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Functional brain imaging of human sleep

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ABSTRACT

This paper presents an overview of the contribution of functional brain mapping to the study of human sleep. Early studies were essentially successful in describing the variations of the global level of cerebral metabolism. More recently, regional distribution of cerebral blood flow was reported. The results suggest that the permissive and executive processes of slow wave sleep and REM sleep are similar in humans and in animals. They also show cortical blood flow distributions specific to each sleep stage. The cellular mechanisms underlying the involvement of these cortical areas in sleep are not yet precisely known. They should be looked for by further investigations in animals. Future research in functional neuroimaging will attempt to explore functional and, hopefully, effective connectivity between cerebral areas involved in sleep processes. This final goal will probably require the co-registration of two or more brain imaging techniques to precisely describe the spatio-temporal course of neuronal interactions occurring during sleep.

KEYWORDS: sleep, cerebral flow, cerebral metabolism, functional neuroimaging.

INTRODUCTION

In the last decade, considerable progress has been made in functional brain imaging (Toga and Mazziotta 1996). New techniques came to maturity and were applied in humans (functional magnetic resonance imaging (fMRI), optical imaging), adding new investigative possibilities to the methods already available (EEG mapping, magnetoencephalography (MEG), positron emission tomography (PET), and single photon emission computed tomography (SPECT)). At the same time, powerful tridimensional statistical techniques appeared that can test, at the voxel level, for significant regional signal modifications. The most popular of these methods is the Statistical Parametric Mapping (SPM), Wellcome Institute for Cognitive Neuroscience, London, UK (Frackowiak *et al.* 1997).
These techniques and methods have now been applied to the study of human sleep [fMRI (Sutton *et al.* 1997); NIRS (Hoshi *et al.* 1994); PET (Braun *et al.* 1997; Hofle *et al.* 1997; Maquet *et al.* 1997; Maquet *et al.* 1996); EEG (Werth *et al.* 1996; Zeitlhofer *et al.* 1993) and MEG (Lu *et al.* 1992)].
In this paper, we first consider the progress that allowed us, using PET, to describe global then regional modifications of cerebral activity during sleep. We then discuss some analyses that may give access to more dynamical aspects of neuronal interactions during sleep in man.

THE OLD DAYS: GLOBAL LEVELS OF CEREBRAL METABOLISM

Cerebral glucose metabolism, as determined by the [^{18}F]fluorodeoxyglucose method was the most popular marker of brain activity measured by PET in the 1980s. The results obtained with this technique reliably showed that brain glucose metabolism was lowest during slow wave sleep (SWS) while, during REM sleep, brain glucose consumption was at waking levels (Buchsbaum *et al.* 1989; Maquet *et al.* 1990). These metabolic variations were in good agreement with the measurements of cerebral blood flow and oxygen utilisation during sleep, obtained independently by the Kety-Schmidt technique (Madsen *et al.* 1991).
At that time, the regional distribution of cerebral activity was not adequately described. This may be due to several factors: poor spatial resolution of the first generation scanners, low anatomical precision in the neuroanatomical placement of regions of interest (ROI), statistical limitations of the ROI method (Ford *et al.* 1991), etc. All these reasons explain why, except for a thalamic deactivation in SWS (Maquet *et al.* 1992; Maquet *et al.* 1990), the regional metabolic pattern of human sleep has not been precisely established. We personally observed scattered cortical activations and deactivations (Maquet *et al.* 1992; Maquet *et al.* 1990) while others described activation in other areas, including white matter regions (Buchsbaum *et al.* 1989).

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THE ASSESSMENT OF REGIONAL CEREBRAL ACTIVITY: $H_2{}^{15}O$ INFUSIONS AND STATISTICAL PARAMETRIC MAPPING

One drawback of the fluorodeoxyglucose (FDG) method consists in the long uptake period (45 min), during which cerebral activity is somehow integrated. This limitation restricted the description to long lasting average changes in glucose metabolism during sleep. More importantly, the physical half-life of ^{18}F (108 min) hampered the repetition of the measurements in the same subject during a single session.
With the advent of ^{15}oxygen-label led water method, multiple (up to 12) acquisitions can be obtained in the same subject, under various conditions, thus allowing the comparison of different brain states. This is possible, due to the very short half-life of ^{15}oxygen (123 s). Furthermore, acquisition times are reduced to 1 or 2 min, giving access to the study of more brief physiological processes. The estimated physiological parameter is the regional cerebral blood flow, which is an indirect marker of neuronal activity (Jueptner and Weiller 1995).
In parallel, statistical methods developed to analyse these data sets increased in sophistication. In the following sections, we will see how three particular modes of analysis were applied to sleep studies: categorical comparisons, parametric designs and psychophysiological interactions.

Categorical comparisons

This type of analysis directly compares the distribution of two (or more) conditions. In our case, we wanted to describe the characteristic distribution of SWS, REM sleep or wakefulness (W). We thus compared one particular state of vigilance with all the others. Our results, which were largely confirmed recently (Braun *et al.* 1997), show that each state of vigilance is characterized by a different distribution of regional cerebral blood flow (rCBF).
In SWS (Maquet *et al.* 1997), we found a significant deactivation of the pons, the mesencephalon, thalami and basal forebrain. These results were in excellent agreement with the animal data on SWS generation (Steriade *et al.* 1993; Steriade and McCarley 1990). Other regions of deactivation were not expected: basal ganglia, anterior cingulate cortex, orbito-frontal cortex and precuneus. Clearly, the cellular basis of these deactivations are not described yet. These results might prompt neurophysiologists to investigate whether and how the rhythms of SWS are modulated in these areas.
Likewise, in REM sleep (Maquet *et al.* 1996), we observed, as expected, an activation of pontine tegmentum and thalamic nuclei, suggesting that the mechanisms of REM sleep generation are similar in humans and in other mammals. While Braun *et al.* (1997) observed an hippocampus activation, our results put a special emphasis on the activation of amygdaloid complexes. Several animal observations had already made a link between amygdala and REM sleep (Calvo *et al.* 1987; Calvo *et al.* 1996; Sanford *et al.* 1995; Smith and Young 1980; Smith and Miskiman 1975). Furthermore, our results suggested that cortical activity would be modulated by amygdaloid complexes: significantly activated cortical areas (anterior cingulate cortex, parietal lobule) receive amygdalar projections while deactivated areas (prefrontal cortex, parietal cortex, precuneus) receive few or no amygdalar output.
It was disappointing that occipito-temporal cortex were not significantly activated during REM sleep: they receive an important amount of amygdalar fibres (Amaral and Price 1984; Amaral *et al.* 1992) and previous PET and SPECT studies had detected their activation in REM sleep (Madsen *et al.* 1991; Maquet *et al.* 1990; Meyer *et al.* 1987). These negative results may in part be explained by the limitations of categorical comparisons: we will present later some more results that suggest that the activity of temporal cortex is indeed modulated by the amygdala during REM sleep.
Finally, wakefulness is characterised by the prominent activity of polymodal prefrontal and parietal cortices. The existence of this typical waking blood flow distribution must be taken into account when direct comparison between sleep and wakefulness are performed (Braun *et al.* 1997).

Parametric designs

Parametric designs look for a significant regression between regional CBF and a covariate. This analysis is much more powerful than categorical comparison since it specifically looks for the brain areas that covary with the explanatory variable of interest.
This strategy has been used in SWS by Hofle *et al.* (1997). These authors show that regional cerebral blood flow tends to decrease in thalamic nuclei and anterior cingulate cortex, as spectral power density increases within the delta frequency range. These data are in good agreement with the results obtained by categorical comparison in SWS (Braun *et al.* 1997; Maquet *et al.* 1997). A similar parametric analysis on our own data provided comparable results (not published).
Furthermore, Hofle *et al.* (Hofle *et al.* 1997) show that thalamic cerebral blood flow is negatively correlated with the power spectral density within the spindle frequency, in good agreement with the data concerning spindle

generation in animals (Steriade *et al.* 1993; Steriade *et al.* 1990).

Psychophysiological interactions

The final aim of functional brain imaging is to describe as precisely as possible the neuronal interactions, at a macroscopic level. Recent advances in statistical analysis precisely provide the logistic background necessary to explore this type of issues. Simple linear models can estimate the cerebral functional connectivity, i.e. the temporal correlation between remote cerebral areas. More comprehensive anatomically constrained models of interactions may provide an estimation of effective connectivity, i.e. the actual influence of one brain area upon the other. As a first step in this direction, we show here a psychophysiological interaction, an analysis which looks for a modulation of the activity of one cerebral region by another, under a specific experimental context (Friston *et al.* 1997).
In the framework of our sleep studies, the lack of activation of temporo-occipital areas was not in favour of the hypothesis of a modulation of cortical areas by amygdaloid complexes. We recently run an interaction analysis on the previously published data. This analysis shows that the cerebral blood flow of temporal cortex varies positively with the amygdala activity in, and only in, REM sleep (Fig. 1). These results suggest a modulation of temporal cortex by the amygdala during REM sleep, in keeping with our hypothesis. Similar interactions were observed on both sides. On the right side, a significant interaction was also shown in some more posterior regions. Interestingly enough, our results do not show such an interaction within brainstem. They do not provide evidence that amygdaloid complexes would favour REM sleep by stimulating brainstem areas, as suggested by animal studies. However, these negative results could be due to artifacts (e.g. partial volume effects on small structures, insufficient number of observations) rather than to the absence of the physiological processes.

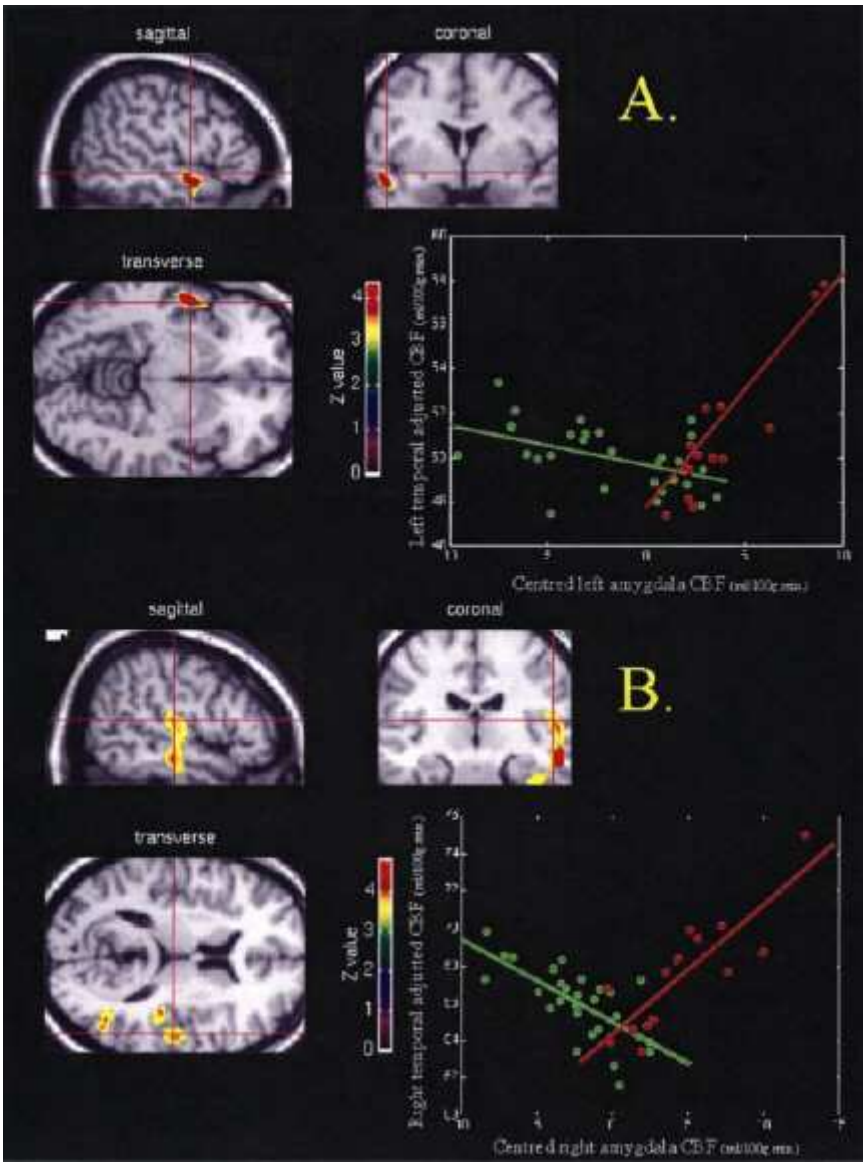

Figure 1. *Psychophysiological interactions. Modulation of temporal activity by the amygdala within the specific context of REM sleep. Amygdalar blood flows were estimated on significant voxels reported in Maquet et al. (1996). Data were reprocessed in SPM96 with a 12 mm gaussian smoothing. (A) Significant interaction in left temporal cortex (Z = 4.36; $p_{corrected}$ = 0.042; coordinates: x = -52 mm; y = 0 mm; z = -8 mm). The significant area is displayed on an MRI image, within the stereotaxic space of Talairach and Tournoux. The plot shows the relations, in terms of regional blood flow, between left amygdalar and the significant temporal voxel in REM sleep (red) and in the other states of vigilance (green). (B) Significant interaction in right temporal cortex (Z = 4.80; $p_{corrected}$ = 0.007; coordinates: x = 58; y = -20; z = -12 mm). The significant area is displayed on an MRI image, within the stereotaxic space of Talairach and Tournoux. The plot shows the relations, in terms of regional blood flow, between right amygdalar and the significant temporal voxel in REM sleep (red) and in the other states of vigilance (green).*

FUTURE PERSPECTIVES

Each neuroimaging technique has its own advantages and drawbacks, in terms of spatial and temporal resolution, technological constraints, cost, safety, etc., (for review, see Toga and Mazziotta 1996). The effort is put now on the coregistration of two or more techniques. Examples of such simultaneous recordings have already been published in the field of cognitive neurosciences (see, for instance, Heinze *et al.* 1994; Kleinschmidt *et al.* 1996). We currently try to obtain the tridimensional coregistration of EEG and PET data. In the framework of sleep studies, dipole modelling is hampered by the fact that no a priori hypothesis should be made on the localization and number of current sources. For this reason, we chose to consider distributed solutions. With this approach, each and every brain voxel is a possible current source and results are presented as clouds of electrical activity, as it is implemented in the Low Resolution Electromagnetic Tomography (LORETA) method (Pascual-Marqui and Michel 1994) or other techniques (Grave de Peralta Menendez *et al.* 1997).
Figure 2 shows the results obtained during sleep in a child presenting with continuous spike-and-wave discharges during sleep and acquired cognitive deterioration.

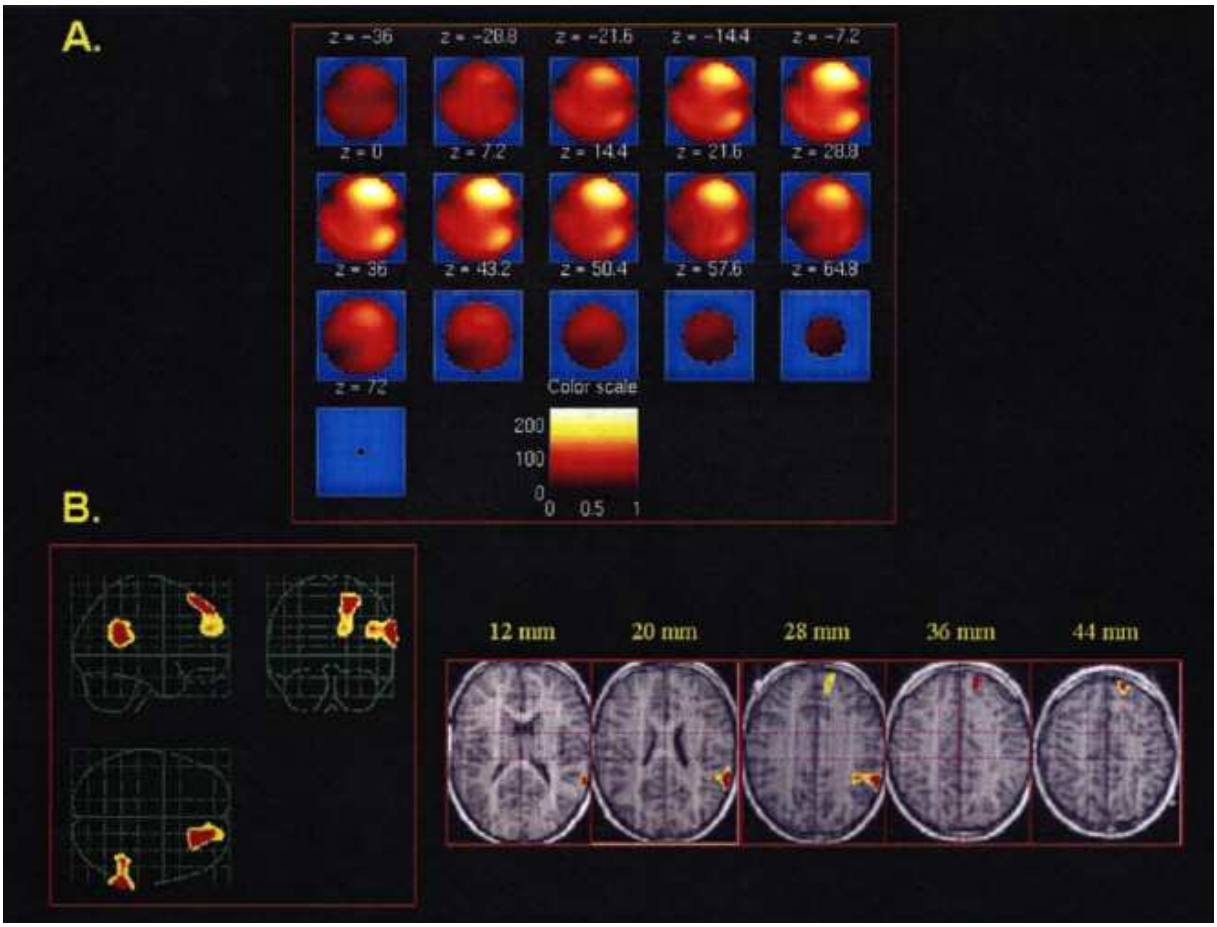

Figure 2. *Comparison of tridimensional EEG mapping of a spike with the corresponding PET data analysed by SPM (SPM96 version gaussian smoothing: 16 mm).* ***(A)*** *Tridimensional reconstruction of current sources of an*

average of 20 spikes, recorded in 17 channels during the uptake period of the FDG sleep scan. The source distribution was calculated using a modified version of Grave de Peralta-Menendez algorithm (1997). Results are shown from bottom to top. The right of the pictures represents the patient's right. The amplitude of the dipole module is color-scaled in arbitrary units. The largest dipole modules are concentrated on right fronto-polar and parietal areas. ***(B)*** *Left panel. Glass brain representation of the two regions where regional glucose metabolism is significantly different from a control population (N = 34; mean age = 44). One region is right fronto-polar (Z = 4.45;* $p_{corrected}$ *= 0.021; coordinates: x = 20; y = 42; z = 52 mm); the other is right parietal (Z = 4.39;* $p_{corrrected}$ *= 0.027; coordinates: x = 68; y = -48; z = 24 mm), in good agreement with EEG data. Right panel. The same results are shown on transverse planes, at different distances from the bicommissural plane. They are displayed over the patient's T1 MRI coregistered to PET data and normalized to the stereotaxic space of Talairach and Tournoux. The right of the pictures represents the patient's right.*

During the fluorodeoxyglucose uptake period, EEG records showed continuous bilateral spike-and-wave discharges with a right frontal predominance. Tridimensional reconstruction of current sources, based on a spherical head model, showed two regions of high activity: right fronto-polar and right parietal. These EEG results were in good agreement with the metabolic data showing, after SPM analysis, that glucose metabolism is significantly increased in the same regions.
The use of realistic, rather than spherical, head models would provide a more accurate representation of current source distribution, that could easily be co registered within a standard space, common to PET and MRI data.

CONCLUSIONS

This paper, by a few examples, has shown that functional neuroimaging studies can provide different kinds of valuable information. Firstly, they can demonstrate that the patterns of activation observed during sleep in humans are consistent with the data obtained in animals on the mechanisms of sleep generation. Secondly, they can point to cerebral areas that have not been thoroughly studied at a cellular level but would deserve further investigations. Thirdly, they should be able to explore the functional and hopefully, in the future, the effective-connectivity in human during sleep. In this respect, these techniques should provide an original contribution to the study of human sleep.

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