

Functional neuroimaging of normal human sleep by positron emission tomography

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SUMMARY Functional neuroimaging using positron emission tomography has recently yielded original data on the functional neuroanatomy of human sleep. This paper attempts to describe the possibilities and limitations of the technique and clarify its usefulness in sleep research. A short overview of the methods of acquisition and statistical analysis (statistical parametric mapping, SPM) is presented before the results of PET sleep studies are reviewed. The discussion attempts to integrate the functional neuroimaging data into the body of knowledge already acquired on sleep in animals and humans using various other techniques (intracellular recordings, *in situ* neurophysiology, lesional and pharmacological trials, scalp EEG recordings, behavioural or psychological description). The published PET data describe a very reproducible functional neuroanatomy in sleep. The core characteristics of this ‘canonical’ sleep may be summarized as follows. In slow-wave sleep, most deactivated areas are located in the dorsal pons and mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain/hypothalamus, prefrontal cortex, anterior cingulate cortex, precuneus and in the mesial aspect of the temporal lobe. During rapid-eye movement sleep, significant activations were found in the pontine tegmentum, thalamic nuclei, limbic areas (amygdaloid complexes, hippocampal formation, anterior cingulate cortex) and in the posterior cortices (temporo-occipital areas). In contrast, the dorso-lateral prefrontal cortex, parietal cortex, as well as the posterior cingulate cortex and precuneus, were the least active brain regions. These preliminary studies open up a whole field in sleep research. More detailed explorations of sleep in humans are now accessible to experimental challenges using PET and other neuroimaging techniques. These new methods will contribute to a better understanding of sleep functions.

INTRODUCTION

Brain function may be investigated at various levels of description, from molecular interactions to the behaviour of organisms (Churchland and Sejnowski 1992). Functional neuroimaging studies describe cerebral function at the systems level, showing macroscopic interactions of brain areas engaged in sensory, motor or cognitive tasks (Frackowiak *et al.* 1997). In the description of the cerebral processes, they act as an interesting link between the cellular level and psychological observation. As such, they are thus likely to provide an original description of brain function.

Several neuroimaging techniques are now available to explore brain dynamics in humans: electroencephalography (EEG), magnetoencephalography (MEG), near infrared spectroscopy (NIRS), single photon emission tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Each of these techniques is based on a particular signal and has its own advantages and disadvantages, in terms of spatial and temporal resolution, safety and cost (Toga and Mazziotta 1996). Most of them have now been successfully applied to sleep studies and have provided valuable contributions to this field. Coverage of all these data is beyond the scope of this review. This paper is devoted mainly to recent advances made by PET in the understanding of human sleep. Indeed, a wealth of data has recently been published in this field. PET has benefited from two technological advances: the iterative

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$H_2^{15}O$ scan technique and statistical parametric mapping (SPM). These methods have allowed the exploration of regional cerebral haemodynamics with a good localizing power. It appeared timely to present an overview of the methodological aspects of these techniques and the results obtained in sleep.

This paper is written for sleep researchers not involved in functional neuroimaging and consists of three main sections. In the methodology section, we present a short description of neuroimaging with PET, $H_2^{15}O$ scans and SPM. We also examine whether cerebral blood flow (CBF) can still be considered a marker of neuronal activity during sleep. These technical discussions expose the validity of PET neuroimaging in sleep as well as several technical points discussed recurrently in the published PET sleep data. The second section reviews the results obtained in wakefulness, slow-wave sleep (SWS) and rapid eye movement (REM) sleep. A short note on dreaming processes is also proposed. The last section presents future development of human sleep neuroimaging, in particular with the advent of fMRI and multimodal coregistrations.

METHODOLOGICAL ASPECTS

The $H_2^{15}O$ paradigm

Activation studies with PET usually imply that multiple CBF measurements are made in the same subject under various conditions, and that several subjects are studied in the same protocol. It is comparison of the blood flow distributions observed in the various conditions or their correlation with a physiological parameter, that provides the localization of activated cerebral areas, suspected to be involved in the sensory, motor or cognitive process explored by the experimental protocol.

CBF is estimated by administering oxygen-15 labelled compounds (water or butanol). The very short half-life of oxygen-15 (123 s) has several advantages. First, as radioactivity becomes negligible after four or five half-lives, the scans can be repeated at 8–10-min intervals and multiple CBF measurements can be obtained within the same experimental session. Routine activation studies consist of four to 12 injections per subject. Second, $H_2^{15}O$ is distributed quickly in the body, in proportion to local blood flow. CBF measurements can thus be made on a timescale ranging from 40 s to 2 min.

If an arterial line is put into the radial artery, arterial blood samples can be obtained during scanning and quantitative values of CBF can be computed, otherwise statistical analysis is based on 'tomographic counts', i.e. the estimated number of disintegrations computed at each voxel.

Some activation studies are based on glucose metabolism. This requires the use of [^{18}F]fluorodeoxyglucose. Fluorine-18 has a longer half life (110 min). Consequently, this compound is less suitable for functional neuroimaging studies, the different scans being necessarily obtained in the same subject on different days.

Cerebral blood flow as a marker of neuronal activity during sleep

Activation studies based on CBF measurements rely on the physiological observation that '...the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity' (Roy and Sherrington 1890). In other words, CBF is used as a marker of neuronal activity.

Here, we show that:

- 1 The activity of local neuronal populations can be traced by regional CBF changes. This assumption is valid although there is a transient uncoupling between oxygen metabolism and regional cerebral blood flow (rCBF) during cerebral activation.
- 2 During sleep, this assumption remains also true.
- 3 The influence of a potential neurogenic tone on rCBF, although possible, is probably negligible. This is also true in sleep.

The precise mechanisms of the haemodynamic response to local neuronal activity are not yet known in every detail. Post-synaptic potentials and action potentials cause ion movement across neuronal membranes which, in turn, induce an increase in metabolism of local neuronal and glial populations (Magistretti and Pellerin 1996a,b). During this metabolic response, several compounds, which mediate the vasodilatory haemodynamic response in the surrounding microcirculation, are produced. The principal vectors of this vascular response are K^+ ions (Paulson and Newmann 1987; Kuchinsky 1997), H^+ ions (Kuchinsky 1997), nitric oxide (NO; Northington *et al.* 1992; Dirnagl *et al.* 1993) and adenosine (Ko *et al.* 1990; Dirnagl *et al.* 1993), although peptides (Edvinsson 1985), prostaglandins (PG; Leffler *et al.* 1993) and kinins (Itakura and Okuno 1993) have also been implicated in these processes. These events occur near the synapses and a number of arguments suggest that regional CBF primarily reflects local synaptic activity (Jueptner and Weiller 1995). On top of these local processes, CBF is also regulated by general factors such as perfusion pressure (autoregulation; Paulson *et al.* 1990), PCO_2 and PO_2 and possibly a neurogenic tone (Lou *et al.* 1987). A local static factor such as capillary density is also functionally related to rCBF: the higher the capillary density, the higher the rCBF (Klein *et al.* 1986; Borowsky and Collins 1989; Kuchinsky 1997).

During cerebral activation, there is a transient uncoupling between the local metabolic rates for oxygen ($CMRO_2$) and rCBF. Although the time courses of these events are still being debated, they can be summarized as follows. When a local neuronal population is firing, the local need for oxygen increases abruptly. The content in deoxy-haemoglobin in the local vasculature increases quickly, during the first hundreds of milliseconds after the activation. This was observed using both optical spectroscopy (Malonek and Grinvald 1996) and magnetic resonance imaging (MRI; Ernst and Hennig 1994). After a very short time, the local CBF increases in response to the neuronal activation. The rCBF increases out of proportion with the local metabolic needs and the local content of

deoxy-haemoglobin actually decreases. As deoxy-haemoglobin is paramagnetic, its decrease can be detected in MRI and this is actually at the origin of the blood oxygen level dependent (BOLD) signal, largely used in functional MRI. Despite this uncoupling between rCBF and oxygen metabolic rates, it should be borne in mind that the vascular changes still localize precisely the cerebral regions at work. They thus can be used reliably in functional neuroimaging.

Little data exist about the metabolic CBF regulation *during sleep* but it is likely that in this condition, rCBF also remains a marker of synaptic activity. The basic mechanisms of CBF regulation investigated to date persist during sleep. The microcirculation does not seem to be modified by sleep. As during wakefulness (Göbel *et al.* 1990; Kuchinsky and Paulson 1992; Villringer *et al.* 1994), all capillaries remain open during sleep in rats (Zoccoli *et al.* 1996). Likewise, it was recently shown in lambs that autoregulation persists during SWS and REM sleep (Grant *et al.* 1998). In sleep, as during wakefulness, acute decreases in cerebral perfusion (by inflating a cuff around the brachiocephalic artery) cause a decrease in cerebral vascular resistance in such a way that CBF returns to normal control values after a few tens of seconds. Although the response and its time course is quantitatively different in active sleep than in quiet sleep or in wakefulness, these results provide clear evidence that the vasoactive mechanisms underlying cerebral autoregulation persist in sleep. Finally, the available data seem to show the persistence of a close relationship between local metabolic needs and rCBF. In goats, global levels of CBF parallel cerebral oxygen consumption, although during REM sleep, the increase in oxygen consumption alone cannot account for the increase in CBF (Santiago *et al.* 1984). In humans, cerebral metabolic rates for oxygen (CMRO₂) and CBF also vary in parallel (Madsen *et al.* 1991b, c; Hoshi *et al.* 1994). The only discrepant data were obtained by NIRS and suggest that *at sleep onset* and only in certain subjects, CBF might decrease while CMRO₂ increases in frontal areas (Hoshi *et al.* 1994). These results must be treated with caution given the great interindividual, intra-individual and spatial variability of metabolic patterns during sleep as well as possible artefacts arising from skin blood volume (Ogata *et al.* 1998; Yamamoto *et al.* 1998).

At the regional level, at this point, it seems reasonable to suggest that, qualitatively, CBF regulation during sleep relies on the same mechanisms as during wakefulness. There might be quantitative differences with waking CBF regulation. For example, in lambs, NO has a major influence on CBF during sleep as well as during wakefulness and its effects seem quantitatively different depending on sleep stage (Zoccoli *et al.* 1998). Likewise, local levels of adenosine are lower during sleep than during wakefulness (Porkka-Heiskanen *et al.* 1997) and might modulate local blood flow differently in sleep. Despite these possible quantitative changes, it remains that modifications in local CBF reflect variations in neural activity.

Although metabolic needs are the major parameter modulating regional vascular supply, the role of neurogenic control has been evoked recurrently. Various arguments have been put

forward to suggest regulation of CBF by direct influences from neural structures. For some authors, the local vasodilatation occurring in an activated area was too quick to be accounted for by metabolic factors and this suggested a direct neural influence on cerebral vessels (Lou *et al.* 1987). However, since the hypothesis was proposed, several humoral compounds have been found which could explain this rapid vascular response: NO, PG, K⁺. Another argument, which was thought to suggest neural control of brain vessels, is the uncoupling between the increase in CBF and oxygen consumption in an activated cerebral area (Lou *et al.* 1987). However, although not completely understood, this phenomenon might, at least in part, rely on metabolic factors (Magistretti and Pellerin 1996a, b).

The most intriguing finding suggesting neurogenic control of local CBF is the presence of nerve fibres in the vicinity of cerebral vessels (Iwayama *et al.* 1970; Edvinsson *et al.* 1972). This innervation is both of extrinsic (ortho- and para-sympathetic) and intrinsic (intracerebral) origin (Pinard 1991). Several brain structures have been shown to have remote vasomotor actions: locus coeruleus (LC), raphe nucleus (RN), basal forebrain (BF), intralaminar thalamic nuclei, parabrachial nucleus, bulbar reticular formation, nucleus of tractus solitarius and fastigial nucleus of the cerebellum (Busija 1993).

In theory, one could imagine a situation in which, because of the neurogenic tone, an increase in rCBF would occur without any change in local metabolism. Such a situation would lead to the detection of spurious cerebral activation by functional neuroimaging. However, it should be stressed that neurogenic CBF control was observed under very unnatural conditions, using stimulations or lesions formed by electrical or chemical means in anaesthetized animal preparations. Their role under physiological circumstances is suspected but remains unclear. Furthermore, possible neurogenic CBF control would alter PET data under only three conditions. First, CBF modifications due to neural mechanisms should be systematic; they should occur in every subject under particular conditions (as it is, stage of sleep), or at least in a vast majority. If this was not the case, i.e. if the neurogenic control is not systematic, group analysis would average them out. Second, CBF modifications due to neural control should be prolonged. In PET, the cerebral activity is integrated over 40–120 s. Transient vasomotor reactions are unlikely to be detected by PET. They might, however, affect fMRI data. Third, CBF variations due to neural control should not be accompanied by modifications in regional metabolism. Indeed, if local metabolism changed simultaneously, the rCBF signal would still reflect modifications of neuronal activity. For these reasons, the effects of neurogenic tone are usually considered negligible during wakefulness and are not a general concern for functional neuroimaging with PET.

As far as sleep studies are concerned, some of the structures mentioned above are involved in both sleep and rCBF regulation. They both modify their activity throughout the sleep/waking cycle and, under the unnatural experimental conditions described above, have some vasoactive actions. It is

thus interesting to examine whether this can explain some variations of regional cerebral blood flow during sleep. In the following, we concentrate on four nuclei: locus coeruleus (LC), raphé nuclei (RN), basal forebrain (BF) and intralaminar thalamic nuclei.

The role of LC in CBF regulation under physiological conditions remains to be established. LC stimulation was shown to decrease CBF, together with cerebral metabolism (Raichle *et al.* 1975; Abraham *et al.* 1979; Goadsby *et al.* 1982; Buchweitz *et al.* 1985), whereas LC lesions by electrolysis or 6-hydroxydopamine have provided controversial results: an increase in CBF (Bates *et al.* 1977) or the absence of any CBF change (Dahlgren *et al.* 1981b; Reddy *et al.* 1986).

Results concerning the vasomotor influence of RN are also controversial. Lesions of RN do not dramatically modify CBF (Dahlgren *et al.* 1981; McBean *et al.* 1990; Underwood *et al.* 1992; Kelly *et al.* 1995) or cerebral glucose metabolism (Cudennec *et al.* 1988; Pappius *et al.* 1988; McBean *et al.* 1990; Kelly *et al.* 1995). Electrical or chemical stimulation of RN does not have univocal effects on CBF: some authors reported an increase in CBF (Goadsby *et al.* 1985a, b; Bonvento *et al.* 1989; Cudennec *et al.* 1993), others observed a decrease in CBF (Underwood *et al.* 1992). The stimulation site seems to be of critical importance: stimulation of ventrolateral RN decreases blood flow while a CBF increase is observed with more caudal stimulations (Underwood *et al.* 1992). In any case, the RN stimulation also causes glucose metabolism increases in various parts of the brain (Cohen *et al.* 1996): manipulations of the 5-HT system actually seem to modify the regression slope between CBF and CMRGlu. Under these conditions, CBF remains a marker of neuronal activity.

Stimulations of BF increase the cortical acetylcholine level (Casamenti *et al.* 1986; Kurosawa *et al.* 1989). Both electrical and chemical BF stimulations cause an ipsilateral increase in cortical blood flow (Biesold *et al.* 1989; Lacombe *et al.* 1989; Adachi *et al.* 1990). The effects predominate on frontal and parietal cortices and are attenuated by muscarinic and nicotinic antagonists. The increase in CBF would not be paralleled by similar changes in cerebral metabolism (Hallström *et al.* 1990; Kimura *et al.* 1990). The effects of BF lesions are controversial. Some authors report a decrease in both CBF and glucose metabolism (Iadecola *et al.* 1983; Orzi *et al.* 1988; Kiyosawa *et al.* 1989; Gomi *et al.* 1991), others do not observe any significant change (Lamarca and Fibiger 1984; Namba *et al.* 1991; Scremin *et al.* 1991). We cannot rule out that, under conditions of high BF activity (wakefulness, REM sleep), an increase in frontal or parietal CBF would be partly due to the intervention of a BF vasomotor effect.

The electrical stimulation of centromedian and parafascicular nuclei of the intralaminar thalamus causes an increase in CBF but not in glucose metabolism (Mraovitch *et al.* 1986; Mraovitch and Seylaz 1987). The changes predominate over the frontal and cingulate cortex, as well as the subthalamic area. Further studies should complement these findings: chemical rather than electrical stimulation as well as lesion studies would confirm or infirm the vasomotor role of these intralaminar

thalamic nuclei. At present, there remains the possibility that frontal and cingulate activations may, in part, be explained by these vascular effects, at least in wakefulness and REM sleep.

Consequently, the available evidence does not lend much support to a significant influence of LC and RN on functional neuroimaging data. There remains the possibility that BF and intralaminar thalamic activity could modify cortical blood flow, especially in frontal regions. The relative importance of these effects, with regard to the CBF regulation by local neuro-glial metabolism remains unknown.

Finally, it should be stressed that, *in the specific context of sleep*, neurogenic control of hypothalamic CBF was suspected in cats. At the beginning of REM sleep episodes, caudate temperature was found to increase while local CBF decreased. After a lesion in the posterior hypothalamus, the decrease in CBF was suppressed, while temperature did not increase further or even decreased. These data were interpreted as reflecting the effects of neurogenic CBF regulation by the posterior hypothalamus (Denoyer *et al.* 1991).

Statistical parametric mapping

Statistical parametric mapping is a statistical process which tests hypotheses about regionally specific effects. The results are presented as statistical maps where voxel values reflect the probability of change in rCBF. Under the null hypothesis, these voxel values are distributed according to a known probability density function (e.g. Gaussian). 'Unlikely' voxel values are interpreted as due to a significant, regionally specific effect attributed to the sensory, motor or cognitive aspects of the experimental protocol.

The most widely used software for statistical parametric mapping is itself known as SPM (statistical parametric mapping). While SPM is now the standard method in functional neuroimaging, it should be emphasized that other methods do exist. They are usually based on similar premises and are not discussed here. A detailed account of statistical parametric mapping can be found in Frackowiak *et al.* (1997). In this section, we summarize the main steps of the analysis of PET activation studies. We stress some points that have been source of discussion in recent sleep studies.

The characterization of brain mapping data essentially relies on two basic principles of brain organization: segregation and integration. Functional segregation pertains to the specialization of certain brain areas for some functions. For instance, Broca's and Wernicke's areas are known to participate in language. In contrast, functional integration reflects how different regions interact to mediate a function. A comprehensive understanding of brain function needs the exploration of both cerebral specialization and connectivity. Examples of each type of contribution in sleep are provided below.

Methods

In SPM, the data analysis proceeds in three steps: spatial transformation, statistical modelling and assessment of significance. In the following, each step is described briefly.

Spatial transformations. Before embarking on a statistical comparison of a particular voxel under the different experimental conditions, spatial transformations are necessary (Friston *et al.* 1995a). Intuitively, one has to ensure that a particular voxel represents the same brain area in all the scans of the same subjects and in the different experimental subjects. Three types of spatial transformation are usually considered: realignment, spatial normalization and coregistration. Realignment of the various scans of the same subject corrects for the subject's head movement during the experimental session (during night in sleep studies). These intramodal intra-individual spatial transformations are based on a 'rigid body' modification of the images. These simple translations and rotations bring all the scans from one subject into register. The second transformation consists of normalizing the individual data into a standard 'stereotaxic' space. The most widely used space is that described by Talairach and Tournoux (1988). This step is mandatory in the analysis of a group of subjects, because of individual differences in brain size and shape. This interindividual intramodal spatial transformation implies not only translations and rotations, but also other linear (scaling, sheering) and nonlinear deformations. These image transformations are not intended to obtain a point-to-point matching of individual brains to a standard brain but allow group analysis and facilitate the communication between laboratories. However, this standard space has several limitations. Talairach's atlas is based on a single hemisphere and does not take into account the interhemispheric asymmetries, or the known interindividual variability of brain anatomy. Furthermore, the localization proposed by Talairach's atlas in certain regions (vermis, medial aspects of occipital and temporal lobes, etc.) may not match exactly the individual anatomy (as estimated by the subject's MRI data). Another spatial transformation consists in coregistering the subject's PET data and his/her structural MRI scan. This (intra-individual intermodal) step increases the localizing power of the analysis. Finally, images are smoothed by a Gaussian kernel in order to increase the signal-to-noise ratio.

Statistical modelling. The second step of the SPM analysis models the data at each and every voxel, using the general linear model (Friston *et al.* 1995b), in terms of the estimates of the model parameters. It partitions the measured responses into various components, including the effects of interest and those of confounding factors. One of these confounding factors is the global flow (discussed later). The difference in parameter estimates (e.g. the treatment effects) are assessed using linear contrasts, leading to a t or a Z statistic. In the most simple case, a contrast is a vector as $[-1 \ 1]$, which simply subtracts the mean observed during the first condition from the mean during the second one. This step provides a first set of significant voxels, before correction for multiple comparisons is applied. The probability level usually used with this first step has been empirically chosen at $P \leq 0.001$ (uncorrected), which corresponds to $Z \geq 3.09$. This first level of inference may

be used in hypothesis-led analysis but should be avoided in exploratory investigations.

Assessment of significance. The final step of statistical inferences takes into account the multiple comparisons that have been made (Friston *et al.* 1991a, 1994). In a typical SPM, several hundred thousand voxels are tested. Consequently, even at a threshold of $P = 0.001$, there should be several hundred voxels exceeding the threshold by chance only. A Bonferroni correction would obviously be too conservative and no significant results could survive such a correction. Furthermore, a Bonferroni correction would consider that voxels are independent while in fact, they are not; the image reconstruction process, and the smoothing performed during the analysis, render adjacent voxels highly correlated. So a procedure was developed, based on the theory of Gaussian random fields, which takes into account the smoothing of the image and corrects the multiple comparisons on the basis of independent elements of the images, the RESELS (resolution elements). Use of the random fields theory puts some constraints on the SPM structure, which should be a good representation of a continuous stationary Gaussian random field. These results are usually reported as significant at 'corrected' P -levels ($P < 0.05$).

Application of SPM in sleep

The use of SPM in sleep studies highlights three issues: head movements during sleep, quantification of CBF values and the choice of contrasts.

Head movements. Head movements are not a greater problem in sleep studies than in studies conducted during wakefulness. However, the experimental session in sleep studies is inevitably longer than in usual daytime protocols, since the subjects have to stay ≈ 8 h in the scanner. The longer the session, the higher the probability of head movements in the scanner. Although head movements are reduced by sleep per se, some movements may be observed at sleep onset or awakening. If these movements are large, attenuation correction is no longer correct. [Attenuation of photons emitted by the object (i.e. the subject's head) causes an underestimation of the true local isotope concentration, especially in the areas situated deep in the object. Correction for this attenuation is usually based on a measure of the density of the head structures by a 'transmission' scan. In this scan, rod sources filled with a positron emitter (usually germanium) turn around the object.] Of course, the correction of the attenuation is valid only if transmission and functional ('emission') scans are in register. Some authors correct for movement between transmission and emission scans (Andersson *et al.* 1998). Furthermore, head movements make heavy corrections necessary during realignment. As a rule of thumb, we discard data from subjects who moved more than the original voxel size (i.e. ≈ 4 mm).

CBF quantification. A debated question is whether CBF should be quantified during PET sleep studies. There is no

univocal answer to this question and the methodology should be adapted to each experimental situation. PET studies may answer two main questions: (i) 'Are there global CBF modifications across states of vigilance (W, SWS, REMS)?'; and (ii) 'Within a specific state, what is the regional distribution of brain activity (i.e. CBF)?'.

There is no doubt that to answer the first question requires CBF quantification. Global CBF modifications are reported by many authors, using various techniques and in different species. Detailed reviews cover these data and summarize their results (Madsen and Vorstrup 1991; Franzini 1992). Briefly, these data show that CBF in REMS is systematically higher than in SWS (Goas *et al.* 1969; Lecas and Bloch 1969; Tachibana 1969; Seylaz *et al.* 1975; Dufour and Court 1977; Milligan 1979; Mukhtar *et al.* 1982; Richardson *et al.* 1985, 1994; Lenzi *et al.* 1987; Meyer *et al.* 1987; Parisi *et al.* 1988; Abrams *et al.* 1990; Zoccoli *et al.* 1993, 1994; Gerashchenko and Matsumura 1996), similar or slightly elevated as compared to W (Kanzow *et al.* 1962; Reivich *et al.* 1968; Townsend *et al.* 1973; Shapiro and Rosendorff 1975; Sakai *et al.* 1980; Santiago *et al.* 1984; Lenzi *et al.* 1986, 1987; Parisi *et al.* 1988; Cote and Haddad 1990; Madsen *et al.* 1991a). Various results are observed during SWS: compared with W, decreases (Townsend *et al.* 1973; Sakai *et al.* 1980; Greisen *et al.* 1985; Meyer *et al.* 1987; Madsen *et al.* 1991a, b; Gerashchenko and Matsumura 1996), increases (Reivich *et al.* 1968; Goas *et al.* 1969; Seylaz *et al.* 1975; Shapiro and Rosendorff 1975) or no change in CBF (Mangold *et al.* 1955; Santiago *et al.* 1984; Lenzi *et al.* 1986, 1987; Parisi *et al.* 1988; Cote and Haddad 1990; Zoccoli *et al.* 1994) are reported. The reasons for these discrepancies remain unclear. The diversity of species investigated and the techniques used are certainly part of the answer. However, other factors are less understood, such as the intriguing possibility of sleep-independent across-night CBF decreases (Hajak *et al.* 1994) or the possible confounding effect of circadian rhythms, which may also be involved. A better knowledge of CBF regulation during sleep is certainly needed at this stage. The measures of global CBF would certainly help in this endeavour.

In contrast, when the *regional distribution* of cerebral blood flow is considered, there seem to be several advantages to the use of raw images (in 'tomographic counts') rather than quantitative CBF images. The main drawback of quantitative CBF studies is that arterial sampling is needed. Usually, subjects are catheterized in one arm for venous infusions and in the other with the arterial line. This position is particularly uncomfortable, especially after several hours of immobility. This severely limits the possibility of observations during a whole night. In contrast, when limiting the analysis to raw images, no arterial line is needed and sleep stability is greatly improved: up to 12 scans may be regularly obtained per subject and per night. This increases the statistical power, by improving the estimation of variance and the assessment of significance [see above and (Frackowiak *et al.* 1997)].

There are also some theoretical considerations that make quantitative CBF data more delicate than raw images for use

with statistical parametric mapping. First, raw images seem particularly suited to SPM. They are created by convolutions of Poisson distributions and by the central limit theorem, voxel values are distributed according to a normal distribution. Second, it is often argued that variations in P_{CO_2} occur during sleep (Sullivan 1980) and that this may change CBF and SPM results. However this possibility seems unlikely, P_{CO_2} changes do not seem to modify the regional CBF distribution (Ramsay *et al.* 1993). Consequently, it is unlikely that P_{CO_2} modifications during sleep could bias the SPM results. Third, raw data images are less prone to condition-dependent global activity changes. Global flow is a confounding factor that masks the regional CBF variations for which SPM is looking. SPM adjusts the regional CBF for possible modifications in global CBF. This can be done either by proportional scaling or by an ANCOVA (global CBF being the confounding covariate; Friston *et al.* 1990). The adjustments may cause some trouble if global CBF changes do actually depend on experimental conditions.

Indeed, if the adjustment is made outside the range of observed values (Fig. 1), one can falsely detect a significant activation (deactivation) in the case of decreased (increased) global flow. Under the same conditions, one may miss a true activation (deactivation) if global CBF increases (decreases). In general, one should be cautious in discussing significant activation when there may be a global flow decrease (e.g. SWS) or significant deactivation in conditions with high global CBF (e.g. REM sleep). Because raw data voxel values depend not only on CBF, but also on P_{CO_2} and on the injected dose, their variance is usually greater but they are less dependent on the vigilance state. In this sense, they are more appropriate than quantitative CBF images in which global flows are likely to depend on the vigilance state. As a rule of thumb, we check scan total counts to ensure the absence of condition-dependent global flow changes before proceeding to the SPM analysis. In sum, to describe global changes in CBF, quantitative CBF measurements are mandatory. To determine rCBF distribution, both quantitative and qualitative CBF measurements may be included in the SPM. In this context, quantitative CBF values are more difficult to obtain and, in theory, more delicate to use in the SPM.

The contrasts. Statistical maps cannot be interpreted without taking into account the contrasts used to create them. It should be clear that no one contrast is right or wrong. Each answers a slightly different question. Thus, it is necessary bear in mind the contrast used in order to interpret each statistical map. In the discussion of the sleep results (see below), the reader should refer to the tables in which the contrasts are specified for each study.

In the case in which one wants to compare the CBF distribution in various states of vigilance (SWS, REM sleep and wakefulness, for instance), the analysis relies on categorical comparisons. The most direct contrast that comes to mind is to compare one particular sleep state with wakefulness. However, it should be borne in mind that wakefulness has its

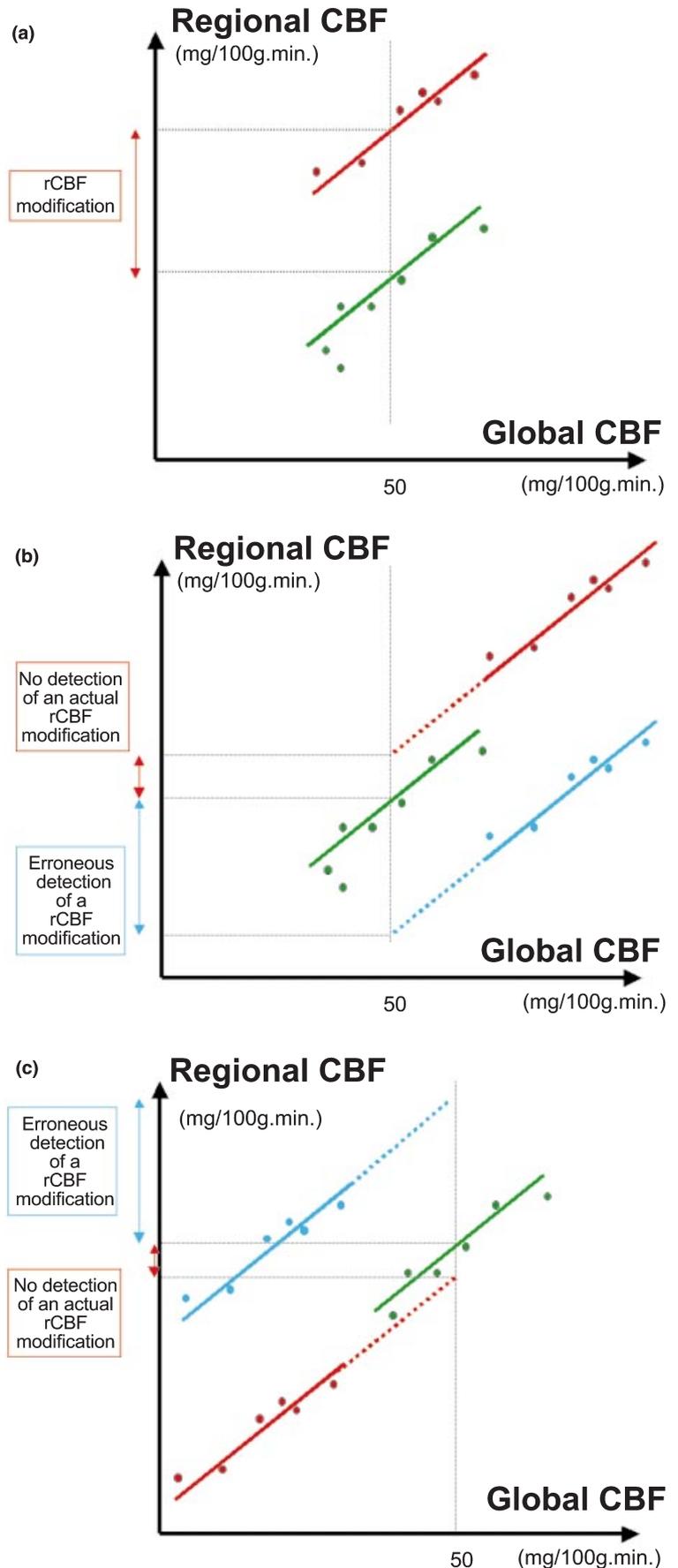


Figure 1. Effects of condition-dependent global flow changes on the estimation of regional activity by ANCOVA. Cerebral blood flow (CBF) observed during the control condition (e.g. rest) is given in green; the experimental condition, CBF observed in a brain region, the activity of which is not altered by the task is given in blue; the experimental condition, CBF observed in a brain region, the activity of which is modified by the task is given in red. (a) A simple situation in which there is no modification of global CBF. The regional increase in rCBF is measured on the axis of the ordinates (red arrow) (Friston *et al.* 1990). (b) Effects of increased global CBF in the experimental condition. In addition to a genuine local increase in rCBF (red regression), there is an increase in global flow (rightward shift). This causes an underestimation of the activation (red arrow). In contrast, a region that is not particularly activated but in which the rCBF follows the increase in global CBF (blue regression) will appear as significantly (and erroneously) deactivated (blue arrow). (c) Effects of decreased global CBF in the experimental condition. In addition to a genuine local decrease in rCBF (red regression), there is a decrease in global flow (leftward shift). This causes an underestimation of the deactivation (red arrow). In contrast, a region that is not particularly deactivated but where the rCBF follows the decrease in global CBF (blue regression) will appear as significantly (and erroneously) activated (blue arrow).

own characteristic CBF distribution (see the following section on wakefulness), which will be subtracted from the sleep haemodynamic pattern.

Another possibility is to try to extract the characteristic CBF distribution of each state, building on the fact that brain organizations in SWS, REM sleep and W are so different that these states may be considered as orthogonal, as exemplified by Jones (1991) (Fig. 2). In this perspective, each state is compared with the rest. For instance, $(REMS - (W + SWS))/2$ provides the brain areas which are specifically activated in REM sleep. This type of contrast leads to more restricted rCBF changes but these are more specific, i.e. characteristic, of each state.

Finally, a more elegant way to analyse PET data is to look for significant regressions between CBF distribution and a physiological parameter in a specific condition such as delta power density in SWS. In this case, regional CBF modifications are specific to the specified parameter.

'CANONICAL' SLEEP AND WAKING BRAIN MAPS

In this section, we describe the brain areas in which local activity is maximally and specifically modified during each state of consciousness: wakefulness, SWS and REM sleep. Some results are interpreted easily in view of the mechanisms of sleep generation described at the cellular level in animals. For other results, cellular correlates of CBF modifications are not yet known completely. In this case, we try to find some support for a link between sleep processes and a brain area at a higher level of description (EEG, psychological effects of sleep or sleep deprivation). The latter situation inevitably leads to a more controversial discussion but may also induce new working hypotheses.

In the following paragraphs, we consider published results that were at least significant at the level $P < 0.001$ uncorrected (corresponding to a Z score of at least 3.09).

Wakefulness

During wakefulness, the rCBF distribution is of course highly variable and depends on the cognitive tasks in which the subject is engaged. This is the foundation of functional neuroimaging in cognitive neuroscience. In the particular case of sleep studies, subjects were scanned while lying still in the dark, with their eyes closed. This condition has long been used as the 'control' resting condition. It is now admitted that this situation is particularly uncontrolled: the subject may be in all sorts of mental conditions, including boredom, anxiety, mental imagery, memory retrieval, etc. These activities may vary from one subject to the other. However, the resting condition is characterized by at least two characteristics: (i) the constant recording of α rhythm on posterior leads by electroencephalography; and (ii) a set of cognitive processes common to all subjects, which include attending and interpreting external stimuli, holding the material in memory as well as adapting

their behaviour to the experimental situation. These processes are known to rely on polymodal associative frontal and parietal cortices, which are significantly activated in this condition. Accordingly, as shown in Fig. 2, the most active brain areas in this condition are located in the prefrontal, anterior cingulate, parietal cortices and in the precuneus.

Similar results concerning the resting condition have been obtained in very different experimental situations. Andreasen and co-workers observed that cerebral regions more active in the resting state than in memory tasks are located in the prefrontal and parietal cortex, in good agreement with our waking CBF distribution (Andreasen *et al.* 1995). Re-analysing PET studies of visual information processing, Shulman *et al.* (1997) showed that the most active areas during the resting state were in the posterior cingulate/precuneus, inferior parietal cortices, left dorso- and ventrolateral prefrontal cortex and medial frontal areas. These brain areas are in very good agreement with those we observed. They report, however, an important activity in the right amygdala, which we did not observe, possibly because this structure is even more active in REM sleep (see below). Although a redistribution of CBF by task performance cannot be ruled out, this CBF distribution was proposed to be due to monitoring by the subjects of the environment and internal state. As mentioned previously, we must also consider the possible vasomotor action of basal forebrain on these frontal and parietal areas.

These results in wakefulness should be kept in mind in the interpretation of sleep data. When the waking state serves as the control for a sleep condition, parieto-frontal hyperactivity is subtracted from the sleep distribution.

Slow-wave sleep

During SWS, large neuronal populations oscillate synchronously within certain frequency bands (Steriade *et al.* 1990a, 1993c, d; Steriade and Amzica 1998). As sleep deepens, spindles then delta rhythms appear, both sculptured by a slow (< 1 Hz) oscillation (Steriade *et al.* 1993b, d). These rhythms have been described in animals at the cellular level but EEG data suggest their existence in humans (Achermann and Borbely 1997; Amzica and Steriade 1997). At the cellular level, these rhythms alternate short bursting periods with long silent lapses of hyperpolarization. To understand PET results, it should be borne in mind that PET averages these cellular processes over time and space.

Over time, brain haemodynamics are integrated for 40–120 s. During this time, neurones discharge in a bursting mode. It turns out that the influence on CBF of the hyperpolarization periods outweighs that of the short bursts; the hallmark of SWS is a decrease in regional CBF. This

Figure 2. Surface rendering of brain areas more active in wakefulness than in sleep (slow-wave or rapid eye movement sleep). The data concern the 11 subjects reported in Maquet *et al.* (1996, 1997) and were analysed with SPM 95. Displayed voxels are significant at $P < 0.05$ after correction for multiple comparisons.

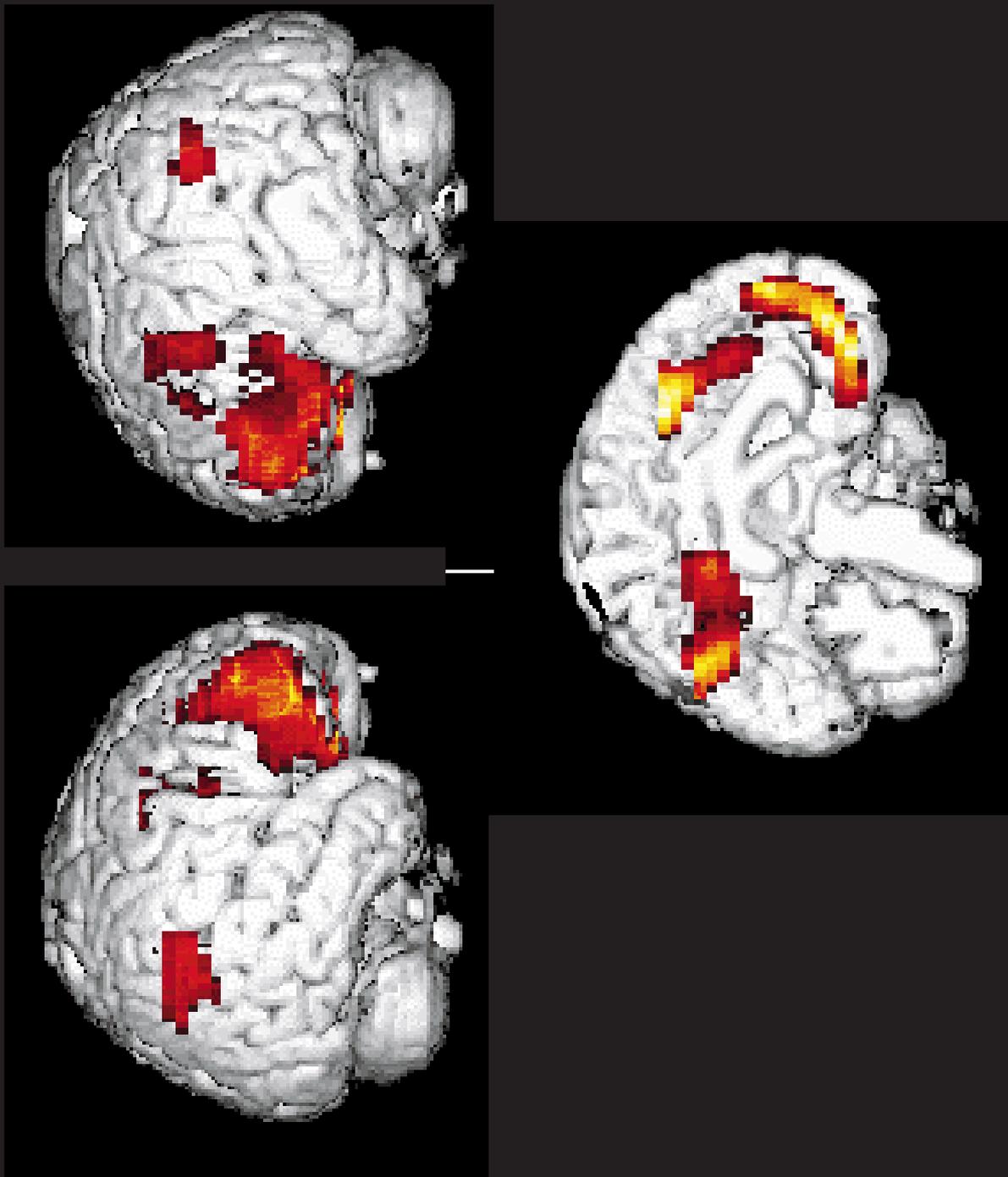


Table 1 Decreases in rCBF during SWS

	<i>Maquet et al.</i> (1997)	<i>Braun et al.</i> (1997)	<i>Andersson et al.</i> (1998)	<i>Kajimura et al.</i> (1999)	<i>Hofle et al.</i> (1997)
Quantification	-	+	+	+	-
Global activity	+	+	+	-	+
Adjustment					
Brainstem	↓	↓		↓	↓
Thalami	↓	↓	↓	↓	↓
Basal forebrain	↓	↓		↓	
Basal ganglia	↓	↓		↓	
Prefrontal cortex	Orbital ↓	DLPFC ↓ Orbital ↓	DLPFC ↓ Orbital ↓	↓	Orbital ↓
Parietal cortex	↓	↓	↓	↓	
Precunes/posterior cingulate cortex	↓	↓	↓	↓	
Anterior cingulate cortex	↓	↓	↓	↓	↓
Mesio-temporal cortex	↓	↓		↓	
Insula-temporal cortex		↓		↓	
Cerebellum		↓		↓	↓
Remarks	CBF [(W + REMS)/2] - SWS	CBF W - SWS	CBF W - SWS	CBF W - SWS*	CBF W - SWS

+, CBF quantification and global activity adjustment have been performed; -, CBF quantification and global activity adjustment have not been performed; DLPFC, dorso-lateral prefrontal cortex.

*Actually, all neocortical areas decrease except the periolandic and occipital cortex.

†Regression with delta power density.

reasoning applies for modifications in local CBF. Global CBF variations in SWS also depend on general factors, as described earlier. In consequence, these periods of hyperpolarization represent the main cellular event that explains the neuroimaging data during SWS.

The degree of deactivation of a particular brain area (in terms of rCBF) is dependent on the local mechanisms of generation of the sleep rhythm. In the thalamus, active inhibition by GABA, as well as intrinsic membrane properties of thalamic neurones, plays an important role in the maintenance and modulation of sleep rhythms (Steriade *et al.* 1993a). In contrast, in the cortex, sleep rhythm is related to disfacilitation of pyramidal neurones and interneurones (Contreras *et al.* 1996). These different mechanisms possibly require different metabolic demand and may explain why thalamic nuclei are the among the most deactivated areas during SWS. Likewise, within the cortex itself, some brain areas might be more deactivated than others (see below), depending on the local modulation of cellular processes underlying sleep rhythms. At present, the cellular bases of such a regional intracortical modulation are not completely understood.

Moreover, the proportion of the local neuronal population engaged in the sleep oscillations may also explain the distribution of rCBF. Because of its limited spatial resolution, PET also averages the local activity over a whole population of neurones. Only a fraction of this population adopts a bursting pattern. For example, in anaesthetized cats, 88, 65 and 44% of neurones were engaged in slow oscillations in the cortex, the reticular thalamus or the dorsal thalamus, respec-

tively (Steriade *et al.* 1993b, d). Similar proportions (82 and 100%, in reticular and thalamocortical cells, respectively) have been reported for delta rhythm (Curro Dossi *et al.* 1992). These figures are usually lower in natural sleep. It seems reasonable to suggest that the higher the proportion of local neurones engaged in sleep oscillations, the lower the local CBF.

In sum, taking into account regionally specific cellular mechanisms, brain areas with a high proportion of neurones committed in abundant synchronous sleep oscillations are likely to have the lowest regional CBF. These areas are described in the following paragraphs as showing a maximal CBF decrease, having a negative association with SWS or being deactivated. This does not imply that these regions 'need' more sleep. However, it seems tempting to suggest that, if synchronous oscillations of SWS have a favourable effect on neuronal function (Steriade *et al.* 1993c), the deactivated areas in particular benefit from these sleep processes. Likewise, the deactivated areas are not necessarily actively involved in sleep generation or maintenance, although it turns out that the cellular processes observed in many of these regions show that this is actually the case.

Five studies (Braun *et al.* 1997; Hofle *et al.* 1997; Maquet *et al.* 1997; Andersson *et al.* 1998; Kajimura *et al.* 1999) reported on regional CBF distribution in SWS (Table 1 and Fig. 3). The functional neuroanatomy of SWS is characterized by a low CBF in central core structures (brainstem, thalamus, basal forebrain), in basal ganglia and cerebellum, as well as in some cortical areas (frontal, parietal, mesiotemporal).

Brainstem deactivations were described in the pontine and mesencephalic tegmentum. This brain area encompasses many nuclear groups among which cholinergic and aminergic reticular nuclei and the mesencephalic reticular formation. In the currently held theory of sleep generation, the activity of the mesencephalic reticular formation and cholinergic reticular nuclei decreases at sleep onset, leading to a disfacilitation of thalamic nuclei (Steriade 1993a). The activity of these brainstem structures must remain low during sleep because resumption of their tonic activity would immediately cause an arousal reaction (Steriade 1993a; McCormick and Bal 1997). Aminergic (serotonergic and catecholaminergic) nuclei also decrease their firing rate during slow sleep (Steriade and McCarley 1990b). Consequently, the low CBF in the brainstem reflects their permissive role on the generation of sleep rhythms.

Thalamic deactivation is the most reproducible pattern observed by neuroimaging techniques in human sleep (stage 2 sleep and SWS). It has already been suggested by early glucose metabolism studies (Buchsbaum *et al.* 1989; Maquet *et al.* 1990, 1992) and was confirmed by recent CBF studies. In stage 2 sleep, Hofle *et al.* (1997) showed that the medial thalamic blood flow was inversely correlated with the power density within the spindle frequency band (12–15 Hz). In deep SWS, all $H_2^{15}O$ studies reported important CBF decreases in the thalamic nuclei (Braun *et al.* 1997; Hofle *et al.* 1997; Maquet *et al.* 1997; Andersson *et al.* 1998). Although the bulk of thalamic nuclei seem deactivated when categorical comparisons are used, CBF is negatively correlated with delta power density (1.5–4 Hz) essentially in the medial thalamus (Hofle *et al.* 1997).

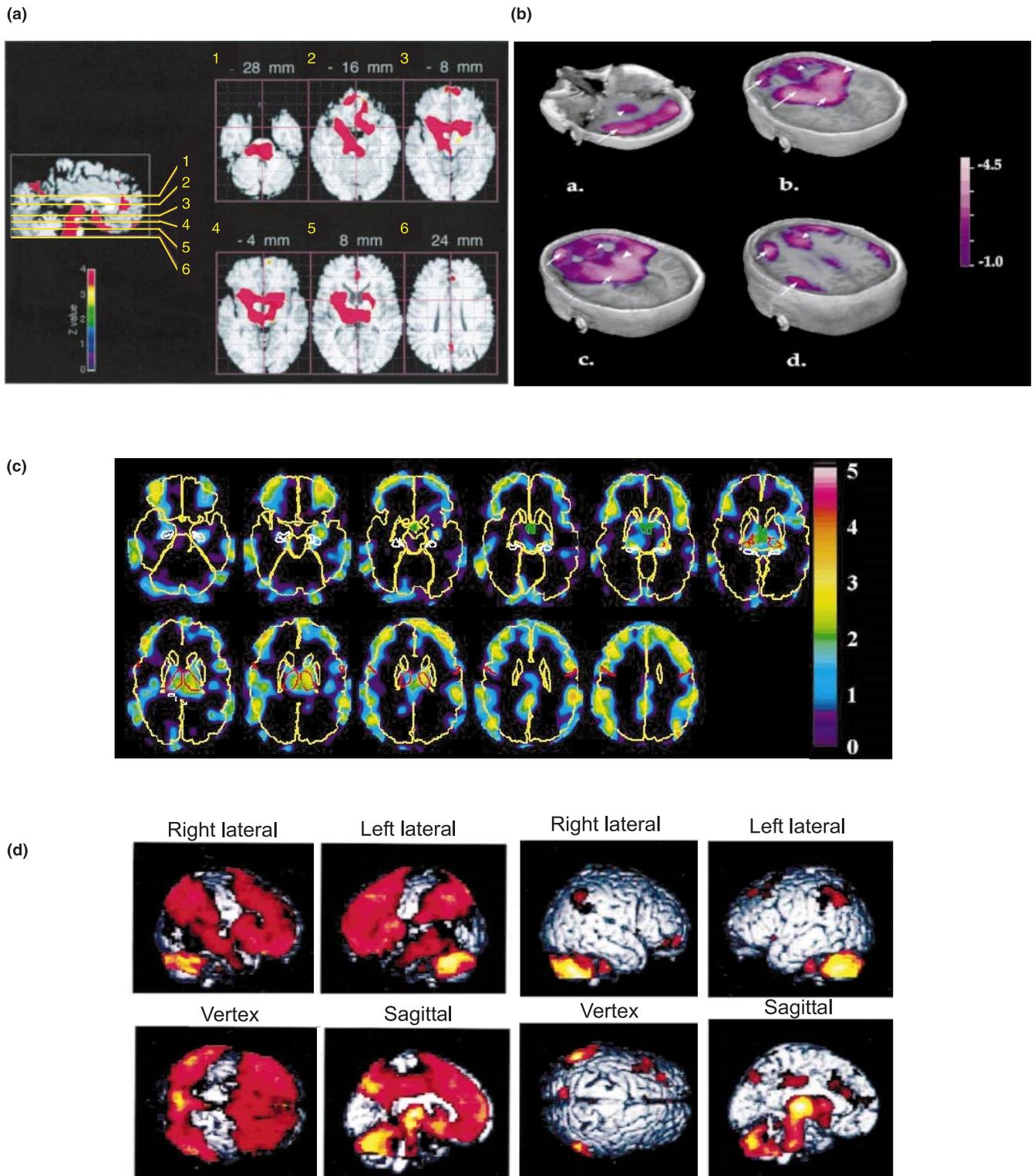
In animals, thalamic neurones, hyperpolarized because of the disfacilitation described above, change their firing mode from tonic to phasic (Steriade *et al.* 1990b, c). First, GABAergic reticular thalamic nucleus bursts in the spindle frequency range and entrains thalamo-cortical neurones in spindle oscillation. As sleep deepens, thalamic neurones become more hyperpolarized and a clock-like delta rhythm appears in thalamocortical cells, due to their intrinsic membrane properties. This delta rhythm arises from the interplay between a low threshold calcium current (I_T) and a hyperpolarization-activated K^+ current (I_h). The thalamic delta rhythm is conveyed to the cortex, which further reorganizes it and incorporates it into a slow, cortically induced, slow rhythm (Steriade and Amzica 1998). Neuroimaging data support the hypothesis that the same mechanisms are at work in humans in stage 2 and SWS.

Basal forebrain/anterior hypothalamus was found to be deactivated during SWS in two studies (Braun *et al.* 1997; Maquet *et al.* 1997). Given the spatial resolution of PET data, the area encompasses the anterior part of the hypothalamus as well as the basal forebrain. These brain areas are structurally and functionally heterogeneous (Szymusiak 1995). On the one hand, BF/AH is a critical site for cortical arousal. Ibotenic acid lesions of basal forebrain reduces acetylcholinesterase cortical staining and results in an ipsilateral increase in slow waves (Buzsaki *et al.* 1988). In contrast, electrical and chemical BF

stimulation elicits a shift of spike discharge pattern of cortical neurones from phasic to tonic and, consequently leads to EEG activation (Metherate *et al.* 1992). By the same token, the unit activity of cortically projecting basal forebrain neurones (most of which are cholinergic), increase their discharge rate during EEG activation (Detari and Vanderwolf 1987). On the other hand, BF/AH is also important for sleep generation. BF/AH lesions with excitatory aminoacids induce a prolonged insomnia (Szymusiak and McGinty 1986a) while its electrical stimulation produces sleep (Siegel and Wang 1974). This region contains cells that increase their firing at sleep onset (Szymusiak and McGinty 1986b; Sherin *et al.* 1996). Despite the functional importance of the latter cellular group, these cells represent only a minority of BF/AH neurones (37%; Nunez 1996). Most of BF/AH neurones increase their firing rate during wakefulness and REM sleep and adopt a bursting mode of firing during SWS (Khateb *et al.* 1992). This bursting pattern would seem to be related to intrinsic membrane properties, notably a low threshold calcium current (Khateb *et al.* 1992). That these findings, obtained in rats may be transposed to humans is suggested only by functional neuroimaging. The low BF/AH blood flow might reflect that in humans also, the majority of BF/AH neurones discharge in bursts during SWS.

Basal ganglia, especially the striatum, were not expected to be among the maximally deactivated brain areas during SWS (Braun *et al.* 1997; Maquet *et al.* 1997). Indeed, they are not usually considered to participate in the networks of SWS generation in animals. For these reasons, we cautiously suggested that these deactivations might reflect the effects of frontal and thalamic activity on the basal ganglia (Maquet *et al.* 1997). Frontal cortex (Selemon and Goldman-Rakic 1985) and intralaminar thalamic nuclei (Macchi *et al.* 1984; Sadikot *et al.* 1990) represent the major sources of afferents to basal ganglia. They are also among the most deactivated brain areas (see related discussions). They might entrain the basal ganglia neuronal population in highly synchronized oscillations. At the cellular level also, the activity of striatal neurones has been shown to depend directly on frontal cortex activity. During sleep or anaesthesia, the striatal membrane potential alternates long phases of hyperpolarization with bursts of discharges (Wilson 1994). Cortical stimulation can elicit membrane potential shifts similar to the spontaneous ones (Wilson 1994).

Braun *et al.* (1997) proposed a more active role for basal ganglia in the generation of SWS. Their proposal is based essentially on the anatomical connectivity of basal ganglia and may be summarized as follows. Basal ganglia are in a position to modulate cortical arousal because they receive information from the reticular core via the intralaminar thalamus and might transfer it to the cortex via the ventral anterior and ventromedial thalamic nuclei. Furthermore, basal ganglia might also regulate the activity of the reticular core via their projections to the pontine and mesencephalic reticular formation. In favour of the role of basal ganglia in SWS regulation, it should be remembered that the mechanical removal of the



striatum (caudate nucleus) causes long-lasting insomnia in cats (Villablanca *et al.* 1976). In contrast, low-frequency electrical stimulation of the caudate nucleus induces EEG synchronization and behavioural inhibition (Siegel and Wang 1974). Furthermore, dopaminergic uptake inhibitors (which, however, may or may not be specifically acting on the basal ganglia)

cause an EEG arousal (Nishino and Mignot 1998). In the same line, modafinil binds with low affinity to the dopamine transporter and this might play a part in its arousing effects (Mignot *et al.* 1994). In addition, dopamine release within the striatum decreases during SWS although the firing rate of VTA neurones is not modified during sleep (Trulson 1985). Finally,

SWS is reduced in Huntington's patients, who suffer from a predominant striatal lesion (Wiegand and Lauer 1991). Whether active or passive, the role of the basal ganglia in the regulation of sleep remains unclear (Nishino and Mignot 1998) and deserves further investigation.

The cerebellar hemispheres are also significantly depressed during SWS. This has been attributed to the reduction of sensorimotor function (decreased muscle tone and proprioception) characterizing the sleeping subject (Braun *et al.* 1997; Hofle *et al.* 1997).

The cortical deactivations are certainly the most intriguing findings from neuroimaging studies. SWS profoundly affects the activity of the whole cortex, not only in the areas in which CBF is lowest. However, in these regions, a larger proportion of the local neuronal population is probably engaged in the highly synchronous oscillation of sleep. Recent neurophysiological studies explored the role of the cortex in the generation of sleep rhythms. The cortical mantle has been involved in the generation of a slow rhythm (<1 Hz) which organizes the thalamically generated rhythms (spindles and delta) and synchronizes oscillations within the cortical and cortico-thalamo-cortical networks (Steriade *et al.* 1993b, d; Steriade and Amzica 1998). The cortex would also seem to be implicated in the generation of a delta rhythm, less regular than the clock-like thalamic delta, although the cellular mechanism of this oscillation has not yet been described in detail (Steriade and Amzica 1998).

The slow rhythm relies on the properties of the cortical networks and the alternate silent periods of hyperpolarization with activity periods (Steriade *et al.* 1993b). The long-lasting silent periods would appear to be due to a cascade of disfacilitation (Contreras *et al.* 1996). Activity periods depend

on aminoacidergic neurotransmission (Steriade *et al.* 1993d). The participation of intracortical inhibitory neurones (Steriade *et al.* 1993a), as well as cortico-cortical connection fibres (Amzica and Steriade 1995a, b), has also been emphasized.

Although neurophysiological studies in animals recorded cortical activity from many sites (sensory, motor, visual) of primary and associative cortices, no regional modulation of sleep oscillations was observed at the cellular level. However, regions such as the orbito-frontal cortex have not been specifically investigated. In this respect, it is important to note that the oscillatory frequency of cortical areas was different on either side of a lidocaine-inactivated brain area (Amzica and Steriade 1995a, Fig. 9). This finding suggests that different local oscillators may exist in the cortical mantle, which are normally synchronized by intracortical or thalamo-cortical networks. However, it clearly appears that the cellular substrate of the regional cortical CBF depression is not yet known. Further arguments suggesting a functional link between sleep processes and the most deactivated areas is thus to be found at higher levels of description.

Braun *et al.* (1997) observed that CBF in fronto-parietal association cortices decreased markedly in SWS while the activity levels of unimodal sensory cortices were preserved. This finding was recently confirmed by Kajimura *et al.* (1999). They found that absolute levels of rCBF were lower in all cortical areas except the perirolandic and occipital cortex during SWS (Kajimura *et al.* 1999). This observation suggested that the first cortical relay areas for exteroceptive stimuli remain active during SWS. Although attractive, this hypothesis is challenged by another way of interpreting the data. It should again be emphasized that polymodal association cortices are the most active areas during wakefulness, whereas primary sensory and motor cortices do not reach such high levels of activity during resting conditions. The differential behaviour of primary and associative cortices could thus be due more to processes occurring during wakefulness than to genuine SWS processes. In keeping with this interpretation, eigenimage analysis of our sleep data shows that 30% of the variance could be explained by a fronto-parietal network which is more active in wakefulness than in sleep (Fig. 4). [The first PC (50% of variance) essentially differentiates REM sleep from both SWS and wakefulness, in relation with negative loadings in the lateral prefrontal cortex and parietal cortex.]

Furthermore, neurophysiological data in animals have shown that exteroceptive afferent volleys are blocked mainly at the thalamic levels during SWS (Steriade *et al.* 1990b, c). This finding minimizes the role of cortical areas in afferent processing during SWS. A third hypothesis, which reconciles the previous suggestions, would be that polymodal associative cortices are both more active during wakefulness and more profoundly influenced by SWS rhythms than primary cortices. Current intracellular recordings indeed show that cellular correlates of SWS rhythms are more pronounced in association cortical areas (Steriade, personal communication). Likewise, in cats involved for some time in a active visual task, neurones in the associative visual cortex may adopt a bursting

Figure 3. Decreases in rCBF during slow-wave sleep (SWS). (a) Data from Maquet *et al.* (1997). Contrast: [(W + REMS)/2] – SWS. Mid-sagittal and transverse sections showing deactivation of the central core structures (brainstem and thalamic nuclei), the basal forebrain, the basal ganglia, the orbito-frontal and anterior cingulate cortices and the precuneus. Section numbers on the sagittal section refer to the respective transverse sections. Reproduced with permission from the *Journal of Neuroscience*. (b) Data from Braun *et al.* (1997). Contrast: presleep W – SWS. Transverse sections showing deactivation of the brainstem, the thalamus, the basal forebrain, the basal ganglia, the orbito-frontal cortex, the frontal and parietal cortices on the convexity. Also note the deactivation of the cerebellum and the insular cortex. Reproduced with permission from the authors and *Brain*. (c) Data from Andersson *et al.* (1998). Contrast: W – SWS. Transverse sections showing deactivation of the thalamus as well as of the frontal and parietal cortices on the convexity. Reproduced with permission from the authors and the *Journal of Cerebral Blood Flow and Metabolism*. (d) Data from Kajimura *et al.* (1999). Contrast: W – SWS. Surface rendering of brain areas deactivated in SWS. For the four images on the left, data were not adjusted for global blood flow changes in SWS. All cortical areas are deactivated with the exception of primary cortices. For the four images on the right, the data were adjusted for global flow changes in SWS. The regional deactivations are localized in brainstem, the thalamus, the cerebellum, the posterior cingulate cortex and left parietal cortex. Reproduced with permission from the authors and the *Journal of Neuroscience*.

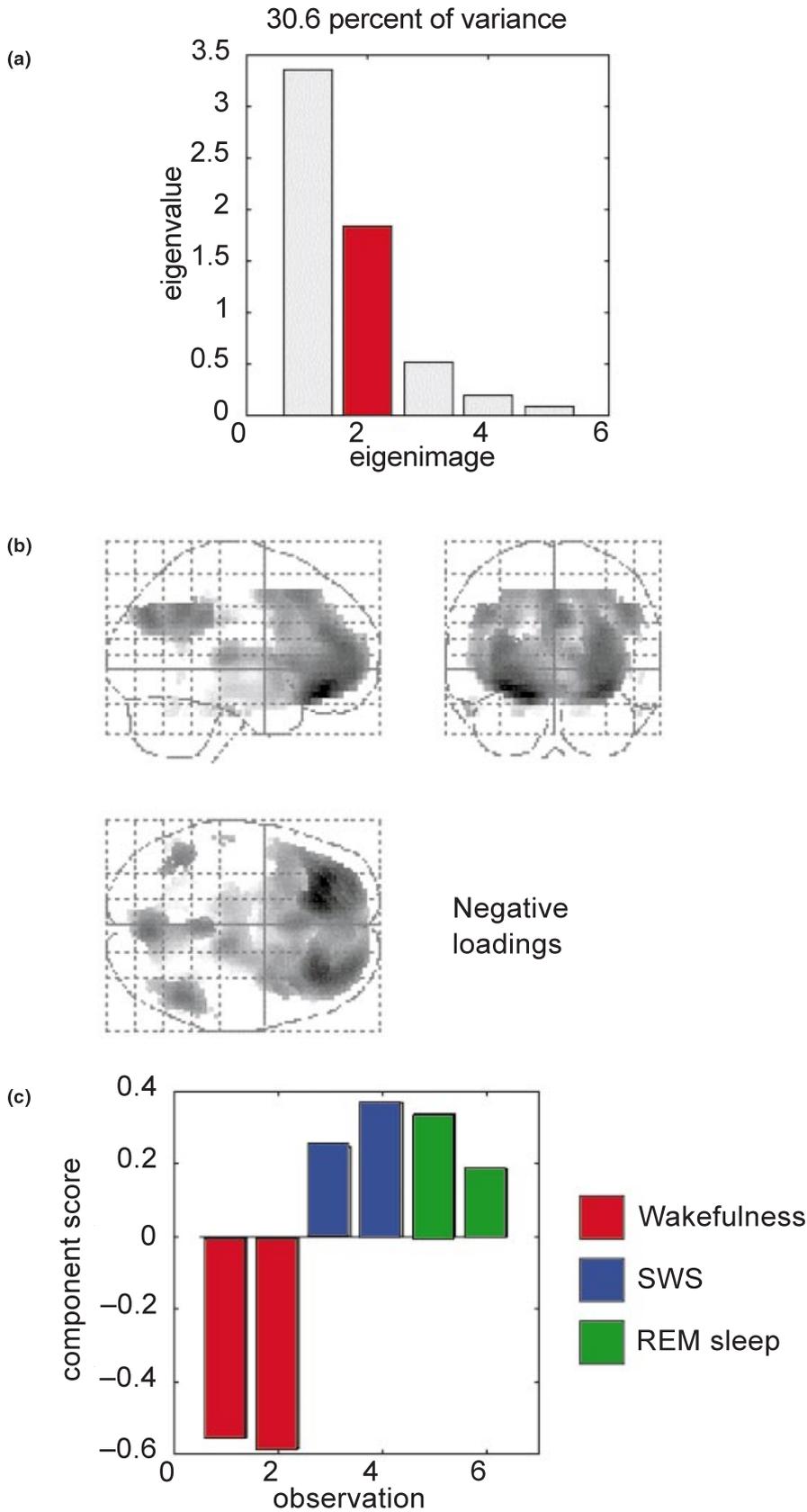


Figure 4. Analysis of the sleep data published in Maquet *et al.* (1996, 1997) by singular value decomposition (Fraczkowiak *et al.* 1997). This analysis is a simple way of measuring a pattern of correlated cerebral activity. Singular value decomposition is an operation that decomposes the original time series (the series of scans) into the patterns in space and time which account for the most variance-covariance of the original data. The identified spatial modes (also called eigenimages) can be interpreted on the basis of their temporal mode, i.e. their expression over different brain states. The figure shows the second eigenimage, which accounts for 30.6% of the variance (a). The spatial mode with negative loadings is characterized by a fronto-parietal network, which also includes the precuneus (b). The corresponding temporal mode (c) indicates that this component is due to the contrast between waking and sleep scans. The negative scores of waking scans echo the negative loadings shown in (b) and suggest that the fronto-parietal network is *most* expressed in wakefulness.

pattern typical for the sleeping cortex and become less responsive to visual stimulation, while the primary visual area maintains a normal response to visual inputs (Pigarev *et al.* 1997).

Below we discuss in more detail three brain areas: the ventro-mesial frontal regions, the precuneus and the mesio-temporal areas.

Ventro-mesial areas of the frontal lobe essentially encompass both the anterior cingulate cortex and the orbito-frontal cortex. This terminology is proposed by Damasio (1994) and is very convenient here because these regions have significantly low CBF during SWS (Braun *et al.* 1997; Hoffle *et al.* 1997; Maquet *et al.* 1997). A functional link between these areas and SWS processes is suggested by three lines of evidence. First, early studies showed that electrical stimulation of the orbito-frontal cortex causes an outbreak of slow waves on EEG recordings and induces behavioural sleep (Sterman and Clemente 1962; Lineberry and Siegel 1971). At present, these results are difficult to reconcile with the prominent theory of sleep generation which invokes mainly a disfacilitation of thalamo-cortical networks under the permissive inactivity of the brainstem structures (see above). However, a detailed description of the functional interactions occurring in sleep between ventro-mesial frontal areas and diencephalic or brainstem structures probably deserves further investigation.

Second, it is noteworthy that the topography of slow wave activity in humans predominates over frontal regions (Zeitlhofer *et al.* 1993; Werth *et al.* 1996). Although the highest delta power densities are observed over the frontal convexity, the limited spatial resolution and spatial sampling of EEG recordings make it difficult to determine the precise localization of frontal areas most intimately related to this higher delta power density.

Third, total sleep deprivation, the effects of which can be attributed primarily to SWS deprivation (Horne 1993), rapidly induces signs and symptoms similar to ventro-mesial frontal lesions. Patients with orbito-frontal or anterior cingulate lesions are usually described as impulsive, disinhibited and distractible. Interestingly, related signs, such as childish humour (Kollar *et al.* 1966), disinhibition and irritability (Bliss *et al.* 1959), distractibility (Norton 1970), and perseverations (Horne 1988) are likewise observed after short-term total sleep deprivation in man. As orbito-frontal and anterior cingulate cortices are closely related to the regulation of emotions and behaviour, it is also noteworthy that a recent meta-analysis shows that one of the main effects of sleep deprivation in humans is modification of affect (Pilcher and Huffcutt 1996). Likewise, ventromesial frontal areas have been implicated in decision-making (Bechara *et al.* 1994; Bechara *et al.* 1995). This process aims to integrate large numbers of facts, past experience and estimations of future consequences in order to adapt the behaviour in the best interest of the individual (Adolphs *et al.* 1996). Once again, sleep deprivation rapidly leads to deficits in decision-making (Harrison and Horne 1998, 1999).

At this point, it is fair to note that other signs observed after short-term sleep deprivation do not depend on ventro-medial but on lateral frontal areas. For instance, verbal fluency (Friston *et al.* 1991b) is known to rely on the dorsolateral prefrontal cortex and is rapidly impaired by sleep deprivation (Horne 1988). Thus, it remains open as to whether the effects of SWS and regional deactivations are restricted to orbito-frontal regions or also involve frontal convexity.

The precuneus, on the medial aspect of the parietal lobe, is significantly deactivated during SWS (Braun *et al.* 1997; Maquet *et al.* 1997; Andersson *et al.* 1998). The interpretation of this deactivation is uncertain. As can be seen in Fig. 2, this association cortex is particularly active during wakefulness. Its activity contrasts the waking state from both SWS and REM sleep (Fig. 4). As for the association cortices of the convexity, the activity of the precuneus would thus appear to reflect more brain operations taking place in conscious wakefulness than in sleep. Curiously, the precuneus and posterior cingulate cortex were shown to be hypoactive in mental states of decreased or abolished consciousness, e.g. pharmacological sedation (Fiset *et al.* 1999), hypnotic state (Maquet *et al.* 1999), vegetative state (Laureys *et al.* 1999). The role of this area in conscious processes certainly deserves further investigation.

Mesio-temporal areas were found to be deactivated during SWS (Maquet *et al.* 1997; Andersson *et al.* 1998). This would suggest that highly synchronous oscillations also occur in these areas. At the cellular level, such activities are indeed observed during SWS in the hippocampal formation of rats. Two main types of activity are observed in the hippocampus in rats: theta rhythm and sharp waves, respectively, associated with γ oscillations and ripples (Chrobak and Buzsaki 1998). Sharp waves and ripples are observed during consumatory behaviours and SWS. They originate from a synchronous discharge of CA3 populations which impinge on CA1 neurones. Sharp waves are transmitted to the superficial layers of the entorhinal cortex where they can also be recorded. The presence of similar activities in primate hippocampal formation is uncertain. Early observations in chimpanzees reported slow waves and K complexes in the hippocampus during non-REM sleep but in the human hippocampal complex, stage 4 sleep was essentially characterized by low voltage fast activity (Freemon and Walter 1970). However, some high voltage M-shaped transients were also recorded (Freemon and Walter 1970). More recently, using single unit recordings in epileptic patients, it was shown that firing rates in the entorhinal cortex were lowest during SWS, while hippocampal neurone activity was less prone to state-related changes (Staba *et al.* 1998).

From the psychological standpoint, the hippocampal formation is intimately involved in explicit memory systems (Squire and Zola 1996). Functional relationships between sleep and memory remain subject to debate (Stickgold 1999). Some recent data show that SWS deprivation has detrimental effects on episodic memory trace consolidation (Plihal and Born 1997).

In consequence, all these arguments suggest that the deactivation of mesio-temporal areas in SWS reflect local slow

synchronous oscillations, possibly related to memory traces processing. At present, further evidence is needed to support this hypothesis.

REM sleep

In contrast to SWS, REM sleep is characterized by sustained neuronal activity (Jones 1990; Steriade *et al.* 1990) and, correspondingly, by high cerebral energy requirements (Maquet *et al.* 1990) and blood flow (Madsen *et al.* 1991a; Madsen and Vorstrup 1991; Franzini 1992). In this working brain, some areas are more active than others; in contrast, other regions have lower than average CBF. This section deals with these two types of structure.

Three studies described the functional neuroanatomy of REM sleep using PET; two used $H_2^{15}O$ CBF measurements (Maquet *et al.* 1996; Braun *et al.* 1997), the third measured the glucose metabolism with [^{18}F]fluorodeoxyglucose (Nofzinger *et al.* 1997). The core functional characteristics of REM sleep are: (i) activation of the mesopontine tegmentum, thalamic nuclei, limbic/paralimbic structures and posterior cortices; and (ii) relative deactivation of frontal and parietal cortices (Tables 2 and 3, Fig. 5).

Activation of the dorsal aspect of the mesopontine tegmentum is in good agreement with the role played by this area in REM sleep generation in animals. It should be emphasized that the activation encompasses many local nuclear structures that cannot be sorted by PET (systems level description) and that the increased regional CBF reflects an intense

Table 2 Increases in rCBF during REM sleep

	<i>Maquet et al.</i> (1996)	<i>Braun et al.</i> (1997)	<i>Nofzinger et al.</i> (1997)
Quantification	-	+	+
Global activity adjustment	+	+	+
Brainstem	↑	↑	
Thalami	↑	↑	↑
Basal forebrain		↑	↑
Amygdala	↑		↑
Hippocampal formation		↑	↑
Orbito-frontal cortex			↑
Parietal lobule	↑		
Extrastriate cortex		↑	
Anterior cingulate cortex	↑	↑	↑
Insula-temporal cortex		↑	↑
Cerebellum		↑	
Remarks	CBF REMS - [(W + SWS)/2]	CBF REMS - SWS	Glucose metabolism REMS - W

+, CBF or glucose metabolism quantification and global activity adjustment have been performed; -, CBF or glucose metabolism quantification and global activity adjustment have not been performed.

Table 3 Decreases in rCBF during REM sleep

	<i>Maquet et al.</i> (1996)	<i>Braun et al.</i> (1997)
Quantification	-	+
Global activity adjustment	+	+
Preformal cortex	↓	↓
Parietal cortex	↓	↓
Precunes/posterior cingulate cortex	↓	↓
Remarks	CBF REMS - [(W + SWS)/2]	CBF REMS - SWS

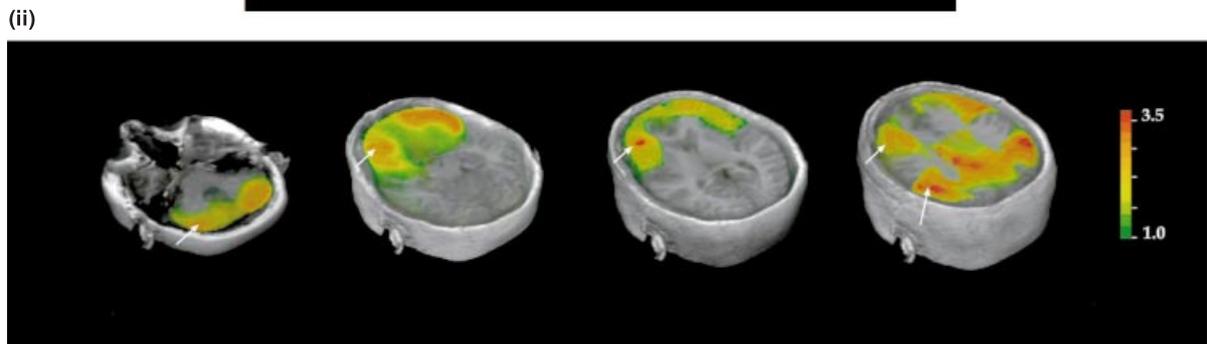
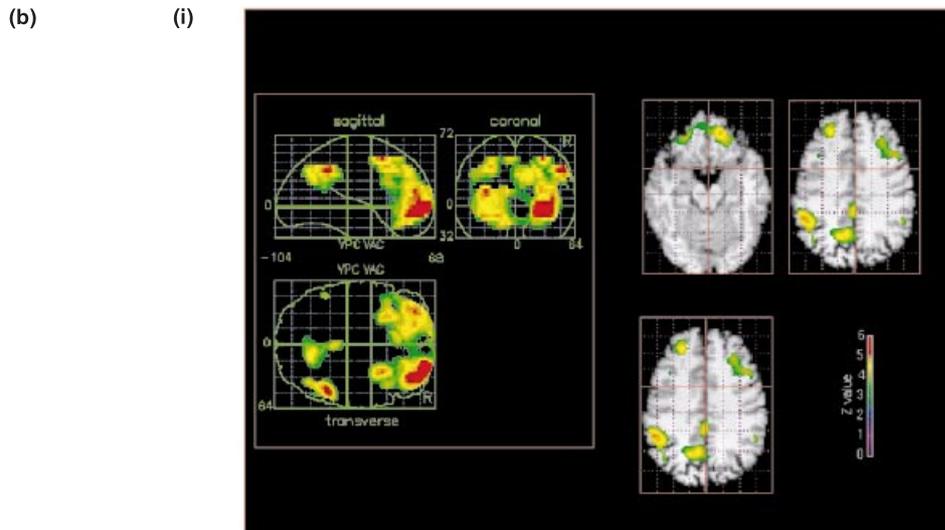
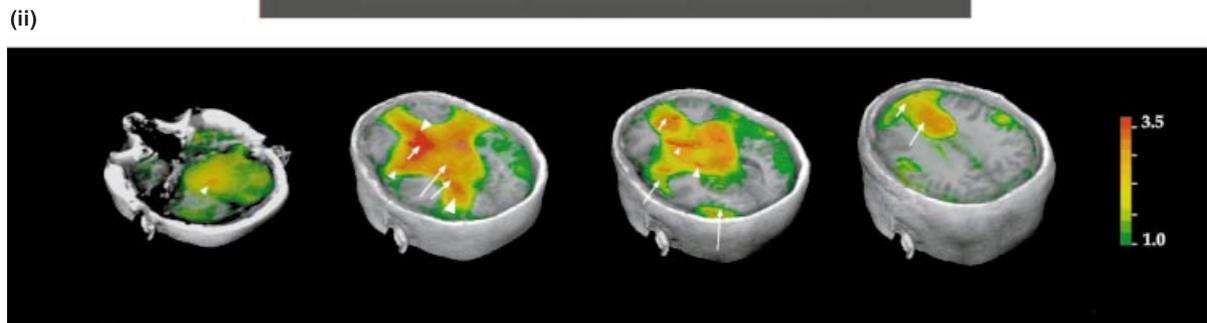
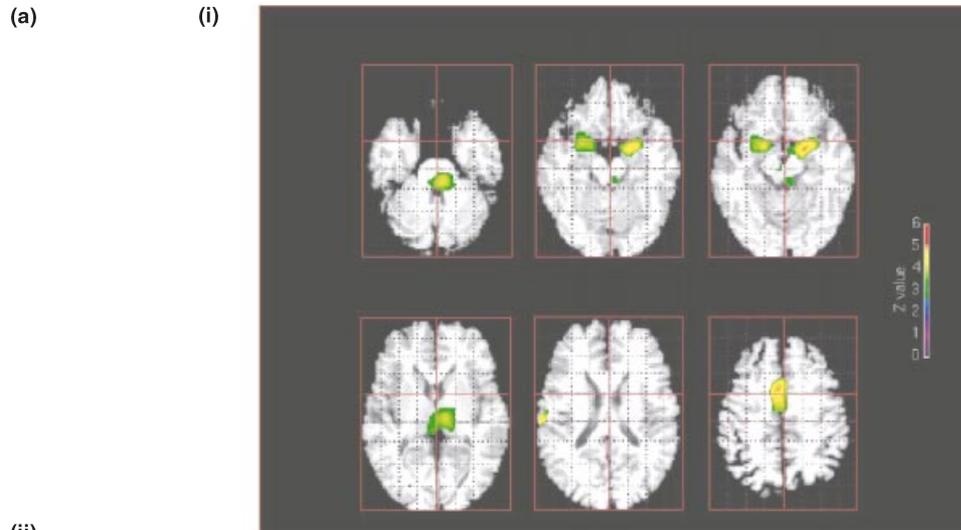
+, CBF or glucose metabolism quantification and global activity adjustment have been performed; -, CBF or glucose metabolism quantification and global activity adjustment have not been performed.

synaptic trafficking in this region during REM sleep. Some of the local neuronal populations monosynaptically project to the thalamic nuclei, which was also found to be activated bilaterally in the three published studies.

It was usually thought that thalamic nuclei, and in particular the intralaminar thalamus, dispatched this activation diffusely and homogeneously to the cortex. Early studies in rats and cats had suggested the heterogeneity of cerebral metabolism during sleep, in particular REM sleep (Ramm and Frost 1983, 1986; Lydic *et al.* 1991). Functional neuroimaging in humans definitely showed that the distribution of telencephalic activity is heterogeneous and specific to REM sleep. The functional significance of the cortical pattern of activity is still open to discussion.

We were intrigued by the bilateral activation of amygdaloid complexes during REM sleep. Furthermore, neuroanatomical evidence in the Macaque showed that cortical areas, which were activated during REM sleep (anterior cingulate cortex, parietal lobule), receive numerous amygdalar projections, whereas deactivated cortices (frontal and parietal) are practically devoid of amygdalar afferents (Amaral and Price 1984; Amaral *et al.* 1992; Aggleton 1993). This anatomical argument suggested that amygdaloid complexes could modulate cortical activity during REM sleep. Our hypothesis was even more likely when we were able to show that functional interactions

Figure 5. (a) Brain areas with significant rCBF increase during REM sleep. (i) Data from Maquet *et al.* (1996). Contrast: REMS - [(W + SWS)/2]. Transverse sections showing activation of pontine tegmentum, the thalami, the anterior cingulate cortices and the right parietal operculum. Reproduced with permission from *Nature*. (ii) Data from Braun *et al.* (1997). Contrast: REMS - SWS. Transverse sections showing activation of the brainstem and the thalamus, as well as the orbito-frontal, anterior cingulate and insular cortices. Note the activation of parahippocampal gyrus on the mesial aspect of the temporal lobe and of lateral occipital areas. Reproduced with permission from the authors and *Brain*. (b) Brain areas with significant rCBF decrease during REM sleep. Note the deactivation of frontal and parietal cortices. (i) Data from Maquet *et al.* (1996). Contrast: [(W + SWS)/2] - REMS. Reproduced with permission from *Nature*. (ii) Data from Braun *et al.* (1997). Contrast: W - REMS. Reproduced with permission from the authors and *Brain*.



between the amygdala and occipito-temporal cortices were different in the context of REM sleep than in SWS or in W (Maquet and Phillips 1998).

Furthermore, animal data suggested a role for amygdala in REM sleep modulation. Early experiments showed that a unilateral daily 1-min stimulation of rat amygdala increased the amount of REM sleep (Smith and Young 1980). Likewise, electrical stimulation of the central nucleus of amygdaloid complexes increases PGO activity (Calvo *et al.* 1987), while carbachol injections in the same nucleus increase both REM sleep and PGO waves (Calvo *et al.* 1996). Intra-amygdalar injections of serotonin produce a shift from SWS to REM sleep in rats (Sanford *et al.* 1995).

However, other neuroimaging studies found activation in the hippocampal formation with (Nofzinger *et al.* 1997) or without (Braun *et al.* 1997) simultaneous amygdalar activation. This suggested that REM sleep would appear to be characterized more by an activation of the limbic system than by an amygdalar hyperactivity alone. As the limbic system is a phylogenetically old structure and is deeply involved in the regulation of affective and social behaviours (MacLean 1990), these results are compatible with, but not decisively supportive of, the hypothesis of a genetic re-programming during REM sleep, a process which would rehearse the repertoire of innate behaviours and maintain the psychological individuation (Jouvet 1998).

The reasons why the hippocampal formation is activated in some studies while the amygdala shows up in others remain unclear. One reason might be that the previous waking experience was different in the experimental populations. Indeed, both the amygdala and hippocampal formation are critical structures for memory systems (Bechara *et al.* 1995). The relationship between sleep and memory processes is beyond the scope of this paper and would deserve a review in itself. In the following, we summarize only data which can provide some explanation for the PET data.

At the cellular level, theta rhythms, together with gamma oscillations, are recorded in hippocampal formation during REM sleep and exploratory behaviour in rats. In a multistep hypothesis, during sleep there would be an interplay between sharp waves/ripples of SWS and theta/gamma oscillations during REM sleep. This interplay would be involved in the consolidation of memory traces (Buzsaki *et al.* 1994).

At the behavioural level, more emphasis has been put on tasks that do not depend on the hippocampal formation. In rats, REM sleep deprivation disturbs the learning of various tasks (Hennevin *et al.* 1995; Smith 1995). These effects are observed only if the deprivation occurs during certain periods, the PS windows, after the learning session (Smith 1985). Furthermore, the amount of REM sleep increases during the learning period (Hennevin *et al.* 1995). This increase in REM sleep is specifically linked to memory processes because: (i) it does not occur in nonlearners; (ii) it is only transient, with REM sleep levels decreasing to baseline levels as soon as the animal masters the task; and (iii) it occurs at specific times after learning sessions.

In humans, REM sleep deprivation is more detrimental to procedural than explicit memory tasks (Smith 1995). For example, REM sleep deprivation alters a perceptual implicit learning of a visual discrimination task (Karni *et al.* 1994). Furthermore, improvement in the same task is correlated with the amount of REM sleep in the second part of the night (Stickgold 1999). Likewise, modifications of the visual field in normal subjects using goggles (which forces them to learn implicitly to move in their environment) causes an increase in REM sleep in the following days (De Koninck and Prévost 1991). In contrast, explicit memory, which depends on the function of the mesio-temporal areas, has not been successfully related to any REM sleep (Smith 1995). Further research is needed to specify the role of REM sleep in memory processes and especially those involving the mesio-temporal areas.

Neocortical activations were observed inconstantly during REM sleep. Early studies mentioned significant increases in glucose metabolism (Maquet *et al.* 1990) or CBF (Madsen *et al.* 1991a) in occipito-temporal areas. More recently, Braun *et al.* (1997) observed such occipital activation while Nofzinger *et al.* (1997) and Maquet *et al.* (1996) did not. The cause of these discrepancies is possibly that posterior cortex activation in REM sleep is variable across subjects and the group analysis averages out the individual activations, unless they occur in the same regions in all (or at least the majority of) individuals.

It is interesting to note that the functional relationships between posterior cortical areas is different in REM sleep than in wakefulness (Braun *et al.* 1998). During REM sleep, a negative correlation is observed between the activity of extrastriate cortex and primary visual areas, in contrast to that usually observed during wakefulness. These results, like the amygdalo-temporal interactions we described (Maquet and Phillips 1998), strongly suggest that not only is the functional neuroanatomy of REM sleep different from wakefulness, but, in addition, functional interactions between neuronal populations are also different in REM sleep than in wakefulness. Further research should explore the characteristics of functional and effective connectivity in REM sleep.

A note on dreaming

Functional neuroimaging of normal subjects during REM sleep also bears on the neural correlates of dreaming activity. In our own study, subjects were systematically awakened after each sleep scan (Maquet *et al.* 1996). All subjects awakened during REM sleep had a dream recall (Maquet *et al.* 1996), whereas only one dream was reported after SWS awakening. As a consequence, at present, the functional maps concern REM sleep with dreaming: we lack any observation of REM sleep without dreaming and a sufficient number of SWS with dreaming. The latter two groups would be interesting to have a comprehensive view of the neural correlates of dreaming in humans.

Consequently, all that can be said is that the distribution of cerebral activity in REM sleep is consistent with some

characteristics of dream recalls (Maquet *et al.* 1996). Their perceptual character, essentially visual and auditory, might rely on the activity of temporo-occipital areas, which were shown to be activated during REM sleep in some glucose metabolism (Maquet *et al.* 1990) and CBF (Madsen *et al.* 1991a; Braun *et al.* 1997) studies. The emotional load in dreams might be related to high limbic activity, especially to amygdalar activation. The peculiar functional connectivity between amygdaloid complexes and temporo-occipital cortices would also contribute to the affective aspect of dreaming (Maquet and Phillips 1998). The relative hypoactivity of the prefrontal cortex would explain the characteristic lack of insight, the alteration of time perception or even the delusional belief of being awake, as recently discussed by Hobson *et al.* (1998).

Any further comment on the functional neuroanatomy of dreaming remains speculative. At this point, it is useful to recall some basic characteristics of dreaming activity. First, dreams, like other cognitive processes (attention, memory, language, mental imagery), result from interactions of neuronal populations, especially in the cortex. Second, dreams are not observable directly. We have access only to dream recall, i.e. the verbal translation of a whole world of perceptions and feelings felt by the dreamer during his sleep. Third, the dreamer is not aware of his dreams until he is awakened and recovers the full consciousness of the waking state: while he is dreaming during sleep, the dreamer is not conscious he is dreaming. We do not consider here the particular case of lucid dreamers, who, to our knowledge, have not yet been explored by functional neuroimaging. Fourth, most dream recall occurs immediately after awakening and their memory rapidly vanishes in a few tens of seconds.

One possible scenario would thus be the following. During REM sleep, in a cholinergic context, brain function is characterized by predominant interactions between mesio-temporal areas and posterior sensory cortices, while supramodal associative cortices in frontal and parietal cortices are relatively quiescent. This mode of brain function carries a low level of consciousness but is favourable to a hallucinatory, oneiric mentation. On arousal, brain activity is reorganized, with a preponderance of frontal and parietal cortex function and the arising of full consciousness. During the transient state of awakening, the subject would become abruptly aware of neuronal interactions going on in REM sleep. As these interactions are replaced by those prevailing in wakefulness, the dream vanishes and gives way to self and environmental awareness. The amnesia of dreams at awakening would appear to be related to the ephemeral character of brain function reorganization. The relative hypoactivity in REM sleep of the prefrontal and parietal cortices, which are involved in working memory and episodic memory processes during wakefulness, might also contribute to the amnesia at awakening. In this view, it clearly appears that a better understanding of the REM sleep neuronal interactions is the core problem on which most research effort should be focused.

CONCLUSIONS AND PERSPECTIVES

Despite a relentless research effort and an increasing number of investigative tools available, sleep is one of the last behaviours, whose function remains unknown. Among the many possible approaches to explore sleep processes, functional neuroimaging enables the study of cerebral specialization and integration during sleep in man at the systems level. The published work is only at a preliminary stage and new data should soon increase our understanding of sleep processes in humans. In this endeavour, progress will come from two types of advance: better experimental protocols, dealing with more specific aspects of sleep and new neuroimaging techniques, including fMRI; and multimodal imaging.

The cerebral organization described above proposes a stereotyped, fixed picture of sleep processes, a picture of 'canonical' human sleep. This description may give the impression that sleep is a stereotypical process. In contrast, we know that sleep may adapt dynamically in response to modifications in the outer or inner environment.

Several specific aspects of sleep deserve further investigation. The correlates of sleep rhythms, EEG transients and phasic events should be specified. Up to now, the results have essentially dealt with SWS and spindle activity (Hofle *et al.* 1997), and many other activities remain to be explored. Concerning the ocular saccades of REM sleep, preliminary results have certainly shown activation of prefrontal and parietal areas (Hong *et al.* 1995), but this deserves confirmation with a more powerful and localizing statistical analysis.

The internal organization of sleep during the night, i.e. the temporal course of sleep processes, is also worth describing in detail. How does brain organization change in relation to the exponential decrease in slow-wave activity in SWS, or with the modification of spindling activity during the night? Are late REM sleep periods comparable with early ones? How is the brain activity organized in non sleep-deprived subjects or during a siesta?

Another line of research concerns the role of sleep in the interaction with the environment. How does the brain process external stimuli during sleep? In particular during REM sleep, how is it that your alarm clock ringing in the morning is incorporated into your dream and does not wake you up? Are stimuli in REM sleep processed differently than in wakefulness at the cortical level? Recent fMRI studies suggest that primary sensory areas continue to process auditory inputs during sleep (Portas *et al.* 1999).

An even more intriguing question is the possible influence of previous experience on brain activity in sleep. This question is related to possible functional links between sleep, memory processes and, more generally, brain plasticity. Slow-wave activity in SWS increases in the central area contralateral to the hand submitted to a vibratory stimulus in the preceding evening (Kattler *et al.* 1994). Likewise, preliminary results suggest experience-related changes in brain CBF distribution during sleep after a training period (Maquet and Phillips 1998, Maquet *et al.* 2000).

Interindividual variability should also be investigated systematically, more probably thanks to fMRI acquisitions. Does every individual organize their his/her brain function during sleep in the same way? Does the functional neuroanatomy of sleep in the elderly differ from young subjects? Along the same lines, pathological populations are worth exploring: how is brain activity organized in depressed, narcoleptic or apnoeic patients in sleep? Do treatments normalize their functional neuroanatomy during sleep? Preliminary data suggest that depressed patients do not activate the anterior cingulate cortex during REM sleep (Nofzinger *et al.* 1998).

Pharmacological trials should explore the effects of hypnotic drugs. Is the regional activity in drug-induced sleep comparable with physiological sleep? Preliminary observations on CBF distribution during sleep induced by zolpidem have been reported (Finelli *et al.* 1998, Finelli *et al.* 2000).

It appears that the PET studies presented in this paper were very crude in their description of sleep functional neuroanatomy but they opened up the way for a whole new field of research. No doubt future studies will provide a picture of more versatile sleep processes, which adjust individual behaviour to various external and internal adaptive constraints.

New neuroimaging techniques now challenge PET as valuable methods for sleep investigations. At present, sleep research in fMRI remains a challenge given its sensibility to movement artefacts, the subject's discomfort and the difficulty of EEG recordings. Some of these problems have already been solved, however (Huang-Hellinger *et al.* 1995), and functional MRI should soon provide a description of sleep processes with better spatial and temporal resolutions. Likewise, a multimodal approach should certainly also be considered. Combining two (or more) neuroimaging techniques would allow a more precise description of the spatio-temporal brain activities and regional interactions during sleep (Maquet and Phillips 1998).

As should appear clear, a new era is on the horizon which should lead to a better understanding of macroscopic sleep processes in humans. This body of data will have to be integrated with the information provided by other techniques and describing similar mechanisms at other levels of observation. This final, multidisciplinary step in the interpretation of experimental data seems essential to unravel the functions of sleep.

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