Frontal Lobe Dysfunction in Secondary Depression

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Depression is common in patients with neurological disease, particularly with diseases involving the basal ganglia. Although the mechanisms of mood disorders in these patients are poorly understood, selective neural pathways affected directly and indirectly by basal ganglia injury provide a strategy for examining these patients with functional imaging techniques. Studies of regional cerebral glucose metabolism by use of positron-emission tomography are reviewed. These studies demonstrate bilateral hypometabolism of orbital–inferior prefrontal cortex and anterior temporal cortex in depressed subjects, independent of disease etiology. This pattern is similar to that seen in patients with primary unipolar depression. These findings suggest that disruption of paralimbic pathways linking frontal cortex, temporal cortex, and striatum may contribute to both primary depression and depression associated with basal ganglia disease. The findings support the evolving concept of a neuroanatomical locus for mood regulation.

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Many neurological disorders are accompanied by depression. Because the clinical presentations of mood symptoms in neurological patients are similar to those seen in primary affective illness, it has been argued that neurological depressions are appropriate and useful models in the study of the pathophysiology of mood disorders in general. A group of hypotheses based on evidence from descriptive, experimental, and theoretical studies have in fact been proposed suggesting involvement of specific neural pathways and a variety of neurotransmitters in depression associated with particular neurological syndromes.[1–13] Although a single unifying mechanism for these depressions has not yet been established, the presence of affective symptoms in specific neurological diseases provides a framework for examining the basic neural systems regulating mood and emotions.

CLINICAL OBSERVATIONS

Clinical studies of depression in neurological patients have focused on three categories of disorders: 1) diseases with generalized or randomly distributed pathologies, such as Alzheimer's disease, multiple sclerosis, and systemic illness with central nervous system involvement;[14–25] 2) conditions where neurochemical or neurodegenerative changes are reasonably well defined, as in Parkinson's disease, Huntington's disease, progressive

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supranuclear palsy, Fahr's disease, Wilson's disease, and carbon monoxide poisoning;[7,26-37] and 3) discrete brain lesions, as seen with trauma, ablative surgery, stroke, tumors, or focal epilepsy.[38-55]

A prominent role for the frontal and temporal lobes and the striatum in the expression and modulation of mood and affect has emerged from these various studies. Classic lesion-deficit correlations, found by using quantitative X-ray CT or MRI, consistently support an association between lesions disrupting frontostriatal or basal-limbic pathways and depressed mood. There is not a consensus, however, as to whether the left or the right hemisphere is dominant in these behaviors. Reports of patients with traumatic frontal lobe injury indicate a high correlation between affective disturbances and right hemisphere pathology.[39] Studies in stroke, on the other hand, suggest that left-sided lesions of both frontal cortex and the basal ganglia are more likely to result in depressive symptoms than right lesions,[46,47,49] where displays of euphoria or indifference predominate.[43,45,48] This view, however, is not shared by all investigators.[44,56] Further evidence supporting the lateralization of emotional behaviors is provided in studies of pathological laughing and crying. Crying is more common with left hemisphere lesions, whereas laughter is seen in patients with right lesions,[57] consistent with subsequent reports of post-stroke mood changes. Lateralization of mood symptoms has also been examined in patients with temporal lobe epilepsy, although here again there is no consensus. Affective disorders have been described with left,[52,53,55] right,[50] and nonlateralized temporal lobe foci.[54] More precise identification of the sites within the temporal lobes most critical for the development of mood symptoms in these patients awaits further study. Studies of plaque loci in multiple sclerosis have also suggested an association of depression with lesions in the temporal lobe,[22] but these reports have not shown lateralized effects.

Despite the many clear similarities, there is still much variability in the location of lesions associated with depression in different neurological conditions. This variability is in part due to the methodological and theoretical limitations of anatomical imaging techniques, which, by definition, restrict lesion identification to those brain areas that are structurally damaged. Functional imaging offers a complementary perspective from which the consequences of anatomic or chemical lesions on global and regional brain function can also be examined. Using these methods, one can probe how similar mood symptoms occur with anatomically or neurochemically distinct disease states, as well as evaluate the paradox that seemingly comparable lesions do not always result in comparable behavioral phenomena.

FUNCTIONAL BRAIN IMAGING STUDIES

Positron-emission tomography is widely used to measure a variety of physiological variables in vivo, including regional brain blood flow,[58,59] oxygen metabolism,[58,60] glucose utilization,[61-63] blood–brain barrier permeability,[64] tissue pH, and amino acid transport.[65] Methods are also available to map and quantify presynaptic and postsynaptic neuroreceptor densities and affinities for many neurotransmitters and neuropeptides, notably benzodiazepine, dopamine, serotonin, acetylcholine, and opiates.[66-68]

An important application of PET and SPECT scanning since their introduction has been to study patterns of abnormal function in patients with well-characterized and, generally, pathologically confirmed diseases.[69,70] The results have had a tremendous impact on both diagnosis and management of patients with epilepsy, brain tumors, and dementia,[71-73] as well as a growing role in the evaluation of stroke, movement disorders, and head trauma.[74-76] Scan abnormalities have also been identified in groups of patients with certain well-defined psychiatric diagnoses. These include depression; schizophrenia; panic, attention-deficit, anxiety, and obsessive-compulsive disorders; alcoholism; and substance abuse, among others.[77-86] Although the sensitivity and specificity of these patterns have not been fully established, these types of studies provide unrivaled tools for identifying previously unrecognized brain abnormalities and potential disease mechanisms in a variety of neuropsychiatric illnesses, including depression.

Functional abnormalities in primary affective disorder patients have been described in a number of published reports. Studies to date, measuring regional glucose metabolism and blood flow, have examined both young and old patients, drug-naïve and medication-refractory disease, state and trait abnormalities, and a variety of patient subgroups.[77,87-94] Despite the obvious clinical heterogeneity of the patient populations examined and differences in data analysis strategies among investigators, abnormalities involving the frontal cortex and, less commonly, temporal cortex have been consistently reported, although the regional localizations within the lobe differ somewhat (Figure 1, p. 431). All of these studies support a role for specific frontal cortical-striatal-thalamic loops[95-98] or paralimbic pathways[3,99-101] in the pathophysiology of depression, although no abnormality is yet considered pathognomonic.

A parallel tactic is to examine the regional localization of depression by using PET in selected neurological patients—specifically, in those with diseases where the predominant gross pathology spares the frontal and tem-

poral cortices, the areas repeatedly implicated in the lesion-deficit literature. Changes in both mood and cognitive performance are extremely common in diseases affecting the basal ganglia, most notably in Parkinson's disease, in Huntington's disease, and following ischemic lesions of the striatum.[8,28,47,102] Bradyphrenia with impaired psychomotor and cognitive performance is often present in basal ganglia disease patients, and it may actually obscure the recognition of a coexisting depressive disorder in some patients.[12,37,103-106] Deficits in attention and motivation, as well as more profound impairments on tasks classically localized to the frontal lobes, are also prominent in these patient groups and appear more pronounced in depressed subjects.

Depressions in patients who are not neurologically impaired share many of the clinical features characteristic of basal ganglia disease, including apathy, bradyphrenia, psychomotor slowing, and disturbed frontal lobe function. These clinical similarities may indicate the involvement of common neuroanatomical and neurochemical systems in the genesis of idiopathic depression and depression associated with basal ganglia disease.

The combination of motor, mood, and cognitive symptoms in these patients and their postulated regional localization provide the basis for focused hypothesis-testing using PET. One can specifically examine whether depressed and nondepressed patients are discriminated by their respective brain glucose metabolic patterns. One can also test the hypothesis that depression is associated with selective dysfunction of frontal-subcortical and paralimbic systems, consistent with the anatomical observations made in other neurological patient populations.

Three basal ganglia disorders have been studied by Mayberg and colleagues[6,10,107-109] to address these hypotheses of selective dysfunction: Parkinson's disease, Huntington's disease, and unilateral ischemic lesions of the striatum. In each disease group, patients with and without depression were matched for age, disease stage, symptom severity, cognitive performance, and medications. CT scans were screened to exclude patients with gross cortical atrophy or coexisting conditions. Our goal was to match, as closely as possible, two sets of patients with a given neurological disease who differed only by the presence or absence of mood symptoms. Patients for all experiments were studied in the awake, resting state in a quiet room, with eyes closed and covered. Scans were acquired by using a preselected imaging plane, parallel to the anterior commissure–posterior commissure (AC-PC) line, determined by using X-ray CT.[110] Absolute metabolic rates for glucose were calculated for average whole brain and individual cortical and subcortical regions by use of standard methods.[61] All intersubject comparisons were made by using regional metabolic rates normalized to the whole brain average. Individual regions of interest were grouped into functional cortical subdivisions derived from human and primate anatomic and physiological studies.[3,95,96] Frontal lobe groupings were specifically selected to differentiate primary motor and premotor areas from dorsolateral prefrontal and inferior-prefrontal/paralimbic cortex regions (Figure 2).

Using this strategy, we first examined each clinical disorder separately to identify disease-specific regional abnormalities for depression. A second analysis compared the pattern of regional abnormalities in depressed patients independent of the underlying disease etiology, testing the hypothesis that mood symptoms correlate with abnormalities in specific brain regions regardless of the underlying pathological condition. We then postulated potential mechanisms for these depressions in relation to the identified functional imaging abnormalities, based on the known pathophysiology of each illness.

Parkinson's Disease

Depression is the most common behavioral disturbance seen in patients with Parkinson's disease (PD), affecting an estimated 50% of patients.[111] The cause of depression in PD is unknown. The loss of mesocortical and mesolimbic dopamine connections to frontal lobe and disruption of monoaminergic afferents from the mesencephalon have been implicated in the pathogenesis of depression in PD on the basis of the reduced brain serotonin, nigral and ventral tegmental area dopamine, and locus ceruleus norepinephrine in patients who die with PD.[112-115] Loss of these brainstem monoaminergic neurons, with degeneration of their respective cortical and subcortical projections, is a plausible mechanism for depression in these patients.[2,4,5,7,102,115]

Clinically, depression in PD has been reported most commonly in patients with right hemiparkinsonism (left-brain dysfunction); this is consistent with the widely supported view that associates depression with left-sided lesions.[29,116-118] Despite these observations, no anatomical differences have been identified that distinguish depressed from nondepressed patients with PD.

Although structural imaging studies have been relatively unhelpful, there is a large PET literature in patients with the disease.[119-123] The findings of increased cerebral blood flow and glucose metabolism in the posterolateral basal ganglia seem proportional to the severity of motor symptoms and are thought to reflect disinhibition of striatal neurons associated with loss of dopamine cell bodies in the substantia nigra. Global cortical decreases have also been observed, as have selective changes in dopamine-innervated regions of frontal cortex. Temporal-parietal hypometabolism, a pattern similar to that

seen in Alzheimer's disease, has also been identified in demented PD patients;[124] the specificity of regional changes for specific cognitive features, however, has only recently been explored.[125]

Using the strategies and methods outlined above, Mayberg and colleagues[6] examined the relationship between mood and regional glucose metabolism in PD. We found bilateral caudate and orbital–inferior frontal hypometabolism in the depressed PD patients compared with both nondepressed patients and control subjects (Figure 4, p. 432). The magnitude of the metabolic change in the inferior prefrontal–orbital frontal region inversely correlated with depression severity as rated by the Hamilton Rating Scale for Depression, but not with measures of cognitive performance. The regional localization is consistent, although not identical, with lesion locations in patients with poststroke depressions and with patterns of hypometabolism described in primary affective disorders. This finding supports a selective frontostriatal or paralimbic defect in the depression of these patients. Because of the strong interaction of depression and cognition,[106,126,127] further studies are needed to separate the relative contributions of specific cognitive deficits to the frontostriatal and basolimbic localization of mood symptoms. In our study, patients were matched for performance on a group of frontal lobe tests as well as overall cognitive functioning, so there were no obvious confounds of these behaviors. Studies to test these issues explicitly with PET are under way.

Findings with respect to biochemical mechanisms for depression in PD have focused on three systems—dopamine, serotonin, and norepinephrine—thus paralleling studies in primary affective disorder.[128–130] Selective in-

FIGURE 1. [^{99m}Tc]HMPAO SPECT images. Sagittal (left images) and axial (right images) views are shown normalized to each subject's cerebellar perfusion for visual comparisons. Symmetric frontal and temporal hypoperfusion is present in the depressed subject (arrows, axial view). Note that frontal perfusion is most abnormal inferiorly (arrows, sagittal view). Patient: 30-year-old woman. Control subject: 28-year-old woman.

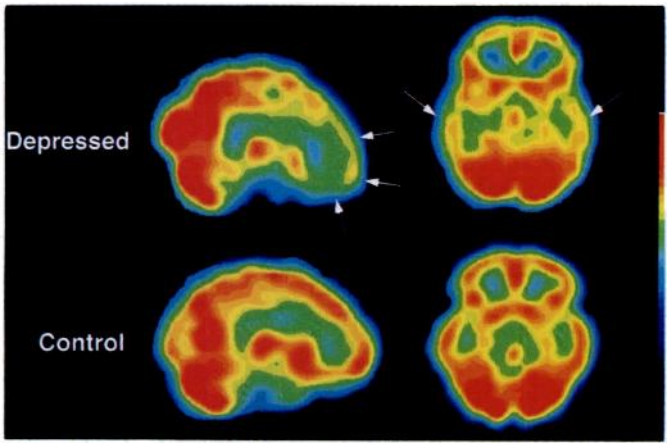


FIGURE 2. PET region of interest template, frontal lobe subdivisions. Frontal lobe regions used for PET data analysis were defined by using standardized landmarks and classification schemes. Shaded regions of interest delineate paralimbic cortex. AC-PC = anterior–posterior commissure line.

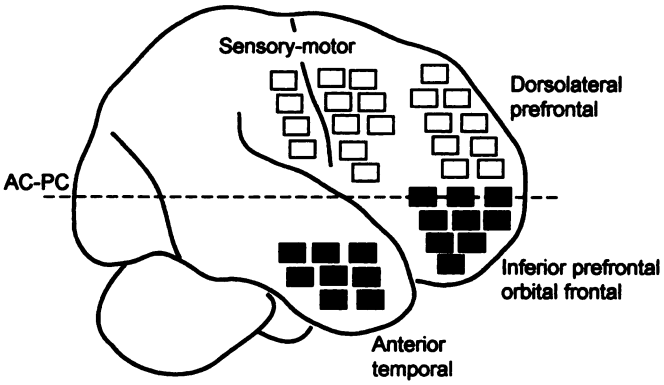
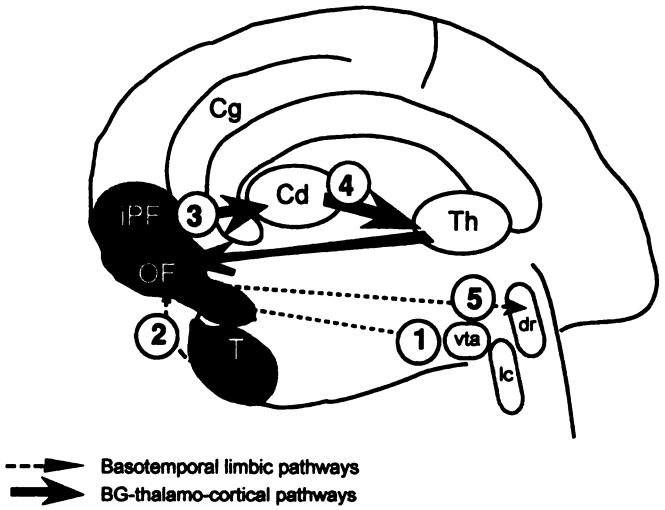


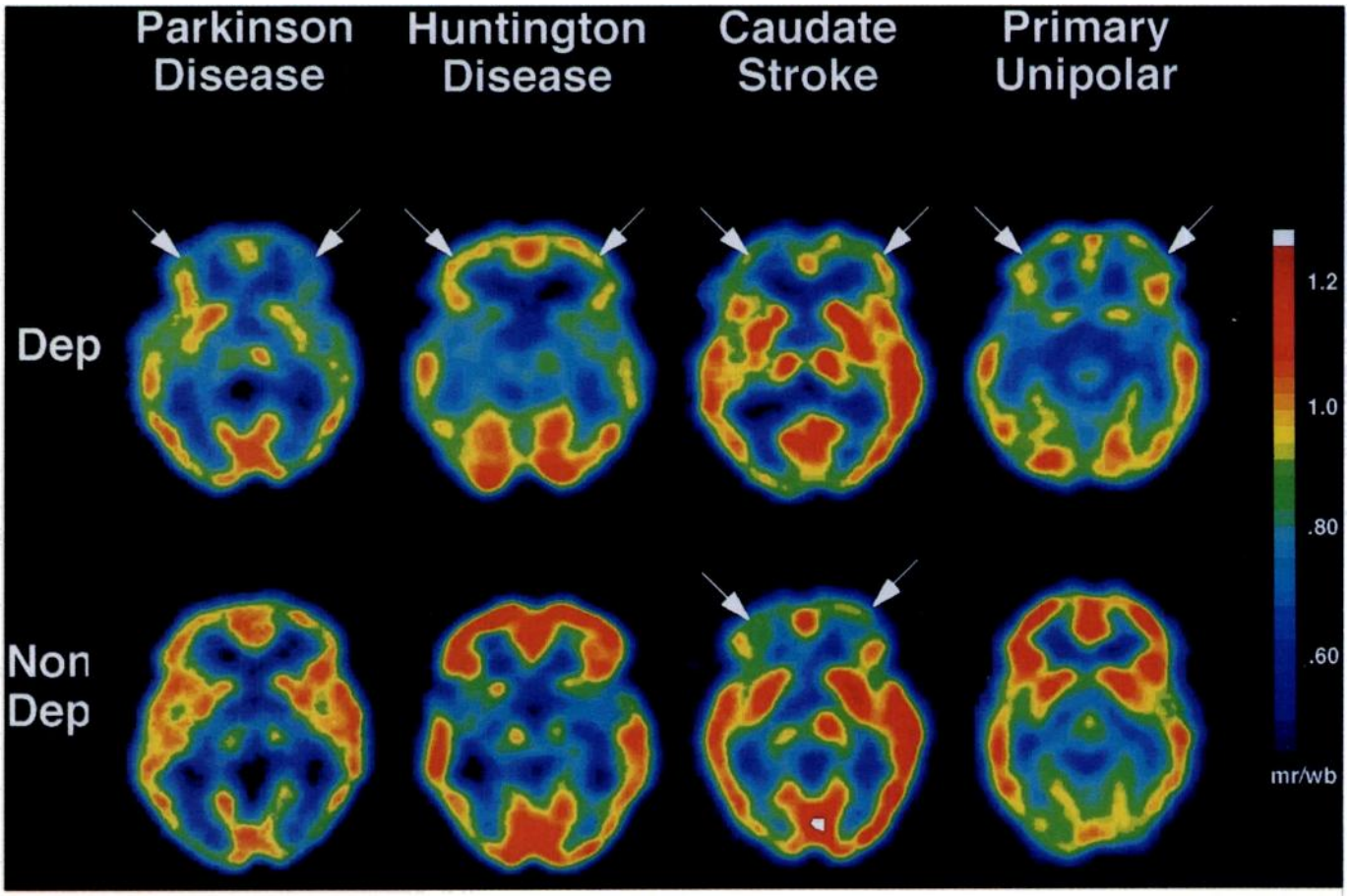
FIGURE 3. Depression model. Possible mechanisms for common paralimbic cortex hypometabolism in primary and secondary depressions include: 1. Degeneration of mesencephalic monamine neurons (vta, dr, lc) and their cortical projections. 2. Remote changes in basotemporal limbic regions, with or without involvement of the amygdala. 3. and 4. anterograde or retrograde disruption of cortico–basal ganglia circuits from striatal degeneration or injury. 5. Secondary involvement of serotonergic neurons via disruption of orbital frontal outflow to the dorsal raphe. Cg = anterior cingulate; Cd = caudate; iPF = inferior prefrontal cortex; OF = orbital frontal cortex; T = temporal cortex; Th = thalamus; vta = ventral tegmental area; dr = dorsal raphe; lc = locus ceruleus; BG = basal ganglia.



volvement of mesocortical or mesolimbic dopamine pathways is an appealing hypothesis for the mechanism of depression in PD, given the prominence of the dopamine deficiency in the illness and the critical role of the ventral tegmental–nucleus accumbens dopaminergic circuit in modulating motivation and reward in general.[131,132] In support of this theory, depressed PD patients, in contrast to nondepressed PD patients and unipolar depressed patients, do not show the expected euphoric response to the central stimulant methylphenidate,[7] a pharmacological effect dependent on the functional integrity of mesocorticolimbic dopamine neurons.[131–135] Morphologic and biochemical studies in PD have identified abnormalities in these brain regions, but results have varied.[112,136–138] Disproportionate degeneration of dopamine neurons in the ventral tegmental area (VTA) has, however, been demonstrated in PD patients with predominance of mood and cognitive symptoms.[115] Cortical projections from this region selectively distribute to the orbitofrontal and prefrontal cortex,[97,139] the areas of hypometabolism observed in the PET studies just described.[6] Despite these compelling lines of evidence, CSF homovanillic acid levels do not correlate with mood,[140] and dopamine agonists have little effect on depressive or cognitive symptoms.[141] These inconsistencies may be explained, however, by the poor correlation between CSF dopamine metabolites and regional brain dopamine metabolism.[142] In addition, levodopa replacement may selectively improve nigrostriatal function at the expense of the mesolimbic system—a phenomenon observed experimentally in rats.[143]

Serotonergic and noradrenergic mechanisms are also strongly implicated, and depression in PD responds, like primary depression, to standard antidepressant therapies.[144,145] Electroconvulsive therapy also improves mood (as well as some of the other motor features of PD),

FIGURE 4. Fluorodeoxyglucose PET images in primary and secondary depression, basal ganglia level. There is bilateral frontal lobe hypometabolism in all depressed patients, independent of disease etiology (arrows, top row). Frontal cortex metabolism is normal in nondepressed patients, except those with strokes (arrows, bottom row). Scale: relative metabolic rate (regional absolute metabolic rate/whole brain metabolic rate).



although the neurochemical mechanisms are likely multidimensional.[146–148] Converging data, however, strongly favor a more selective serotonergic etiology for depression in PD. Reduced CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been demonstrated in depressed but not in nondepressed PD patients withdrawn from dopaminergic agonist therapy,[5,127,149] a finding consistent with studies in depressed patients without PD.[150] Treatment with 5-hydroxytryptophan and L-tryptophan also improve mood symptoms in PD; as in primary affective disorder, this improvement correlates with increases in CSF 5-HIAA levels.[140,151–153] Selective serotonin reuptake blockers such as fluoxetine and fluvoxamine are also effective in treating depression.[154,155] In total, these observations support a more critical role for serotonin than for norepinephrine in modulating mood symptoms in PD. These findings also suggest strategies for future studies.

The question remains of whether a common mechanism can account for both 1) the selective orbital and inferior prefrontal hypometabolism and 2) the evidence of dopaminergic and serotonergic dysfunction documented in depressed patients with PD. The regional localization of the metabolic abnormalities is consistent with both the orbital frontal–basal ganglia–thalamic pathways[96] and basotemporal limbic circuit[100,101,156] (Figure 3, p. 431). These particular brain areas exhibit several relevant neurochemical properties. Available evidence in primates, rodents, and humans suggests that ascending monoaminergic projections from the dorsal raphe and VTA terminate in the cortex, but in different regions. Dopaminergic efferents from the VTA show regional specificity for the orbitofrontal and prefrontal cortex,[139] whereas serotonergic projections are more widely distributed.[157] Furthermore, the major cortical outflow to the dorsal raphe originates in the orbitofrontal cortex.[99] It might be postulated, then, that primary degeneration of mesocorticolimbic dopamine neurons in patients with PD may lead to dysfunction of the orbitofrontal cortex, which secondarily affects serotonergic cell bodies in the dorsal raphe. Theoretically, disruption of connections at any point along these pathways might result in the metabolic and biochemical defects previously observed, focusing attention on both dopamine and serotonin and their interactions in the depression of PD[158,159] (Figure 3).

FIGURE 5. X-ray CT and FDG PET scans in two patients with unilateral basal ganglia strokes (see p. 436). The motor stroke (black arrow, top left image) is associated with diffuse hypometabolism involving the entire ipsilateral hemisphere (white arrows, top right image). Note change in the ipsilateral thalamus. The nonmotor stroke (black arrow, bottom left image) is associated with a more restricted abnormality of cortical metabolism—in this case, ipsilateral prefrontal cortex (arrow, lower right image).

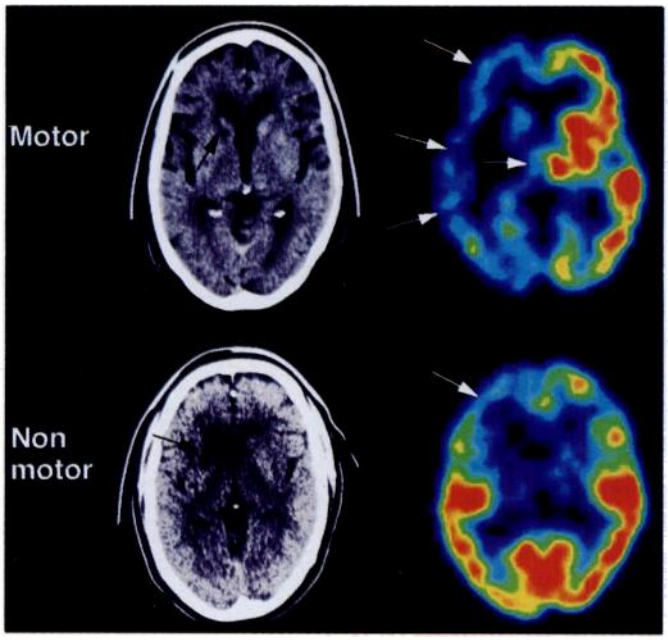
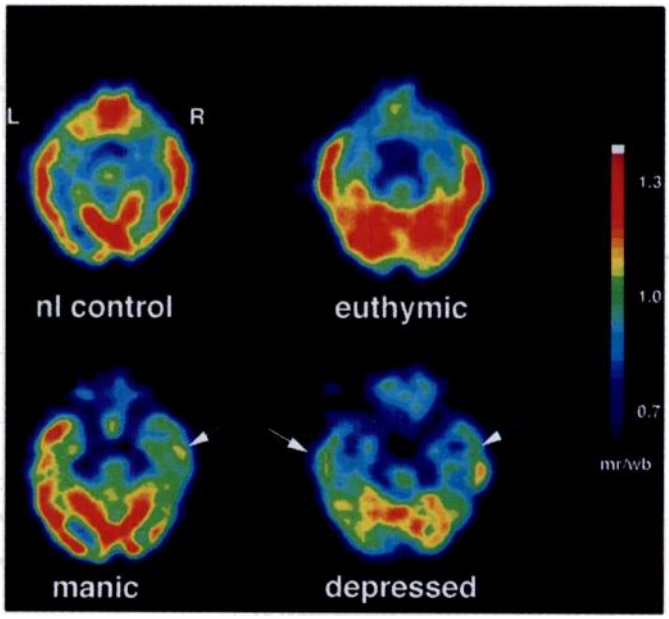


FIGURE 6. FDG PET scans in patients with single caudate lesions and varying mood states (see p. 436). Single scans at the level of the temporal lobe are shown in 4 subjects. Euthymic stroke patients, like healthy control subjects, have normal, symmetric temporal lobe metabolism. In contrast, manic patients show unilateral (right-sided) temporal hypometabolism, and depressed patients show bilateral temporal hypometabolism. Scale: relative metabolic rate (regional absolute metabolic rate/whole brain metabolic rate).



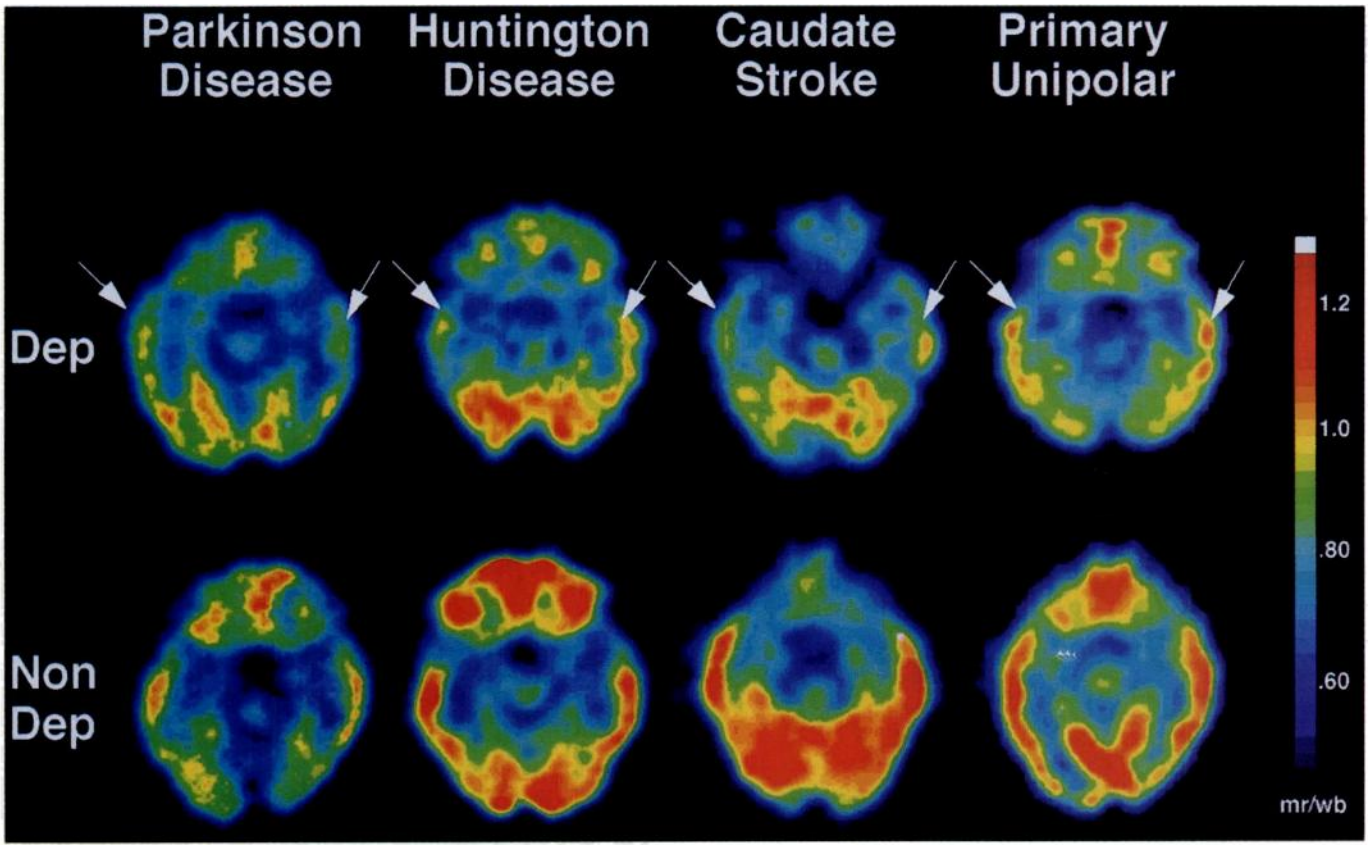
Huntington's Disease

George Huntington, in his 1872 description of hereditary chorea, was the first to observe that "the tendency to insanity and sometimes to that form of insanity which leads to suicide is marked."[160] Depression occurs in up to 40% of patients with Huntington's disease (HD)[31,32] and often precedes the more familiar motor and cognitive features that characterize the illness. The consistent association of involuntary movements, dementia, and mood change with striatal degeneration has given rise to hypotheses in which dysfunction of specific motor and nonmotor basal ganglia–thalamic–cortical pathways is implicated in the pathogenesis of these symptoms.[8,161] Motor pathways have been studied in the most detail; in these studies, loss of spiny neurons in the caudate and putamen as well as neurochemical changes in the pallidum and substantia nigra are described.[162–164] Although the mechanisms underlying the cognitive and mood disorders are less well understood, selective involvement of limbic and prefrontal striatal pathways has been proposed.

There have been no detailed anatomical studies of regional atrophy and mood disturbance in Huntington's disease, although CT studies have shown correlations between cognitive performance and subcortical atrophy, as measured with the bicaudate ratio.[165] As in PD, there are many published PET studies in patients with HD, and decreases in striatal, frontal, and cingulate cortex glucose metabolism have been reported.[166–171]

The relationship between the mood disorder and regional metabolic abnormalities has also been tested by Mayberg et al.[10] using methods identical to those in the study of PD patients described above.[6] Depressed and nondepressed HD patients, matched for age, years of duration of involuntary movements, functional disability, and measures of apathy, irritability, and global and frontal cognitive function, were studied with fluorodeoxyglucose PET. Caudate, putamen, and cingulate metabolism was significantly lower in the HD patients compared with the control subjects, independent of mood state; these results were comparable with previously published studies. Orbital–inferior prefrontal

FIGURE 7. FDG PET images in primary and secondary depression, temporal lobe level (see p. 437). There is symmetric bitemporal hypometabolism in the depressed patients, independent of disease diagnosis (arrows, top row). Temporal metabolism is normal in all nondepressed patients. Scale: relative metabolic rate (regional absolute metabolic rate/whole brain metabolic rate).



cortex and thalamic hypometabolism, on the other hand, differentiated depressed patients from both the nondepressed HD patients and normal control subjects, in a pattern similar to that seen in the depressed parkinsonian patients (Figure 4, p. 432). These findings again suggested that disruption of pathways linking paralimbic frontal cortex and the basal ganglia is integral to the development of depression in Huntington's disease, but that the disruption occurs via different mechanisms than those proposed for Parkinson's disease.

Although the predominant chemical and anatomical changes in HD occur in the striatum, pathological changes in cortex have not been appreciated in early stages of the disease, although both cortical atrophy[172] and cell loss in the frontal cortex[173] have been documented in more advanced cases. Atrophy alone, however, did not explain the findings in the described PET study; depressed and nondepressed patients had comparable quantitative measures of atrophy by MRI.

The established connections between specific striatal subnuclei and exclusive regions of cortex, via the pallidum and thalamus, provide a cogent physiological mechanism by which specific cortical areas are selectively affected in the depressed group of HD patients (Figure 3, p. 431). Primary dysfunction or degeneration of neurons in the frontal cortex is one explanation for the hypometabolism seen in this region in the depressed HD patients. Although specific neuroreceptor changes in frontal cortex, demonstrated at the time of autopsy, have been shown to correlate with the atrophy that occurs late in the course of the disease,[172,174] differences between depressed and nondepressed patients have not been studied. Alternatively, disproportionate involvement of the dorsomedial caudate, which is known to undergo early degeneration in HD,[172] may be present in some, but not all, patients, accounting for the affective disorder seen in a significant subset of HD patients. Preferential involvement of the dorsomedial caudate can also be directly addressed by postmortem pathological studies in psychiatrically well characterized HD patients who die early in the course of illness. Anterograde or retrograde degeneration of pathways linking dorsomedial caudate, dorsomedial thalamus, and orbitofrontal–inferior prefrontal cortex might similarly result in remote hypometabolism in appropriate regions of thalamus and cortex.[173] Changes in basotemporal limbic pathways linking the orbitofrontal cortex with the amygdala, temporal pole, and dorsomedial thalamus[156,175] would also explain the observed pattern of focal hypometabolism. Although amygdala metabolism was not reliably sampled in our PET study, atrophy of the amygdala has been reported in HD.[176] Correlations with depression have yet to be explored.

Neurochemical mechanisms are more obscure. Degeneration of VTA neurons or their projections have not been demonstrated in HD, although dopaminergic projections from the VTA have regional specificity for the orbitofrontal and prefrontal cortex. Striatal monoaminergic, peptidergic, and glutamatergic changes, on the other hand, are well documented,[163,164] but there are no systematic studies of these pathways in depressed HD patients. Future in vitro and in vivo neurochemical studies targeting these specific brain regions may help to delineate further the pathophysiological mechanisms specific to depression in HD.

Stroke Studies

Clinicians have long recognized that depression is a frequent consequence of stroke. Systematic studies examining the relationship between changes in mood, alterations in specific neurotransmitters, and discrete lesion locations have evolved more recently. Results suggest that the development of clinically significant depression after stroke depends on two variables: the location of the brain injury and the time elapsed since the stroke.[45] Although severe depressions have been described with lesion sites in both hemispheres, left frontal and left basal ganglia lesions appear more likely to be associated with mood changes than any other lesion location.[46–48]

The prevailing hypotheses concerning mechanisms for depressions following stroke involve direct injury to midbrain catecholamine neurons or disruption of their cortical projections. Experimental stroke lesions in rodents and primates have demonstrated decreases in norepinephrine, dopamine, and serotonin concentrations early after brain injury. Changes in central monoamines and their metabolites in the spinal fluid of stroke patients have also been measured.[177,178] Lower levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) have been demonstrated in patients with left compared to right hemisphere strokes and have been found to correlate with clinical measures of depression severity. These neurochemical changes support the theory that mood disorders result from changes in functionally available biogenic amines.[128]

It is also postulated that mood changes do not result solely from the stroke lesion but are due to the interruption of well-established subcortical-cortical connections—"remote diaschisis."[179] This thesis readily explains the high association of both basal ganglia and frontal lesions with depression. Functional imaging can be used to test this disconnection theory directly and offers a complementary approach to lesion-mapping studies in the evaluation of brain areas critical for the maintenance of normal mood after brain injury. These methods enable us to ask what pattern of cortical or

subcortical dysfunction is common to patients with similar phenomena and different brain lesions or what is different about patients with seemingly similar lesions but different mood symptoms.

The examination of regional changes in metabolism or blood flow in patients with specific clinical deficits is a well-described strategy. The pattern of cortical hypometabolism has been shown to correlate with persistent disturbances of language, memory, and attention.[179-181] Applying this strategy to subcortical lesions has definite advantages over studies of patients with cortical infarctions; with subcortical lesions there are no confounding effects of direct tissue damage or atrophy in brain areas where metabolic measurements are of the greatest interest. The high association of behavioral sequelae, including mood disorders, with lesions of the striatum makes these patients highly suitable for these types of studies. Finally, the known pathways linking the basal ganglia and specific areas of frontal cortex, which have been studied in primates,[95,96,99] provide a logical analysis strategy. The hypothesis that disruption of specific motor and nonmotor loops linking the basal ganglia, thalamus, and cortex accounts for specific clinical deficits can be tested by examining the patterns of regional glucose metabolism in relation to specific lesions.[107,108,182]

To this end, Mayberg et al.[108] divided patients with chronic unilateral subcortical strokes into two groups: 1) those with lesions of motor nuclei (putamen with or without posterior internal capsule) and 2) those with lesions of nonmotor nuclei (head of the caudate alone, or caudate plus anterior limb of internal capsule). Patients with putamen lesions had widespread ipsilateral cortical and thalamic hypometabolism and were clinically identified by motor deficits (Figure 5, p. 433). In contrast, patients with caudate lesions had ipsilateral hypometabolism involving more restricted areas of frontal, temporal, or cingulate cortex (Figure 5). Clinically, these patients as a group had selective disturbances of cortical function without motor impairment. Although the pattern of remote cortical hypometabolism was not identical among individual patients with nonmotor clinical deficits, all subjects had focal rather than hemispheric changes in metabolism ipsilateral to their stroke lesions. The clinical and metabolic phenomenology seen in this small group of patients[108] is consistent with segregated motor and nonmotor behavioral circuits described in primates.[96,98] The data suggest that precise localization of structural lesions with MRI, combined with mapping of remote metabolic phenomena with PET, may be useful in differentiating functionally separate pathways connecting the basal ganglia and cortex and may contribute to understanding the mechanisms underlying lesion-induced disturbances of motor control, mood, and cognition.

A similar strategy was then used to examine patients with comparable basal ganglia lesions but variable mood symptoms.[107,182] Patients with single lesions of the basal ganglia restricted to the head of the caudate, with or without extension into the anterior limb of the internal capsule, were identified from an ongoing clinical study of patients with poststroke mood disorders. Patients were subdivided by DSM-III mood disorder diagnosis into three groups: euthymic, depressed, and manic. Patients in the euthymic and depressed groups all had left-sided lesions, whereas manic patients all had right-sided lesions.

Patients with mood changes (depressed and manic patients together) were compared with euthymic patients, and bilateral hypometabolism was seen in all the limbic regions of interest: orbital–inferior frontal cortex, anterior temporal cortex, and cingulate cortex. The most pronounced changes occurred in the temporal lobes, and metabolism in this region differentiated patients by mood diagnosis (Figure 6, p. 433). Manic patients showed temporal hypometabolism ipsilateral to the lesion only. Depressed patients had bilateral temporal as well as cingulate hypometabolism. Euthymic patients had normal temporal and cingulate metabolism. Interestingly, lesion location did not predict mood change, although the precision of lesion localization was limited by the structural imaging techniques used. Furthermore, the role of lesion side was not fully addressed because patients with right-sided lesions and depression were not available for this study. Notably, bilateral inferior frontal hypometabolism was seen in all subjects and was not useful in differentiating depressed from nondepressed stroke patients, as was clearly demonstrated in the studies of Parkinson's disease[6] and Huntington's disease[10] (Figure 4, p. 432).

The mechanisms underlying these cortical changes remain uncharacterized. It nonetheless can be postulated that the remote metabolic effects that occurred in the orbital–inferior frontal cortex may be lesion-specific, disrupting orbitofrontal–striatal–thalamic circuits in all patient subgroups. These bilateral changes were unexpected and have no obvious explanation. Temporal lobe abnormalities, on the other hand, appear to be mood state–specific, implicating selective disruption of basotemporal limbic pathways in the patients with mood changes. Undercutting of the medial forebrain bundle as it passes ventral to the caudate, with disruption of selective ascending monoaminergic cortical projections, might also result in secondary changes in regional limbic metabolism. Further studies, including selective lesion studies in animals, are necessary to test these hypotheses.

COMPARISON OF PRIMARY AND SECONDARY DEPRESSIONS

From this series of studies of depression in Parkinson's disease, Huntington's disease, and isolated basal ganglia lesions, it became apparent that basolimbic regions (anterior temporal cortex, orbitofrontal–inferior prefrontal cortex) were consistently abnormal in the depressed, but not the nondepressed, patients in each disease group.

A subsequent study by Mayberg et al.[183] tested the hypothesis that primary and secondary depressions, regardless of disease etiology, have comparable patterns of abnormal metabolism involving brain areas with limbic connections. In this study groups of patients with the three neurological diseases were compared with a group of primary affective disorder patients. Depressed patients, independent of disease group, had significantly decreased metabolism bilaterally in both paralimbic frontal and temporal cortex (Figures 4, p. 432, and 7, p. 434). Further analyses showed no statistical differences between patients with primary and secondary depression—although the magnitude of the abnormalities was greatest in patients with basal ganglia disease. Unlike the original studies performed in each disease independently, these studies showed the frontal and temporal changes in all three depressed patient groups. The temporal lobe abnormalities were not appreciated when each disease was analyzed separately, probably because of inadequate statistical power.

As hypothesized, depressed mood correlated with changes in stereotypic brain regions and was state-specific rather than disease-specific. The potential confound of associated cognitive impairments in these patients was not directly addressed. However, depressed and nondepressed patients were matched for their cognitive performance in all experiments. Although no published studies have explicitly tested these mood–cognitive function interactions, primate experiments have examined the effects of precise cortical lesions on tasks such as delayed response and delayed alternation (behavioral deficits also described in depressed and basal ganglia disease patients), and these primate studies have identified selective involvement of dorsolateral prefrontal and orbitofrontal cortex in these behaviors.[184,185] Preliminary studies in primary affective disorder patients have demonstrated that global cognitive impairment is highly correlated with medial prefrontal hypoperfusion, whereas psychomotor slowing correlates most strongly with decreases in the dorsolateral prefrontal cortex.[186,187] Prospective examination of specific cognitive deficits awaits future studies in both unipolar depression and depression in neurological patients.

A UNIFYING VIEW OF SECONDARY DEPRESSION

The repeated observations from these independent studies of patients with Parkinson's disease, Huntington's disease, and caudate strokes is the common involvement of paralimbic regions (orbital–inferior prefrontal and temporal cortex) in patients with mood disorders, independent of disease diagnosis. These findings make it possible to propose a functional lesion-deficit map of brain areas involved in depression. The regional localization of the metabolic abnormalities matches two known pathways: the orbitofrontal–basal ganglia–thalamic circuit[95,96] and the basotemporal limbic circuit that links the orbitofrontal cortex and anterior temporal cortex via the uncinate fasciculus.[97–101] Unfortunately, the precise mechanisms responsible for these metabolic changes cannot be delineated by these experiments.

Hypotheses based on the known neurochemical and degenerative defects present in these three disorders can, however, be offered to account for the selective disruption of these corticostriatal and basotemporal limbic pathways (Figure 3, p. 431). These hypotheses include

1. Primary degeneration of the ventral tegmental area, seen in PD, with disruption of dopamine projections to the mesolimbic frontal cortex.
2. Primary degeneration of the basal amygdaloid nucleus, also reported in HD, which has direct connections with both the orbitofrontal and basotemporal areas via limbic pathways.
3. Cell dropout in frontal cortex, which has been reported in HD.
4. Anterograde or retrograde degeneration along basal ganglia–thalamic–cortical pathways secondary to caudate degeneration in either HD or stroke lesions.
5. Secondary changes in brainstem monoamines from dysfunction of the orbitofrontal cortex, the major cortical outflow to the mesencephalon.

Disease-specific interruptions of individual connections could explain the characteristic paralimbic frontal and temporal metabolic defects that have been identified and could reconcile the presence of similar clinical symptomatology in the settings of different disease etiologies.

In summary, patients with depression and neurological disease are useful models in the study of the functional neuroanatomy of mood. Imaging techniques provide a focused and novel approach for exploring the biological similarities and differences between primary and secondary depressed patients. Future studies designed to identify specific in vivo neurochemical markers in patients with depression of different etiologies may

advance our understanding of the pathogenesis of these disorders and contribute to the full characterization of neural systems regulating normal mood and emotions.

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