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# Using proton magnetic resonance imaging and spectroscopy to understand brain "activation"

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**Abstract**

Upon stimulation, areas of the brain associated with specific cognitive processing tasks may undergo observable physiological changes, and measures of such changes have been used to create brain maps for visualization of stimulated areas in task-related brain "activation" studies. These perturbations usually continue throughout the period of the stimulating event, and then subside when the event is terminated. In this communication, we consider the nature and meaning of these task-related brain activations. Since stimulation usually results in an increase in the frequency of neuron depolarizations or "spikes", an energy expensive activity that requires ATP for restoration of ionic gradients, additional energy supplies must be rapidly deployed to the stimulated areas or rates of re-polarization could be decreased, and refractory periods between spikes increased. As a result, maximum spiking rates may be decreased and some frequency-encoded information lost. The energy available to brain cells to re-synthesize ATP from ADP is a function of levels of glucose and oxygen in blood, and their availability to stimulated neurons is a function of the rate at which focal blood supplies can be increased (hyperemia). In this review we explore how neurons transmit meaningful encoded information; how the integrity of that information is dependent on a continuous supply of energy, and how proton magnetic imaging and spectroscopy may aid in understanding the process. Finally, evidence is presented that the neuropeptide, *N*-acetylaspartylglutamate, is a neuronal astrocyte-vascular feedback signal that regulates activation induced focal hyperemic responses.


*Keywords:* Cognition; Hyperemia; Metabotropic glutamate receptor 3; NAAG peptidase; *N*-Acetylaspartate: *N*-Acetylaspartylglutamate

## 1. Introduction

### 1.1. Physiological components associated with brain activation

There are a number of distinguishable, but linked physiological components associated with any task-related brain "activation" that occur on different timescales following experimental stimulation, and that can be measured in vivo independently of one another. An early component is the initiation of a change in rate of spiking by stimulated neurons, which occurs within 1–2 ms and can be measured using implanted electrodes. A later component is an increase in focal blood flow (hyperemia) in response to that stimulation, which occurs in approximately 3–10 s and can be measured using a variety of minimally invasive procedures. A related component is a change in rates of metabolism, and as a result, of the tissue content of a variety of substances. These become apparent in the period from 10 to 100 s after initiation of the experimentally induced stimulation, and some of the changes in levels of specific metabolites can be measured in vivo using proton magnetic resonance

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spectroscopy ($^1$H MRS),[1] and others by spectroscopic analyses of additional elements and their isotopes. In order to measure such metabolic changes, prolonged stimulation periods of minutes in duration may be required. Although these components related to brain activity occur on different timescales, it is important to recognize that all are a result of the initial task activation and comprise a linked sequence, each providing some evidence of the initial and of subsequent physiological responses to that activation. In addition, the temporal window of opportunity for measuring these changes due to activation is short, being of the order of up to100 s after such activation. Measurements of one or more of these components have been used to prepare a variety of dynamic brain activation maps associated with specific cognitive tasks.

As an example of the temporal variability, in studies of the visual cortex, the evoked electrophysiological changes associated with subsequent blood flow changes demonstrated the completely different orders of time, about 0.001 s (1 ms) for neurostimulatory events, compared to hyperemic effects that are observed in >3 s (3000 ms) (Huettel et al., 2004). Such observations suggest that the hyperemic response is a reflection or "afterglow" of the information-transfer events. The large temporal discrepancy also indicates that these functions are likely due to very different physiological processes, and that the much later hyperemic effect is probably due to a slower intercellular molecular diffusion-related function. While the induced hyperemia may only be a reflection of more rapid information-transfer events, it is a vital component of the entire process. This is because it is in the period immediately following any increased signaling activity, that the neuronal ATP energy stores used for restoration of ionic gradients in support of that increase in signaling must be rapidly replenished. During short interim periods between neuronal stimulation and hyperemic responses, the phosphocreatine (PCr) pool may be used to maintain ATP levels.

[1] *Abbreviations used:* ADC, apparent diffusion coefficient; Ac, acetate; AcCoA, acetyl-coenzyme A; Asp, aspartic acid; ADP, adenosine diphosphate; ATP, adenosine triphosphate; BOLD, blood oxygen level-dependent imaging; CBF, cerebral blood flow; CD, canavan disease; CNS; central nervous system; Cr, creatine; Cho, choline; ECF, extracellular fluid; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; fMRS, functional magnetic resonance spectroscopy; Glc, glucose; Gln, glutamine; Glu, glutamic acid; $^1$H-MRS, proton magnetic resonance spectroscopy; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; mGluR, metabotropic Glu receptor; NAA, *N*-acetyl-L-aspartic acid; NAAG, *N*-acetylaspartylglutamic acid; NMR, nuclear magnetic resonance; PCr, phosphocreatine; PET, positron emission tomography; P, phosphate; 2-PMPA, 2-(phosphonomethyl) pentanedioic acid; PRESS, point-resolved spectroscopy; SNR, signal to noise ratio; STEAM, stimulated acquisition mode; tCr, total creatine and phosphocreatine; Te, echo time; tNAA, total NAA + NAAG; ROI, region of interest; $T_2^*$, apparent proton transverse relaxation time.

### *1.2. Hyperemic and related responses to specific neurostimulatory events can be quantified*

#### *1.2.1. Methods for measurement of changes*

There are several minimally invasive investigative methods that provide results that can be correlated with brain activation. These include near-infrared spectroscopy (Fallgatter, Ehlis, Wagener, Michel, & Herrmann, 2004), positron emission tomography (PET) and magnetic resonance imaging (MRI). Functional MRI (fMRI) has become a widespread technique for mapping brain activity. The most commonly employed fMRI contrast mechanism is based on the action of deoxyhemoglobin as a paramagnetic contrast agent. A change in the blood oxygenation level leads to a change in the MR signal. This contrast is referred to as blood oxygenation level dependent (BOLD) (Ogawa et al., 1993).

Other MR methods may provide additional information, such as the ADC contrast method. Using this method it is reported that activated areas of the brain appear to be more closely coupled to neuronal activity than those observed using fMRI (Song et al., 2003), and precedes that from MRI with a timing offset of about 1 s (1000 ms) (Gangstead & Song, 2002). While ADC measurements represent a different form of MRI measurements, it is proposed that by mapping and comparing the two measures in brain, that certain inferences regarding various vascular contributions to MRI signals can be made from the diffusion values (Song, Fichtenholtz, & Woldorff, 2002). MRS, in conjunction with MRI, while difficult, can be used to assess changes in metabolites associated with specific areas of brain activation (Chen et al., 2001).

#### *1.2.2. MRI BOLD measurements*

*1.2.2.1. The BOLD signal.* Brain blood oxygen levels can be evaluated based on the magnetic properties of substances in blood, which in turn are dependent on the oxygenation state of hemoglobin. Since oxygenated hemoglobin is diamagnetic, and deoxygenated hemoglobin is paramagnetic (Hyder et al., 2001), deoxygenated hemoglobin acts as an MRI intra-vascular paramagnetic "contrast" agent. Thus, hemoglobin deoxygenation results in an increased magnetic susceptibility difference, producing an attenuation of the water signal, measured by changes in its apparent proton transverse relaxation time ($T_2^*$). Because the changes in blood oxygenation levels that affect the water signal are also directly associated with the use of oxygen in the neuron re-polarization process, this technique is used to image areas of the brain that appear to be "activated" as a function of specific tasks.

The changes in BOLD signals are also correlated with changes in cerebral blood flow (CBF) (Feng et al., 2004), thus coupling brain stimulation not only with increased oxygen utilization, but with increased focal CBF, the source of replenishment of both oxygen and the glucose (Glc) that are required to support neurophysiological activities. In addition to BOLD measurements,