

Alterations in Regional Cerebral Glucose Metabolism Across Waking and Non–Rapid Eye Movement Sleep in Depression

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Background: Depression is associated with sleep disturbances, including alterations in non–rapid eye movement (NREM) sleep. Non–rapid eye movement sleep is associated with decreases in frontal, parietal, and temporal cortex metabolic activity compared with wakefulness.

Objective: To show that depressed patients would have less of a decrease than controls in frontal metabolism between waking and NREM sleep and to show that during NREM sleep, they would have increased activity in structures that promote arousal.

Design: Subjects completed electroencephalographic sleep and regional cerebral glucose metabolism assessments during both waking and NREM sleep using [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography.

Setting: General clinical research center.

Patients: The study included 29 unmedicated patients who met the Structured Clinical Interview for DSM-IV criteria for current major depression and who had a score of 15 or greater on a 17-item Hamilton Rating Scale for Depression and 28 medically healthy subjects of comparable age and sex who were free of mental disorders.

Main Outcome Measures: Electroencephalographic sleep and regional cerebral metabolism during waking and NREM sleep.

Results: Depressed patients showed smaller decreases than healthy subjects in relative metabolism in broad regions of the frontal, parietal, and temporal cortex from waking to NREM sleep. Depressed patients showed larger decreases than healthy subjects in relative metabolism in the left amygdala, anterior cingulate cortex, cerebellum, parahippocampal cortex, fusiform gyrus, and occipital cortex. However, in post hoc analyses, depressed patients showed hypermetabolism in these areas during both waking and NREM sleep.

Conclusions: The smaller decrease in frontal metabolism from waking to NREM sleep in depressed patients is further evidence for a dynamic sleep-wake alteration in prefrontal cortex function in depression. Hypermetabolism in a ventral emotional neural system during waking in depressed patients persists into NREM sleep.

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ALTERATIONS IN NON-RAPID eye movement (NREM) sleep have been observed in patients with mood disorders.¹⁻⁷ The neurobiological basis of these alterations, however, has not been defined. Combined with preclinical knowledge of sleep regulation, new findings from human functional neuroimaging studies of NREM sleep can be used to develop a brain-based model of the NREM sleep alterations in depression. Preclinical studies show that the regulation of behavioral state involves interactions between brain structures that promote arousal, such as the ascending reticular activating system and the hypothalamus and basal fore-

brain, and those structures that produce the brain rhythms of NREM sleep, which include extensive thalamocortical networks.⁸⁻¹⁰ Human functional neuroimaging studies of sleep have provided evidence for changes both in general arousal systems and in thalamocortical function, as indicated by the preclinical work. Blood flow and metabolism in the brain decline globally from waking to NREM sleep. These declines are greatest in the heteromodal association cortex and in the thalamus.¹¹⁻¹⁶ Decreased metabolism and blood flow in arousal networks from waking to NREM sleep, including the pons and mesencephalon and the basal forebrain/hypothalamus, have also been reported.¹²⁻¹⁵

The function of NREM sleep is not known. At the electroencephalographic (EEG) level, sleep has been shown to discharge a wake-dependent sleep drive, as measured by EEG spectral power in the delta frequency band.¹⁷⁻²⁰ At the molecular and neuronal levels, hypothesized functions include the restoration of brain energy metabolism through the replenishment of brain glycogen stores that are depleted during wakefulness^{21,22} and the downscaling of synapses that have been potentiated during waking brain function.²³ It is increasingly recognized that sleep has regional selectivity. Slow wave sleep rhythms have both thalamic and cortical components.²⁴ Decreases in brain activity from waking to NREM sleep are most pronounced in the frontoparietal cortex. An anterior dominance of EEG spectral power in the delta EEG spectral power range has been reported.²⁵⁻²⁷ A frontal predominance for the increase in delta power following sleep loss has also been reported.²⁷⁻³³ This region of cortex plays a prominent role in waking executive functions, which are preferentially impaired following sleep deprivation.³⁴⁻³⁷ These sleep deprivation-induced cognitive impairments have been related to declines in frontal metabolism after sleep loss.³⁸ Evidence such as this suggests that NREM sleep changes in depressed patients may be related to alterations in prefrontal cortex function.

Alterations in NREM sleep may also be related to altered function in structures that promote arousal and thereby inhibit sleep generation. Primary structures that have activating influences on cerebral activity include the posterior hypothalamus, the reticular activating system arising from the brainstem, and the basal forebrain driven from the upper reticular core.^{39,40} The amygdala and anterior cingulate cortex (ACC) influence emotional arousal and may interact with this more specific arousal network in modulating generalized cortical arousal.⁴¹⁻⁴³ As such, alterations in NREM sleep in depressed patients may be related to abnormally increased activity in arousal centers or in an emotional arousal network that may moderate function in these centers.

We hypothesize that altered NREM sleep in depression may reflect abnormal frontal cortex function and/or overactivity of an arousal network that alters the expression of NREM sleep. To test this model, we assessed waking and NREM sleep regional cerebral metabolism in 29 depressed patients and 28 healthy control subjects of comparable age and sex using the [¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) positron emission tomography (PET) method.⁴⁴

METHODS

SUBJECTS

We studied 29 right-handed depressed subjects (22 women and 7 men, mean \pm SD age, 39.7 \pm 10.9 years) and 28 right-handed healthy subjects (21 women and 7 men, mean \pm SD age, 37.2 \pm 10.5 years). The research study was reviewed and approved by the University of Pittsburgh Institutional Review Board. All subjects provided written informed consent after the procedures were fully explained and were compensated for participation in the study. Partial data (NREM scans only) from 12 patients and 13 controls were included in another report.⁴⁵

Depressed subjects met the DSM-IV criteria for major depression on the basis of an interview using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition, version 2.0.⁴⁶ Depressed subjects had a minimum score of 15 on the first 17 items of the Hamilton Rating Scale for Depression⁴⁷ or a score of 17 or greater on the Beck Depression Inventory.⁴⁸ They were excluded if they met the DSM-IV criteria for schizophrenia, lifetime history of substance abuse or alcoholism, borderline or antisocial personality disorder, organic affective disorder, schizoaffective disorder, psychotic subtype of major depression, or bipolar depression. Healthy subjects were required to have a score of 6 or lower on the first 17 items of the Hamilton Rating Scale for Depression⁴⁷ and to be free of any lifetime history of a mental disorder, as previously described.⁴⁹ All subjects were required to be free of medications that could affect mood or sleep for at least a 2-week period (8 weeks for fluoxetine) prior to EEG sleep and PET studies. Subjects who could not remain free of drugs or alcohol during the study, as verified by nightly drug screens, were excluded. All subjects met the previously described medical exclusion criteria.⁴⁹ Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index. Psychological distress was assessed using the Symptom Checklist 90—Revised. Any subject with an Apnea-Hypopnea Index of 10 or greater on the night 1 screening was excluded from further study. All subjects underwent magnetic resonance scanning prior to their EEG sleep and PET studies using a Signa 1.5-T scanner (GE Medical Systems, Milwaukee, Wis), as previously described.¹⁶ To determine whole-brain metabolism, a whole-brain mask was created by applying a brain-nonbrain segmentation to the magnetic resonance data that minimized the dilution of whole-brain metabolic values by the individually variable contribution of cerebrospinal fluid spaces.⁵⁰

EEG SLEEP METHODS

The EEG sleep studies were performed at the University of Pittsburgh General Clinical Research Center, Pittsburgh, Pa. Electroencephalographic sleep was monitored on nights 1, 2, and 3. Night 1 was an adaptation night, and subjects were screened for sleep disorders. Night 2 data were used for the collection of baseline EEG sleep data. Bedtime was determined by the mean bedtime over the 7 days preceding sleep studies as determined by sleep diary. On nights 1 and 2, subjects had sham intravenous tubing taped over their forearms. This tubing was inserted through a cannula portal to a monitoring room to simulate the mobility restrictions of an indwelling intravenous tube used on night 3 to inject the radioisotope. The EEG sleep montage consisted of a C4/A1-A2 EEG channel, two electrooculogram channels (right and left eyes) referenced to A1-A2, and a submental electromyogram channel. All electrode impedances were determined to be less than 5000 Ω . The EEG signal was collected using Grass 7P511 amplifiers. Filter settings for the EEG were 0.3 to 100 Hz. The electromyogram was bipolar, with a filter setting of 10 to 90 Hz. Electroencephalographic sleep was scored visually by raters blind to clinical information, according to the criteria of Rechtschaffen and Kales.⁵¹ Interrater sleep scoring reliability for major sleep variables was checked periodically, with κ values ranging from 0.76 to 0.85. Definitions for visually scored sleep variables have been provided elsewhere.⁵²

PET METHODS

Regional cerebral glucose metabolism was assessed during both waking and NREM sleep using the [¹⁸F]FDG PET method.⁴⁴ The waking PET study occurred on the morning following the sec-

ond night of sleep. The NREM sleep PET study occurred on the third night of study. All PET studies used a 4- to 6-mCi dose of [^{18}F]FDG injected via the cannula portal method so that subjects would be minimally disturbed. The time of [^{18}F]FDG injection for the waking study was approximately 2 to 4 hours following awakening from the second night of sleep. The time of [^{18}F]FDG injection for the NREM sleep study was either 5 to 7 minutes following the identification of the first sleep spindle (13 healthy and 12 depressed subjects) or 20 minutes after sleep onset, which was defined as the first of 10 consecutive minutes of stage 2, 3, or 4 sleep (15 healthy and 17 depressed subjects). These different criteria were used because subjects were pooled from two protocols that had slightly different criteria for injection start times. The distribution of subjects injected by each of the two criteria did not differ between controls and depressed subjects in either the waking or NREM sleep study (Pearson $\chi^2=0.15$, $df=1$, two-sided $P=.70$). In both the waking and NREM sleep conditions, subjects were monitored via polysomnography while lying on a bed. They were left undisturbed for a 20-minute period following injection of the radioisotope. For the waking study, they were given instructions to remain awake but with eyes closed in a dimly lit room. Twenty minutes after injection, subjects were transported to the PET imaging room. Scanning included a 30-minute emission scan (6 summed sequential 5-minute PET emission scans beginning 60 minutes after injection of the [^{18}F]FDG), followed by a 15-minute rod-windowed transmission scan. A modified simplified kinetic method⁵³ was used as an indirect measure of absolute glucose metabolism (metabolic rate of deoxyglucose [MRD_{glc}]), as described previously.⁵⁴ In this approach the plasma integral was estimated from 6 nonarterialized venous plasma samples collected every 8 minutes from 45 to 95 minutes after [^{18}F]FDG injection. The acquisition protocol included the 3-dimensional mode with septa retracted in an ECAT HR+ PET scanner. The head was positioned so that the lowest scanning plane was parallel to and 1.0 cm below the canthomeatal line. All PET images were reconstructed as 63 transaxial slices (each 2.4 mm thick) using standard commercial software, as previously described.¹⁶ All subsequent alignments and coregistrations were performed using a modification of Roger Woods' automated algorithms for PET-PET alignment and PET-magnetic resonance cross-modality registration, as previously described.^{49,55-58} The methods used to translate the PET images into a common Talairach space for use in the grouped Statistical Parametric Mapping program, 1999 version (SPM99),^{59,60} analyses have been previously described.⁴⁹

STATISTICAL ANALYSES

We used χ^2 tests and t tests to test group differences in categorical and continuous clinical and demographic measures, respectively. Group differences in EEG sleep measures were determined using a multivariate analysis of variance (MANOVA) to help control for problems of multiple comparisons. Variables entered into the MANOVA included total recording period; sleep efficiency; percentages of stage 1, 2, 3-4, and rapid eye movement (REM) sleep; REM latency; and density of REM sleep in the first REM period. Post hoc analyses of variance were performed on individual variables after a significant group effect was detected in the MANOVA. For the measure MRD_{glc} , a repeated-measures analysis of variance (control and depressed groups; the repeated measure was MRD_{glc} while awake and during NREM sleep) was used to test for group and time effects and group \times time interactions. The above analyses were done using SPSS software. To determine differences in relative regional metabolism between waking and NREM sleep for each group as well as group \times time (awake vs NREM sleep) interactions, we used SPM99. This program was also used to test

post hoc group differences in waking relative regional metabolism and in NREM sleep relative regional metabolism. Following the coregistration and spatial normalization of the PET data into a common Talairach space as described above, the PET data were smoothed ($10 \times 10 \times 10$ mm). The control and depressed waking and NREM sleep PET images were entered into an analysis of covariance using global metabolism and age as covariates. Age was used as a covariate because of known variations in regional cerebral metabolism with age.⁶¹ Statistic images (t scores converted to z scores) were created for each analysis. Local statistical maxima in these images were identified by their Talairach atlas (x , y , z axis) coordinates.⁶²

IDENTIFICATION OF REGIONS IN REGION OF INTEREST ANALYSES

Regions were identified that showed group \times time interactions. To determine whether the interactions were predominantly due to a group difference in either waking metabolism or NREM sleep metabolism, we first created a binary mask of the regions demonstrating the initial statistical interaction using the ImCalc feature of SPM99. These masks were then used as image files in small-volume correction secondary analyses assessing group differences in either waking or NREM sleep using SPM99.

RESULTS

CLINICAL

The depressed and healthy groups did not differ in age or sex (**Table**). Depressed subjects had moderately severe depressive symptoms, subjective sleep disturbance, and global distress. Twenty-five had recurrent major depression, and 4 were in their first episode. The average duration of the current episode of depression was 41.7 weeks. The average age of onset of major depression was 24.5 years.

EEG SLEEP

The MANOVA revealed that the EEG sleep (from the second undisturbed baseline night of sleep) of depressed patients differed significantly from that of the healthy controls ($F=3.0$, $df=48$, $P=.008$). Secondary analyses showed increases in sleep latency, awake time, and stage 1 and REM sleep percentages as well as decreases in sleep maintenance and sleep efficiency (**Table**). No significant group differences were found in the EEG sleep distribution of waking, REM, and NREM sleep during the initial [^{18}F]FDG uptake period of the NREM sleep study. The mean \pm SD number of minutes of NREM, waking, and REM sleep, respectively, in the 20 minutes following injection of [^{18}F]FDG were 19.6 ± 0.6 , 0.4 ± 0.6 , and 0 ± 0 minutes for the controls and 18.9 ± 2.0 , 0.8 ± 1.8 , and 0.3 ± 1.1 minutes for the depressed patients.

WHOLE-BRAIN METABOLISM

A repeated-measures analysis of variance tested group (depressed vs control), state (wake vs NREM sleep), and group \times state interactions of the indirect measure MRD_{glc} . No group \times state interaction or group effects were ob-

Table. Clinical, Demographic, and Electroencephalographic Sleep Variables*

	Controls (n = 28)	Depressed Patients (n = 29)	Statistics		
			t Score	df	P Value
Clinical and Demographic Variables					
Sex, No. (female/male)	21/7	22/7	0.94†	1	>.99
Age, y	37.2 ± 10.5	39.7 ± 10.9	−0.85	55	.40
BDI total	1.2 ± 2.1	25.0 ± 8.3	−14.3	52	<.001
HRSD total	0.8 ± 1.3	20.9 ± 3.5	−27.1	51	<.001
PSQI total	2.6 ± 1.9	9.5 ± 3.5	−8.4	44	<.001
SCL-90-R GSI	0.1 ± 0.2	1.2 ± 0.4	−11.9	52	<.001
Sleep Continuity Variables					
Total recording period, min	457.6 ± 47.7	456.6 ± 58.6	0.07	55	.95
Sleep latency, min	13.7 ± 10.1	23.7 ± 11.4	−3.51	55	.001
Awake, min	20.1 ± 18.6	35.5 ± 31.6	−2.23	55	.03
Sleep maintenance, %	95.5 ± 4.0	91.8 ± 7.4	2.37	55	.02
Sleep efficiency, %	92.8 ± 4.8	87.1 ± 8.1	3.22	55	.002
Non-Rapid Eye Movement (NREM) Variables					
% Stage 1	4.4 ± 2.3	6.1 ± 3.2	−2.20	55	.03
% Stage 2	62.9 ± 9.4	59.3 ± 8.5	1.53	55	.13
% Stage 3	6.4 ± 5.0	5.0 ± 4.8	1.02	55	.31
% Stage 4	2.9 ± 4.5	3.3 ± 6.0	−0.25	55	.81
% Delta	9.3 ± 7.9	8.3 ± 8.8	0.44	55	.66
Delta power	38.6 ± 25.2	33.3 ± 31.0	0.71	55	.48
Delta ratio	1.4 ± 0.8	1.4 ± 0.5	0.42	55	.68
Rapid Eye Movement (REM) Variables					
% REM	23.4 ± 4.3	26.3 ± 5.0	−2.39	55	.02
REM latency, min	59.9 ± 28.1	58.3 ± 29.5	0.21	55	.83
REM density in first REM period	5.6 ± 4.4	6.3 ± 5.4	−0.55	55	.59

Abbreviations: BDI, Beck Depression Inventory; GSI, Global Severity Index; HRSD, Hamilton Rating Scale for Depression; PSQI, Pittsburgh Sleep Quality Index; SCL-90-R, Symptom Checklist 90–Revised.

*Unless indicated otherwise, values are mean ± SD.

† χ^2 Analysis.

served. A significant state effect was noted (NREM $MRD_{glc} < \text{wake } MRD_{glc}$; $F = 27.94$; $df = 1, 39$; $P < .001$).

CHANGES IN REGIONAL METABOLISM FROM WAKING TO NREM SLEEP IN HEALTHY AND DEPRESSED SUBJECTS

In healthy subjects (**Figure 1**, left-hand column), relative metabolism decreased from waking to NREM sleep in the bilateral frontal, parietal, occipital, anterior cingulate, and temporal cortex and in the thalamus (cluster level $P < .05$ corrected for multiple comparisons). In the depressed subjects (**Figure 1**, right-hand column), a generally similar pattern of decline in relative metabolism from waking to NREM sleep was observed (cluster level $P < .05$ corrected for multiple comparisons), although the spatial extent showed differences. In the frontal cortex and ACC, depressed patients showed a smaller extent of decline (3825 voxels in depressed subjects vs 5771 voxels in healthy subjects). Other differences were analyzed by the interaction analysis described below.

GROUP × STATE INTERACTIONS

Depressed subjects (**Figure 2**, left column) showed smaller reductions in relative metabolism from waking to NREM sleep than healthy subjects in a broadly dis-

tributed region of predominantly right-hemispheric dorsolateral prefrontal, parietal, and temporal cortex (cluster level $P = .002$ corrected for multiple comparisons; 1591 voxels in cluster; voxel of maximum significance within cluster at Talairach coordinates $x = 50$, $y = -48$, $z = -24$). Secondary analyses (**Figure 2**, right-hand column) revealed extensive overlap between structures demonstrating this interaction (smaller reductions in relative metabolism from waking to NREM sleep) and waking relative hypometabolism (bilateral dorsolateral prefrontal cortex and temporal cortex) but not NREM relative hypermetabolism (data not shown) in the depressed group.

We then analyzed structures in which depressed subjects showed greater reductions than controls in relative metabolism from waking to NREM sleep (**Figure 3**). These areas (**Figure 3**, left-hand column) included portions of the cerebellum, parahippocampal cortex, fusiform gyrus, and occipital cortex as well as more anterior, ventral, and mesial structures such as the brainstem, ventral striatum/basal forebrain, left amygdala, and pregenual and subgenual ACC. Post hoc analyses revealed that, in most of these areas, depressed patients showed relative waking hypermetabolism (**Figure 3**, center column). Inspection of NREM analyses, however, also showed that depressed patients had persistent relative hypermetabolism in these structures during NREM sleep (**Figure 3**, right-hand column). Depressed patients showed

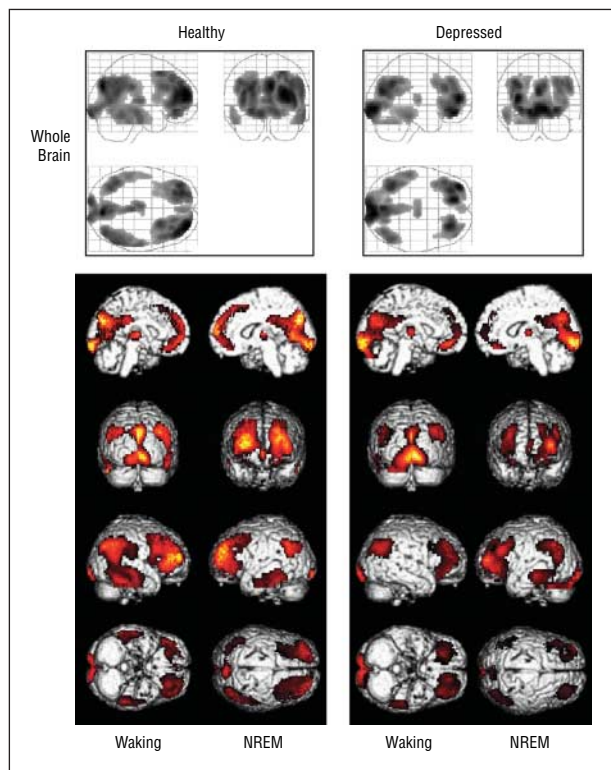


Figure 1. Glass brain and 3-dimensional brain-rendering images showing regions with significant declines in relative metabolism from waking to non-rapid eye movement (NREM) sleep. Left column, Healthy subjects. Regions include the prefrontal cortex ($x=28$, $y=54$, $z=20$; $t_{\max}=7.32$; 5771 voxels); cuneus, precuneus, and left temporoparietal cortex ($x=6$, $y=-78$, $z=32$; $t_{\max}=6.70$; 3396 voxels); and right temporoparietal cortex ($x=56$, $y=-54$, $z=20$; $t_{\max}=4.78$; 2305 voxels). Right column, Depressed subjects. Regions include the cuneus, precuneus, and temporoparietal cortex ($x=8$, $y=-90$, $z=-8$; $t_{\max}=7.60$; 5303 voxels); left prefrontal cortex ($x=-34$, $y=52$, $z=12$; $t_{\max}=6.95$; 2500 voxels); and right prefrontal cortex ($x=26$, $y=36$, $z=-8$; $t_{\max}=6.08$; 1325 voxels). All clusters reported are significant at $P < .05$, corrected. Coordinates refer to local cluster maxima in Talairach sections.

increased relative metabolism in the thalamus during NREM sleep compared with healthy subjects.

COMMENT

Changes in regional brain activity from waking to NREM sleep in healthy adults include a reduction in activity in the thalamus and in the frontal, parietal, and temporal association cortex.^{12,13,16} While both healthy and depressed patients showed this general overall pattern in the current study, depressed patients showed less of a decline in broad regions of the frontal, parietal, and temporal cortex from waking to NREM sleep. Depressed patients showed greater reductions in relative metabolism in the cerebellum, left amygdala, ACC, fusiform gyrus, parahippocampal cortex, basal forebrain, and occipital cortex. Post hoc analyses, however, demonstrated relative hypermetabolism in these areas during waking in the depressed patients and persistence of relative hypermetabolism in these same areas during NREM sleep.

Depressed patients showed less of a decline in relative metabolism from waking to NREM sleep than did the healthy subjects in many regions. These results may reflect a change in brain function during either wakeful-

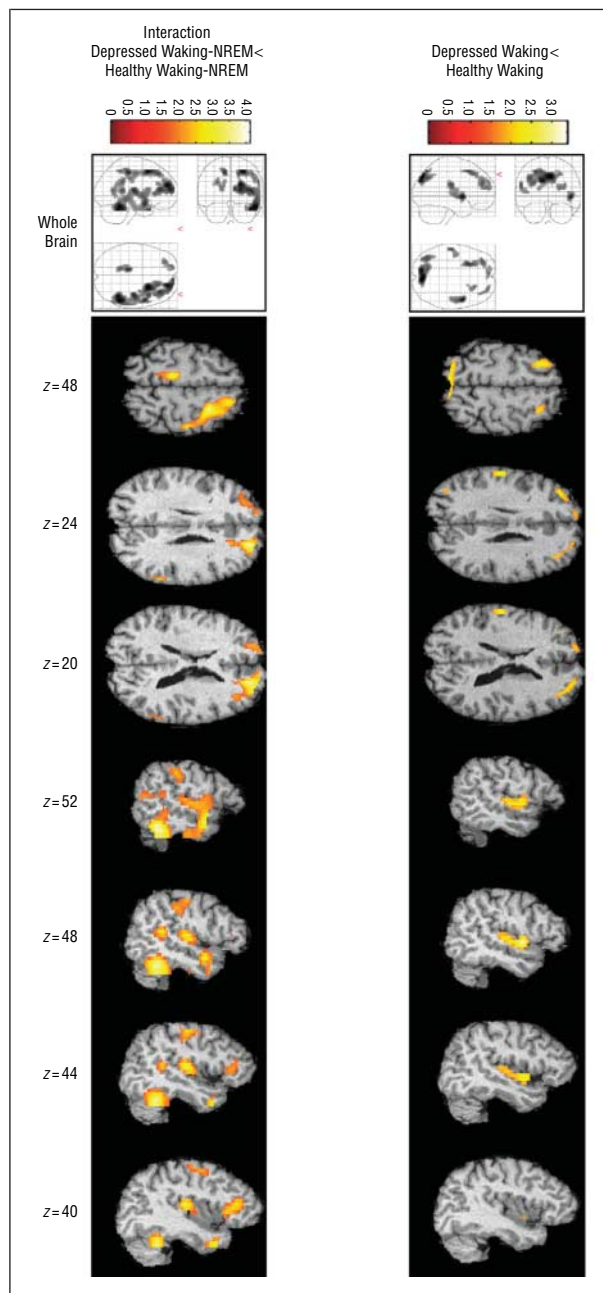


Figure 2. Left column, Regions where healthy subjects had greater declines than depressed patients in relative metabolism from waking to non-rapid eye movement (NREM) sleep, including the right frontoparietal cortex ($x=50$, $y=-48$, $z=-24$; $t_{\max}=3.81$; 1591 voxels; cluster significant at $P < .05$, corrected). Right column, Regions where depressed patients showed relative hypometabolism during waking compared with healthy subjects, including the left prefrontal cortex ($x=-26$, $y=14$, $z=52$; $t_{\max}=2.64$; 379 voxels; cluster significant at $P < .05$, uncorrected). Coordinates refer to local cluster maxima in Talairach sections.

ness or sleep or some dynamic interaction between the two. Secondary analyses suggest that this finding is in part related to a waking hypofrontality in the depressed group that does not decline further in NREM sleep. Waking hypofrontality may result from a lack of a sleep-related reversal in some wake-dependent process, such as a depletion of glycogen stores, or a potentiation of synaptic activity. In this sense, poor sleep in depressed patients may not allow for some sleep-related function to occur

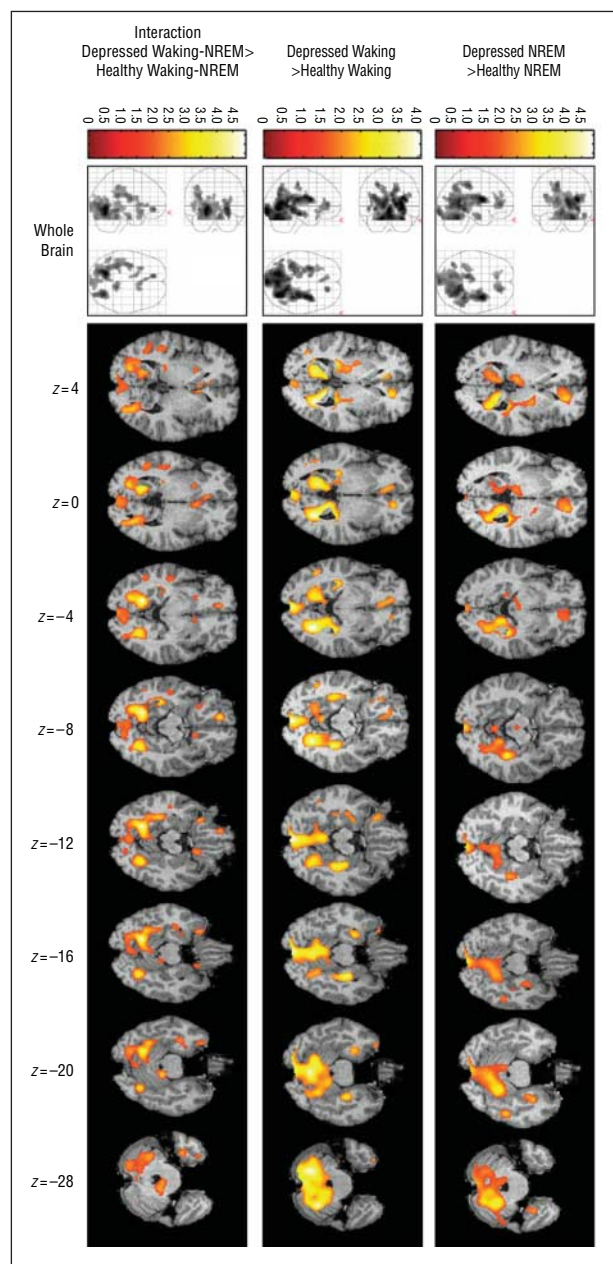


Figure 3. Left column, Regions where depressed patients had greater declines than healthy subjects in relative metabolism from waking to non-rapid eye movement (NREM) sleep, including the cerebellum, parahippocampal cortex, fusiform gyrus, and occipital cortex, including the primary visual cortex, as well as more anterior, ventral, and mesial structures, such as the brainstem, ventral striatum/basal forebrain, left amygdala, and pregenual and subgenual anterior cingulate cortex ($x=-18$, $y=-62$, $z=-4$; $t_{\max}=4.88$; 2200 voxels). Center column, Regions where depressed patients showed relative hypermetabolism during waking compared with healthy subjects ($x=28$, $y=-68$, $z=-4$; $t_{\max}=4.05$; 7216 voxels). Note significant overlap with the regions shown in the left column. Right column, Regions where depressed patients showed relative hypermetabolism during NREM sleep compared with healthy subjects ($x=34$, $y=2$, $z=16$; $t_{\max}=4.84$; 5690 voxels; cluster significant at $P<.05$, corrected). Note significant overlap with the regions shown in the left and center columns. Coordinates refer to local cluster maxima in Talairach sections.

efficiently. Consistent with this, both extended sleep deprivation in healthy subjects and inefficient sleep in primary insomnia subjects⁶³ have been associated with reduced waking metabolism in the prefrontal cortex.³⁸

Alternatively, waking prefrontal cortex function may be fundamentally altered in depressed patients. In this case, there may be less depletion of glycogen stores or less synaptic potentiation in depressed patients relative to healthy controls during waking, resulting in less of a need for repletion or downscaling, respectively, during sleep. The prefrontal cortex plays an important role in a dorsal neural emotional system.⁶⁴ It has also been shown to play an important role in executive function, including selective attention, planning, and effortful regulation of affective states. Functional neuroimaging studies consistently report reduced function in the dorsolateral prefrontal cortex in depressed patients⁶⁵⁻⁶⁸ and increased function in this area following recovery from a major depressive episode.^{65,67,69-72} The current studies extend these observations of altered prefrontal cortex function in depression and raise the question as to whether altered prefrontal cortex function may be mediated by an alteration in a dynamic sleep-wake interaction in this area.

Depressed patients also showed a greater decline than healthy subjects in relative metabolism from waking to NREM sleep in a large collection of ventral and posterior structures. Post hoc analyses suggest that this is related to increased metabolism in these structures during waking in the depressed patients. Even within NREM sleep, however, depressed patients continued to show hypermetabolism in these regions. Preclinical studies suggest that brain structures involved in promoting arousal may interfere with the production of sleep.^{9,10,39,40,73-89} Consistent with this, regions of the reticular activating system and basal forebrain were shown to be hypermetabolic in the depressed patients. Depressed patients also showed hypermetabolism in the amygdala, pregenual and subgenual ACC, cerebellum, parahippocampal gyrus, fusiform gyrus, thalamus, and occipital cortex. Preclinical and functional neuroimaging studies in humans suggest that these structures may play a broader role as part of a ventral emotional neural system in depressed patients⁴¹ that is fundamental to the initial experience of emotions and to the automatic generation of emotional responses. Given the connections of these areas with the brainstem, basal forebrain, and hypothalamic centers involved in promoting arousal, it is conceivable that hypermetabolism in this broader network may modulate arousal in depressed patients and thereby adversely affect any function of sleep across the night. Important components of this network include the amygdala and ACC.

Considerable evidence from both animal and human research supports the hypothesis that the amygdala, when activated by emotional arousal, modulates memory storage processes in other brain regions.^{90,91} In humans, the amygdala shows increased activation in response to a variety of emotional stimuli, including unfamiliar faces,⁹² fearful⁹³⁻⁹⁶ and sad⁹⁷ faces, threatening words,⁹⁸ fearful vocalizations,⁹⁹ and unpleasant olfactory¹⁰⁰ and gustatory¹⁰¹ stimuli. A reactive "motor" role for the amygdala includes the recruitment and coordinating of cortical arousal and vigilant attention for optimizing sensory and perceptual processing of stimuli associated with underdetermined contingencies.^{102,103} With some consistency, studies have demonstrated increased baseline activity in the

amygdala in depressed patients,¹⁰⁴⁻¹⁰⁷ a positive correlation between depressive severity and amygdalar metabolism,^{104,108} and increased amygdalar responses to fearful faces and reductions in amygdalar responses following treatment.¹⁰⁹ Amygdala hyperactivation has been implicated in the maintenance of depression.¹¹⁰ The amygdala has been shown to play a role in sleep regulation.^{111,112}

Ventral and subgenual and pregenual but not dorsal portions of the ACC demonstrated hypermetabolism during waking and NREM sleep and a greater decline from waking to NREM sleep in depressed vs healthy subjects. The ACC is a highly differentiated structure that participates in both a ventral and a dorsal neural system for emotional behavior.⁴¹⁻⁴³ The subgenual ACC region has been associated specifically with mood reactivity (eg, Drevets et al¹⁰⁷) and is considered a component of the ventral neural system for emotional behavior.⁴¹ After correction for volume deficits in this region, depressed patients have increased metabolism in this area that normalizes following treatment.^{67,71,113} The rostral, pregenual part of the ACC has been more strongly implicated in the evaluation of emotional information (eg, Whalen et al¹¹⁴). This region of the ACC appears to be intermediate in its relations to the ventral and dorsal neural systems involved in emotional behavior. While many studies demonstrate increased activity in this region in depressed patients, there have been mixed findings as to whether treatment increases or decreases activity here.^{69,115,116}

Depressed patients showed hypermetabolism in the cerebellum during waking and NREM sleep and a greater decline compared with healthy subjects from waking to NREM sleep. Activation of the cerebellum in response to arousing stimuli affecting the autonomic nervous system has been reported previously.^{117,118} Critchley et al¹¹⁸ have suggested that the cerebellum may act as a functional relay between cortex and brainstem through which brainstem autonomic nuclei are modulated by cortical activity related to cognitive, motor, and emotional behaviors. Increased relative metabolism in the cerebellum in depressed patients across waking and NREM sleep therefore is consistent with its involvement in mediating emotional arousal.

Depressed patients also showed increased metabolism in the thalamus, especially in NREM sleep (Figure 3, right-hand column, levels $z=4$ and $z=0$). Preclinical studies show that the thalamus is a critical site for the generation of the thalamocortical rhythms that characterize the synchronous EEG activity of NREM sleep.⁸⁻¹⁰ Increased metabolism in the thalamus during NREM sleep in depressed patients is consistent with a fundamental alteration in the thalamic generation of NREM sleep in this population.

Ho et al¹¹⁹ compared regional cerebral metabolism during the first NREM sleep period between 10 depressed men and 12 healthy men. They found increased whole-brain metabolism during NREM sleep in the depressed subjects, most noticeable in the posterior cingulate, amygdala, hippocampus, occipital and temporal cortex, and pons. Hypofrontality was noted in the depressed subjects. The depressed subjects also had reduced relative metabolism compared with controls in the anterior cingulate, caudate, and medial thalamus. Ho et al inter-

preted these findings as evidence for a generalized hyperarousal in depressed patients. We did not replicate the finding of increased global metabolism during NREM sleep in depressed patients. This may reflect different sex distributions between the two studies or differences in controlling for the effects of age. We did, however, replicate the regional changes that are consistent with a hyperarousal in the central nervous system of depressed patients. Specifically, we showed increased relative metabolism in the depressed patients during NREM sleep in the posterior cingulate, hippocampus, occipital and temporal cortex, and pons. These structures can be conceptualized as part of a ventral emotional neural system in which persistent activity within sleep may prevent the normal deactivation of thalamocortical activity that may play an important role in NREM sleep function.

The waking comparison PET scan in the current study provides an additional perspective from which to view altered prefrontal cortex activity in depression. Ho et al¹¹⁹ reported hypofrontality during NREM sleep in depressed patients. In the current study, depressed patients demonstrated hypofrontality during waking but less of a decline in metabolism from waking to NREM sleep than did the healthy subjects. The addition of a waking study helped show that depressed patients have an alteration in the dynamic sleep-wake interaction in the prefrontal cortex. Finally, the addition of a waking PET scan in the current study demonstrated that abnormally elevated function in the ventral emotional neural system in depressed patients may also play a role in preventing the normal occurrence of sleep.

The current findings can also be compared with those in the study reported by Germain et al.⁵ In that study 12 depressed patients and 13 healthy subjects underwent [¹⁸F]FDG PET studies during presleep waking and during the first NREM period. Germain et al reported less of a decrease in frontal metabolism in depressed patients than in healthy subjects between presleep waking and NREM sleep, just as we found in the present study. We studied a larger sample of depressed and control subjects. The timing of the waking [¹⁸F]FDG PET study in the current study was chosen to maximize cerebral activity associated with late morning wakefulness. We found increased metabolic activity in a ventral emotional neural system across waking and NREM sleep in depressed patients. Increased metabolism in this system may increase emotional arousal and adversely moderate the generation of sleep in depressed patients. This disruption of sleep in turn may prevent sleep from increasing waking efficiency in prefrontal cortex function in depressed patients.

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