Brain Structure and Function and the Outcomes of Treatment for Depression

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Background: Depressed patients have a variety of brain structural alterations, the most common being atrophy and deep white-matter lesions. Alterations in brain function also are common, particularly regional decreases in cerebral metabolism and perfusion. ***Method:*** We review here the evidence that alterations in brain structure and function may explain some of the heterogeneity in outcomes of depression. We also report initial results suggesting that measurement of brain structure and function may help to predict outcomes of treatment for depression. Brain structure was examined using three-dimensional reconstruction and volumetric analysis of magnetic resonance imaging (MRI) scans. Brain function was examined using quantitative electroencephalography (QEEG), performed at baseline and serially during the course of treatment. QEEG measures included coherence (a measure of synchronized activity between brain regions) and cordance (a measure strongly associated with regional cerebral perfusion). ***Results:*** Depressed patients have been reported to have larger volumes of white-matter lesions than controls. We have found that some types of white-matter lesions are associated with lower coherence and that subjects with low coherence had significantly poorer outcomes of treatment for depression at 2-year follow-up. Depressed subjects had low cordance at baseline, which decreased further during the course of effective treatment. Subjects who did not improve had little or no change in cordance. Changes in cordance were detected prior to the onset of clinical response, with decreases seen as early as 48 hours after the initiation of treatment in subjects who showed eventual response. ***Conclusion:*** These preliminary results suggest that functional imaging using QEEG may be useful for assessing, and possibly predicting, outcomes of treatment for depression.

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There is considerable heterogeneity in the outcomes of treatment for depression. Some patients achieve rapid remissions and remain well for extended periods; others suffer from prolonged, refractory illness; and still others achieve remission but suffer frequent recurrences or relapses of depression.[1] Research has identified several risk factors for poor outcomes based on patient history and symptoms. The presence of multiple previous depressive episodes,[2] psychotic symptoms,[3] and comorbid conditions such as panic disorder[4] all are associated with a decreased likelihood of an early, complete, and sustained treatment response.

There is evidence that alterations in brain structure or function may be more powerful predictors of outcome than history or symptoms alone. It also is possible that functional imaging can be used to guide decisions regarding the treatment of depression. We review here the evi-

dence that brain structural and functional changes serve as indicators of the outcome of depressive illness.

BRAIN STRUCTURAL CHANGES AND DEPRESSION

For nearly 30 years, investigators have reported brain structural changes in depressed patients.[5] Surprisingly, it is not yet clear under what circumstances structural alterations constitute a risk factor for the development of depressive illness. Four types of structural change have been reported in depressed patients: stroke, atrophy, white-matter lesions, and deep-gray lesions.

Strongest evidence supporting a causal link between structural changes and depressive illness has been found in patients with stroke. The most powerful predictor of the development of poststroke depression is the location and size of the lesion; left anterior lesions that affect the caudate nucleus confer the greatest risk of depressed mood, regardless of the level of disability caused by the stroke.[6,7]

Other types of structural abnormality have been shown to have increased prevalence in patients with depression, but their role in the pathogenesis of depression is less clear. Atrophy is a common finding in both computed tomography (CT) and magnetic resonance imaging (MRI) studies of depressed patients. These patients commonly have a smaller frontal-lobe volume[8] and/or temporal-lobe volume[9] than age-matched controls. Atrophy is a nonspecific finding, however, seen also in "normal" aging and dementia, and it is not clear that it is associated with increased risk for depression.

Other structural abnormalities are deep gray-matter lesions of the brain seen with MRI scanning. These are seen with a higher prevalence in patients with late-life depression than in control subjects.[8] Interestingly, these lesions are seen with highest prevalence in elderly patients with late-onset depression, suggesting that such lesions may be a significant risk factor for this subgroup of subjects.[10]

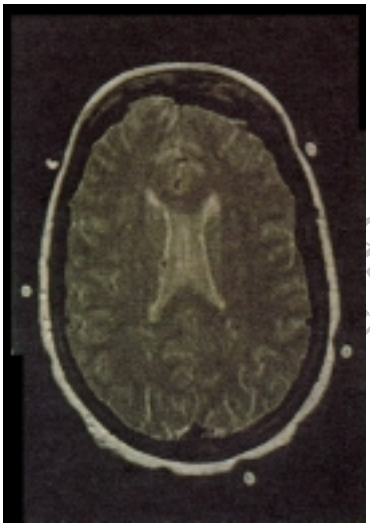
One of the most common structural alterations seen in depressed patients is that of white-matter hyperintensities seen on T_2-weighted MRI scanning. There are two types of such lesions: hyperintensities seen in the periventricular white-matter (PVH) and hyperintensities seen in the subcortical deep white matter (DWMH). Such lesions are found with an increased prevalence in the frontal lobes of patients with depression[10–12] and may constitute a risk factor for late-onset depression.[6,8,10] Some evidence, however, calls into question a causal link. White-matter lesions are found with high prevalance in demented and normal elderly, as well as among depressed patients.[13–16] Evidence suggests that the presence of these lesions is related both to age and to risk factors for cerebrovascular disease.[17–19] At least one study has found that healthy depressed subjects with no risk factors for cerebrovascular disease have no greater prevalence of these lesions than normal control subjects.[20]

In addition to possibly conferring added risk for the development of depression, structural alterations may be related to the heterogeneity in outcomes of depressive illness. Several different structural alterations appear to be related to outcome, although the specific poor outcomes associated with different alterations remain unclear. The presence of extensive brain atrophy on CT has been reported to be a predictor of increased 2-year mortality in depressed subjects,[21–23] as well as decreased likelihood of response to antidepressant medications.[24] Several studies reported that patients with white-matter lesions are at risk for poor outcome, although the results are in part conflicting. Some investigators have reported that patients with lesions respond well to treatment but are at risk for the development of delirium during treatment with electroconvulsive therapy (ECT) or medications.[11,25–27] In contrast, a recent study reported that patients with DWMH had a significantly poorer response to treatment with ECT or medications.[28] Still another study found that the initial response rate to treatment was just as good for patients with white-matter lesions but that these patients may suffer a higher rate of relapse of depressive illness.[29]

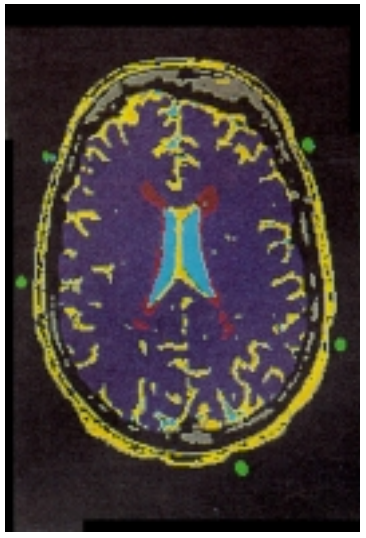
The apparent inconsistencies among studies regarding the significance of structural lesions may reflect the variability of lesion placement and volume. Boone and colleagues[30] demonstrated that white-matter lesions are associated with decrements in brain function, but only after a critical area of brain tissue is affected (as measured with two-dimensional MRI analysis). This quantitative analysis of lesion area is valuable in that it may identify subjects with functionally significant lesions. The two-dimensional approach, however, has limitations. While sensitive to lesion area, it does not measure lesion volume. Furthermore, it is difficult to examine the relationship of lesions to critical brain structures using two-dimensional methods.

In order to further explore the relationship between white-matter lesions and brain dysfunction, we are conducting experiments using three-dimensional reconstructed MRI scanning. In this technique, scans are performed with a double-echo pulse sequence and 3-mm contiguous sections, to maximize accuracy in the measurement of lesion volumes and distribution. MRIs are performed after completion of an EEG recording, with surface markers placed at EEG recording sites. The resulting image permits not only volumetric lesion analysis, but also measurement of the precise relationship between lesions and surface electrical activity (Figure 1). The series of images are segmented, and the distinct structures (i.e., ventricles, white matter, white-matter lesions) are assigned unique color codes (Figure 1B). The series of segmented images then can be reconstructed in three-dimensional space to examine the entire brain (Figure 1C); the green "net" over the surface of the brain is created by the network of EEG recording electrodes. Embedded within this three-dimensional brain are both normal and abnormal

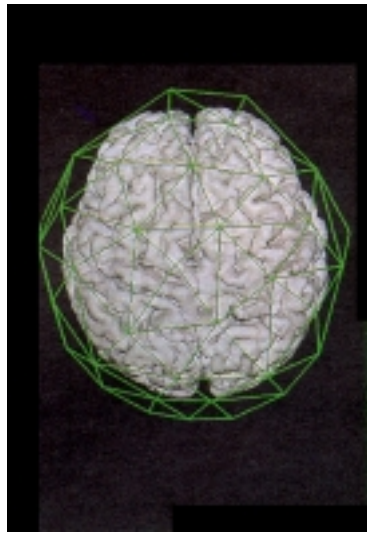
Figure 1A–1E. Steps in Three-Dimensional Reconstruction and Volumetric Analysis of MRI Scans and in Integrating These Images With QEEG Data*



A: The raw image has been acquired with external markers at EEG recording sites

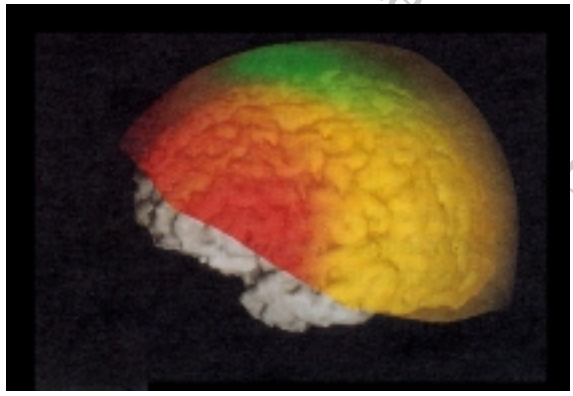


B: The image is then "segmented" such that different structures are assigned unique color codes



C: Three-dimensional reconstruction of all segmented images can then take place

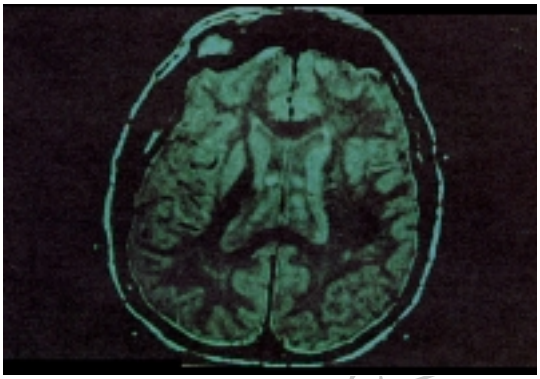
D: During three-dimensional reconstruction, normal and abnormal structures such as white-matter lesions (shown in red) are embedded within the brain



E: EEG activity can be projected onto the surface of the brain using an isosurface created from external markers

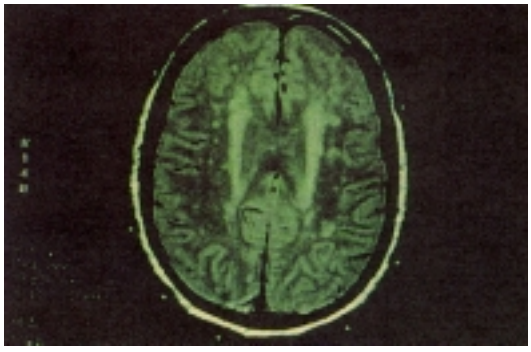
*1A–1D from reference 56, with permission.

Figure 2. T_2-Weighted MRI Image From Subject X, Showing Minimal Periventricular White-Matter Hyperintensities (PVH) at the Anterior and Posterior Ventricular Horns*



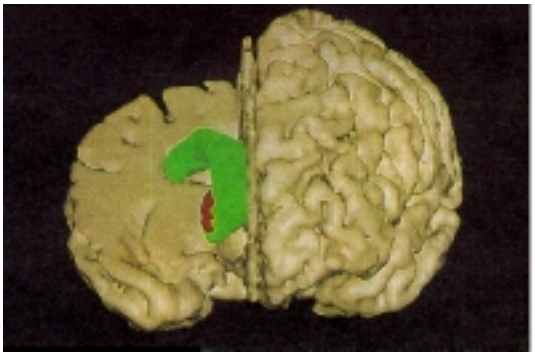
*From reference 56, with permission.

Figure 3. T_2-Weighted MRI Image From Subject Y, Showing Marked PVH Along the Bodies and the Horns of the Lateral Ventricles*

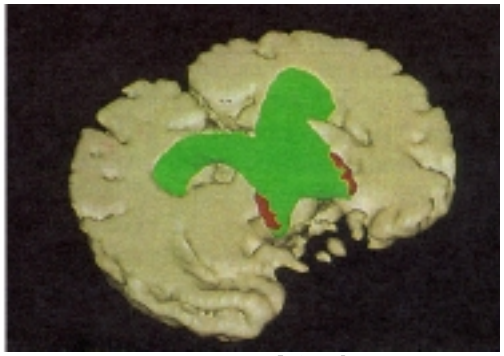


*From reference 56, with permission.

Figure 4. Three-Dimensional Reconstruction of the Brain of Subject X*



A: Partial Cutaway



B: Complete Cutaway

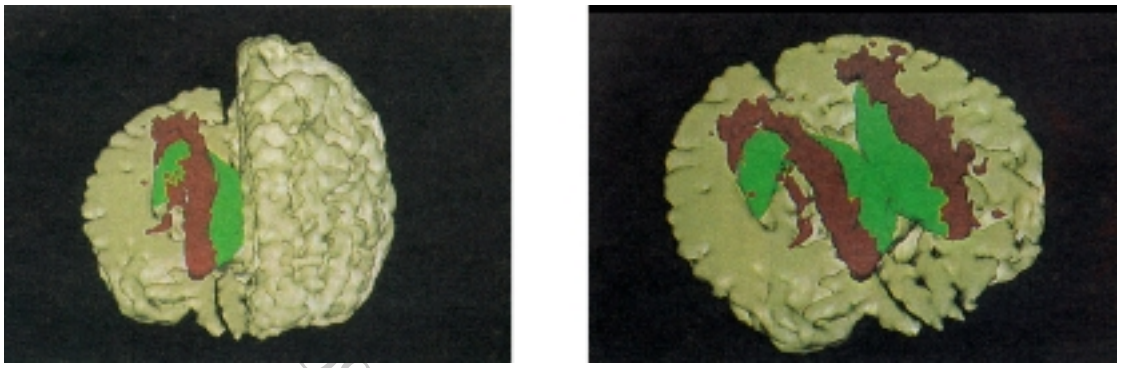
*4B from reference 56, with permission. Cutaways show the volume of reconstructed PVH (in red). A minimal volume of lesions is immediately adjacent to the ventricles.

brain structures, such as ventricles and white-matter lesions (Figure 1D), which can be revealed in cutaway images. EEG measures can be displayed on an isosurface created from the recording electrodes (Figure 1E).

The usefulness of the three-dimensional technique is shown by two subjects, whose MRIs appear in Figures 2 and 3.[56] Both were 89-year-old men living independently in the community who volunteered as normal control subjects. Both had 17 years of higher education and were without significant cognitive complaints. Subject X (Figure 2) was in excellent health, while subject Y (Figure 3) was in good health with relatively well-controlled hypertension and diabetes. The MRI of subject Y shows more extensive white-matter lesions, particularly in the periventricular white matter. The volume of these lesions is more apparent in the three-dimensional reconstructions, in which subject X has a low volume (less than 5 cc) of white-matter lesions (Figures 4A and 4B, indicated by the red structures), while subject Y has notably larger lesions (Figures 5A and 5B). The presence of these lesions is associated with subtle changes in cognition and mood in subject Y. Although he did not have a diagnosable cognitive impairment and did well on most measures of cognitive function (such as memory and vocabulary), he showed impairment compared with subject X in more demanding tasks involving executive (frontal lobe) function, such as the Wisconsin Card Sorting Test (Table 1). He also showed subtle increases in mood-related complaints, although he did not meet criteria for a mood disorder. We have found similar results from a study of 25 additional normal control subjects, which is in preparation for publication.

Since white-matter lesions disrupt many of the fiber tracts linking cortical and subcortical gray-matter structures, it is reasonable to hypothesize that they could compromise the function of systems responsible for mood regulation. Recent articles have postulated the existence of subcortical "circuits" involved in mood regulation.[12,31] Since these circuits are dependent upon positive and nega-

Figure 5. Three-Dimensional Reconstruction of the Brain of Subject Y*



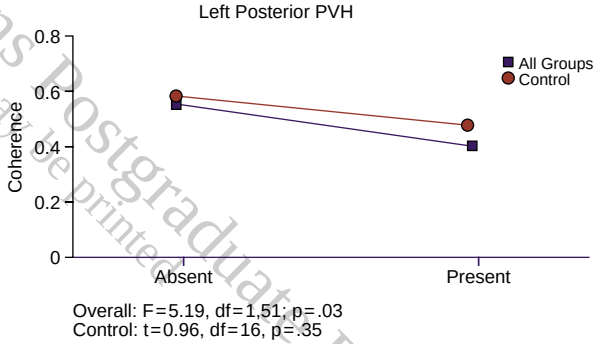
*5B from reference 56, with permission. Cutaways show the volume of reconstructed PVH. A substantial volume of lesions is adjacent to the ventricles, extending out into the deep white matter.

Table 1. Clinical Characteristics and Test Results of Subjects X and Y*†

Parameters	Subject X	Subject Y
Age (y)	89	89
Sex	Male	Male
Education (y)	17	17
Blessed	1	1
Hachinski	1	1
MMSE	30	30
Vocabulary	33	36
Words remembered	30	32
Words C	18	31
Words F	12	1
Wisconsin Card Sorting		
Categories	6	6
Perservative errors	3	5[a]
Total errors	4	7[a]
MRI lesion volume (cc)	4.5	11[a]
Abstract thinking	15	7[a]
HAM-D	2	14
FAS	40	10[a]

*Data from reference 56.
†Abbreviations: FAS = Word-List Generation Test; HAM-D = Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging.
[a]Areas where subject Y does worse than subject X.

Figure 6. Level of Coherence in Subjects Without (left) Versus With (right) White-Matter Lesions*



*Adapted from Leuchter et al.[13] All subjects (blue line) showed a significant decrease in coherence associated with the presence of lesions, while control subjects alone (red line) showed a trend toward decreased coherence.

Table 2. Two-Year Outcome of Treatment for Depression, Stratified by Coherence*

Coherence Group	Recovered	Residual Symptoms	Deceased	Total
Low	3	6	7	16
High	11	8	2	21
Total subjects (%)	14 (38)	14 (38)	9 (24)	37 (100)

*Adapted from Leuchter et al.[33]

tive "feedback" pathways between brain structures, white-matter lesions could make some patients more vulnerable to depression by damaging one or more limbs of these pathways. A neurophysiologic method that could detect an effect of lesions on the integrity of these pathways could be useful in the study of depression.

One method for the assessment of the integrity of these pathways is EEG coherence. Coherence is a measure of the functional connections between brain regions, analogous to the square of a correlation coefficient: a value near 1 denotes highly shared activity, while a value near 0 denotes little shared activity. Shared EEG activity presumably is mediated in part by white-matter fiber tracts[32] and therefore should be affected by the presence of lesions that disrupt these tracts. We examined EEG coherence in normal and demented elderly subjects with and without white-matter lesions[13] and found that subjects with white-matter lesions had significantly lower coherence than those without white-matter lesions (Figure 6). In many instances, the lesions were not extensive, suggesting that even modest amounts of white-matter disease may have neurophysiologic effects on the brain.

Coherence appears to be useful as a predictor of long-term outcome in patients with late-life depression. We per-

formed quantitative EEG (QEEG) studies at baseline in 37 subjects with late-life depression and carried out a 2-year follow-up to examine associations between baseline QEEG measures and outcome.[33] The results of this study are shown in Table 2. Overall, the depressed subjects in this study had a 2-year mortality rate of 24%, which was consistent with previous studies showing increased 1-year mortality rates of approximately 8%–15% in subjects with depression.[34–38] Decreased coherence was a significant risk factor for mortality; 44% of those with low coherence died, and of those who died, 78% had low coherence. The surviving subjects with low coherence had lower functional status than their counterparts with high coherence. The subjects with low coherence could not be distinguished from those with high coherence on the basis of clinical factors, such as baseline severity of depression, health status, or level of disability. Structural imaging data were not available on these subjects to determine if the low coherence was associated with the presence of white-matter lesions. We now are prospectively examining MRI and coherence in subjects with depression to determine if white-matter lesions or other structural changes are associated with increased mortality or poor functional status in subjects with depression.

BRAIN FUNCTIONAL CHANGES AND DEPRESSION

A number of investigators have reported abnormal brain function in depression. Studies examining cerebral metabolism (with 18-fluorodeoxyglucose positron emission tomography [FDG PET]) or cerebral perfusion (using ^{15}O-PET, or 99m technetium hexamethylpropyleneamine oxime single-photon emission computed tomography [HMPAO SPECT], or ^{133}xenon [Xe] SPECT) have repeatedly shown regional decreases in perfusion or metabolism. The precise distribution of the decreased cerebral function is not clear. Most studies have found the greatest decreases in the left hemisphere, particularly the left prefrontal cortex; some studies have reported primarily right-sided decreases in cortical activity; still other studies have shown normal cortical activity but decreased activity in the subcortical gray nuclei (particularly the caudate nucleus).[39–42]

Disagreement among studies regarding the nature and distribution of functional abnormalities probably reflects several factors. First, although cerebral perfusion and metabolism are closely related physiologically, and the various PET and SPECT techniques are comparable, there are differences in (1) the characteristics and distribution of the different radioactive tracers; (2) the temporal resolution of the different techniques (ranging from 30 seconds to 45 minutes to obtain an image); and (3) the recording conditions for the various studies (i.e., eyes-open versus eyes-closed states). In addition to technical differences, variation in subject populations could account for differing patterns of brain dysfunction. Subjects in different phases of depressive illness or with distinct constellations of symptoms (such as obsessive-compulsive features) may have different brain imaging findings.[31,42,43] Any combination of technical and clinical differences could account for substantial interstudy variability.

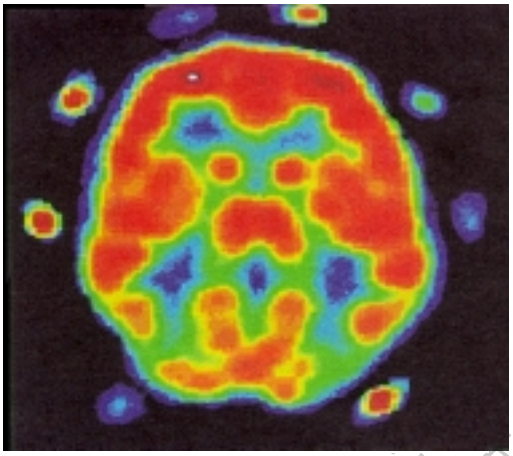
Limited studies of subjects with late-life depression suggest that brain functional changes may be more prominent among these subjects. Studies by Sackeim and colleagues using Xe SPECT,[44] Lesser and colleagues using HMPAO SPECT,[45] and Kumar and coworkers using FDG PET[46] all reported marked global decreases in metabolism or perfusion, with possible lateralization of the decreased activity to the right hemisphere.[45] These marked functional abnormalities may make the elderly population particularly interesting for functional imaging studies.

Several studies suggest that functional abnormalities in depressed subjects are altered by effective antidepressant treatment. Baxter and colleagues[39,47] were among the first to report increases in brain metabolism (measured with ^{18}FDG-PET) in the left prefrontal cortex and the caudate nucleus after effective antidepressant treatment. Comparable results have been reported by Martinot and colleagues[48] and by Bench and coworkers[49] using ^{15}O-PET. In subjects with late-life depression, Kumar and colleagues[50] found global increases in cerebral perfusion after treatment using SPECT.

It is not clear that normalization of blood flow occurs in most patients with depression. Several studies suggest that effective treatment is associated with further reductions in cerebral perfusion and metabolism. Drevets and coworkers[31,43] studied the effects of medication treatment with ^{15}O-PET, and found significant decreases in perfusion in the left frontal cortex. Nobler and his colleagues[52] studied the effects of ECT treatment using SPECT and found decreases in cerebral perfusion in response to effective treatment. The findings of further decreases in perfusion are consistent with animal literature that shows that chronic administration of antidepressant medication is associated with decreased rCBF and rCMR.[41] Some studies, however, have no consistent effect of treatment: Hurwitz and colleagues[51] found no significant change in metabolism measured with ^{18}FDG-PET after medication treatment.

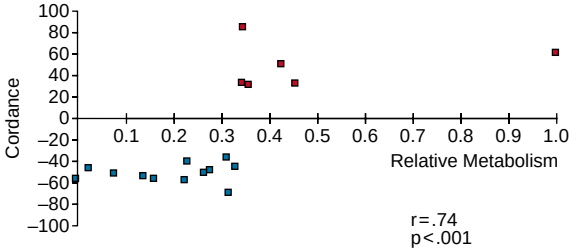
At least two factors may account for the inconsistent relationship between clinical improvement and functional changes in these studies. First, most studies have included small numbers of subjects who were heterogeneous in their clinical characteristics (i.e., age, health status, number of prior episodes); it is likely that subjects with different clinical presentations will have different patterns of change in cerebral activity.[42] Second, subjects in previous studies have differed in the type and intensity of treatments assigned; these differences may profoundly affect clinical outcome. It will be necessary to study larger numbers of well-characterized subjects on multiple occasions

Figure 7. Transaxial PET Scan Image Showing the Brain With External Radioactive Markers at EEG Recording Sites*



*These markers permit a "digital punch biopsy" measurement of the metabolism directly underlying each recording electrode.

Figure 8. Association Between Cordance and Relative Metabolism Measured With PET*



*Each point represents a single recording electrode. Electrodes with above-average metabolism show high cordance values (indicated by red marks), while electrodes with low metabolism show low cordance values (indicated by blue marks).

during the course of treatment, in order to clarify the circumstances under which metabolism or perfusion normalizes after treatment.

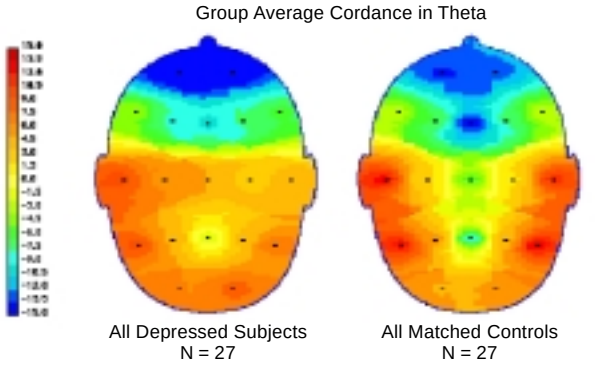
From a practical standpoint, it is difficult to study a large number of subjects on multiple occasions during antidepressant treatment using PET and SPECT. While these are powerful techniques, they are relatively expensive to perform; a combination of cost and radiation dosimetry considerations limit the number of studies an individual may undergo. To overcome these limitations of PET and SPECT, we worked to develop a noninvasive, low-cost method to assess cerebral perfusion and metabolism.

We recently reported the development of a new technique for processing QEEG data, called cordance,[53,54] which derives from brain electrical-output information which is substantially similar to that collected with PET or SPECT. Cordance is derived from measures of absolute EEG power (the intensity of energy in a single EEG band measured in μV^2) and relative EEG power (the proportion of total energy found in a given frequency band, measured in percentage of total power). These two power measures are normalized across recording sites and combined to yield cordance values. Cordance has been validated as a measure of perfusion and metabolism through the simultaneous acquisition of QEEG and PET data. An example of the resultant associations is shown in Figures 7 and 8. Figure 7 shows an ^{18}FDG-PET image from a normal subject; the "satellites" surrounding the brain are lucite markers containing ^{22}Na, a positron-emitting compound also detected by the PET scanner. These markers permit measurement of cerebral metabolism directly underlying each recording electrode, and the association between cordance and PET for this subject is shown in Figure 8. Electrodes overlying cortex with relatively high metabolism (above the mean) have high cordance values; those overlying cortex with relatively low metabolism (below the mean) have low cordance values. The correlation between the two measures for this individual was .74. We now have examined a series of subjects with ^{15}O-PET and cordance acquired simultaneously and have found cordance to be a reliable indicator of cerebral perfusion in normal subjects performing motor tasks (Leuchter AF. Unpublished data).

We have used the cordance technique to study subjects with late-life depression to determine what pattern of brain activity could be detected in these subjects.[55] We examined 27 elderly depressed subjects and 27 matched normal elderly controls, with the hypothesis that the depressed subjects would show global alterations in cordance (possibly worse in the right hemisphere), similar to the decreases in perfusion and metabolism seen using PET or SPECT. This hypothesis proved to be correct, as shown in Figure 9. The average cordance map for the group of control subjects shows maximum cordance in the temporal regions bilaterally, with the lowest cordance in the frontal regions; this pattern commonly is seen in subjects at rest. The depressed subjects show a disruption of the normal anteroposterior gradient, with lower cordance frontally and diminished cordance in the temporal regions. The lower cordance was particularly prominent over the right temporal region, an asymmetry that was statistically significant ($p < .05$)[55] and similar to that reported in previous PET and SPECT studies.[45]

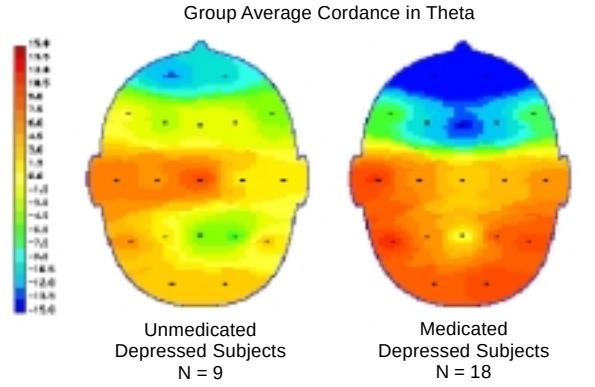
It is important to note that many of our depressed subjects (18/27, or 67%) were receiving antidepressant medication at the time of the cordance study. We therefore analyzed the data from the medicated and nonmedicated depressed subjects separately. Those subjects not receiving medication lost the normal anteroposterior gradient of cordance values compared with control subjects and had the greatest decreases over the right temporal region. The average cordance map for the subjects on medication (Figure 10) shows an "overcorrection" of the normal cordance pattern, with a steeper antero-posterior gradient than that

Figure 9. Average Cordance Maps for Depressed and Control Subjects*



*Adapted from Cook et al.[55] Depressed subjects show a disruption of the normal antero-posterior gradient, with lower cordance values in the frontal regions (indicated by blue-green colors) and decreased cordance in the temporal regions, which is most marked on the right. Cordance maps show the head as viewed from above, with red colors indicating higher cordance values and blue colors indicating lower cordance values.

Figure 10. Average Cordance Maps for Subjects Not Receiving and Receiving Antidepressant Medications*



*Adapted from Cook et al.[55] Subjects not receiving medication show a marked loss of the normal antero-posterior gradient, while subjects receiving medication show an "overcorrection" of the antero-posterior gradient. This finding suggests that antidepressant treatment is associated with relative suppression of frontal brain activity.

seen in the control group. Thus, it appears that medication is associated with a further reduction in frontal cordance,[55] consistent with PET and SPECT studies showing relative decreases in frontal metabolism and perfusion resulting from medication treatment.[41]

Because of these results suggesting that cordance detects changes in brain function associated with treatment, we are studying a series of subjects with depression during the course of antidepressant treatment (Leuchter AF. Unpublished data). Through these serial studies, we are planning to address two questions. First, is the "overcorrection" in cordance during antidepressant treatment specific for effective treatment? Preliminary data suggest that suppression of cordance is seen only during a stable remission of a depressive episode. Figure 11 shows a series of studies from a 76-year-old woman during the course of treatment for depression. Prior to antidepressant treatment (Figure 11A), the patient had loss of the normal gradient, as well as a prominent decrease in cordance in the right temporal region. The patient had a good clinical response to paroxetine, but the cordance map did not show either an increase in right temporal cordance or a robust decrease in frontal cordance (Figure 11B). The absence of overcorrection in cordance was worrisome, because these maps lacked the hallmarks of a lasting antidepressant response. The patient did in fact suffer a relapse of depression within several months, and despite an increased dose of paroxetine, right temporal cordance remained low and frontal cordance did not show a marked decrease (Figure 11C). The patient was switched to fluoxetine but did not have a therapeutic response and had little change in her cordance maps (Figure 11D). Finally, the subject was treated with venlafaxine and had a rapid and complete remission of symptoms. This was associated with a robust bilateral suppression of frontal cordance and a return of right temporal cordance to normal levels (Figure 11E).

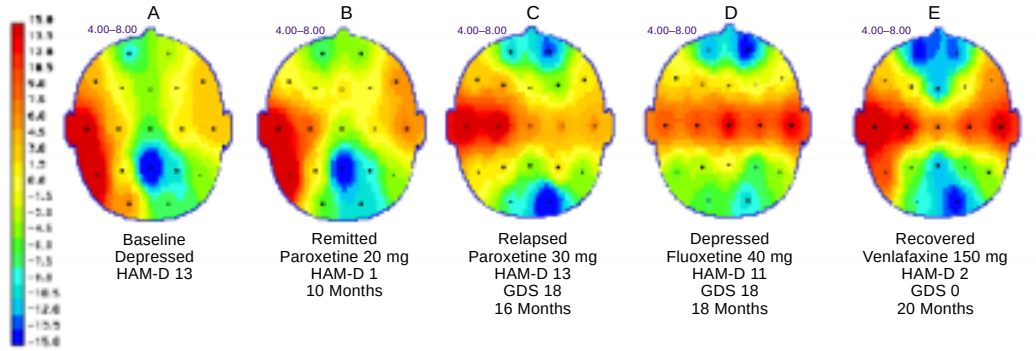
A second question is, how early in the course of antidepressant treatment can suppression of frontal cordance be detected? Preliminary data suggest that decreases in cordance precede clinical improvement, and may be seen as soon as 2 days after the start of treatment. The maps shown (Figure 12) were recorded from a 32-year-old woman in a double-blind, placebo-controlled study of venlafaxine. After 2 days on a low dose of venlafaxine (Figure 12B), this patient demonstrated decreases in frontal cordance; this decrease was seen before any significant change in depression scores was seen (Figure 12C). A graph of average frontal cordance values (Figure 13) shows that cordance decreased before significant clinical change was detected.

A physiologic method for assessing a patient's response to antidepressant medications could have significant benefits for clinical care. Such a method could help to shorten unsuccessful medication trials and to select the medication that is most likely to benefit an individual patient. Since cordance is both noninvasive and inexpensive, it could be used to examine many subjects with depression serially during the course of treatment for depression and help to make therapeutic decisions.

CONCLUSION

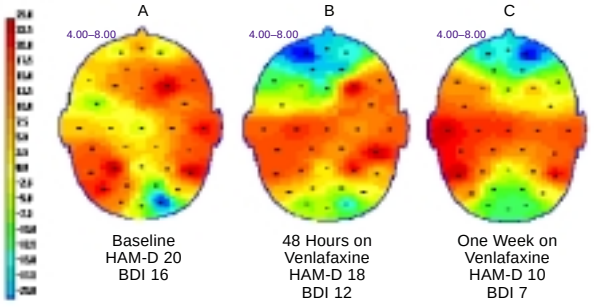
Brain imaging has the potential to be a useful clinical method for assessing subjects with depression. Alterations in brain structure may be important prognostic factors in determining which patients are at risk for poorer outcomes from treatment with antidepressant medication. Such patients may require different forms of treatment. Functional

Figure 11A–11E. Series of Cordance Maps From a Subject Undergoing Treatment for Depression*



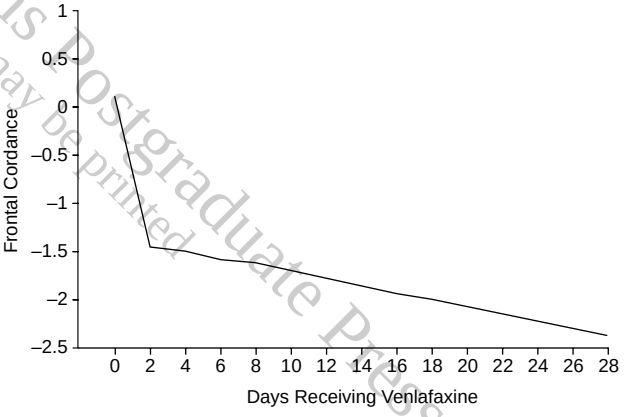
*At baseline (A), subject had low cordance over the frontal regions and the right temporal region. Although symptoms resolved after treatment with paroxetine (B), the frontal cordance did not decrease further and the temporal cordance did not increase. The subject relapsed, and an increased dose of paroxetine did not resolve the depression (C). Fluoxetine in a dosage up to 40 mg also was ineffective (D). Finally, the subject was treated with venlafaxine, which led to a complete remission of symptoms. The cordance map showed a large bilateral decrease in frontal cordance and a bilateral increase in temporal cordance, consistent with effective treatment (E).
Abbreviations: GDS = Yesavage Geriatric Depression Scale; HAM-D = Hamilton Rating Scale for Depression.

Figure 12A–12C. Series of Cordance Maps From a 32-Year-Old Female Subject, Recorded During the First Week of Venlafaxine Treatment*



*Subject started to show resolution of depressed cordance pattern as early as 2 days after medication was started (B), before clinical symptoms improved. The cordance continued to decrease over the next week as depression scores decreased (C).
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression.

Figure 13. Time Course of Response to Venlafaxine*



*Graph shows the decrease in frontal cordance values that preceded a change in clinical symptoms.

imaging may help to identify which treatments will be of greatest use to individual patients. Prospective controlled studies will be necessary to determine the usefulness of cordance and other imaging techniques for predicting treatment outcome.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), venlafaxine (Effexor).

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