Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS

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Article abstract—Objective: To study the association between the cortical cerebral metabolic rate of glucose (CMRglc), MRI T2-weighted total lesion area (TLA), cognitive dysfunction, and neurologic disability in MS. Background: MRI lesion load is widely used in the clinical evaluation of the MS patient but little is known about the associated changes in cortical activation. Methods: Twenty-three patients with clinically definite MS underwent measurements of CMRglc, TLA, motor evoked potentials (MEPs), and cognitive and neurologic disability. CMRglc was calculated using PET and 18-F-deoxyglucose and compared with nine normal control subjects. Results: Reductions in CMRglc ($p < 0.01$) were found in the cortical global and regional lobar measurements. Furthermore, regional CMRglc ($r$CMRglc) was reduced in the dorsolateral prefrontal cortex, orbitofrontal cortex, caudate, putamen, thalamus, and hippocampus. Global cortical CMRglc correlated with TLA (Spearman rank correlation coefficient [SRCC] $= -0.66$, $p = 0.001$), and $r$CMRglc correlated with regional lesion load in all cerebral lobes ($p \leq 0.05$). Global cortical CMRglc and cognitive disability also correlated (SRCC $= 0.58$, $p = 0.015$), and stepwise regression analysis showed a significant association between $r$CMRglc of the right thalamus and cognitive performance as well as TLA. There was no correlation between CMRglc and neurologic disability (Expanded Disability Status Scale) or MEP. Conclusion: Global and regional cortical CMRglc is reduced significantly in MS patients compared with normal control subjects. Furthermore, the CMRglc reductions correlate with TLA as well as with cognitive dysfunction, which indicates that MRI white matter lesion burden has a deteriorating effect on cortical cerebral neural function. Key words: MS—PET—MRI—Cognitive dysfunction—Disability—Motor evoked potential.

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White matter hyperintensities (WMH) on T2-weighted MR images are regarded as a sensitive measure of MS-related pathologic cerebral changes, and are widely used in clinical trials to monitor disease progression. Still, the association between isolated WHM and corresponding neurologic deficits is often poor, and the correlation between total lesion area (TLA) and physical disability is weak or moderate. MRI measurements such as T1 “black holes” and magnetization transfer ratios of normal-appearing white matter, as well as spinal cord and cerebral atrophy, have shown a stronger correlation with clinical symptoms, which indicates that focal as well as diffuse pathologic changes determine the clinical impact of the disease. Although these data question the clinical value of T2-weighted lesion load, a consistent relationship has been shown between TLA and cognitive dysfunction.

Similar conclusions have been reported in functional imaging studies, showing an association between measures of global cerebral activation and cognitive dysfunction, where the most pronounced reductions have been detected in the frontal lobes, whereas isolated memory deficits are related to metabolic changes in the basal frontal as well as the hippocampal regions. Controversy still exists about the association between clinical disability and cerebral metabolic rate of glucose (CMRglc) because reports have reached different conclusions.

MRI and emission tomographic studies thus show converging results, and a direct relationship would therefore be expected, although a previous study was not able to draw this conclusion. In our opinion the question needed additional investigation. Therefore we tested the hypothesis that lesions on T2-weighted MRI reflect pathologic processes that cause neural dysfunction, corresponding to metabolic reductions measured by PET. In addition we investigated the correlation between cortical metabolic changes and cognitive as well as neurologic disability.
Methods. Subjects. We studied 23 patients (9 men, 14 women) with clinically definite MS\textsuperscript{18} who were recruited from the MS clinic at the Copenhagen University Hospital, Rigshospitalet. The mean age of the patients was 41 years (range, 26 to 67 years), the mean disease duration was 11 years (range, 3 to 19 years), and the mean score on the Expanded Disability Status Scale (EDSS)\textsuperscript{19} was 5.2 points (range, 2.5 to 7.5 points). The control group consisted of nine healthy subjects (five men, four women) with a mean age of 37 years (range, 24 to 60 years), with no report of physical or mental illness. Informed consent was obtained after written information, according to the Declaration of Helsinki II, and the study was approved by the Central Scientific Ethical Committee of Denmark (jr. no. c-1992-30). All subjects were studied while their eyes were closed; in a darkened, quiet room; and were instructed to pause medication (within 24 hours before examination) and not to smoke, or consume carbohydrates or coffee (within 3 hours before the examination). No patients had acute exacerbation of the disease (within 1 month before the examination).

Positron emission tomography. We used a GE 4096-15 WB tomograph\textsuperscript{20} (General Electric, Milwaukee, WI) that yielded 15 consecutive image slices parallel to the canthomeatal line and separated by 6.5 mm. Spatial resolution in the image plane was approximately 7 mm, and the axial field of view was 97.5 mm. The head was fixed using an individually molded head holder of polystyrene foam and was positioned in the PET scanner. A transmission scan was performed immediately before tracer injection for attenuation correction. A dose of approximately 200 MBq\textsuperscript{18} fluorodeoxyglucose was administered as a slow bolus through an antecubital vein, and arterial blood samples were drawn manually from the distal part of the radial artery. Blood glucose was monitored throughout the examination. Global CMRglc was calculated using the autoradiographic single-scan method as described by Sokoloff et al.\textsuperscript{21} and revised by Huang et al.\textsuperscript{22} A 15-minute scan obtained 45 to 60 minutes after the injection was used for calculation purposes. We used a lumped constant of 0.82\textsuperscript{23} and kinetic rate constants determined for normal gray matter.\textsuperscript{24} The following image analysis was therefore restricted to gray matter regions, which are rarely affected by the pathophysiologic processes in MS.\textsuperscript{25} To test our data for underestimation of CMRglc in hypometabolic regions, due to the use of fixed kinetic rate constants, we calculated the kinetic rate constants in a cortical region of five patients with high as well as low CMRglc. The largest relative difference between CMRglc calculated with individual rate constants, and CMRglc calculated with standard rate constants, was 2.6% and was therefore considered negligible. One patient was excluded from the study because it became evident that medication (anticholinergic and antidepressant drugs) were not paused before examination.

PET image analysis. PET image analysis was performed using a computerized brain atlas (CBA; CBA software, Uppsala, Sweden, version 3.1).\textsuperscript{26} All images were reformatted (normalized) to a standard stereotactic space and thereby aligned to the intercommisural (anterior commissure-posterior commissure [AC-PC]) line. Regions of interest (ROIs) were drawn manually, guided by the anatomic information of the CBA. Because regions extended through several image slices, weighted average values were calculated.

Magnetic resonance imaging. MRI studies were made on a Siemens Magnetom SP 4000 1.5-T (slice thickness, 5 mm; double-spin echoes, 15 and 90 msec; repetition time [TR], 2,500 msec) or a Siemens H15 1.5-T (slice thickness, 4 mm; double-spin echoes, 15 and 90 msec; TR, 1,800 msec) scanner (Erlangen, Germany).

MR images were obtained in the intercommisural horizontal image plane. If the images deviated from the AC-PC line they were aligned using a three-dimensional algorithm (automated image registration [AIR] software, version 2.0; Department of Radiology, UCLA, Los Angeles, CA)\textsuperscript{27} on a voxel-by-voxel basis. The subsequent data analysis was carried out by a radiologist using Displimage (Display Image Software, version 4.5; Department of Medical Physics and Bioengineering, University College London, UK),\textsuperscript{28} and the TLA of the T2-weighted images were recorded and corrected for differences in slice thickness. To compare MRI and stereotactically normalized PET data, the lesion area was corrected further for differences in brain volume. All lesions were classified according to their topographic localization in the major cerebral lobes, the basal ganglia, the cerebellum, or the brainstem, although the majority of MS lesions are usually classified as periventricular. This was done because neural transmission in the periventricular region is related to the function of the superficial cortex, and in this way the quantification of our MRI data could be compared directly with changes in corresponding regional CMRglc (rCMRglc).

Motor evoked potentials (MEPs). A Dantec magnetic stimulator (Dantec MagPro; Copenhagen, Denmark) was used for cortical and root excitation. Facilitated MEPs were recorded bilaterally from the brachial biceps, the radial carpal flexor, the first dorsal interosseus muscle of the hand, the anterior tibial muscle, and the abductor hallucis muscle. We calculated central motor conduction time as well as a central motor conduction index (CMCI; the average deviation from the mean of 50 healthy subjects).\textsuperscript{29} Three patients refused to participate in the neurophysiologic examination.

Neuropsychological assessment. Twenty MS patients were examined with a battery of 19 neuropsychological tests, measuring skills within the following cognitive domains: visuoperception (Street Gestalt Completion Test),\textsuperscript{30} Block design [four cubes version, 10 tasks]\textsuperscript{31,32}; language (sentence repetition,\textsuperscript{33,34} Boston Naming Test,\textsuperscript{34} Proverbs [multiple-choice version\textsuperscript{35}], Controlled Oral Word Association Test,\textsuperscript{35} Naming of Famous Faces [Danish version\textsuperscript{36}]; memory (Digit Span [forward],\textsuperscript{32,33} List Learning\textsuperscript{32,34}); attention (Stroop [modified version],\textsuperscript{37} Auditory Motor Attention,\textsuperscript{31} Digit Span Backward\textsuperscript{35,36}); executive functions (WAIS Picture Arrangement,\textsuperscript{38} Design fluency,\textsuperscript{39} Mental Arithmetic,\textsuperscript{40} Tower of London,\textsuperscript{41} Wisconsin Card Sorting Test\textsuperscript{42}); and speed of mental processing (Tower of London [time to solve 12 tasks],\textsuperscript{41} Proverbs [multiple choice version]).\textsuperscript{31}

The raw scores were standardized to z scores using the mean and SD from a group of normal control subjects (n = 23) comparable with the patients on a number of background variables (age, years of schooling and vocational training). For each of the six cognitive domains, an average z score was computed and the cognitive deterioration
Table 1 Average values of regional and global cortical cerebral metabolic rate of glucose (CMRglc) (μmol/100 g/min) with SDs are listed for normal control subjects (n = 9) and MS patients (n = 23)

<table>
<thead>
<tr>
<th>Area</th>
<th>Normal control subjects</th>
<th></th>
<th>MS patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>24.6 ± 2.6</td>
<td>24.4 ± 2.4</td>
<td>19.8 ± 3.2*</td>
<td>19.7 ± 3.3*</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>23.5 ± 2.7</td>
<td>23.6 ± 2.2</td>
<td>18.8 ± 3.2*</td>
<td>18.7 ± 3.2*</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>24.9 ± 2.9</td>
<td>24.9 ± 2.8</td>
<td>19.4 ± 3.1*</td>
<td>19.2 ± 3.2*</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>21.8 ± 2.6</td>
<td>21.9 ± 2.7</td>
<td>17.6 ± 2.8*</td>
<td>17.4 ± 3.0*</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>26.2 ± 2.9</td>
<td>25.2 ± 2.4</td>
<td>21.0 ± 3.4*</td>
<td>20.7 ± 3.6</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>24.3 ± 2.9</td>
<td>23.6 ± 3.1</td>
<td>18.2 ± 3.4*</td>
<td>18.9 ± 3.0*</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>23.7 ± 3.8</td>
<td>25.2 ± 2.5</td>
<td>19.3 ± 4.2</td>
<td>19.3 ± 3.7</td>
</tr>
<tr>
<td>Caput nucleus caudatus</td>
<td>24.4 ± 4.5</td>
<td>22.9 ± 4.7</td>
<td>18.9 ± 3.3*</td>
<td>20.8 ± 3.8</td>
</tr>
<tr>
<td>Putamen</td>
<td>29.7 ± 2.5</td>
<td>30.8 ± 2.8</td>
<td>24.2 ± 4.8</td>
<td>24.3 ± 4.3*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>25.9 ± 4.1</td>
<td>26.1 ± 3.1</td>
<td>18.0 ± 5.3*</td>
<td>19.8 ± 5.1</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>15.3 ± 2.2</td>
<td>16.7 ± 2.1</td>
<td>11.1 ± 2.3*</td>
<td>12.8 ± 2.3*</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>21.7 ± 4.0</td>
<td>20.8 ± 3.9</td>
<td>15.4 ± 5.0</td>
<td>15.2 ± 4.9</td>
</tr>
<tr>
<td>Global cortical CMRglc</td>
<td>23.6 ± 2.8</td>
<td>—</td>
<td>18.6 ± 2.9*</td>
<td>—</td>
</tr>
</tbody>
</table>

Values of regions marked with an asterisk in the MS group are reduced significantly (p < 0.01) compared with those of the normal control subjects.

score was computed as the mean of the six cognitive domains. Three patients refused to participate in the neuropsychological examination. Two patients did not complete the tests due to severe cognitive impairment, and one patient was excluded from the study because it became evident that medication was not paused before PET examination (as described earlier).

Statistical analysis. Global and regional values of CMRglc of the normal subjects and the MS patients were compared using an F-test which demonstrated equal variance, and therefore followed by a two sample t-test, with Bonferroni's corrections for multiple comparisons. We used Spearman's rank correlation coefficient to examine the relationships among the global PET data, the neurophysiologic data, the neuropsychological data, and the clinical data. When comparing the neurophysiologic, the neuropsychological, and the clinical data with the regional PET data, we used stepwise multiple regression analysis.

Results. Reduced CMRglc (p < 0.01) was detected in global cortical measurements (table 1) as well as in all regional lobar measurements. Furthermore, CMRglc was reduced (p < 0.01) in the dorsolateral prefrontal cortex, orbitofrontal cortex, caudate, putamen, thalamus, and hippocampus.

Table 2 shows the results of the MRI lesion area calculations with a symmetric pattern in paired hemispheric regions, and a preponderance of lesion area in the frontal regions compared with the rest of the brain. Lesion scores in the cerebellum were low.

MSEP central conduction times ranged from normal values to increases of approximately 45 SDs. Peripheral conduction latencies were abnormal in seven patients (>2 SDs), and total conduction latencies were distributed in a similar way as the central conduction data.

Global CMRglc and TLA correlated (Spearman rank correlation coefficient [SRCC] = -0.66, p = 0.001; table 3, figure 1), and values of rCMRglc correlated with regional lesion area in all cerebral lobes (p ≤ 0.05; table 4). The stepwise regression analysis showed an association between TLA and rCMRglc of the right thalamus (R = 0.77, p = 0.002), whereas other regional CMRglc data were not associated with lesion burden.

Global CMRglc correlated to the general cognitive index (SRCC = 0.58, p = 0.015; see table 3, figure 2), and step-
**Table 3** Spearman’s correlations between global cortical CMRglc, clinical disability (EDSS), CMCI, MRI T2-weighted total lesion area, and cognitive index

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Spearman’s correlation quotient</th>
<th>p Value</th>
<th>MS patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRglc/EDSS</td>
<td>0.05</td>
<td>0.84 (NS)</td>
<td>23</td>
</tr>
<tr>
<td>CMRglc/CMCI</td>
<td>0.30</td>
<td>0.20 (NS)</td>
<td>20</td>
</tr>
<tr>
<td>CMRglc/TLA</td>
<td>-0.66</td>
<td>0.001</td>
<td>23</td>
</tr>
<tr>
<td>CMRglc/Cognitive index</td>
<td>0.58</td>
<td>0.015</td>
<td>17</td>
</tr>
<tr>
<td>TLA/Cognitive index</td>
<td>-0.57</td>
<td>0.017</td>
<td>17</td>
</tr>
</tbody>
</table>

CMRglc = cerebral metabolic rate of glucose; EDSS = Expanded Disability Status Scale; CMCI = central motor conduction index; TLA = total lesion area; NS = not significant.

wise regression analysis showed an association between cognitive performance and rCMRglc of the right thalamus (R = 0.63, p = 0.006), whereas other regional CMRglc data were not associated with cognitive performance.

There was no correlation between global cortical metabolism and EDSS score or CMCI (see table 3), and the result of the stepwise regression analysis likewise showed no association between rCMRglc and EDSS or CMCI.

Cognitive dysfunction and TLA correlated (SRCC = -0.57, p = 0.017; see table 3).

**Discussion.** Our PET results (see table 1) show reduced global CMRglc as well as reduced rCMRglc in all cerebral lobes. These metabolic reductions were more substantial than reported in former SPECT studies of cerebral blood flow, in which frontal and temporal lobes were affected significantly. A recent longitudinal PET study of MS patients has shown that the time-related reductions in cerebral metabolism are most pronounced in the frontal and parietal regions, and because lesion load has a preponderance for the frontal and parietal regions (see table 2), it would be expected that early changes in cortical metabolic reductions were seen in these regions. The divergent nature of the results between studies is therefore most likely the result of differences in clinical disability of the MS patients at the time of examination, but could also be caused by differences in the variance of the CMRglc measurements, which of course would influence the outcome of the statistical tests.

We found a significant correlation between global CMRglc and TLA (see table 3), which disagrees with the conclusions of a previous report by Paulesu et al. One obvious reason for this difference could be that severely impaired patients were not included in the study by Paulesu et al. In our study the patients comprised a broad range of EDSS scores, which was reflected in a corresponding span of pathology and was presumably decisive for the statistical outcome. The application of ROIs also differed between the two studies. Paulesu et al. used manual application of circular ROIs with a diameter of 9.6 mm, whereas the application of ROIs in our study covers continuously the cerebral and lobar cortical surface, as well as an approximately 25-mm-thick selection of the cortical rim. In this way our data analysis expresses mean values of larger cortical selections, which could be of statistical importance to a set of data that contains a considerable amount of variance. The methodological approach regarding the MRI data also differed because these

**Table 4** Spearman’s correlations between rCMRglc and regional MRI T2-weighted lesion area in lobar subdivisions of the brain

<table>
<thead>
<tr>
<th>Correlation (rCMR vs rLA)</th>
<th>Spearman’s correlation quotient</th>
<th>p Value (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal R</td>
<td>-0.63</td>
<td>0.001</td>
</tr>
<tr>
<td>Frontal L</td>
<td>-0.54</td>
<td>0.009</td>
</tr>
<tr>
<td>Temporal R</td>
<td>-0.48</td>
<td>0.022</td>
</tr>
<tr>
<td>Temporal L</td>
<td>-0.54</td>
<td>0.008</td>
</tr>
<tr>
<td>Parietal R</td>
<td>-0.58</td>
<td>0.004</td>
</tr>
<tr>
<td>Parietal L</td>
<td>-0.41</td>
<td>0.050</td>
</tr>
<tr>
<td>Occipital R</td>
<td>-0.48</td>
<td>0.022</td>
</tr>
<tr>
<td>Occipital L</td>
<td>-0.49</td>
<td>0.019</td>
</tr>
</tbody>
</table>

rCMR = regional cerebral metabolic rate; rLA = regional lesion area.

**Figure 1. Measurements of global cortical cerebral metabolic rate of glucose (CMRglc) versus total MRI T2-weighted lesion area (TLA) of the MS patients (n = 23).**
were normalized in our study according to the stereotactic normalization carried out during the analysis of the PET images. Therefore, a number of reasons could explain the difference in results of the two studies.

The clinical impact of WMH seen on MRI has been widely discussed in MS and is to some extent still a matter of controversy. The strongest clinical association has been found with cognitive dysfunction, which has been reported in several studies. It has also been shown that TLA bears little relation to the degree of disability whereas a recent report has shown a moderate correlation in a larger group of MS patients. Although other MRI measurements presumably have stronger clinical correlates, such as magnetization transfer ratios, normal-appearing white matter spectroscopy, and T1 black hole analysis, we conclude from the current study that T2 lesion burden has a demonstrable impact on cerebral neural activity.

Apart from the relationship between TLA and global CMRglc, we found that the correlation between regional lesion burden and rCMRglc is strong in all cerebral lobes (see table 4), which emphasizes the notion that local aggregations of MS plaques affect the neural function of the superficial cortex.

Our neuropsychological measurements of general cognitive dysfunction showed strong correlation with measures of global CMRglc (see table 3), which have also been reported in previous studies. The most consistent finding in cognitive testing of MS patients is the impairment of memory function. The initial coding of memory has been ascribed classically to the function of the hippocampus being the primary site for retrieval of long-term memory whereas PET studies have shown that a network of structures is activated during long-term and working memory tasks, including large cortical areas in the prefrontal cortex. We found bilateral metabolic reductions in frontal cortical regions as well as in the hippocampus, which is in accordance with a previous study. The function of the hippocampus is related closely to the anterior thalamic nucleus, illustrated by clinical observations in thalamic degenerative diseases leading to severe memory impairment. Furthermore, all subcortical connections from the frontal lobe incorporate thalamic neurons in the circuit, as well as the thalamic nuclei receive input from most cerebral areas. The neurotransmission between the thalamus and other cerebral structures would therefore be expected to be affected in MS caused by the widespread white matter lesions. This was confirmed further in our results because the stepwise regression analysis showed that reductions of rCMRglc of the right thalamus was associated statistically with general cognitive dysfunction as well as with the total MRI lesion burden.

TLA and cognitive disability also correlated (see table 3), which again illustrates the intercorrelation between our PET, MRI, and psychometric measurements. Table 3 also shows that PET and MRI measurements correlate quite equally to cognitive disability, although they are correlated primarily and strongly to each other, which indicates that MRI and PET in the clinical evaluation of the MS patient provide information of similar etiology. In this regard the study validates MRI T2-weighted lesion load as a surrogate marker used widely in clinical trials, and encourages the use of PET in future clinical studies of MS patients.

Acknowledgment
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