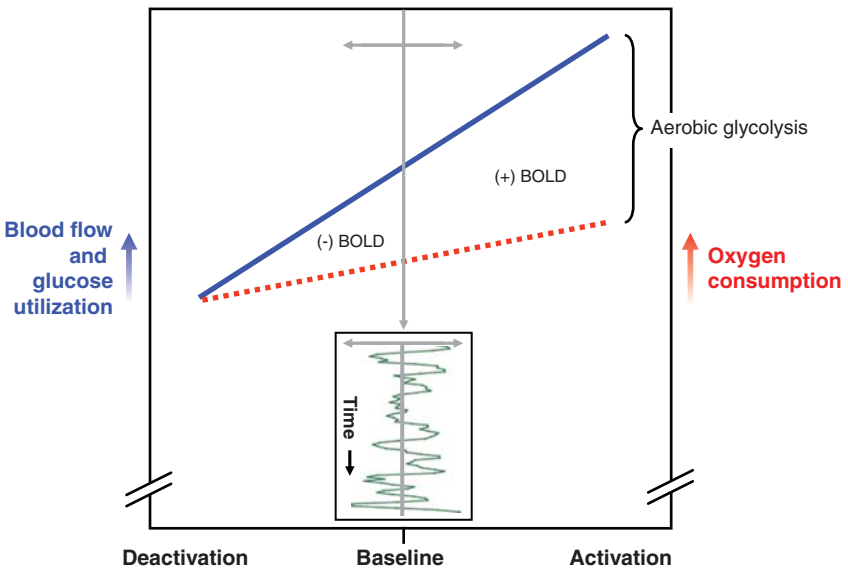

Figure 6

A schematic representation of the relationship of blood flow and glucose utilization (*blue*) to oxygen consumption (*red*) and cellular activity (*x-axis*) at baseline and during increases (activation) and decreases (deactivation) in neuronal activity. The presence of aerobic glycolysis causes activity-dependent variations in oxygen availability in the brain (see **Figure 1**) that are detectable by fMRI. Activations as seen by fMRI result from a disproportionate increase in blood flow and glucose utilization, whereas deactivations result from the opposite. At baseline, time-varying fluctuations in neuronal activity are seen as spontaneous fluctuations in the fMRI BOLD signal (*insert, green line*).

phosphorylation, the OGI is observed to be less than six.

If at baseline the molar ratio of oxygen used to glucose consumed were six, then a decrease in energy requirements accompanying a decrease in cellular activity would be expected to produce parallel decreases both in glycolysis and oxidative phosphorylation. Assuming an accompanying decrease in blood flow, which is likely, there would be no change in local blood oxygen content. As a result there would be no change in the fMRI BOLD signal. Yet, fMRI BOLD readily detects activity decreases from a physiologic baseline (Raichle 1998, Simpson et al. 2000), clearly implying the presence of ongoing aerobic glycolysis in the baseline state of normal human subjects.

Thus, aerobic glycolysis provides for us a window (a "glycolytic window") through which we can observe changes in brain activity with fMRI BOLD (**Figure 6**). This includes both increases and decreases in activity from a physiologic baseline. We suggest ongoing aerobic glycolysis in the baseline state is necessary for the observation of activity decreases with fMRI BOLD. Interestingly evidence for ongoing aerobic glycolysis in the baseline state has been extant for quite some time in the form of positive arteriovenous difference for lactate (Gibbs et al. 1942, Raichle et al. 1970, Siesjo 1978) and the presence of lactate in the brain as detected by magnetic resonance spectroscopy in humans (Prichard et al. 1991). An average value for the human brain OGI is approximately 5.3 (Raichle et al. 1970). As discussed above (see The Lactate Shuttle), this probably represents the lower bound because shuttled lactate is invisible in arterio-venous difference measurements.

The presence of aerobic glycolysis in the physiologic baseline state has another important implication for brain imaging as well as brain function. That emerges from an examination of spontaneous fluctuations in the fMRI BOLD signal in the resting state (resting quietly but awake with eyes closed).

SPONTANEOUS FUNCTIONAL ACTIVITY

All who have done fMRI BOLD imaging are aware that the unaveraged MRI signals are quite noisy. Some of the noise is created by such uninteresting yet troublesome sources as scanner electronics, subject movement, respiration, and variations in systemic cardiovascular dynamics (Triantafyllou et al. 2005). However, a considerable fraction of the variance in the BOLD signal in the frequency range below 0.1 Hz appears to reflect fluctuating neuronal activity (see insert in **Figure 6**).

Biswal and colleagues (1995) at the Medical College of Wisconsin began the work on the surprising significance of these spontaneous fluctuations in the fMRI BOLD signal. They were the first to note that spontaneous fluctuations in the fMRI BOLD signal at rest in one area of the cerebral cortex exhibit system-relevant correlations with signal fluctuations in other areas. Their initial observation in somatomotor cortices has since been replicated and extended to many other brain systems (for a recent example and review of this literature, see Fox et al. 2005). These studies have provided a rich new view of the intrinsic activity of the human brain characterized by spatially consistent, temporally varying activity within distinct brain systems (**Figure 7**).

Correlated spontaneous fluctuations in the fMRI BOLD signal should be considered in the context of the rich neurophysiological literature on coherent neuronal fluctuations or oscillations. Synchronous neuronal fluctuations have been reported across a broad range of frequencies and spatial scales (Buzsaki & Dragulm 2004). Furthermore, it has been suggested that neuronal fluctuations at high and low frequencies may be related, with lower-frequency fluctuations corresponding to power modulations of higher-frequency bands, both demonstrating coherence at their respective spatial scales (Bruns et al. 2000, Leopold et al. 2003). Thus, future research may determine that

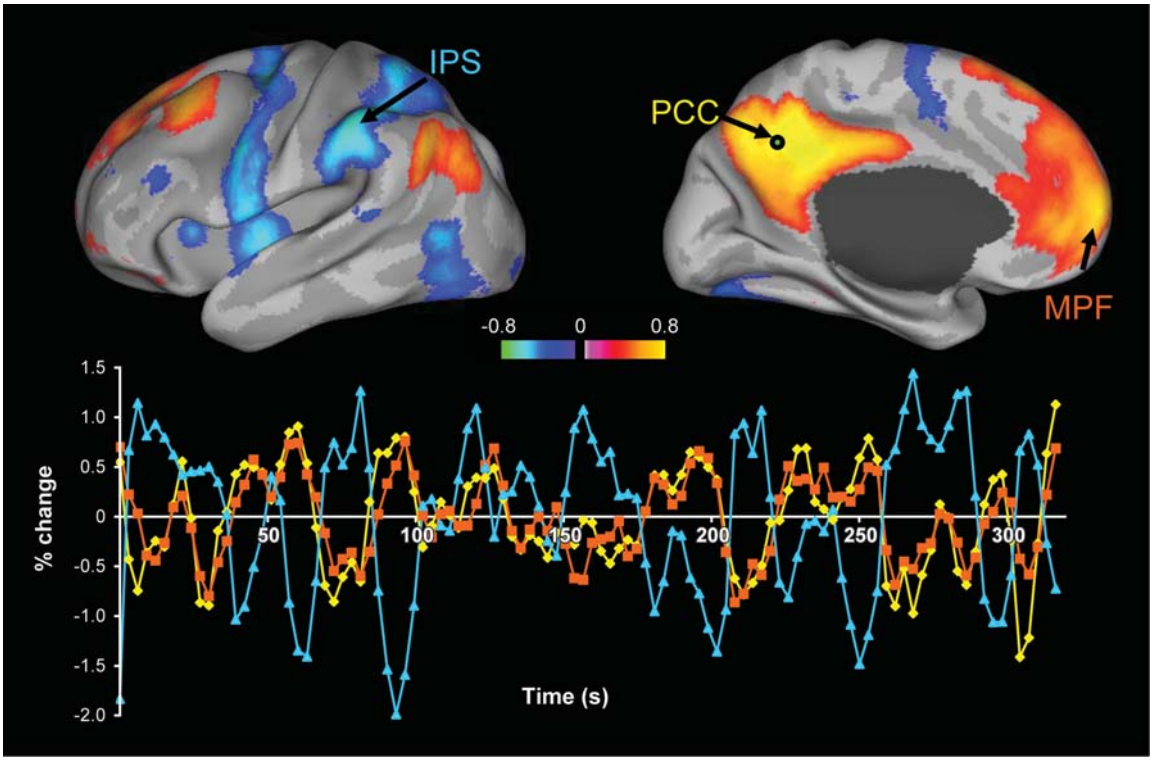

Figure 7

Intrinsic correlations in spontaneous fluctuations in the fMRI BOLD signal between a seed region in the posterior cingulate cortex (PCC) and all other voxels in the brain for a single subject during resting fixation. The spatial distribution of correlation coefficients shows both correlations (positive values) and anticorrelations (negative values) threshold at $R = 0.3$. The time course for a single run is shown for the seed region (PCC, *yellow*), a region positively correlated with this seed region in the medial prefrontal cortex (MPF, *orange*), and a region negatively correlated with the seed region in the intraparietal sulcus (IPS, *blue*). Note the similarity between the positively correlated regions and those shown in **Figure 5**). Data from Fox et al. 2005 with permission.

low-frequency fMRI BOLD signal oscillations (<0.1 Hz) actually represent power fluctuations at higher frequencies (e.g., frequencies in the gamma range of 30–100 Hz). Organized in this way, oscillations could facilitate the coordination and organization of information processing across several spatial and temporal ranges. Future research on the neurobiology of spontaneous as well as task-evoked fMRI BOLD signals must consider these complexities when attempting to understand the underlying cellular events.

In the context of this review it is important to point out that the presence of these relatively slow, systems-relevant spontaneous fluctuations about an average baseline level of activity occur in the same glycolytic window as the increases and decreases evoked by task performance. Otherwise, we argue, they would not be seen in the fMRI BOLD signal. Accordingly they provoke many of the same interpretive questions we address throughout this review in relation to evoked responses.

Finally, an interesting question arises from our analysis regarding the genesis of the activity decreases (deactivations). Conceptually they could arise as the result of a decrease in the magnitude of the spontaneous

fluctuations themselves or as a result of a decrease in the overall mean level of aerobic glycolysis without a change in the spontaneous fluctuations or as some combination of the two. A useful metaphor might be the sea, which rises and falls as the result of two largely independent processes, tide and wind-generated surface waves. As we probe more deeply the meaning of these spontaneous fluctuations in brain function organization, it is of particular interest to determine how these components behave when the systems they represent are attenuated in their activity.

THE OVERALL COST OF BRAIN FUNCTION

This review approaches functional brain imaging from the perspective of measurements that relate changes in brain function to changes in brain energy consumption (i.e., brain work). We examine the manner in which this may be orchestrated in brain cells and the vasculature that serve them. Above, however, we do not speak explicitly about the actual costs involved in these changes nor how they relate to the overall cost of brain function. Below, we examine these relationships and put what we discuss above into a broader perspective.

In the average adult human, the brain represents approximately 2% of the total body weight but approximately 20% of the energy consumed (Clark & Sokoloff 1999), 10 times that predicted by its weight alone. Relative to this high rate of ongoing or "basal" metabolism (usually measured while resting quietly awake with eyes closed), the amount dedicated to task-evoked regional imaging signals is remarkably small.

The regional increases in absolute blood flow associated with imaging signals as measured with PET are rarely more than 5%–10% of the resting blood flow of the brain. These are modest modulations in ongoing circulatory activity that rarely affect the overall rate of brain blood flow during even the most arousing perceptual and vigorous motor activity (Fox et al. 1987, Friston et al. 1990, Lennox 1931, Madsen et al. 1995, Roland et al. 1987, Sokoloff et al. 1955).

The modest nature of these task-induced increases in blood flow is further underscored when one considers the increase in energy consumption they represent. One should recall, as discussed in detail above, the average resting metabolic activity of the brain is supported by the nearly complete (>90%) oxidation of glucose to carbon dioxide and water, producing approximately 32 mol of ATP per mole of glucose consumed (Siesjo 1978). Imaging signal activations, conversely, are associated with increases in glucose utilization that are not accompanied by a proportionate increase in oxygen consumption (Blomqvist et al. 1994, Fox et al. 1988, Madsen et al. 1995), resulting in the production of only 2 mol of ATP per mole of glucose consumed, typical of glycolysis. Estimates of the actual increases in oxygen consumption vary somewhat (Fox & Raichle 1986, Fox et al. 1988, Fujita et al. 1999, Mintun et al. 2002, Roland et al. 1989) but are always less than that predicted by the increase in blood flow. From knowledge of these relationships, one can estimate that if blood flow and glucose utilization increase by 10%, but oxygen consumption does not, the local energy consumption increase owing to a typical task-related response could be as little as 1%. It becomes clear, then, that the brain continuously expends a considerable amount of energy even in the absence of a particular task (i.e., when a subject is awake and at rest). What is the nature of this intrinsic activity present even at rest that commands such a large amount of the brain's energy resources?

It is tempting to assume this intrinsic or resting state–energy utilization reflects simple housekeeping functions such as neuronal repair or protein trafficking. However, the preponderance of evidence suggests such functions consume a relatively small fraction of the brain's energy budget. Measurements of brain energy metabolism using magnetic resonance spectroscopy (Sibson et al. 1997, 1998;

Shulman et al. 2001, 2004) in a variety of experimental settings have indicated that up to 80% of the entire energy consumption of the brain at rest is devoted to glutamate cycling and, hence, neural signaling processes. Complementary analyses using extant anatomic, physiologic, and metabolic data (Ames 2000, Attwell & Laughlin 2001, Lennie 2003, Wong-Riley 1989) to assess the cost of different components of excitatory signaling in the gray matter have arrived at similar conclusions. Such estimates leave for future consideration the demands placed on the brain's energy budget by the functional activity of inhibitory interneurons (Ackerman et al. 1984, Chatton et al. 2003, McCasland & Hibbard 1997, Patel et al. 2005, Waldvogel et al. 2000). That evidence notwithstanding, it is likely to remain the case that a significant fraction of the energy consumed by the brain (quite possibly the majority) is a result of functionally significant intrinsic neuronal activity. The majority of that energy is produced by oxidative phosphorylation coupled to glycolysis with a small additional fraction, whose size remains to be determined quantitatively, by glycolysis alone.

From this cost-based analysis of brain functional activity, it seems reasonable to conclude that intrinsic activity may be as significant as, if not more so than, evoked activity in terms of overall brain function. Taking this position converts one's view of the brain as a system primarily responding to changing contingencies to one operating on its own, intrinsically, with sensory information interacting with rather than determining the operation of the system. This view has historical (Llinas 1988) and recent theoretical (Olshausen & Field 2005) as well as experimental support (Arieli et al. 1996, Fiser et al. 2004, Kenet et al. 2003). It seems highly likely that ultimate constraints on the behaviors we study with neuroimaging or any other technique will be significantly determined by this intrinsic activity.

SUMMARY

Although a great deal has been learned about the neurobiology of functional brain imaging signals, note that we still do not know what function moment-to-moment changes in blood flow serve. As we point out above, oxygen delivery does not appear to be a convenient explanation, intuitively appealing as it might at first seem. Likewise, the delivery of additional glucose also seems not to be responsible. In both cases adequate reserves are available (i.e., unextracted oxygen in circulating blood and glucose and glycogen in astrocytes). One is forced to conclude that a more likely explanation will emerge from future research that examines the manner in which a change in blood flow may regulate an effect of the activity change. For example, one might consider the possibility that it is used for the removal of the excess lactate produced during an increase in activity or the adjustment of the acid-base or ionic balance of the tissue. Likewise, temperature regulation, a long-overlooked subject, may be playing some role. At present no evidence exists for any of these speculative ideas. Our challenge will be to identify a role for the changes in blood flow associated with brain activity changes and to understand how a multitude of factors known to alter blood flow are orchestrated to serve this role (for an excellent recent review, see Iadecola 2004, Lauritzen 2005).

FUTURE ISSUES TO BE RESOLVED

1. What function(s) does regional brain–blood flow perform when neuronal activity changes?
2. Why is glycolysis obligatorily used in providing energy for membrane-bound Na^+/K^+-ATPase in astrocytes and, possibly, neurons as well?

3. Does glycolysis serve regulatory or mnemonic functions in neurons that might also affect brain imaging signals?
4. How are the energy-generating resources of astrocytes and neurons coordinated and how does this affect functional brain imaging signals?
5. What do inhibitory interneurons contribute in the imaging signals?

LITERATURE CITED

Ackerman RF, Finch DM, Babb TL, Engel JJ. 1984. Increased glucose utilization during long-duration recurrent inhibition of hippocampal pyramidal cells. *J. Neurosci.* 4:251–64

Aguirre CK, Detre JA, Zarahn E, Alsop DC. 2002. Experimental design and the relative sensitivity of BOLD and perfusion MRI. *NeuroImage* 15:488–500

Amedi A, Malach R, Pascual-Leone A. 2005. Negative BOLD differentiates visual imagery and perception. *Neuron* 48:859–72

Ames AI. 2000. CNS energy metabolism as related to function. *Brain Res. Rev.* 34:42–68

Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, et al. 1995. Remembering the past: Two facets of episodic memory explored with positron emission tomography. *Am. J. Psychiatry* 152:1576–85

Arieli A, Sterkin A, Grinvald A, Aertsent A. 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. *Science* 273:1868–71

Aston-Jones G, Cohen JD. 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.* 28:403–50

Attwell D, Laughlin SB. 2001. An energy budget for signaling in the grey matter of the brain. *J. Cereb. Blood Flow Metab.* 21:1133–45

Aubert A, Costalat R, Magistretti PJ, Pellerin L. 2005. Brain lactate kinetids: modeling evidence for neuronal lactate uptake upon activation. *Proc. Natl. Acad. Sci. USA* 102:16448–53

Bandettini PA, Kwong KK, Davis TL, Tootell RBH, Wong EC, et al. 1997. Characterization of cerebral blood oxygenation and flow changes during prolonged brain activation. *Hum. Brain Mapp.* 5:93–109

Bandettini PA, Wong EC, Hinks RS, TIkofsky RS, Hyde JS. 1992. Time course EPI of human brain function during task activation. *Magn. Reson. Med.* 25:390–97

Batini C, Benedetti F, Buisseret-Delmas C, Montarolo PG, Strata P. 1984. Metabolic activity of intracerebellar nuclei in the rat: effects of inferior olive inactivation. *Exp. Brain Res.* 54:259–65

Binder JR, Frost JA, Hammeke TA, Bellgowan PSF, Rao SM, Cox RW. 1999. Conceptual processing during the conscious resting state: a functional MRI study. *J. Cogn. Neurosci.* 11:80–93

Binzegger T, Douglas RJ, Martin KAC. 2004. A quantitative map of the circuit of cat primary visual cortex. *J. Neurosci.* 24:8441–53

Biral G, Cavazzuti M, Porro C, Ferrari R, Corazza R. 1984. [^{14}C]Deoxyglucose uptake of the rat visual centres under monocular optokinetic stimulation. *Behav. Brain Res.* 11:271–75

Biswal B, Yetkin F, Haughton V, Hyde J. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med.* 34:537–41

Blomqvist G, Seitz RJ, Sjogren I, Halldin C, Stone-Elander S, et al. 1994. Regional cerebral oxidative and total glucose consumption during rest and activation studied with positron emission tomography. *Acta Physiol. Scand.* 151:29–43

Boynton GM, Engel SA, Glover GH, Heeger DJ. 1996. Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci.* 16:4207–21

Brodersen P, Paulson OB, Bolwig TG, Rogon ZE, Rafaelsen OJ, Lassen N. 1973. Cerebral hyperemia in electrially induced epileptic seizures. *Arch. Neurol.* 28:334–38

Brown AM. 2004. Brain glycogen re-awakened. *J. Neurochem.* 89:537–52

Bruns A, Eckhorn R, Jokeit H, Ebner A. 2000. Amplitude envelope correlation detects coupling among incoherent brain signals. *Neuroreport* 11:1509–14

Buxton RB. 2001. The elusive initial dip. *Neuroimage* 13:953–58

Buxton RB, Uludag K, Dubowitz DJ, Liu TT. 2004. Modeling the hemodynamic response to brain activation. *Neuroimage* 23:S220–33

Buzsaki G, Draguhn A. 2004. Neuronal oscillations in cortical networks. *Science* 304:1926–29

Cacioppo JT, Berntson GG, Adolphs R, Carter CS, Davidson RJ, et al., eds. 2002. *Foundations in Social Neuroscience*. Cambridge, MA: MIT Press

Cacioppo JT, Visser PS, Pickett CL, eds. 2005. *Social Neuroscience: People Thinking About Thinking People*. Cambridge, MA: MIT Press

Campbell JD, Paul RJ. 1992. The nature of fuel provision for the Na^+, K^+-ATPase in procine vascular smooth muscle. *J. Physiol.* 447:67–82

Chatton JY, Pellerin L, Magistretti PJ. 2003. GABA uptake into astrocytes is not associated with significant metabolic cost: implications for brain imaging of inhibitory transmission. *Proc. Natl. Acad. Sci. USA* 100:12456–61

Chesler M, Kraig RP. 1987. Intracellular pH of astrocytes increases rapidly with cortical stimulation. *Am. J. Psychol.* 253:R666–70

Chih CP, Roberts ELJ. 2003. Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. *J. Cereb. Blood Flow Metab.* 23:1263–81

Clark DD, Sokoloff L. 1999. Circulation and energy metabolism of the brain. In *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, ed. GJ Siegel, BW Agranoff, RW Albers, SK Fisher, MD Uhler, pp. 637–70. Philadelphia: Lippincott-Raven

Cohen LB, De Weer P. 1977. Structural and metabolic processes directly related to action potential propagation. In *Handbook of Physiology: The Nervous System*, ed. JM Brookhart, VB Mountcastle, pp. 137–59. Bethesda, MD: Am. Physiol. Soc.

Cooper R, Crow HJ. 1975. Changes in cerebral oxygenation during motor and mental tasks. In *Brain Work: The Coupling of Function, Metabolism and Blood Flow in the Brain*, ed. DH Ingvar, NA Lassen, pp. 389–92. Copenhagen: Munksgaard

Detre JA, Wang J. 2002. Technical aspects and utility of fMRI using BOLD and ASL. *Clin. Neurophysiol.* 113:621–34

Drevets WC, Burton H, Videen TO, Snyder AZ, Simpson JRJ, Raichle ME. 1995. Blood flow changes in human somatosensory cortex during anticipated stimulation. *Nature* 373:249–52

Erecinska M, Silver IA. 1994. Ions and energy in mammalian brain. *Prog. Neuorobiol.* 43:37–71

Fan J, Fossella J, Sommer T, Wu Y, Posner MI. 2003. Mapping the genetic variation of executive attention onto brain activity. *Proc. Natl. Acad. Sci. USA* 100:7406–11

Fiser J, Chiu C, Weliky M. 2004. Small modulation of ongoing cortical dynamics by sensory input during natural vision. *Nature* 431:573–78

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. 2005. The human brain is intrinsically organized into dynamic anticorrelated functional networks. *Proc. Natl. Acad. Sci. USA* 102:9673–78

Fox PT, Burton H, Raichle ME. 1987. Mapping human somatosensory cortex with positron emission tomography. *J. Neurosurg.* 67:34–43

Fox PT, Raichle ME. 1986. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc. Natl. Acad. Sci. USA* 83:1140–44

Fox PT, Raichle ME, Mintun MA, Dence C. 1988. Nonoxidative glucose consumption during focal physiologic neural activity. *Science* 241:462–64

Frahm J, Kruger G, Merboldt KD, Kleinschmidt A. 1996. Dynamic uncoupling and recoupling of perfusion and oxidative metabolism during focal brain activation in man. *Magn. Reson. Med.* 35:143–48

Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RSJ. 1990. The relationship between global and local changes in PET scans. *J. Cereb. Blood Flow Metab.* 10:458–66

Fujita H, Kuwahara H, Reutens O, Gjedde A. 1999. Oxygen consumption of cerebral cortex fails to increase during continued vibrotactile stimulation. *J. Cereb. Blood Flow Metab.* 19:266–71

Gazzaniga M, ed. 2004. *The Cognitive Neurosciences*. Cambridge, MA: MIT Press

Ghatan PH, Hsieh JC, Petersson KM, Stone-Elander S, Ingvar M. 1998. Coexistence of attention-based facilitation and inhibition in human cortex. *Neuroimage* 7:23–29

Gibbs EL, Lennox WG, Nims LF, Gibbs FZ. 1942. Arterial and venous cerebral blood arterial-venous differences in man. *J. Biol. Chem.* 18:325–32

Gusnard DA, Raichle ME. 2001. Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2:685–94

Harik SI, Busto R, Martinez E. 1982. Norepinephrine regulation of cerebral glycogen utilization during seizures and ischemia. *J. Neurosci.* 2:409–14

Harik SI, LaManna JC, Light AI, Rosenthal M. 1979. Cerebral norepinephrine: influence on cortical oxidative metabolism in situ. *Science* 206:69–71

Hershey T, Revilla FJ, Wernle AR, McGee-Minnich L, Antenor JV, et al. 2003. Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. *Neurology* 61:816–21

Hounsfield GN. 1973. Computerized transverse axial scanning (tomography). Part I. Description of system. *Br. J. Radiol.* 46:1016–22

Howse DC, Plum F, Duffy TE, Salford LG. 1973. Cerebral energy metabolism and the regulation of cerebral blood flow. *Trans. Am. Neurol. Assoc.* 98:153–55

Iadecola C. 2004. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat. Rev. Neurosci.* 5:347–60

Ido Y, Chang K, Williamson JR. 2004. NADH augments blood flow in physiologically activated retina and visual cortex. *Proc. Natl. Acad. Sci. USA* 101:653–58

Ido Y, Chang K, Woolsey T, Williamson JR. 2001. NADH: sensor of blood flow need in brain, muscle and other tissues. *FASEB J.* 15:1419–21

Illes J, Kirschen MP, Gabrieli JDE. 2003. From neuroimaging to neuroethics. *Nat. Neurosci.* 6:205

Kasischke KA, Vishwasrao HD, Fisher PJ, Zipfel WR, Webb WW. 2004. Neural activity triggers neuronal oxidative metabolism followed by astrocytic glycolysis. *Science* 305:99–103

Kawashima R, O'Sullivan BT, Roland PE. 1995. Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the "mind's eye". *Proc. Natl. Acad. Sci. USA* 92:5969–72

Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, Arieli A. 2003. Spontaneously emerging cortical representations of visual attributes. *Nature* 425:954–56

Kevles BH. 1997. *Naked To The Bone: Medical Imaging in the Twentieth Century*. New Brunswick, NJ: Rutgers Univ. Press. 378 pp.

Kim DS, Duong TQ, Kim SG. 2000. High-resolution mapping of iso-orientation columns by fMROI. *Nat. Neurosci.* 3:164–69

Kim SG, Rostrup E, Larsson HBW, Ogawa S, Paulson OB. 1999. Determination of relative $CMRO_2$ from CBF and BOLD changes: significant increase in oxygen consumption rate during visual stimulation. *Magn. Reson. Med.* 41:1152–61

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weiskoff RM, et al. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Natl. Acad. Sci. USA* 89:5675–79

Laschet J, Minier F, Kurcewicz I, Bureau MH, Trottier S, et al. 2004. Glyceraldehyde-3-phosphate dehydrogenase is a GABA receptor kinase linking glycolysis to neuronal inhibition. *J. Neurosci.* 24:7614–22

Lassen NA, Ingvar DH, Skinhoj E. 1978. Brain function and blood flow. *Sci. Am.* 239:62–71

Lauritzen M. 2001. Relationship of spikes, synaptic activity and local changes of cerebral blood flow. *J. Cereb. Blood Flow Metab.* 21:1367–83

Lauritzen M. 2005. Reading vascular changes in brain imaging: Is dendritic calcium the key? *Nat. Rev. Neurosci.* 6:77–86

Lennie P. 2003. The cost of cortical computation. *Curr. Biol.* 13:493–97

Lennox WG. 1931. The cerebral circulation. XV. Effect of mental work. *Arch. Neurol. Psychiatry* 26:725–30

Leopold DA, Murayama Y, Logothetis NK. 2003. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. *Cereb. Cortex* 13:423–33

Lightman SL, Hunt SP, Iversen LL. 1982. Effects of opiates and osmotic stimuli on rat neurophypophyseal metabolic activity monitored with [^{3}H]-2-deoxyglucose. *Neuroendocrinology* 35:104–10

Llinas R. 1988. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science* 242:1654–64

Logothetis NK. 2000. Can current fMRI techniques reveal the micro-architecture of the cortex? *Nat. Neurosci.* 3:413–14

Logothetis NK. 2003. The underpinnings of the BOLD functional magnetic resonance imaging signal. *J. Neurosci.* 23:3963–71

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150–57

Logothetis NK, Wandell BA. 2004. Interpreting the BOLD signal. *Annu. Rev. Physiol.* 66:735–69

Madsen PL, Hasselbalch SG, Hagemann LP, Olsen KS, Bulow J, et al. 1995. Persistent resetting of the cerebral oxygen/glucose uptake ratio by brain activation: evidence obtained with the Kety-Schmidt technique. *J. Cereb. Blood Flow Metab.* 15:485–91

Magistretti PJ, Chatton JY. 2005. Relationship between L-glutamate-regulated intracellular Na^+ dynamics and ATP hydrolysis in astrocytes. *J. Neural Trans.* 112:77–85

Magistretti PJ, Morrison JH, Shoemaker WJ, Sapin V, Bloom FE. 1981. Vasoactive intestinal polypeptide induces glycogenolysis in mouse cortical slices: a possible regulatory mechanism for the local control of energy metabolism. *Proc. Natl. Acad. Sci. USA* 78:6535–39

Magistretti PJ, Pellerin L, Martin JL. 1995. Brain energy metabolism: an integrated cellular perspective. In *Psychopharmacology: The Fourth Generation of Progress*, ed. FE Bloom, DJ Kupfer, pp. 657–69. New York: Raven Press

Magistretti PJ, Pellerin L, Rothman DL, Shulman RG. 1999. Energy on demand. *Science* 283:496–97

Martin A. 1999. Automatic activation of the medial temporal lobe during encoding: lateralized influences of meaning and novelty. *Hippocampus* 9:62–70
Martin WR, Powers WJ, Raichle ME. 1987. Cerebral blood volume measured with inhaled C15O and positron emission tomography. *J. Cereb. Blood Flow Metab.* 7:421–26
Mata M, Fink DJ, Gainer H, Smith CB, Davidsen L, et al. 1980. Activity-dependent energy metabolism in rat posterior pituitary primarily reflects sodium pump activity. *J. Neurochem.* 34:213–15
Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, et al. 2001. Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res. Bull.* 54:287–98
McCasland JS, Hibbard LS. 1997. GABAergic neurons in barrel cortex show strong, whisker-dependent metabolic activation during normal behavior. *J. Neurosci.* 17:5509–27
McGilvery RW, Goldstein GW. 1983. *Biochemistry: A Functional Approach*. Philadelphia: Saunders
Mercer RW, Dunham PB. 1981. Membrane-bound ATP fuels the Na/K pump. Studies of membrane-bound glycolytic enzymes on inside-out vesicles from human red cell membranes. *J. Gen. Physiol.* 78:547–68
Mintun MA, Lundstrom BN, Snyder AZ, Vlassenko AG, Shulman GL, Raichle ME. 2001. Blood flow and oxygen delivery to human brain during functional activity: theoretical modeling and experimental data. *Proc. Natl. Acad. Sci. USA* 98:6859–64
Mintun MA, Raichle ME, Martin WR, Herscovitch P. 1984. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J. Nucl. Med.* 25:177–87
Mintun M, Shulman GL, Snyder AZ, Raichle ME. 2000. Cerebral blood flow during regional activation is not regulated to maintain oxygen delivery. *Soc. Neurosci. Abstr.* 26:1729
Mintun M, Vlassenko AG, Rundle MM, Raichle ME. 2004. Increased lactate/pyruvate ratio augments blood flow in physiologically activated human brain. *Proc. Natl. Acad. Sci. USA* 101:659–64
Mintun M, Vlassenko AG, Shulman GI, Snyder AZ. 2002. Time-related increase of oxygen utilization in continuously activated human visual cortex. *Neuroimage* 16:531–37
Mosso A. 1881. *Ueber den Kreislauf des Blutes im Menschlichen Gehirn*. Leipzig: Verlag von Veit & Co.
Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R. 2005. Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science* 309:951–54
Mulligan SJ, MacVicar BA. 2004. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature* 431:195–99
Nichols MJ, Newsome WT. 1999. The neurobiology of cognition. *Nature* 402:C35–38
Offenhauser N, Thomsen K, Caesar K, Lauritzen M. 2005. Activity-induced tissue oxygenation changes in rat cerebellar cortex: interplay of postsynaptic activation and blood flow. *J. Physiol.* 565:279–94
Ogawa S, Lee TM, Kay AR, Tank DW. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc. Natl. Acad. Sci. USA* 87:9868–72
Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, et al. 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* 89:5951–55
Okamoto K, Wang W, Rounds J, Chambers EA, Jacobs DO. 2001. ATP from glycolysis is required for normal sodium homeostasis in resting fast-twitch rodent skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* 281:E479–88
Olshausen BA, Field DJ. 2005. How close are we to understanding V1? *Neural Comput.* 17:1665–99

Patel AB, de Graaf RA, Mason GF, Rothman DL, Shulman RG, Behar KL. 2005. The contribution of GABA to glutamate/glutamine cycling and energy metabolism in the rat cortex in vivo. *Proc. Natl. Acad. Sci. USA* 102:5588–93

Pauling L, Coryell CD. 1936. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proc. Natl. Acad. Sci. USA* 22:210–16

Pellerin L, Magistretti PJ. 2003. Food for thought: challenging the dogmas. *J. Cereb. Blood Flow Metab.* 23:1282–86

Pellerin L, Magistretti PJ. 2004. Let there be (NADH) light. *Science* 305:50–52

Pessoa L, Kastner S, Ungerleider LG. 2003. Neuroimaging studies of attention: from modulation of sensory processing to top-down control. *J. Neurosci.* 23:3990–98

Peters A, Payne BR. 1993. Numerical relationships between geniculocortical afferents and pyramidal cell modules in cat primary visual cortex. *Cereb. Cortex* 3:69–78

Peters A, Payne BR, Budd J. 1994. A numerical analysis of the geniculocortical input to striate cortex in the monkey. *Cereb. Cortex* 4:215–29

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, et al. 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. 8:828–34

Plum F, Duffy TE. 1975. The couple between cerebral metabolism and blood flow during seizures. In *Brain Work: The Coupling of Function, Metabolism and Blood Flow in the Brain*, ed. DH Ingvar, NA Lassen, pp. 197–214. Copenhagen: Munksgaard

Plum F, Posner JB, Troy B. 1968. Cerebral metabolic and circulatory responses to induced convulsions in animals. *Arch. Neurol.* 18:1–13

Porras OH, Loaiza A, Barros LF. 2004. Glutamate mediates acute glucose transport inhibition in hippocampal neurons. *J. Neurosci.* 24:9669–73

Powers WJ, Hirsch IB, Cryer PE. 1996. Effect of stepped hypoglycemia on regional cerebral blood flow response to physiological brain activation. *Am. J. Physiol.* 270:H554–59

Prichard JW, Rothman DL, Novotny E, Hanstock CC, Shulman RG. 1991. Lactate rise detected by 1H NMR in human visual cortex during physiological stimulation. *Proc. Natl. Acad. Sci. USA* 88:5829–31

Raichle ME. 1987. Circulatory and metabolic correlates of brain function in normal humans. In *Handbook of Physiology: The Nervous System, V. Higher Functions of the Brain*, ed. F Plum, pp. 643–74. Bethesda: Am. Physiol. Soc.

Raichle ME. 1998. Behind the scenes of functional brain imaging: a historical and physiological perspective. *Proc. Natl. Acad. Sci. USA* 95:765–72

Raichle ME. 2000. A brief history of human functional brain mapping. In *Brain Mapping: The Systems*, ed. AW Toga, JC Mazziotta, pp. 33–75. San Diego: Academic

Raichle ME. 2003a. Functional brain imaging and human brain function. *J. Neurosci.* 23:3959–62

Raichle ME. 2003b. Images of body and brain. In *A Century of Nature: Twenty-One Discoveries That Changed Science and the World*, ed. L Garwin, T Lincoln, pp. 189–95. Chicago: Univ. Chicago Press

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. 2001. A default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98:676–82

Raichle ME, Martin WR, Herscovitch P, Mintun MA, Markham J. 1983. Brain blood flow measured with intravenous H2(15)O. II. Implementation and validation. *J. Nucl. Med.* 24:790–98

Raichle ME, Posner JB, Plum F. 1970. Cerebral blood flow during and after hyperventilation. *Arch. Neurol.* 23:394–403

Ritchie JM. 1967. The oxygen consumption of mammalian non-myelinated nerve fibres at rest and during activity. *J. Physiol.* (*Lond.*) 188:309–29

Roland PE, Eriksson L, Stone-Elander S, Widen L. 1987. Does mental activity change the oxidative metabolism of the brain. *J. Neurosci.* 7:2373–89

Roland PE, Eriksson L, Widen L, Stone-Elander S. 1989. Changes in regional cerebral oxidative metabolism induced by tactile learning and recognition in man. *Eur. J. Neurosci.* 1:3–17

Schwartz WJ, Smith CB, Davidsen L, Savaki H, Sokoloff L, et al. 1979. Metabolic mapping of functional activity in the hypothalamo-neurohypophysial system of the rat. *Science* 205:723–25

Sharp FR. 1976. Relative cerebral glucose uptake of neuronal perikarya and neuropil determined with 2-deoxyglucose in resting and swimming rat. *Brain Res.* 110:127–39

Sherrington C. 1906. *The Integrative Action of the Nervous System*. New Haven: Yale Univ. Press. 413 pp.

Shimojyo S, Scheinberg P, Kogure K, Reinmuth OM. 1968. The effect of graded hypoxia upon transient cerebral blood flow and oxygen consumption. *Neurology* 18:127–33

Shmuel A, Yacoub E, Pfeuffer J, Van de Moortele PF, Adriany G, et al. 2002. Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. *Neuron* 36:1195–210

Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, et al. 1997. Common blood flow changes across visual tasks. II. Decreases in cerebral cortex. *J. Cogn. Neurosci.* 9:648–63

Shulman RG, Hyder F, Rothman DL. 2001. Cerebral energetics and the glycogen shunt: neurochemical basis of functional imaging. *Proc. Natl. Acad. Sci. USA* 98:6417–22

Shulman RG, Rothman DL, Behar KL, Hyder F. 2004. Energetic basis of brain activity: implications for neuroimaging. *Trends Neurosci.* 27:489–95

Sibson NR, Dhankhar A, Mason GF, Behar KL, Rothman DL, Shulman RG. 1997. In vivo ^{13}C NMR measurements of cerebral glutamate synthesis as evidence for glutamate-glutamine cycling. *Proc. Natl. Acad. Sci. USA* 94:2699–704

Sibson NR, Dhankhar A, Mason GF, Rothman DL, Behar KL, Shulman RG. 1998. Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proc. Natl. Acad. Sci. USA* 95:316–21

Siesjo BK. 1978. *Brain Energy Metabolism*. New York: Wiley & Sons

Sillito A, Jones HE. 2002. Corticothalamic interactions in the transfer of visual information. *Philos. Trans. R. Soc. Lond. B* 357:1739–52

Silver IA, Deas J, Erecinska M. 1997. Ion homeostasis in brain cells: differences in intracellular ion responses to energy limitation between cultured neurons and glial cells. *Neuroscience* 78:589–601

Simpson JRJ, Ongur D, Akbudak E, Conturo TE, Ollinger JM, et al. 2000. The emotional modulation of cognitive processing: an fMRI study. *J. Cogn. Neurosci.* 12(Suppl. 2):157–70

Smith AJ, Blumenfeld H, Behar KL, Rothman DL, Shulman RGFH. 2002. Cerebral energetics and spiking rate: the neurophysiological basis of fMRI. *Proc. Natl. Acad. Sci. USA* 99:10765–70

Sokoloff L, Mangold R, Wechsler R, Kennedy C, Kety SS. 1955. The effect of mental arithmetic on cerebral circulation and metabolism. *J. Clin. Invest.* 34:1101–8

Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, et al. 1977. The [^{14}C]deoxyglucose method for the measurement of local glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat. *J. Neurochem.* 28:897–916

Somers DC, Dale AM, Seiffert AE, Tootell RB. 1999. Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proc. Natl. Acad. Sci. USA* 96:1663–68

Stark CEL, Squire LR. 2001. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *Proc. Natl. Acad. Sci. USA* 98:12760–66

Stettler DD, Das A, Bennett J, Gilbert CD. 2002. Lateral connectivity and contextual interactions in macaque primary visual cortex. *Neuron* 36:739–50

Stone EA, Ariano MA. 1989. Are glial cells targets of the central noradrenergic system? A review of the evidence. *Brain Res. Rev.* 14:297–309

Swanson RA, Morton MM, Sagar SM, Sharp FR. 1992. Sensory stimulation induces local cerebral glycogenolysis: demonstration by autoradiography. *Neuroscience* 51:451–61

Takano T, Tian G-F, Peng W, Lou N, Libionka W, et al. 2006. Astrocyte-mediated control of cerebral blood flow. *Nat. Neurosci.* 9:260–67

Thompson JK, Peterson MR, Freeman RD. 2003. Single-neuron activity and tissue oxygenation in cerebral cortex. *Science* 299:1070–72

Thompson JK, Peterson MR, Freeman RD. 2004. High-resolution neurometabolic coupling revealed by focal activation of visual neurons. *Nat. Neurosci.* 7:919–20

Thomsen K, Offenhauser N, Lauritzen M. 2004. Principal neuron spiking: neither necessary nor sufficient for cerebral blood flow in rat cerebellum. *J. Physiol.* 560:181–89

Triantafyllou C, Hoge RD, Krueger G, Wiggins CJ, Potthast A, et al. 2005. Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. *Neuroimage* 26:243–50

Triveda B, Danforth WH. 1966. Effect of pH on the kinetics of frog muscle phosphofructokinase. *J. Biol. Chem.* 241:4110–14

Ui M. 1966. A role of phosphofructokinase in pH-dependent regulation of glycolysis. *Biochim. Biophys. Acta* 124:310–22

Van Essen DC, Dickson J, Harwell J, Hanlon D, Anderson CH, Drury HA. 2001. An integrated software system for surface-based analyses of cerebral cortex. *J. Am. Med. Inform. Assoc.* 41:1359–78

Vanzetta I, Grinvald A. 1999. Increased cortical oxidative metabolism due to sensory stimulation: implications for functional brain imaging. *Science* 286:1555–58

Vlassenko AG, Rundle MM, Raichle ME, Mintun MA. 2006. Regulation of blood flow in activated human brain by cytosolic NADH/NAD^+ ratio. *Proc. Natl. Acad. Sci. USA* 103:1964–69

Waldvogel D, Van Gelderen P, Muellbacher W, Ziemann U, Immisch I, Hallett M. 2000. The relative metabolic demand of inhibition and excitation. *Nature* 406:995–98

Webb S. 1990. *From the Watching of Shadows*. New York: Adam Hilger. 350 pp.

Weibel ER. 1984. *The Pathway for Oxygen*. Cambridge, MA: Harvard Univ. Press

Williamson JR. 1970. General features of metabolic control as applied to the erythrocyte. *Adv. Exp. Med. Biol.* 6:117–36

Wong-Riley MT. 1989. Cytochrome oxidase: an endogenous metabolic marker for neuronal activity. *Trends Neurosci.* 12:94–101

Wu K, Aoki C, Elste A, Rogalski-Wilk AA, Siekevitz P. 1997. The synthesis of ATP by glycolytic enzymes in the postsynaptic density and the effect of endogenously generated nitric oxide. *Proc. Natl. Acad. Sci. USA* 94:13273–78

Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, et al. 2003. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat. Neurosci.* 6:43–50

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