ON-LINE APPENDIX

Additional details about the procedure of the segmentation for the metabolite concentrations are presented here.

The basic principle of the segmentation method is that the metabolite concentration measured in every voxel is a linear combination of the WM (NAWM or LWM) and GM concentrations. We suppose negligible concentrations in CSF. We can therefore express any concentration in a voxel v as

1)

$$C_v = \begin{cases} C_v^{NAWM} \cdot P_v^{NAWM} + C_v^{GM} \cdot P_v^{GM} & \text{if lesion } PVE < 1\% \\ C_v^{LWM} \cdot P_v^{LWM} + C_v^{GM} \cdot P_v^{GM} & \text{if lesion } PVE > 5\% \end{cases}$$

where C_v^{NAWM}, C_v^{LWM}, and C_v^{GM} are the concentrations in, respectively, NAWM, LWM, and GM in voxel v and P_v^{NAWM}, P_v^{LWM}, and P_v^{GM} are the corresponding partial volume estimates (PVEs). Because of the short TE (30 ms) and the long TR (3000 ms) of the 2D-MRSI sequence, we did not correct the metabolite concentration for possible in vivo against in vitro relaxation time differences.

An extrapolation of the distinct tissue type concentrations is possible if we suppose them constant over a region containing ≥2 voxels and by minimizing the sum square of the regression error:

2)

$$E_{reg}^2 = \sum_{v \in reg} \begin{cases} (C_{reg}^{NAWM} \cdot P_v^{NAWM} + C_{reg}^{GM} \cdot P_v^{GM} - C_v)^2 & \text{if lesion } PVE < 1\% \\ (C_{reg}^{LWM} \cdot P_v^{LWM} + C_{reg}^{GM} \cdot P_v^{GM} - C_v)^2 & \text{if lesion } PVE > 5\% \end{cases}$$

where reg is a region (ensemble of voxels) with corresponding extrapolated concentrations C_{reg}^{NAWM}, C_{reg}^{LWM}, and C_{reg}^{GM}. As indicated in Fig 1*C*, GM was designated as either frontal or parietal, whereas WM was defined as frontal, semiovale, or parietal.

To increase the precision, we performed 3 conditional consecutive minimizations of Equation 2 in all separate regions. In step 1, we included all voxels containing <1% lesion PVE to compute C_{reg}^{NAWM} and C_{reg}^{GM}. In step 2, we repeated the extrapolation for C_{reg}^{GM}, including only voxels containing >10% GM PVE with <1% lesion PVE and replacing C_{reg}^{NAWM} by the value computed in step 1. In step 3, the LWM concentration C_{reg}^{LWM} was extrapolated, including only the voxels containing >5% lesion PVE and replacing C_{reg}^{GM} by the value calculated in step 2.

The quality of the concentration segmentation was verified by the computation of a concentration conservation factor throughout the extrapolation method: The sum of the regional and tissue-specific concentrations multiplied by the respective PVEs (voxels with lesion PVE <5% was considered as NAWM) was divided by the average of the concentrations of the included voxels (with either NAWM or LWM) of the 64-voxel original concentrations. In the ideal case of an exact concentration segmentation, the factor is 1. If it is <1, the segmented concentrations are underestimated and if it is >1, they are overestimated. For all groups, metabolites, and time points, the concentration conservation factor values had a mean of 1.00 ± 0.015, within a total range of 0.93–1.06.