ORIGINAL ARTICLE

Increased Activation of Anterior Paralimbic and Executive Cortex From Waking to Rapid Eye Movement Sleep in Depression

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Background: Depression is associated with sleep disturbances, including alterations in rapid eye movement (REM) sleep, that may relate to the neurobiology of the disorder. Given that REM sleep activates limbic and anterior paralimbic cortex and that depressed patients demonstrate increases in electroencephalographic sleep measures of REM, we hypothesized greater activation of these structures during waking to REM sleep in depressed patients.

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

Setting: Patients and healthy subjects recruited from the general community to participate in a research study of depression at an academic medical center.

Patients: Twenty-four unmedicated patients who met the *Structured Clinical Interview for DSM-IV* criteria for current major depression and who had a score of 15 or higher on a 17-item Hamilton Rating Scale for Depression; 14 medically healthy subjects of comparable age and sex who were free of mental disorders.

Main Outcome Measures: Electroencephalographic sleep, semiquantitative and relative regional cerebral metabolism during waking and REM sleep.

Results: Depressed patients showed greater REM sleep percentages. While both healthy and depressed patients activated anterior paralimbic structures from waking to REM sleep, the spatial extent of this activation was greater in the depressed patients. Additionally, depressed patients showed greater activation in bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, as well as in the midbrain reticular formation.

Conclusions: Increased anterior paralimbic activation from waking to REM sleep may be related to affective dysregulation in depressed patients. Increased activation of executive cortex may be related to a cognitive dysregulation. These results suggest that altered function of limbic/anterior paralimbic and prefrontal circuits in depression is accentuated during the REM sleep state. The characteristic sleep disturbances of depression may reflect this dysregulation.

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DEPRESSION HAS BEEN CONsistently linked with sleep dysregulation,[1-8] including alterations in electroencephalographic (EEG) measures of rapid eye movement (REM) sleep. In addition, changes in REM sleep have been linked with the clinical course of the disorder,[9-12] and most effective antidepressant medications suppress REM sleep. Therefore, clarification of the neurobiology of REM sleep in depression may provide clinically relevant insights into the pathophysiology of the disorder.

Rapid eye movement sleep is generated by brainstem mechanisms.[13] Recent functional neuroimaging studies demonstrate that REM sleep preferentially activates anterior limbic and paralimbic structures, such as the amygdala and the anterior cingulate cortex, in the absence of prefrontal activation.[14-18] *Activation* of limbic and paralimbic cortex in these studies refers to a relatively greater level of blood flow or metabolism during REM sleep in relation to a waking baseline condition. Given the lower functional activity of these structures in the preceding nonrapid eye movement (NREM) period,[17,19,20] one could conceptualize this as a reactivation of limbic and paralimbic cortex within REM sleep. The persistence of this waking vs REM sleep pattern across blood flow and metabolic functional neuroimaging studies led us to propose that such a comparison may serve as a naturalistic probe of limbic and paralimbic function in patients with mental disorders, such as depression.[18,21] Given the involvement of these structures in emotional regulation and motivated behavior, we hypothesize that

alterations in REM sleep in depressed patients may reflect a functional alteration in these structures that may be central to the neurobiology of depression. Since depressed patients have increased REM sleep in relation to healthy subjects, we hypothesized that depressed patients would exhibit a greater activation of limbic and paralimbic cortex from waking to REM sleep relative to healthy subjects. To test this hypothesis, we compared waking to REM sleep changes in regional cerebral metabolism between 28 depressed patients and 14 healthy control subjects using the [^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]-FDG) positron emission tomography (PET) method.[22]

METHODS

SUBJECTS

We studied 24 depressed subjects (15 women and 9 men; mean ± SD age, 41 ± 10 years; right-handed only) and 14 healthy subjects (11 women and 3 men; mean ± SD age, 37 ± 10 years; right-handed only). Preliminary analyses of 6 of the depressed patients and 8 of the healthy controls have been reported earlier.[21] 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 they were compensated for participation in the study. Depressed subjects met Research Diagnostic Criteria[23] for major depression on the basis of an interview with either the Schedule for Affective Disorders and Schizophrenia or the *Structured Clinical Interview for DSM-III-R*.[24] Depressed subjects were required to have a minimum score of 15 on the first 17 items of the Hamilton Rating Scale for Depression[25] or a score of 17 or greater on the Beck Depression Inventory.[26] They were excluded if they met Research Diagnostic Criteria for schizophrenia, lifetime history of substance abuse or alcoholism, borderline or antisocial personality disorder, organic affective disorder, schizoaffective disorder, or 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 Depression and to be free of any lifetime history of a mental disorder as previously described.[21] All subjects were required to be free of medications that could affect mood or sleep for at least a 2-week period of time (8 weeks for fluoxetine) prior to EEG sleep and PET studies. Subjects who could not remain drug- or alcohol-free during the study, as verified by nightly drug screens, were excluded. Medical exclusion criteria for all subjects were met, as previously described.[21] Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index. Psychological distress was assessed using the Symptom Check List-90-Revised. Any subject with an Apnea-Hypopnea Index of 10 or higher on night 1 screening was excluded from further study. All subjects underwent magnetic resonance scanning prior to their EEG sleep and PET studies using a 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, Wis), as previously described.[19] 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.[27]

EEG SLEEP METHODS

Electroencephalographic sleep studies were performed at the University of Pittsburgh General Clinical Research Center. Electroencephalographic sleep was monitored on nights 1, 2, and 3. Night 1 was an adaptation night and sleep disorders screening night. Night 2 data were used for the collection of baseline EEG sleep data. Bedtime was determined by the mean bedtime during the 7 days preceding sleep studies, as determined by review of a 7-day sleep diary. On nights 1 and 2, subjects had sham intravenous tubing taped over their forearms. This was inserted through a cannula portal to a monitoring room for the purpose of accommodation to an indwelling intravenous tube used on night 3 for injection of the radioisotope. The EEG sleep montage consisted of a C4/A1-A2 EEG channel, 2 electro-oculography channels (right and left eyes) referenced to linked mastoids, and a submental electromyography channel. All electrode impedances were determined to be greater than 5000 Ω. The EEG signal was collected using Grass 7P511 amplifiers (Grass-Telefactor, West Warwick, RI). Filter settings for the EEG were 0.3 to 100 Hz. The electromyograph 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 Rechtschaffen and Kales criteria.[28] In addition to sleep continuity and sleep architecture measures, the primary REM sleep dependent variables included REM sleep percentage, REM latency (time between sleep onset and first REM period minus any wakefulness occurring during the interval), and REM density in the first REM period (average automated REM counts per minute of REM sleep in the first REM period[29]). Interrater sleep scoring reliability for major sleep variables were checked periodically with κ values ranging from 0.76 to 0.85. Definitions for visually scored sleep variables have been provided elsewhere.[30]

PET METHODS

Regional cerebral glucose metabolism was assessed during both waking and REM sleep using the [^{18}F]-FDG PET method.[22] The waking PET study occurred on the morning following the second night of sleep. The REM sleep PET study occurred on the third night of study. All PET studies used a 4- to 6-mCi (148- to 222-mBq) dose of [^{18}F]-FDG injected via the cannulas portal method in order to minimally disturb subjects. 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 REM sleep study immediately followed the identification of the first REM of the second REM period of the third night of sleep in the laboratory. While depressed patients often exhibit changes in REM sleep in the first REM period, the first REM period is often too brief for an [^{18}F]-FDG PET imaging study. In both the waking and REM sleep periods, subjects were monitored via polysomnography while lying on a bed. They were left undisturbed for a 20-minute period following injection of the radioisotope. Subjects were allowed to leave the laboratory environment following their morning waking PET scan. 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 method[31] was used as an indirect measure of absolute glucose metabolism (MRDglc), as previously described.[32] In this approach, the plasma integral was estimated from 6 nonarteriolized venous plasma samples collected every 8 minutes from 45 to 95 minutes after [^{18}F]-FDG injection. The acquisition protocol included 3-dimensional (septa retracted) mode in an ECAT HR+ PET scanner (CTI Molecular Imaging Inc, Knoxville, Tenn). The head was positioned such that the lowest scanning plane was parallel to and 1 cm below the canthomeatal line. All PET images were reconstructed using standard commercial software as 63 transaxial slices (each 2.4 mm thick), as previously

described.[19] All subsequent alignments and coregistrations were performed using a modification of Roger Woods' automated algorithms for PET to PET alignment and PET to magnetic resonance cross modality registration, as previously described.[33-36,21] The methods for translating the PET images into a common Talairach space for use in the grouped Statistical Parametric Mapping program, 1999 version,[37,38] analyses have been previously described.[21]

STATISTICAL ANALYSES

χ^2 Tests and *t* tests were used to test group differences in categorical measures and continuous clinical and demographic measures. Group differences in EEG sleep measures were determined using a multivariate analysis of variance (MANOVA) to minimize errors related to performing multiple comparisons. Variables entered into the MANOVA included total recording period; sleep efficiency; percentages of stage 1, 2, delta, and REM sleep; REM latency; and the density of REM sleep in the first REM period. Post hoc analyses of variance were performed on individual variables after detecting a significant group effect in the MANOVA. For the measure, MRDglc, a repeated-measures analysis of variance (groups = control and depressed; repeated measure = wake and REM sleep MRDglu), was used to test for group × time interactions and group and time effects. The above analyses were performed using SPSS software (SPSS Inc, Chicago, Ill). To determine differences in relative regional metabolism between waking and REM sleep for each group, as well as group (control vs depressed) by time (wake vs REM sleep) interactions, we used the Statistical Parametric Mapping program. This program was also used to test post hoc group differences in waking relative regional metabolism and in REM sleep relative regional metabolism. The control and depressed waking and REM sleep PET images were entered into an analysis of covariance using global metabolism and age as covariates. Age in years was used as a covariate given known variations in regional cerebral metabolism with age.[39] 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-, and z-axis) coordinates (see Talairach and Tournoux[40]). Regions of interest were defined from preliminary analyses reported earlier.[21] Results were corrected for multiple comparisons based on number of voxels in the whole brain and within regions of interest.

Table 1. Clinical and Demographic Measures

Variable	Mean ± SD: Controls n = 14	Mean ± SD: Depressed n = 24	t_{36}	*df*	*P* Value
Sex, F/M	11/3n	15/9n	1.06	36	.3
Age, y	37.4 ± 10.4	40.8 ± 10.0	–0.99	36	.33
Beck Depression Inventory score	1.0 ± 1.8	21.2 ± 7.8	–9.22	35	<.001
17-Item Hamilton Depression score	1.2 ± 1.5	20.2 ± 3.9	–17.16	35	<.001
Pittsburgh Sleep Quality Index	2.5 ± 2.2	8.9 ± 3.9	–4.99	28	<.001
Hopkins Global Symptom Index	0.1 ± 0.2	1.1 ± 0.5	–6.55	34	<.001

Table 2. Electroencephalographic Sleep Measures

Variable	Mean ± SD: Controls n = 14	Mean ± SD: Depressed n = 24	t_{36}	*P* Value
Sleep Continuity				
Total record period	464.4 ± 45.8	452.1 ± 45.6	0.8	.43
Sleep latency	15.8 ± 12.3	23.7 ± 13.0	–1.85	.07
Awake minutes	23.3 ± 21.1	40.0 ± 36.9	–1.55	.13
Sleep maintenance	94.8 ± 4.5	90.5 ± 8.9	1.68	.10
Sleep efficiency	91.7 ± 5.7	85.9 ± 10.0	2	.05
Nonrapid Eye Movement (NREM)				
% Stage 1	4.9 ± 1.6	7.6 ± 3.3	–2.87	.01
% Stage 2	64.2 ± 9.6	58.7 ± 8.3	1.83	.08
% Stage 3	5.6 ± 5.3	4.4 ± 4.5	0.71	.48
% Stage 4	2.1 ± 3.7	2.7 ± 5.5	–0.36	.72
% Delta	7.7 ± 7.3	7.1 ± 8.2	0.21	.84
Rapid Eye Movement (REM)				
% REM	23.3 ± 5.4	26.5 ± 4.5	–1.99	.05
REM latency	65.6 ± 23.2	56.0 ± 22.1	1.26	.21
REM density in first REM period	4.6 ± 4.2	6.4 ± 5.3	–1.11	.28

RESULTS

CLINICAL

Depressed and healthy groups did not differ in age or sex (**Table 1**). Depressed subjects had mild to moderate severity of depression, global distress, and subjective sleep disturbance. Twenty-one depressed subjects had recurrent major depression (average age at onset, 28 ± 5 years [mean ± SD]; average duration, 49 ± 52 weeks [mean ± SD]), while 3 had single-episode major depression (average age at onset, 28 ± 5.5 years [mean ± SD]; average duration, 51 ± 29 weeks [mean ± SD]). According to the insomnia questions on the Hamilton Rating Scale for Depression,[25] sleep disturbances were moderately severe and distributed evenly across the night (initial, middle, and delayed).

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 control group ($F_{29} = 2.8$, $P = .02$). Secondary analyses showed differences in measures of sleep continuity, NREM sleep, and REM sleep (**Table 2**). 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 REM sleep study. The mean ± SD number of 20-second epochs of REM, wake, and NREM sleep, respectively, in the 20 minutes following injection of [^{18}F]-FDG were 49 ± 9, 2 ± 2, and 8 ± 8 for the controls and 50 ± 11, 3 ± 4, and 8 ± 8 for the depressed group.

WHOLE-BRAIN METABOLISM

We predicted that the decline in whole-brain MRDglc from waking to REM sleep would be less in depressed patients than in healthy subjects. A trend towards this group (depressed vs control) × state (wake vs REM sleep) interaction was noted (1-tailed $P = .08$). We predicted that depressed patients would show greater MRDglc in REM sleep. A trend was noted (1-tailed $P = .09$). No signifi-

cant difference in waking MRDglc was found (depressed = 8.14 ± 2.18 μmol/(100 mL · min) and control = 8.66 ± 1.51 μmol/(100 mL · min) $t_{31} = .71$, 2-tailed t test, $P = .48$). A main effect of state was noted (REM MRDglc < wake MRDglc, $F_{1,30} = 9.2$, $P = .005$).

CHANGES IN REGIONAL METABOLISM FROM WAKING TO REM SLEEP IN HEALTHY SUBJECTS

In healthy subjects (**Figure**), relative metabolism increased from waking to REM sleep in a broad collection of anterior limbic and paralimbic structures with some tendency towards right hemispheric increases (cluster level $P = .002$ corrected for multiple comparisons; voxels in cluster = 1765; voxel of maximum significance within cluster at Talairach x, y, and z coordinates 6, 44, and 16). One large confluent region extended posteriorly and superiorly from the supplementary motor area, then arched anteriorly and inferiorly in the dorsal anterior cingulate and medial prefrontal cortex. This region continued into pregenual and subgenual anterior cingulate cortex, the nucleus accumbens, anterior ventral pallidum, anterior ventral caudate, and lateral hypothalamus. Inferiorly and laterally in the right hemisphere, this region continued into the amygdala and uncus, then arched laterally and posteriorly along the right hippocampal gyrus. Finally, this region extended into the right medial temporal cortex and into the right insular cortex.

CHANGES IN REGIONAL METABOLISM FROM WAKING TO REM SLEEP IN DEPRESSED SUBJECTS

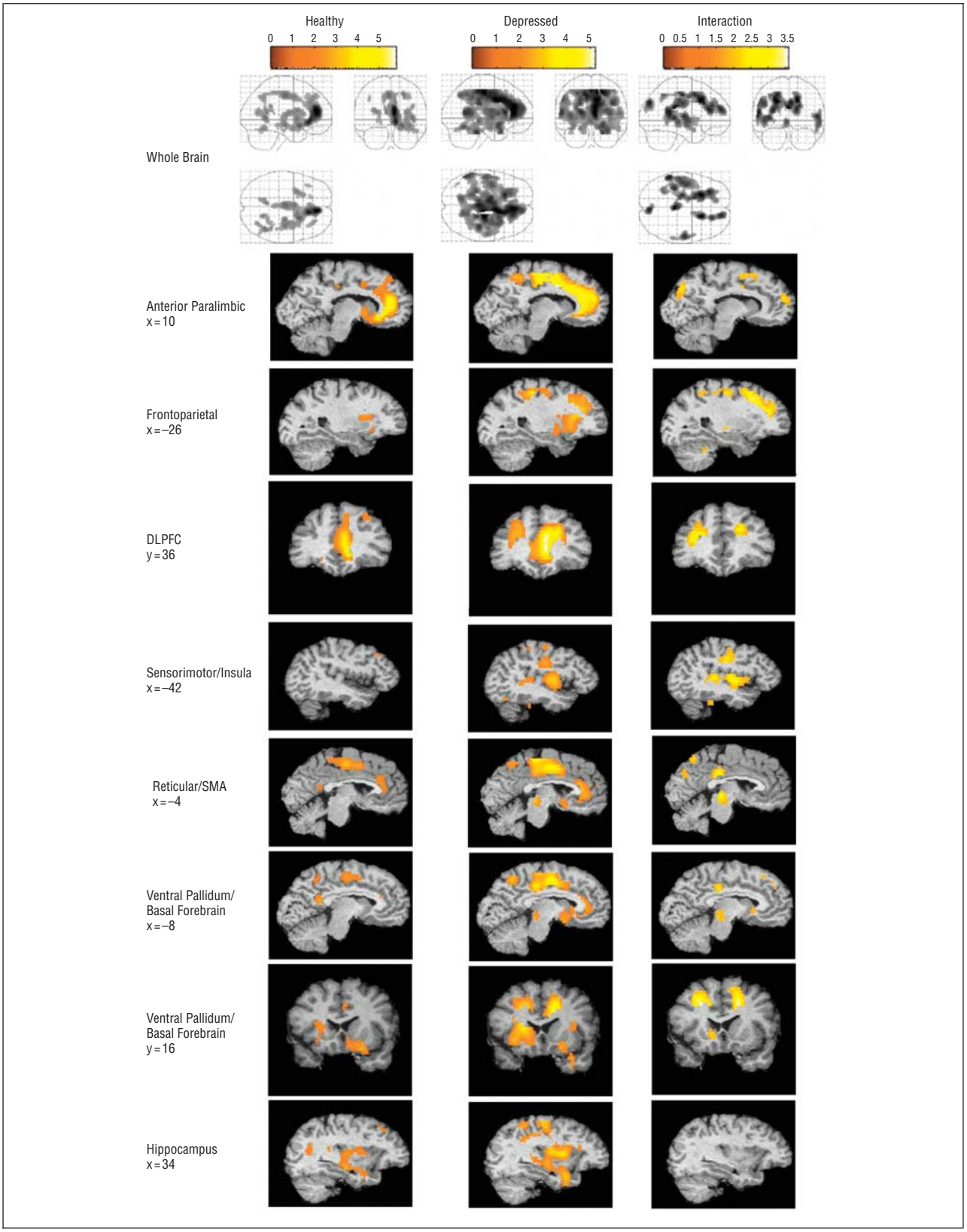
In the depressed subjects (Figure), relative metabolism increased from waking to REM sleep in a broad collection of anterior paralimbic structures (cluster level $P < .001$ corrected for multiple comparisons; voxels in cluster = 9883; voxel of maximum significance with cluster at Talairach x, y, and z coordinates 8, 4, and 32). The spatial extent of activation in depressed patients was much broader (9883 voxels in anterior paralimbic cortex cluster in depressed subjects vs 1765 voxels in this region in healthy control subjects) and more bilateral in nature, and some regional variations seemed apparent (see results of interaction analysis below). The posterior limit of the anterior paralimbic region bilaterally was in the superior parietal cortex (Brodmann area [BA] 7), extending anteriorly including primary sensorimotor cortex bilaterally (BA 1-5), cingulate cortex bilaterally (BA 23, 24), the supplementary motor area, and the premotor area (BA 6). Laterally, this region continued bilaterally into dorsolateral prefrontal cortex. Medially, beginning at the dorsal anterior cingulate (BA 24, 32), this region continued predominantly on the right hemisphere into pregenual anterior cingulate and medial prefrontal cortex. This region did not extend prominently into the subgenual anterior cingulate cortex (BA 25). More posteriorly increased relative metabolism was seen in ventral pallidum/basal forebrain. Increased relative metabolism of basal ganglia was present only on the left side. There was increased relative metabolism of bilateral insular cortex. Significant increases in relative metabolism were seen in the right but not left hippocampus. In the brainstem, the midbrain reticular formation showed increased relative metabolism in REM sleep (voxel level $P = .002$; voxels in cluster = 266; voxel of maximum significance at Talairach coordinates –2, –30, –4). On the left side, this area was confluent with a region of relatively increased metabolism in the anterior lobe of the cerebellum. A similar increase in relative metabolism was noted in the anterior lobe of the cerebellum on the right side.

GROUP × STATE INTERACTIONS

After correcting for multiple comparisons across all brain voxels, depressed subjects showed greater increases in relative metabolism from waking to REM sleep than healthy subjects in a broadly distributed region of predominantly left hemispheric dorsolateral prefrontal, parietal, and temporal cortex (Figure; cluster level $P = .04$ corrected; voxels in cluster = 1005; voxel of maximum significance within cluster at Talairach x, y, and z coordinates –22, 16, 36). The largest region was in the left dorsolateral prefrontal and parietal cortex extending anteriorly from the frontal cortex at Talairach x, y, and z coordinates –25, 43, 15, then arching dorsally along the cortical mantle to a posterior border in parietal cortex at x, y, and z coordinates –34, –58, 47. This area included the dorsolateral prefrontal cortex (BA 46), the Frontal Eye Field in the superior precentral sulcus (x, y, and z coordinates –25, –12, and 53), and the Parietal Eye Fields in the superior and inferior parietal lobule (x, y, and z coordinates –25, –57, and 52 to –31, –41, and 40).

After correcting for multiple comparisons within a priori regions of interest, 3 additional areas reached significance. One area included left hemispheric insular and superior temporal cortex (BA 22, 38, 41, and 42) ranging from y = –20 to 0 and from x = –39 to –53 (cluster level $P = .023$ uncorrected; voxels in cluster = 451; voxel of maximum significance within cluster at Talairach x, y, and z coordinates –42, –12, and 4). A second area included left hemispheric primary sensorimotor cortex (BA 1, 2, 3, 4) (cluster level $P = .04$ uncorrected; voxels in cluster = 378; voxel of maximum significance within cluster at Talairach x, y, and z coordinates –48, –18, and 32). A third area was in the left-sided midbrain reticular formation including the pretectal area (voxel level $P = .007$ uncorrected; voxels in cluster = 92; voxel of maximum significance at Talairach x, y, and z coordinates –4, –28, and 0).

To control for the possibility that overall lower waking metabolism in depressed patients may be driving the results, we first created a binary image mask that included all voxels showing a significant group × state interaction. We then used this mask in a small-volume correction analysis in a group comparison (depressed vs control) of waking metabolism. Structures showing both the interaction and waking hypometabolism in depressed patients included bilateral superior temporal gyrus (right hemisphere 164 voxels, $P < .001$ at x, y, and z coordinates –56, –16, and 16; left hemisphere 57 voxels, $P = .03$ at x, y, and z coordinates 58, –14, and 12) and a trend towards significance in the left superior frontal gyrus (BA 10) (37 voxels, $P = .07$ at x, y, and z coordinates –22, 52, and –4). To see if the observed interactions were associated with relative REM sleep hyperme-



Waking to rapid eye movement sleep activations in healthy subjects (column 1), depressed subjects (column 2), and interactions showing regions where the depressed subjects' waking to rapid eye movement activations are greater than those of healthy subjects (column 3). DLPFC indicates dorsolateral prefrontal cortex; SMA, supplementary motor area; and x and y, Talairach x and y coordinates, respectively.

tabolism in the depressed patients, we used the same binary image mask in a small-volume correction analysis in a group comparison (depressed vs control) of REM sleep metabolism. Structures showing both the interaction and REM sleep hypermetabolism in depressed patients included a large cluster (316 voxels, $P<.001$) in-

clusive of left primary sensorimotor cortex, inferior parietal cortex, and left temporal cortex; a second large cluster (381 voxels, $P < .001$) inclusive of the left superior temporal gyrus and the left frontal eye fields, at Talairach x, y, and z coordinates –28, 20, 36 (90 voxels, $P = .01$).

After we corrected for multiple comparisons across all brain voxels, healthy subjects did not show greater increases in relative metabolism in any area from waking to REM sleep than depressed subjects.

We performed a contrast that corrected for multiple comparisons within a priori regions of interest. Control subjects showed greater increases from waking to REM sleep in both the subgenual anterior cingulate cortex (Talairach x, y, and z coordinates 10, 26, and –4) and the pregenual anterior cingulate cortex (x, y, and z coordinates 6, 44, and 16). In depressed patients, waking hypermetabolism in this region of the anterior cingulate was noted (302 voxels; $P<.05$ corrected; maximum significance at Talairach x, y, and z coordinates –8, 32, and 20).

COMMENT

Depressed patients showed increases in relative metabolism from waking to REM sleep in the midbrain reticular formation and in a larger region of anterior paralimbic cortex than did healthy control subjects. In addition, relative to controls, depressed patients showed greater activation of executive cortex, including cortical eye fields and bilateral dorsolateral prefrontal cortex, from waking to REM sleep. These findings support our hypothesis that depressed patients would demonstrate a greater activation of limbic and anterior paralimbic structures in a waking to REM sleep functional neuroimaging probe.

While the EEG sleep profile of the depressed group was similar to prior reports, some features did not differ from our control sample. Depressed patients displayed poorer sleep efficiency and longer sleep latencies, and they had a greater percentage of stage 1 sleep, although no reductions in slow-wave sleep were observed. They also had a greater REM sleep percentage. The differences for REM density and REM latency were in expected directions but did not reach statistical significance.

The first primary finding in this study is the increased activation of the brainstem reticular formation from waking to REM sleep in depressed patients. This is consistent with the model of an altered balance in brainstem monoaminergic (norepinephrine and serotonin) systems and brainstem acetylcholine neuronal systems in depressed patients as proposed by McCarley.[41] Rapid eye movement sleep is generated by cholinergic nuclei in the brainstem interacting reciprocally with monoaminergic cell groups.[13] As inhibitory monoaminergic input declines from waking to NREM sleep and ceases in REM sleep,[42] cholinergic REM–generating cells are disinhibited. This altered balance may be related to a supersensitive cholinergic system in depressed patients, as evidenced by supersensitive responses to cholinergic REM–generating agents in depression.[43-45] Alternatively, or in addition, a fundamental alteration in monoaminergic tone could lead to the observed findings. For example, application of 5-hydroxytryptamine 1A (5HT1A) agonists into the raphe decreases postsynaptic serotonin release, leading to an increase in REM sleep.[46,47] Boutrel et al[48] described increased amounts of REM sleep in 5-HT1A knockout mice. In light of other work,[49-51] the tonic inhibitory role of serotonin on REM sleep in the 5-HT1A knockout study may be mediated by postsynaptic 5-HT1A receptors in mesopontine cholinergic REM-on neurons.

A second primary finding in this study is the increased activation of limbic and anterior paralimbic (hippocampus, basal forebrain/ventral pallidum, anterior cingulate, and medial prefrontal) cortex from waking to REM sleep in the depressed patients. Activation of these areas in REM sleep has previously been noted in cats[15] and healthy human subjects.[16-18] Mesulam et al[52] have shown that the highest density of cholinergic axons is in core limbic structures such as the hippocampus and amygdala, followed by nonisocortical then isocortical sectors of paralimbic cortex, and lastly in primary sensory, unimodal, and heteromodal association areas. Limbic and anterior paralimbic cortices also have high densities of inhibitory 5-HT1A postsynaptic receptors in relation to other areas of the cortex.[53-55] Increased activation of limbic and anterior paralimbic structures from waking to REM sleep in depressed patients, therefore, may also reflect a monoaminergic/cholinergic imbalance in the forebrain in addition to that seen in the brainstem reticular formation.

A third primary finding in this study is the relatively greater activation of executive cortex from waking to REM sleep in depressed patients. Studies have shown reduced executive function in depression.[56] A fundamental difference between waking brain function and REM-sleep brain function is the degree to which cortical activation is influenced by monoaminergic vs cholinergic ascending projections.[57] In waking, depression-associated reductions in monoaminergic function may account in part for reductions in executive cortex function. In REM sleep, a cholinergically driven state, the depression-associated increased cholinergic tone and reduced monoaminergic tone may not only activate cholinergically rich limbic and paralimbic cortex but also provide significant activation of other cortical areas not activated in healthy subjects during REM sleep. This activation may occur via brainstem cholinergic projections to the cortex or via basal forebrain cholinergic projections that are also under modulatory influence of monoaminergic systems.[58]

Findings in affective neuroscience suggest that our PET findings may be fundamentally related to the behavioral features of depression. Functional neuroimaging studies have found that hippocampus, amygdala, and anterior cingulate cortex, structures showing supersensitive activation in REM sleep in depressed patients, also activate in response to negatively valenced stimuli or increased affective states.[59-64] Given the negative affect of depressed patients during waking, we speculate that the increased activation of these structures in depressed patients may reflect a susceptibility of depressed patients to experience stimuli in a more affectively intense, negative context. Some support for this comes from EEG sleep studies in depressed patients, which showed an association of increased REM density with greater intensity of affect.[65] Both REM density and intensity of affect declined following resolution of depressive symptoms.

Observations from cognitive neuroscience suggest that our findings in the dorsolateral prefrontal cortex may reflect a greater involvement of executive function during REM sleep in depressed patients, perhaps in response to the increased affective state produced by the abnormal activation of limbic and paralimbic cortex during REM sleep in depressed patients. Studies of cognitive control suggest that the anterior cingulate cortex plays a role in the monitoring of cognitive performance, while the dorsolateral prefrontal cortex plays a role in the implementation of cognitive control.[66,67] Activation of the anterior cingulate cortex within REM sleep[16-18] may reflect an internal monitoring process assessing the presence of affectively arousing stimuli. In depressed subjects, the additional bilateral activation of the dorsolateral prefrontal cortex is consistent with the recruitment of higher-order cognitive processes that may be recruited by depressed patients to process the negative affective state. The increased activation of the frontal and parietal eye fields during REM sleep in depressed patients, which are known to underlie the awake control of eye movements,[68] further support an increased cognitive involvement within REM sleep in the depressed subjects. If they were solely related to the eye movements of REM sleep, we would have expected them to be right- as opposed to left-lateralized, given that eye movements are strongly right lateralized.[69]

In relation to prior EEG sleep studies on depression, therefore, alterations in REM sleep may reflect an increased sensitivity of the brainstem cholinergic REM–generating system, an increased stimulation of limbic and paralimbic cortex, and an additional involvement of executive cortex in REM sleep. These alterations in forebrain function in depression may be attributed to an imbalance in monoaminergic/cholinergic function in depression that affects not only the brainstem generation of REM sleep but also the manner in which the forebrain responds to the stimuli of REM sleep. In the context of affective and cognitive neuroscience studies of the behavioral roles of these structures, the increased activation of limbic and paralimbic cortex may reflect an increase in affective responsivity in depression. Involvement of executive cortex during REM sleep in depression may reflect the recruitment of the cortex to develop strategies for managing the heightened affective arousal in depressed patients. Future studies are needed to clarify the relationships between these forebrain patterns and an imbalance in monoaminergic/cholinergic systems that may underlie depressive neurobiology. Future studies are also needed to characterize the relationship between affective and cognitive processes that may be abnormal in depression and that may produce these forebrain patterns observed in REM sleep.

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