SEARCHING FOR A BASELINE: FUNCTIONAL IMAGING AND THE RESTING HUMAN BRAIN

Debra A. Gusnard[*‡] *and Marcus E. Raichle*[*§]

Functional brain imaging in humans has revealed task-specific increases in brain activity that are associated with various mental activities. In the same studies, mysterious, task-independent decreases have also frequently been encountered, especially when the tasks of interest have been compared with a passive state, such as simple fixation or eyes closed. These decreases have raised the possibility that there might be a baseline or resting state of brain function involving a specific set of mental operations. We explore this possibility, including the manner in which we might define a baseline and the implications of such a baseline for our understanding of brain function.

LOCAL FIELD POTENTIAL
A weighted average of dendrosomatic pre- and postsynaptic currents, which might include dendritic spikes or activity of small interneurons. So, it predominantly reflects the input to and the local processing in an area, rather than output from the area. The local field potential is an important determinant of the fMRI and PET signals.

A fundamental aspect of scientific experimentation is the identification of a control or baseline against which the condition of interest can be compared. This has been an important issue in cognitive neuroscience — a field of research in which functional brain-imaging techniques are used to measure changes in brain activity that are associated with specific mental operations. Many suspect that, left unconstrained, this activity would vary unpredictably. In this review, we introduce the concept of a physiological baseline in the 'awake' human brain, defined in terms of its metabolism and circulation. This concept arose from studies of the function of the normal human brain, using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

We begin our review by examining data from functional imaging experiments and considering the interpretation of the observed increases and decreases in activity. We also discuss how providing a definition of a physiological baseline might facilitate a greater understanding of these changes. We then introduce a definition of the baseline based on quantitative measurements of brain circulation and metabolism. Finally, we explore the functional implications that arise from this conceptualization.

Background

Studies using PET and fMRI have consistently revealed expected task-induced increases (BOX 1) in regional brain activity during goal-directed behavioural activities (see REFS 1,2 for brief reviews). These changes are detected when comparisons are made between a task state designed to place specific demands on the brain and an investigator-defined control state. These changes are commonly referred to as 'activations', and are thought to represent increases in the local cellular activity of the brain[3,4], which have been suggested to relate predominantly to changes in LOCAL FIELD POTENTIALS[5].

However, researchers have also frequently encountered task-induced decreases in brain activity in functional imaging experiments. These are sometimes referred to as 'deactivations', but not all decreases are deactivations. Deactivations are generally considered to be attenuations in regional brain activity, and are thought to be attributable to specific physiological mechanisms that are incompletely understood at present (BOX 1). On the other hand, perceived decreases in functional imaging experiments may have a variety of explanations (BOX 2).

For example, some decreases arise simply on the basis of how control tasks and tasks of interest are manipulated in the image-analysis strategy. A simple

**The Mallinckrodt Institute of Radiology and the Departments of §Neurology, ‡Psychiatry, §Neurobiology and §Psychology, Washington University, St Louis, Missouri 63110, USA.
Correspondence to M.E.R.
e-mail: marc@npg.wustl.edu*

example involves 'reverse subtraction' (BOX 2). A reverse subtraction arises when two tasks that differ in their mental operations (for example, one might contain a hand movement and the other not) are compared with each other. Depending on which of the two tasks serves as the control condition (and investigators occasionally switch the roles of the two tasks), the change in activity in given areas that is associated with the unique components of a particular task can appear as an increase or as a decrease. So, in this example, the motor hand area might well appear as a decrease. This explanation relates to the way in which the data are analysed, and clearly does not involve specific concepts of brain physiology. Unfortunately, in some instances, insufficient information exists about the tasks and the operations that they involve to judge whether the observed decrease arose in this manner.

Not everything that is referred to as a decrease can be explained in this way, however. Other explanations for some decreases have been tendered, with brain physiology specifically in mind. One relates to brain haemodynamics. It has been proposed[6] that when there is an increase in local blood flow within the brain, adjacent areas will show a decrease simply because of a need to divert blood flow away from them to meet the needs of the activated tissue (the so-called 'vascular-steal' phenomenon). This explanation could have some validity at the level of the microvasculature[7], but seems to have little relevance for decreases that are appreciated at the level of functional imaging for several reasons. First, the actual changes in local blood flow that are associated with increased cognitive activity are very small (a few per cent locally in the cortex) relative to the overall blood flow to the brain. In fact, these local changes are so small that changes in total brain blood flow cannot be measured during cognitive activity[8]. Second, and related to the first, the haemodynamic reserve of the brain is very large[9]. So, the brain has the capacity to as much as double its blood flow when the need arises (for example, during an epileptic seizure[10]). Finally, the decreases can occur remote from the site of the increases[11–13], or in the absence of increases altogether[14], making a steal within a given vascular territory an unlikely explanation.

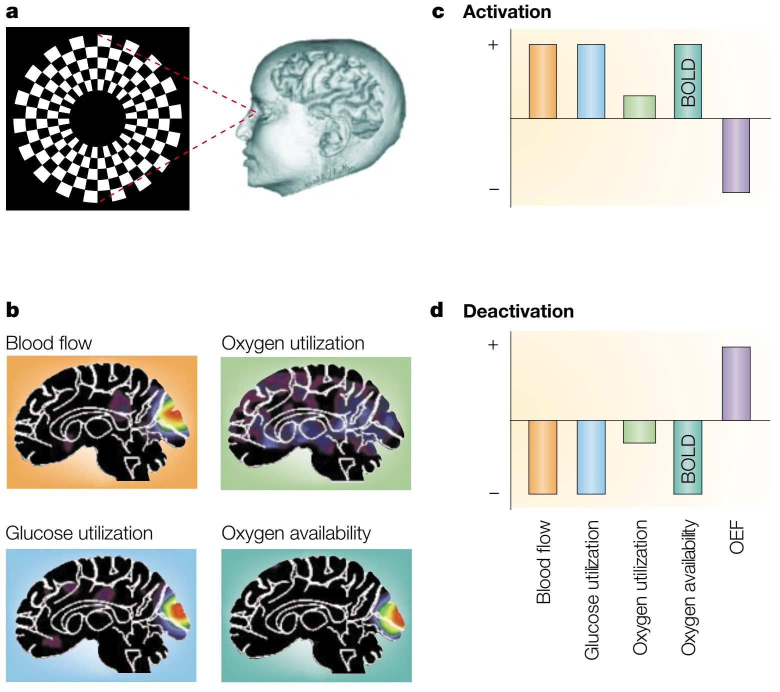
Another explanation for decreases from the perspective of brain physiology involves the consideration of their functional significance. It has been posited that some of the decreases that are observed in areas remote from activations might reflect the suppression or 'gating' of information processing in areas that are not engaged in task performance[15]. This gating is thought to facilitate the processing of information that is expected to carry behavioural significance by filtering out unattended (sensory) input. These decreases have been observed both within and across sensory modalities and are task specific[15–17]. We shall refer to these as task-dependent decreases.

There is another class of functionally related decreases that was often not reported initially. As investigators paid increasing attention to it, however, an important feature of these task-induced decreases began to emerge. Although cortical increases in activity, as well as some decreases (see above), had been shown to be task specific

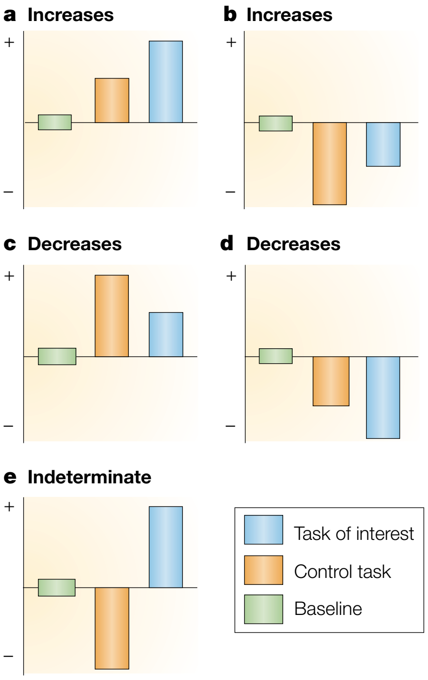
Box 1 | **Brain activation and functional imaging**

Brain activation can be produced experimentally in various ways. For example, the presentation of a visual stimulus such as a reversing annular chequerboard (**a**), when compared with viewing a blank screen, produces marked changes in activity in visual areas of the brain, as shown in positron emission tomographic (PET) images (**b**). These changes consist of an increase in blood flow and glucose utilization, but little if any increase in oxygen utilization. As a result, the amount of oxygen available in the area of activation increases (supply transiently exceeds demand), which accounts for the blood-oxygen-level-dependent (BOLD) signal of functional magnetic resonance imaging (fMRI). The changes that define a typical 'activation' are depicted graphically in panel **c**. The absence of these changes in an image defines the baseline. A more formal description of the change in oxygen availability is derived from the technique that is used with PET imaging to determine brain oxygen use[84]. Oxygen use is measured through the acquisition of data from two PET-imaging measurements: one made after the intravenous injection of $^{15}O_2$-radiolabelled water, and the other made after the inhalation of $^{15}O_2$-radiolabelled oxygen. By comparing the uptake of the two tracers in a region of the brain, the fraction of available oxygen that is extracted by the brain and converted to water of metabolism — the oxygen extraction fraction, OEF — can be directly determined. It can be expressed as the percentage of the oxygen delivered to the brain that is utilized by the brain. The 'oxygen use' can be computed as the product of the OEF, the measurement of blood flow (BF) obtained with $^{15}O_2$-radiolabelled water, and the measurement of the arterial blood oxygen content (C_A). So, oxygen use = BF × OEF × C_A. It follows from a simple rearrangement of this equation that the OEF is the ratio of oxygen utilization to BF or oxygen delivered. When BF increases more than oxygen utilization, as it does in brain activation, the OEF decreases (**c**).

The opposite happens when deactivation occurs from the baseline[14]. Deactivation (**d**) represents the opposite spectrum of metabolic and circulatory changes to those observed with activation (**c**). What mechanism(s) is responsible for deactivation? It is unlikely to be a result of the increased activity of local inhibitory interneurons, as both excitation and inhibition increase local glucose utilization in laboratory animals[85,86]. That is, both excitation and local inhibition should be seen as increases in activity (activations) by fMRI or PET (**c**). One possible explanation for the decrease in activity that is observed in an area of the brain with functional imaging is that it might reflect a decrease in the activity of the cells that are projecting to the area. A possible source of this modulatory influence could be the thalamus, with involvement of the basal ganglia.



Box 2 | How do increases and decreases arise from functional imaging strategies?



There are two ways in which both increases and decreases can be obtained in the interpretation of functional imaging data. These depend, first, on the direction of the change in regional brain activity relative to the baseline for both the control task and the task of interest and, second, on the way in which these two tasks are compared.

For example, increases can be obtained when a task of interest is associated with greater activity than an investigator-defined control task relative to the baseline. This can arise under two circumstances. In the first instance (**a**), the task of interest has a greater increase above baseline than the control task. In the second instance (**b**), the task of interest has less of a decrease from the baseline. In both cases, the difference in activity between the control task and the task of interest would be interpreted as an increase.

Decreases can be obtained when a task of interest is associated with less activity than the control task relative to the baseline. This can also arise under two circumstances. In the first instance (**c**), the task of interest has a lower increase above baseline than the control task. In the second instance (**d**), the task of interest involves a greater decrease below the baseline. In both cases, the difference in activity between the control task and the task of interest would be interpreted as a decrease. Note that merely switching the task and control, as depicted in **a** compared with **c**, for example, would be recognized by most as a 'reverse subtraction' and would result in an obvious decrease. This is sometimes done when investigators wish to emphasize the contributions of control states and refer to their results as activations[18].

Finally, under circumstances in which the control task and the task of interest cause changes in brain activity that move in opposite directions relative to the baseline, the result could range from no perceptible change in the area to an increase or a decrease that is underestimated (**e**). The infrequent use of a true baseline (passive) task makes estimates of the occurrence of these confounding factors difficult to determine.

and, therefore, to vary in location depending on the demands of the task, many of these particular decreases (FIG. 1) seemed to be largely task independent, varying little in their locations across a wide range of tasks (for example, visual and auditory attention, language processing, memory and motoric activity)[13,18]. The consistency with which certain areas of the brain participated in these decreases indicated that there might be an organized mode of brain function, which is attenuated during various goal-directed behaviours. We shall refer to these as task-independent decreases.

Such functional conceptualizations regarding task-dependent and task-independent decreases require us to determine a reference point or baseline from which these decreases might arise (BOX 2). An inherent problem has been the lack of agreed characteristics to define such a baseline. Without the knowledge of such a reference point or baseline, it is impossible to exclude the possibility that such decreases merely represent the product of a reverse subtraction, as mentioned above. Providing a definition of a physiological baseline should facilitate a greater understanding of all changes in activity, both decreases and increases, that are encountered in functional brain-imaging experiments (BOX 2).

In response to this challenge to define a baseline, we begin with a generally accepted, quantitative circulatory and metabolic definition of brain activation (BOX 1). From this definition, we specify the criteria for a baseline. We can then demonstrate that areas that consistently show decreases during specific goal-directed behaviours (task-independent decreases[13]) do so from this baseline[14].

Definition of the baseline

We define the physiological baseline of the brain as the absence of activation. Activation may be defined in the context of functional imaging as an increase in blood flow that is not accompanied by a commensurate increase in oxygen consumption (BOX 1). As a result, less oxygen is extracted from the blood, leading to an increase in the local blood oxygen content in the brain. This represents a change in the relationship between oxygen delivery, which increases, and oxygen utilization, which does not. This relationship is defined in terms of the oxygen extraction fraction (OEF; BOX 1), which decreases during brain activation. Research into blood flow and metabolic relationships in the brain has highlighted the close relationship between local blood flow and oxygen utilization in the resting state (for example, lying quietly in a scanner with eyes closed, although awake; FIG. 2), which is reflected in the spatial uniformity of the OEF. This spatial uniformity exists despite marked regional differences in both blood flow and oxygen consumption between grey matter and white matter, as well as among areas of grey matter (FIG. 2).

Before now, the OEF was used almost exclusively to characterize the relationship between regional blood flow and oxygen consumption in the diseased brain, particularly in various forms of cerebrovascular disease that compromise blood flow[19,20]. The uniformity of the

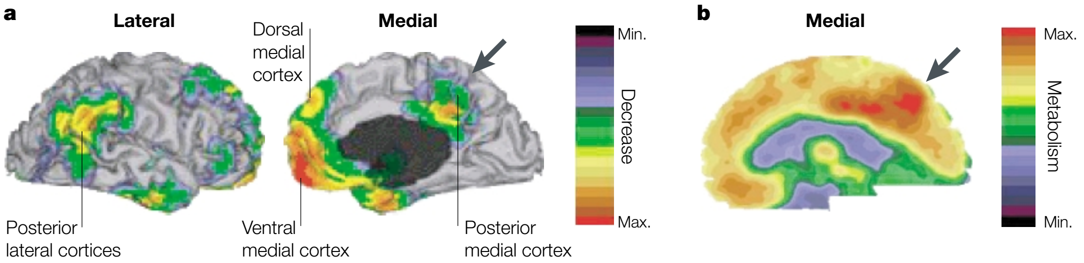


Figure 1 | **Task-independent decreases observed in functional imaging experiments. a** | The coloured areas on the lateral and medial surfaces of the cerebral cortex[80] summarize the decreases observed in nine functional brain-imaging studies that were carried out using positron emission tomography (PET)[13]. In these studies, which involved 132 normal adults, subjects had to process various visual stimuli in the tasks of interest, such as detecting targets, setting up sequencing task operations, establishing an intention and performing language-related tasks; in the control state, they passively viewed the same visual stimuli. The results were similar when a simple visual-fixation task was used. These decreases are remarkable for their task independence. The only common feature among the tasks, beyond the fact that they involved visual stimuli, was that they required active goal-directed behaviour. **b** | Areas showing task-independent decreases along the midline of the brain, particularly posteriorly in medial parietal cortex and the posterior cingulate cortex (arrows), are associated with the highest resting metabolic rates in the human cerebral cortex. This is illustrated in this PET image of resting glucose metabolism in 22 normal individuals[81], which was measured with ^{18}F-fluorodeoxyglucose[82]. Images in **a** courtesy of D. Van Essen and A. Z. Snyder, Washington University, USA.

OEF at rest in the normal brain had not been considered in defining a functional baseline. Here, we propose to do so.

The uniformity of the OEF at rest indicates that equilibrium has been reached between the local metabolic requirements that are necessary to sustain a long-term continuing level of neural activity, and the level of blood flow in that region. We propose that this equilibrium state defines a baseline level of neuronal activity. Consequently, those areas with a reduced OEF relative to the mean OEF of the brain (the 'brain mean OEF') are defined as 'activated' (that is, neural activity is increased above the baseline level). Those areas that do not differ 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 (that is, neural activity is decreased below the baseline level).

Importantly, obvious decreases in the OEF from the brain mean, reflecting areas of activation[1], are not apparent when subjects rest quietly with their eyes either closed or open. Specifically, the task-independent decreases that are noted in functional imaging studies do not correspond to 'activations' in the resting state as suggested by Mazoyer and colleagues[18]. Rather, they arise from the baseline[14]. Therefore, we suggest that they might be more appropriately referred to as areas that, in the resting state, are active rather than 'activated'.

When the eyes of a subject are closed, areas of apparent deactivation (increased OEF) are clearly seen, primarily in extrastriate visual areas (FIG. 2, bottom row). The same regional increases in OEF were also noted in some of the earliest PET work on normal humans[21], although their possible significance was not appreciated. Their presence indicates that the baseline for extrastriate visual areas might be associated with open eyes. In support of this hypothesis, eye opening increases blood flow in these areas[14].

So, we propose that there exists a physiological baseline of the human brain, which can be observed when subjects are awake and resting with their eyes closed (an exception might exist for some extrastriate visual areas — see above). Substituting simple visual fixation or passive viewing of stimuli has little effect on this physiological baseline, except to increase blood flow in the visual areas, as mentioned above[13].

We turn now to a discussion of the possible functionality that resides in the baseline. Others have considered the related issue of the functions that are inherent in the resting state[18,22], but they have not considered the significance of a physiological baseline. We believe that the consideration of these two issues — functions and baseline — together will enrich our understanding of the significance of the findings that arise from functional imaging studies.

Functions in the baseline

In the awake resting state, the brain receives 11% of the cardiac output and accounts for 20% of the total oxygen consumption of the body[23], despite the fact that it represents only 2% of body weight. However, the changes in brain activity that are the focus of most functional brain-imaging experiments, although easily identified using functional imaging techniques such as PET and fMRI, produce changes in global measurements of blood flow and metabolism that are too small to be measured[8] (BOX 3). This raises the question of why the brain consumes all of this energy in the baseline or resting state. A possible explanation comes from observations indicating that up to 50% of this baseline energy consumption is devoted to the functional aspects of synaptic transmission[3–5,24], implying significant functionality in the baseline or resting state.

Task-independent decreases in activity, coming as they do from the baseline, provide a means of probing the functionality of the baseline or resting state of the human brain. These decreases are remarkable in their consistency, as demonstrated by two large meta-analyses (a total of 18 PET studies involving 197 subjects that performed visual, auditory and motor tasks) that came to their findings from very different perspectives.

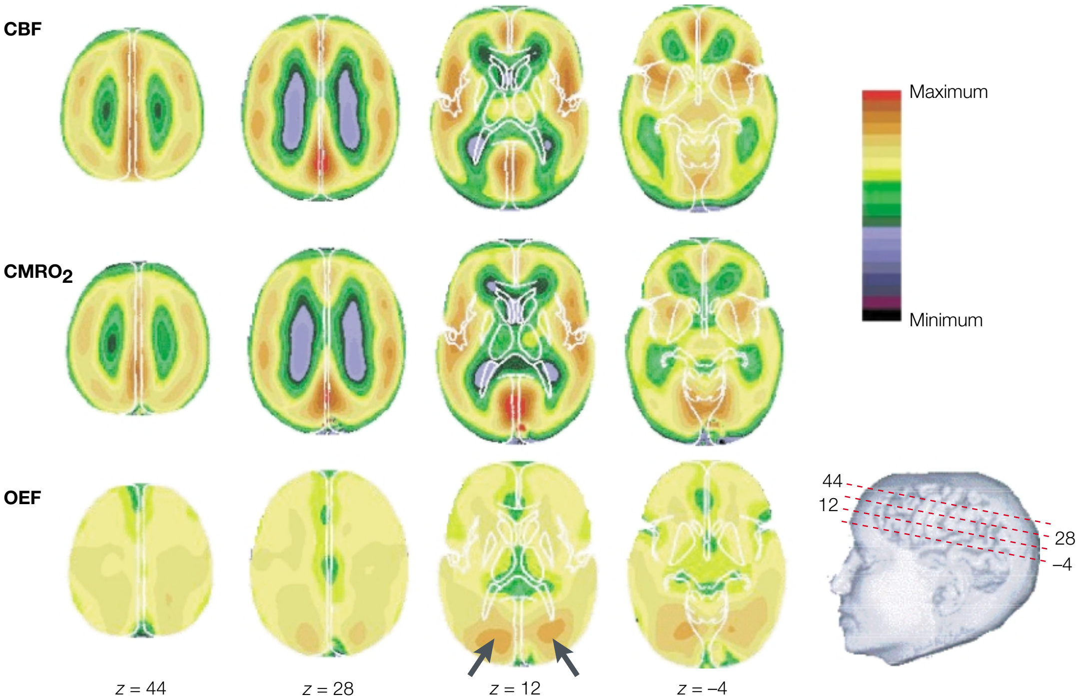


Figure 2 | **Resting measurements of brain blood flow, oxygen consumption and oxygen extraction fraction.** Transverse images of cerebral blood flow (CBF) and oxygen consumption ($CMRO_2$) in the normal adult human brain, measured with positron emission tomography. Note the marked, up to fourfold, variability in both blood flow and oxygen consumption. Despite this variability, there is a remarkable correspondence between these two sets of images. This close matching of regional blood flow to oxygen consumption is exemplified in the map of the oxygen extraction fraction (OEF), which reflects the ratio of these two measurements (BOX 1). There are areas of increased OEF (arrows) in the occipital regions bilaterally, most prominently at $z = 12$. These represent areas of deactivation relative to the baseline in visual cortices when eyes are closed (see text). These data came from 19 normal adults who were resting quietly, but awake, with their eyes closed[14]. The numbers beneath each column represent the millimetres above or below a transverse plane (the z axis) running through the anterior and posterior commissures[83], as shown in the three-dimensional lateral view of the head and brain (bottom right; created using magnetic resonance imaging).

In the first study by Shulman and colleagues[11–13], the objective was to determine whether activations in the cerebral cortex were present across various visual tasks that reflected the use of common attentional strategies. The control task for all nine studies, which involved 132 subjects, was the passive viewing of the visual stimuli that were used in each individual study. Another control task, that of visual fixation, was also included in several of the studies. Although common increases outside the visual cortices were not observed[12], the meta-analysis did reveal a striking and consistent set of decreases[13] (FIG. 1), indicating the presence of processes that were attenuated during the performance of goal-directed actions when compared with either visual fixation or passive stimulus viewing.

In the second study, by Mazoyer and co-workers[18], the objective was to explore the functional nature of the resting state. Various tasks were compared to an eyes-closed resting condition, in which the subjects were instructed to “keep their eyes closed, to relax, to refrain from moving, and to avoid any structured mental activity such as counting, rehearsing, etc.” The task of interest was the resting state rather than the active behaviour, which served as the control. Using a reverse-subtraction strategy (see above), they observed changes in almost the same areas reported by Shulman and colleagues. However, because of the analysis strategy that was used, the changes were reported as activations rather than as decreases or deactivations.

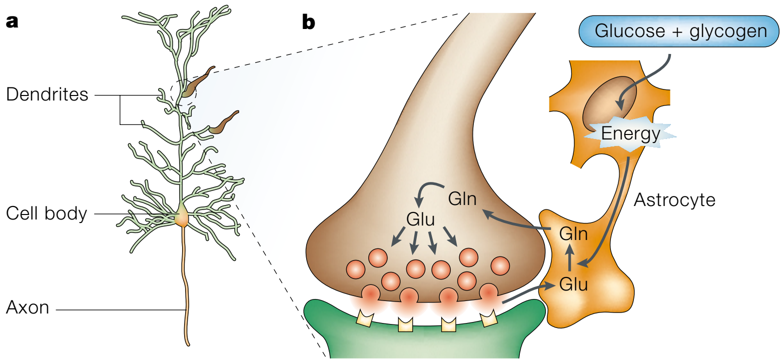
These two large meta-analyses[13,18] converge on the same conclusion — that there is a consistent set of brain areas that are active at rest with eyes closed, as well as during visual fixation and the passive viewing of simple visual stimuli. The activity in these areas is attenuated during the performance of various goal-directed actions. Because these areas arise from the baseline activity of the brain in these passive conditions, we suggest that they are functionally active, although they are not ‘activated’[14]. In contrast to the transient nature of typical activations (BOXES 1 AND 3), the presence of this functional activity in the baseline implies the presence of sustained information processing.

Understanding the exact functions served by such tonically active areas will require much more work, but some indication of the directions that future research might take is suggested by our current knowledge of these areas. In the remainder of this section, we will organize our discussion by dividing these areas into four general groups on the basis of their anatomical location. We recognize, however, that this segregation might obscure important subdivisions within areas, and relationships among these areas that presumably work together in the baseline or resting state.

Box 3 | **Cellular mechanisms**

The metabolic and circulatory changes associated with the blood-oxygen-level-dependent (BOLD) signal are driven by electrical potentials arising from the input to, and information processing within, the dendrites of neurons[5] (**a**). The signals obtained in functional brain imaging are associated with local increases in blood flow as well as glucose consumption, without commensurate changes in oxygen consumption (glycolysis; BOX 1). An attractive explanation for the BOLD signal invokes the preferential use of glycolysis in the metabolism of neurotransmitters participating in brain activation. Specifically, the communication between neurons occurs at synapses (**b**), and requires the release of neurotransmitters from a presynaptic neuron and their detection by a postsynaptic nerve cell. Glutamate (Glu) is the main excitatory neurotransmitter in the brain. After it is released, glutamate is removed promptly from the synapse by uptake into an adjacent astrocyte. There, glutamate is converted to glutamine (Gln) before being returned to the neuron and recycled. The energy needed for processing glutamate is provided by glycolysis, using glucose obtained from blood and, during sudden increases in activity, from a glycogen store in astrocytes[87,88].

The baseline metabolic rate of the brain is very high and does not change appreciably over time, hence the analogy with marathon running (**c**). The energy needed is supplied by glucose oxidation and the brain vasculature is precisely organized to meet the accompanying continuing need for oxygen. Changes in activity associated with activation, however, although requiring only a small and brief increment in energy expenditure, occur in milliseconds. The brain vasculature simply cannot respond quickly enough to meet these energy requirements in a timely fashion[5]. How does the brain deal with this mismatch? It resorts to glycolysis, like a sprinter. Although glycolysis yields less energy overall, it produces this energy nearly twice as fast as glucose oxidation (**d**).



c **Baseline** **d** **Activation**

Posterior medial cortices

Areas in the medial parietal cortex are particularly prominent among those areas of the brain that show task-independent decreases from the baseline during the performance of goal-directed actions. The posterior cingulate, precuneus and retrosplenial cortices together show the highest level of glucose use (the primary fuel for brain energy metabolism) of any area of the cerebral cortex in humans (FIG. 1) and other species[25]. This is consistent with there being a high level of information processing in this region of the cortex in the baseline or resting state[3,5], which is attenuated during many goal-directed behaviours.

Evidence indicates that the functions to which this region of the cerebral cortex contributes include those concerned with aspects of visuospatial processing. Animal studies indicate that the posterior cingulate cortex and adjacent precuneus are involved in both orientation within, and interpretation of, the environment (see REF. 26 for a recent review). The work of Colby[27] and Allman[28] and their colleagues also draws attention to the fact that elements of the dorsal stream of extrastriate visual cortex (area M in the owl monkey and area PO in the macaque) are part of a network of areas that are concerned with the representation of the visual periphery. These areas are primarily located along the dorsal midline, and can be distinguished in various ways from those areas of the visual system of the monkey that represent the macular region (the central 10 degrees of the visual field). From these and other data[26] emerges a specific hypothesis: activity within the posterior cingulate cortex and adjacent precuneus in the baseline state in humans is associated with the representation (monitoring) of the world around us.

Posterior cingulate and retrosplenial cortex might be involved in emotional processing. Activations in this region were noted in a review of 51 emotion-related studies[29], in which Maddock suggests that these regions might participate in emotional processing as a consequence of their role in episodic memory.

The idea that this area participates in aspects of emotional processing is also supported by observations in the fields of psychology and communication. Images shown on larger screens elicit greater 'attention' and 'arousal', as measured by heart rate and skin conductance, than the same images shown on medium-sized or small screens[30]. Although related functional imaging studies have not been carried out, it is anticipated that larger screens would stimulate the visual periphery and would, therefore, be associated with activity in this area.

So, posterior cingulate cortex and adjacent precuneus might be tonically active regions of the brain that continuously gather information about the world around, and possibly within, us. This seems to be a default activity of the brain with 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 the successful performance of a task demands focused attention should this broad information-gathering activity be curtailed.

Posterior lateral cortices

Task-independent decreases in the posterior lateral cortex occur bilaterally in BRODMANN AREAS (BA) 40 and 39 (parietal lobe), and in BA 22 (temporal lobe) and 19 (occipital lobe)[13,18] in a broad area at the posterior end of the Sylvian fissure and the superior temporal sulcus (FIG. 1). Functional imaging studies in humans and single-unit studies in behaving monkeys provide an interesting perspective on the possible functionality of these decreases.

The functional imaging data can be roughly grouped according to the location of the responses in this region. A more dorsal, right-lateralized group[31,32] identifies an area that responds to targets at unfamiliar or unexpected (invalid) locations, and to novel movement patterns[33]. Single-unit recordings in monkeys are consistent with this formulation, showing enhanced activity with the redirection of attention to stimuli that appear at unattended locations[34,35]. Another functional imaging study[36] indicates that the equivalent area on the left side might be engaged obligatorily or unintentionally in the recall of episodic memory information. The authors make the specific point that this process need not be controlled or driven by current task demands, which is consistent with a baseline or resting-state function. Future research should address the role of the personal saliency of episodic memory information in eliciting such responses.

A more ventral group along the posterior portion of the superior temporal sulcus seems to be concerned with the detection and analysis of biological motion. Stimuli in these functional imaging experiments have consisted of structured, moving-dot patterns[37–39], complex, intentional-movement patterns instantiated in simple geometric shapes[40], complex facial stimuli with moving eyes and mouths (REF. 41; see also REF. 42 for review), and movies of everyday social activities[43]. Like the more dorsal area, this area might also be engaged passively or unintentionally, independent of the demands of the current task[43]. This area can be distinguished from adjacent areas (MT and MST) that seem to be more concerned with non-biological motion[37]. Recordings of single-unit activity in monkey superior temporal sulcus, obtained while the monkey viewed particular whole-body movements (such as walking), revealed similar findings[44].

So, the task-independent decreases in the posterior lateral cortex seem to occur in areas that orient individuals to salient novel[31–33] or familiar[36] stimuli, especially when they contain animate and socially relevant components. We posit that some degree of this activity is continuous in the baseline or resting state. These areas are distinguishable from adjacent areas in parietal lobe that are concerned with shifts of attention and eye movements during goal-directed behaviours. The latter areas seem to be involved mainly in activities in which subjects respond to visual targets at expected locations[45].

The medial and lateral parietal cortices, which participate in the task-independent decreases, also have decreased activity in other settings. For example, under several circumstances in which awareness of the environment is altered, the medial and lateral parietal areas that show task-independent decreases in activity (FIG. 1) seem to be involved (FIG. 3). Maquet and colleagues[46] used PET to show activity reductions in these areas (along with prefrontal areas) during rapid-eye-movement and slow-wave sleep. A PET study with the general anaesthetic propofol[47] complements these studies. Deepening anaesthesia was associated with a progressive reduction in activity, predominantly in the medial parietal area. Finally, patients in a persistent VEGETATIVE STATE show marked reductions in activity in both medial and lateral parietal cortices, portions of which resume their activity if patients recover conscious awareness[48]. Together, these observations indicate that these medial and lateral cortices might participate in conscious awareness in a way that has not yet been defined.

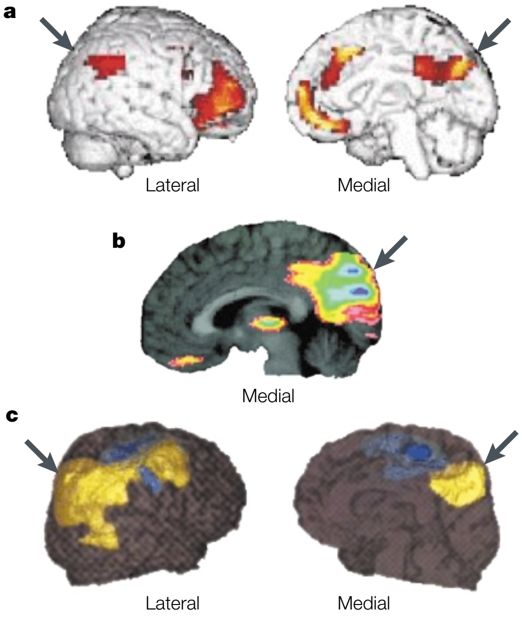


Figure 3 | **Parietal cortices and conscious awareness.** Under several circumstances in which conscious awareness of the environment is altered, the medial and lateral parietal cortices that show task-independent decreases (FIG. 1) seem to be involved. These circumstances include **a** | sleep[46], **b** | general anaesthesia[47] and **c** | recovery from coma associated with the vegetative state[48]. In the case of sleep, the highlighted areas are more active in wakefulness than in either slow-wave or rapid-eye-movement sleep. With general anaesthesia, the highlighted areas were selectively depressed. In the case of recovery from the vegetative state, the yellow areas denote regions that returned towards normal. The blue areas, however, remained decreased in their activity after recovery. Images in **a** reproduced with permission from REF. 46 © 2000 Blackwell Science Ltd; image in **b** reproduced with permission from REF. 47 © 1999 Society for Neuroscience; images in **c** reproduced with permission from REF. 48 © 1999 Journal of Neurology, Neurosurgery & Psychiatry.

Ventral medial prefrontal cortex

Another area of the cortex that shows prominent decreases in activity during a wide variety of goal-directed behaviours is the ventral medial prefrontal cortex (FIG. 1). Anatomically, the ventral prefrontal cortex can be divided into orbital and medial networks. The

BRODMANN AREAS
(BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions based on cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains subdivisions including BA 44, BA 45, BA 47 and others). Modern derivatives of his maps are commonly used as the reference system for discussion of brain-imaging findings.

VEGETATIVE STATE
A disorder of consciousness wherein arousal, sleep–wake cycles, ventilation and autonomic control persist but external awareness, including all cognitive function and emotion, is abolished. It can result from a variety of causes including carbon monoxide intoxication, cardio-respiratory arrest, traumatic head injury and drug overdose.

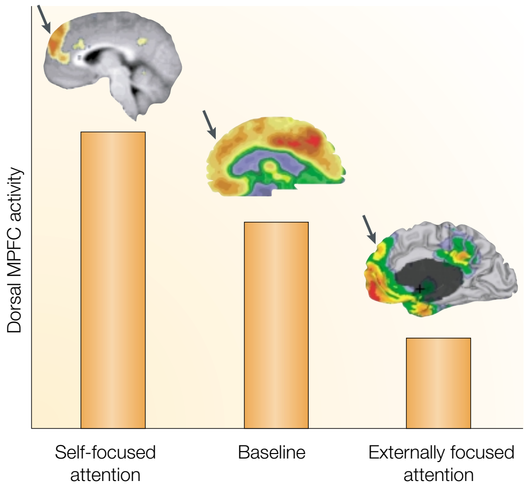


Figure 4 | **Dynamic range of dorsal medial prefrontal cortex activity.** There is evidence for a dynamic functional range in the dorsal medial prefrontal cortex (MPFC), which encompasses increases in tasks that involve self-referential mental activity[40,61] or self-focused attention (left, arrow), and decreases in tasks that involve externally focused attention (right, arrow)[13]. The latter is consistent with the observation that there is an attenuation of self-focused attention during goal-directed behaviours. This indicates that there should be some degree of self-referential mental activity engaging this region at the baseline (middle, arrow). Recent functional imaging data support this suggestion[62].

orbital network is composed of cytoarchitectonically discrete areas that receive a range of sensory information from the body and the external environment[49,50]. This information is relayed to the ventral medial prefrontal cortex through a complex set of interconnections. Areas within the ventral medial prefrontal cortex are also heavily connected to limbic structures, such as the amygdala, ventral striatum, hypothalamus, midbrain periaqueductal grey region and brainstem autonomic nuclei[49,51,52]. Such anatomical relationships indicate that these medial areas might mediate the integration of the visceromotor aspects of emotion with information gathered from the internal and external environments.

Because these anatomical data implicate ventral medial prefrontal cortex in aspects of emotional processing, it has been suggested that decreases in this area during focused attention might reflect a dynamic interplay between continuous cognitive and emotional processes, as shown in many functional imaging studies[53–58]. More specifically, it has been proposed that, in humans, the ventral medial prefrontal cortex might contribute to the integration of emotional and cognitive processes by incorporating emotional biasing signals or markers into decision-making processes[59]. This has been suggested to involve a continuous process of online monitoring of associations between sensory information, responses and outcomes under changing circumstances[60].

Dorsal medial prefrontal cortex

The dorsal medial prefrontal cortex often decreases its activity along with the ventral medial prefrontal cortex during goal-directed activities (FIG. 1). However, its activity can sometimes be dissociated from decreases in ventral medial prefrontal cortex[61]. On some occasions, this occurs as the result of an increase above baseline in its activity. It is instructive to examine the nature of these increases, as they point to the possible functions of this area.

A recent report and review by Castelli and colleagues[40] summarizes many of the functional imaging experiments that have reported increases in activity in dorsal medial prefrontal cortex (BA 8, 9 and 10) and the adjacent paracingulate sulcus. The cognitive processes that are covered fall into two general categories. The first involves monitoring or reporting one's own mental state, such as self-generated thoughts[62], intended speech[63] and emotions[61,64–67]. A second category of experiments that engage this region involves attributing mental states to others[40,68]. On the basis of these imaging results, the Friths[69] have postulated that dorsal "medial prefrontal regions are concerned with explicit representations of states of the self", which we posit are attenuated during (non-self-referential) goal-directed behaviour.

Similar mental activity arises spontaneously when subjects are not actively engaged in goal-directed behaviour. This spontaneous kind of mental activity has been referred to, for example, as "stimulus-independent thoughts" or daydreams[70,71], "task-unrelated imagery and thought"[72] and "free association" or "stream of consciousness"[73]. A recent PET study[62] has associated stimulus-independent thoughts with activity in this dorsal medial prefrontal area. We suggest that this spontaneous activity does not simply represent 'noise'[22,74] but, as Ingvar first proposed[75,76], it might imply a continuous "simulation of behaviour", "an inner rehearsal" and "an optimization of cognitive and behavioural serial programs" for the individual's future, which represents another feature of continuous activity in the baseline or resting state.

So, functional imaging studies indicate that dorsal medial prefrontal cortex is important for spontaneous and task-related self-referential or introspectively oriented mental activity. And, consequently, its dynamic range encompasses both enhanced and attenuated activity (FIG. 4).

Conclusions

Functional brain-imaging studies using PET have provided a means of identifying a physiological baseline level of activity within the human brain. Knowledge of the baseline is of great practical importance in interpreting functional imaging studies with both PET and fMRI. It also emphasizes the functional importance of the passive resting state. The frequently expressed concern that, left unconstrained, brain activity would vary unpredictably, does not apply to the passive resting state of the human brain. Rather, it is intrinsically constrained by the default functionality of the baseline or resting state.

Can we, at present, propose a unifying concept for this default functionality of the baseline? Its functions are spontaneous and virtually continuous, being attenuated only when we engage in goal-directed actions. This is consistent with the continuity of a stable, unified perspective of the organism relative to its environment (a 'self').

This unified perspective is generally under appreciated, because it largely operates in the background, as do many of the functions we review above. However, it is crucial for normal human performance. Its importance is most often recognized when it is impaired by diseases of the brain such as stroke[77] and Alzheimer's disease[78,79].

Future research in functional imaging should consider the need to obtain information about the baseline. Without it, experiments will harbour an unnecessary degree of ambiguity. But the recognition of the baseline or resting state challenges researchers at all levels of neuroscience. Important information regarding the dynamics of neural activity during the resting state will be of vital importance for understanding basic neurophysiological mechanisms that operate in the baseline. This work will require both human and animal experimentation involving the direct recording of neural activity. Likewise, theoretical approaches to understanding these baseline operations and their features (for example, coherence, stability and the significance of 'noise') will probably provide guidelines for research at all levels.

1. Raichle, M. E. Behind the scenes of functional brain imaging: a historical and physiological perspective. *Proc. Natl Acad. Sci. USA* **95**, 765–772 (1998).
2. Raichle, M. E. The neural correlates of consciousness: an analysis of cognitive skill learning. *Phil. Trans. R. Soc. Lond. B* **353**, 1–14 (1998).
3. Schwartz, W. J. *et al.* Metabolic mapping of functional activity in the hypothalamo–neurohypophysial system of the rat. *Science* **205**, 723–725 (1979).
4. Mata, M. *et al.* Activity-dependent energy metabolism in rat posterior pituitary primarily reflects sodium pump activity. *J. Neurochem.* **34**, 213–215 (1980).
References 3 and 4 provide the first evidence that the increased metabolic activity associated with neural activity occurs in nerve terminals (axon terminals and dendrites) rather than cell bodies.
5. Logothetis, N. K., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* **412**, 150–157 (2001).
An important paper showing clearly for the first time the relationship between changes in neural activity (single- and multiple-unit activity and local field potentials) and the signals obtained with fMRI. The study was completed in monkeys, in which simultaneous measurements were carried out with fMRI and indwelling microelectrodes in the visual cortex.
6. Shmuel, A. *et al.* Negative BOLD response and its coupling to the positive response in the human brain. *Neuroimage* **13**, S1005 (2001).
7. Woolsey, T. A. *et al.* Neuronal units linked to microvascular modules in cerebral cortex: response elements for imaging the brain. *Cereb. Cortex* **6**, 647–660 (1996).
8. Sokoloff, L., Mangold, R., Wechsler, R., Kennedy, C. & Kety, S. S. The effect of mental arithmetic on cerebral circulation and metabolism. *J. Clin. Invest.* **34**, 1101–1108 (1955).
An important early paper demonstrating the often-overlooked fact that local changes in functional activity within the human brain, although associated with regionally increased blood flow, are not associated with perceptible changes in global blood flow or metabolism.
9. Heistad, D. D. & Kontos, H. A. in *Handbook of Physiology. The Cardiovascular System* (eds Sheppard, J. T. & Abboud, F. M.) 137–182 (American Physiological Society, Bethesda, Maryland, 1983).
10. Plum, F., Posner, J. B. & Troy, B. Cerebral metabolic and circulatory responses to induced convulsions in animals. *Arch. Neurol.* **18**, 1–13 (1968).
A classic demonstration of the haemodynamic reserve of the brain.
11. Shulman, G. L. *et al.* Top–down modulation of early sensory cortex. *Cereb. Cortex* **7**, 193–206 (1997).
12. Shulman, G. L. *et al.* Common blood flow changes across visual tasks: I. Increases in subcortical structures and cerebellum, but not in non-visual cortex. *J. Cogn. Neurosci.* **9**, 624–647 (1997).
13. Shulman, G. L. *et al.* Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J. Cogn. Neurosci.* **9**, 648–663 (1997).
14. Raichle, M. E. *et al.* A default mode of brain function. *Proc. Natl Acad. Sci. USA* **98**, 676–682 (2001).
This paper presents the PET data that support the use of the oxygen extraction fraction (OEF) in defining the baseline of the human brain.
15. Drevets, W. C. *et al.* Blood flow changes in human somatosensory cortex during anticipated stimulation. *Nature* **373**, 249–252 (1995).
16. Haxby, J. V. *et al.* The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. *J. Neurosci.* **14**, 6336–6353 (1994).
17. Kawashima, R., O'Sullivan, B. T. & Roland, P. E. Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the 'mind's eye'. *Proc. Natl Acad. Sci. USA* **92**, 5969–5972 (1995).
18. Mazoyer, B. *et al.* Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res. Bull.* **54**, 287–298 (2001).
19. Grubb, R. L. J. *et al.* Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *J. Am. Med. Assoc.* **280**, 1055–1060 (1998).
20. Marchal, G. *et al.* PET imaging of cerebral perfusion and oxygen consumption in acute ischaemic stroke: relation to outcome. *Lancet* **341**, 925–927 (1993).
21. Lebrun-Grandie, P. *et al.* Coupling between regional blood flow and oxygen utilization in the normal human brain. *Arch. Neurol.* **40**, 230–236 (1983).
22. Binder, J. R. *et al.* Conceptual processing during the conscious resting state: a functional MRI study. *J. Cogn. Neurosci.* **11**, 80–93 (1999).
23. Clark, D. D. & Sokoloff, L. in *Basic Neurochemistry. Molecular, Cellular and Medical Aspects* (eds Siegel, G. J., Agranoff, B. W., Albers, R. W., Fisher, S. K. & Uhler, M. D.) 637–670 (Lippincott-Raven, Philadelphia, 1999).
24. Astrup, J., Sorensen, P. M. & Sorensen, H. R. Oxygen and glucose consumption related to Na^+–K^+ transport in canine brain. *Stroke* **12**, 726–730 (1981).
25. Harley, C. A. & Bielajew, C. H. A comparison of glycogen phosphorylase α and cytochrome oxidase histochemical staining in rat brain. *J. Comp. Neurol.* **322**, 377–389 (1992).
26. Vogt, B. A., Finch, D. M. & Olson, C. R. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb. Cortex* **2**, 435–443 (1992).
27. Colby, C. L., Gattass, R., Olson, C. R. & Gross, C. G. Topographic organization of cortical afferents to extrastriate visual area PO in the macaque: a dual tracer study. *J. Comp. Neurol.* **238**, 1257–1299 (1988).
28. Baker, J. F., Petersen, S. E., Newsome, W. T. & Allman, J. M. Visual response properties of neurons in four extrastriate visual areas of the owl monkey (*Aotus trivirgatus*): a quantitative comparison of medial, dorsomedial, dorsolateral, and middle temporal areas. *J. Neurophysiol.* **45**, 397–416 (1981).
29. Maddock, R. J. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci.* **22**, 310–316 (1999).
A review of the functional imaging findings that relate emotion to changes in the posterior cingulate cortex, retrosplenial cortex and precuneus.
30. Reeves, B., Lang, A., Kim, E. Y. & Tatar, D. The effects of screen size and message content on attention and arousal. *Media Psychol.* **1**, 49–67 (1999).
31. Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P. & Shulman, G. L. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neurosci.* **3**, 292–297 (2000).
32. Decety, J. *et al.* Brain activity during observation of actions: influence of action content and subject's strategy. *Brain* **120**, 1763–1777 (1997).
33. Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S. J. & Passingham, R. E. Motor sequence learning: a study with positron emission tomography. *J. Neurosci.* **14**, 3775–3790 (1994).
34. Constantinidis, C. & Steinmetz, M. A. Neuronal responses in area 7a to multiple-stimulus displays: I. Neurons encode the location of the salient stimulus. *Cereb. Cortex* **11**, 581–591 (2001).
35. Constantinidis, C. & Steinmetz, M. A. Neuronal responses in area 7a to multiple stimulus displays: II. Responses are suppressed at the cued location. *Cereb. Cortex* **11**, 592–597 (2001).
36. Donaldson, D. I., Petersen, S. E. & Buckner, R. L. Dissociating memory retrieval processes using fMRI: evidence that priming does not support recognition memory. *Neuron* (in the press).
37. Grezes, J. *et al.* Does perception of biological motion rely on specific brain regions? *Neuroimage* **13**, 775–785 (2001).
38. Grossman, E. D. *et al.* Brain areas involved in perception of biological motion. *J. Cogn. Neurosci.* **12**, 711–720 (2000).
39. Grossman, E. D. & Blake, R. Brain activity evoked by inverted and imagined biological motion. *Vision Res.* **41**, 1475–1482 (2001).
40. Castelli, F., Happe, F., Frith, U. & Frith, C. Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. *Neuroimage* **12**, 314–325 (2000).
41. Puce, A., Allison, T., Bentin, S., Gore, J. C. & McCarthy, G. Temporal cortex activation in humans viewing eye and mouth movements. *J. Neurosci.* **18**, 2188–2199 (1998).
42. Allison, T., Puce, A. & McCarthy, G. Social perception from visual cues: role of the STS region. *Trends Cogn. Sci.* **4**, 267–278 (2000).
A useful review, which summarizes human functional imaging data as well as animal experimental work on the involvement of the STS region in social perception.
43. Zacks, J. M. *et al.* Human brain activity time-locked to perceptual event boundaries. *Nature Neurosci.* **4**, 651–655 (2001).
44. Oram, M. W. & Perrett, D. I. Responses of anterior superior temporal polysensory (STPa) neurons to 'biological motion' stimuli. *J. Cogn. Neurosci.* **6**, 99–116 (1994).
45. Corbetta, M. *et al.* A common network of functional areas for attentional and eye movements. *Neuron* **21**, 761–773 (1998).
46. Maquet, P. Functional neuroimaging of normal human sleep by positron emission tomography. *J. Sleep Res.* **9**, 207–231 (2000).
A review of the small, but important, group of functional imaging studies detailing the regional changes in brain activity that are associated with stages of sleep.
47. Fiset, P. *et al.* Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. *J. Neurosci.* **19**, 5506–5513 (1999).
48. Laureys, S., Lemaire, C., Maquet, P., Phillips, C. & Franck, G. Cerebral metabolism during vegetative state and after recovery to consciousness. *J. Neurol. Neurosurg. Psychiatry* **67**, 121–122 (1999).
49. Barbas, H. Anatomic basis of cognitive–emotional interactions in the primate prefrontal cortex. *Neurosci. Biobehav. Rev.* **19**, 499–510 (1995).
50. Ongur, D. & Price, J. L. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex* **10**, 206–219 (2000).
A detailed description of the cytoarchitectonics and connectivity of the orbital and ventral medial prefrontal cortices, which also discusses the significance of these areas in emotional processing.
51. Carmichael, S. T. & Price, J. L. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J. Comp. Neurol.* **363**, 615–641 (1995).
52. Haber, S. N., Kunishio, K., Mizobuchi, M. & Lynd-Balta, E. The orbital and medial prefrontal circuit through the primate basal ganglia. *J. Neurosci.* **15**, 4851–4867 (1995).
53. Drevets, W. C. & Raichle, M. E. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions

between emotion and cognition. *Cogn Emotion* **12**, 353–385 (1998).
References 53 and 55 summarize functional imaging data that characterize the interplay between aspects of cognitive and emotional processing.

54. Mayberg, H. S. Limbic–cortical dysregulation: a proposed model of depression. *J. Neuropsychiatry* **9**, 471–481 (1997).
55. Bush, G., Luu, P. & Posner, M. I. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci.* **4**, 215–222 (2000).
56. Simpson, J. R. Jr *et al.* The emotional modulation of cognitive processing: an fMRI study. *J. Cogn. Neurosci.* **12** (Suppl. 2), 157–170 (2000).
57. Simpson, J. R. J., Drevets, W. C., Snyder, A. Z., Gusnard, D. A. & Raichle, M. E. Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. *Proc. Natl Acad. Sci. USA* **98**, 688–691 (2001).
58. Simpson, J. R. J., Snyder, A. Z., Gusnard, D. A. & Raichle, M. E. Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. *Proc. Natl Acad. Sci. USA* **98**, 683–687 (2001).
59. Bechara, A., Damasio, H., Tranel, D. & Damasio, A. R. Deciding advantageously before knowing the advantageous strategy. *Science* **275**, 1293–1295 (1997).
An interesting experimental approach, which explores the functions of the ventral medial prefrontal cortex in social decision making.
60. Elliott, R., Dolan, R. J. & Frith, C. D. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb. Cortex* **10**, 308–317 (2000).
61. Gusnard, D. A., Akbudak, E., Shulman, G. L. & Raichle, M. E. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl Acad. Sci. USA* **98**, 4259–4264 (2001).
62. McGuire, P. K., Paulesu, E., Frackowiak, R. S. J. & Frith, C. D. Brain activity during stimulus independent thought. *Neuroreport* **7**, 2095–2099 (1996).
63. McGuire, P. K., Silbersweig, D. A. & Frith, C. D. Functional neuroanatomy of verbal self-monitoring. *Brain* **119**, 907–917 (1996).
64. Lane, R. D., Fink, G. R., Chau, P. M. -L. & Dolan, R. J. Neural activation during selective attention to subjective emotional responses. *Neuroreport* **8**, 3969–3972 (1997).
65. Pardo, J. V., Pardo, P. J. & Raichle, M. E. Neural correlates of self-induced dysphoria. *Am. J. Psychiatry* **150**, 713–719 (1993).
66. Reiman, E. M. *et al.* Neuroanatomical correlates of externally and internally generated human emotion. *Am. J. Psychiatry* **154**, 918–925 (1997).
67. George, M. S., Ketter, T. A., Parekh, P. I., Herscovitch, P. & Post, R. M. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biol. Psychiatry* **40**, 859–871 (1996).
68. Goel, V., Grafman, J., Tajik, J., Gana, S. & Danto, D. Modelling other minds. *Brain* **120**, 1805–1822 (1998).
69. Frith, C. D. & Frith, U. Interacting minds — a biological basis. *Science* **286**, 1692–1695 (1999).
An important synthesis of functional imaging experiments related to the topic of mentalizing, and the roles of the medial prefrontal cortex and STS in this process.
70. Antrobus, J. S. & Singer, J. L. Mindwandering and cognitive structure. *Trans. NY Acad. Sci.* **32**, 242–252 (1970).
71. Teasdale, J. D. *et al.* Stimulus-independent thought depends on central executive resources. *Mem. Cogn* **23**, 551–559 (1995).
72. Giambra, L. M. A laboratory method for investigating influences on switching attention to task-unrelated imagery and thought. *Conscious. Cogn* **4**, 1–21 (1995).
73. Andreasen, N. C. *et al.* Remembering the past: two facets of episodic memory explored with positron emission tomography. *Am. J. Psychiatry* **152**, 1576–1585 (1995).
74. Christoff, K. & Gabrieli, J. D. E. The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology* **28**, 168–186 (2000).
75. Ingvar, D. H. Memory of the future: an essay on the temporal organization of conscious awareness. *Hum. Neurobiol.* **4**, 127–136 (1985).
76. Ingvar, D. H. in *Brain Work and Mental Activity* (eds Lassen, N. A., Ingvar, D. H., Raichle, M. E. & Friberg, L.) 346–359 (Munksgaard, Copenhagen, 1991).
References 75 and 76 are two early papers by one of the pioneers in functional brain imaging, whose insights anticipated much of the rationale underlying the concept of the baseline or resting state.
77. Feinberg, T. Some interesting perturbations of the self in neurology. *Semin. Neurol.* **17**, 129–135 (1997).
78. Damasio, A. R. *The Feeling of What Happens: Body and Emotion in the Making of Consciousness* (Harcourt Brace, New York, 1999).
79. Reiman, E. M. *et al.* Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N. Engl. J. Med.* **334**, 752–758 (1996).
This study presents a demonstration of the location of early metabolic changes in Alzheimer's disease, predominantly in the posterior medial and lateral parietal cortices, which coincide remarkably with areas that show task-independent decreases in functional imaging studies (figure 1).
80. VanEssen, D. C. & Drury, H. A. Structural and functional analyses of human cerebral cortex using a surface-based atlas. *J. Neurosci.* **17**, 7079–7102 (1997).
81. Drevets, W. C. *et al.* Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **386**, 824–827 (1997).
82. Reivich, M. *et al.* The $[^{18}\text{F}]$fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ. Res.* **44**, 127–137 (1979).
83. Talairach, J. & Tournoux, P. *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme Medical, New York, 1988).
84. Mintun, M. A., Raichle, M. E., Martin, W. R. & Herscovitch, P. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J. Nucl. Med.* **25**, 177–187 (1984).
85. Ackerman, R. F., Finch, D. M., Babb, T. L. & Engel, J. J. Increased glucose utilization during long-duration recurrent inhibition of hippocampal pyramidal cells. *J. Neurosci.* **4**, 251–264 (1984).
86. Batini, C., Benedetti, F., Buisseret-Delmas, C., Montarolo, P. G. & Strata, P. Metabolic activity of intracerebellar nuclei in the rat: effects of inferior olive inactivation. *Exp. Brain Res.* **54**, 259–265 (1984).
References 85 and 86 are important experiments that characterize the spectrum of our current understanding of the metabolic changes associated with increased inhibitory activity in the cerebral cortex of man and experimental animals. These two papers also show the limitations of this current understanding.
87. Magistretti, P. J., Pellerin, L., Rothman, D. L. & Shulman, R. G. Energy on demand. *Science* **283**, 496–497 (1999).
88. Shulman, R. G., Hyder, F. & Rothman, D. L. Cerebral energetics and the glycogen shunt: neurochemical basis of functional imaging. *Proc. Natl Acad. Sci. USA* **98**, 6417–6422 (2001).
References 87 and 88 provide an up-to-date synthesis of our current understanding of the cellular metabolic changes underlying the fMRI BOLD signal.

Acknowledgements

The National Institutes of Health and the Charles A. Dana Foundation supported this work.

Online links

DATABASES

The following terms in this article are linked online to:

Medscape DrugInfo:
http://promini.medscape.com/drugdb/search.asp
propofol
MIT Encyclopedia of Cognitive Sciences:
http://cognet.mit.edu/MITECS/
magnetic resonance imaging | positron emission tomography
OMIM:
http://www.ncbi.nlm.nih.gov/Omim/
Alzheimer's disease