



A default mode of brain function

Marcus E. Raichle*, Ann Mary MacLeod*, Abraham Z. Snyder*, William J. Powers†, Debra A. Gusnard*§, and Gordon L. Shulman*

*Mallinckrodt Institute of Radiology and Departments of †Neurology and §Psychiatry, Washington University School of Medicine, St. Louis, MO 63110

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected on April 30, 1996.

Contributed by Marcus E. Raichle, October 26, 2000

A baseline or control state is fundamental to the understanding of most complex systems. Defining a baseline state in the human brain, arguably our most complex system, poses a particular challenge. Many suspect that left unconstrained, its activity will vary unpredictably. Despite this prediction we identify a baseline state of the normal adult human brain in terms of the brain oxygen extraction fraction or OEF. The OEF is defined as the ratio of oxygen used by the brain to oxygen delivered by flowing blood and is remarkably uniform in the awake but resting state (e.g., lying quietly with eyes closed). Local deviations in the OEF represent the physiological basis of signals of changes in neuronal activity obtained with functional MRI during a wide variety of human behaviors. We used quantitative metabolic and circulatory measurements from positron-emission tomography to obtain the OEF regionally throughout the brain. Areas of activation were conspicuous by their absence. All significant deviations from the mean hemisphere OEF were increases, signifying deactivations, and resided almost exclusively in the visual system. Defining the baseline state of an area in this manner attaches meaning to a group of areas that consistently exhibit decreases from this baseline, during a wide variety of goal-directed behaviors monitored with positron-emission tomography and functional MRI. These decreases suggest the existence of an organized, baseline default mode of brain function that is suspended during specific goal-directed behaviors.

Functional brain imaging studies in normal human subjects with positron-emission tomography (PET) and functional MRI (fMRI) have consistently revealed expected task-induced increases in regional brain activity during goal-directed behaviors (for brief reviews see refs. 1 and 2). These changes are detected when comparisons are made between a task state, designed to place demands on the brain, and a control state, with a set of demands that are uniquely different from those of the task state.

Researchers have also frequently encountered task-induced decreases in regional brain activity even when the control state consists of lying quietly with eyes closed or passively viewing a stimulus. Whereas cortical increases in activity have been shown to be task specific and, therefore, vary in location depending on task demands, many decreases (Fig. 1) appear to be largely task independent, varying little in their location across a wide range of tasks (3). This consistency with which certain areas of the brain participate in these decreases made us wonder whether there might be an organized mode of brain function that is present as a baseline or default state and is suspended during specific goal-directed behaviors.

The primary issue this paper will address is whether these unexplained decreases merely arise from unrecognized increases (i.e., activation in the jargon of functional brain imaging) present only in the “control state.” Thus, on this argument, any control state, no matter how carefully it is selected, is just another task state with its own unique areas of activation. Unfortunately, in most instances there is insufficient information about the control state to judge whether the observed decrease arose in this manner.

We believe conceptual progress has suffered because of our inability to exclude explanations of the above type for regional decreases in brain activity and, more generally, to understand whether a specific level of activity in a given area of the brain can be considered its baseline. At the heart of the problem is the lack of agreed-upon characteristics defining a baseline state. In response to this dilemma we began with a generally accepted, quantitative circulatory and metabolic definition of brain activation (see *Background*, below). From this definition we specified criteria for a baseline state (i.e., the absence of activation by this definition). In so doing, we were able to determine that areas consistently exhibiting decreases in activity during specific goal-directed behaviors (3) did so from this baseline state. We believe these findings are consistent with our idea of a baseline or default state of the brain, the functions of which are revealed by those areas whose activities are suspended during many transient, attention-demanding, goal-directed activities.

Background

Although the human brain accounts for only about 2% of the body weight, it consumes nearly 20% of the oxygen we extract from the air we breathe. This dependence of the brain on oxygen is highlighted by the fact that failure of oxygen delivery to the brain, usually the result of a stoppage of the heart, results in unconsciousness within seconds. An examination of the relationship between oxygen delivery to the brain and flowing blood regionally within the brain (Fig. 2) highlights the nature of this dependency.

The signal used by PET to map changes in neural activity in the human brain is based on local changes in blood flow (1). Increased neural activity in a local brain region increases blood flow in that region. Scientists have known of this robust relationship for well over 100 years through repeated demonstrations in laboratory animals and humans (1). It was thought to reflect the changing needs of the brain for oxygen during changing mental activity.

Surprisingly, more recently it has been appreciated that these changes in blood flow are accompanied by smaller changes in oxygen consumption (4). This leads to a decrease in the amount of oxygen extracted from blood when blood flow increases and an increase in the amount of oxygen extracted when blood flow decreases. Thus, changes in blood flow accompanying local changes in brain activity are associated with significantly smaller changes in the amount of oxygen used by the brain (1). As a result of these relationships the local blood oxygen content parallels the change in brain activity because the amount of oxygen supplied changes more than the demand (Fig. 3). At the present time we do not fully understand why the relationship between

Abbreviations: OEF, oxygen extraction fraction; fMRI, functional MRI; PET, positron-emission tomography; CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate for oxygen; MPFC, medial prefrontal cortex.

[†]To whom reprint requests should be addressed at: Washington University School of Medicine, 4525 Scott Avenue, Room 2116, St. Louis, MO 63110. E-mail: marc@npg.wustl.edu.

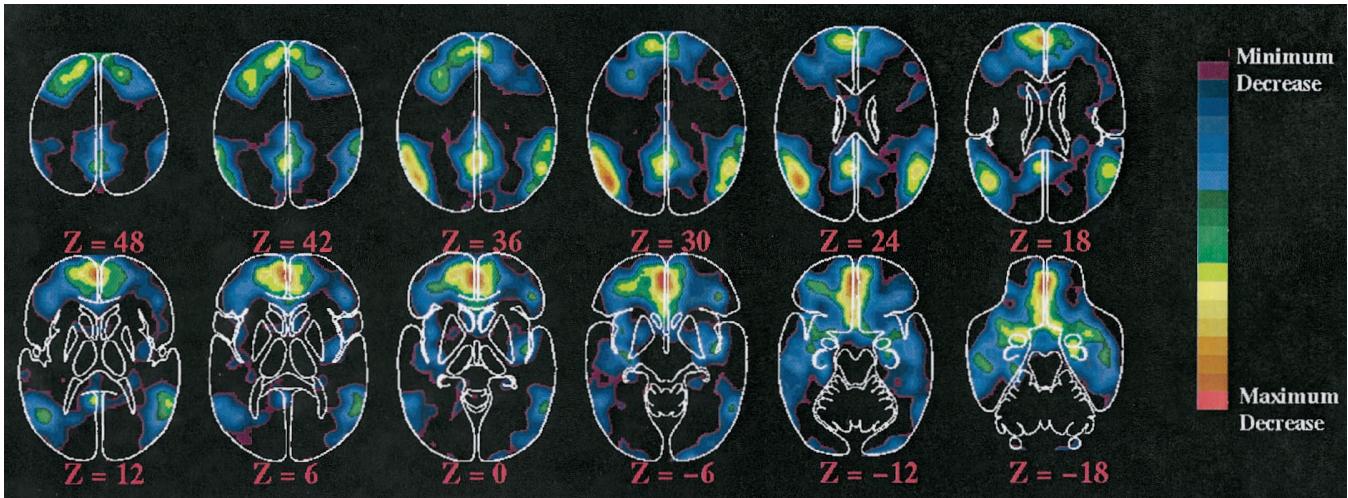


Fig. 1. Regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks. These data represent a metaanalysis of nine functional brain imaging studies performed with PET and analyzed by Shulman and colleagues (49). In each of the studies included, the subjects processed a particular visual image in the task state and viewed it passively in the control state. One hundred thirty-two individuals contributed to the data in these images. These decreases appear to be largely task independent. The images are oriented with the anterior at the top and the left side to the reader's left. The numbers beneath each image represent the millimeters above or below a transverse plane running through the anterior and posterior commissures (26).

oxygen delivery and oxygen consumption changes during changes in brain activity (see ref. 1 for a review), but this phenomenon has had great practical value for our ability to view changes in brain activity with fMRI.

Because fMRI signal intensity is sensitive to the amount of oxygen carried by hemoglobin (5–7), this change in blood oxygen content at the site of increased brain activity can be detected with fMRI. This phenomenon is the basis for fMRI (8, 9) and is usually referred to as the blood oxygen level-dependent (BOLD) signal, following Ogawa and colleagues (6).

The relationship of oxygen delivery to oxygen utilization can be measured quantitatively in the human brain 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) (10–12). Researchers interested in blood flow and metabolic relationships in the brain

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; see Fig. 4). This spatial uniformity exists despite considerable variation in resting 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 (Figs. 2 and 4). This relationship is altered in the normal brain only when areas briefly change their activity during specific behaviors (4, 13).

Heretofore the uniformity of the OEF at rest has not been considered in defining a baseline state of the human brain. Here we specifically propose to do so. The brain mean OEF was chosen as the baseline level of activity on the basis of its general uniformity in the eyes closed, resting state. This uniformity suggests that equilibrium has been reached between the local metabolic requirements necessary to sustain a long-term modal

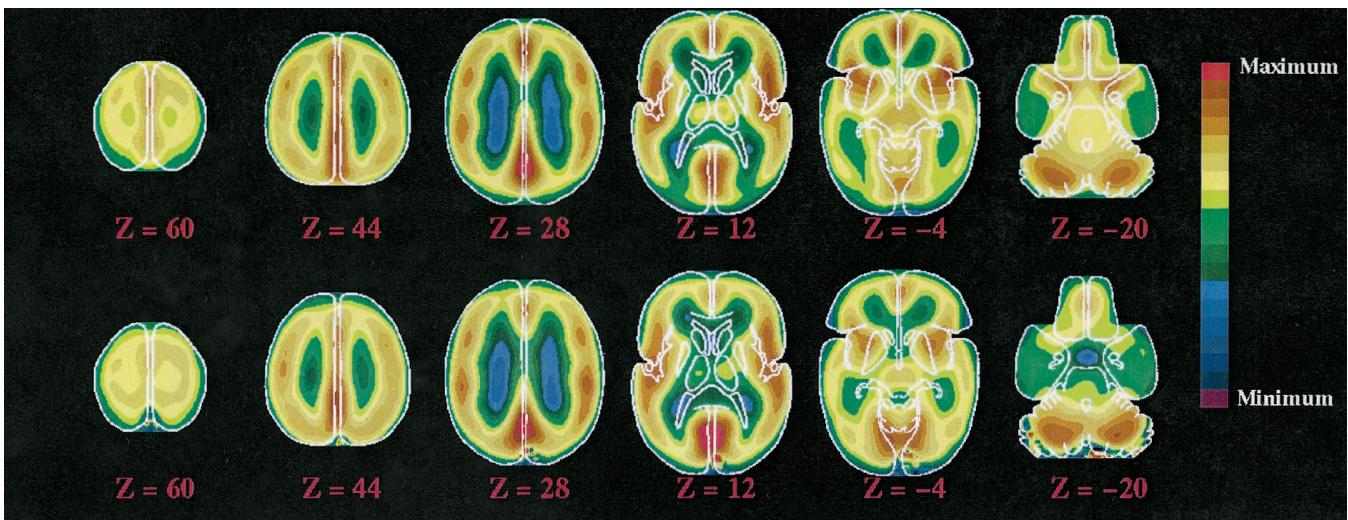


Fig. 2. Quantitative maps of blood flow (Upper) and oxygen consumption (Lower) in the subjects from group I while they rested quietly but awake with their eyes closed. The quantitative hemisphere mean values for these images are presented in Table 1. Note the large variation in blood flow and oxygen consumption across regions of the brain. These vary most widely between gray and white matter. Despite this variation, blood flow and oxygen consumption are closely matched, as also reflected in the image of the oxygen extraction fraction (i.e., the ratio of oxygen consumption to blood flow; see Fig. 4).

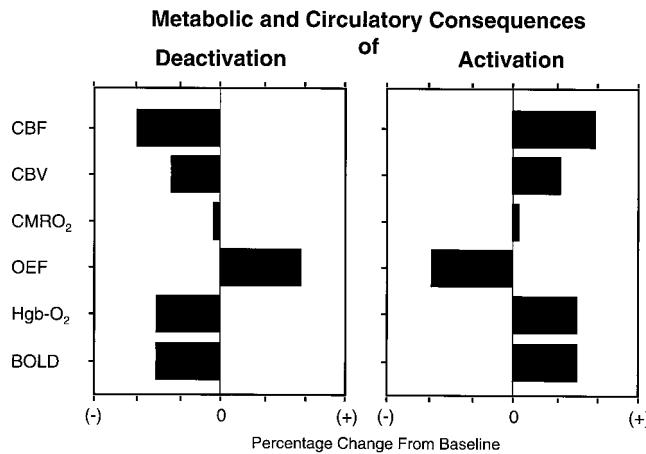


Fig. 3. A schematic representation of the metabolic and circulatory relationships occurring in areas of the brain with transient increases (Activation) or decreases (Deactivation) in the level of neural activity from a baseline or equilibrium state. Typically increases (Right) are characterized by increases in the cerebral blood flow (CBF) and the cerebral blood volume (CBV), with much smaller changes in the cerebral metabolic rate for oxygen (CMRO_2). As a result, there is a fall in the oxygen extraction fraction (OEF) and an increase in the amount of oxygen attached to hemoglobin exiting the brain (HbO_2). This latter change is responsible for the blood oxygen level-dependent (BOLD) signal used in functional magnetic resonance imaging (fMRI). Decreases from baseline (Left) are characterized as the opposite pattern of change.

level of neural activity and the level of blood flow in that region. We propose that this equilibrium state defines a baseline level of local neuronal activity. Consequently, those areas with a reduced OEF relative to the brain mean are defined as activated (i.e., neural activity is increased above the baseline level). Those areas not differing from the brain mean OEF are considered to be at baseline. In this scheme, increases in the OEF from the brain mean then define areas of deactivation (i.e., neural activity is decreased below the baseline level).

With these definitions in mind (Fig. 3) we used quantitative measurements of the OEF obtained with PET to examine those

brain areas regularly observed to exhibit reductions in blood flow and blood oxygen level-dependent signal during goal-directed behaviors (3). Our reason for choosing these regions was to test the hypothesis that such decreases occur relative to a baseline state of brain activity (here defined as resting quietly but awake with eyes closed). In other words, decreases in brain activity do not have to be increases simply looked at from the opposite side of the equation. Rather, they are decreases from a true baseline or zero set point. If this hypothesis is correct, the chosen regions should exhibit an OEF similar to that of the rest of the brain in this baseline state. The OEF in these areas was measured in two independent groups of 19 normal adults resting quietly with eyes closed. These results were then extrapolated to a more complex control or baseline state (passive visual fixation) in a third group of 11 normal adults.

Methods

Subjects. Data from three subject groups were used for this analysis. The first two groups had served as control subjects in previously published studies from this laboratory (3, 14, 15). The third group was culled from previously unpublished data. All subjects were recruited from the Washington University community. None had any history of neurological or psychiatric illness. The Human Studies Committee and the Radioactive Drug Research Committee of Washington University approved all studies. Informed consent was obtained in accordance with their guidelines.

Group I consisted of 19 subjects (eight females) in whom quantitative CBF, CBV, OEF, and the CMRO_2 were measured while the subjects rested quietly but awake with eyes closed in a Siemens model 961 PET scanner (see below). Their ages ranged from 19 to 77 years, with a mean age of 43 years. Seventeen were right handed. They are described in greater detail elsewhere (15).

Group II consisted of 19 subjects (10 females) in whom quantitative CBF, CBV, OEF, and CMRO_2 were measured while the subjects rested quietly but awake with eyes closed in the PETT VI PET scanner (see below). Their ages ranged from 19 to 84 years, with a mean age of 42 years. Fourteen were right handed. They are described in greater detail elsewhere (14).

Group III (previously unpublished) consisted of 11 subjects

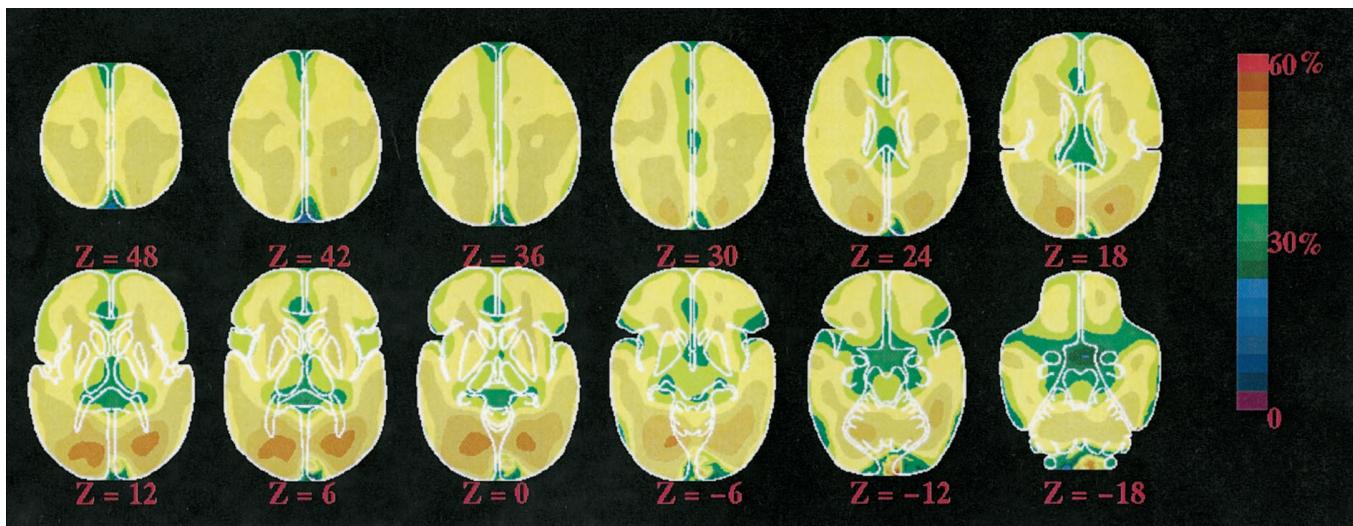


Fig. 4. Maps of the fraction of oxygen extracted by the brain from arterial blood (oxygen extraction fraction or OEF expressed as a percentage of the available oxygen delivered to the brain). The data come from 19 normal adults (group I, Table 1) resting quietly but awake with their eyes closed. The data were obtained with PET. Despite an almost 4-fold difference in blood flow and oxygen consumption between gray and white matter, the OEF is relatively uniform, emphasizing the close matching of blood flow and oxygen consumption in the resting, awake brain. Areas of increased OEF can be seen in the occipital regions bilaterally (see text for discussion).

Table 1. Data obtained from subjects in group I while they rested quietly but awake with their eyes closed

Area	x	y	z	OEF	P	CBF	P	CMRO ₂	P	
A	M 31/7	-5	-49	40	1.010	0.62	1.374*	<0.0001	1.397*	<0.0001
B	L 40	-53	-39	42	0.901	0.07	0.735*	<0.0001	0.695*	<0.0001
C	L 39/19	-45	-67	36	0.987	0.66	0.813*	0.0008	0.805*	0.0003
D	R 40	45	-57	34	0.978	0.26	1.002	0.96	0.998	0.97
E	L lateral 8	-27	27	40	0.981	0.52	0.991	0.74	0.986	0.74
F	L 8/9	-11	41	42	0.902	0.04	0.874	0.006	0.803*	0.001
G	R 8/9	5	49	36	0.887	0.004	0.893	0.01	0.813*	0.001
H	L 9	-15	55	26	0.943	0.35	0.813*	0.0001	0.785*	0.002
I	L 10	-19	57	8	0.971	0.06	0.940	0.01	0.927	0.01
J	M 10	-1	47	-4	0.933	0.01	1.284*	<0.0001	1.203*	<0.0001
K	L 10/47	-33	45	-6	0.930	0.25	0.920	0.03	0.879	0.04
L	M 32	3	31	-10	0.946	0.20	1.111	0.005	1.058	0.26
M	L 20	-49	-19	-18	0.972	0.46	0.821*	<0.0001	0.814*	0.0002

The values for OEF, CBF, and CMRO₂ are expressed as local-to-global ratios (see *Methods*). For the 19 subjects in group I the global values for OEF and CBF (\pm SD) were 0.40 ± 0.09 (dimensionless) and 46 ± 8 ml/(min \times 100 g), respectively. The mean arterial oxygen content for this group was 16.6 ± 0.16 ml/ml. From these data quantitative images of the CMRO₂ were created that yielded a mean cerebral hemisphere value of 2.94 ± 0.41 ml/(min \times 100 g) or 1.31 ± 0.18 μ mol/(min \times g). The asterisks denote values that differ significantly from the global mean after correction for multiple comparisons.

(five females) in whom qualitative CBF was measured while the subjects rested quietly but awake with eyes closed and again while they passively viewed a visual fixation cross hair in the middle of a television monitor. Five such paired measurements were obtained. Their ages ranged from 19 to 40 years, with a mean age of 27 years. Eight subjects were right handed. There is no record of the handedness of the other three. The data for group III were also acquired with the PETT VI PET scanner (see below).

Imaging Methods. The subjects in group I were scanned with a Siemens model 961 scanner (Siemens Medical Systems, Hoffman Estates, IL) (16, 17). Images were reconstructed by using filtered back projection and scatter correction with a ramp filter at the Nyquist frequency. All images were then filtered with a three-dimensional Gaussian filter to a uniform resolution of 16-mm full width at half-maximum.

In the subjects in groups II and III, studies were performed on the PETT VI scanner (18, 19). The PETT VI system was used in the low-resolution mode. Images were then filtered with a three-dimensional Gaussian filter to a uniform resolution of 17-mm full width at half-maximum.

Quantitative regional OEF, CBF, and CMRO₂ were measured by using a combination of O¹⁵-labeled radiopharmaceuticals as

described (11, 12, 20–22). Qualitative CBF was measured in the subjects in group III. In this instance H₂¹⁵O images consisting of normalized PET counts were used to create maps of the distribution of blood flow in the brain (21, 23, 24).

Regions of Interest. The location of each region of interest analyzed in this study was obtained directly from the right hand side of table 1 of the study by Shulman and colleagues (3). These regions were chosen because they reliably predict the location of areas of the human brain exhibiting reductions in activity, as measured with either PET or fMRI, during the performance of a variety of cognitive tasks (3). Their coordinates are listed in Tables 1 and 2 of the present study. The regions are referred to by the Brodmann area originally assigned to them by Shulman *et al.* (3).

Furthermore, a center-of-mass algorithm (25) was used to search the OEF data sets for any significant deviations from the hemisphere mean outside of the specific areas chosen for analysis (preceding paragraph).

Data Analysis. A 12-mm sphere was centered on the stereotaxic coordinates of each region of interest (see Tables 1 and 2) for each subject's individual images of CBF, OEF, and CMRO₂. Each regional value was divided by the subject's mean global

Table 2. Data obtained from subjects in group II while they rested quietly but awake with their eyes closed

Area	x	y	z	OEF	P	CBF	P	CMRO ₂	P	
A	M 31/7	-5	-49	40	1.035	0.62	1.278*	<0.0001	1.345*	<0.0001
B	L 40	-53	-39	42	0.903	0.04	0.804	0.0042	0.756*	0.003
C	L 39/19	-45	-67	36	0.997	0.94	0.805*	<0.0001	0.820*	0.0004
D	R 40	45	-57	34	0.994	0.77	0.941	0.04	0.957	0.11
E	L lateral 8	-27	27	40	1.001	0.93	0.964	0.05	0.996	0.93
F	L 8/9	-11	41	42	0.707	0.04	0.893	0.03	0.756	0.02
G	R 8/9	5	49	36	0.871	0.02	0.926	0.15	0.858	0.02
H	L 9	-15	55	26	0.983	0.54	0.876*	0.0002	0.878*	0.0009
I	L 10	-19	57	8	1.042	0.06	0.967	0.02	1.012	0.61
J	M 10	-1	47	-4	0.984	0.36	1.187*	<0.0001	1.166*	<0.0001
K	L 10/47	-33	45	-6	1.037	0.12	0.913*	<0.0001	0.964	0.27
L	M 32	3	31	-10	0.984	0.54	1.080*	<0.0001	1.061	0.03
M	L 20	-49	-19	-18	0.962	0.35	0.865*	<0.0001	0.877	0.005

The values for OEF, CBF, and CMRO₂ are expressed as local-to-global ratios (see *Methods*). For the 19 subjects in group II the global values for OEF and CBF (\pm SD) were 0.30 ± 0.09 (dimensionless) and 48 ± 10 ml/(min \times 100 g), respectively. The mean arterial oxygen content for this group was 17.0 ± 0.02 ml/ml. From these data quantitative images of the CMRO₂ were created that yielded a mean cerebral hemisphere value of 2.17 ± 0.41 ml/(min \times 100 g) or 0.97 ± 0.17 μ mol/(min \times g). The asterisks denote values that differ significantly from the global mean after correction for multiple comparisons.

Table 3. Areas with maximum absolute deviation of the OEF from the hemisphere mean in subjects from group I

Brodmann area	x	y	z	OEF	P
11	8	33	-22	1.491	0.0007
19	-23	-79	6	1.217	<0.0001
19	29	-67	4	1.201	<0.0001
18	-29	-93	12	1.194	0.001
18	23	-79	18	1.182	0.0002
18	23	-81	10	1.181	<0.0001
37	33	-51	-8	1.138	0.0005
31	23	-47	40	1.121	<0.0001
31	17	-33	50	1.103	0.0003
19	21	-83	30	1.098	0.08

Note that these are all increases in the OEF signifying areas of deactivation in the baseline state of resting but awake with eyes closed. With the exception of Brodmann area 11 located in the right gyrus rectus, these areas cluster in visual areas of the occipital and parietal cortices. The conventions used are similar to those of Tables 1 and 2.

value for that image, creating a local to global ratio for that region. A two-tailed, one-sample Student's *t* test was performed to determine whether this ratio differed from a predicted value of 1. The level of significance was adjusted for multiple comparisons.

Results

Regional as well as whole-brain measurement values of CBF, OEF, and CMRO₂ for groups I and II are presented in Tables 1 and 2. None of the areas selected for study (3) exhibited an OEF significantly different from the hemispheric mean (compare Figs. 1 and 4). The correlation between the regional values of OEF obtained independently on the two groups was excellent (*r* = 0.89). By our definition (see *Background*), therefore, none of these areas was activated in subjects who were awake but resting quietly with their eyes closed (two independent groups of 19 subjects each).

To complete our analysis, the data sets from groups I and II were automatically searched (25) for any deviations in the OEF above or below the hemisphere mean. No significant decreases in OEF were found signifying areas of activation. In arriving at this determination we had to exclude several "areas" falling in high-noise areas at the edge of the brain or, in some instances, clearly outside of the brain. However, we did find, bilaterally, areas within extrastriate visual cortices that exhibited a significantly increased OEF from the hemisphere mean. These changes are readily apparent in Fig. 4, and their locations are given in

Table 4. Areas with maximum absolute deviation of the OEF from the hemisphere mean in subjects from group II

Brodmann area	x	y	z	OEF	P
18	19	-79	10	1.189	<0.0001
18	-19	-93	14	1.169	<0.0001
19	35	-75	10	1.163	<0.0001
19	-27	-79	8	1.145	0.001
17	-9	-75	6	1.123	0.003
19	21	-81	28	1.112	0.03
18	-13	-69	30	1.109	0.002
7	21	-59	32	1.107	<0.0001
19	-23	-87	28	1.104	.05
7	17	-63	46	1.073	0.02

Note that these are all increases in the OEF signifying areas of deactivation in the baseline state of resting but awake with eyes closed. These areas cluster in visual areas of occipital and parietal cortices. The conventions used are similar to those of Tables 1 and 2.

Tables 3 and 4. By our definition these apparent visual areas are deactivated when subjects are awake but resting quietly with their eyes closed.

Although none of the areas selected for study appear to be activated by our definition, two areas in both groups (i.e., M31/7 and M10) have both resting CBF and CMRO₂ significantly above the global mean (criteria: *P* < 0.0038 for both measurements in both groups). Likewise, two additional areas in both groups (i.e., L39/19 and L9) have both resting CBF and CMRO₂ significantly below the global mean.

Resting quietly awake with the eyes closed is much less frequently used as a control state in functional imaging studies than visual fixation of a cross hair on a television monitor or passive viewing of a stimulus. The data presented in Tables 1 and 2 as well as Figs. 1 and 4 do not tell us whether areas exhibiting significant reductions in activity during active task performance (3) become more active in the control states of visual fixation than when the eyes are closed. If this were to occur, reduced activity seen in the task state could simply reflect the absence of this increase in activity during fixation and passive viewing.

The data from group III resolved this issue. No significant change in blood flow was found for any of the regions listed in Tables 1 and 2 when subjects went from the eyes closed and awake but resting state to passively viewing a fixation cross hair in the middle of a television monitor. Furthermore, it should be noted that those areas of extrastriate visual cortex exhibiting deactivation in the eyes closed state (Fig. 4) increase their BF when the eyes are opened (details to be published separately). This observation is consistent with the hypothesis that the baseline state of these areas is more nearly approximated when subjects rest quietly with their eyes open.

Discussion

Our study represents a comprehensive analysis of the uniformity of the OEF in the normal human brain while adult subjects are awake and resting quietly with their eyes closed. These data affirm the long-held impression of a relatively consistent relationship between oxygen delivery and oxygen consumption in the human brain (Fig. 2). Obvious decreases in the OEF from the brain mean, reflecting areas of activation (1), are not apparent in our data when subjects rest quietly with their eyes closed or open.

Areas of deactivation (i.e., increased OEF), primarily in extrastriate visual areas, were clearly apparent from our data (Fig. 4 and Tables 3 and 4). It is of interest to note that these same increases in OEF were also noted in some of the earliest PET work on normal humans (27), although their possible significance was not appreciated. Their presence suggests that the baseline state for these areas may well be associated with the eyes being open. This hypothesis receives support from our comparison of eyes closed versus passive visual fixation, in which we noted an increase in the blood flow in these areas as subjects opened their eyes. Further work remains, including actual measurements of OEF in these areas in the eyes open and closed states. Nevertheless, these data are consistent with our hypothesis that the baseline state of these areas is more nearly approximated when the eyes are open.

More generally our data are consistent with the hypothesis that the brain mean OEF defines a baseline level of neuronal activity. The uniformity of the OEF in the absence of specific goal-directed activities supports our belief that an established equilibrium exists between the local metabolic requirements necessary to sustain a long-term modal level of neural activity and the level of blood flow in a particular region. Deviations from this equilibrium produced by transient changes in this modal level of neural activity manifest themselves as changes in the OEF and provide us with the signals underlying modern functional brain imaging with fMRI.

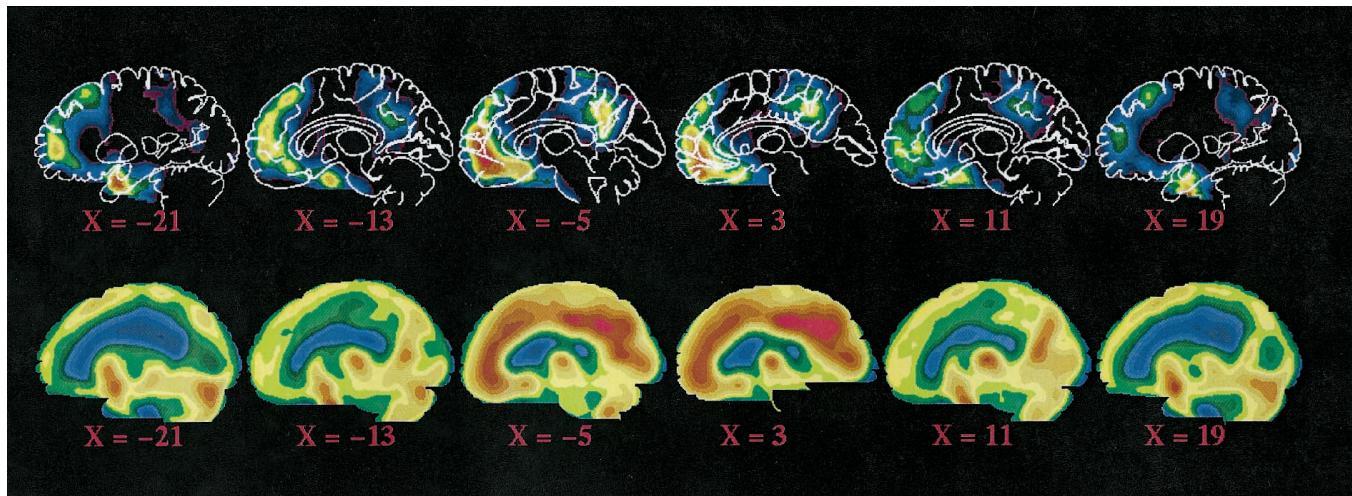


Fig. 5. Regions of the brain regularly observed to decrease their activity during attention-demanding cognitive tasks shown in sagittal projection (*Upper*) as compared with the blood flow of the brain while the subject rests quietly but is awake with eyes closed (*Lower*). The data in the top row are the same as those shown in Fig. 1, except in the sagittal projection, to emphasize the changes along the midline of the hemispheres. The data in the bottom row represent the blood flow of the brain and are the same data shown in horizontal projection in the top row of Fig. 2. The numbers below the images refer to the millimeters to the right (positive) or left (negative) of the midline.

Areas consistently observed to decrease their activity in a variety of goal-directed, cognitive activation paradigms (Fig. 1) do not exhibit a reduced OEF (i.e., evidence of activation) in this typical resting state (Tables 1 and 2). While a null result such as this (i.e., the regional OEF does not differ from the hemisphere mean) might be received with some caution, the relatively tight 95% confidence limits for the measurement of OEF ($\pm 3\%$, based on an analysis of the group I data) make it very unlikely that significant reductions in OEF, of even lesser magnitude than the increases seen in the visual system (Fig. 4 and Tables 3 and 4), would have been missed. Thus, we believe our findings indicate that these localized decreases in activity (Figs. 1 and 5) (3) occur as decreases from a baseline level of activity rather than the return to baseline of an area of unsuspected activation.

The presence of a consistent set of decreases in activity within a select set of brain areas strikingly independent of the goal-directed behaviors with which they are associated suggests to us that specific brain functions unique to the baseline state itself are being temporarily suspended. We posit that areas decreasing their activity in this manner may be tonically active in the baseline state, as distinguished from areas that are transiently activated in support of varying goal-directed activities. Understanding the exact functions served by such tonically active areas would require much additional work, yet some indication of the directions this research might profitably take is revealed by our current knowledge about two of them. These are midline areas within the posterior cingulate and precuneus and within the medial prefrontal cortex (MPFC) (see Fig. 5).

The response of posterior cingulate and precuneus neurons to visual stimuli, for example, crucially depends on the physical characteristics of the stimulus (for a recent review see ref. 28). Small spots of light to which a monkey may be attending and responding do not elicit neuronal responses in this area. In contrast, large, brightly textured stimuli elicit responses, even if they are totally irrelevant to tasks the animal is performing. These observations are consistent with the fact that elements of the dorsal stream of extrastriate visual cortex [area M in the owl monkey (29) and area PO in the macaque (30)] are part of a network of areas concerned with the representation of the visual periphery.

Severe damage to the parietal cortex, when it extends medially to include the precuneus and the posterior cingulate, produces

a condition known as Balint's syndrome (31), the cardinal feature of which is the inability to perceive the visual field as a whole (i.e., a fixed form of tunnel vision usually referred to as simultanagnosia), despite intact visual fields, during simple confrontation with single small stimuli. Furthermore, patients with Alzheimer's disease show early reductions of metabolic activity in this area (32) and have been reported to show abnormalities in the processing of extrafoveal information (33).

Thus, the posterior cingulate cortex and adjacent precuneus can be posited as a tonically active region of the brain that may continuously gather information about the world around, and possibly within, us. It would appear to be a default activity of the brain with rather obvious evolutionary significance. Detection of predators, for example, should not, in the first instance, require the intentional allocation of attentional resources. These resources should be allocated automatically and be continuously available. Only when successful task performance demands focused attention should such a broad information gathering activity be curtailed. The central importance of such a function is underscored by the observation that restoration of consciousness from a vegetative state (or at least external awareness, as it can be assessed at the patient's bedside) is primarily heralded by a restoration of metabolism in parietal areas, including the precuneus (34).

Finally, we note the selective vulnerability of the posterior cingulate and precuneus in such conditions as carbon monoxide poisoning [i.e., acute hypoxia (34)], diffuse brain ischemia (35), and Alzheimer's disease (32). This vulnerability, in the case of hypoxia and ischemia, has been ascribed to the position of the posterior cingulate and precuneus in the border zone between two of the main arteries supplying blood to the brain. We wonder whether the exceptionally high metabolic rate exhibited by the posterior cingulate and precuneus adds to their vulnerability (Tables 1 and 2 and Fig. 5). This hypothesis receives some support from animal models of schizophrenia (36), based on pharmacologically induced, excitatory amino acid toxicity that preferentially (but without explanation to date) targets this area.

Another midline area of the cortex exhibiting prominent decreases in activity during focused attention is MPFC (Figs. 1 and 5). Because of the large body of data implicating, in particular, the ventral aspects of this area of the brain and its connections in emotional processing within the brain, it has been

posed that decreases during focused attention reflect a dynamic interplay between ongoing cognitive processes and the emotional state of the subject (37–40), a hypothesis we explore in more detail in our accompanying papers (41, 42). More specifically, it has been proposed that in humans the MPFC may play a role in the integration of emotional and cognitive processes by incorporating emotional biasing signals or markers into decision-making processes (43).

Anatomically, the ventral MPFC is composed of a number of cytoarchitectonically discrete areas that receive a wide range of sensory information from the body and the external environment (44–46) and are heavily interconnected with limbic structures such as the amygdala, ventral striatum, hypothalamus, midbrain periaqueductal gray region, and brainstem autonomic nuclei (44, 45). Electrophysiological studies in monkeys indicate that orbital and medial prefrontal neurons respond to stimuli based on their reward and nonreward associations (for a review see ref. 47).

Thus, as we come to associate general monitoring of sensory information with the posterior cingulate and adjacent precuneus, we may also come to associate an evaluation of the salience of this information with medial and orbital frontal cortices. We posit that when an individual is awake and alert and yet not actively engaged in an attention-demanding task, a default state of brain activity exists that involves, among other areas, the MPFC and the posterior cingulate and precuneus. Information

broadly arising in the external and internal milieu is gathered and evaluated. When focused attention is required, particularly if this activity is novel, activity within these areas may be attenuated. This attenuation in activity reflects a necessary reduction in resources devoted to general information gathering and evaluation. The MPFC with the posterior cingulate and medial parietal cortices may well be the “sentinels” to which William James referred (see ref. 48, p. 73), which, “when beams of light move over them, cry ‘who goes there’ and call the fovea to the spot. Most parts of the skin do but perform the same office for the fingertips.”

More generally, an appreciation of the important activities that may underlie the baseline state of the human brain will certainly enrich our understanding of its function. Strong hints about the direction research in this area might take come, we believe, from the heretofore mysterious activity reductions routinely seen by modern functional brain imaging techniques during the performance of goal-directed behaviors. In addition to the midline areas we have discussed, it is necessary to consider as well the role(s) of more lateral cortical areas (especially prominent in parietal cortex), which also appear as elements of this default system.

This work was supported by National Institutes of Health Grants NS06833, DA07261, and NS10196 and the Charles A. Dana Foundation.

1. Raichle, M. E. (1998) *Proc. Natl. Acad. Sci. USA* **95**, 765–772.
2. Raichle, M. E. (1998) *Philos. Trans. R. Soc. London B* **353**, 1–14.
3. Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E. & Petersen, S. E. (1997) *J. Cognit. Neurosci.* **9**, 648–663.
4. Fox, P. T. & Raichle, M. E. (1986) *Proc. Natl. Acad. Sci. USA* **83**, 1140–1144.
5. Thulborn, K. R., Waterton, J. C., Matthews, P. M. & Radda, G. K. (1982) *Biochim. Biophys. Acta* **714**, 265–270.
6. Ogawa, S., Lee, T. M., Kay, A. R. & Tank, D. W. (1990) *Proc. Natl. Acad. Sci. USA* **87**, 9868–9872.
7. Ogawa, S., Lee, T. M., Nayak, A. S. & Glynn, P. (1990) *Magn. Reson. Med.* **14**, 68–78.
8. Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S.-G., Merkle, H. & Ugurbil, K. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 5951–5955.
9. Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weiskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., et al. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 5675–5679.
10. Frackowiak, R. S. J., G. L., L., Jones, T. & Heather, J. D. (1980) *J. Comput. Assist. Tomogr.* **4**, 727–736.
11. Mintun, M. A., Raichle, M. E., Martin, W. R. & Herscovitch, P. (1984) *J. Nucl. Med.* **25**, 177–187.
12. Altman, D. I., Lich, L. L. & Powers, W. J. (1991) *J. Nucl. Med.* **32**, 1738–1741.
13. Fox, P. T., Raichle, M. E., Mintun, M. A. & Dence, C. (1988) *Science* **241**, 462–464.
14. Perlmutter, J. S., Herscovitch, P., Powers, W. J., Fox, P. T. & Raichle, M. E. (1985) *J. Cereb. Blood Flow Metab.* **5**, 476–480.
15. Grubb, R. L., Derdeyn, C. P., Fritsch, S. M., Carpenter, D. A., Yundt, K. D., Videen, T. O., Spitznagel, E. L. & Powers, W. J. (1998) *J. Am. Med. Assoc.* **280**, 1055–1060.
16. Wienhard, K., M., D., L., E., Michel, C., Bruckbauer, T., Pietrzyk, U. & Heiss, W. D. (1994) *J. Comput. Assist. Tomogr.* **18**, 110–118.
17. Spinks, T. J., Jones, T., Bailey, D. L., Townsend, D. W., Grootoont, S., Bloomfield, P. M., Gilardi, M. C., Casey, M. E., Sipe, B. & Reed, J. (1992) *Phys. Med. Biol.* **37**, 1637–1655.
18. Ter-Pogossian, M. M., Ficke, D. C., Hood, J. T., Yamamoto, M. & Mullani, N. A. (1982) *J. Comput. Assist. Tomogr.* **6**, 125–133.
19. Yamamoto, M., Ficke, D. C. & Ter-Pogossian, M. M. (1982) *IEEE Trans. Nucl. Sci.* **NS-29**, 529–533.
20. Videen, T. O., Perlmutter, J. S., Herscovitch, P. & Raichle, M. E. (1987) *J. Cereb. Blood Flow Metab.* **7**, 513–516.
21. Herscovitch, P., Markham, J. & Raichle, M. E. (1983) *J. Nucl. Med.* **24**, 782–789.
22. Raichle, M. E., Martin, W. R. W., Herscovitch, P., Mintun, M. A. & Markham, J. (1983) *J. Nucl. Med.* **24**, 790–798.
23. Fox, P. T. & Mintun, M. A. (1989) *J. Nucl. Med.* **30**, 141–149.
24. Fox, P. T., Mintun, M. A., Raichle, M. E. & Herscovitch, P. (1984) *J. Cereb. Blood Flow Metab.* **4**, 329–333.
25. Mintun, M. A., Fox, P. T. & Raichle, M. E. (1989) *J. Cereb. Blood Flow Metab.* **9**, 96–103.
26. Talairach, J. & Tournoux, P. (1988) *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme Medical Publishers, New York).
27. Lebrun-Grandie, P., Baron, J.-C., Soussaline, F., Loch'h, C., Sastre, J. & Bousser, M.-G. (1983) *Arch. Neurol.* **40**, 230–236.
28. Vogt, B. A., Finch, D. M. & Olson, C. R. (1992) *Cereb. Cortex* **2**, 435–443.
29. Baker, J. F., Petersen, S. E., Newsome, W. T. & Allman, J. M. (1981) *J. Neurophysiol.* **45**, 397–416.
30. Colby, C. L., Gattass, R., Olson, C. R. & Gross, C. G. (1988) *J. Comp. Neurol.* **238**, 1257–1299.
31. Hecaen, H. & Ajuriaguerra, J. (1954) *Brain* **77**, 373–400.
32. Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L. & Kuhl, D. E. (1997) *Ann. Neurol.* **42**, 85–94.
33. Benson, D. F., Davis, J. & Snyder, B. D. (1988) *Arch. Neurol.* **45**, 789–793.
34. Laureys, S., Lemaire, C., Maquet, P., Phillips, C. & Franck, G. (1999) *Lancet* **67**, 121–133.
35. DeVolder, A. G., Goffinet, A. M., Bol, A., Michel, C., de Barsy, T. & Laterre, C. (1990) *Arch. Neurol.* **47**, 197–204.
36. Oliny, J. W., Newcomer, J. W. & Farber, N. B. (1999) *J. Psychiatric Res.* **33**, 523–533.
37. Drevets, W. C. & Raichle, M. E. (1998) *Cognit. Emotion* **12**, 353–385.
38. Mayberg, H. S. (1997) *J. Neuropsychiatry* **9**, 471–481.
39. Bush, G., Luu, P. & Posner, M. I. (2000) *Trends Cognit. Sci.* **4**, 215–222.
40. Simpson, J. R., Jr., Ongur, D., Akbudak, E., Conturo, T. E., Ollinger, J. M., Snyder, A. Z., Gusnard, D. A. & Raichle, M. E. (2000) *J. Cognit. Neurosci.*, in press.
41. Simpson, J. R., Jr., Snyder, A. Z., Gusnard, D. A. & Raichle, M. E. (2001) *Proc. Natl. Acad. Sci. USA* **98**, 683–687.
42. Simpson, J. R., Jr., Drevets, W. C., Snyder, A. Z., Gusnard, D. A. & Raichle, M. E. (2001) *Proc. Natl. Acad. Sci. USA* **98**, 688–693.
43. Bechara, A., Damasio, H., Tranel, D. & Damasio, A. R. (1997) *Science* **275**, 1293–1295.
44. Barbas, H. (1995) *Neurosci. Biobehav. Rev.* **19**, 499–510.
45. Carmichael, S. T. & Price, J. L. (1995) *J. Comp. Neurol.* **363**, 615–641.
46. Rolls, E. T. & Baylis, L. L. (1994) *J. Neurosci.* **14**, 5437–5452.
47. Rolls, E. T. (1999) *The Brain and Emotion* (Oxford Univ. Press, Oxford, U.K.).
48. James, W. (1893) *Psychology* (Henry Holt, New York).
49. Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E. & Petersen, S. E. (1997) *J. Cognit. Neurosci.* **9**, 648–663.