

Neuroanatomic Correlates of Psychopathologic Components of Major Depressive Disorder

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Background: The Hamilton Depression Rating Scale (HDRS) is widely used to measure the severity of depression in mood disorders. Total HDRS score correlates with brain metabolism as measured by fludeoxyglucose F 18 (^{18}F)-FDG positron emission tomography. The HDRS comprises distinct symptom clusters that may be associated with different patterns of regional brain glucose metabolism.

Objective: To examine associations between HDRS component psychopathologic clusters and resting glucose cerebral metabolism assessed by ^{18}F -FDG positron emission tomography.

Patients: We evaluated 298 drug-free patients who met the DSM-III-R criteria for major depressive disorder.

Main Outcome Measures: Five principal components were extracted from the 24-item HDRS for all subjects and ProMax rotated: psychic depression, loss of motivated behavior, psychosis, anxiety, and sleep disturbance. The ^{18}F -FDG scans were acquired in a subgroup of 43 drug-free patients in twelve 5-minute frames. Voxel-

level correlation maps were generated with HDRS total and factor scores.

Results: Total HDRS score correlated positively with activity in a large bilateral ventral cortical and subcortical region that included limbic, thalamic, and basal ganglia structures. Distinct correlation patterns were found with the 3 individual HDRS factors. Psychic depression correlated positively with metabolism in the cingulate gyrus, thalamus, and basal ganglia. Sleep disturbance correlated positively with metabolism in limbic structures and basal ganglia. Loss of motivated behavior was negatively associated with parietal and superior frontal cortical areas.

Conclusions: Different brain regions correlate with discrete symptom components that compose the overall syndrome of major depression. Future studies should extend knowledge about specific regional networks by identifying responsible neurotransmitters related to specific psychopathologic components of mood disorders.

Arch Gen Psychiatry. 2005;62:397-408

MAJOR DEPRESSIVE EPISODES (MDEs) involve several psychopathologic components. Brain imaging studies¹⁻²⁸ have identified abnormalities associated with MDEs, but most have not attempted to identify brain regions related to symptom components of MDEs. Symptom components may correlate with different brain regions. If so, given the variation in psychopathologic features and their severity between episodes, even within the same individual,²⁹ considering only global depression severity in mapping brain activity patterns in MDEs introduces noise into the results of studies.

One approach to obtaining a map of the anatomic correlates of the symptom components of MDEs is to decompose the overall depression rating scale scores into components. The internal structure of clinical psychometric scales can be explored by fac-

tor analysis. Despite progress in resolving the technical³⁰ and conceptual³¹⁻³⁵ issues, previous factor analyses of the Hamilton Depression Rating Scale (HDRS)³⁶⁻⁵⁴ identified 1 to 7 factors. The lack of consistent results reflects methodologic and study population differences.^{30,37,48} For ordered-category ratings, the polychoric correlation technique (see the "Methods" section) is an option⁵⁵⁻⁶¹ that avoids potential artifacts and yet, to the best of our knowledge, has never been applied to determine the correlation between HDRS factors and relative regional brain activity as measured by glucose uptake (rCMRglu).

To our knowledge, only 3 studies⁶²⁻⁶⁴ have evaluated the correlation between the severity of symptom clusters obtained by factor analysis and rCMRglu^{63,64} or relative regional cerebral blood flow (rCBF).⁶² All these studies found indications of regional differences in patterns of correlation with symptom components, al-

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though 1 study⁶³ examined only treatment effects. These studies used small, diagnostically heterogeneous samples, limiting the confidence in the factors derived.

To overcome the limitations of the previous studies, we conducted factor analysis of depressive symptom clusters in 298 medication-free patients with a current DSM-III-R MDE using a polychoric correlation matrix of 24-item HDRS (HDRS-24)^{42,65} scores that generated 5 nonorthogonal symptom factors. We then examined the relationships between these factors and the HDRS-24 total score at a voxel level to rCMRglu measured by fludeoxyglucose F 18 ([¹⁸F]-FDG) and positron emission tomography (PET) in 43 of the 298 patients.

METHODS

PATIENTS

Medication-free patients with a current MDE in the context of major depressive disorder, diagnosed based on the *Structured Clinical Interview for DSM-III-R, Patient Version*,⁶⁶ and with a score greater than 16 on the 17-item HDRS^{41,42,65} were entered into the study after giving written informed consent as approved by the Columbia University and New York State Psychiatric Institute institutional review boards. Demographic data and psychiatric, medical, and family histories were recorded on the Columbia Baseline Demographic Form. Patients were administered the HDRS within 24 hours of undergoing PET.

Data are reported as mean \pm SD. Patients in the PET analysis had an age of 38.4 ± 13.2 years and 15.6 ± 2.9 years of education. Age at the first episode of major depression was 23.8 ± 14.7 years. The cohort comprised 61% women and had 4.2 ± 3.5 lifetime episodes of major depression. The Global Assessment of Functioning Scale score for the current episode was 43.6 ± 10.2 . The HDRS-24 total and factor scores for patients in the PET analysis were as follows: HDRS-24 total score, 29.7 ± 6.2 (scale range, 0-74); factor 1, 12.5 ± 3.3 (scale range, 0-28); factor 2, 5.1 ± 2.3 (scale range, 0-10); factor 3, 1.6 ± 1.7 (scale range, 0-12); factor 4, 5.3 ± 2.1 (scale range, 0-14); and factor 5, 2.8 ± 1.7 (scale range, 0-6).

Patients were medication free for a minimum of 14 days except for benzodiazepines and 1 patient receiving buspirone hydrochloride (6 weeks in the case of fluoxetine hydrochloride and 1 month in the case of oral antipsychotic agents). The median number of days not taking each type of medication before PET was as follows: anticonvulsants and mood stabilizers¹ ($n=5$), 19 (range, 13-34 days); antidepressant, other² ($n=7$), 43 (range, 7-13 days); benzodiazepines ($n=17$), 25 (range, 9-956 days); selective serotonin reuptake inhibitor, non-fluoxetine³ ($n=8$), 26.5 (range, 9-461 days); and fluoxetine ($n=7$), 64, (range, 41-984 days). Eighteen patients had no previous medication use. The following medications were taken by 1 patient each: lithium carbonate (terminated 43 days before PET), the monoamine oxidase inhibitor phenelzine sulfate (41 days), and levothyroxine sodium (16 days). The following medications were taken by 2 patients each: the antiparkinsonian drugs bromocriptine and pergolide mesylate (terminated 101 and 29 days before PET), risperidone (41 and 29 days), the typical antipsychotic agents haloperidol and thioridazine (44 and 30 days), the stimulants dextroamphetamine sulfate and methylphenidate hydrochloride (19 and 16 days), and electroconvulsive therapy (56 and 57 days). Three patients each took the following medications: buspirone hydrochloride (terminated 9, 17, and 44 days before PET), the tricyclic antidepressants clomipramine hydrochloride ($n=2$) and nortriptyline hydrochloride ($n=1$) (19, 82, and 956 days),¹ divalproex sodium and carbamazepine,² trazodone hydrochloride, venlafaxine hydrochloride,

ride, mirtazapine, nefazodone hydrochloride, bupropion hydrochloride,³ paroxetine, and sertraline hydrochloride.

Patients were free of medical illnesses based on history, physical examination findings, and laboratory test results. Pregnant women were excluded. Premenopausal women were studied within 5 days of the onset of menses.

FACTOR ANALYSIS

The factor analysis was performed on the polychoric correlation matrix of the HDRS-24 scores. For completeness of content coverage of components of MDEs, we used HDRS-24 scores for the factor analysis. The polychoric correlation (for ordered-category ratings) is preferable to correlation or covariance matrices for the measurement of correlations between psychometric scale items⁵⁵⁻⁵⁹ because it is theoretically invariant across changes in the number or "width" of rating categories. Otherwise, owing to the truncated range of scores (inclusion criteria of the 17-item HDRS total score of ≥ 17) and the stepwise nature of the subitem scores (each item ordered into a few categories and scored from zero to a single digit upper limit, which varies from item to item), the standard factor analysis of a correlation matrix or covariance matrix can generate false associations between items. We previously used this method in an analysis of the Beck Suicide Intent Scale.⁶⁷ However, we also ran our factor analysis using standard Pearson correlations and the raw data, and we obtained the same 5 factors that we obtained with the polychoric matrix (all items loaded on the same factors). Because we did not weight factor scores by their loadings, the Pearson correlation matrix produced identical factor scores. Correlations with ¹⁸F-FDG uptake remained unchanged.

Furthermore, we used a nonorthogonal (ProMax) rotation. Applying a mathematical rotation to the axes can greatly simplify the relationships between factors (axes) and variables (HDRS item scores). A multidimensional factor plot may have multiple distinct clusters, which are isolated from each other but vectorially less than orthogonal to each other. In such a case, orthogonal rotation of the axes would not necessarily stop variables from loading equally on several axes or factors. A nonorthogonal rotation of the axes is necessary to find a useful factor solution to variables that tend to form clusters that are not orthogonal to each other.

The same factor structure of depressive symptoms was found in the subsample that underwent PET ($n=43$) and the larger sample ($n=298$). The 2 groups also did not differ in HDRS total or factor scores or demographic variables except that the PET group was more educated by a mean of 1.5 years ($t_{60.76}=-3.13$; $P=.003$).

PET STUDIES

As reported in previous publications,^{12,68-70} a bolus injection of approximately 10 mCi of ¹⁸F-FDG was administered intravenously. Patients gazed at crosshairs in a room with dimmed lighting during the first 15 minutes of the ¹⁸F-FDG distribution phase and then rested quietly for another 15 minutes before moving to the scanner (ECAT EXACT 47; Siemens Corp, New York, NY), where they were supine for 10 minutes before undergoing PET.

IMAGE ANALYSIS

As reported elsewhere,^{12,68-70} the twelve 5-minute PET frames were aligned using automated image registration⁷¹ and then summed. Statistical analysis was performed using Statistical Parametric Mapping (SPM99; Institute of Neurology, University College of London, London, England) implemented in Matlab 5 (The Mathworks Inc, Natick, Mass).^{72,73} To determine which regions correlate with HDRS-24 total and factor scores, a voxel-level correlation analysis was performed using the general lin-

ear model with rCMRglu. Height threshold was set a priori to $P < .01$, and the extent threshold was set to $P < .05$ after correction for multiple comparisons by Statistical Parametric Mapping. Stereotaxic coordinates reported are based on Talairach atlas⁷⁴ coordinates, converted from Montreal Neurological Institute coordinates.⁷⁵⁻⁷⁷

RESULTS

FACTOR ANALYSIS

Factor analysis of the HDRS-24 on the population of 298 depressed patients yielded a 5-factor solution (**Table 1**). When factors are correlated owing to nonorthogonal rotation, sums of square loadings cannot be added to obtain a total cumulative variance. However, from the eigenvalues, it can be determined that the variance in HDRS-24 scores explained by the individual factors ranges from 9.4% to 13.1%. For descriptive statistics on the subscale (or factor) scores, see the “Methods” section.

rCMRglu CORRELATION WITH HDRS SCORES

HDRS-24 Total Score

There are positive correlations between rCMRglu and the HDRS-24 total score in multiple ventral brain regions (**Figure 1** and **Table 2**). These structures form a single contiguous brain region (6960 voxels) in which rCMRglu shows significant (cluster level $P < .001$, corrected for multiple comparisons) positive correlation (partial $R = 0.551$; global maximum at Talairach coordinates 10 13 -12) with HDRS-24 total scores. These brain regions involve the bilateral mesiotemporal cortex, parts of the ventral subgenual basal forebrain, and most of the thalamus, hypothalamus, ventral striatum, and midbrain. The HDRS-24 total score shows no significant negative correlation with any brain region.

Factor 1: Psychic Depression

Factor 1 correlates positively with a large central, ventral cortical and subcortical area that extends into the left temporal lobe (**Figure 1**, **Figure 2**, and **Table 2**). These structures form 3 clusters (3557, 3793, and 1561 voxels) in which rCMRglu shows significant ($P \leq .001$, .001, and .03) positive correlations (partial $R = 0.6$, 0.5, and 0.6 for maxima at Talairach coordinates -38 -45 -11, 10 -17 8, and -12 -23 40) with factor 1. This area includes most of the dorsal posterior cingulate, thalamus, ventral striatum, hypothalamus, subgenual anterior cingulate, and subgenual basal forebrain. Factor 1 shows no significant negative correlation with rCMRglu.

Factor 2: Loss of Motivated Behavior

Factor 2, in contrast to the total HDRS-24 and factor 1, shows only a significant negative correlation with largely dorsal cortical regions. These structures form 3 clusters (2873, 3765, and 3172 voxels) in which rCMRglu shows a significant ($P \leq .001$) negative correlation (partial $R = 0.6$, 0.6, and 0.5 at 42 -70 33, -22 -70 33, and -30 23 34

Table 1. Factor Structure of the Hamilton Depression Rating Scale (HDRS)

24-Item HDRS	Factor Loading*
Factor 1: Psychic depression	
1. Depressed mood	0.59
2. Feelings of guilt	0.46
3. Suicide	0.67
8. Retardation	0.44
22. Helplessness	0.41
23. Hopelessness	0.65
24. Worthlessness	0.79
Factor 2: Loss of motivated behavior	
7. Work and activities	0.42
12. Somatic symptoms (appetite)	0.84
14. Genital symptoms (libido)	0.50
16. Weight loss	0.74
Factor 3: Psychosis	
17. Insight	0.74
19. Depersonalization and derealization	0.41
20. Paranoid symptoms	0.68
21. Obsessive and compulsive	0.68
Factor 4: Anxiety	
9. Agitation	0.74
10. Anxiety—psychic	0.62
11. Anxiety—somatic	0.52
15. Hypochondrias	0.68
Factor 5: Sleep disturbance	
4. Insomnia—early	0.74
5. Insomnia—middle	0.83
6. Insomnia—late	0.59

*Each number represents the correlation between the item and the rotated factor. The extraction method used was principal components analysis, and the rotation method used was ProMax with Kaiser normalization. Only items with factor loading of 0.5 or higher were retained for further analysis.

Talairach coordinates) with factor 2. Factor 2 is negatively correlated with an extensive network of dorsal cortical regions (**Figures 1** and **2** and **Table 2**), including the dorsolateral prefrontal cortex (PFC), dorsal parietal cortex, and dorsal temporal association cortices.

Factors 3 and 4: Psychosis and Anxiety

Factors 3 and 4 show no significant positive or negative correlation with rCMRglu in any brain regions.

Factor 5: Sleep Disturbance

Factor 5 correlates positively with rCMRglu in a series of regions almost encircling the area associated with factor 1 (**Figures 1** and **2** and **Table 2**). These structures form 2 clusters (1582 and 5224 voxels) in which rCMRglu shows a significant ($P \leq .003$) positive correlation (partial $R = 0.6$ and 0.5 at 42 -20 32 and -24 -25 14 Talairach coordinates) with factor 5. The sleep disturbance factor shows no significant negative correlation with any brain region.

We found no correlations between HDRS total or factor scores and age, sex, or any other demographic variables reported in the “Methods” section. Nevertheless, for completeness we repeated the entire analysis controlling for age and sex. Despite the decreased statistical power, and correcting for multiple comparisons, the correlations between rCMRglu and the depression severity

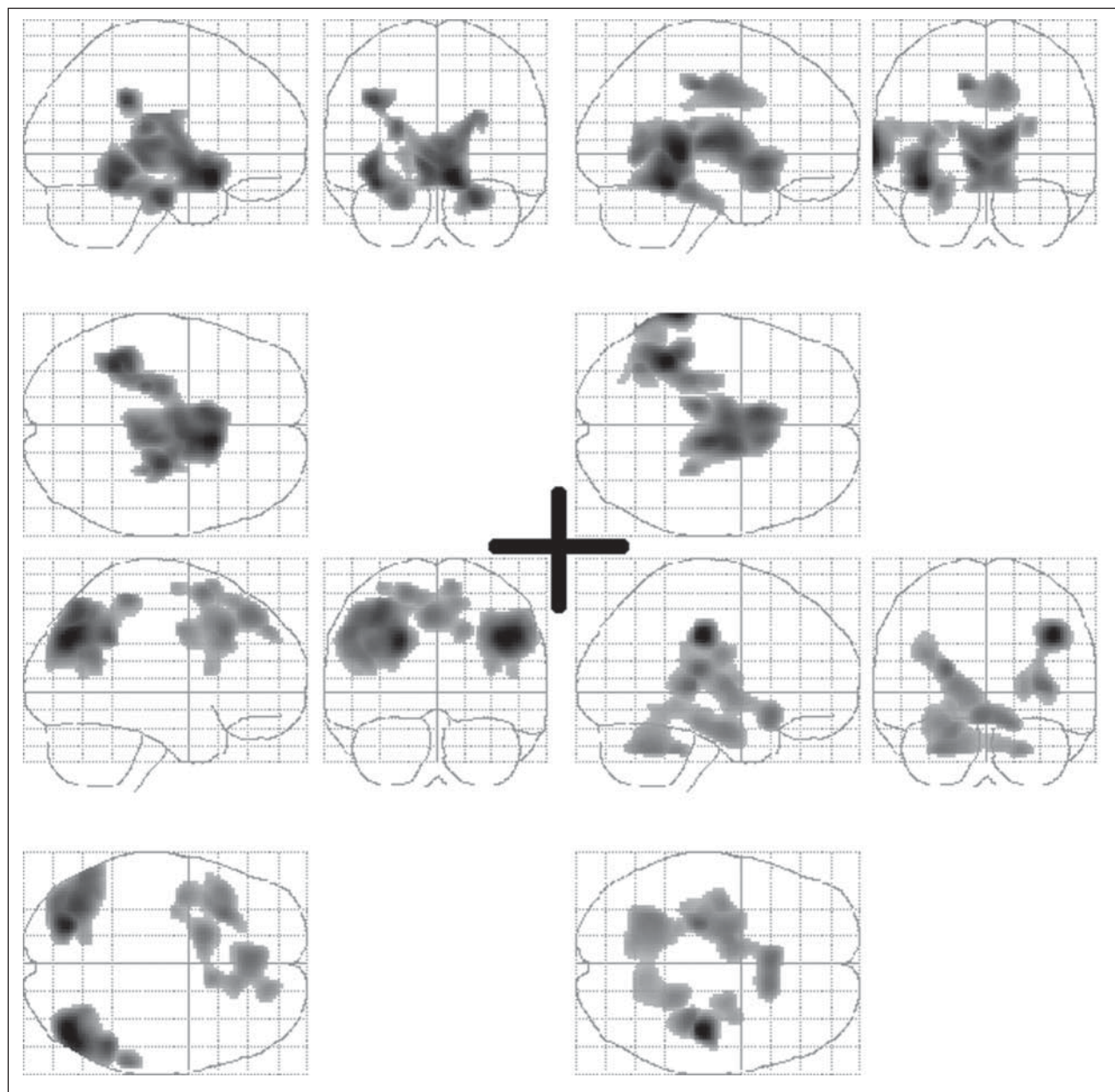


Figure 1. Regions shown as a volume in the glass brain. Maps of correlations of relative regional glucose metabolic rate in human brain in major depression, with severity of depression measured by the 24-item Hamilton Depression Rating Scale. Upper left, overall depression (total score). Upper right, Factor 1: psychic depression. Lower left, Factor 2: loss of motivated behavior. Lower right, Factor 5: sleep disturbance.

scores remained statistically significant in all but 1 case. Factor 2 lost significance when including age in the statistical design.

COMMENT

To our knowledge, this is the first study that maps the neuroanatomic correlates of the symptom components of major depression based on factor analysis of the polychoric correlation matrix (instead of the correlation matrix or covariance matrix that is used routinely) of the HDRS-24. We found distinct correlation maps of brain activity for 3 of the 5 factors. There is minimal overlap in the parametric maps of the 3 factors such that their brain distributions are strikingly distinct. This is best il-

lustrated in Figure 2, where the panel shows the area unique to the corresponding factor separately from the area that overlaps with other factors. Two factors did not reveal any statistically significant correlations with specific brain regions in this population.

OVERALL DEPRESSION SEVERITY AND RELATIVE REGIONAL BRAIN ACTIVITY

Overall depression severity shows a positive correlation with rCMRglu in a large contiguous volume that includes parts of the limbic system, the ventromedial prefrontal and temporal cortices, parts of the inferior parietal cortex, the thalamus, the ventral aspects of the basal ganglia, and the midbrain. No negative correlation of over-

Table 2. Regions in Which Relative Cerebral Glucose Metabolism Shows Significant Correlations With Hamilton Depression Rating Scale (HDRS) Total and Factor Scores*

	HDRS Total†	Factor 1†	Factor 2‡	Factor 5†
Right mesiotemporal	28, 35, 36
Left mesiotemporal	37, 19, 28, 35, 36	35, 36	...	19, 28, 30, 34, 35, 36, 37, amygdala, hippocampus
Ventromedial prefrontal cortex	BL 25	BL 25	...	R 11, R 13, BL 25, R 47
Dorsomedial prefrontal cortex	BL 6, 8, 9	...
Dorsolateral prefrontal cortex	L 44, 45	...
Ventral anterior cingulate	BL 25	BL 25	...	L 25, L 32
Dorsal anterior cingulate	...	BL 24
Pregenual cingulate
Dorsal posterior cingulate	...	BL 31
Insula	BL 13	BL 13	...	BL 13
Left parietal cortex	7, 19, 39, 40	...
Right parietal cortex	19, 39, 40	...
Left temporal cortex	20, 37	20, 21, 22, 37	39	...
Right temporal cortex	19, 22, 39	...
Left occipital cortex	19, 39	...
Right occipital cortex	19	...
Thalamus	BL mammillary body, BL MDN, BL pulvinar, BL VAN, BL VLN	Entire (BL)
Hypothalamus	BL	BL
Caudate	...	BL head	...	R tail
Putamen	BL
Globus pallidus	BL
Midbrain	BL most
Cerebellum	BL anterior lobe

Abbreviations: BL, bilateral; L, left; MDN, medial dorsal nucleus; R, right; VAN, ventral anterior nucleus; VLN, ventral lateral nucleus; ellipses, not applicable.

*Numbers represent Brodmann areas.

†Positive correlation.

‡Negative correlation.

all depression score with rCMRglu was found in any brain region. Like our findings, others have found overall severity of depression to be positively correlated with rCMRglu or rCBF in the ventral brain regions, such as the bilateral medial frontal and right anterior cingulate,⁷⁸ right dorsolateral⁷⁸ and anterolateral⁷⁹ PFCs and in the hippocampus,⁸⁰ cingulate, and other paralimbic areas.⁸¹ In addition, positive correlations are reported in the left anterior temporal, left dorsolateral prefrontal, right prefrontal, and right posterior temporal cortices.⁸² Some studies report no correlation between overall severity of depression and central nervous system activity estimated by either rCBF^{83,84} or rCMRglu.^{85,86}

There is less clear agreement among studies that find negative correlations between global depression severity and regional brain activity in terms of the specific regions involved. For example, overall severity of depression is reported to be negatively correlated with rCMRglu or rCBF in whole slice,⁸⁷ right cingulate cortex, bilateral PFC, insula, basal ganglia, and temporoparietal cortex (right > left)¹⁴; globally,^{88,89} inferior anterior cingulate cortex,⁹⁰ anterofrontal and left prefrontal regions⁹¹; widespread anterior,⁹² frontal, central, superior temporal, and anterior parietal regions²¹; ventral anterior cingulate; and orbitofrontal cortex with the caudate nuclei in an acute tryptophan depletion-induced relapse paradigm.⁹³ Similarly, low gray matter rCBF was reported to correlate with severity of depression as measured by the HDRS.⁸⁹ Some regions showing correlation with overall severity scores in that study⁸⁹ were identified in our study as correlat-

ing with specific clinical components of the HDRS. One explanation for the inconsistency in reported findings is that the diversity of clinical manifestations of MDE between and within patients²⁹ may obscure associations of global severity with specific brain regions in functional imaging studies. Psychopathologic item clusters correlate differently with activity of specific brain regions such that combining factor scores from different subjects may obscure important associations between brain regions and symptom severity of depression.

Normalization of higher rCMRglu in the limbic system associated with improvement in MDEs⁶³ after treatment, and increases in limbic-paralimbic rCBF (subgenual cingulate and anterior insula) and decreases in neocortical rCBF in other regions (right dorsolateral prefrontal and inferior parietal)⁹⁴ indicate partial normalization with recovery from depression, namely, limbic metabolic decreases and neocortical metabolism increases. A significant inverse correlation between subgenual cingulate and right dorsolateral prefrontal activity is demonstrated in the state of induced sadness and recovery.⁹⁴

Caution should be exercised in interpreting negative findings in this study. The fact that this study did not find regions in the brain that negatively correlate with overall depression does not mean that such regions do not exist. The composition of the group in terms of severity of factor 2, which has negative correlations with large bilateral parts of the PFC and parietotemporal cortex, may be part of the reason for the absence of a global severity negative correlation.

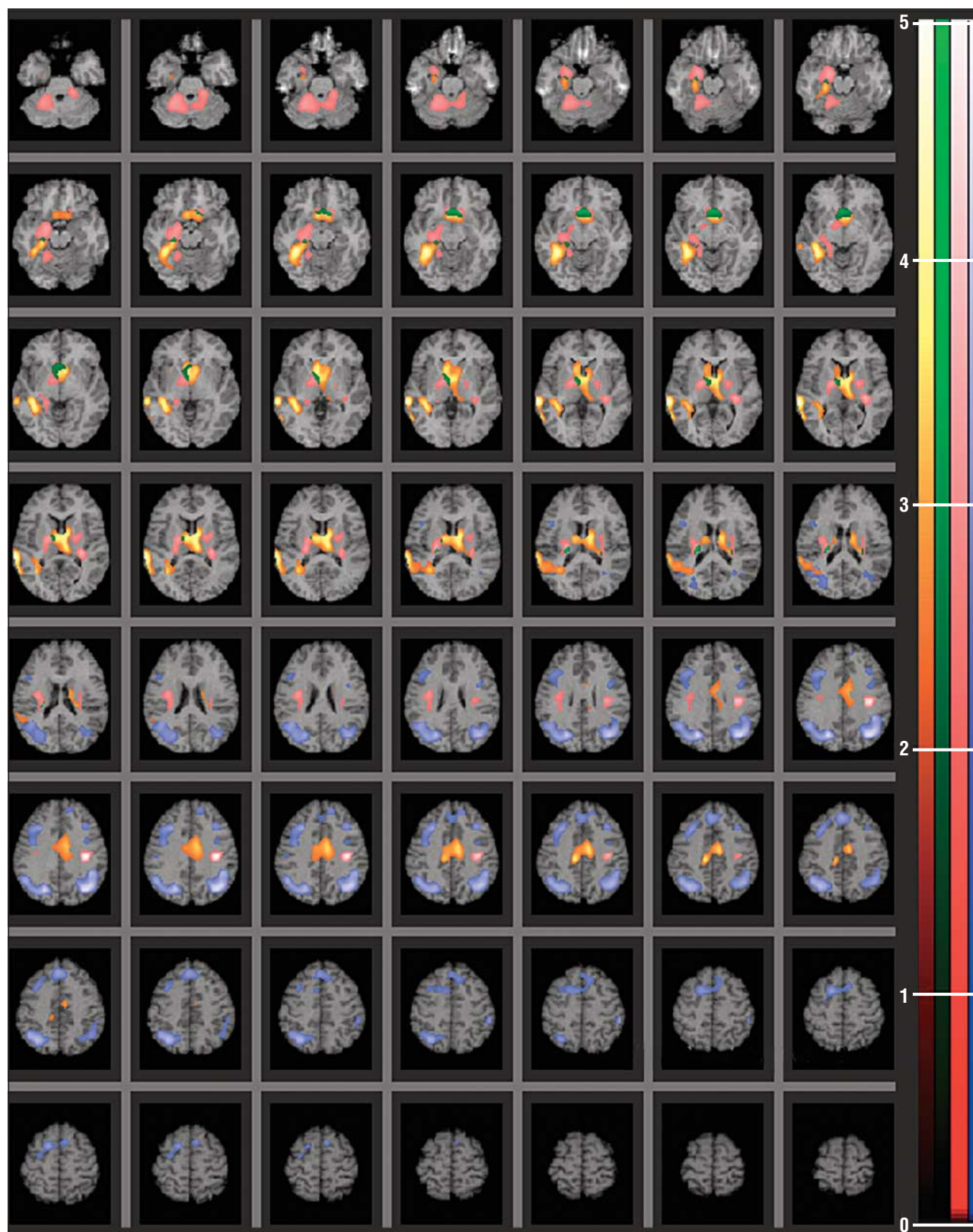


Figure 2. A map of correlations of relative regional glucose metabolic rate in human brain in major depression, with severity of depression measured by factors 1, 2, and 5 of the 24-item Hamilton Depression Rating Scale. The color scales indicate the strength (t score) of the correlation (t score maps are overlaid on a series of transaxial slices [2 mm apart] of a coregistered magnetic resonance image from 38 mm below to 72 mm above the line connecting the anterior and posterior commissures). Red to orange regions are uniquely positively correlated with factor 1, green to light green regions correlate with factors 1 and 5, blue to light blue regions are uniquely negatively correlated with factor 2, and red to light red regions are uniquely positively correlated with factor 5, the sleep disturbance factor.

CORRELATIONS WITH DEPRESSIVE PSYCHOPATHOLOGIC COMPONENTS

Factor 1: Psychic Depression

This factor, which includes items that reflect depressed mood, depressive cognitions, and suicidality, correlates positively with a large ventral and midline area. Subjective severity of negative cognitions in major depression is reported by other researchers⁶⁴ to also correlate with metabolism bilaterally in ventral brain regions. Minor differences in involved brain regions compared with our study may be attributable to differences in the clinical measures used. Although the HDRS-derived factors in a treatment study⁶³ differ somewhat from ours, there is convergence in the results because improvement in symptom severity was associated with a decrease in metabolic activity in ventral structures, a normalization of the findings we made in the depressed state.

Factor 2: Loss of Motivated Behavior

Factor 2 is negatively correlated with an extensive network of dorsal cortical regions (Figures 1 and 2 and Table 2). Consistent with this finding, psychomotor change–anhedonia is reported to correlate robustly with lower normalized rCMRglu in the right dorsolateral prefrontal and temporal cortices,⁶⁴ and lower normalized rCBF in the dorsolateral anteroposterior PFC correlates with psychomotor slowing, poverty of speech, and cognitive impairment.^{62,95-98} On the other hand, psychomotor retardation–anhedonia correlated with lower absolute metabolism in the right insula, caudate, anteroventral caudate/putamen, and temporal cortex and with higher normalized metabolism in anterior cingulate in another study.⁶⁴ Consistent with our results, rCMRglu in the left anterolateral and dorsolateral PFC increases proportionately with antidepressant treatment response.^{63,79}

We found that loss of motivation in depression was also associated with changes in the parietal, temporal, and frontal cortices. Some studies⁹⁹⁻¹⁰³ have noted associations in planning or other measures of motivation to parietal and frontal cortex activity. In addition, one model¹⁰⁴ has postulated that depression involves the frontal, limbic, and subcortical regions, with the subcortical regions playing a primarily gating role. Our findings that multiple regions are involved in this dimension of depression are in keeping with such a model and are further supported by studies that suggest specific deficits in the parietal and frontal cortices that are associated with motivation or its inverse, apathy.¹⁰²

Although in animal¹⁰⁵ and human^{106,107} studies, reward-related motivation has been linked to the striatum and to limbic projections from the midbrain tegmentum in paradigms using tasks in which some operantly conditioned behavior is coupled with the anticipation of instant gratification, it is not surprising that the metabolic abnormality of an extensive network of frontal, parietal, and temporal association cortices correlates with the severity of the loss of motivated behavior. This is in keeping with the model that dopaminergic input to the stri-

tum gates the glutamatergic sensorimotor and incentive motivational input signals to the striatum,¹⁰⁵ and it is also supported by studies of brain injuries in which reduced goal-directed behavior due to lack of motivation (apathy) has been found to be associated with specific cognitive deficits related to frontal cortical dysfunction.¹⁰²

Factor 3: Psychosis

Factor 3 shows no significant associations with rCMRglu in the present study. These items are the least cohesive group of items, forming a cluster in our factor analysis that seems to encompass a dimension that is related to psychosis. Distinct patterns of central nervous system correlates of various measures of formal thought disorder and other psychotic symptoms are extensively reviewed¹⁰⁸ in the context of schizophrenia. The severity of psychosis was low in our sample, providing minimal statistical power to find meaningful correlations.

Factor 4: Anxiety

We found no correlations with this factor, in contrast to other voxel-based correlational analyses that derived anxiety factors from the Beck Depression Inventory or other scales.^{62,63} However, most region of interest–based studies do not agree on correlations with anxiety severity. Positive correlations are reported with 1 brainstem region of interest between rCBF and subjective anxiety scores.¹⁰⁹ A “probable association” was reported⁸¹ between an increase in the anxious-depression factor and reduced frontal neocortical perfusion. No clear association was reported¹¹⁰ between subjective or physiologic variables and changes in rCBF as a consequence of anxiety induction. Based on an anxiety induction study, it has been suggested¹¹¹ “that some of the temporal cortex rCBF activation peaks previously reported in humans in association with drug- and non-drug-induced anxiety, as well as the increase in rCBF in the claustrum-insular-amygdala region, may be of vascular and/or muscular origin” instead of a reflection of central nervous system activity. On the other hand, there are rCMRglu¹¹² and rCBF¹¹³ studies that show disparate but unique patterns of correlation between their measures of anxiety and tracer uptake. Another possible explanation for the disparate findings, besides differences in patient populations and definitions of anxiety symptoms, may lie in the uncoupling of metabolism and blood flow in many brain regions.¹¹⁴ This double-isotope ¹⁸F-FDG and technetium Tc 99m–hexamethylpropylene amine oxime single-photon emission computed tomography technique indicates that a dynamic coupling between rCBF and rCMRglu exists only in a few distinct brain regions even in healthy individuals, and depressive illness may have a further uncoupling effect on this correlation in some brain regions.

Factor 5: Sleep Disturbance

Factor 5 shows positive correlations with a series of cortical and subcortical structures in our awake patients. Abnormalities in brain activity in the limbic and paralimbic structures that overlap with regions we find to correlate

with the depression sleep disturbance factor are reported to be more active in relation to sleep disturbances found in major depression¹¹ and to decreases in activity after sleep deprivation treatment of major depression.¹¹⁵

These results are also consistent with findings from human functional neuroimaging studies of sleep (for a review see Maquet¹¹⁶). It is currently assumed that for the successful initiation or maintenance of physiologic phases of normal sleep, the deactivation of these areas is important. Consequently, it is not surprising that insomnia (a lack of normal sleep) may positively correlate with the degree to which some of these areas are overactivated and, therefore, perhaps fail to deactivate and thereby interfere with the development of normal sleep architecture. In contrast, a dissenting study⁶³ found that improvement in sleep disturbance was negatively associated with change in right anterior medial temporal, left ventral frontal, and right ventral frontal metabolism.

IMPLICATIONS FOR THE NEURAL CIRCUITRY OF MAJOR DEPRESSION

The evolution of emotion likely stems from the absolute need to identify and appraise threatening and rewarding stimuli in the environment and form quick and appropriate goal-directed behavior in response.^{117,118} This process has been divided into identification and appraisal of the emotional significance of the stimulus and the production of an affective state, including the automatic physiologic and somatomotor responses to the stimuli.¹¹⁹⁻¹²¹ Phillips et al¹²² propose a third process, the effortful regulation of the affective state and behavioral responses, which in turn involves the inhibition or modulation of the first 2 processes so that the affective state and behavior produced are contextually appropriate. The neural basis of these 3 processes have been extensively reviewed recently.^{122,123} Briefly, amygdala, which has extensive interconnections with insula, together with the ventromedial PFC, thalamus, hypothalamus, and periaqueductal gray, is thought to form part of a network that participates in perceiving aversive stimuli and organizing autonomic responses to them. Numerous lines of evidence,^{124,125} human stimulation,¹²⁶ human central nervous system lesions,¹²⁷⁻¹³¹ and functional brain imaging studies¹³²⁻¹⁴³ support the involvement of these structures in the perception of aversive stimuli^{124,125} or the identification of expressions of fear,^{128-130,144} disgust,^{76,131,136,145,146} sadness,¹³⁹ and happiness¹³⁴ and in the attention¹⁴⁷ to emotionally charged information.

Findings from animal and human studies suggest that these structures participate not only in the perception and identification of the emotional salience of stimuli but also in the second process mentioned in the previous paragraph, that is, the production of affective states and emotional behavior. Animal studies implicate the ventral tegmental area, nucleus accumbens,^{148,149} putamen, and caudate¹²⁵ in reward processing; the amygdala¹⁵⁰⁻¹⁵⁵ in the production of various affective states; the subgenual anterior cingulate¹⁵⁶⁻¹⁶⁰ in autonomic and conditioned responses to emotionally salient stimuli; and the subgenual ventral PFC¹⁶¹⁻¹⁶³ in the evaluation of the reward value of stimuli and the regulation of autonomic and

endocrine responses to fear.¹⁶⁴ Human lesion¹⁶⁵⁻¹⁶⁸ and stimulation^{169,170} studies support the involvement of these structures (the amygdala,^{165,166,169} subgenual anterior cingulate,^{167,168,170} and ventromedial PFC¹⁷¹⁻¹⁷⁴) in the production of affective states and emotional behavior in human. Findings from human functional brain imaging studies support the involvement of these structures (found in the present study to correlate with depression severity) in the production of affective states and emotional behavior (the ventral striatum,¹⁷⁵⁻¹⁷⁹ amygdala,¹⁸⁰⁻¹⁸⁴ subgenual anterior cingulate,^{94,185,186} orbitofrontal/ventromedial PFC,¹⁸⁶⁻¹⁹³ and dorsal anterior cingulate¹⁹⁴⁻¹⁹⁸). Parts of the dorsolateral PFC, found to have a negative correlation with factor 2 in our study (which included items such as work and activities and loss of motivated behavior), have been implicated in the performance of cognitive tasks in which attention needs to be directed away from the affective charge associated with the task.¹⁹⁹

These findings suggest that regions found to correlate with one or another aspect of depression severity in our study are involved in the identification and appraisal of the emotional significance of the stimulus and in the production of affective states, including the automatic physiologic and somatomotor responses to the emotional content of stimuli.

On the other hand, there is a lack of correlation in this study with regions such as the dorsal anterior and rostral anterior cingulate, which are thought to be associated with attention to subjective emotional states and experiences,²⁰⁰ and with regions such as the paracingulate gyrus, which has been associated with representation of mental states of self²⁰¹ and self-reflecting thoughts.²⁰² We suggest that this has to do with the fact that the HDRS is a clinician-rated instrument. Consequently, it is likely that the severity of depression as scored by clinicians, who tend to give more credence to objective or behavioral and neurovegetative signs of depression, is more likely to correlate with the activities of structures that are involved in the perception and regulation of unconscious and autonomic, physiologic, and somatomotor responses to the affective contents of stimuli. We hypothesize that a self-rated scale, such as the Beck Depression Inventory, would be more likely to correlate with structures such as the anterior cingulate that are thought to be involved in the effortful regulation of affective states and reflective awareness of affect (the third process suggested by Phillips et al¹²²).

We find that different brain regions contribute to discrete psychopathologic components that compose the overall syndrome of major depressive disorder. There is a correlation between the HDRS total score and the component scores. Therefore, although the brain regions that correlate with different factors are largely different, it is not surprising that there still is some overlap between the factors in terms of involved brain regions. Global severity correlates with brain regions that overlap with most of the factors.

The overall pattern is striking in that the positive correlations with aspects of depression severity are mostly subcortical ventral, ventral prefrontal, and limbic structures and the negative correlations are mostly or almost exclusively dorsal cortical; this overall pattern is consistent with the literature.⁹⁴

Ultimately, understanding the functional neuroanatomy of major depressive disorder will depend on understanding the unique association of specific regional networks and neurotransmitter systems to specific symptom components rather than to an overall composite severity score. The widespread correlation of depressive symptom clusters with rCMRglu reported herein is most consistent with abnormalities in the distributed neuromodulatory role of monoaminergic neurotransmitter systems. Correlating regional brain abnormalities in catecholaminergic, serotonergic, and dopaminergic synaptic transmission with symptom components of depression and neuropsychologic deficits of depression may provide further insights into the neurobiologic processes of major depression.

Submitted for Publication: October 8, 2003; final revision received September 13, 2004; accepted September 29, 2004.

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Funding/Support: This study was supported in part by grants MH40695, MH62185, and RR00645 from the National Institutes of Health, Bethesda, Md, and by the National Alliance for Research on Schizophrenia and Depression, Great Neck, NY.

Previous Presentation: This study was presented in part at the Annual Meeting of the Organization for Human Brain Mapping; June 19, 2003; New York, NY.

Acknowledgment: We thank our imaging core for analyzing the images, our clinical evaluation core for recruiting the patients and performing the clinical ratings, and Shuhua Li, PhD, for his assistance with the polychoric statistics.

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