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Research report

Forebrain activation in REM sleep: an FDG PET study [1]

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Abstract

Rapid eye movement (REM) sleep is a behavioral state characterized by cerebral cortical activation with dreaming as an associated behavior. The brainstem mechanisms involved in the generation of REM sleep are well-known, but the forebrain mechanisms that might distinguish it from waking are not well understood. We report here a positron emission tomography (PET) study of regional cerebral glucose utilization in the human forebrain during REM sleep in comparison to waking in six healthy adult females using the ^{18}F-deoxyglucose method. In REM sleep, there is relative activation, shown by increased glucose utilization, in phylogenetically old limbic and paralimbic regions which include the lateral hypothalamic area, amygdaloid complex, septal–ventral striatal areas, and infralimbic, prelimbic, orbitofrontal, cingulate, entorhinal and insular cortices. The largest area of activation is a bilateral, confluent paramedian zone which extends from the septal area into ventral striatum, infralimbic, prelimbic, orbitofrontal and anterior cingulate cortex. There are only small and scattered areas of apparent deactivation. These data suggest that an important function of REM sleep is the integration of neocortical function with basal forebrain-hypothalamic motivational and reward mechanisms. This is in accordance with views that alterations in REM sleep in psychiatric disorders, such as depression, may reflect dysregulation in limbic and paralimbic structures.

Keywords: REM sleep; Limbic system; Cerebral glucose metabolism

1. Introduction

Sleep is a behavioral state characterized by a lack of interaction with the environment and a relative motor quiescence. With the development of the electroencephalogram (EEG), it was recognized that within sleep there are two primary behavioral states. One is characterized by relative EEG activation, rapid eye movements (REM) and muscular atonia and is designated REM sleep. The other is characterized by EEG deactivation, the relative absence of eye movements and relative preservation of muscle tone, and is designated non-REM (NREM) sleep. The behavior associated with sleep is dreaming. While dreaming occurs in all stages of sleep, awakenings from REM sleep more commonly result in story-like, affect-laden dream reports. The neurobiology of REM sleep has been investigated actively for more than 30 years. REM sleep is generated by brainstem mechanisms [18,32]. The physiology and pharmacology of these mechanisms is now quite well understood. What remains to be elucidated is the function of REM sleep, and particularly, the exact nature and significance of the forebrain activation associated with that sleep state. One approach to this problem is an analysis of dreaming behavior and this has a long [4,8,11,20], but controversial, [9,17] history. More recent analyses, largely based on electrophysiological data, have posited a role for REM sleep in brain development [27], brain plasticity and learning [6,19,21,22,36] and as a homeostatic balance for NREM sleep [3]. Another approach to understanding REM sleep is to analyze patterns of brain activation associated with REM sleep using either the deoxyglucose method [33]

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in animals or functional brain imaging in the human. In the cat, Lydic and coworkers [24] found increased glucose utilization in REM sleep compared to waking in a series of limbic and paralimbic structures. Similar findings have been reported using positron emission tomography (PET) in the human [5,26]. The present study was carried out to further characterize the patterns of forebrain activation in REM sleep by determining regional cerebral glucose utilization in the human using PET in normal, healthy subjects.

2. Materials and methods

The current study used ^{18}FDG PET methodology to study cerebral glucose metabolism during wakefulness and REM sleep in healthy women. This method allows the subject to sleep relatively undisturbed in a comfortable bed in a private room during the uptake and metabolism of the ^{18}FDG. To minimize the effects of sex and handedness on cerebral glucose metabolism, we restricted the sample to right-handed women. To maximize the contrast between the global brain states of waking and REM sleep, we performed the waking PET study at a circadian time associated with maximal alertness [28].

2.1. Subjects

Six right-handed healthy adult women (age, 34.6 ± 7.4 years; years of education, 17.0 ± 1.3; mean $\pm$ S.D.) were studied. The absence of a lifetime diagnosis of any psychiatric disorder was assessed by an interview with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version [34]. Subjects who could not remain drug- or alcohol-free verified by nightly urine drug screens during the study were excluded. A medical history was taken and a physical examination was conducted. Laboratory tests included an ECG, urinalysis, CBC with differential, electrolytes, BUN, serum creatinine, serum calcium, phosphate and uric acid, plasma bilirubin, alkaline phosphatase, SGOT, serology, glucose, T_3, T_4 and TSH. Subjects were required to have a negative serum pregnancy test within 24 h of both PET scans. Medical exclusion criteria included diabetes mellitus, hypertension (blood pressure $\geq 140/90$ mmHg on repeated testing), cardiovascular disease, cerebrovascular disease, neurologic disorders and endocrinopathies. Any subject with a specific sleep disorder was excluded from further study. Any subject with an apnea/hypopnea index ≥ 5 on night 1 screening was excluded from further study, due to potential alterations in cerebral metabolism related to sleep apnea.

2.2. EEG sleep procedures

Studies were performed at a General Clinical Research Center, University of Pittsburgh Medical Center using hole-in-the-wall techniques to minimize sleep disruption. EEG sleep was monitored for three nights, screening for sleep apnea and periodic limb movements on night 1. Bedtime and awakening times were defined by the mean bedtime over the 7 days preceding sleep studies as determined by review of a 7-day sleep log. On nights 1 and 2, subjects received a normal saline i.v. for accommodation to an indwelling i.v. used on night 3 for bolus injection of the radioisotope. The routine montage (nights 2 and 3) consisted of a single EEG channel (C4/A1–A2), two EOG channels (right and left eyes) referenced to linked mastoids, and a sub-mental EMG channel. EEG sleep from nights 2 and 3 was scored manually according to Rechtschaffen and Kales criteria [30] as well as by automated EEG sleep analyses as defined previously [23]. In addition to sleep continuity and sleep architecture measures, the primary REM sleep-dependent variables include: REM sleep time, percent, and latency (time between sleep onset and first REM period – any wakefulness occurring during the interval), activity (a measure of the number of REMs over the night), and density (a measure of the frequency of REMs during the night).

2.3. PET scan procedures

For the waking baseline comparison assessment of regional brain glucose utilization (rCMRglu), the subjects received an injection of 5 mCi ^{18}fluorodeoxyglucose (^{18}FDG) within 2–4 h [28] following awakening from the second night of sleep. The subjects were lying supine, eyes closed, ears open in the same bedroom used for the sleep studies for 15 min accommodation prior to injection and for 20 min following the injection. Subjects were monitored by EEG throughout the waking study. No subject fell asleep. They were then taken to the PET scanner for the rCMRglu analysis. For the REM sleep assessment of rCMRglu, FDG was injected via an indwelling catheter immediately after onset of the first REM sleep period, defined with appropriate EEG, EMG and EOG correlates [30], during the third night of recorded sleep. No subject awoke in response to the injection. After 20 min, the subjects were awakened and transferred to the PET scanner.

All PET scans were initiated 60 min after injection of the ^{18}FDG and consisted of 30 min emission followed by a 15-min transmission scan. An individually molded, thermoplastic headholder (marked with laser guidance for repositioning) was made for each subject to minimize head movement and to allow for head positioning for scanning. The head was positioned such that the lowest scanning place (visualized by a system of laser lines within the scanner gantry) was parallel to and 1.0 cm above the canthomeatal line. A 15-min transmission scan was obtained immediately after the emission scan (rather than prior to injection as is typical) to allow quantitative correction of attenuation. The use of a 4-mCi FDG dose, rather than the conventional clinical dose (e.g. for brain tumors) of 10 mCi, and the use of electronic windowing of the rod

source to reject head activity allowed this convenient timing of the transmission scan.

The uptake of ^{18}FDG from plasma to tissue is 70–80% maximal in the first 7–10 min after an i.v. injection and approximates completion at 25 min. The pattern of rCMRglu shown by PET for the injection of ^{18}FDG during waking will reflect brain activity during a resting, waking state. Since the duration of the REM period averaged 14 min, and was followed by a period of non-REM sleep in which ^{18}FDG uptake is low [16,25], the pattern of rCMRglu obtained during the period following injection will reflect brain activity during REM sleep almost exclusively.

For the purposes of using high resolution anatomic information in statistical analyses of the PET dataset, each subject was assessed by magnetic resonance imaging. For this study, a single spoiled gradient recoil (SPGR) MR pulse sequence was used with the following parameters: TE = 5, TR = 25, flip angle = 40°, NEX = 1, 1.5 mm slice thickness, contiguous slices. MR imaging was performed on a 1.5 T MR unit (Signa, General Electric).

PET images were reconstructed using standard commercial software as 31 transaxial slices (each 3.375 mm) with approximately 8 mm full-width half-maximum transaxial resolution. The image sets from each of the two scanning sessions were co-registered by Automatic Image Registration (AIR) software [38]. After registration, the PET data was summed and then registered to the subject's volume magnetic resonance MR study by AIR [39] which was then reviewed to ensure adequate registration (error < 1 pixel).

Analysis of group differences between waking and REM sleep was performed using the Statistical Parametric Mapping (SPM 1995) method [12,13]. The MR data were transformed to a Standard Atlas MR data set by linear affine transformation within an expanded form of AIR. The coregistered PET data was then similarly transformed into the standard space by using the same transformation equations as for the subjects MR thereby utilizing the high density of anatomical information in the MR for coordinate transformation [37]. Subsequently, images were convolved with a low-pass filter to increase the signal-to-noise ratio and confounding effects of differences in global rCMRglu were removed by analysis of covariance. Waking and REM sleep adjusted mean rCMRglu values and error variance were calculated for each pixel in the stereotaxic atlas space. Means between waking and REM sleep at each pixel were compared using a *t*-statistic. Whole-brain parametric maps distributed according to the *t*-values (displaying all pixels significant at $P < 0.01$) were created. Regions are reported only if they were among a contiguous group of pixels over more than one transverse plane which all reached significance at the $P < 0.01$ level.

In order to display these subjects' grouped significant regions of activation on their own averaged MR image, we aligned each subject's MR to the Talairach MR provided in the SPM95 program using Woods' intersubject AIR algorithm. The aligned MRs were then averaged and saved in Analyze format for use with SPM95. The background brain image in the figures reported, therefore, represent the averaged MR image for the actual subjects in the study.

3. Results

3.1. Subjects

Six healthy women (age, 34.6 ± 7.4, mean ± S.D.) with no history of depression or other psychiatric disorder who met inclusion/exclusion criteria as noted above were stud-

Table 1
EEG sleep variables for baseline (night 2) and PET assessment night

Parameters	Values (mean ± S.D.)
Baseline night	
Total recording period (min)	461.83 ± 48.79
Sleep maintenance (%)	96.52 ± 2.78
Sleep latency (min)	17.33 ± 18.22
Minutes awake	16.00 ± 13.22
Total delta counts	5723.50 ± 2910.34
REM latency minus awake	62.50 ± 9.96
REM density	1.00 ± 0.41
Minutes stage 1	13.16 ± 9.01
Minutes stage 2	259.01 ± 22.23
Minutes stage 3	22.33 ± 18.39
Minutes stage 4	13.34 ± 21.27
Delta counts (NREM period 1)	1785.17 ± 956.02
Total minutes of REM	120.50 ± 10.00
PET assessment night	
Minutes awake (prior to REM)	4.50 ± 5.24
Total automated delta counts (NREM 1)	2034.83 ± 856.42
Sleep latency	14.67 ± 9.03
REM latency minus wake after sleep onset	68.83 ± 10.01
REM minutes during FDG uptake	14.17 ± 4.40

Table 2
Regions of activation from waking to REM sleep

Region size for confluent area (pixels)	Region of maximal difference in confluent area	Coordinates of maxima			*Z* for maxima	*P*
		x	*y*	*z*		
188	Ant. cingulate	20	0	40	4.16	< 0.001
17	L. dorsolateral prefrontal	−30	46	12	3.90	< 0.001
49	L. insula	−42	2	12	3.58	< 0.001
728	L. infralimbic	−8	18	−8	3.57	< 0.001
	R. medial prefrontal	4	44	12	3.57	< 0.001
	R. frontal	10	48	24	3.40	< 0.001
	R. medial prefrontal	10	38	28	3.29	0.001
	R. gyrus rectus	8	52	−8	3.10	0.001
	L. anterior inferior caudate	−6	18	0	3.06	0.001
	L. inferior orbitofrontal	−6	26	−12	3.03	0.001
7	R. dorsolateral prefrontal	36	40	4	3.49	< 0.001
51	R. parahippocampal gyrus	22	−46	−8	3.48	< 0.001
29	L. amygdala	−22	−18	−8	3.22	0.001
15	R. middle temporal	50	−46	4	3.22	0.001
19	L. parahippocampal gyrus	−18	−46	−8	3.14	0.001
114	R. superior temporal	48	−4	4	2.93	0.002
7	R. lateral hypothalamus	8	−12	−12	2.51	0.006

ied. Their mean ($\pm$S.D.) Hamilton Rating Scale for Depression [15] score was 0.5 ± 1.2 and mean Beck Depression Inventory [1] score was 0.83 ± 2.0. Table 1 documents the normality of their EEG sleep profile during a routine night of sleep (night 2) and during the first NREM/REM cycle corresponding to the PET study night (night 3). The durations of REM sleep following the injection of FDG for each subject were 14, 18, 20, 11, 14, and 8 min.

3.2. PET results

Fig. 1 shows the whole brain statistical parametric map revealing all areas which had statistically ($P < 0.01$) greater normalized rCMRglu during REM sleep than during waking. Removal of the data from the one subject whose REM duration following FDG uptake was 8 min in a separate SPM analysis did not alter the general pattern of activation. Table 2 shows the regions of significant activation ($P < 0.01$) from waking to REM sleep, including the number of contiguous pixels within a region significant at the $P < 0.01$ level; an anatomical description of the pixel of maximum significance within the region; the exact Tailarach axis coordinates of the pixel of maximum significant activation; the *z*-score for the pixel; and the level of statistical significance. While the analysis was performed at a significance level of $P < 0.01$, it is apparent in nearly every case that the pixel of maximum significant difference within a region was significant at the $P \leq 0.001$ level. For one large contiguous region spanning 728 significant pixels in the anterior midline of the brain, multiple regions of maximal significance within the overall region are given in order to clarify the anatomical extent of the region.

Fig. 2 provides an illustrative display of regions with increased rCMRglu which reached statistical significance mapped onto select sagittal, transverse and coronal sections of the averaged MR images of the actual subjects used in the analysis. Descriptively, the largest area of activation during REM sleep in relation to waking occurred in anterior midline structures best viewed in a midline sagittal section 4 mm to the right of midline (Fig. 2A) and in a transverse section 8 mm superior to the anterior–posterior commissural line (Fig. 2B). Posteriorly, this region begins in the septal nuclei, then extends anteriorly and inferiorly through adjacent ventral striatum (nucleus accumbens, substantia innominata area) and infralimbic cortex (Brodmann area 25). Continuing anteriorly, this activation extends beneath and around the corpus callosum into the orbital frontal cortex (areas 11 and 12) as seen in a transverse section 8 mm below the AC–PC line (Fig. 2C). Superiorly, this region then arches around the corpus callosum in the anterior cingulate cortex (Brodmann area 24), and the medial prefrontal or prelimbic cortex (Brodmann area 32). Additional midline limbic activation of the right lateral hypothalamic area, the left

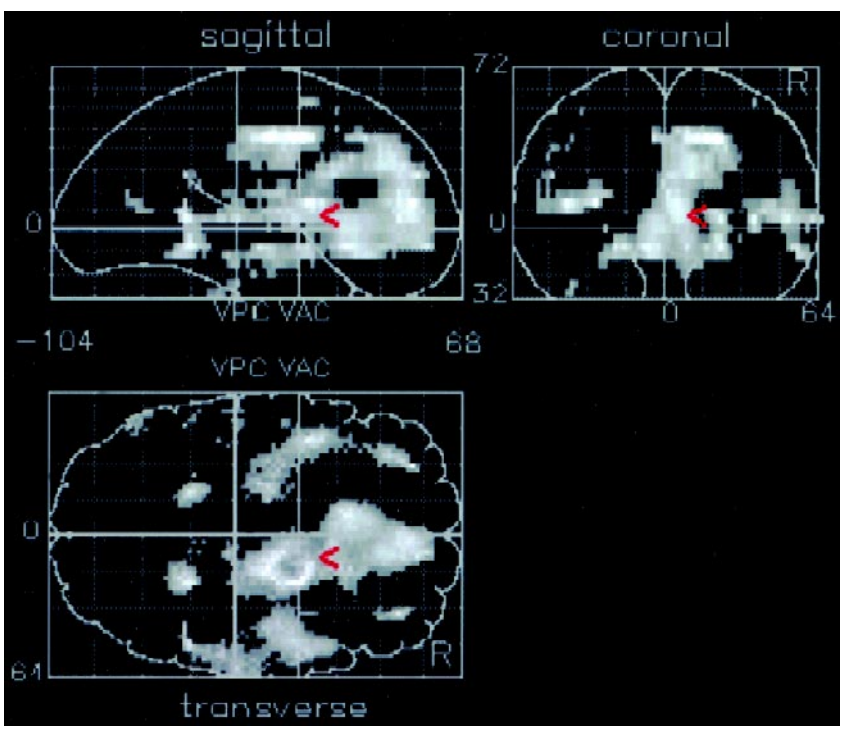

Fig. 1. All regions in the brain which have statistically greater ($P < 0.01$) relative cerebral glucose metabolism during REM sleep than during wakefulness are shown in this statistical parametric image.

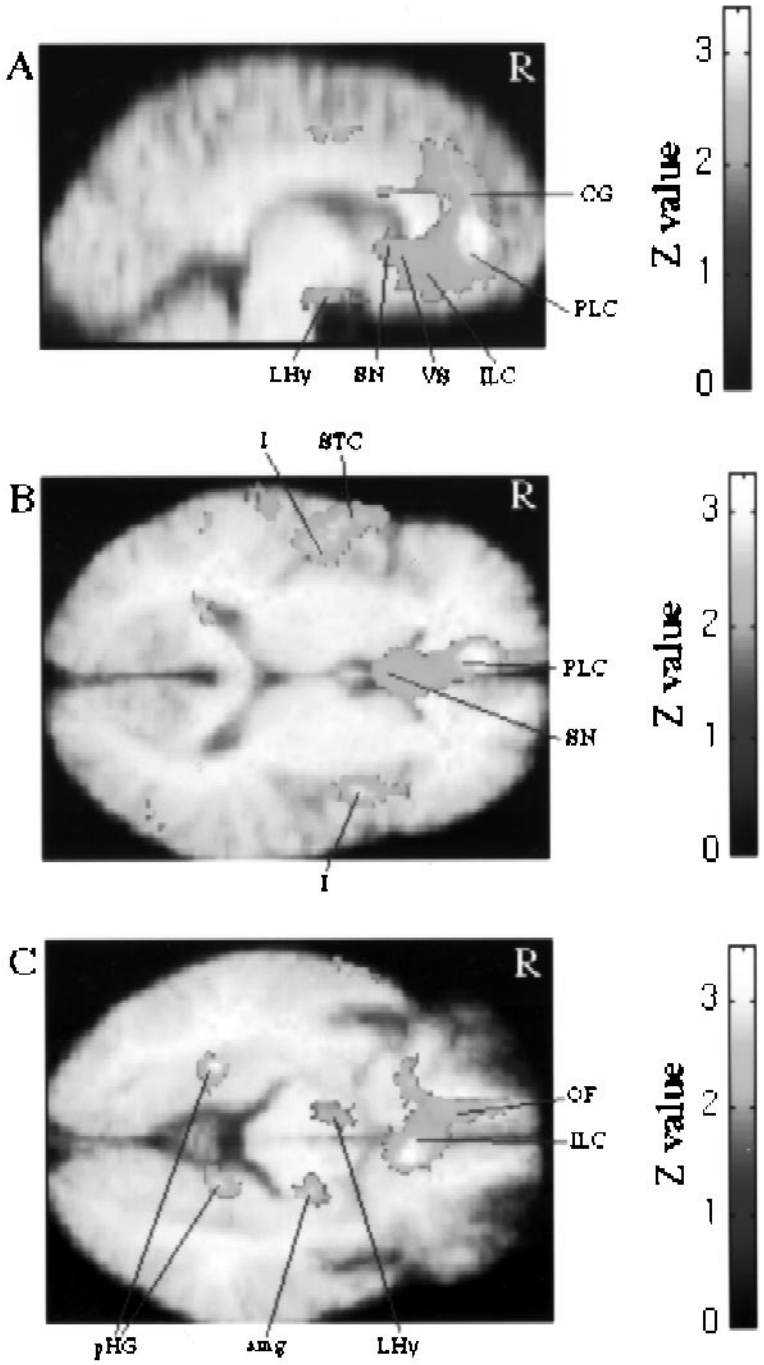

Fig. 2. In contrast to the whole brain statistical parametric map in Fig. 1, these figures show selected individual sections of the brain on which corresponding regions of significance have been overlaid. In order to display these subjects' grouped significant regions of activation on their own averaged MR image, we aligned each subject's MR to the Talairach MR provided in the SPM95 program using Woods' intersubject AIR algorithm. The aligned MRs were then averaged and saved in Analyze format for use with SPM95. The background brain image in these figures, therefore, is the averaged MR image for the actual subjects in the study. amg, amygdala; Cg, cingulate gyrus; ILC, infralimbic cortex; I, insula; LHy, lateral hypothalamus; of, orbitofrontal cortex; pHG, parahippocampal gyrus; PLC, prelimbic cortex; PRC, perirhinal cortex; SN, septal nuclei; STC, superior temporal cortex; VS, ventral striatum.

amygdala and a localized region in both parahippocampal gyri, can also be seen in the low transverse section (Fig. 2C). No activation of the posterior cingulate cortex was noted. Bilaterally, areas of activation of the insular cortex extending into the medial aspect of the superior temporal cortex on the right were noted maximally between 0 and 15 mm above the anterior–posterior commissural line (Fig. 2B). There also was a small, bilateral area of activation in the fusiform gyrus, probably entorhinal cortex. There are small areas of decreased rCMRglu. The largest of these

Table 3
Reliability of baseline EEG sleep in a healthy subject separated by 18 months

Measure	Time 1	Time 2
Baseline sleep continuity		
Sleep efficiency	94	91
Total sleep time	375	398
Sleep latency	14	5
Baseline sleep stages		
Stage 1 (%)	5.6	5.8
Stage 2 (%)	59.5	61.3
Stage 3 (%)	6.1	8.0
Stage 4 (%)	0.0	0.0
Stage REM (%)	28.8	24.9
Baseline REM measures		
REM latency	76	76
REM period 1		
REM activity	14	32
REM density	1.0	1.0
REM period 2		
REM activity	17	8
REM density	0.8	0.7
REM period 3		
REM activity	27	23
REM density	0.8	0.8
Whole night REM		
REM activity	91	86
REM density	0.8	0.9

was in the occipital lobes and smaller areas are present in the left frontal area and right posterior cingulate area. The significance of these scattered small areas of posterior decreased glucose utilization is unclear.

3.3. Reliability of limbic and paralimbic activation during REM sleep

One subject, a 32-year-old healthy woman had identical 3-night EEG sleep, waking and REM sleep PET assessments at two time points separated by 18 months. Baseline EEG sleep measures and clinical variables were similar at both times (Table 3). Mean change in normalized glucose metabolism in 20 regions which showed activation at time 1 was 2.46 ± 1.08. At time 2, the mean change in these 20 identical regions was 2.57 ± 1.20 (Fig. 3). A paired *t*-test between the two time points showed no statistically significant difference in the degree of activation from waking to REM sleep ($t = 0.34$, $P = 0.73$, $df = 19$). In each of the structures which showed increases from waking to REM sleep at time 1, there also was an increase at time 2. Substitution of her time 2 PET measures for her time 1 measures in the SPM (REM–wake) for 6 healthy subjects shown in Fig. 1 did not change the overall pattern of limbic and paralimbic activation.

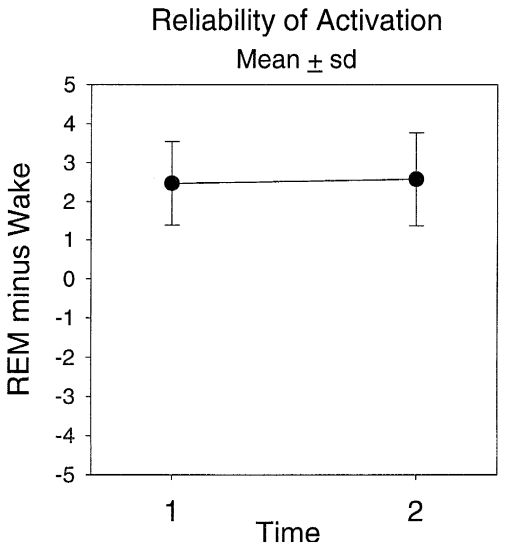

Fig. 3. Reliability of activation across 18 months in normalized cerebral glucose metabolism for 20 structures activated at time 1 in a healthy subject.

4. Discussion

The principal objective of this study was to use PET with analysis of rCMRglu to define the forebrain areas that are activated in REM sleep in comparison to waking in healthy, young subjects. The data obtained indicate that there are three primary sites of activation as shown by increased rCMRglu. The largest of these is an extensive confluent area along the midline that includes the lateral hypothalamic area, septal area, ventral striatum–substantia innominata, infralimbic cortex, prelimbic and orbitofrontal cortex and the anterior cingulate cortex. Much of this is bilateral, but the involvement of cingulate cortex is predominantly on the right. The second area is the frontotemporal operculum and the insula bilaterally and the third is the parahippocampal gyrus (entorhinal area) bilaterally. The left amygdala is also activated. There are scattered areas of decreased glucose utilization, but these are small, and their distribution does not appear to be functionally significant. These observations are quite similar to those reported by Lydic [24] from a study comparing regional glucose utilization in the cat in REM sleep and waking using the Sokoloff [33] method. A larger study similarly reported activation of the anterior cingulate during REM sleep [5]. They are also similar to those reported by Maquet et al. [26] in the human also comparing REM sleep and waking. In their study, Maquet et al. use ^{15}O-H_2O to determine rCBF in each state. Increased rCBF was observed in their study in the anterior cingulate and amygdala bilaterally and in the right parietal operculum, left thalamus and pons. They also observed decreased rCBF in the dorsolateral prefrontal cortex and parietal cortex bilaterally and in the posterior cingulate cortex. The main differences between the studies are in the extent of the confluent paramedian area of activation observed in our study and our finding of activation in the temporal opercula and insular cortex. In addition, we do not observe significant areas of decreased rCMRglu. There are four differences in methodology that may account for some, or

all, of the differences between the two studies. First, there is the difference between studying rCBF and rCMRglu. It would seem unlikely that this technical issue accounts for all of the differences. Second, the Maquet et al. study [26] had subjects sleeping in the PET scanner, whereas our subjects slept in the somewhat more naturalistic setting of a Clinical Research Center. Third, all of the subjects in their study were male whereas all of ours were female. To determine whether the differences in the observations between the studies reflects gender would require a further study testing that hypothesis. Fourth, and likely to be more significant, their subjects were scanned in late night REM periods whereas ours were uniformly studied in the first REM period. The only way to determine the importance of this methodological difference would be to do a direct comparison of early and late REM periods using a single PET method.

The predominant areas of activation in our study are limbic and paralimbic regions which form an interface between the neocortex on one side and the basal forebrain-hypothalamus on the other [7,31]. These areas are involved in behavioral activation, motivation–reward mechanisms [35] and in the integration of homeostatic regulatory mechanisms, including autonomic control, with adaptive behavior. This realm of function is consistent with a role in synaptic plasticity [27] and memory consolidation [14,22] and it is quite in accordance with older, more general views that REM sleep, and specifically dream content, is associated with internally generated, or instinctual behaviors that subserve adaptive mechanisms. These considerations emphasize that there are two components to REM sleep. The first is the neurological mechanisms, the brainstem mechanisms which cannot be shown readily with PET and the activation of limbic and paralimbic structures shown in this study. These form the neurobiological foundation of the sleep state. The second aspect of REM sleep is the associated behavior, dreaming [17]. The function of REM sleep and dreaming is not known with certainty. We presume that the pattern of activation shown in our study reflects a part of the substrate of dreaming behavior. This does not help, of course, in understanding either the meaning or the function of dreams and we cannot exclude the possibility that the dream is merely an evanescent, random product of cortical activation that is no more essential to the fundamental function of REM sleep than memories of the dream are to waking behavior. It is evident, though, that the extent of neocortical activation in waking and REM sleep is essentially the same. Finally, while ‘dreaming’ has been reported to occur throughout all stages of sleep [10], the current findings of limbic and paralimbic activation during REM sleep, in light of prior findings of increased cortical activation, and increased metabolism during REM sleep, as well as global, regionally non-selective cortical deactivation and decreased metabolism during NREM sleep, are generally supportive of the traditional notion that more story-like affect-laden dreams are more attributable to the REM sleep, than NREM sleep behavioral state.

A second aim of the current study was to develop a feasible, reliable, and valid functional brain imaging paradigm to assess limbic and paralimbic function, or dysfunction, in pathological states in which alterations in REM sleep have been observed, for example, in depression. With respect to feasibility, we suggest that the FDG paradigm described here offers several advantages over other available functional brain imaging methods. The primary limitation of PET blood flow and functional MR studies for imaging sleep states is the requirement that subjects sleep in a scanner with their heads immobilized. In order to facilitate sleep in this non-naturalistic setting, some investigators sleep deprive their subjects, an intervention known to result in REM sleep enhancement. In one such study [26], only seven of 30 original subjects were able to complete sufficient periods of sleep for inclusion in analyses. In the current paradigm, no subject was rejected due to inability to sleep and no subject was aroused sufficiently by the recording and injection procedure to exclude them from subsequent analyses. These findings demonstrate that the current paradigm is feasible for use in clinical studies where subject attrition and the study of naturalistic sleep are important considerations. With respect to reliability, in the one subject for whom repeated assessments were performed, there was a striking consistency in the activation of structures during REM sleep at both time points. With respect to validity, the similarities between our findings in female humans, those of Maquet et al. [26] in male humans, and those reported in cats suggest that REM sleep activates similar limbic and paralimbic structures in both human sexes and among mammals. While the FDG PET method offers advantages in the ‘naturalistic’ study of sleep states, its primary limitation is that FDG PET studies generally study steady-state conditions over a 30-min period of time, whereas the duration of REM sleep for individual subjects may be shorter and cannot be reliably predicted.

The current findings have important implications for the interpretation of previous findings in EEG sleep in patients with mental disorders. Alterations in EEG measures of REM sleep have been described for diverse mental disorders [2,29], including schizophrenia, post-traumatic stress disorder, obsessive–compulsive disorder and a reliable alteration in REM sleep early in the night has been proposed to be pathognomonic for patients with mood disorders. The current finding of selective activation of limbic and paralimbic structures during REM sleep, suggests that the EEG sleep findings may reflect dysregulation in limbic and paralimbic structures, regions known to be associated with affective and adaptive behavior. Difficulties in defining EEG sleep markers specific to a disorder [2] may reflect a lack of sensitivity of EEG sleep measures to accurately define diverse pathophysiologic processes in limbic function which may independently lead to diverse

mental disorders. The use of functional brain imaging studies in conjunction with EEG sleep measures offers the promise of more directly studying dysregulation of limbic and paralimbic structures which, in turn, may offer enhancements in specifying discrete limbic or paralimbic functional lesions unique to a mental disorder.

In summary, REM sleep is associated with a preferential activation of a wide region of midline limbic and paralimbic structures, temporal and insular cortex and entorhinal cortex not evident during quiet waking. These data are in accordance with the view that one function of REM sleep is the integration of neocortical activity with hypothalamic-basal forebrain regulatory and motivational–reward mechanisms. We have demonstrated that the FDG PET paradigm using a waking to REM sleep contrast offers a feasible, reliable, and valid assessment of limbic and paralimbic activation as defined by increased normalized glucose metabolism. We suggest that the finding of activation of limbic and paralimbic structures during REM sleep in healthy subjects may have important implications for understanding the pathophysiology of alterations in REM sleep previously seen in diverse mental disorders and that the use of this paradigm in patients with mental disorders could provide insights into the pathophysiology of these disorders.

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