Depression in MS: Is brain imaging helpful?

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Disclosures

- MS Society of Canada
- Canadian Institute of Health Research
- Biogen
- Teva, Merck-Serono, Novartis
Aims

• To appreciate the structural brain changes that can occur in depressed MS patients.
• To understand some of the functional brain changes linked to alterations in mood.
• To appreciate how the structural brain changes linked to depression differ from those seen in pseudobulbar affect

Is brain imaging helpful in assessing depression in MS?
MRI: lesion change over time

- MRI with Gd every two weeks
- 6 months of scanning
- > 90 new lesions
- Little change in physical disability
- 5 secs = 1 week in the patient’s life

Acknowledgement: Prof. W. I. McDonald et al: Institute of Neurology, Queen Square

Major Depression
Prevalence

- lifetime prevalence in patients attending MS clinics approaches 50%
- However, prevalence is also raised in a community based sample.
  - In a study of 115,071 Canadians, the 12 month prevalence of depression in MS patients exceeded that in healthy subjects (odds ratio: 3.4)
  - In subjects ages 18-45 years, the 12 month prevalence was 25.7%.
- Rates increased in relation to other neurological disorders.
Major Depression
Diagnostic criteria

- Five or more of the following during the same two week period:
- Depressed mood most of the day
- Markedly diminished interest or pleasure in all activities
- Appetite change with significant weight loss, or weight gain
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation (observable by others)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness, excessive, inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death

Rating scales
Etiology of depression

MS, depression and brain imaging

Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis

J. Pojol, MD; J. Bello, MD; J. Duenas, PhD; J.L. Marti-Vila, MD; and A. Capdevila, MD

Abstract—Depression is a common mood disturbance in multiple sclerosis (MS) patients. Epidemiologic data suggest a causative relationship between depressive symptoms and cerebral demyelination, although a specific lesion site responsible for depressed mood has not been identified. Given that depression in neurologic disease is closely related to frontal and temporal lobe damage, we focused our study on investigating the extent to which lesions in the white matter connecting both cortical lobes may account for depressive symptoms in MS. Forty-five patients were assessed using the Beck Depression Inventory and an MRI protocol consisting of quantitative images separately in the basal, medial, and lateral frontotemporal white matter. The presence of lesions in the left supramarginal white matter, the region that mainly includes the arcuate fasciculus, was specifically associated with depressive symptoms, accounting for a significant 17% of the depression score variance. Although a multifactorial origin is suspected for depression in MS, this finding gives support to the existence of a direct negative effect of demyelination on mood.
Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis.

Pujol, J; Bello, J; Deus, J; Martí-Vilalta, J; Capdevila, A


Figure 1. Sagittal reformatted images (left in A, B, and C) showing the level and extent of the three different white matter regions considered in the axial analysis (basal [A], periventricular [B], and lateral [C]), and representative proton density axial images (right in A, B, and C) on which lesion measurements were performed.

Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis.

Pujol, J; Bello, J; Deus, J; Martí-Vilalta, J; Capdevila, A


Figure 3. Plot of Beck scores with coronal lesion areas of the left arcuate fasciculus region. Although the relationship was significant ($r = 0.43$, $p = 0.002$), high depression scores were registered in patients with no lesions in this region.
Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis.
Pujol, J; Bello, J; Deus, J; Martí-Vilalta, J; Capdevila, A

Figure 4. (A-F) Representative coronal inversion-recovery images of the six patients with the highest lesion scores of the left arcuate fasciculus region. Note that the bulk of the left arcuate fasciculus was substantially damaged in each case (arrow). L = left; R = right; IP = inferoposterior; IA = inferoanterior.

MS, Depression and MRI changes

Structural brain abnormalities in multiple sclerosis patients with major depression
A. Feinstein, FRCP; P. Roy, MS; N. Lobaugh, PhD; K. Feinstein, MA; P. O'Connor, FRCP; and S. Black, FRCP

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 with current-defined major depression and 19 without. The groups did not differ on demographic, illness, 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 ($p = 0.009$) and more extensive T2-weighted lesion volume in the left superior frontal periventricular cortex ($p = 0.01$) and less gray matter volume ($p = 0.01$) and more CSF volume in the left anterior temporal region ($p = 0.000$). A logistic regression analysis identified two independent predictors of depression: left medial temporal periventricular T2 lesion volume and left anterior temporal CSF volume. These variables accounted for 42% of the depression variance. Conclusions: Whether both lesion burden and atrophy are important in the ambivalence of depression in MS, environmental influences should also be considered.
Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients

A Feinstein, P O’Connor, N Akbar, L Moradzadeh, CJM Scott and NJ Lobaugh
MS, Depression, brain parcellation

Figure 1. Magnetic resonance imaging sagittal view demarcating medial brain regions using Semi-Automated Brain Region Extraction. ABG/T, anterior basal ganglia/thalamus; AT, anterior temporal; IF, inferior frontal; MIF, medial inferior frontal; MOF, medial orbitofrontal; MSF, medial superior frontal; O, occipital; PBG/T, posterior basal ganglia/thalamus; PT, posterior temporal; SF superior parietal.

MS, Depression, diffusion tensor imaging

Figure 2. Depression produces ultra-structural alterations (UA) and non-diffuse (ND) from normal appearing brain tissue (NABT) and normal appearing (NA) white matter (WM). (A) NA-GM parcellation according to the normal appearing brain region (NABR) method. (B) ND images: (a) parcellation according to the normal appearing brain region (NABR) method; (b) NA-GM images; (c) ND images; (d) ND-GM overlap.
MS, Depression, lesions, atrophy, DTI

Figure 4. Differences in regional lesion and atrophy volumes between depressed (n=19) and non-depressed (n=32) patients with multiple sclerosis. BDI, Beck Depression Inventory.

<table>
<thead>
<tr>
<th>MRI variables</th>
<th>Percentage variance</th>
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<tbody>
<tr>
<td>Lesions + atrophy</td>
<td>23.7%</td>
</tr>
<tr>
<td>Lesions + atrophy + regional DTI indices (MD of NAGM and FA of NAWM)</td>
<td>35.1%</td>
</tr>
<tr>
<td>Lesions + atrophy + regional DTI indices (MD of NAGM and FA of NAWM + MD of right inferior frontal lesions)</td>
<td>43.6%</td>
</tr>
</tbody>
</table>
The importance of the hippocampus

Smaller Cornu Ammonis 2–3/Dentate Gyrus Volumes and Elevated Cortisol in Multiple Sclerosis Patients with Depressive Symptoms

Gold et al, Biological Psychiatry 2010, 68, 553-9
Hypothalamic–pituitary–adrenal axis dysregulation in patients with comorbid relapsing–remitting multiple sclerosis (RRMS) and major depressive disorder (MDD).

From: Mood Disorders and Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis in Multiple Sclerosis: Association With Cerebral Inflammation

Figure Legend:
Mean±SEM scores on depression and anxiety scales for patients with multiple sclerosis (MS) with and without gadolinium-enhancing MS plaques. HRSD indicates Hamilton Rating Scale for Depression; SDS, Zung Self-Reporting Depression Scale; HRSA, Hamilton Rating Scale for Anxiety; and SASS, Zung Self-Reporting Anxiety Scale. Asterisk indicates P<.05; dagger, P<.01.
Figure Legend:
Mean ± SEM serum levels of cortisol in patients with multiple sclerosis (MS) with and without gadolinium enhancement of MS plaques.

Processing emotions in MS
(patients without Major Depression and PBA excluded)

### MS, Depression and brain imaging: summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Imaging modality</th>
<th>Number of subjects</th>
<th>Ratings Scale</th>
<th>Clinical diagnosis</th>
<th>Imaging findings</th>
<th>Laterality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolatsis, U. et al.</td>
<td>1996</td>
<td>SPECT</td>
<td>N=20 (10 depressed &amp; 10 non depressed)</td>
<td>DSM-III</td>
<td>Major depression</td>
<td>Increased perfusion in frontier areas.</td>
<td>Left</td>
</tr>
<tr>
<td>P剿, J. et al.</td>
<td>2000</td>
<td>MRI</td>
<td>N=47</td>
<td>RCT-B</td>
<td>None</td>
<td>Increased 12 lesion in the anterior thalamus associated with aminergic and efferent system.</td>
<td>Left</td>
</tr>
<tr>
<td>Fischeder, K. et al.</td>
<td>1998</td>
<td>MRI + Gal</td>
<td>N=33 (23 RBDMS, 10 healthy control group, 10 non depressed)</td>
<td>DSM-III-R, RCT-B, RCT-D</td>
<td>Major depression</td>
<td>Increased 4G+ lesions linked to increased cortisol and a positive autonomic suppression test.</td>
<td>None reported</td>
</tr>
<tr>
<td>Hatai, R. et al.</td>
<td>2000</td>
<td>MRI</td>
<td>N=40 (19 depressed &amp; 21 non depressed)</td>
<td>DSM-III-R</td>
<td>Major depression</td>
<td>Superior frontal, superior parietal and temporal 11 lesions, lateral and third ventricular enlargement, frontal atrophy.</td>
<td>Left</td>
</tr>
<tr>
<td>Hasegawa, D. et al.</td>
<td>2000</td>
<td>MRI</td>
<td>N=78</td>
<td>DSM-III-R</td>
<td>Major depression</td>
<td>Increased 12 lesion in whole brain, parietal and frontal lobe and the cingulum.</td>
<td>Right</td>
</tr>
<tr>
<td>Fischeder, A. et al.</td>
<td>2004</td>
<td>MRI</td>
<td>N=49 (21 depressed &amp; 21 non depressed)</td>
<td>DSM-III-R</td>
<td>Major depression</td>
<td>T2 and T1 lesions volume in medial inferior prefrontal cortex, anterior temporal atrophy.</td>
<td>Left</td>
</tr>
<tr>
<td>Fu et al., L. et al.</td>
<td>2005</td>
<td>SPECT</td>
<td>N=20 (15 MS subjects, 5 healthy control subjects)</td>
<td>None</td>
<td>None</td>
<td>Reduced fractional connectivity between ventral and prefrontal cortex.</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Ueda, S.M. et al.</td>
<td>2018</td>
<td>DTI</td>
<td>N=49</td>
<td>None</td>
<td>None</td>
<td>Hippocampal atrophy particularly in CA1-3 and dentate gyrus linked to increased cortisol.</td>
<td>Left</td>
</tr>
<tr>
<td>Fischeder, A. et al.</td>
<td>2018</td>
<td>MRI plus DTI</td>
<td>N=45 (25 depressed, 20 non depressed)</td>
<td>SPECT-B</td>
<td>None</td>
<td>Increased T1 lesion in right medial inferior frontal region, atrophy of left superior frontal region, lesion T5; higher MD in left superior temporal non-dominant white and gray matter; higher MD at right inferior frontal superior striae.</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Ueda, S.M. et al.</td>
<td>2018</td>
<td>MRI</td>
<td>N=109 (healthy only)</td>
<td>GE-B</td>
<td>None</td>
<td>Reduced hippocampus thickness.</td>
<td>Right</td>
</tr>
</tbody>
</table>

### Psychosocial causes of depression

- From the journal: *June 15, 1917.*
  - I sit all day in my chair, moving 8 feet to my bed at night, and 8 feet from it to my chair in the morning—and wait. The assignment is certain.

- From the journal: *October 3, 1918.*
  - I am grateful to-day for some happy hours plucked triumphantly from under the very nose of Fate, and spent in the warm sun in the garden... A Lark sang... I sat by some Michaelmas Daisies and watched the Bees, Flies and Butterflies.
Depression
Psychosocial etiology

- Uncertainty (Lynch et al, 2001)
- Inadequate coping strategies (Mohr et al, 1997; Pakenham et al, 1997; Aikens et al, 1997; Jean et al, 1997; Pakenham 1999)
- Helplessness (Shnek et al, 1997; Patten et al, 2002; van der Werf, 2003)
- Poor social relationships (Maybury and Brewin, 1984)
- Loss of recreational activities (Voss et al, 2002)
- High levels of stress (Patten et al, 2000)
- Fatigue (Lobentanz et al, 2004)

Treating Major Depression:
Medication

- Only Two RCTs
- Desipramine (tricyclic antidepressant)
- Paroxetine (SSRI)
- Medication effective
- Side effects troubling: anticholinergic problems
  - Dry mouth
  - Constipation
  - Sedation
  - Blurred vision
  - Sexual difficulties
Stress management

- 24 weeks of treatment
- Less Gd+ lesions
- Less cumulative lesion load
- Effects not sustained beyond 24 weeks
- No clinical benefits, including mood

MRI can predict response to depression treatment

Abstract

This study examined the effects of brain lesions and neuropsychological impairments on the efficacy of treatment for depression in patients with comorbid diagnoses of multiple sclerosis (MS) and major depressive disorder (MDD). Thirty patients meeting criteria for MS and MDD received 1 of 3 16-week treatments for depression and were followed for 6 months following treatment cessation. T2-weighted magnetic resonance imaging and neuropsychological evaluations were also obtained. End-of-treatment Beck Depression Inventory (BDI) A. T. Beck, D. H. Ward, M. Mendelson, J. Mock, & J. Erbaugh, 1961 results resubmitted for baseline BDI were related to right temporal periventricular lesion volume (R2 = .32, p < .002) and left temporal gray-white junction lesion volume (R2 = .19, p < .02) but were not statistically related to lesion volume in any other brain region or to neuropsychological function. BDI results at 6-month follow-up, resubmitted for end-of-treatment BDI, were predicted by total lesion volume (R2 = .22, p < .005), lesion volume in many discrete areas, and neuropsychological functioning (R2 = .30, p < .000). The effect of total lesion volume on 6-month follow-up BDI results was fully mediated by neuropsychological function.
Pathological laughing and crying

(Pseudobulbar affect)

- Crying without sadness
- Laughter without happiness (mirth)
- Up to 10% of MS patients affected to various degrees

Prevalence and Neurobehavioral Correlates of Pathological Laughing and Crying in Multiple Sclerosis

Audrey Kempton, PhD; M. Debra Fonknechten, MD; Kermit Gray, MD; Paul O'Connor, MD

Objectives: To establish the prevalence of pathological laughing and crying in Multiple Sclerosis (MS). To define associated neurologic, emotional, and cognitive correlates of PCL.

Design: A consecutive sample of 155 patients with clinically definite or laboratory supported MS was screened for PCL. All subjects had an MRI and neuropsychological assessment (Montreal Cognitive Assessment, Brief Examination of Attention, and Stroop Color-Word Test). Depression was screened with the Beck Depression Inventory, Anxiety with the Fear Survey Schedule, and Quality of Life with the Multiple Sclerosis Quality of Life-54 scale. Crying and mirth were assessed with the Presence of Pathological Crying and Mirth Scale.

Results: The prevalence of PCL was 31.3%. Patients with MS had higher scores on the Brief Examination of Attention, Stroop Color-Word Test, and Fear Survey Schedule than controls. The presence of PCL was significantly correlated with depression, anxiety, and lower quality-of-life scores.

Conclusions: Pathological laughing and crying are frequent in MS. Patients with MS, in contrast to controls, are more likely to demonstrate pathological laughing and crying. This observation suggests a role for depression, anxiety, and quality of life in the development of pathological laughing and crying in MS.

Arch Neurol. 1997;54(6):626-632
Pseudobulbar affect in MS: an MRI study

- Two groups of MS subjects
- PBA versus normal mood/affect change (n=14 for each group).
- All underwent neurological examination, cognitive testing (BRNB) and detailed MRI scanning

Ghaffar et al. (2008) J. Neurology

PBA associated with more lesions in the following areas:

<table>
<thead>
<tr>
<th>Region</th>
<th>Sig.</th>
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<tbody>
<tr>
<td>Global lesion volume</td>
<td>T2</td>
</tr>
<tr>
<td>Brain stem</td>
<td>T1</td>
</tr>
<tr>
<td>Medial inferior frontal L</td>
<td>T2</td>
</tr>
<tr>
<td>Medial inferior frontal R</td>
<td>T2</td>
</tr>
<tr>
<td>Medial superior frontal R</td>
<td>T2</td>
</tr>
<tr>
<td>Inferior parietal L</td>
<td>T2</td>
</tr>
<tr>
<td>Inferior parietal R</td>
<td>T2</td>
</tr>
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MRI regions

Pseudobulbar Affect: Associated With Lesions at Various Locations
Major Depression and Pathological Laughing and Crying: Comparison of MRI variance

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<tbody>
<tr>
<td>Major Depression</td>
<td>40%</td>
</tr>
<tr>
<td>Pathological laughing and crying</td>
<td>~ 75%</td>
</tr>
</tbody>
</table>

Pseudobulbar affect

- **R**:
  - low dose amitriptyline
  - SSRI
  - levodopa and amantadine
  - Neudexta (dextromethorphan/quinidine)

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<tr>
<td>Response to treatment in PBA</td>
<td>48-72 hours</td>
</tr>
<tr>
<td>Response to treatment in major depression</td>
<td>10-14 days</td>
</tr>
</tbody>
</table>
Treatment of PBA

Randomized, Controlled Trial of Dextromethorphan/Quinidine for Pseudobulbar Affect in Multiple Sclerosis

Hild S. Piro, MD,1 Bernard A. Thalheim, PhD,2 Richard A. Smeed, MD,3 Daniel R. Wyner, MD,4 James P. Wyman, MD, PhD5 Anne Albinson, MD, PhD6 Timmery L. Yeffner, MD7 Paul N. Maizlis, MD8 Denise W. Daniels, MD9 Melissa Fletcher, LECOP, MRCSc,9 Laura R. Pope, PhD,10 James E. Eng, BA11 and Axel Miller, MD, PhD,12 for the Pseudobulbar Affect in Multiple Sclerosis Study Group

Objective: To evaluate the efficacy and safety of DMPQ (dextromethorphan/quinidine) and placebo (P) capsules in patients with pseudobulbar affect in multiple sclerosis.

Methods: A total of 120 patients were randomized in a double-blind, placebo-controlled study to receive dextromethorphan capsules with the standard care for multiple sclerosis or placebo capsules with standard care for multiple sclerosis. Each patient received 2 capsules of dextromethorphan or placebo daily for 12 weeks. The primary outcome measure was the total score on the Pseudobulbar Affect Questionnaire (PAQ), which was assessed at baseline and at each visit. A secondary outcome measure was the total score on the Multiple Sclerosis Impact Scale (MSIS-29), which was assessed at baseline and at each visit. A third outcome measure was the total score on the Multiple Sclerosis Quality of Life Inventory (MSQOL-54), which was assessed at baseline and at each visit. All secondary outcome measures were analyzed using an analysis of variance (ANOVA) model with treatment and visit as factors. The results were significant at the 0.05 level.

Data: The results were significant at the 0.05 level for all secondary outcome measures. The results were also significant at the 0.05 level for the primary outcome measure. The results were also significant at the 0.05 level for the secondary outcome measures. The results were also significant at the 0.05 level for the tertiary outcome measures. The results were also significant at the 0.05 level for the quaternary outcome measures.

Conclusions: DMPQ capsules are effective in reducing pseudobulbar affect in patients with multiple sclerosis. The results were also significant at the 0.05 level for the quinary outcome measures. DMPQ capsules may be beneficial in reducing pseudobulbar affect in a variety of neurological disorders.

Ann Neurol. 2006;59:760–767

Is brain imaging helpful in assessing depression in MS?
Acknowledgments

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