Brain Energy Supports the State of Consciousness

Abstract

Following the pragmatic practices of anesthesiologists, a person is defined to be in the state of consciousness by the ability to respond to stimuli. ^{13}C MRS studies have shown that brain energy consumption is mainly used for neuronal signaling. PET measurements have shown widespread ~45% energy reduction during anesthesia-induced loss of consciousness. We propose that high energy consumption is a necessary property of the conscious state. Additional properties are losses at deep anesthesia in fMRI activation patterns and high frequency signaling of neuronal populations. These necessary properties begin to create a physical understanding of the conscious state and differ from the causal use of brain activities that locate hypothesized mental processes assumed to be necessary and sufficient representations of consciousness..

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Non-invasive methods of studying brain chemistry have taken a central place in modern neuroscience. Results from these studies have raised hopes of relating brain activity to mental processes supporting behavioral states, such as consciousness. In recent years, functional Magnetic Resonance Imaging (fMRI), ^{13}C Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET), and electrophysiology experiments have been directed towards these goals. These studies have measured brain energy production in the form of glucose oxidation in the resting baseline and anesthetized states and have followed regional changes during stimulation from these states. PET and MRS methods have measured the total or baseline energies while neuroimaging studies, by fMRI and PET, have determined the incremental energies during cognitive or sensory stimulations. The most striking result is that the energy consumption supporting neuronal firing in the conscious- awake, baseline state is one to two orders of magnitude larger than the energy changes during stimulation (Shulman & Rothman, 1998; Shulman, Rothman, & Hyder, 1999; Shulman, Rothman, & Hyder, 2007). Nonetheless, most research relating brain activity to mental processes has been based upon the smaller fMRI or PET increments induced by stimulation, which generally are interpreted as localizing differences in mental processes supporting the two activities.

Early functional imaging studies by Posner and Raichle (1994), using PET scanning, posited that a connection between hypothesized mental processes and brain activities can be made by comparing brain images taken of subjects performing different tasks. An experimental example they used was comparing subjects reading proper and nonsense words. Differences between two functional images were interpreted as providing a quantitative map of the difference in neuronal activity and to have localized the neuronal underpinnings of the hypothesized mental processes (sometimes called modules); in the case at hand that mental process would be semantics. This experimental paradigm, based on cognitive psychology, was adopted for fMRI

studies, a technology which made functional brain imaging widely accessible.

It soon became clear, however, that the brain did not follow the simple assumptions of "pure insertion" which expects the incremental brain neuronal response to a mental process to be independent of its context. The dependence of brain responses upon their context created problems for cognitive psychology, which had assumed, for example, that all acts of remembering would require brain to use a similar module of "memory". Jerry Fodor, a founder of the field, concluded in 2000 that this original formulation was not supported experimentally and in his book with that title recognized that "the mind does not work that way" (Fodor, 2000). The dependence upon context undercut the causality claimed for the concepts of Cognitive Neuroscience derived from cognitive psychology. Early PET and fMRI results, including the influence of context in psychologically-based fMRI or PET studies, led us to question the value of such concepts for functional brain imaging. We suggested that the field would be better served by using the functional imaging data to question, test or better yet, to avoid the use of hypothesized mental processes, rather than considering those assumptions proven when a difference image is acquired (Shulman, 1996). A primary goal of the present paper is to show how brain activity supporting behavior can be studied without making mentalistic/psychological assumptions about the unobserved processes presumably involved in observed behaviors or behavioral states.

In the face of these results, prominent neuroimagers tried to retain the potential value of cognitive concepts by considering that the dependence upon context arose from the non-linear nature of brain responses (Friston, Price, Fletcher, Moore, Frackowiak, & Dolan, 1996). Methods for parametric studies were designed to overcome the presumed non-linearity and thereby to retain modularity of the input activities (Buchel, Wise, Mummery, Poline, & Friston, 1996). With the hopes that more and more corrections for non-linear brain responses could be eventually found, the simplifications of assuming pure insertion of concepts remain the prevailing interpretation of functional imaging. A strong version of that goal, which represents the present popular position despite continual empirical set-backs, was described by Michael Gazzaniga who said that "we now understand that changes in our brain are both necessary and sufficient for changes in our mind" and continues by praising Cognitive Neuroscience for having identified the mechanisms of cognitive phenomena (Gazzaniga, 2005, p. 88).

In this report we examine what neuroimaging can tell us about a human in the state of consciousness by using an alternate approach which does not assume that consciousness is supported by hypothesized mental processes. In our study, brain experiments are used to determine neuronal and energetic properties of a behavioral state, as distinguished from the claims that imaging results localize theorized mental processes in the brain. Furthermore, we include a central role for the high baseline level of neuronal activity that is removed by differencing in the large majority of functional imaging studies. In both these respects they offer a previously untried methodology for relating brain activities to observable behavior. We believe that baseline brain activities provide necessary support for behavioral processes that are characteristic of the human or rodent in the state of consciousness. In our view, memory, intent, etcetera are contingent assumptions of mental processes presumed to underlie actions performed by the person.

Rather than hypothesizing and then localizing psychological assumptions about the contents of consciousness, in our studies the subjects, rat or human, are defined as being in a conscious state by observations of reproducible behavior. In our definition, the state of consciousness enables a person to perform the many actions that Zeman (2002) called the

contents of consciousness. These are the actions, feelings, thoughts, sensory interconnections, etcetera, which are described in common parlance as being caused by mental processes. These observables are postulated in neuroimaging studies to be identified with concepts, for example, memory, attention or recognition, and are then sought in localized brain activities. Uncertainties in this methodology have been revealed by the widely recognized dependence of these concepts upon the context in which they are embedded. To avoid these complexities we are correlating brain activities not with such specific assumptions about the contents of consciousness, but rather with the state of consciousness of a human or of the rat. We describe the state of consciousness simply by the subject's ability to respond to stimuli using the criteria established in anesthesia (Katoh, Bito, & Sato, 2000). The role of consciousness in the different stages of sleep or seizure are too complex (Tononi & Koch, 2008) to be discussed in the present report, but they do serve to remind us that a certain high level of brain energy is certainly not sufficient for the person to be in a state of consciousness; an otherwise functioning individual is necessary.

We propose that high cerebral energy (and by inference its coupled neuronal activity) in the awake state defines a necessary property of the consciousness state; when the energy is reduced sufficiently, there is loss of consciousness. Two additional brain properties that we have measured are the fMRI activation patterns and neuronal population activity with change with baseline state. In this paper, we first review the methods developed (primarily in our laboratory) to measure brain energy consumption and their use in studies of the coupled neuronal signaling, which is the work of the brain (Section I). These studies have shown that, above a relatively small level of non-functional energy, brain energy consumption is coupled to the firing of glutamatergic neurons in the cerebral cortex and the coupled ATP consumption during neuronal signaling (e.g., action and field potentials, neurotransmitter release, and recycling, etc).

Then we describe experimental measurements of brain properties of the state of consciousness (Section II). The brain energy distribution and the range of energy consumption in the fully awake state measured by PET and fMRI studies are reviewed. Overall, it is shown that in the state of consciousness, the brain energy, and by inference the neuronal signaling, is evenly distributed throughout the cortex. Fluctuations in energy are small compared to the resting brain energy in the fully awake state. PET reports of subjects undergoing graded anesthesia are then reviewed to show the reduced energy levels (and its regional distribution) at which subjects lose consciousness, as defined by the loss of response to stimuli. Next we discuss two additional brain properties, fMRI activation patterns and the firing rates of neuronal populations that change significantly with baseline energy. Finally, we discuss implications of our proposal that measurable brain properties provide insight to the state of consciousness (Section III). Current definitions, philosophies, and theories for the state of consciousness are discussed to demonstrate how measurable brain properties are beginning to sketch a physical understanding of the interconnected behavior representing that state, without a priori assumptions about underlying mental processes.

I. Relations Between Brain Work and Brain Energetics

A. ^{13}C MRS and Calibrated fMRI Studies of Energetics

We review here studies we have performed using ^{13}C MRS studying the relationship between neuronal firing and energetics. Although we primarily describe our own work, related

studies have been performed in other laboratories (for a review, see Hyder, Patel, Gjedde, Rothman, Behar, & Shulman, 2006). The studies were based on the ability of MRS, in combination with ^{13}C labeled substrates such as glucose and acetate, to measure various metabolic pathways in vivo. For example, the cerebral energy production rates in neurons (by the rate of glucose oxidation ($CMR_{glc(ox),N}$) in the tri-carboxylic acid cycle) and the coupled rates of neurotransmitter glutamate and GABA release; and recycling (V_{cyc}) (Sibson, Dhankhar, Mason, Rothman, Behar, & Shulman 1998). In the initial study the rates of glucose oxidation and neurotransmitter cycling were measured over a wide range of brain activities in the rat (Fig. 1), taking the animals from iso-electric pentobarbital anesthesia under which there is no neuronal signaling to lighter states with higher neuronal signaling activity (as measured by electroencephalography (EEG) or magnetoencephalography (MEG)). It was found that the V_{cyc} plotted versus neuronal $CMR_{glc(ox),N}$ in Fig. 1 was fitted very well with a straight line of

$$CMR_{glc(ox),N} = V_{cyc} + 0.10 \qquad\qquad [1]$$

all in units of μmol/g/min. The plot of the original rat data from 1998 (Sibson et al., 1998), and subsequent results from other laboratories (Choi, Lei, & Gruetter, 2002; de Graaf, Mason, Patel, Rothman, & Behar, 2004; Hyder et al., 2006; Oz et al., 2004; Patel et al., 2004), is significant in several respects. First, it establishes a quantitative molecular relationship between cortical oxidative energy production and the glutamate neurotransmitter flux, which is coupled to the rate of neuronal firing. Second, it provides a convenient measurement of these rates. Third, at the intercept where V_{cyc} falls to zero, the rate of neuronal glucose oxidation $CMR_{glucose(ox),N}$ had fallen to 0.1 μmol/g/min which is only ~15% of the value in the awake rat brain (of 0.8 μmol/g/min). Hence, in the resting-awake basal state, ~85% of the neuronal energy consumption is devoted to supporting neuronal signaling. A similar high ratio of V_{cyc} to $CMR_{glucose(ox),N}$ was found in ^{13}C MRS studies in the awake human brain (Lebon et al., 2002; Shen et al., 1999; Shulman, Rothman, Behar, & Hyder, 2004). Fig. 1 shows that the human data from several groups plotted as neuronal glucose oxidation versus the rate of the glutamate/glutamine cycle falls upon the line found in the rodent cerebral cortex. This high level of neuronal signaling in the absence of specific stimulations was a novel neuroscientific finding from these experiments and required fundamental re-evaluations of results from higher level brain studies, including those using functional imaging (Shulman & Rothman, 1998).

A unique feature of the data plotted in Fig. 1 is the slope of unity, when the cycling flux (V_{cyc}) is plotted vs. the rate of neuronal glucose oxidation ($CMR_{glc(ox),N}$). The value of unity means that above a baseline level, for every additional glucose molecule oxidized in a neuron, one glutamate molecule is released as a neurotransmitter and cycles through glutamine in astrocytes. This stoichiometry allows changes in neurotransmitter flux (which can only be measured directly in the ^{13}C MRS experiment) to be derived from measured changes in oxygen consumption. These results have been extended to include GABAergic neurons and astrocytes (Deelchand, Nelson, Shestov, Ugurbil, & Henry, 2009; Hyder et al., 2006; Patel et al., 2005).

When there is an increase in cortical neuronal activity, there is a concomitant increase in blood flow and volume (CBF and CBV) in order to bring more oxygen to the brain to provide fuel for the neurons and glial cells (Hyder, 2009). The blood-oxygenation level dependent (BOLD) fMRI signal is sensitive to these changes, as well as to changes to the rate of oxygen consumption (Ogawa et al., 1993). Recent work combining BOLD measurements with measurements of CBF (and CBV), using calibrated fMRI, have allowed incremental oxygen consumption (ΔCMR_{O2}) to be derived from BOLD fMRI results (Davis, Kwong, Weisskoff, & Rosen, 1998; Hoge , Atkinson, Gill, Crelier, Marrett, & Pike, 1999; Hyder et al., 2001; Kida,

Kennan, Rothman, Behar, & Hyder, 2000; Zijl et al., 1998). Because fMRI has good spatiotemporal resolution and allows ample brain coverage, it has become attractive to calculate ΔCMR_{O2} with calibrated fMRI even for event-related paradigms (Herman, Sanganahalli, Blumenfeld, & Hyder, 2009; Sanganahalli, Herman, Blumenfeld, & Hyder, 2009), which is desired in cognitive fMRI studies (Blamire et al., 1992; Rosen, Buckner, & Dale, 1998).

B. Relationship Between Energy Consumption and Electrical Activity

The chemical relationship between the metabolic rates of glutamate neurotransmitter release and neuronal oxidative energy production/consumption (Fig 1) were experimentally related to electrophysiological measurements of neuronal firing rates. A series of high resolution calibrated fMRI studies, developed an analogous relationship between changes in neuronal oxygen consumption during sensory stimulation (of rats) and the average rate of neuronal firing (Maandag et al., 2007; Smith et al., 2002). A direct relation was found between the change in CMR_{O2}, in an fMRI voxel, and the change in the neuronal firing frequencies of a representative ensemble of neurons in that voxel

$$\Delta CMR_{O2} = G \sum N_i \,(^A v_i - {}^B v_i) \qquad\qquad [2]$$

where the running index i spans the entire range of frequencies in the histogram representative of the neuronal population, N_i is the number of cells firing at the frequency v_i, G is a scaling factor that accounts for neuronal density and metabolic rate per neuron, and A and B are two independent energy states. If the same neuronal population is measured across different states (i.e., N_i does not change in eq. [2] across states), then relative changes in CMR_{O2} can be related to shifts in firing rates within the neuronal ensemble. In combination with ^{13}C MRS measurements of total neuronal oxygen functional consumption it was found that the relationship of eq. [2] holds, provided the baseline oxygen consumption is subtracted out (Hyder, Rothman, & Shulman, 2002). Similar relationships have been suggested by several groups (Pasley, Inglis, & Freeman, 2007; Uludag et al., 2004; Zhu, Zhang, Zhang, Ugurbil, & Chen, 2009).

In summary, the large majority of energy consumption of the brain produced by the oxidation of glucose is devoted to the work required by the electrical activity of neurons (and astrocytes). The excellent correlation between neuronal firing rates and their energy consumption relates the activity of neurons in a voxel to firing rates of representative ensembles of their constitutive neurons, by expressing both as CMR_{O2}. This agreement between metabolic measurements of neurotransmission and electrical measurements of neuronal firing rate reflects the equivalence of both approaches to electrochemical brain work and allows conversion of imaging signals to neuronal activity.

II. Brain Properties of the State of Consciousness

A. Effect of Baseline Energy on Regional and Temporal Variations

1.   Energetic basis of the awake conscious state.

In the resting- awake human brain the ratio of the rate of neuronal glucose oxidation to the rate of glutamate neurotransmitter cycling is consistent with that found in the rat (Fig. 1). Therefore, to a first-order approximation, either the CMR_{O2} or CMR_{glc} images can be interpreted as images of neuronal activity once the energetics not directly associated with neuronal

communication (e.g., maintenance of resting membrane potentials in neurons and astrocytes) are subtracted. From ^{13}C MRS studies in gray matter, the non-signaling contribution is 10-30% of the awake state value (de Graaf et al., 2004).

Tab. 1 (right column) shows regional PET measurements of CMR_{glc} for resting-awake human brain (Alkire et al., 1995; Alkire et al., 1999; Kaisti et al., 2003). CMR_{glc} in gray matter is relatively uniform throughout the neocortex and subcortex. Correcting for difference across regions of gray and white matter, most cortical regions are within 10% of whole brain CMR_{glc}.

Temporal fluctuations of energy are difficult to measure with PET or ^{13}C MRS directly because of the low temporal resolution of these methods. An estimate, however, may be obtained from the maximum amplitude of the spontaneous BOLD signal fluctuations, which is about 1% in the resting- awake human brain (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007). Since most of the amplitude variations are not activity related (e.g., instead are due to factors like respiration, brain motion with the cardiac cycle, and fMRI scanner instability), the 1% value represents an upper limit. Based on calibrated BOLD measurements (Hoge & Pike, 2001; Kida & Hyder, 2006), a 1% fluctuation using standard parameters at 3T, corresponds approximately to, at most, a 10% variation in CMR_{O2}, although most likely the variation is much lower due to most of the fluctuations coming from non-brain activity related sources. This upper limit is consistent with measurements during maximum sustained cognitive and sensory stimuli, which range from 5 to 15% respectively (Chiarelli et al., 2007; Restom, Perthen, & Liu, 2008).

In summary, in the resting-awake state, baseline cerebral energy consumption is high compared with small regional variations and spontaneous fluctuations in energy consumption. The energy consumption is distributed rather uniformly across the cerebral cortex. These results suggest that a high and widely distributed level of brain energy exists in the conscious human brain. Similar results are available for rodents (de Graaf et al., 2004; Hyder et al., 2000; Hyder et al., 2006; Oz et al., 2004; Sibson et al., 1998; Sokoloff et al., 1977).

2. *Energetic basis of the loss of consciousness.*

Studying loss of consciousness with anesthesia is an active neurophysiological research area (Cariani, 2000; Franks, 2008; Kulli & Koch, 1991), with the majority of studies trying to identify specific brain regions or signaling patterns that change significantly when consciousness is lost. We have, similar to anesthesiologists, defined the loss of the conscious state as occurring when a person or animal can no longer respond to stimulus (Fig. 2). Although studies explicitly designed to correlate the change in energy consumption with the loss of consciousness have not been performed, several PET studies have been performed on human subjects at deep levels of anesthesia (Alkire et al., 1995; Alkire et al., 1999; Kaisti et al., 2003). These subjects were not conscious based upon their inability to respond to sensory stimuli and questions from the anesthesiologist (Katoh et al., 2000; Kurita et al., 2001).

Tab. 1 (left columns) shows PET data of homogenous reduction in energy metabolism with anesthesia for 12 different brain regions. To a first approximation, these suppressions were not region or anesthesia specific. In addition, anesthesia-induced metabolic depression does not differ significantly in sub-cortical and cortical areas. Although the authors of the PET studies, summarized in Tab. 1 (left columns), subsequently interpreted these results as indicating selective regional loss of energy consumption (Alkire & Miller, 2005; Kaisti et al., 2003), our meta-analysis of the same PET results suggests that any such localized metabolic effects of anesthetics are very small compared to the global reductions.

Three target sites have been identified for the anesthetics used in these studies, and all three sites directly or indirectly inhibit glutamate neurotransmitter activity (Franks, 2008). The most common target up-regulates GABA activity. Since GABA is an inhibitor of glutamate neurotransmission, the binding of anesthetics to those sites decreases glutamate signaling, neuronal firing and therefore the brain energy consumption. The other two targets that have been identified (NMDA receptors and potassium uptake) also decrease the rates of glutamatergic neuronal firing with similar lowering of energy consumption. Hence, the actions of all known anesthetic agents (with the exception of ketamine, which is anomalous in that it raises metabolic activity at low dosages) are consistent with decreases in the glutamate-GABA synaptic activity and would cause the reductions observed in cerebral energy consumption. Since glutamatergic neurotransmission is widely spread throughout the brain, its responsiveness to anesthetics (small molecules that diffuse readily throughout the brain) supports a global reduced neuronal firing consistent with the uniform energy reduction observed in the PET experiments.

In summary, the conscious state in the resting-awake human is supported by a high and relatively uniform state of baseline brain energy consumption and (by inference) neuronal activity. Loss of consciousness during anesthesia occurs when regional energy levels are uniformly reduced by 40-50% from the resting-awake values. We hypothesize from these results that high baseline cerebral energy consumption and its associated neural activity are necessary properties of the state of consciousness.

B. Effect of Baseline Energy on Sensory Activation Patterns

The total energy of neuronal activity in a brain volume, and the incremental energy during a stimulus, can be measured both separately and non-invasively by ^{13}C MRS and calibrated fMRI methods (described above). For fMRI experiments, it has been conventional to describe the total energy in the unstimulated state as the "baseline" energy (Shulman, Rothman, & Hyder, 1999). The different meanings attributed to the term baseline are simplified if we simply consider it as an operational term. In this usage baseline is an adjective that describes a property of the brain state that exists before a stimulation of interest (Shulman et al., 2007). That state has values of "baseline" energy, "baseline" BOLD signal, and "baseline" blood flow etcetera, and upon stimulation we detect changes of these parameters. The neuronal and imaging consequences of baseline energies were explored by experiments in rats at two anesthetic states characterized by very different baseline energies (Maandag et al., 2007), where energy in the lower state (α-chloralose) was 40-60% lower than in the higher energy state (halothane). Forepaw stimulation was administered in both states to excite the contralateral primary somatosensory cortex. There were major differences between fMRI activations in the two states. At high baseline there were weak activations in anterior brain regions (Fig. 3A), which included primary and secondary somatosensory cortices in the contralateral side along with other distal regions. At low baseline, however, strong activations were primarily confined to the contralateral primary somatosensory cortex (Fig. 3B). Upon stimulation, as previously reported (Hyder et al., 2002; Shulman et al., 1999), the absolute and percent energy in the primary somatosensory cortex is greater from the low energy baseline state (Armstrong-James & George, 1988; Chapin & Lin, 1984; Chapin, Waterhouse, & Woodward, 1981; Chen, Friedman, & Roe, 2005; Huttunen, Grohn, & Penttonen, 2008; Kroeger & Amzica, 2007; Masamoto, Kim, Fukuda, Wang, & Kim, 2007). There are limited reports for baseline-dependent delocalized activity patterns beyond the primary area because most neurophysiological experiments focus on

designated regions of the brain, not on the majority of brain regions covered easily by fMRI. Nevertheless, several neuroscience studies have suggested that activity patterns become more localized upon deep anesthetized states (Chapin & Lin, 1984; Chapin et al., 1981; Chen et al., 2005; Erchova et al., 2002). Recent fMRI studies in awake primates and humans are supportive of our findings (Antognini, Buonocore, Disbrow, & Carstens, 1997; Disbrow, Slutsky, Roberts, & Krubitzer, 2000; Dueck et al., 2005; Heinke et al., 2004; Ishizawa, 2007).

In summary, these results indicate that at higher baseline energy consumption, the increment in energy consumption due to sensory stimuli are smaller on a percentage and absolute basis, and are spread across a larger cortical area. At present, owing to experimental limitations, fMRI studies of awake rodents are limited. The few that have been performed, however, are consistent with greater delocalization of the fMRI activation patterns compared with anesthetized rodents (Peeters, Tindemans, De Schutter, & Van der Linden, 2001; Sachdev et al., 2003).

C. Effect of baseline energy on distributions of neural firing.

The baseline energy level affects the spatial pattern of activation and also influences the distribution of neuronal firing rates in the activated volumes (Maandag et al., 2007). Neuronal histograms in the two states showed that the population can be divided into sub-groups of slow and rapid signaling neurons (i.e., SSN and RSN, respectively), where greater SSN and RSN sub-populations were observed in the lower (Fig. 4A) and higher (Fig. 4B) energy baseline states, respectively. The halothane state had nearly equal sub-populations in SSN and RSN, whereas the α-chloralose state was heavily weighted towards SSN. The most conspicuous difference between the two anesthetized states of different energy was the dominance of RSN activity (or energy by eq. [2]) under halothane in contrast to α-chloralose where the RSN/SSN ratio is low. Similar anesthesia-dependent shifts in high versus low frequency neuronal signaling have been reported (Alkire, 1998; Jugovac, Imas, & Hudetz, 2006).

The populations of SSN and RSN sub-groups correlated with the dissimilar delocalization of fMRI activations in the two states. At high baseline energy, with greater RSN activity, widespread activations were observed throughout dispersed brain regions, mainly of the contralateral hemisphere (Fig. 3A). At low baseline energy, however, strong activations were mainly confined to the contralateral primary somatosensory cortex with insignificant activity elsewhere (Fig. 3B). High frequency signaling, including γ-band electrical activity, has been extensively studied with EEG (Freeman, 2004a, 2004b) and has been shown to be attenuated by anesthesia (Kulli & Koch, 1991). The γ-band activity tends to be synchronized between the homologous sensorimotor regions of both hemispheres (MacDonald, Brett, & Barth, 1996) and can be modified by variations in global activity and energy (Engel, Konig, Kreiter, & Singer, 1991). These results gave rise to the hypothesis that the RSN activity supports intracortical signaling and synchronization, in accord with previous assignments of similar frequencies observed as the γ band-type signaling in EEG (Maandag et al., 2007).

III. Discussion

A. Definitions and Properties of the State of Consciousness

When asked what is meant by consciousness, Zeman distinguished between a state of consciousness which is used to describe someone who is "awake- rather...than asleep, or

concussed, comatose, dead drunk etc" and the contents of consciousness which are "sensory or perceptual" (Zeman, 2002, pp. 16-17). Zeman's second definition might be considered as "the contents of conceptual experience" which are the goals of many cognitive neuroscience studies (Zeman, 2002, p. 18). By using Zeman's operational, behavioral definition of the state of consciousness (i.e., the ability to respond to stimuli), no assumption about mental processes (e.g., working memory, attention or intention) underlying either the state of consciousness or the contents of consciousness are needed. In identifying the state of consciousness of the subject by his/her ability to respond, we depend on an observation that has the reliability of stimulus and response. While responsiveness may not have the objective scientific methodology available from physical measurements of neuronal activity and energy, it is very reliable and straightforward to measure.

We define the state of consciousness by the person's ability to respond to stimuli using criteria established in anesthesiology (Katoh et al., 2000; Kurita et al., 2001). We acknowledge that there are many circumstances where humans cannot respond (i.e., sleep, coma, physical impairment, etc). For the sake of avoiding a proliferating terminology, we limit discussion to individuals who have full expressive faculties, and acknowledge that there are caveats to this definition, conspicuously in altered human states of sleep, intoxication, coma etcetera. In the awake rat, the state of consciousness has been distinguished from the deeply anesthetized state by the loss of righting reflex (Antkowiak, 2001). Based on these behavioral criteria of the loss of consciousness, humans and rats have the same dose response curves for the common anesthetics (Franks, 2008). In addition to the response to stimuli, the properties of the state of consciousness presented here are the measurable brain neurophysiological results. These include the fMRI responses, and the amount, patterns, and time evolution of neuronal firings, which occur in the state of consciousness and which change during its loss. These properties can be observed at many experimental scales: the activity of a single synapse, the activity of a single neuron, the coordinated activity of networks of neurons such as in an ocular dominance column, and finally the coordinated activity of the whole brain.

Our survey of the neurophysiological literature shows that in the conscious-awake state the cortical energetics (and by inference the neuronal activities) are uniformly distributed with regional differences in energies (approximately proportional to the amount of grey matter) being small compared with the baseline energetics. With loss of consciousness induced by anesthesia, there is uniform reduction of cerebral energy (Tab 1). In addition to the reductions in energy in Tab 1, PET measurements of CBF reduction by anesthesia have been reported (Fiset et al., 1999). All reports found global reduction of activities (CMR_{O2}, CMR_{glc} or CBF) with anesthesia. Based on these observations we propose that the state of consciousness is supported by a high level of rather uniformly distributed neuronal activity. The ground-breaking PET results (Tab 1) by Alkire et al. (1995, 1999) and Kaisti et al. (K 2003) report a global energy reduction during the loss of consciousness under anesthesia. In subsequent publications, however, they have identified a complex set of brain areas comprising the lateral tempero-parieto-occipital junction and perhaps a mesial cortical core as possibly responsible for anesthetic-induced unconsciousness (Alkire, Hudetz, & Tononi, 2008). They have assigned the action of anesthesia to such specific broad brain regions by considerations from lesions, functional imaging, clinical observations, default modes, and sleep, etcetera. We believe their direct measurements of the uniformly, lowered energies provide a more reliable localization of the site of action of anesthetics, which is quite global and rather uniform. Although we admire these PET results, we do not find the claims of regional specificity to be convincing when we contrast the large

homogenous anesthesia-induced reductions in baseline energies with small percentage differences between regions in the degree of CMR_{glc} reduction (Tab. 1).

The properties of the state of consciousness, as compared with the loss of consciousness, are reviewed and somewhat generalized in Tab. 2. Since these characterizations have been derived from limited data presented above, they should be regarded as hypotheses that could be judged, and perhaps extended, by subsequent results. They describe an extremely active brain, with high neuronal activity, supported by the elevated energy consumption, in the conscious-awake state. High firing frequencies, with commensurate elevated baseline energies, correlate with γ-band EEG signals which are associated with inter-cortical communication (Ebner & Armstrong-James, 1990; Franowicz & Barth, 1995; MacDonald & Barth, 1995) (Fig 4). The γ-band signaling measured at the scalp as EEG or evoked potentials are reduced with loss of consciousness (Kulli & Koch, 1991). In the conscious- unstimulated state the highly active neurons stand ready to respond with ubiquitous, brain-wide high frequency firings to external stimuli. Neuronal properties of a state of consciousness, i.e., responding to a sensory stimulus, are shown in the dispersed BOLD activation maps at the higher energy state (Fig 3). Calibrated fMRI has shown that the energetic increments are no larger than ~10% of baseline value for the strongest sensory stimuli (Hoge & Pike, 2001), whereas for cognitive stimuli, they are smaller and at the lower limits of detection, corresponding to ≤ 1% of baseline energy. Our limited BOLD results on forepaw stimulation reveal the delocalized nature of the stimulated response spread across dispersed brain regions in the higher energy state. We do not interpret these responses as locating particular mental processes which would attempt to identify the contents of consciousness. Rather we emphasize that the state of consciousness is associated with brain-wide responses to stimuli. The relative energetics of BOLD responses and baseline show that the neuronal responses to stimuli which are often interpreted as caused by the contents of consciousness are much smaller than the neuronal activity maintaining the baseline state. Implications of this "tip-of-the iceberg" are far reaching when we consider models of brain function. Some consequences of the results are as follows.

A majority of fMRI experiments on the contents of consciousness have focused primarily on regional difference between signals in order to localize the brain activities (Posner & Raichle, 1994). However these experiments had not evaluated the difference energies. Modular (computer-like) models, originally adapted to functional imaging from cognitive psychology, implicitly assumed negligible brain energy expenditure in the absence of tasks allowing the small incremental energy differences to be interpreted as supporting the complete neuronal activity of a region. As already noted by Shulman and Rothman in 1998 (1998), however, the finding that the majority of energy consumption in the baseline state is directly supporting neuronal activity is not consistent with a computer model of brain activity, where in the absence of external stimulation, neuronal activity has no function. Since then, Gusnard and Raichle (2001) have incorporated a "default" baseline activity into a psychologically based model to reconcile the high neuronal activity of the brain in the baseline or resting state with standard interpretations of functional imaging. In their approach the properties of the conscious brain are assumed to be supported by different brain regions based on modular models of differencing. Regions that show larger percent changes upon stimulation, either positive or negative, are assigned to hypothesized sub-processes of consciousness. This approach assigns the large baseline energies consumed globally during consciousness by small localized changes during stimulation. Although the high baseline activity is acknowledged by Gusnard and Raichle (2001), the assignments of function are still based on psychological assumptions about processes that occur in the conscious state.

Consciousness is a state of a human being. The contents of consciousness include the sensations of touch, smell, feelings, intentions, and observation and our understanding of them are contingent, since they depend upon formulation of an individual's history, genes, experience and reflections, amongst other factors. Philosophers often refer to these contents collectively as qualia. The contents cannot be expressed in exact terms because they are uniquely individualistic and transient. Therefore, there is no complete explanation of the contents of consciousness in objective, neuronal terms. Similarly, we cannot describe the state of consciousness by objective neuronal properties, but its existence for a human is reliably identified by observations of behavior. In pragmatic criteria, long recognized by anesthesiologists, the state of consciousness can be assessed by behavioral responses to stimuli. The patient is defined as having lost consciousness when she/he is no longer able to respond to simple questions.

The similarities between our definition of consciousness as a state that enables response to a stimulus and the once popular psychology called behaviorism, is apparent in J.B Watson's definitive summary (Britannica, 1932), which starts with the clear statement, "Behavior can be observed like the phenomena of all other natural sciences." While we do not share Watson's enthusiasm about the explanatory powers of behavior, we share his confidence in the objective and reliable nature of observing stimulus and response.

We describe the state of consciousness simply by the subject's ability to respond to stimuli using the criteria established in anesthesia (Katoh et al., 2000). We propose that the object of study should be the person, an entity whose observable behavior derives from brain and body processes that cooperate to interact with the environment and the individual's history. The dependence of brain activities upon this web of factors is shown by the empirical failure of functional imaging to consistently localize hypothesized brain concepts. The dependence of brain activities upon more extensive bodily functioning has been championed by Antonio Damasio, a neurologist and neuroscientist, who has supported the idea that the study of "mental activity, from its simplest aspects to its most sublime, requires both brain and body" (Damasio, 1994, p.xvii). The neurophysiological basis of this belief is documented in an account of how body and brain are in continual back and forth interactions via chemical and neuronal impulses. The brain influences body chemistry by hormones and second messengers while the body's chemical reactions change the signal sent back to the brain. Within this cycle of coupled reactions it is not possible, Damasio argues, to consider either brain or body separately. Although Damasio proposes that once bodily functions are included it is then possible to localize cognitive concepts, the empirical failures to do so, shown by the context dependence of the localization by imaging, is consistent with our position that this kind of localization is not available (for a review see Eijsden, Hyder, Rothman, & Shulman, 2009).

Our position also has some overlap with a comprehensive analysis of Cognitive Neuroscience developed by Bennett and Hacker (2008). Their argument is that mental functions are performed by the person and therefore they are not located, represented, or encrypted in a brain. A person adds, subtracts, feels pain or decides to marry, not the brain. Since in Wittgenstein's formulation the person is the agent responsible for the behavior, it is not permissible, they conclude, to assign the behavior to a part of the person, that is, the brain. In this interpretation, brain activities can be necessary for a person's behavior but they are not sufficient to explain it. Our agreement with Bennett & Hacker, that brain activity is not sufficient to cause behavior, comes more from Wittgenstein's position that the subjective concepts needed to identify a causative brain activity cannot be defined with the rigor needed for a physical mechanism. Once again our reservations are supported by the inability to localize such cognitive

brain areas independent of their context. This can be seen in studies of working memory, an intensely studied cognitive concept, which have become more delocalized as short-term memory is studied under different conditions representing different contexts (for a review see Eijsden et al., 2009).

B. Philosophies for Studying the State of Consciousness

Our understanding of the state of consciousness grows from measurements of its properties. We have proposed that high global neuronal energy supporting neuronal activity is a necessary property of the state of consciousness (Tab 2). It is an independent variable, which if reduced by anesthesia, contributes to the loss of consciousness. High brain activity is not consciousness; it is a brain property that provides necessary, but not sufficient, support of the state of consciousness. Objective, reliable understandings of the state of consciousness are expected to gradually emerge from measurable brain properties, just as our understanding of water, DNA, or glycogenolysis grows as we make additional physical measurements of these respective systems. This growing understanding of the brain's support of the state of consciousness, while impoverished compared to philosophical and quotidian formulations of the contents of consciousness, enjoys the scientific reliability supplied by the straightforward behavioral measurements that are used to define it.

The relative energetics of the contents of consciousness and the state of consciousness offer clarification to ongoing debates about the role of brain activities in mental processes. The distinction allows us to separate different mental activities and to reformulate their relationships in terms of what is necessary and what is sufficient. The brain/mind question is a generalization of the experimental hopes for understanding the relation between subjective mental processes and objective brain function. Christof Koch overcomes this divide by biting the bullet: "I take subjective experience as given and assume that brain activity is both necessary and sufficient for biological creatures to experience something" (2004, p.19). He assumes that there "must be an explicit correspondence between any mental event and its neuronal correlates" (Koch, 2004, p. 17). His research on the neuronal correlates of consciousness (NCC) starts with visual processes with the hopes of proceeding from them to more complex, more subjective correlates. Koch is studying the contents of consciousness. Hierarchical neurophysiological and imaging results of sensory stimulation do find reproducible and well isolated brain activations and allow the claim that in the future better and better NCC of sensory actions could be found. However, we and others have repeatedly found it necessary to distinguish between the neuronal responses to sensory stimuli and the prospects for identifying NCC of subjective concepts (Llinas, 2001; Shulman, 2001; Shulman, Hyder & Rothman, 2003). Koch recognizes that even if NCC of visual processes were found, the Cartesian divide has not yet been crossed. He postulates that even with NCC in hand, additional activities would be needed to link them with subjectivity, and introduces an enabling factor (NCCe) that supports the contents of consciousness (2004, p. 88).

The need for some enabling circumstances was taken up by John Searle, who in a review of Koch's book agrees and emphasizes that "we will not understand consciousness until we understand how the brain creates the conscious field to begin with" (2005). We have come to a somewhat more modest view of our ability to describe properties of the state of consciousness. In contrast to prevailing views in the field as expressed by Koch and echoed by Searle, we do not accept that mental phenomena, defined by psychological theories, for example working memory, are "themselves features of the brain" (Searle, 2005). Our approach does not start with

a priori assumptions about the nature of mental processes including the concept of consciousness. In investigating brain properties of the state of consciousness, we make no assumptions about the contents of consciousness, which are hypothesized mental processes such as cognition, perception and intention that are frequently studied by fMRI.

In our interpretation of the experimental results, we were influenced by Philosophical Pragmatism, a contemporary direction in philosophy, descended from Wittgenstein. Pragmatic philosophers like Richard Rorty emphasize Wittgenstein's conclusion that generalizations can never have the validity of mathematical or logical definitions and recognize the contingent nature of philosophical and psychological descriptions of Mind (Rorty, 1989). For pragmatists, the weaknesses of generalizations mean that the concepts of Mind are to be judged not by ontological primacy but by their usefulness in understanding the world. The decision on whether or not to use mental concepts in the study of brain functioning becomes a pragmatic question. It is optional, on this basis, as to whether we should start fMRI experiments with these concepts. Our evaluation of recent results, however, finds that the goal of explaining a priori psychological concepts with fMRI has not been useful relative to concepts in other scientific fields (Eijsden et al., 2009). The disappointing usefulness of hypothesized mental processes has been accepted by Jerry Fodor, one of the original proponents of their value (Fodor, 1984), as results have shown that the brain's response to sensory and cognitive tasks depends upon context (Fodor, 2000). Our proposed approach does not question the value of using concepts - such as intention, memory, attention, or love - in everyday life, or the value of using a psychological level description of human behavior. However, in our opinion, the hypothesized mental processes underpinning these concepts are not proving useful in physical studies of brain properties.

C. Gradations of the State of Consciousness

The experimental results presented above -- reduced global energy at deep levels of anesthesia, the differences in fMRI activation maps at different baseline energies, and histograms of neuronal firing patterns in different behavioral states --have been used to illustrate the properties of the state of consciousness by studying extreme conditions. In using these examples, however, we are not proposing that the brain only exists in either of the two extreme states, one conscious the other not. Rather, existing data suggests that there is a continuous variation of brain activity and the behavioral properties associated with consciousness as the brain energy level gradually falls. Heinke and Schwarzbauer (2002) and others (Qiu, Ramani, Swetye, Rajeevan, & Constable, 2008) have shown that secondary processing regions in the human fMRI maps are decreased more at a moderate level of anesthesia than are the primary sensory regions. Presumably the gradual decreases in the widespread brain activations supporting consciousness continue with depth of anesthesia until the neuronal activities necessary for even simple response are lost. We agree with the view that consciousness is not a quantized or two-state phenomena (Alkire et al., 2008) and that while the awake fully conscious state can be distinguished clearly from its loss, future experiments should be dedicated to delineating the details of these transitions. We propose that neuronal activity, as mapped by imaging measurements of regional energy utilization, would be a unifying parameter in such experiments.

D. Energies and Neuronal Theories of Consciousness

Other explorations of the state of consciousness, in particular by Rudolfo Llinas, are

similar to our proposal that the global state of consciousness is maintained by a large amount of distributed neuronal activity, while responses to sensory and cognitive inputs, as shown in BOLD images, are relatively small perturbations of the conscious state. We had reached this conclusion earlier from consideration of energy consumption in the stimulated and baseline state (Shulman & Rothman, 1998). The different magnitudes of baseline and incremental energies provides a quantitative basis for Llinas when he says: "The significance of sensory cues is expressed mainly by their incorporation into larger, cognitive states ... sensory cues earn representation via their impact upon the pre-existing functional disposition of the brain" (Llinas, 2001, p. 8).

Llinas, following many reports especially by Singer and Gray (Gray, Konig, Engel & Singer, 1989), proposed that the 40 Hz electrical signals recorded on the scalp measure consciousness, and he further suggests that their synchronicity (Singer, 1999) binds together separate brain activities into a "substrate of self" (Llinas, 2001, p. 126). The correlation of 40 Hz waves generated during stimulation with consciousness was made in an early review of experimental results by Kulli and Koch (1991, pp. 6-10). From a survey of the literature, they proposed the 40 Hz oscillations observed by Singer and Gray to be the "most promising measure of 'consciousness' or 'awareness'" (1991). Crick and Koch (1990) extended this role to propose that the 40 Hz oscillations bind together the different inputs to thereby create awareness. From this extended role for these signals, Kulli and Koch conclude that the loss of the 40 Hz signals "could go a long way towards explaining the effects of at least some anesthetics" (1991).

From the standpoint of measurements of overall brain energetics, the increase in the 40 Hz signal in the conscious-awake state is a component of the general increase in energy (and by inference of neuronal activity) in the state. Based upon histogram measurements of neuronal firing frequency in the rat (Fig. 4), and consistent with measurements in other species (Antognini et al., 1997; Disbrow et al., 2000; Ishizawa, 2007), the increase in activity is across a broad band of frequencies. The 40 Hz signal involves synchronous neuronal firing, which shows it to be strong in the conscious state by EEG and MEG type measurements (John, 2002). Although the 40 Hz coherence may play a role in binding together brain activities (Crick & Koch, 1990), the increased magnitude of high frequency firing in the conscious state (Kulli & Koch, 1991; Llinas, 2001) is inseparable from the high baseline energy.

Brain energy levels can be measured non-invasively for a human in coma. If subsequent experiments support our hypothesis that regards a high level of brain energy as necessary for the person to be in the richly endowed state of consciousness, then non-invasive energy measurements could provide a valuable clinical assay of the subject's potential for a normal life.

IV. Summary and Conclusions

We have described an experimental protocol for using functional imaging to study the neuronal support of consciousness that is independent of prior assumptions about localized mental processes. The state of consciousness is defined by the human's observable response to stimuli which avoids having to postulate mental processes that underlie the observations. Results from earlier PET imaging studies of glucose metabolism at different levels of anesthesia are converted to an estimate of neuronal activity based upon MRS and calibrated fMRI studies. The awake- conscious state in humans, often referred to as the "baseline" or "default" state in recent imaging studies, is characterized by a relatively spatially and temporally uniform high level of neuronal activity. Anesthesia results in a uniform global decrease in the neuronal activity (as

assessed from glucose consumption) from the awake state with consciousness being lost when the reduction is 40% to 50%. fMRI studies of rats anesthetized at different levels suggest that the high energy state involves a greater degree of interaction between brain regions as evidenced by distributed activation patterns. We hypothesize that the high distributed neuronal activity associated with consciousness supports extensive inter-regional communication necessary for the conscious state.

Certainly the property of responding to a stimulus does not compare with the richness of mental processes usually attributed to consciousness. However the very jarring nature of this observable, behavioral test for the state of consciousness illustrates an important point that we have made above and elsewhere (Shulman, 2001; Shulman et al., 2003). Namely, in order to study neuronal activities that provide necessary, but not sufficient, support for the state of consciousness (as defined here), we have not assumed that consciousness at the level of the brain can be described in terms of component mentalistic, philosophical and folk-psychological concepts that are commonly used in everyday speech and most neuroimaging experiments. However we do note that concepts like fear, memory, attention or consciousness are of great utility in everyday life. The abstraction of these concepts into mental processes located within the brain has not in our opinion been satisfactorily supported by imaging data. At the cost of complexity we hope that by confining experimental goals to measuring bottom up neuronal properties that are necessary but not sufficient to explain behaviorally defined states, imaging studies of brain function will gain scientific objectivity.
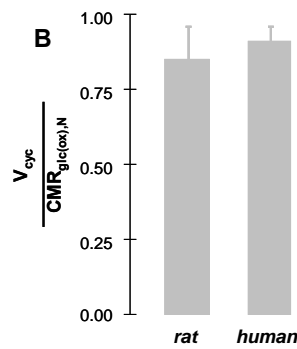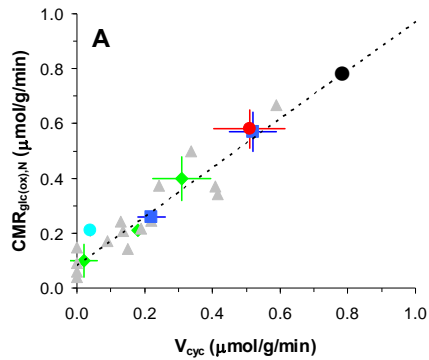
Acknowledgements

Figure 1. (A) Experimental results of V_{cyc} and $CMR_{glc(ox),N}$. Values of V_{cyc} and $CMR_{glc(ox),N}$ for the rat brain reported in studies published between 1998 and 2006. The dark blue squares are from Patel et al. (2004), the red circle is from Oz et al. (2004), the light blue circle is from Choi et al. (2002), the green diamonds are from de Graaf et al. (2004), and the gray triangles are from Sibson et al. (1998) (for details , see Hyder et al., 2006).

Modified from Hyder et al. (2006)with permission. (B) The ratio of $V_{cyc}/CMR_{glc(ox),N}$ in the non-anesthetized resting -awake state in rat (extrapolated from A; see ●) and human brain (for details see Hyder et al., 2006)). Similarity of $V_{cyc}/CMR_{glc(ox),N}$ ratio in rats and humans suggests that relation between V_{cyc} and $CMR_{glc(ox),N}$ are similar.

Figure 2. Behavioral index of the ability to respond during anesthesia depth variation. Relationship between probability of no response to stimuli (i.e., loud verbal command) to the end-tidal sevoflurane concentration in adult, healthy human subjects (Katoh et al., 2000). The ability to respond decreases as sevoflurane concentration increases, and vice versa. Modified from Katoh et al. (2000) with permission.
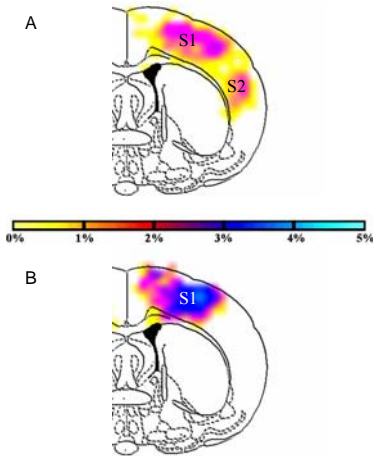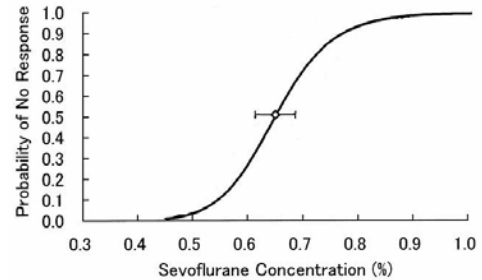

Figure 3. Averaged fMRI maps (from two subjects, two single runs, 30 s block design, forepaw stimulation) of anterior coronal slices (A) under halothane showed widespread activities beyond contralateral primary (S1) and secondary (S2) somatosensory cortices, whereas (B) under α-chloralose demonstrated localized activation in contralateral S1. Darker colors represent greater overlap across experiments (i.e., reproducibility). All activation maps were thresholded at the same value (p < 0.02). Modified from Maandag et al.(2007) with permission.

Figure 4. Total activity represented by distribution of firing rates (ν; 10 s bins) in the primary somatosensory ensemble of ~200 neurons for (A) halothane and (B) α-chloralose states. Activity under halothane is dominated by the rapid signaling neurons (RSN) sub-group which seems unaffected by stimulation. The slow signaling neurons (SSN) sub-group shifts to higher frequencies upon stimulation are similar in both states, but more significant under α-chloralose. Modified from Maandag et al. (2007) with permission.
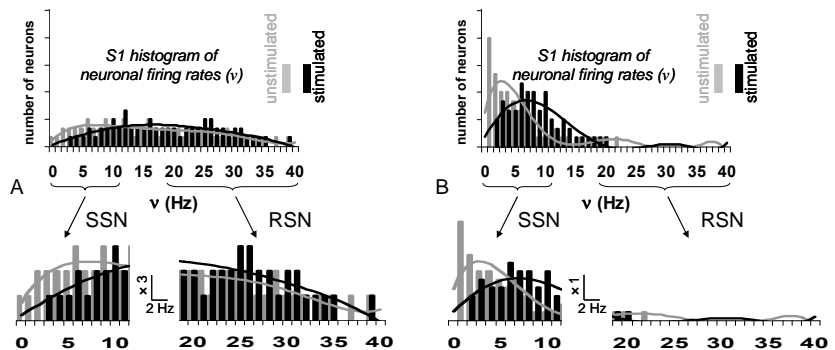
Table 1. Anesthesia-induced decrease in metabolism and awake values of glucose metabolism measured by PET.

	ΔCMR_{O2} [†]Sevoflurane	ΔCMR_{O2} [†]Propofol	ΔCMR_{glc} [‡]Propofol	ΔCMR_{glc} [||]Halothane	ΔCMR_{glc} [||]Isoflurane	[§]Awake CMR_{glc} μmol/g/min
Frontal Cortex	29 %	38 %	58 %	47 %	52 %	0.39±0.05
Parietal Cortex	31 %	42 %	53 %	41 %	55 %	0.37±0.01
Temporal Cortex	26 %	36 %	52 %	48 %	47 %	0.35±0.07
Occipital Cortex	43 %	50 %	59 %	50 %	40 %	0.37±0.04
Anterior Cingulate	-	-	53 %	46 %	48 %	0.34±0.01
Caudate	30 %	33 %	-	-	-	0.32±0.06•
Putamen	31 %	32 %	-	-	-	0.40±0.07•
Thalamus	41 %	43 %	55 %	52 %	53 %	0.34±0.01
Basal Ganglia	-	-	52 %	48 %	44 %	0.36±0.03
Hippocampus	-	-	42 %	50 %	45 %	0.29±0.08
Midbrain	-	-	44 %	54 %	50 %	0.15±0.01
Cerebellum	44 %	43 %	56 %	54 %	55 %	0.26±0.06

[§]Awake CMR_{glc} values were mainly derived from averaged value in refs. ‡ and || except for caudate and putamen.
•Awake CMR_{glc} values were derived from CMR_{O2} values in ref †.
Awake CMR_{glc} values show that the average of the whole brain (0.33±0.04 μmol/g/min) is within 10% and 3% of the gray matter regions in the neocortex (0.36±0.03 μmol/g/min) and subcortex (0.34±0.05 μmol/g/min), % respectively. Therefore brain metabolism of gray matter regions in the awake human is quite high and uniform.
Values for anesthesia-induced decrease in metabolism were approximations made from graphical representations of data in the original papers (refs. †, ‡, and || below). Decreased metabolism in whole brain, neocortex, and subcortex were 40-50%, 45-50%, and 35-45%, respectively. Therefore brain metabolism of gray matter regions in anesthetized humans is uniformly suppressed.† (Kaisti et al., 2003); ‡ (Alkire et al., 1995); ||(Alkire et al., 1999).

Table 2. Measurable properties of the state of consciousness.

Property	Measure	Conscious State	Unconscious State
Behavior	Response to stimuli	Yes	No
Baseline energy	^{13}C MRS, calibrated fMRI, PET	High and uniform	Uniformly reduced by ~40%
Activation spreading	fMRI (conventional, calibrated)	Distributed	Localized
Neuronal firing patterns	Electrophysiology	Low and high frequencies	Low frequencies

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