Sleep, 14(2):155–162

The Effect of Sleep Deprivation on Cerebral Glucose Metabolic Rate in Normal Humans Assessed with Positron Emission Tomography

*Joseph C. Wu, †J. C. Gillin, *Monte S. Buchsbaum, *Tamara Hershey, *Erin Hazlett, *Nancy Sicotte, and *William E. Bunney, Jr.

**University of California, Irvine, California;*
†Department of Psychiatry, University of California, San Diego, and San Diego Veterans Administration Medical Center, San Diego, U.S.A.

Summary: This study is the first report on the effects of total sleep deprivation (about 32 h) on regional cerebral glucose metabolism during wakefulness in man, using positron emission tomography (PET) with F-18 deoxyglucose (FDG). Sleep deprivation leads to a significant reorganization of regional cerebral metabolic activity, with relative decreases in the temporal lobes and increases in visual cortex. Absolute glucose metabolic measurements indicate a decrease in thalamus, basal ganglia, white matter, and cerebellum. No overall decrease in whole brain metabolism was noted after sleep deprivation. As expected, sleep deprivation significantly reduced visual vigilance as assessed by the continuous performance test and this decrease was correlated significantly with reduced metabolic rate in thalamic, basal ganglia, and limbic regions. **Key Words:** Vigilance—Continuous performance test—Sleep—PET—Humans—Sleep deprivation—Regional cerebral glucose metabolism.

Studies of total or selective stage sleep deprivation have not fully clarified the functions or mechanisms of normal sleep (1–4). Sleep deprivation shortens sleep latency (5), enhances electroencephalographic (EEG) delta waves during recovery sleep (6), alters average evoked responses (7,8), interferes with performance on tasks requiring motivation and sustained attention (1,9), and activates epileptic EEG patterns and seizures in some patients (10,11). It also has a brief but significant antidepressant effect in about 50% of depressed patients (12). In contrast to these effects of short-term sleep deprivation, prolonged sleep deprivation (for 2 weeks or more) has a hypermetabolic effect and causes death in rats (13,14).

Slow wave sleep decreases both whole body metabolic rate (15,16) and cerebral metabolic rate in rhesus monkey (17,18) and man (19) as measured by the 2-deoxyglucose (2-dG) method and positron emission tomography (PET) with F-18 deoxyglucose (FDG). Cerebral blood flow is also diminished (20), suggesting diminished cerebral metabolic rate. Adam (21) hypothesized that cellular work was decreased during sleep thus allowing a net anabolic activity increase. This decrease in cellular work might imply a decrease in metabolism. Thus, the initial observations on cerebral metabolic rate in the monkey are consistent with the rest or restoration theory of sleep (21–23).

To our knowledge, the effects of sleep deprivation on cerebral metabolism have not previously been reported. In an early study, however, Mangold et al. (24), using the nitrous oxide method, reported nonsignificantly reduced cerebral blood flow in fatigued (about 20 h sleep deprived) subjects compared to well-rested subjects. In addition, Nakamura et al. (18) found no difference in 2-DG cerebral metabolism between rested and sleepy monkeys (who had just been awakened from sleep).

METHODS

In this study, eight normal controls (six males, two females, mean age = 25.3 years) were studied with two separate FDG PET scans. Seven of the eight subjects had their first PET scan after a night of normal sleep and the second PET scan several weeks to months later following all night sleep deprivation. All subjects re-

Accepted for publication June 1990.
Address correspondence and reprint requests to Joseph Wu, M.D., D402, Med Sci I, UCI-CCM, Irvine, CA 92717, U.S.A.

ceived a psychiatric interview, physical examination, and routine laboratory screening. All subjects were free of physical and mental disorders. None had a first degree relative with a major psychiatric illness. All subjects are right-handed.

Sleep deprivation and task

Subjects were sleep deprived under continuous supervision from approximately 0700 h until after the scanning procedure the following afternoon at 1300–1700 h. The FDG PET procedure has been described previously (25). During the uptake of FDG the subjects did the continuous performance test (CPT), a visual vigilance task (26), which they had practiced previously. This requires a button press response to stimuli occurring at 3-s intervals, ensuring that subjects remain awake during FDG uptake.

Plasma glucose concentration measured after a normal night's sleep (mean 77 ± 12 mg/dl) and after sleep deprivation (mean 78 ± 11 mg/dl) did not differ.

Image collection

Approximately 45 min following the injection of FDG, nine slice images were obtained on the NeuroECAT scanner in the Brain Imaging Center of the Department of Psychiatry, University of California, Irvine as described elsewhere. The scan was transformed to glucose metabolic rate according to the model of Sokoloff et al. (27), using our adaptaion of the program developed by Sokoloff. Kinetic constants and lumped constant from Phelps et al. (28) were used.

Image analysis

Cortical metabolic rates were measured using our cortical peel technique (19), which is shown in Figure 1. First, each PET slice is visually matched to an anatomical slice in the Matsui and Hirano atlas without knowledge of sleep condition. Next, a strip of pixels around the circumference of each slice is identified by computer algorithm and the proportional distance on the strip corresponding to the cortical area identified. Pixels in the cortical edge are averaged across all slices in which the cortical area appears in the atlas. In this way, we obtain values for the metabolic rate of the four lobes of the brain for each hemisphere.

Subcortical structures were assessed using stereotaxic coordinates derived from the same neuroanatomical atlas (29), as we have previously described (30). The region of interest is 3 × 3 pixels or 6 × 6 mm. This area fits well within most structures listed in the tables, allowing minor variation from person to person. The accuracy of this application for the basal ganglia is adequate as discussed elsewhere (30). It should also be noted that random deviations from the true coordinates due to head shape and tilt variation between scans would tend to create type II statistical error, rather than producing spurious findings. Data were analyzed both as absolute metabolic rate (μmol/100 g/min) and as relative rates (region of interest divided by whole slice metabolic rate). Because individual whole brain metabolic rates vary widely, relative metabolic rates may reveal regional changes with greater statistical power (31,32). The data were analyzed with repeated measures analysis of variance (ANOVA) to minimize the chance of type I error with multiple t tests on many brain regions. The dimensions were previous night's sleep condition (normal sleep vs. sleep deprived), brain structures (with eight brain systems as described below), and hemisphere (left, right). This approach allows testing for sleep deprivation effects on the whole brain, brain system regional differences, and hemispheric effects of sleep deprivation in one systematic operation. We used the Huynh-Feldt corrected degrees of freedom. All significant interactions are reported. Follow-up simple interactions are given to further define the effects and simple effects analysis are reported to facilitate future direct comparison of our data with those of other investigators.

We divided the brain into eight main systems and averaged acrose several regions of interest: lateral cortex (average of frontal, temporal, parietal and occipital lobes), medial cortex (frontal—Brodmann area 32, rectal gyri; parietal—paracentral; occipital—precuneus, calcarine; and medial temporal), limbic system (amygdala, hippocampus, and cingulate), basal ganglia (caudate, putamen, globus pallidus), thalamus, white matter (frontal white matter, corpus callosum, and optic radiations), midbrain, and cerebellum.

RESULTS

Psychophysical performance

As expected, vigilance performance significantly declined after sleep deprivation (d′ = 2.05) compared with normal sleep (d′ = 2.53, t = 2.47, df = 7, $p < 0.05$).

Whole brain metabolism

Mean cerebral metabolic rate across the nine slices (weighted for the number of pixels/slice) did not change significantly with sleep deprivation (15.6 μmol/100 g/min before, 14.5 μmol/100 g/min afterward) (Figs. 2 and 3).

TABLE 1. *Relative regional metabolism before and after sleep deprivation*[a]

	Baseline		Sleep deprived		Difference	
System/structure	x	SD	x	SD	x	SD
Cortical surface	1.06	0.03	1.06	0.04	0.006	0.04
Frontal lobe	1.17	0.05	1.13	0.05	−0.03	0.05
Parietal lobe	1.08	0.08	1.16	0.09	0.08	0.11
Temporal lobe	0.95	0.06	0.88	0.06	−0.07	0.05[b]
Occipital lobe	1.04	0.04	1.08	0.03	0.04	0.03[b]
Medial cortex	1.15	0.09	1.18	0.06	0.03	0.09
Limbic	0.94	0.05	0.95	0.10	0.01	0.11
Thalamus	1.08	0.05	0.94	0.18	−0.14	0.19
Basal ganglia	1.15	0.08	1.08	0.09	−0.07	0.13
White matter	0.76	0.11	0.79	0.19	0.03	0.10
Midbrain	0.89	0.12	0.89	0.15	−0.001	0.09
Cerebellum	1.10	0.19	0.99	0.14	0.11	0.10[b]

[a] Three-way ANOVA with condition (baseline, sleep deprivation), hemisphere (left, right) and structure (eight system/structures). Significant condition by structure interaction ($F = 3.5$; df = 4.30,30.09; p = 0.0165). Three-way ANOVA done the same way with structures only from the cortical surface (frontal, parietal, temporal, occipital) showed a significant condition by lobe interaction ($F = 9.03$; df = 1.37,9.56; p = 0.0099).

[b] $p < 0.05$, simple effects analysis, baseline vs. sleep deprivation.

TABLE 2. *Relative regional metabolism before and after sleep deprivation*[a]

	Baseline		Sleep Deprived		Difference	
System	x	SD	x	SD	x	SD
Cortical surface						
Left	1.04	0.04	1.06	0.05	0.01	0.05
Right	1.07	0.05	1.07	0.05	−0.002	0.04
Medial cortex						
Left	1.16	0.11	1.18	0.07	0.02	0.13
Right	1.13	0.09	1.18	0.05	0.05	0.09
Limbic system						
Left	0.92	0.06	0.96	0.09	0.05	0.09
Right	0.96	0.05	0.93	0.12	−0.02	0.14
Thalamus						
Left	1.08	0.08	0.91	0.19	−0.17	0.19[b]
Right	1.08	0.09	0.97	0.18	−0.12	0.23
Basal ganglia						
Left	1.17	0.07	1.06	0.09	−0.11	0.13
Right	1.12	0.13	1.09	0.11	−0.03	0.14
White matter						
Left	0.69	0.06	0.79	0.20	0.09	0.18
Right	0.83	0.19	0.80	0.21	−0.03	0.08
Midbrain						
Left	0.85	0.11	0.88	0.17	0.03	0.17
Right	0.94	0.18	0.90	0.16	0.03	0.11
Cerebellum						
Left	1.07	0.18	0.99	0.14	−0.08	0.13
Right	1.13	0.22	0.99	0.17	−0.14	0.13[b]

[a] Three-way ANOVA with condition (baseline, sleep deprivation), hemisphere (left, right) and structure (eight) showed significant condition by structure by hemisphere interaction (multivariate T-square; df = 1,7; p = 0.0011). Follow-up simple interaction two-way ANOVA (condition by structure) for the left hemisphere showed a two-way interaction ($F = 3.63$; df = 6.6,46.1; p = 0.004). The right hemisphere showed no significant interaction. Follow-up simple interaction two-way ANOVA (condition by hemisphere) for the cerebellum showed a two-way interaction ($F = 9.12$; df = 1,7; p = 0.02). The other brain systems showed no significant interaction.

[b] $p < 0.05$, simple effects analysis, baseline vs. sleep deprivation.

Brain systems

After sleep deprivation, the thalamus, basal ganglia, and cerebellum metabolic ratios show a decrease, whereas little change is seen in the cortical surface as a whole, limbic system, medial cortex, or midbrain metabolic ratios after sleep deprivation. These findings were confirmed by ANOVA (see Table 1, significant condition by structure interaction, $F = 3.5$; df = 4.30,30.09; p = 0.0165).

A significant brain system by hemisphere by condition interaction was also seen for brain metabolic ratios (Table 2). Three-way ANOVA with condition (baseline, sleep deprivation), hemisphere (left, right) and structure (eight structures) showed significant condition by structure by hemisphere interaction (multivariate T-square, df = 1,7; p = 0.0011) for Table 2. Significant decrease was seen in left but not in right thalamic ratios after sleep deprivation.

A similar three-way ANOVA for absolute metabolic rates did not show a significant condition effect or interaction. Simple effects analysis confirmed a significant decrease in thalamic system and cerebellum (see Table 3), not dissimilar to the relative metabolic rate data.

Cortical lobes

A three-way ANOVA (sleep condition by lobe by hemisphere) showed a significant condition by lobe interaction for absolute (condition by lobe interaction, TSQ = 7.3; df = 3,5; p = 0.02; see Table 3) and relative (TSQ = 9.49; df = 3,5; p = 0.02; see Table 1) values. Frontal and temporal lobes showed a significant decrease in absolute metabolic rate whereas the parietal lobes showed an increase and occipital lobes showed no change. Similar results were seen for relative metabolic ratios for the cortical lobes as was seen with absolute glucose metabolic rates. Simple effects analysis confirmed a decrease in relative temporal lobe metabolism and an increase in relative occipital lobe metabolism.

Regional metabolic correlation with task

In this study, the greater the decrease in attention scores from rest to sleep deprivation, the greater the reduction in absolute metabolic rates (data combined for right and left side). These correlations were positive

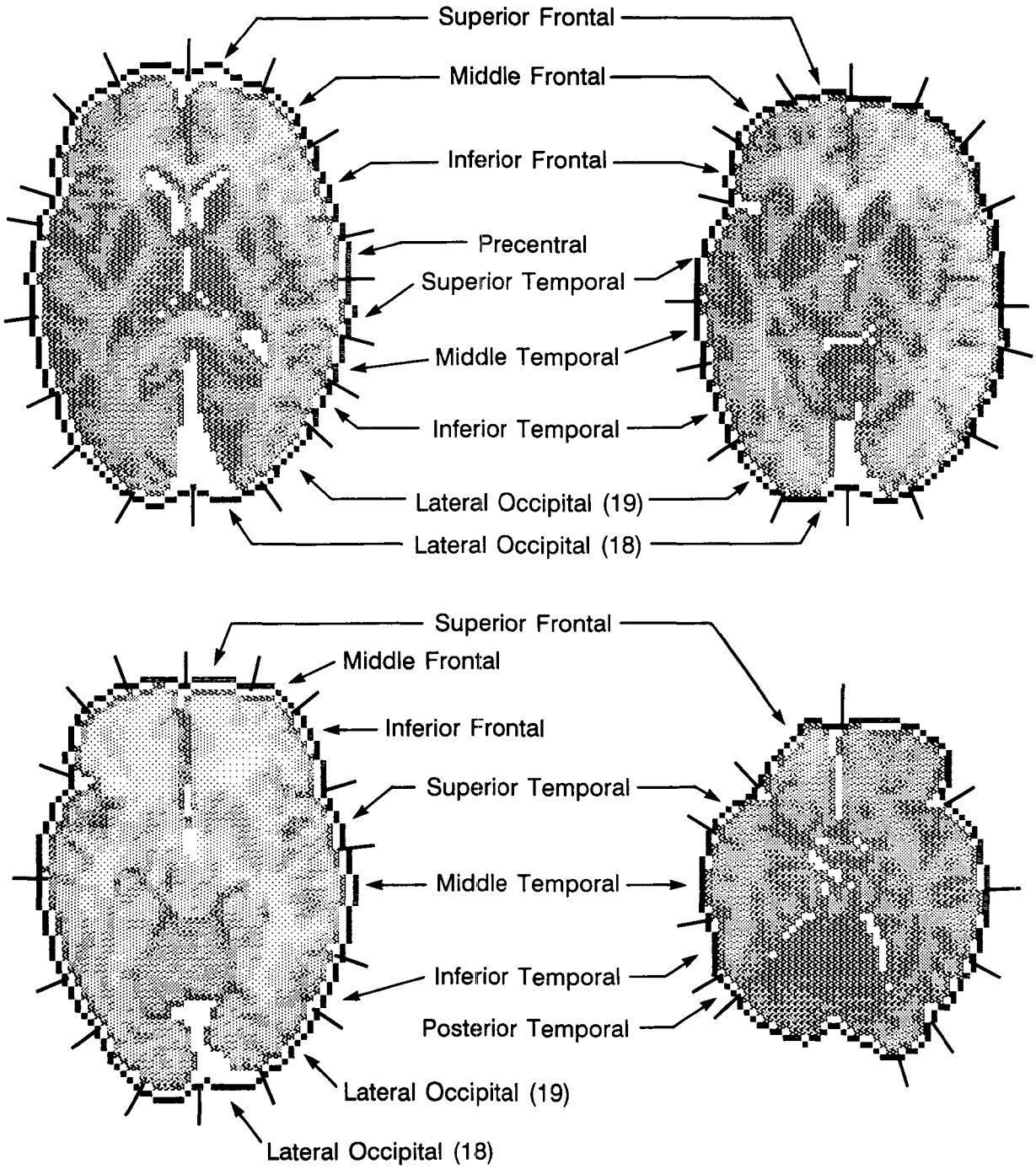
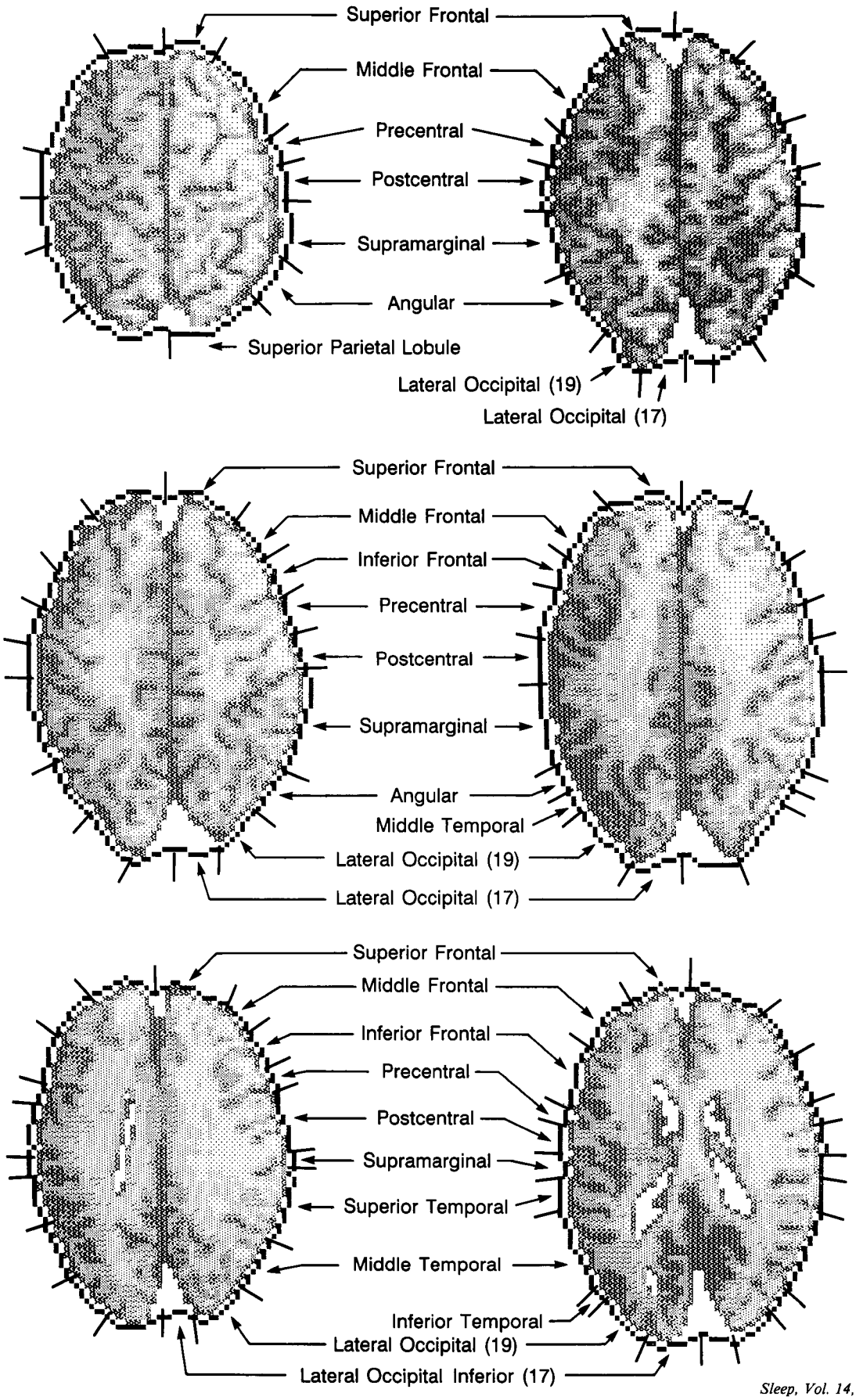


FIG. 1. Photographic brain atlas (29) outlined by computer algorithm. The relative coordinates of the 16 cortical gyri, which are the constitutents of the four lobes of the cortical surface, are shown by dividing lines along the perimeter. Figure 1 continued at right.

in all brain areas of Table 1 and reached $p < 0.01$ in the amygdala ($r = 0.90$), thalamus ($r = 0.93$), caudate ($r = 0.83$), and putamen ($r = 0.90$). No lateral cortical lobe correlations reached significance.

DISCUSSION

In comparison to the changes in cerebral metabolic rates seen in nonrapid eye movement (NREM) sleep or rapid eye movement (REM) sleep (19), sleep deprivation appears to be distinct from NREM sleep and REM sleep. Unlike NREM sleep where a large decrease from waking was observed, the lateral cortical areas did not decrease with sleep deprivation. However, in central gray regions, sleep deprivation shows a decrease (of approximately 14%) in metabolism, which is intermediate compared to the drop seen with NREM



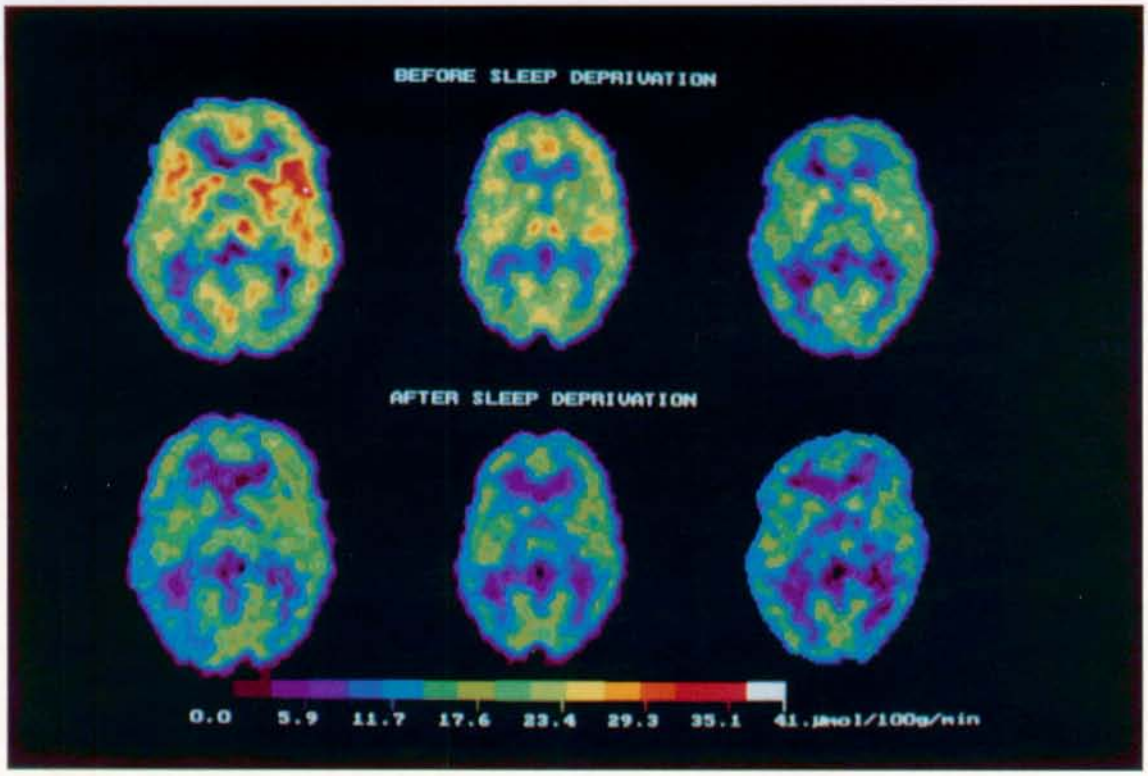


FIG. 2. Brain images of cerebral glucose metabolic rate before (above) and after (below) sleep deprivation in the same individuals. The slice level is approximately 55 mm above the canthomeatal line. The scale bar shows glucose metabolic rate in µmol glucose/100 g brain/min. Note decreased metabolism in the frontal lobe, temporal lobe, thalamus, and basal ganglia.

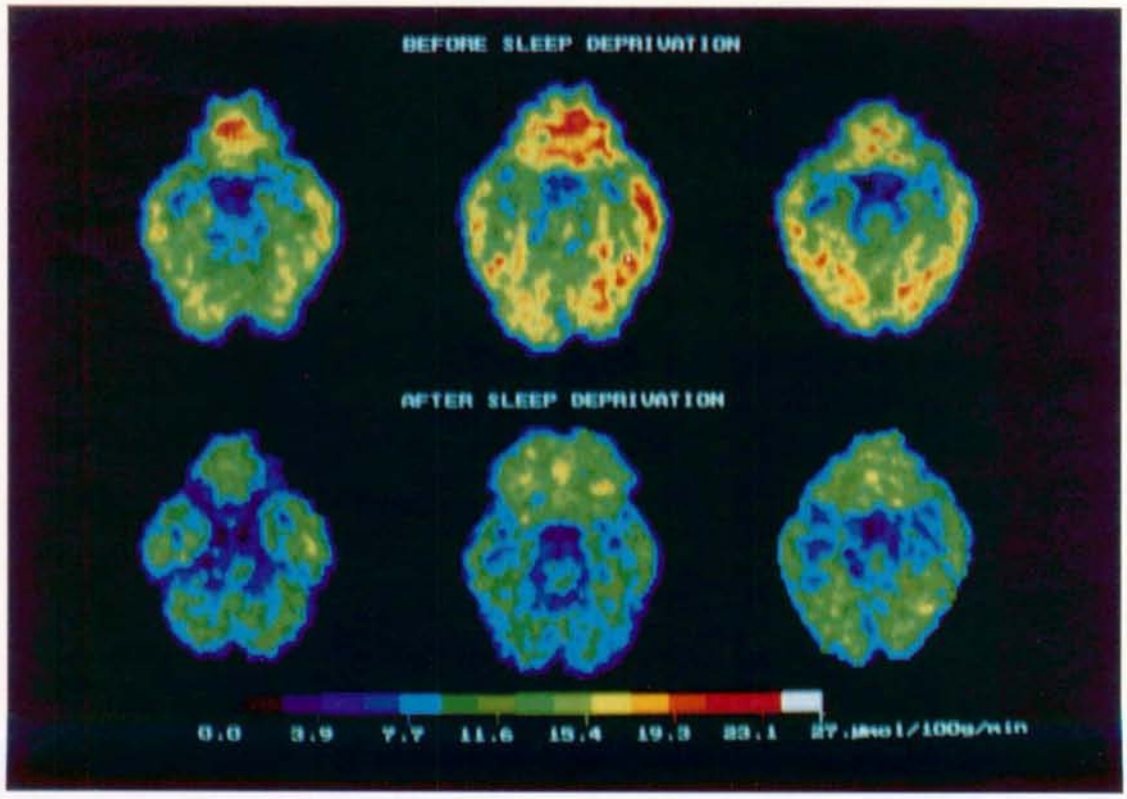


FIG. 3. Brain images at 25 mm above canthomeatal line. Note decrease in temporal poles and midbrain.

TABLE 3. *Absolute regional metabolism before and after sleep deprivation*[a]

	Baseline		Sleep Deprived		Difference	
System/structure	x	SD	x	SD	x	SD
Cortical surface	23.6	3.6	22.3	4.3	−1.3	4.3
Frontal lobe	25.9	3.9	23.6	4.4	−2.3	4.6
Parietal lobe	24.0	4.1	24.4	5.2	0.4	5.6
Temporal lobe	21.1	3.3	18.4	3.5	−2.7	3.3
Occipital lobe	23.1	3.2	22.5	4.1	−0.6	4.1
Medial cortex	27.3	3.4	26.9	4.9	−0.4	5.2
Limbic	18.9	2.5	17.2	2.3	−1.7	2.5
Thalamus	25.6	4.2	20.3	3.1	−5.3	4.9[b]
Basal ganglia	25.9	3.3	22.0	2.7	−3.9	3.7
White matter	20.1	3.4	19.2	4.6	−0.9	2.7
Midbrain	18.1	2.9	15.7	3.0	−2.4	2.8
Cerebellum	20.3	3.9	16.3	4.2	−4.0	3.0[b]

[a] Three-way ANOVA with condition (baseline, sleep deprivation), hemisphere (left, right) and structure (eight system/structures) showed no significant interactions with condition. Three-way ANOVA done the same way with structures only from the cortical surface (frontal, parietal, temporal, occipital lobes) showed significant condition by structure interaction ($F = 6.11$; df = 1.35,9.45; $p = 0.0275$). Follow-up tests of simple interactions by two-way ANOVA (condition by hemisphere) for each lobe revealed no significant effects.

[b] $p < 0.05$, simple effects analysis.

sleep (of approximately 25%). In contrast to the decreases seen in NREM sleep and sleep deprivation, REM sleep shows relative increases in medial cortical areas in comparison to the awake state.

Because the order effect in this study (baseline vs. sleep deprivation) was not randomized, we realize that changes in brain metabolism reported here may reflect effects other than sleep deprivation, including accommodation and changes in anxiety levels. However, PET studies have been done indicating high reliability for repeat PET scans (33). Consequently, although our subjects were not perfectly counterbalanced with respect to order, we feel that effect of order was smaller than all-night sleep deprivation.

Because we did not continuously monitor EEG or other physiological measures of sleep, we cannot exclude the possibility that subjects experienced microsleep epidoses during sleep deprivation or CPT. However, subjects were observed during the uptake to ensure that their eyes remained open and looking at the visual stimuli. Furthermore, the subjects did press the button to respond to stimuli at 3-s intervals, indicating that microsleep episodes would have to have been extremely short.

On the basis of the rest theory of sleep, we might have predicted that sleep deprivation would increase cellular work relative to the sleeping state. Increased cellular work could be reflected by increased metabolic rate. As the studies of prolonged sleep deprivation in the rat suggest, whole body metabolic rate increases dramatically without sleep (13), although the effects on brain metabolism have not yet been reported. The results of the present study are inconsistent with this prediction. Thus, in keeping with the data on single cell activity during sleep (23), the present data do not support a simple linear hypothesis relating sleep, short-term sleep deprivation, and cerebral metabolism.

As a preliminary interpretation of these data, we assume that sleep deprivation dampens brain arousal mechanisms. For example, the reduction in absolute metabolic rate at the midbrain might cause absolute deactivation of the rostrally projecting arousal systems to basal ganglia, thalamic, limbic, and temporal cortical areas. Decrements in metabolic rates in limbic, basal ganglia, and thalamic areas were particularly associated with poor CPT performance. At the same time, however, the brain was faced with state-dependent demands, in the present study, to remain awake and to perform the CPT. Thus, subjects who suffered the least decrement on the CPT showed the least change in regional metabolic rate. In addition, in this particular study, sleep deprivation significantly increased relative metabolic rate in the occipital cortex but decreased in the temporal cortex. These differential effects may reflect the CPT, which placed greater demands upon the visual than the auditory system. Alternatively, subjects who were motivated enough to overcome the decreases associated with sleep deprivation may have been able to perform better on the CPT. No cause and effect relationship, however, can be inferred at this time.

According to this interpretation, the effects of sleep deprivation on cerebral neurophysiology are a compromise between nonspecific deactivating influences upon brain arousal systems and state-dependent demands upon specific brain functional systems.

Acknowledgements: This work was supported in part by the National Institute of Mental Health [MH 42955 (J.C.W.), MH 38738 (J.C.G.)], the UCSD Mental Health Clinical Research Center [MH 30914 (J.C.G.)], the Veterans Administration Medical Research Service (J.C.G.), and the MacArthur Foundation (W.E.B., M.S.B.). We also thank the following students: P. Duong, T. Ma, C. Wu, and T. Kim.

REFERENCES

1. Wilkinson RT. Sleep deprivation. In: Edholm OG, Bacharach AL, eds. *The physiology of human survival.* London: Academic Press, 1965, pp 399–430.
2. Naitoh P, Pasnau RV, Koeller EJ. Psychophysiological changes after prolonged deprivation of sleep. *Biol Psychiatry* 1971;3: 309–20.
3. Daan S, Beersma D, Borbely AA. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol* 1984;246:R161–78.
4. Inoue S, Borbely AA, eds. Tokyo: Japan Scientific Societies Press, 1985.
5. Berger RJ, Walker JM, Scott TD, Magmison LJ, Pollack S. Diurnal and nocturnal sleep stage patterns following sleep deprivation. *Psychonom Sci* 1971;23:23–5.
6. Borbely AA, Buamann F, Brandeis D, Strauch I, Lehmann D.

Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol* 1981;51:483–93.
7. Buchsbaum MS, Gerner R, Post RM. The effects of sleep deprivation on average evoked responses in depressed patients and in normals. *Biol Psychiatry* 1981;16:351–63.
8. Gauthier P, Gottesman C. Influence of total sleep deprivation on event-related potentials in man. *Psychophysiology* 1983;20;351–5.
9. Martin BJ, Eur J. Effects of sleep deprivation on tolerance of prolonged exercise. *European J Appl Physiol Occup Physiol* 1981;47:345–54.
10. Gunderson GH, Dunne PB, Feyer T. Sleep deprivation seizures. *Neurology* 1973;23:678–86.
11. Schwarz JR, Zangemeister WH. The diagnostic value of the short sleep EEG and other provocative methods following sleep deprivation. *J Neurol* 1978;218:179–86.
12. Wu JC, Bunney WE. Sleep deprivation and relapse (biological basis: review and hypothesis). *Am J Psychiatry* 1990;147:14–21, 1990.
13. Bergman BM, Everson Ca, Kushida CA, et al. Sleep deprivation in the rat: V. Energy use and mediation. *Sleep* 1989;12(1):31–41.
14. Gilliland MA, Wold C, Wollman R, Eschenback K, Rechtschaffen A. Pathology in sleep deprived rats is not reflected in histologic abnormalities. *Sleep Res* 1984;13:190.
15. Horn JA. Factors relating to energy conservation during sleep in mammals. *Physiol Psychol* 1977;5:403–8.
16. Berger RJ. Bioenergetic functions of sleep and activity rhythms and their possible relevance to aging. *Fed Proc* 1975;34:97–102.
17. Kennedy C, Gillin JC, Mendelson WB, et al. Local cerebral glucose utilization in non-rapid eye movement sleep. *Nature* 1982;297:325–7.
18. Nakamura RK, Kennedy C, Gillin JC, et al. Hypnogenic center theory of sleep: no support from metabolic mapping in monkeys. *Brain Res* 1983;268:372–6.
19. Buchsbaum MS, Gillin JC, Wu JC, et al. Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. *Life Sci* 1989;45:1349–54.
20. Sakai F, Meyer JS, Karacan I, et al. Normal human sleep: regional cerebral hemodynamics. *Ann Neurol* 1980;7:471–8.
21. Adam K. Sleep as a restorative process and a theory to explain why. *Prog Brain Res* 1980;53:289–306.
22. Morruzzi G. The sleep–waking cycle. *Ergeb Physiol* 1972;64:1–165.
23. Steriade M, Hobson JA. Neuronal activity during the sleep waking cycle. *Prog Neurobiol* 1976;6:155–376.
24. Mangold R, Sokoloff L, Conner E, et al. The effects of sleep and lack of sleep on the cerebral circulation and metabolism of normal young men. *J Clin Invest* 1955;34:1092–100.
25. Buchsbaum MS, Wu J, Haier R, et al. Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorders. *Life Sci* 1987;40:2393–400.
26. Nuechterlein KH, Parasuraman R, Jiang Q. Visual sustained attention: image degradation produces rapid sensitivity decrement over time. *Science* 1983;220:327–9.
27. Sokoloff L, Reivich M, Kennedy C, et al. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 1977;28:897–916.
28. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 1979;6:371–88.
29. Matsui T, Hirano A. *An atlas of the human brain for computerized tomography.* Tokyo: Igaku-Shoin, 1978.
30. Buchsbaum MS, Wu J, DeLisi LE, et al. Positron emission tomography studies of basal ganglia and somatosensory cortex neuroleptic drug effects: differences between normal controls and schizophrenic patients. *Biol Psychiatry* 1987;479–94.
31. Fox PT, Mintun MA. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2{}^{15}O$ tissue activity. *J Nucl Med* 1989;30:141–9.
32. Buchsbaum MS, DeLisi LE, Holcomb HH, et al. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry* 1984;41:1159–66.
33. Reivich M, Alavi A, Wolf A, et al. Use of 2-deoxy-D[1-^{11}C] glucose for the determination of local cerebral glucose metabolism in humans: variations within and between subjects. *J Cereb Blood Flow Metab* 1982;2:307–19.