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 ([18F]-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 [18F]-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 [18F]-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.

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though 1 study 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) 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, and with a score greater than 16 on the 17-item HDRS 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±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; factor 1, 12.5±3.3; factor 2, 5.1±2.3; factor 3, 1.6±1.7; factor 4, 5.3±2.1; and factor 5, 2.8±1.7. HDRS-24 total score for the current episode was 43.6±10.2. The Global Assessment of Functioning Scale score for the current episode was 43.6±10.2.

PET STUDIES

As reported elsewhere, 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, the twelve 5-minute PET frames were aligned using automated image registration 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.). To determine which regions correlate with HDRS-24 total and factor scores, a voxel-level correlation analysis was performed using the general linear model.
factor scores, see the “Methods” section. 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.

### 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 significant (cluster level $P < .001$, corrected for multiple comparisons) positive correlation (partial $R = 0.39$; global maximum at Talairach coordinates $10, 13, 12$) with HDRS-24 total scores. These brain regions involve the bilateral mesiotemporal cortex, parietal, and medial temporal association cortices.

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...
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 illustrated 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-
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, right dorsolateral76 and anterolateral79 PFCs and in the hippocampus, insula, 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 HDRS89. Some regions showing correlation with overall severity scores in that study89 were identified in our study as correlating 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 patients 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 MDEs 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.

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

<table>
<thead>
<tr>
<th>HDRS Total†</th>
<th>Factor 1†</th>
<th>Factor 2‡</th>
<th>Factor 5†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right mesiotemporal</td>
<td>28, 35, 36</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Left mesiotemporal</td>
<td>37, 19, 28, 35, 36</td>
<td>35, 36</td>
<td>...</td>
</tr>
<tr>
<td>Ventromedial prefrontal cortex</td>
<td>BL 25</td>
<td>BL 25</td>
<td>...</td>
</tr>
<tr>
<td>Dorsomedial prefrontal cortex</td>
<td>...</td>
<td>...</td>
<td>BL 6, 8, 9</td>
</tr>
<tr>
<td>Ventral anterior cingulate</td>
<td>BL 25</td>
<td>BL 25</td>
<td>...</td>
</tr>
<tr>
<td>Dorsal anterior cingulate</td>
<td>...</td>
<td>BL 24</td>
<td>...</td>
</tr>
<tr>
<td>Pregenual cingulate</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dorsal posterior cingulate</td>
<td>...</td>
<td>BL 31</td>
<td>...</td>
</tr>
<tr>
<td>Insula</td>
<td>BL 13</td>
<td>BL 13</td>
<td>...</td>
</tr>
<tr>
<td>Left parietal cortex</td>
<td>...</td>
<td>...</td>
<td>7, 19, 39, 40</td>
</tr>
<tr>
<td>Right parietal cortex</td>
<td>...</td>
<td>...</td>
<td>19, 39, 40</td>
</tr>
<tr>
<td>Left temporal cortex</td>
<td>20, 37</td>
<td>20, 21, 22, 37</td>
<td>39</td>
</tr>
<tr>
<td>Right temporal cortex</td>
<td>...</td>
<td>...</td>
<td>19, 22, 39</td>
</tr>
<tr>
<td>Left occipital cortex</td>
<td>...</td>
<td>...</td>
<td>19, 39</td>
</tr>
<tr>
<td>Right occipital cortex</td>
<td>...</td>
<td>...</td>
<td>19</td>
</tr>
<tr>
<td>Thalamus</td>
<td>BL mammillary body, BL MDN, BL pulvinar, BL VAN, BL VLN</td>
<td>Entire (BL)</td>
<td>...</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>BL</td>
<td>BL</td>
<td>...</td>
</tr>
<tr>
<td>Caudate</td>
<td>...</td>
<td>BL head</td>
<td>...</td>
</tr>
<tr>
<td>Putamen</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Midbrain</td>
<td>BL most</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

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.

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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 researchers 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 study 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, and lower normalized rCBF in the dorsolateral anteroposterior PFC correlates with psychomotor slowing, poverty of speech, and cognitive impairment. On the other hand, psychomotor retardation—anhedonia correlated with lower absolute metabolism in the right insula, claustrum, anteroventral caudate/putamen, and temporal cortex and with higher normalized metabolism in anterior cingulate in another study. Consistent with our results, rCMRglu in the left anterolateral and dorsolateral PFC increases proportionately with antidepressant treatment response.

We found that loss of motivation in depression was also associated with changes in the parietal, temporal, and frontal cortices. Some studies have noted associations in planning or other measures of motivation to parietal and frontal cortex activity. In addition, one model 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.

Although in animal and human 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 stratum gates the glutamatergic sensorimotor and incentive motivational input signals to the striatum, 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.

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 reviewed 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. 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. A “probable association” was reported between an increase in the anxious-depression factor and reduced frontal neocortical perfusion. No clear association was reported between subjective or physiologic variables and changes in rCBF as a consequence of anxiety induction. Based on an anxiety induction study, it has been suggested 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 rCMRglu and rCBF 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. This double-isotope 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 depression\textsuperscript{11} and to decreases in activity after sleep deprivation treatment of major depression.\textsuperscript{115}

These results are also consistent with findings from human functional neuroimaging studies of sleep (for a review see Maquet\textsuperscript{116}). 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 study\textsuperscript{63} 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.\textsuperscript{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 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.\textsuperscript{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,\textsuperscript{124,125} human stimulation,\textsuperscript{120} human central nervous system lesions,\textsuperscript{127-131} and functional brain imaging studies\textsuperscript{132-143} support the involvement of these structures in the perception of aversive stimuli\textsuperscript{124,125} or the identification of expressions of fear,\textsuperscript{128-130,144} disgust,\textsuperscript{76,131,136,145,146} sadness,\textsuperscript{130} and happiness\textsuperscript{134} and in the attention\textsuperscript{147} 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,\textsuperscript{148,149} putamen, and caudate\textsuperscript{125} in reward processing; the amygdala\textsuperscript{150,155} in the production of various affective states; the subgenual anterior cingulate\textsuperscript{156-160} in autonomic and conditioned responses to emotionally salient stimuli; and the subgenual ventral PFC\textsuperscript{161-163} in the evaluation of the reward value of stimuli and the regulation of autonomic and endocrine responses to fear.\textsuperscript{164} Human lesion\textsuperscript{165-168} and stimulation\textsuperscript{169,170} studies support the involvement of these structures (the amygdala,\textsuperscript{165,166,167} subgenual anterior cingulate,\textsuperscript{167,168,170} and ventromedial PFC\textsuperscript{171-174}) 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,\textsuperscript{173-175} amygdala,\textsuperscript{183-184} subgenual anterior cingulate,\textsuperscript{185-186} orbitofrontal/ventromedial PFC,\textsuperscript{186-193} and dorsal anterior cingulate\textsuperscript{194-198}). 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.\textsuperscript{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,\textsuperscript{200} and with regions such as the paracingulate gyrus, which has been associated with representation of mental states of self\textsuperscript{201} and self-reflecting thoughts.\textsuperscript{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 al\textsuperscript{122}).

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.\textsuperscript{84}
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 neuro-modulatory 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.

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