Structural brain abnormalities in multiple sclerosis patients with major depression
Neurology 2004;62;586
DOI 10.1212/01.WNL.0000110316.12086.0C

This information is current as of April 15, 2013

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/content/62/4/586.full.html

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2004 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.
Structural brain abnormalities in multiple sclerosis patients with major depression

A. Feinstein, FRCPC; P. Roy, MS; N. Lobaugh, PhD; K. Feinstein, MA; P. O’Connor, FRCPC; and S. Black, FRCPC

Abstract—Objective: To assess the association between major depression and structural brain abnormalities in patients with multiple sclerosis (MS). Methods: Two groups of patients with clinically definite MS were studied: 21 with Diagnostic and Statistical Manual of Mental Disorders (4th ed.)–defined major depression and 19 without. The groups did not differ on demographic, disease, or cognitive measures. All subjects underwent brain MRI. Tissue segmentation and regional brain masking were applied to the MRI data. Results: Compared with the euthymic subjects, those with major depression had a greater T2-weighted lesion volume (p = 0.003) and more extensive T1-weighted lesion volume in the left medial inferior prefrontal cortex (p = 0.01) and less gray matter volume (p = 0.01) and more CSF volume in the left anterior temporal region (p = 0.005). A logistic regression analysis identified two independent predictors of depression: left medial inferior prefrontal cortex T2 lesion volume and left anterior temporal CSF volume. These variables accounted for 42% of the depression variance score. Conclusion: Whereas both lesion burden and atrophy are important in the pathogenesis of depression in MS, psychosocial influences should also be considered.

Multiple sclerosis (MS) is frequently associated with major depression, with lifetime prevalence rates ranging from 25 to 50%.¹ Reasons include psychosocial factors, MS disease characteristics (e.g., exacerbations, chronic progressive illness course) and MRI-demonstrated brain abnormalities.² It is, however, with respect to the latter that data have been inconsistent. Unlike brain correlates of cognitive difficulties in MS patients, where the associations have been robust,³ the results from the few published MRI–mood studies have been either more modest or negative.

An early 1.5 T MRI study in a sample of eight subjects reported an increased temporal lobe lesion score in those who were depressed,³ but subsequent studies failed to replicate this.⁵⁻⁷ More recently, an MRI study of 45 MS patients revealed that those with depression had significantly more T2-weighted lesions in the left arcuate fasciculus, although these could explain only 17% of the depression score variance.⁸ Other reports have, however, noted a closer association between depression and hypointense lesions in superior frontal and parietal areas or the presence of contrast-enhancing lesions.⁹¹⁰

The reasons for these inconsistent findings may reflect not only the complex pathogenesis of mood change but also some methodologic limitations in the studies undertaken thus far. These include the use of symptom questionnaires for the assessment of depression, which does not allow for the diagnosis of major depression; failure to exclude patients whose depression predated the onset of MS; neglecting to control for cognitive function between depressed and nondepressed subjects, a potentially serious confounder given the robust associations between cognitive function and brain lesion load in MS; and MRI protocols that focused exclusively on a single aspect of brain pathology, that is, lesion load. A better understanding of the important relationship between structural brain changes in MS and depression is, however, required more so as preliminary data suggest lesion location may influence treatment response in depressed MS patients.¹¹

Methods. Sample selection. Depressed group. A consecutive sample of patients with clinically definite MS attending an outpatient clinic were screened for the presence of depression using the self-report Hospital Anxiety and Depression Rating Scale.¹² All patients with a score of ≥10, the designated cut-off for clinically significant depression, were then interviewed with the Mood Disorder Section of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) to establish a diagnosis of major depression.¹³ This in-depth interview can be used to generate current and lifetime estimates of mental illness. The DSM-IV requires the presence of five of nine possible symptoms of depression. For the purpose of this MS study, the fatigue question was removed from the analysis, given the virtually ubiquitous nature of this symptom in MS patients, thereby strengthening the diagnostic validity of major depression (i.e., the presence of five of eight symptoms).
Furthermore, a set of exclusion criteria were applied to those MS subjects with major depression to remove those in whom depression may have been a chance co-morbid diagnosis. Thus, subjects with a premorbid history of psychiatric illness (including depression), traumatic brain injury, past or current history of substance abuse, family history of mood disorder, and co-existing medical conditions were excluded. Given that the methodology of the study was dependent on MRI-detectable brain changes, depressed subjects on disease-modifying drugs (the interferons) were also ruled out because of the propensity for the medication to reduce lesion burden. An additional reason for excluding these patients was the potentially deleterious effects of such treatment on MRI. Similarly, patients who had been on steroid treatment during the last 3 months were excluded. A sample of 21 MS patients with major depression meeting these criteria were selected.

Nondepressed group. Nineteen nondepressed MS subjects were also chosen to ensure the two groups did not differ with respect to the following demographic and disease variables: age, gender, duration of MS, disease course, and exacerbations and physical disability as defined by the Expanded Disability Status Scale. The matching process was not pairwise but rather based on group profiles. The nondepressed subjects were also screened for the absence of a past history of mood or substance disorder, a history of traumatic brain injury, and a family history of mood disorder. Similarly, if nondepressed patients were taking disease-modifying drugs or steroids (the latter in the last 3 months), they were excluded.

Cognitive testing. Subjects from both groups underwent cognitive assessment with the Brief Repeatable Neuropsychological Battery. This brief cognitive battery, developed specifically for MS patients, has been widely used and is considered a valid and reliable indicator of cognitive dysfunction in MS patients. It consists of four tests: the Controlled Oral Word Association Test (COWAT), the Paced Auditory Serial Addition Task (PASAT), an abbreviated form (12-word and 6-recall trials) of the Consistent Long-Term Retrieval (CLTR) from the Selective Reminding Test, and the 7/24 Spatial Recall Test. These measures probe verbal fluency (COWAT), sustained attention (PASAT), and recent verbal (CLTR) and nonverbal (7/24) memory and are considered among the most sensitive indexes of cognitive decline in MS patients. According to testing protocol, performance on two or more tests below the 5th percentile is indicative of cognitive impairment.

MRI protocol. Scanning. All methods described in this article were developed on images acquired on a 1.5 T Sigma scanner (GE Medical Systems, Milwaukee, WI). These images include a T1-weighted acquisition (axial three-dimensional spoiled gradient echo sequence with a 5-millisecond echo time [TE], 35-millisecond repetition time [TR], 1 excitation, 35° flip angle, 22 × 22 × 16.5–cm field of view, 0.859 × 0.859–mm in-plane resolution, and 1.2–mm slice thickness) and a proton density acquisition (interleaved axial spin echo with TE of 30 and 80 milliseconds, 3-second TR, 0.5 excitation, 22 × 22–cm field of view, 0.859 × 0.859–mm in-plane resolution, and 3-mm slice thickness).

Lesion analysis. MR images were processed on a Sun computer workstation (Palo Alto, CA) using the ANALYZE AVW 6.0 software package (Biomedical Imaging Resonance, Mayo Clinic, Rochester, MN). Lesions were semiautomatically traced based on intensity thresholds. Hyperintense lesions were traced on proton density/T2-weighted images, and hypointense lesions were traced on T1-weighted images. Lesions <3 mm in diameter were excluded from analysis. The measurement technique used was a “high intrarater” (intraclass correlation coefficient [ICC] = 0.98) and interrater (ICC = 0.99) reliability on a sample of 20 brains that were not part of the study sample.

Tissue segmentation. This was accomplished using two in-house protocols. The first protocol generated an intracranial cavity mask (brain extraction), and the second performed automatic segmentation into three tissue types: gray matter (GM), white matter (WM), and CSF. For brain extraction, an automatic segmentation algorithm classified all voxels into either brain or non-brain matter, using the proton density and T2-weighted images. A small amount of manual editing was used as necessary to remove nonbrain tissues such as eyes. The T1-weighted image was then masked and segmented. The segmentation algorithm was fixed to that used in a previous study and fitted four Gaussian curves to local intensity histograms to derive cut-offs to classify each voxel as CSF, GM, or WM.

Regional analysis. Regional brain analysis was based on the Talairach proportional grid system, which served as the foundation for the semiautomatic parcellation of each brain into 13 regional volumes of interest per hemisphere. The regional boundaries were delineated using a combination of predefined proportional co-ordinate positions (see below): the three orthogonal planes of the Talairach system, the edges of the brain, and four user-defined points on each brain (i.e., central sulcus, Sylvian fissure, occipital and parietal sulci). The optimal co-ordinate positions for the predefined boundaries were derived by hand-tracing boundaries on 10 brains and using the co-ordinate positions that produced the largest concordance across the images. The interrater reliability of the method varied between an ICC of 0.93 and 0.97, depending on the region. The use of the proportional grid system to obtain the regional volumes reduced the impact of head size variability. Thus, segmentation results for each region were normalized by expressing them as a proportion of the regional volume. For purposes of this report, atrophy was defined based on the percentage CSF in each region.

The brain regions demarcated were as follows: medial superior frontal, lateral superior frontal, medial inferior frontal, lateral inferior frontal, medial orbitofrontal, lateral orbitofrontal, anterior temporal, posterior temporal, anterior basal ganglia, posterior basal ganglia, superior parietal, inferior parietal, and occipital (figure).

Statistical analysis. In the primary analysis, between-group comparisons were undertaken using two t-tests for normally distributed data, Mann–Whitney U tests for nonparametric continuous data, and χ² analyses (with Yates correction) for ordinal data. For statistical comparisons, a was set at 0.01.

In the secondary analysis, MRI predictors of depression were sought with a stepwise logistic regression (forward selection). To limit the number of potential predictor variables, only those MRI values from anatomic areas in which differences had been found between depressed and nondepressed subjects in the primary analysis were entered into the regression analysis. Significance was set at p ≤ 0.05 for variable entry into the equation.

Results. The depressed and nondepressed MS groups did not differ on any demographic or disease-related variables (table 1). In addition, there were no between-group cognitive differences on the Brief Repeatable Battery of Neuropsychological Tests with respect to either a global
estimate of impairment or any of the four specific cognitive indexes (table 2).

MRI brain comparisons revealed depressed patients had more extensive hyperintense \( (t|df = 38| = 3.3, p = 0.003) \) and hypointense \( (t|df = 38| = 2.6, p = 0.01) \) lesions in the left medial inferior frontal region and less GM volume \( (t|df = 38| = -2.5, p = 0.01) \) and a greater CSF volume in the left anterior temporal region \( (t|df = 38| = 4.0, p = 0.005) \). Depressed subjects did not, however, have a greater total lesion load, nor did they show greater total WM and GM volume loss. Furthermore, no regional differences were present between the groups in any of the remaining 11 brain regions.

The degree to which these brain abnormalities contributed to the development of major depression was explored using a logistic regression model. Two left-sided brain areas were found to be significant independent predictors of major depression. They were the left medial inferior frontal hyperintense lesion load and the left anterior temporal CSF volume (an index of regional cerebral atrophy), which accounted for 42% of the variance when it came to explaining the presence of major depression.

**Discussion.** The essential findings in our study are that MS patients who are depressed have more hyperintense lesions in left inferior medial frontal regions and greater atrophy of left anterior temporal regions. The depressed and nondepressed groups were matched on disease and demographic characteristics. By demonstrating that almost half the variance in the diagnosis of depression is directly attributable to brain pathology, the data extend findings from previous MS studies and provide more compelling evidence of a direct brain–mood relationship in patients with MS.

In a study that focused exclusively on hyperintense lesions, it was reported that lesions in the arcuate fasciculus accounted for only 17% of the depression variance score. This would overlap with our data had we, too, confined our analysis to this one imaging index. However, cerebral pathology in MS patients is not limited to WM lesions but may also involve cortical lesions and atrophy. Furthermore, it has been noted that there is an association

### Table 1 Demographic and disease-related comparisons between depressed (n = 21) and nondepressed (n = 19) MS patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Depressed MS group, n = 21</th>
<th>Nondepressed MS group, n = 19</th>
<th>t-test/( \chi^2 )</th>
<th>Significance, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD), y</td>
<td>46.4 (9.6)</td>
<td>48.3 (6.3)</td>
<td>( t</td>
<td>df = 38</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>4/17</td>
<td>5/14</td>
<td>( \chi^2 = 0.7 ) (Fisher exact)</td>
<td>0.7</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>( \chi^2 (</td>
<td>df - 2</td>
</tr>
<tr>
<td>Single</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>15</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (SD), y</td>
<td>9.9 (7.6)</td>
<td>10.6 (4.9)</td>
<td>( t</td>
<td>df = 35.9</td>
</tr>
<tr>
<td>Disease course</td>
<td></td>
<td></td>
<td>( \chi^2 (</td>
<td>df - 2</td>
</tr>
<tr>
<td>RR</td>
<td>8</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS (SD)</td>
<td>4.7 (1.9)</td>
<td>4.6 (1.3)</td>
<td>( t</td>
<td>df = 38</td>
</tr>
</tbody>
</table>

MS = multiple sclerosis; RR = relapsing remitting; PP = primary progressive; SP = secondary progressive; EDSS = Expanded Disability Status Scale; df = degrees of freedom.

### Table 2 Cognitive comparisons between depressed (n = 21) and nondepressed (n = 19) MS subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Depressed MS group, n = 21</th>
<th>Nondepressed MS group, n = 19</th>
<th>t-test/( \chi^2 )</th>
<th>Significance, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cognitive</td>
<td>7 (33.3%)</td>
<td>4 (21.1%)</td>
<td>( \chi^2 (</td>
<td>df - 2</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLTR</td>
<td>26.1 (16.6)</td>
<td>32.6 (18.0)</td>
<td>( t</td>
<td>df = 38</td>
</tr>
<tr>
<td>7/24 Recall</td>
<td>28.7 (7.2)</td>
<td>30.1 (6.9)</td>
<td>( t</td>
<td>df = 38</td>
</tr>
<tr>
<td>PASAT</td>
<td>26.0 (12.6)</td>
<td>31.3 (7.9)</td>
<td>( t</td>
<td>df = 38</td>
</tr>
<tr>
<td>COWAT</td>
<td>36.3 (14.3)</td>
<td>32.2 (13.1)</td>
<td>( t</td>
<td>df = 38</td>
</tr>
</tbody>
</table>

Numbers in parentheses for CLTR, 7/24 Recall, PASAT, and COWAT indicate the number of correct responses. MS = multiple sclerosis; CLTR = Controlled Long-Term Retrieval Task; 7/24 = Spatial Recall Test; PASAT = Paced Auditory Serial Addition Test (number correct); COWAT = Controlled Oral Word Association Test (total words generated).
between depression and cortical atrophy in MS patients, a finding that our data also replicated. Our results indicate that the combined influence of two indexes of pathology, that is, T2-weighted hyperintensities plus regional cortical atrophy, was critical in determining the presence of major depression. The strength of this relationship likely arose because depressed and nondepressed groups were carefully matched on demographic and disease-related variables. In addition, we excluded MS patients whose history of depression predated the onset of MS (thereby reducing the possibility of a chance co-morbidity), adhered to DSM-IV diagnostic criteria for depression, with fatigue removed as a potential confounder, combined tissue segmentation and regional masking, and controlled for cognitive dysfunction between the groups. Failure to address the latter, given robust cognitive–MRI correlates, could either negate significant between-group differences or misleadingly skew the result in favor of greater brain pathology in the depressed cohort.

Whereas our data bring together different, albeit significant, results from two earlier studies, not all inconsistencies have been resolved. Our lesion localization to the left medial inferior frontal regions does not overlap with a report citing the arcuate fasciculus as the pivotal brain region, whereas the presence of left anterior temporal lobe atrophy in depressed subjects falls short of temporal, frontal, and parietal atrophy noted by others. Furthermore, although we did find differences between depressed and nondepressed groups in terms of regional hypointense lesion volume, as others have, this variable did not emerge in our study as an independent predictor of depression. Reasons for these inconsistencies are most likely due to differences in sensitivity of the methodologies used for brain analysis in the previous studies and variability in patient recruitment.

Our conclusion that frontal brain regions are pivotal in mood regulation is not without controversy. Support has come from functional imaging studies in Parkinson and Huntington diseases that revealed depression was associated with hypoperfusion affecting the orbital inferior prefrontal cortex. In stroke patients, a specific connection between left frontal cortical lesions has also been reported and replicated, although a recent meta-analysis of stroke data challenges this view, citing selection bias as a major confounder. Although acknowledging this concern (our study screened close to 300 subjects to satisfy our stringent exclusion criteria), our data fit with current neural hypotheses explaining the pathogenesis of depression. What may therefore link depression in a disparate set of neurologic disorders is a disruption in neural circuits originating in the prefrontal cortex and then sequentially relaying in the striatum, globus pallidus, and thalamus, before looping back to its prefrontal site of origin. Three such discrete circuits have been identified, one of which, the medial orbitofrontal circuit, is considered important in mood regulation. This circuit traverses medial inferior frontal brain areas where increased pathology in our MS sample differentiated depressed from nondepressed subjects. We postulate that a combination of inflammation, demyelination (hyperintense lesions), and atrophy within medial inferior frontal areas would disconnect neural connectivity with an associated perturbation in several neurotransmitters and modulators known to be involved in frontal subcortical circuits, of which the monoamines are most intimately tied to disorders of mood.

Our finding that pathology within the anterior temporal lobe was also a predictor of depression is not incompatible with the above model. A PET study comparing depressed and nondepressed stroke patients with single lesions of the basal ganglia restricted to the caudate nucleus noted hypometabolism in a number of limbic regions. These included the medial inferior cortex and anterior cingulate cortex, but the most marked differentiation between depressed and nondepressed patients was present in the anterior temporal cortex. Lesions within the basal ganglia leading to alterations in temporal lobe blood flow thus illustrate that there are both open and closed aspects to the frontal subcortical circuits. It is in the former that projections to and from limbic association areas within the temporal lobes have the potential to influence mood. A comprehensive review of neuroimaging data in patients with depression secondary to neurologic disease emphasizes this point.

Whether this model can be applied to MS patients with subthreshold major depression cannot be answered here, although the question raises further intriguing hypotheses. Subthreshold depression, or a constellation of depressive symptoms insufficient to meet syndromal criteria for major depression, is very common in MS patients and represents a significant source of morbidity. Given the degree of symptom overlap with major depression, it is plausible to speculate that the posited disconnection in the open frontal subcortical circuits with their afferent and efferent connections to temporal lobe limbic areas may not be as marked in the subsyndromal group. This threshold hypothesis, linking the severity of mood change to the severity of cerebral dysfunction, deserves further exploration.

Although our data establish a firmer link between depression in MS patients and the degree and location of cerebral pathology, >50% of the depression variance score remained unaccounted for. Possible reasons for this include the fact that structural MRI can, at best, provide only part of the equation in brain–behavior relationships. Other MRI modalities focusing on normal-appearing WM, such as magnetization transfer and diffusion-weighted imaging, offer the possibility of an enhanced understanding of brain changes linked to depression. In addition, the search for brain correlates of low mood is likely to defy a reductionist approach. MS is a disease of the young and middle aged. It can cause devastating physical disability, is without cure, and its course is
difficult to predict—all reasons enough to precipitate and perpetuate depression. It is therefore not surprising that an association, perhaps bidirectional, has been noted between depression in MS and degrees of coping ability, physical disability, uncertainty over the future, loss of recreational activities, perceived levels of social support, disease exacerbations, and levels of stress. Of note is that one study that factored in many of these variables reported that disability, uncertainty, hope, and coping accounted for 40% of the depression variance, a figure that, when viewed alongside our imaging data, provides a more encompassing explanation for the high rates of depression in MS patients.

Acknowledgment

The authors thank Dr. Jill Fisher for helpful comments.

References

Structural brain abnormalities in multiple sclerosis patients with major depression
Neurology 2004;62;586
DOI 10.1212/01.WNL.0000110316.12086.0C

This information is current as of April 15, 2013

Updated Information & Services
including high resolution figures, can be found at:
http://www.neurology.org/content/62/4/586.full.html

References
This article cites 38 articles, 13 of which can be accessed free at:
http://www.neurology.org/content/62/4/586.full.html#ref-list-1

Citations
This article has been cited by 21 HighWire-hosted articles:
http://www.neurology.org/content/62/4/586.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Depression
http://www.neurology.org/cgi/collection/depression
MRI
http://www.neurology.org/cgi/collection/mri
Multiple sclerosis
http://www.neurology.org/cgi/collection/multiple_sclerosis

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/addir.xhtml#reprintsus

AMERICAN ACADEMY OF NEUROLOGY®