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Quantitative fMRI and oxidative neuroenergetics

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Abstract

The discovery of functional magnetic resonance imaging (fMRI) has greatly impacted neuroscience. The blood oxygenation level-dependent (BOLD) signal, using deoxyhemoglobin as an endogenous paramagnetic contrast agent, exposes regions of interest in task-based and resting-state paradigms. However the BOLD contrast is at best a partial measure of neuronal activity, because the functional maps obtained by differencing or correlations ignore the total neuronal activity in the baseline state. Here we describe how studies of brain energy metabolism at Yale, especially with ^{13}C magnetic resonance spectroscopy and related techniques, contributed to development of quantitative functional brain imaging with fMRI by providing a reliable measurement of baseline energy. This narrative takes us on a journey, from molecules to mind, with illuminating insights about neuronal-glial activities in relation to energy demand of synaptic activity. These results, along with key contributions from laboratories worldwide, comprise the energetic basis for quantitative interpretation of fMRI data.

Keywords

calibrated fMRI; GABA; glutamate; glutamine; field potentials; multi-unit activity; neuroimaging

Introduction

In 1992, while the first demonstrations of blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) (Bandettini et al., 1992; Blamire et al., 1992; Frahm et al., 1992; Kwong et al., 1992; Ogawa et al., 1992) caused great excitement in the functional brain imaging community, there were concerns about how well the BOLD signal reflected underlying changes in neuronal activity (Barinaga, 1997; Fitzpatrick and Rothman, 1999). This personal account by the authors describes how studies at Yale, in particular those utilizing ^{13}C magnetic resonance spectroscopy (MRS) in conjunction with calibrated fMRI techniques and electrophysiology, helped reveal fundamental relationships between brain function and energy metabolism in the context of BOLD signal change, as well as the overall importance of baseline neuronal activity. These studies arose from basic work on brain energy metabolism using ^{13}C MRS that had begun at Yale in the 1980's under the

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direction of Professor Robert G. Shulman (Behar et al., 1986; Petroff et al., 1986; Rothman et al., 1985). Although we focus on work at Yale, we cover key contributions made at sites worldwide and apologize for any work we may have neglected due to space limitations.

Human brain mapping became possible about three decades ago with positron emission tomography (PET). Within a decade, however, PET functional measurements were replaced by fMRI. But the basic concepts for mapping brain function are similar (for a historical perspective see (Raichle, 2009)). PET measured changes in blood flow or volume (CBF, CBV) and/or changes in glucose or oxygen metabolism (CMR_{glc}, CMR_{O2}) induced by external stimuli, and fMRI uses the blood oxygenation level-dependent (BOLD) contrast, which is a consequence of a complex combination of changes in CBV, CBF, and CMR_{O2} (Ogawa et al., 1990). The main advantage of fMRI over PET is that BOLD signal can be mapped repeatedly in the same session because no external tracer is needed as the changing concentrations of oxyhemoglobin and deoxyhemoglobin (i.e., diamagnetic and paramagnetic respectively) during functional hyperemia provide the contrast.

However both contrasts revealed by PET and fMRI are qualitative because localization of brain regions ignores the total neuronal activity in the baseline state. But both methods have a key underlying assumption that changes in neuronal activity will be proportional to changes in neuronal energy consumption (Shulman and Rothman, 1998). This energy consumption may be measured directly via CMR_{O2} in PET and calibrated fMRI, as described later which is a method that extracts change in CMR_{O2} with CBF and CBV imaging by combining other magnetic resonance imaging (MRI) methods with BOLD contrast. However PET mostly used CBF to reflect the neuronal activity indirectly, whereas fMRI used BOLD contrast.

When the first PET and fMRI studies were performed in the human brain it was not known what the relationship between functional parameters familiar to neuroscientists such as neurotransmission or spiking activity and neuronal energy consumption. The work described in this article focuses on two main questions relevant to interpretation of neuroimaging data:

- What is the relationship between changes quantitative measures of neuronal activity (such as neurotransmitter cycling, synaptic and spiking activity) and oxygen consumption?
- What fraction of total neuronal activity does the contrast measured by BOLD represent?

Early PET and ^{1}H MRS studies suggest non-oxidative energy contribution during brain function

It had long been established that glucose is the main energy substrate in the brain and its oxidation efficiently produces energy to support its function (Siesjo, 1978). However in the late 1980's Fox et al published some PET data that revealed diminished glucose oxidation during sensory processing in awake human brain, where CMR_{glc} and CBF changed significantly but CMR_{O2} did not (Fox and Raichle, 1986; Fox et al., 1988). These PET results, along with early theoretical calculations by Creutzfeld, supported a model of brain function in which neuronal signaling had minimal oxidative energy costs (Creutzfeldt, 1975). This conclusion was surprising based on the generally accepted view of disproportionately high energy costs of human brain function at rest, given its size relative to the body (Aiello and Wheeler, 1995; Sokoloff, 1991). An implication of this model is that the changes in activity mapped by fMRI were much larger than the brain activity in the resting-state, and therefore to a first approximation, the resting brain activity could be neglected. As we will describe below that MRS and other results, initially form Yale and

later from elsewhere, showed that in fact the opposite is true. But the concept of negligible resting-state activity still has a strong influence on the interpretation of fMRI results.

Since the radioactivity in PET lacks specificity, the molecular basis of MRS signals provided an opportunity to test the Fox et al PET findings (Prichard and Shulman, 1986). Unlike ^{1}H MRI, which measures water in all compartments, ^{1}H MRS measures other endogenous molecules specific to intracellular and/or extracellular milieu. MRS is similar to MRI, except that it uses differences in resonance frequency between dissimilar chemical groups to measure the regional concentrations of endogenous molecules, including lactate, glucose, glutamate, GABA, glutamine, etc. However, as discussed in more detail below, ^{13}C MRS in combination with infusion of ^{13}C-labeled substrates like glucose, acetate, etc. the rates of ^{13}C label incorporation into cell-specific pools – e.g., glutamate and GABA are predominantly neuronal, glutamine is predominantly glial – can be detected (for a recent review see (Rothman et al., 2011)).

In the early in 1990's, the Yale group utilized ^{1}H MRS to measure transient lactate increase and glucose decrease in the human brain during a similar visual stimulation paradigm as in Fox et al (Chen et al., 1993; Prichard et al., 1991). While these results suggested some level of non-oxidative glycolysis, the amount of lactate produced was quantitatively much smaller than predicted by the Fox et al PET studies. Moreover, subsequent PET, ^{1}H MRS, and calibrated fMRI (see below) studies have shown there is several-fold larger increase in CMR_{O2} with functional activation than originally measured by Fox et al, especially in relation to the change in CBF which gives rise to the CMR_{O2}-CBF coupling underlying the BOLD contrast (Hyder et al., 2000; Hyder et al., 1998) – an issue which is discussed below for calibrated fMRI. Therefore there was still a significant role for oxidative energy during brain function that could potentially be tracked by ^{13}C MRS (see below). These early ^{1}H MRS results from Yale were in good agreement with independent measurements from other laboratories using ^{1}H MRS and PET, at that time (Frahm et al., 1996; Merboldt et al., 1992; Roland et al., 1987; Sappey-Marinier et al., 1992; Seitz and Roland, 1992; Vafaee et al., 1998; Vafaee et al., 1999) and more recent measurements (Mangia et al., 2007; Mintun et al., 2002).

^{13}C MRS studies reveal high demand for oxidative energy during functional activation

Pioneering studies by Shulman and colleagues, originally at Bell Laboratories and later at Yale, showed that ^{13}C MRS had the potential to provide detailed measurements of metabolic fluxes (for a historical perspective see (Alger and Shulman, 1984)). Following initial studies in the late 1970's in cell suspensions and perfused organs, the ^{13}C MRS method, and a related ^{1}H MRS method called proton observe carbon edit (POCE), was applied to the rodent and human brain (Behar et al., 1986; Cerdan et al., 1990; Fitzpatrick et al., 1990; Gruetter et al., 1992; Petroff et al., 1986; Rothman et al., 1985; Rothman et al., 1992). A surprising initial finding from the in vivo studies was that there was rapid ^{13}C labeling of glutamate and glutamine from glucose or acetate, which stood in contrast with results from brain slices (Badar-Goffer et al., 1990; Badar-Goffer et al., 1992). Because the brain slices were not activated, this feature (i.e., significant ^{13}C labeling of glutamate and glutamine) provided a clue about the relation of energy metabolism and function discussed in the next sections. Based on the ability to detect in vivo turnover of ^{13}C label from substrates (e.g., glucose or acetate) into various metabolites (e.g., glutamate, glutamine, lactate, or aspartate) in real time, several metabolic fluxes (e.g., tricarboxylic acid cycle, glutamine synthesis, neurotransmitter cycle, etc.) could be extracted with compartmental modeling of neuronal-glial trafficking of metabolites (Gruetter et al., 1996; Mason et al., 1995; Mason et al., 1992). The rate determined for glucose oxidation has been shown to be in good agreement with CMR_{glc} measured by other methods in animal models (e.g., in rats with arterio-venous

difference or 2-deoxyglucose autoradiographic methods (Hyder et al., 2000) or in primates with PET (Boumezbeur et al., 2005)) and in humans (Rothman et al., 2011)).

To test the oxidative energy demand of functional brain activation, studies were performed in animal and human visual cortex. At Yale, POCE was used in an anesthetized rat model to demonstrate a large increase in neuronal glucose oxidation in the somatosensory cortex during forepaw activation (Hyder et al., 1996; Hyder et al., 1997). Because the earliest interpretations of BOLD signal increase were interpreted to reflect minimal rise in CMR_{O2} (Kim and Ugurbil, 1997; Ogawa et al., 1993), this Yale finding was especially controversial at the time because a large increase in CMR_{O2} in the presence of a positive BOLD signal was considered an artifact. This issue will be discussed more below in context of calibrated BOLD and electrical activity recordings, but POCE studies of the human brain conducted independently at Universities of Minnesota and Nottingham also showed a substantial increase in CMR_{O2} with visual stimulation in the primary visual cortex (Chen et al., 2001; Chhina et al., 2001). These POCE studies along with parallel studies using calibrated fMRI (see below) have led to the general acceptance that increases in brain activity are primarily fueled by ATP for oxidative glucose consumption, which in primary sensory cortices can be metabolically quite significant (Shulman et al., 2001b). However the mechanism and function of the enhanced non-oxidative metabolism remains an intense area of research, although several models have been proposed (Chih et al., 2001; Magistretti et al., 1999; Shulman et al., 2001a).

Relationship between oxidative energy and glutamatergic neurotransmission

While ^{13}C MRS and POCE (and early calibrated fMRI, see below) studies provided insights into changes in oxidative energy metabolism with brain function, they did not deliver a quantitative relationship between a parameter measuring neuronal function such as glutamate neurotransmission or neuronal signaling as conventionally represented by electrical activity. A potential way to study this relationship was inferred from the rapid ^{13}C labeling from glucose of glutamine in human and animal ^{13}C MRS and POCE studies. In the cerebral cortex, glutamate released from nerve terminals is taken up by surrounding glial cells and returned to the nerve terminals as glutamine (for details of the process see (Rothman et al., 1999)). The glutamatergic neurotransmission pathway is referred to as the glutamate-glutamine cycle. If glutamine labeling from the glutamate-glutamine cycle could be distinguished from other labeling sources for glutamine (e.g., removal of brain ammonia in the glia by glutamine synthesis) this pathway of glutamatergic neurotransmission could be quantitated by ^{13}C MRS.

At Yale, the first study that tried to disentangle the contribution of the glutamateglutamine cycle to glutamine synthesis was performed by measuring the increase in the rate of ^{13}C labeling of glutamine (from glucose) as a function of ammonia concentration and then extrapolating to basal ammonia level. This study lead to an estimate of de novo glutamine synthesis to remove ammonia being no more than a 10–20% contribution even in the anesthetized rat cerebral cortex when metabolic rates are extremely slow compared to the awake state (Sibson et al., 1997). These early ^{13}C MRS studies of the glutamate-glutamine cycle were supported by other studies at Yale and California Institution of Technology using alternate labeling strategies with ^{15}N and ^{13}C labeled precursors enabling separate and direct measurement of glutamine labeling from both de novo synthesis and the glutamate-glutamine cycle (Kanamori et al., 1993; Kanamori et al., 1995; Shen et al., 1998; Sibson et al., 2001). These heteronuclear MRS studies, in conjunction with advanced metabolic modeling (Gruetter et al., 2001; Gruetter et al., 1998; Mason and Rothman, 2004), have been

consistent with the glutamate-glutamine cycle accounting for the majority of mass flow into the brain glutamine pool (for a recent review see (Rothman et al., 2011)).

After the demonstration that ^{13}C MRS could measure the glutamate-glutamine cycle, the Yale group performed a study in a rat model in which they measured the rate of the glutamate-glutamine cycle and neuronal glucose oxidation (both fluxes measured in the same ^{13}C MRS experiment) at different brain electrical activities to address the question of the neuronal energy cost of function (Sibson et al., 1998). ^{13}C MRS was used to measure the rates of neuronal glucose oxidation ($CMR_{glc(ox),N}$) and neurotransmitter flux ($V_{cyc(tot)}$), localized in the rat somatosensory cortex over a wide range of activities: from isoelectric pentobarbital anesthesia, under which there is no neuronal signaling, to mildly anesthetized states with higher neuronal signaling. The study found a linear relationship between $V_{cyc(tot)}$ vs. $CMR_{glc(ox),N}$ which is significant in several respects (Figure 1). Firstly it demonstrated a linear relationship between neuronal activity as measured by glutamatergic function and neuronal energy metabolism. Furthermore at the intercept where $V_{cyc(tot)}$ falls to zero, $CMR_{glc(ox),N}$ is about 0.1 μmol/g/min. Hence in the awake brain approximately 80% of the neuronal energy demand is devoted to events associated with neuronal signaling, which contrasted expectations at the time that majority of resting brain energy not being related to signaling (see discussion above). ^{13}C MRS experiments looking simultaneously at neuronal energy consumption and the rate of the glutamate glutamine cycle have subsequently been performed by several laboratories in both rats and humans (Bluml et al., 2002; Boumezbeur et al., 2010; Chen et al., 2001; Chhina et al., 2001; Choi et al., 2002; Chowdhury et al., 2007; de Graaf et al., 2004; Duarte et al., 2011; Gruetter et al., 2001; Gruetter et al., 1998; Henry et al., 2010; Jiang et al., 2011; Lebon et al., 2002; Mason et al., 1995; Mason et al., 2007; Oz et al., 2004; Pan et al., 2000; Patel et al., 2005a; Patel et al., 2005b; Serres et al., 2008; Shen et al., 1999; van Eijsden et al., 2010; Wang et al., 2010; Yang and Shen, 2005). The results of these studies have been highly consistent with the original findings of Sibson et al and furthermore the human results also agree with the findings in rodent brain (Figure 1).

A third highly significant finding of the Sibson et al study is that the slope between glutamate release/recycling and neuronal glucose oxidation is close to 1:1, or approximately one molecule of glucose is consumed for every glutamate released. The high value of this slope indicated that the glutamate-glutamine cycle is a major metabolic flux in the brain – on the order of the tri-carboxylic acid cycle and glucose consumption (which has considerable importance for models of glutamate excitotoxicity in disease). Furthermore the close to stoichiometric 1:1 ratio implies a molecular mechanism for the coupling of the two fluxes. The early 13C MRS results of Sibson et al were consolidated into a model of neuronal-glial interactions proposing a novel role for lactate, which conventionally had been thought to be an end product of glycolysis (Magistretti et al., 1999). The fundamental hypothesis was that glial glycolytic ATP was produced rapidly enough to clear glutamate from the extracellular space to prepare the nerve terminal for the next synaptic event. The recycling of one mole of glutamate neurotransmitter between glia and neurons was associated with oxidation of one mole of glucose molecule in neurons. However only by glia took up the glucose whereas all the lactate generated by glycolysis in the glia was transferred to neurons for subsequent oxidation.

While this model was consistent with the 1:1 observed relationship between $\Delta CMR_{glc(ox),N}$ and $\Delta V_{cyc(tot)}$ measured by ^{13}C MRS, it could not specify the energetics of glia and GABAergic neurons because quantitative values for these pathways were not available back then. Later we revised this model to include more up-to-date measurements (Hyder et al., 2006). The revised model showed that glia could produce around 10% of total oxidative ATP and GABAergic neurons could potentially generate about 20% of total oxidative ATP

in neurons. Neurons could produce around 90% of total oxidative ATP and could be required to take up directly as much as 25% of the total glucose oxidized. However glial lactate would still make a major contribution to neuronal oxidation, but about 30% less than predicted before. The relationship observed between $\Delta CMR_{glc(ox),N}$ and $\Delta V_{cyc(tot)}$ could still be determined by glial glycolytic ATP as before. Quantitative aspects of this model (Figure 2) are currently being tested, but so far the Yale group has shown that interruption of glutamate release/recycling affects both BOLD contrast and oxidative demand (Kida et al., 2001; Kida et al., 2006).

It should be pointed, however, that other models have been proposed to explain the relationship based upon other molecular mechanisms, including redox potential balancing requirements and the need of glycolytic ATP to pump glutamate into vesicles (Hertz et al., 2007; Mangia et al., 2009; Simpson et al., 2007). The hopeful discovery of the molecular/cellular mechanism(s) underlying the relationship between $\Delta CMR_{glc(ox),N}$ and $\Delta V_{cyc(tot)}$ will provide important insight into why the brain requires glucose as its major fuel and may be of importance in understanding the finding of altered brain glucose metabolism in a variety of diseases. Thus the most up-to-date ^{13}C MRS data from the rat and human brain suggest that about 20% of neuronal energy demand in the awake brain is dedicated for non-signaling or housekeeping needs, whereas the remaining 80% fraction of the energy supports the signaling needs within cortical networks. This large 80% of the baseline energy, which is necessary for consciousness (Shulman et al., 2009), as discussed below remains largely unexplored in brain studies.

Implications of the ^{13}C MRS findings for the interpretation of fMRI

As described above, due to the belief of minimal resting brain activity at the time the most accepted model for interpreting fMRI was based on the changes seen being proportional to the total neuronal activity engaged in the task, an assumption that was inherent in the early versions of statistical parametric mapping which remains the most popular method for analyzing functional imaging data (Frackowiak et al., 2004). However by the mid 1990's there were findings of negative changes in the BOLD signal (as well as negative CBF changes reported from PET studies), which represented a paradox from the viewpoint of there being little resting neuronal activity compared with activated state. In 1998, Shulman and Rothman proposed an explanation for the negative BOLD signal by applying the relationship discovered by the ^{13}C MRS results between neuronal glucose oxidation and neuronal activity (as assessed by the glutamate-glutamine cycle) to estimate the total resting brain activity versus the change in activity measured in the increments reported by PET and early quantitative fMRI studies (Shulman and Rothman, 1998). They concluded, contrary to common belief at the time, that the task-induced changes measured by BOLD signal were substantially lower than the neuronal activity in the same regions when no task was present. From this perspective the negative BOLD was no longer paradoxical – it simply meant the brain region exhibiting the change during the task had less neuronal activity than in the resting state. They also presented examples of how the large resting activity could change the interpretation of an fMRI study. For example, no change in BOLD signal during a task did not mean the region was not involved in its performance – its neuronal activity devoted to the task could be the same as that used in its resting state (see the later section regarding studies that examined the question of how much neuronal activity is needed for function). Soon after the publication of the initial ^{13}C MRS studies looking at the energy costs of neuronal activity and resting state activity, Raichle and colleagues at Washington University incorporated these findings along with other results from PET and fMRI to develop a model explaining the function of resting state activity in terms of a default state of function, which has extensively influenced the analysis and interpretation of fMRI studies of the resting-state paradigm (Gusnard and Raichle, 2001).

Calibrating the BOLD contrast to reflect oxidative demand during task paradigms

From the earliest descriptions of BOLD contrast (Boxerman et al., 1995; Kennan et al., 1994; Ogawa et al., 1993), it was clear that CMR_{O2} could be extracted, provided that CBF and CBV were measured with the baseline BOLD signal. As fMRI and ^{13}C MRS developments continued to flourish in the 1990's, several groups focused on novel MRI methods for CBF and CBV imaging in vivo which proved to be seminal for the development of calibrated fMRI studies (Detre et al., 1992; Kennan et al., 1998; Kim, 1995; Mandeville et al., 1998; Williams et al., 1992). Because magnetic labeling of arterial blood proved to be a sensitive enough perfusion tracer in brain tissue, the CBF method did not require exogenous contrast agents and thus could be imaged reliably in both humans and animals. The CBV method, however, was based on intravascular-borne exogenous paramagnetic contrast agents that drowned out the diamagnetic BOLD effect during functional hyperemia. Because this contrast agent-based CBV method was limited to animals, early human "calibrated fMRI" studies combined BOLD and CBF measurements to estimate CMR_{O2} changes during functional activation (Davis et al., 1998; Hoge et al., 1999; Kastrup et al., 1999; Kim et al., 1999; Kim and Ugurbil, 1997),

$$\frac{S}{S_0} - 1 = M\left[1 - \left(\frac{CMR_{O2}}{CMR_{O2_0}}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right] \qquad \text{eq. [1]}$$

where the subscript "o" represents the baseline state values for each parameter, S represents the BOLD signal, M represents the baseline BOLD signal which is the product of the transverse relaxation rate (with either spin-echo or gradient-echo) and the echo time, and the parameters α and β are assumed to be 0.4 and 1.5, respectively, for field strengths of 1.5T.

Because ^{13}C MRS methods can measure CMR_{O2} changes directly, an opportunity presented itself at Yale to test the validity of eq. [1] by conducting multi-modal measurements of CMR_{O2}, CBF, CBV, and BOLD signal (with both spin-echo or gradient-echo) under various levels of brain activity in rats at 7.0T (Hyder et al., 2001; Kida et al., 1999; Kida et al., 2000). Some important observations from these studies have relevance for calibrated fMRI studies, especially for those conducted at fields higher than 1.5T. First, it was observed that the parameter β, which designates the CMR_{O2}-CBF coupling in relation to the BOLD effect, is closer to 1 at 7.0T (or higher). This β value is within expectations from stimulations of the BOLD effect extrapolated to fields beyond 1.5T (Boxerman et al., 1995; Kennan et al., 1994; Ogawa et al., 1993). Second, the value of the parameter α which describes the CBV-CBF coupling is probably less than 0.4 and was estimated by PET in primate brain during CO_2 challenges (Grubb et al., 1974).

Most early human calibrated fMRI studies assumed a specific value of α because CBV could not be independently measured. Animal studies at Yale suggested that the α value could range from 0.1 to 0.2 (Hyder et al., 2001) because CBV and CBF dynamics were not fixed during the time course of the functional activation (Mandeville et al., 1999). These suggestions are now independently supported by subsequent findings from studies in rat, cat, and human brain where CBV and CBF have been measured in the same session (Chen and Pike, 2009; Jin and Kim, 2008; Kida et al., 2007). However it should be noted that these CBV measurements reflect the entire blood volume in the vascular branching, whereas the BOLD effect is sensitive to mainly the venous compartment. Recently some novel CBV methods developed at University of Pittsburgh, which allows separation of the arterial and venous compartments, suggest that the contribution of CBV changes incorporated into

calibrated fMRI may be too large because it is the arterial compartment that contributes most during functional hyperemia (Kim and Kim, 2005, 2011). These results have serious consequences for calibrated fMRI because of the potential to underestimate changes in CMR_{O2} by exaggerated contributions from CBV in eq. [1].

Another intrinsic problem in calibrated fMRI is the assessment of an independent measure (or assumption) about the baseline BOLD signal (i.e., the so-called *M* parameter), which is affected by a variety of experimental settings including the static magnetic field shim, which can vary from study to study. By comparing ΔCMR_{O2} predicted from calibrated fMRI and ΔCMR_{O2} measured from POCE, the Yale group showed good accuracy of calibrated fMRI in animals with independent CBF and CBV imaging and direct *M* measurement under optimal shim conditions (Hyder et al., 2001; Kida et al., 2000). An important component of this early work was that *M* can be directly measured, from both spin-echo and gradient-echo calibrated fMRI studies, a point that has been raised recently in the literature (Blockley et al., 2012; Gauthier et al., 2011).

The use of calibrated fMRI has advanced considerably in many different laboratories (Bulte et al., 2012; Chen and Pike, 2010; Chiarelli et al., 2007a; Chiarelli et al., 2007b; Leontiev and Buxton, 2007; Leontiev et al., 2007; Lin et al., 2009; Liu et al., 2004; Restom et al., 2007; Restom et al., 2008; Shen et al., 2008; Stefanovic et al., 2005; Uludag et al., 2004). However the neuronal basis of the CMR_{O2} changes derived from calibrated fMRI remained unresolved until recently. The Yale group compared neuronal activity recordings of local field potential (LFP) and/or multi-unit activity (MUA) with calibrated fMRI results, in an animal model, to show tight neurovascular and neurometabolic couplings in block-design (Maandag et al., 2007; Smith et al., 2002) and event-related paradigms (Herman et al., 2009; Sanganahalli et al., 2009) of normal brain and various types of epileptic seizure models (Englot et al., 2008; Mishra et al., 2011; Schridde et al., 2008). Although relationships between neuronal activity and stimulus features can range from linear to nonlinear, associations between hyperemic components (i.e., BOLD, CBF, CBV) and neuronal activity (i.e., LFP, MUA) are linear. These results showed that CMR_{O2} changes are correlated with LFP and MUA in cerebral cortex.

Overall, the calibrated fMRI studies at Yale quantitatively explained the presence of large CMR_{O2} changes observed during sensory stimulation in anesthetized rats with a positive BOLD signal (Hyder et al., 1996; Hyder et al., 1997) with concomitant large changes in CBF (Hyder et al., 2000; Silva et al., 1999). Notably, both in human and animal studies, the measured $\Delta CBF/CBF$ and calculated $\Delta CMR_{O2}/CMR_{O2}$ from calibrated fMRI studies (i.e., the CMR_{O2}-CBF coupling) show a linear trend suggesting rapid oxygen equilibration between blood and tissue pools within the physiological range (Hyder et al., 1998). In support of this hypothesis, independent studies from Universities of Pennsylvania and Pittsburgh show that tissue pO_2 dynamics are just as fast as the CBF dynamics during functional activation (Ances et al., 2001; Vazquez et al., 2008). Together, these results propose that calibrated fMRI at high magnetic fields can provide high spatiotemporal mapping of CMR_{O2} changes (Hyder et al., 2010).

What fraction of neuronal ensemble's activity is needed for brain function?

Although BOLD signal had been shown to correlate with LFP and MUA dynamics (Logothetis et al., 2001), no specific mechanism for this linkage had been identified yet. The Yale group sought an energetic basis for this question because the model on the basis of the Sibson et al ^{13}C MRS studies (Figure 2) proposed a testable hypothesis that neurotransmitter flux, and consequently oxidative demand, should be proportional to spiking frequency of glutamatergic neurons (Smith et al., 2002). In an anesthetized rat model, Smith et al derived

change in oxidative energy ($\Delta CMR_{O2}/CMR_{O2}$) from calibrated fMRI during sensory stimulation and compared it to changes in spiking frequency of a neuronal ensemble ($\Delta\nu/\nu$) within activated voxels identified by BOLD contrast. Smith et al examined the relationships from two anesthetized levels and found good agreement between $\Delta CMR_{O2}/CMR_{O2}$ and $\Delta\nu/\nu$, thereby relating the energetic basis of neuronal spiking frequency and neurotransmitter flux.

A surprising finding by Smith et al was that not all neurons in the recorded ensemble responded the same way to the forepaw stimulation (Figure 3). The histograms of neuronal firing rates showed different distributions in the resting and stimulated states. For example, in the deeply anesthetized level (or a low baseline state) about 60% of the population showed an increase in firing, about 10% of the population showed a decrease in firing, and about 30% of the population showed no change in firing. But these fractional responses of the population were different from the lightly anesthetized level (or a high baseline state), where the fraction that decreased their firing remained at 10% (see (Smith et al., 2002) and (Hyder et al., 2002). for details). These fMRI and electrophysiology results from Yale showed that the fraction of neuronal ensemble's activity that underlies BOLD contrast is highly dependent on the baseline state. Similar observations had been made with electrophysiological measurements under a variety of conditions (McCasland and Woolsey, 1988; Scannell and Young, 1999). Overall these studies suggest that collaboration among a large number of neurons – some of which are firing faster and others slower but all requiring energy – is crucial for neuronal signaling.

Another interesting feature of the Smith et al studies was that the same forepaw stimulation was applied from two anesthetized levels (i.e., low and high baseline states). Although the histograms representing the two rest conditions showed different distributions, the histograms for the two stimulated conditions were nearly identical (Figure 3). In other words, the final values of CMR_{O2} and ν (and thus BOLD signal) reached upon stimulation were approximately the same from both baselines (Hyder et al., 2002). If only increments were required to support function then magnitudes should be independent of the baseline. But if particular magnitudes of activity were required, then incremental sizes should inversely correlate with baseline, being larger from a lower baseline (Shulman et al., 1999). In support of this hypothesis, the results of Smith et al showed that particular magnitudes of activity support neural function. These results confirmed that disregard of baseline activity in fMRI experiments by differencing (or correlations) removes a large and necessary component of the total neuronal activity in the resting brain.

The Smith et al findings are supported by other results, which have been measured by a variety of techniques (e.g., fMRI, optical imaging, electrophysiology), applied to different sensory systems (e.g., somatosensory cortex, visual cortex, olfactory bulb), across a wide range of species (e.g., rat, cat, monkey, human), and under quite diverse behavioral states (e.g., awake, sleep, and anesthetized. Measurements show that the magnitude of the evoked response upon stimulation is, to a first-order, inversely related to the level of baseline activity (Chen et al., 2005; Issa and Wang, 2008, 2009; Li et al., 2011; Masamoto et al., 2007; Pasley et al., 2007; Portas et al., 2000; Smith et al., 2002; Uludag et al., 2004; Zhu et al., 2009).

More recent studies at Yale by Maandag et al showed that the spatial extent of activation spreading is also inversely conditional on the level of baseline activity (Maandag et al., 2007). Since the separation of the two baseline states (e.g., as reflected by ΔCMR_{O2}) in the Smith et al and Maandag et al studies differed significantly, these early results about the relevance of baseline for fMRI studies suggest that careful consideration about an absolute measure of resting state is necessary. These results from Maandag et al also find support

from other studies in the literature (Antognini et al., 1997; Disbrow et al., 1999; Disbrow et al., 2000; Dueck et al., 2005; Erchova et al., 2002; Heinke et al., 2004; Imas et al., 2006; Sperling et al., 2002). Most of these studies, which used either an anesthetic or a sedative to alter the baseline state, suggest that evoked activity is more localized under levels of deep anesthesia or higher sedation (i.e., low baseline state), whereas the response patterns expand beyond the primary area under levels of light anesthesia or lower sedation (i.e., high baseline state).

Thus contrary to the traditional approach of just varying the stimulus input, the brain's input can also be treated as an independent variable, because perception measured at the cortical level depends on both exogenous and endogenous inputs (Ebner and Armstrong-James, 1990). While recent experimental evidence is changing the opinion that spontaneous neuronal activity is simply "noise" (for recent reviews see (Hyder and Rothman, 2011; Northoff et al., 2010; Ringach, 2009; Shulman et al., 2007)), it should be noted that classical studies had raised the importance of spontaneous activity for understanding brain function (Adrian, 1941). Future studies need considerations about properties of the stimulus (e.g., amplitude, contrast, etc.) in relation to baseline to study interactions of exogenous and endogenous inputs (Davis et al., 2007; Silva et al., 2011). Since anesthetics and sedatives are the primary means to experimentally alter the baseline states, better mechanistic understanding is needed (Alkire et al., 2008; Franks, 2008). An alternate means of varying resting brain activity without exogenous chemicals, as recently featured in studies from Universities of California in San Diego and Berkley (Pasley et al., 2007; Uludag et al., 2004), are needed for translation to humans.

Understanding healthy aging with multi-modal studies of ^{13}C MRS and calibrated fMRI

As applications of fMRI to disease states rise (Matthews et al., 2006), there is a growing need to assess effects of healthy human aging because alterations in brain morphology, cellular density, or metabolism could significantly influence the BOLD contrast (d'Esposito et al., 2003). Alterations in mitochondrial function have been implicated in age-related neurodegenerative diseases through reactive oxygen species hypothesis and have been suggested to have a role in the loss of brain function with healthy aging (Reddy, 2007). Healthy human aging is associated with a decline in cognitive, memory, and sensory processes (Hedden and Gabrieli, 2004). But is there a quantitative neuroimaging correlate of these cognitive findings?

Recent task-based fMRI studies in healthy human aging show that the BOLD response is greater in younger subjects, but the CMR_{O2}-CBF couplings established from calibrated fMRI in aging and younger subjects are nearly identical (Ances et al., 2009). Moreover, the resting-state fMRI studies show very little difference between the networks revealed in the healthy young and aging brains (Koch et al., 2010). PET studies have noted 10–20% reductions in overall CMR_{glc} and CMR_{O2} with normal aging (Kalpouzos et al., 2009; Martin et al., 1991), but these may not all be related to mitochondrial changes. Furthermore, it is unclear whether these metabolic decreases are due to changes at the cellular level or are secondary to brain shrinkage (Ibanez et al., 2004). Recent ^{13}C MRS studies from the Yale group shows that, compared with young subjects, neuronal mitochondrial metabolism and neurotransmitter cycle flux (assessed with ^{13}C-labelled glucose) was approximately 30% lower in elderly subjects, but glial mitochondrial metabolism (assessed with ^{13}C-labelled acetate) was approximately 30% higher in elderly subjects (Boumezbeur et al., 2010). Taken together, these multi-modal studies suggest that healthy aging is associated with reduced neuronal mitochondrial metabolism and altered glial mitochondrial metabolism, which may in part be responsible for declines in brain function.

Concluding remarks

Functional brain imaging methods like PET and fMRI that highlight areas of activity in vivid hues have revolutionized neuroscience, but has been limited by these methods not directly capturing changes in neuronal activity or reflecting a measure of total neuronal activity. Studies using multi-modal MRI, MRS, and electrical recordings have contributed to quantitating the energetic changes underlying the BOLD signal and directly relating them to changes in neurotransmission and electrical activity. They also have shown that the baseline neuronal activity is much larger than the changes in activity induced by tasks, which in turn has contributed to the recent interest in understanding its functional significance. The response to task has been shown to be dependent on this baseline activity, which strongly argues for its functional relevance, and thus every attempt should be made to image the resting brain activity and metabolism quantitatively and new schemes should be sought for its inclusion in data analysis. The underlying theme in these early Yale studies, and those that continue today in several other laboratories around the world, is that functional brain imaging studies can go beyond just mapping indirect correlates of function and instead directly study total brain activity as well as the neurometabolic and neurovascular components that support it in health and disease.

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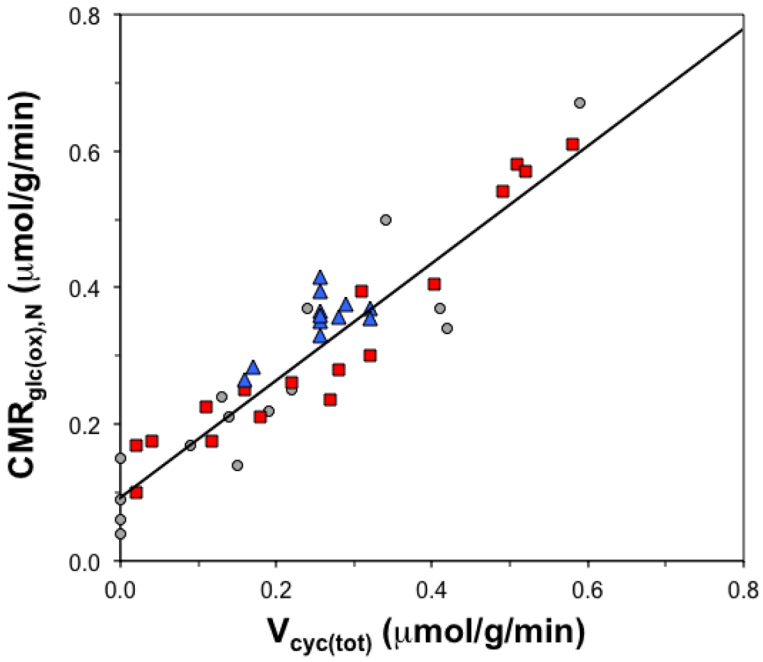

Figure 1.

High neuronal energy demand and its relation to neurotransmitter cycling reveal a sizeable level of neuronal activity in the awake brain. Experimental estimates of relationship between total neurotransmitter cycling rate ($V_{cyc(tot)}$) and the cerebral metabolic rate of glucose oxidation in neurons ($CMR_{glc(ox),N}$ derived using ^{13}C MRS localized to the rat somatosensory cortex (grey circles for Sibson et al (1998) and red squares are for all other studies since then) and human visual cortex (blue triangles). The results suggest that about 80% of the resting energy consumption in the awake rat brain is dedicated to events associated with neuronal activity. The trends, to a first-order, are similar between rat and human brain ^{13}C MRS data.

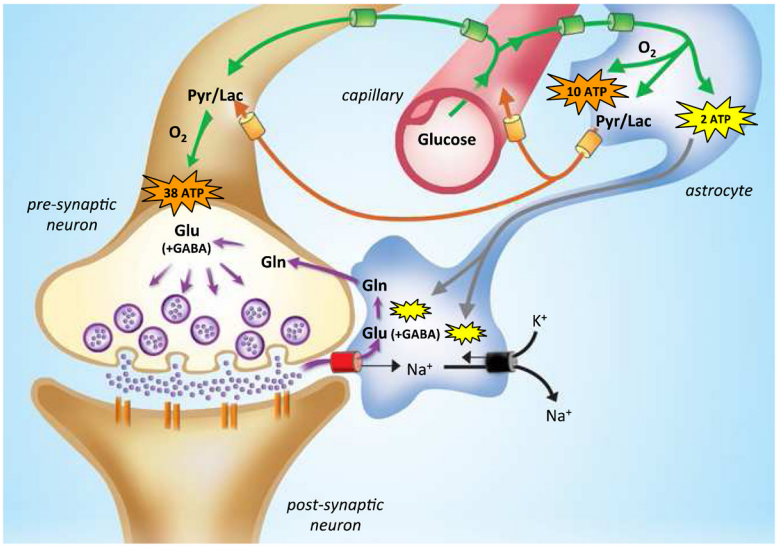

Figure 2.

A revised coupling between synaptic activity and glucose metabolism. Glucose uptake (green) is now ubiquitous. Astrocytic lactate flow (orange) to neurons is now less, with a small amount being effluxed to blood. ATP is produced oxidatively (orange) in neurons and astrocytes. ATP produced by glycolysis (yellow) fuels ion pumping and glutamine synthesis in astrocytes. Abbreviations: Glu, glutamate; Gln, glutamine; Pyr, pyruvate; Lac, lactate in astrocytes. See Hyder et al (2006) for details. Modified from Hyder et al (2006), Journal of Cerebral Blood Flow and Metabolism, NPG.

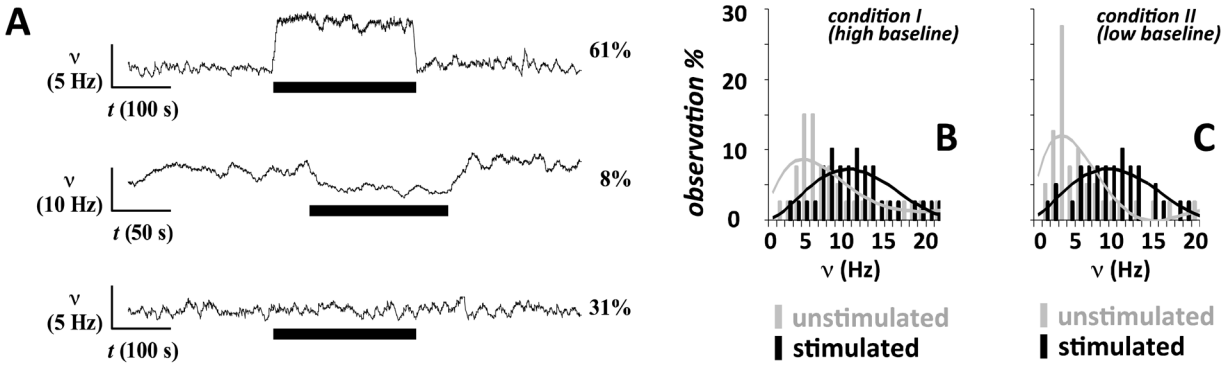

Figure 3.

Neuronal ensemble recordings. (A) Experimental variations across electrophysiological measurements (shown for condition II, i.e., high baseline state, only) from the contralateral forepaw region. Significant increases and decreases in spiking frequency (ν) within were observed in ~60% and ~10% of the recordings, respectively (top and middle), whereas in ~30% of the recordings the stimulation did not induce any significant changes in n (bottom). The vertical and horizontal bars represent the scales for ν and time, respectively. The thick black horizontal bar represents the stimulus duration. (B and C) The comparison in a small neuronal ensemble (72 neurons) between basal activity achieved with two dosages of α-chloralose shows significantly different spiking frequencies at rest ($P < 0.01$), whereas upon stimulation the spiking frequencies became similar ($P > 0.25$). See Smith et al (2002) for details. Modified from Smith et al (2002), Proceedings of National Academy of Sciences, USA.