

Paralimbic Hypoperfusion in Unipolar Depression

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Methods: Relative regional cerebral blood flow was measured with SPECT using ^{99m}Tc -hexamethylpropyleneamine oxime in 13 patients with severe unipolar depression that was nonresponsive to drug therapy and 11 age-matched nondepressed controls. **Results:** All patients were clinically depressed and taking antidepressant drugs at the time of the study. The relative blood flow was significantly decreased bilaterally in the frontal cortex, anterior temporal cortex, anterior cingulate gyrus and caudate in the depressed patients compared with the nondepressed healthy controls. The greatest decreases were seen in the paralimbic regions, specifically, the inferior frontal and cingulate cortex. No significant changes were seen in the parietal cortex, occipital cortex or thalami. Psychiatric rating scales correlated poorly with regional blood flow, except for the degree of psychomotor slowing, which was negatively correlated with frontal and cingulate perfusion. **Conclusion:** These findings implicate selective dysfunction of paralimbic brain regions in clinically depressed patients, independent of their medication use, and support the concept of specific neural systems that regulate mood. Recognition of these regional abnormalities may have clinical utility in both the diagnosis and treatment of depression.

Key Words: depression; primary affective disorder; technetium- ^{99m}Tc -HMPAO; SPECT

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Depression is one of the most common psychiatric illnesses, affecting nearly one in 12 people at some point during their lifetime (1). Although the diagnosis is generally considered straightforward and antidepressant medications usually alleviate symptoms (2), a significant number of patients easily relapse or do not respond. In others, the diagnosis may actually be obscured by other neurologic or psychiatric conditions, delaying the proper treatment of those patients who might benefit (3–6). These diagnostic and management difficulties only underscore the fact that the biologic cause of this illness is still unknown, although

a number of hypotheses have been proposed. These include abnormalities of specific neurotransmitter and peptide systems (7–10), focal lesions in specific brain regions (3, 11–13) and selective dysfunction of known neural pathways (14, 15). These hypotheses are supported by a growing body of evidence generated by using both anatomic and functional lesion-mapping studies that demonstrate global and regional abnormalities in depressed patients with both primary affective disorders (16–24) and depressions associated with specific neurologic diseases (25–28). Taken together, these studies support a role for selective frontal, temporal and striatal dysfunction in the pathophysiology of depression, although no single abnormality has been consistently identified. This is often believed to be caused by differences in test conditions, patient groups, medication status or imaging method.

Given the widespread availability of SPECT and these previous results as a foundation, brain perfusion was measured in a homogeneous group of refractory, familial, unipolar depressed patients using ^{99m}Tc -hexamethylpropyleneamine oxime (^{99m}Tc -HMPAO) and SPECT to test explicitly the hypothesis that selective dysfunction of the paralimbic cortex, e.g., orbital frontal, cingulate and anterior temporal cortex, is present in depressed patients.

METHODS

Patient Selection

Men and women, aged 20 to 55 yr, who were hospitalized with major depression, were identified on the inpatient psychiatry service of the Johns Hopkins Hospital. Before scanning, the clinical diagnosis of major depression was confirmed by using a structured psychiatric interview, the Present State Examination (PSE) (29) and the *Diagnostic and Statistical Manual of Mental Disorders*, third edition-revised (DSM-III-R) criteria (30). All patients had experienced at least two prior illness episodes with comparable symptoms and had a positive family history of unipolar type depression. All patients were hospitalized because of a poor response or a refractory course of their mood disorder, despite therapeutic drug levels of one or more antidepressant medications (Table 1).

The patients were screened by history and examination for superimposed medical, neurologic or other psychiatric disorders. Those with histories, examinations or laboratory tests that suggested thyroid disease, stroke, head trauma, epilepsy, multiple

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TABLE 1
Demographics, Clinical Characteristics and Neuropsychiatric Ratings

Subjects	13
Gender	3 men and 10 women
Age	42 ± 11 yr
Antidepressant medications	Tricyclics 9 of 13 patients
	MAOI 1
	SSRI 4
	Trazodone 2
	Bupropion 1
Present State Examination	42 ± 9
Hamilton depression scale	22 ± 5
Mini-Mental State Examination	29 ± 1
Hamilton anxiety scale	18 ± 6
Apathy scale	24 ± 9
Motor slowing	3 none, 5 mild and 5 severe

MAOI = monoamine oxidase inhibitors; SSRI = selective serotonin reuptake inhibitors.

sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease or other movement disorders, present or past manic or hypomanic episodes, obsessive compulsive disorder or psychotic symptoms were excluded. Patients with clear cerebrovascular risk factors, such as hypertension, diabetes and coronary artery disease, or those with global cognitive impairment, as evidenced by a Folstein Mini-Mental State Examination (31) score less than 28 were also deemed ineligible. Neuroleptic, vasodilator or dopamine-agonist medication, polysubstance abuse or electroconvulsive therapy within 6 mo were also grounds for exclusion from the study.

Thirteen patients (10 women and 3 men) with major depression meeting these criteria (mean age 42 ± 11 yr) were enrolled. Informed consent, using guidelines established by the Johns Hopkins University School of Medicine Joint Committee on Clinical Investigation, was obtained from each subject before all imaging studies. Eleven healthy volunteer subjects (2 women and 9 men, mean age 35 ± 13 yr) with normal neurologic and psychiatric histories and examinations were studied under identical conditions.

Psychiatric and Cognitive Evaluation

The patients were each examined just before the SPECT study by using a standardized assessment battery. In addition to re-administering the PSE to confirm the presence of a major depression, the Hamilton Rating Scale for Depression (32) was scored to rate the severity of the depression. Four additional tests, which were selected to characterize clinical signs that commonly accompany depression, were performed. Ratings of anxiety (33), apathy (34), global cognitive function (31) and motor speed (35) were made using standardized scales. More selective testing of language, memory and frontal lobe function was not part of this evaluation. Detailed psychiatric and neuropsychologic assessments were not obtained from control subjects.

Scan Acquisition and Image Processing

All subjects were studied in the awake resting condition in a quiet room, seated, with their eyes and ears closed and covered. Technetium-99m-HMPAO was prepared according to the manufacturer's recommendations (Ceretec, Amersham International, England) and a 20-mCi (740-MBq) dose was administered by

intravenous bolus injection. Image acquisition began after approximately 15 min. The subjects were immobilized in the scanner using a thermoplastic face mask to minimize movement artifacts. Scans were acquired using a Hitachi NeuroSpect 2000 (Twinsburg, OH), four-head high-resolution dedicated head SPECT scanner operating with a high-resolution low-energy collimator. The imaging protocol acquired 64 frames at 30 sec per frame with 360° rotation of the camera. Two-pixel (8-mm) attenuation-corrected images were reconstructed in the transaxial plane parallel to the canthomeatal line (CML). Images were then smoothed with a Butterworth filter, using a 0.2 cutoff, creating images with a final inplane resolution of 9 mm, and in the z-axis of 13 mm (FWHM).

Data Analysis

Six transaxial scans corresponding to predefined anatomic levels (+16, +24, +32, +40, +48 and +64 mm relative to the CML) were identified for quantitative analysis. Thirty paired right and left brain regions (16–24 mm³) were manually positioned on appropriately matched scans by using visual inspection and a generalized template modified from the brain atlas of Matsui and Hirano (36) (Fig. 1). Individual cortical regions were combined to define seven cortical areas: inferior frontal cortex, superior frontal cortex, anterior temporal cortex, posterior temporal cortex, anterior cingulate, parietal cortex and occipital cortex. Additional regions of interest were placed in the cerebellum, thalamus and basal ganglia (caudate nucleus). Frontal cortex groupings were specifically selected to differentiate the two primary subdivisions

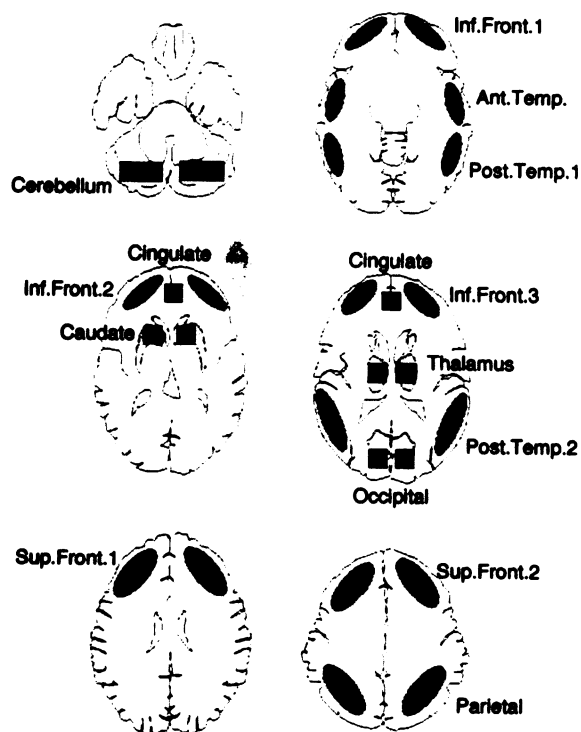


FIGURE 1. SPECT region of interest template: transaxial views at six standardized brain levels. The rCBF was measured in standardized brain regions by using a generalized template modified from the Matsui and Hirano brain atlas (36). The regions of interest were defined in cortical and subcortical regions, as shown. Individual cortical regions were combined into seven functional areas by using standardized landmarks and classification schemes: inferior frontal cortex, superior frontal cortex, anterior temporal cortex, posterior temporal cortex, anterior cingulate cortex, parietal cortex and occipital cortex.

of prefrontal cortex: the more rostral heteromodal lateral prefrontal cortex (Brodmann areas 9, 10 and 46) and the more caudal orbital frontal-inferior prefrontal (paralimbic) cortex (Brodmann areas 10, 11, 12 and 47). Region selections were based on human and primate anatomic and physiologic studies (14,15) and defined to match approximately a published CT-based region-of-interest template used to study glucose metabolism in neurologically depressed patients (25,26).

A relative blood flow ratio (rCBF) was calculated for each region of interest using the average tissue activity in the region divided by activity in the cerebellum. This method was selected after comparing regional rCBF measures normalized to cerebellum, whole brain and occipital cortex. Variance in the normal control subjects was lowest for the region/cerebellum data (results not shown). This rCBF ratio was subsequently used for all statistical comparisons.

Intergroup comparisons were made using two-way repeated-measures analysis of variance (ANOVA) and post hoc planned t-tests, when appropriate. Nine regions were examined to allow the analysis of regions previously implicated in PET and SPECT studies of depression, i.e., inferior frontal (orbital-inferior) cortex, superior frontal (lateral prefrontal) cortex, anterior temporal cortex, anterior cingulate cortex and caudate, with those that were not, i.e., posterior temporal cortex, parietal cortex, occipital cortex and thalamus. When significant differences were obtained using ANOVA, planned t-tests were performed using the Fisher's protected least-significant difference test to determine which group, region or side was accountable. Regional rCBF was correlated with clinical ratings using Spearman rank correlations and the Bonferroni correction for multiple comparisons.

RESULTS

Demographic and Clinical Characteristics

All 13 patients met DSM-III-R criteria for major depression on the day of the SPECT study. None of the control subjects were clinically depressed. No significant correlations existed among scores of depression severity, anxiety, apathy, motor speed and global cognitive function. The clinical characteristics and neuropsychiatric ratings of the patients are summarized in Table 1.

TABLE 2
Relative Regional Perfusion:
Region Right-Left Average/Cerebellum

Region	Patients (n = 13)	Controls (n = 11)
Anterior cingulate*	0.84 ± 0.06†	0.94 ± 0.04
Inferior frontal cortex*	0.76 ± 0.07†	0.86 ± 0.04
Superior frontal cortex	0.81 ± 0.05†	0.88 ± 0.04
Anterior temporal cortex*	0.76 ± 0.06†	0.82 ± 0.04
Posterior temporal cortex	0.80 ± 0.06	0.84 ± 0.03
Parietal cortex	0.82 ± 0.06	0.86 ± 0.04
Occipital cortex	0.91 ± 0.07	0.93 ± 0.07
Caudate	0.89 ± 0.06†	0.98 ± 0.05
Thalamus	0.91 ± 0.10†	0.99 ± 0.03
Whole cortex	0.83 ± 0.08	0.90 ± 0.07

*Limbic cortex.

†Post hoc, planned t-tests; $p < 0.001$.

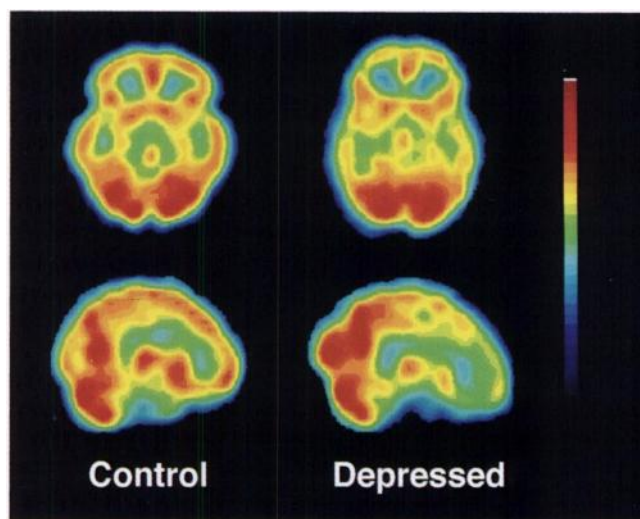


FIGURE 2. Technetium-99m-HMPAO SPECT images from a depressed patient and a nondepressed control subject. Axial (upper images) and sagittal (lower images) views from two age- and sex-matched subjects—one depressed (woman, age 30 yr) and one nondepressed (woman, age 28 yr). Scans are normalized to each subject's cerebellar perfusion for visual comparisons. There is normal homogeneous flow in the normal volunteer, with a similar distribution in the inferior and superior frontal regions (left images). This pattern contrasted with that seen in the depressed subject (right images). There is gross hypoperfusion of the frontal cortex, which is worse inferiorly (sagittal view), and hypoperfusion in the anterior cingulate and anterior temporal cortex (axial view).

SPECT Results

The rCBF values were decreased in depressed patients compared with the control subjects across all regions examined (group effect: $F[1,22] = 15.7$, $p = 0.0007$), but there was significant regional variability (group \times region interaction: $F[8,176] = 3.6$, $p = 0.0006$) (Table 2). The most robust decreases were seen in the paralimbic cortex: inferior frontal cortex, anterior cingulate gyrus and anterior temporal cortex, although significant changes were also present in the superior frontal cortex, striatum and thalamus. These decreases were not lateralized (side effect: $F[1,22] = 0.003$, $p = 0.96$), i.e., the right and left hemispheres were equally affected. Paralimbic regional changes were of comparable magnitude. No significant changes were seen in the posterior temporal, parietal or occipital cortex. Scans demonstrating these regional abnormalities are shown in Figure 2.

Correlational analysis of regional perfusion and clinical ratings demonstrated no relationship between depression severity and regional perfusion ($\rho < 0.2$ for all regions). There was, however, a significant inverse correlation between psychomotor slowing and both paralimbic (frontal and temporal cortex) and prefrontal perfusion ($\rho = -0.54$, $p < 0.03$ for all three regions). Depression scores did not correlate with psychomotor speed.

DISCUSSION

Paralimbic cortex (inferior frontal, anterior temporal and anterior cingulate) hypoperfusion was the predominant re-

gional abnormality identified in this study of clinically depressed medically refractory patients with familial unipolar depression. The mechanisms underlying these changes are not understood. Disease-specific pathologic changes in the cortex have not been identified in primary depressed patients, and brain anatomy is grossly normal. Recent anatomic imaging studies have, however, demonstrated non-specific changes in ventricular size and T2-weighted MRI abnormalities in subcortical gray and periventricular white matter in some patient subgroups (37–39).

Neurochemical mechanisms that would account for the selective perfusion defects in paralimbic frontal, temporal and cingulate cortex in depressed patients are compelling but somewhat circumstantial. A large literature exists to support changes in a variety of monoaminergic and peptidergic markers in depression, but there has been little focus on the target regions identified in this and previous imaging studies. Dopaminergic projections from the ventral tegmental area (VTA) show regional specificity for the orbital frontal and prefrontal cortex (40). Dysfunction of these particular dopaminergic pathways has been proposed to explain the orbital frontal hypometabolism observed in depressed patients with Parkinson's disease (10,25,41). This hypothesis is appealing, given the mood-enhancing properties and clinical utility of methylphenidate in treating some depressed patients, although dopaminergic stimulation alone is inadequate to alleviate all depressive symptoms. Degeneration of VTA neurons or their projections has not been demonstrated in primary unipolar depression, however.

Serotonergic and noradrenergic mechanisms, on the other hand, have dominated the neurochemical literature on depression because most typical antidepressant drugs affect synaptic concentrations of these two transmitters (2). Changes in both serotonergic and noradrenergic metabolites have been reported in subsets of depressed patients, but the relationship of these peripheral measures to specific changes in specific brain stem nuclei or their cortical projections is unknown. Postmortem studies of the brains of depressed suicide victims report changes in serotonergic and noradrenergic receptors (42). 5₂-serotonin receptor changes, measured with PET, were described in the temporal cortex of depressed patients who had strokes (43), but these measures have not yet been examined in nonneurologically impaired depressed patients. Increases in paralimbic mu-opiate receptors were demonstrated with PET in unipolar depressed patients (44), which was consistent with the results of autoradiography studies in depressed suicide victims (9). These preliminary findings suggest a primary or secondary role of opioids in depression. The relationship of these biochemical changes to regional perfusion defects awaits continued investigation.

Although the causal relationship between neurochemical abnormalities in depression and regional perfusion abnormalities is unclear, the localization of these defects is consistent with converging data from a variety of clinical, anatomic and functional imaging observations. A promi-

nent role for paralimbic cortex, particularly the frontal and temporal cortex in the expression and modulation of mood and emotions has long been recognized from classic lesion-deficit studies in depressed patients with discrete brain lesions, such as occur with trauma, ablative surgery, stroke, tumors or focal epilepsy (3,13,28,45–48). The importance of these cortical regions is further supported by studies in patients with well-characterized neurochemical or neurodegenerative diseases, such as Parkinson's disease and Huntington's disease, in which the interactions between the frontal cortex and striatum are well documented (6,49,50).

PET studies of regional glucose metabolism in depressed patients with Parkinson's disease, Huntington's disease and strokes of the basal ganglia identify consistent hypometabolism of the paralimbic frontal and temporal cortex, similar to the findings observed here, which differentiated depressed from nondepressed patients, independent of disease etiology (25,26,51). The present findings are also similar, although not identical, to PET findings reported in patients with primary affective disorders. Decreases in caudate, frontal cortex and temporal cortex metabolism and flow were identified in depressed patients of varying types, including unipolar depression, bipolar depression and obsessive compulsive disorder with depression (16–18,23,24). A single study of frontal and amygdala hyperperfusion was also reported (52). Increases in caudate and frontal metabolism in depressed patients who recovered following antidepressant therapy have also been observed (18,53), suggesting that regional metabolic changes may be useful state and trait markers in patients with mood disorders. Some of these studies emphasized left lateralized abnormalities, but this finding was inconsistent.

The true differences across these various studies are difficult to assess because data analysis strategies and acquisition methods vary. Nonetheless, it can be hypothesized that disruption of circuits linking frontal cortex, temporal cortex, cingulate cortex and striatum, whether structural or functional, may underlie depressive phenomena, independent of the cause. This also suggests a specific role for frontal cortical-striatal-thalamic loops or paralimbic pathways in the pathophysiology of depression (14,15,54).

Of direct clinical interest is that the perfusion defects identified in this study were statistically robust despite the presence of a variety of antidepressant drugs to which the patients were having little to no clinical response. This issue has been long debated as a potential source of variability among PET and SPECT studies performed in patients with clinically heterogeneous types of depression. The findings from this study suggest that the clinical state of the patient at the time of the study, i.e., persistent clinical signs and symptoms of depression, may have the greatest influence on the pattern of brain perfusion, with no apparent attenuation of regional abnormalities by concurrent antidepressant use. Obviously, a controlled study of the effects of medication, independent of the clinical state,

will be required to resolve this issue with certainty. Direct comparisons of refractory-depressed versus de novo-depressed patients and patients without clinical improvement versus medication-responsive patients are needed. Similarly, longitudinal studies that examine the time course of the change in blood flow abnormalities relative to the course of the clinical improvement will help to determine whether serial scans in clinically treated patients can be used to monitor drug therapy effectively. The sensitivity and specificity of regional paralimbic defects to identify depression in heterogeneous subsets of mood-disordered patients in whom associated clinical features, such as psychomotor slowing, apathy, anxiety and selective cognitive impairment, may be present are not known and also need to be addressed experimentally.

In summary, this study identified a specific and selective perfusion defect in the paralimbic cortex that differentiated a clinically homogeneous group of medically refractory patients with familial unipolar depression from nondepressed control subjects. The regional localization was similar to the pattern of hypometabolism and hypoperfusion previously identified with PET in both primary affective disorder and depression associated with specific neurologic diseases. Clinically, future use of SPECT perfusion scans in mood-disordered patients may be useful in reassessing patients who do not respond to standard therapy, in identifying depression in patients whose clinical presentation is atypical but who may already be taking psychoactive medications or in recognizing depression that may be confounded by the presence of concurrent neurologic or other psychiatric diagnoses. Continued studies in clinically depressed patients may improve our understanding of the pathogenesis of these disorders, help develop more specific and effective treatments and contribute to the elucidation of the neural systems that regulate normal moods and emotions.

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