Appraising the brain's energy budget

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In the average adult human, the brain represents about 2% of the body weight. Remarkably, despite its relatively small size, the brain accounts for about 20% of the oxygen and, hence, calories consumed by the body (1). This high rate of metabolism is remarkably constant despite widely varying mental and motoric activity (2).

Despite these well-known facts about the brain's large energy budget, a clear understanding of how it is apportioned among the many ongoing functional processes in neurons and glial cells has not been clearly spelled out. Understanding these relationships has assumed new importance because of the rapidly increasing use of modern imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to study the functions of the living human brain in both health and disease. Both of these techniques and their derivatives [e.g., single photon emission tomography (SPECT) and various optical imaging techniques] use measurements related to the brain's metabolism and circulation to draw inferences about brain function in terms of its cellular activity (for review, see ref. 3).

In this issue of PNAS, two papers from investigators at Yale University (4, 5) provide important new information on the relationship between brain energy metabolism and cellular activity. This information, when understood in the context of other extant information, allows new insights into the manner in which we employ both neuroimaging and neurophysiological techniques to probe the functions of the human brain. Together with other work, it also lends considerable support to conceptualization of the instantiation of functional processes themselves.

The two reported studies in this issue of PNAS (4, 5) combined magnetic resonance spectroscopy (MRS) techniques with the extracellular recording of neuronal activity in the cerebral cortex of the anesthetized rat. With MRS, the investigators were able to assess changes in brain oxygen consumption as well as changes in the flux of the excitatory amino acid glutamate, the brain's primary excitatory transmitter during somatosensory stimulation. These MRS measurements were complemented by measurements of the change in neuronal activity (i.e., spike frequency, or cell firing rate in this instance) during somatic sensory stimulation. The experimental strategy used two levels of anesthesia (i.e., deep and shallow) designed to achieve two different levels of *baseline* activity to which stimulus-induced changes could be related.

Two observations emerge from this work. First, the change in oxygen consumption produced by stimulation was proportional to the change in excitatory or glutamatergic neurotransmitter flux, which, in turn, was proportional to the change in spike frequency. Establishing these relationships was important to the second phase of this work showing that the maximum values of oxygen consumption and spike frequency achieved during stimulation were approximately the same from both baselines (i.e., both levels of anesthesia). The authors assert that an overall *level* of ongoing activity must be achieved for a particular function to occur. Thus, if the baseline level of activity of the brain is artificially suppressed, as it was in this case by anesthesia, it must be "restored" to the level found in the awake state as a necessary component of the functionally related activity. To put this second point into proper perspective, it is important to establish some possible ground rules about what is meant by the term "baseline" or ongoing activity; what this might reflect in terms of brain function; and how this baseline activity relates to transient changes in activity that have been generally termed "activations."

The metabolic activity of the brain is remarkably constant over time.

The Cost of Ongoing or Baseline Activity

As already mentioned, the metabolic activity of the brain is remarkably constant over time. This ongoing metabolic activity consists largely of the oxidation of glucose to carbon dioxide and water resulting in the production of large amounts of energy in the form of ATP. This high metabolic activity is present when we are completely passive and resting as well as when we are observably doing something. Two lines of investigation have recently converged in their analysis on how this energy is being used. Both have focused on the metabolic requirements associated with glutamate signaling in the brain. This focus would seem reasonable, considering that greater than 80% of neurons are excitatory and greater than 90% of synapses release glutamate (6, 7). Attwell and Laughlin (8) have taken a bottom up modeling approach using extant data on the blowfly retina and the mammalian cerebral cortex. Estimates from their approach indicate that most of the energy used in the brain is required for the propagation of action potentials and for restoring postsynaptic ion fluxes after receptors have been stimulated by the neurotransmitter. In contrast, maintenance of the resting potential in neurons and glial cells accounts for less than 15% of the total energy consumption. Shulman and his colleagues (9, 10) in a very different approach using MRS in anesthetized rats have shown remarkably converging evidence that a very large fraction (≈80%) of the energy use in the brain is correlated with glutamate cycling and, hence, active signaling processes.

Thus, in contemplating the functional significance of the high fixed cost of brain function (i.e., 10 times that expected on the basis of its weight alone), activities directly associated with this ongoing neuronal activity must be strongly considered. The question then arising is just what kind of neuronal activity are we talking about. A possible step in the direction of answering that question is first to examine what is meant by the term "activations" (i.e., transient changes in brain activity) used in the context of modern functional brain imaging with PET and fMRI.

The Cost of Transient Changes in Activity ("Activations")

Brain activation can be distinguished both qualitatively and quantitatively from resting metabolic activity referred to above (for a brief review, see ref. 3). To understand the

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unique qualitative features of brain activation, it is important, first, to recall how blood flow and oxygen consumption are related to each other in the human brain. This relationship is striking for its spatial consistency. It can be measured quantitatively with PET as the fraction of available oxygen (i.e., the arterial oxygen concentration) used by the brain. This measurement is usually referred to as the oxygen extraction fraction (OEF) and represents the balance between oxygen delivery (i.e., blood flow) and oxygen consumption. Researchers have come to appreciate the spatial uniformity of the OEF measured in a resting state (e.g., lying quietly in a scanner with eyes closed but awake) when ongoing metabolic activity is relatively constant (for an introduction to this literature, see refs. 11 and 12). This spatial uniformity in the OEF exists despite considerable variation in the ongoing oxygen consumption and blood flow within gray matter and an almost 4-fold difference between gray and white matter in both oxygen consumption and blood flow. This relationship is altered to a measurable degree in the normal brain only when areas briefly *change* their activity (i.e., so-called "activations") during specific behaviors (13–15).

The signal used to map activations in the brain with PET or fMRI is based on local changes in blood flow. It has been known for more than a century that increased neuronal activity in a region of the brain is associated with an increase in blood flow (for a historical review, see ref. 16). Surprisingly, these changes in blood flow are accompanied by significantly smaller changes in oxygen consumption (13–15). As a result, the local blood oxygen content follows closely the change in brain activity because the amount of oxygen supplied increases more than the demand. This phenomenon has been of great practical value in enabling us to view changes in brain activity with fMRI (17, 18) because aspects of the MR signal intensity are sensitive to the amount of oxygen carried by hemoglobin (19–21).

Whereas oxygen consumption increases less than blood flow, glucose utilization appears to increase in proportion to the change in blood flow (14, 22). Therefore, the increase in metabolism accompanying brain activation is, in part, an increase in glycolysis, which is now thought to occur in astrocytes related to a transient increase in glutamate cycling (23, 24). Thus, brain activation distinguishes itself from ongoing brain metabolism in a unique qualitative manner, with blood flow and glucose utilization increasing more than oxygen consumption.

Quantitatively, metabolic and circulatory changes associated with activations are also distinctive. These changes are *very small* relative to the ongoing hemodynamic and metabolic activity of the brain. Attempts to measure whole brain changes in blood flow and metabolism during intense mental activity have failed to demonstrate any change (2). This finding is not entirely surprising considering both the accuracy of the methods and the small size of the observed changes. For example, *local changes* in blood flow measured with PET during most cognitive tasks are often 5% or less.

Despite their small size, cognitive neuroscientists using modern imaging techniques have focused on these transient changes in activity almost exclusively, ignoring the potential significance of the far larger amount of ongoing functional activity. The papers from the Yale group in this issue of PNAS (4, 5), along with the work of others (for a summary, see ref. 12), provide a stimulus to extend our inquiry into the nature of this ongoing functional activity. Several lines of investigation provide clues to the road ahead.

The Nature of the Ongoing Activity

Neurophysiologists have noted the existence of spontaneous, ongoing electrical activity in the brain for as long as electrical recordings of the brain have been made. This ongoing activity is observed broadly in the electroencephalogram (EEG) recorded from the scalp, as well as in the firing of individual neurons (i.e., "spikes") and local field potentials (LFPs)[†] both recorded from microelectrodes within the brain. Although easily detected, this spontaneous ongoing activity has received far less attention from researchers than has the electrical activity associated with specific perceptual and cognitive activities (there have been exceptions; see, e.g., ref. 30). With regard to such studies, those working with the EEG average activity across many iterations of a task looking for so-called event-related potentials or ERPs, whereas those working with microelectrodes look for changes in spiking frequency. In both instances, researchers correlate elements of task performance with ERPs or changes in spike frequency.

Recently, interest in the spontaneous electrical activity of the brain has accelerated (e.g., see refs. 29 and 31–35). Researchers have been able to demonstrate its importance in simulations as well as the actual analysis of empirical data. Central to this work are attempts to understand how functional connections arise within neural circuits and how temporally correlated activity affects this process. A crucial component in establishing these functional connections is the sensitivity of the involved neurons to correlations in their inputs.

An intriguing hypothesis has emerged that the responsiveness of neurons to changes in their input depends on a continuous, high-level but balanced input of both excitatory and inhibitory activity (for review, see ref. 29). Importantly, it is the balance between this continuous excitatory and inhibitory input that determines the gain or responsiveness of the neurons to correlations in their input. In this formulation, spontaneous ongoing activity becomes a critical enabling factor in the creation of functional connections within circuits responsible for specific behaviors. Furthermore, this correlation-induced functional connectivity can be modified without causing variations in the mean firing rates of the involved cells. As Salinas and Sejnowski have pointed out in their review (29), balanced neurons have rich dynamics and can react to external stimuli on effective timescales that are much smaller than the membrane time constant of a single neuron.

So, how might this relate to our analysis of the energy budget of the brain? It should be noted that most of the neurophysiology discussed above concerns synaptic activity at the input to neurons. Because the highest energy-demanding processes in the brain are centered at these sites (27, 28), it suggests that much of the ongoing or baseline metabolism is devoted to processes occurring there. We might therefore posit that, in the brain, a large majority of its metabolic activity is devoted to ongoing synaptic processes associated with maintaining a proper balance between excitatory and inhibitory activity. Maintenance of this balance allows neurons to respond appropriately to correlational changes in their input and establish the functional connectivity as required for a particular task.

So, where does the above leave cognitive neuroscientists in their quest to use functional imaging data to understand brain function? In part, it would seem to place an emphasis on transient metabolic *changes* associated with alterations in the correlational structure of a neural circuit. This emphasis would be consistent with the importance of synaptic activity in brain metabolism and the close relationship between synaptic activity, LFPs, and functional imaging signals.[†] Furthermore, it would be consistent with success in using functional brain imaging to establish task-related functional connectivity in the human brain (for a brief review, see ref. 36).

But the role for functional imaging does not necessarily end there. Some have raised the intriguing possibility that the spontane-

[†]LFPs are the electric fields recorded from microelectrodes in the brain and are thought to reflect a weighted average of input signals on the dendrites and cell bodies of neurons in the vicinity of the electrode. In terms of functional brain imaging, LFPs are thought to have a much greater influence on the signals generated than spiking activity of neurons (25, 26), which is consistent with the very high metabolic demands of the cell processes thought to be involved in the LFPs (27, 28). The papers by the Yale group in this issue of PNAS report only changes in spiking activity. Although changes in spiking activity and changes in LFPs can be correlated, the latter may sometimes vary independently (29).

ous, ongoing activity of the brain may actually generate globally coherent processes by itself (e.g., ref. 33). Functional brain imaging studies have actually provided some important support for this suggestion. Two overlapping empirical observations are of interest. First, task-independent deactivations appear consistently within the same configuration of areas when subjects engage in a wide variety of goal-directed behaviors (for a review, see ref. 12). Importantly, these deactivations arise in areas that exhibit a normal OEF in the resting state [i.e., they are supported by the full oxidation of glucose to carbon dioxide and water and not by glycolysis alone as are the typical activations (11)]. Thus, they can be viewed as "active" but not "activated" in the resting state. Second, some very recent functional imaging studies have now documented changes consistent with functional connectivity in these same areas in the resting state.[‡§] Together, these data strongly support the hypothesis that these areas represent a unique and sustained functionality resident within the ongoing activity of the brain.

Thus, we may entertain the possibility that the very high baseline or ongoing metabolic activity of the brain not only supports processes necessary for the maintenance of the proper responsiveness of neurons for the transient and ever changing functions of the brain but also instantiates a sustained functionality.

Conclusions

The use of modern imaging techniques such as PET and fMRI in the study of the functional organization of the human brain has opened up enormously exciting new frontiers in the neuroscience of human behavior. As this work has moved forward, it has become increasingly obvious that understanding the relationship between the signals generated by these imaging devices and the underlying physiology of the brain is critically important to the success and long-range goals of this enterprise. It is heartening that important research work is now emerging on this subject, as exemplified in the two papers in this issue of PNAS. A somewhat unexpected feature of this work more generally is that it is not simply a confirmation of preexisting notions about the relationship between the spiking activity of neurons in the brain, blood flow, and metabolism, but, rather, it is opening up new ways of thinking about the manner in which the considerable resources of the brain are being harnessed in the service of human mental activities. The picture that emerges suggests that neurophysiologists, theoretical neurobiologists, and cognitive neuroscientists, with their imaging devices, all bring important and unique perspectives to an enterprise that is enormously exciting to participants and observers alike.

[‡]Greicius, M. D., Krasnow, B., Reiss, A. L. & Menon, V., Eighth International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. Available on CD-Rom in *NeuroImage* **16,** No. 2, (abstr. 1032).

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