Proton MR spectroscopy of the thalamus in early relapsing-remitting multiple sclerosis

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TARGET AUDIENCE: Multiple sclerosis (MS) researchers, neurologists, spectroscopists

PURPOSE: Recently, converging evidence from quantitative MR studies suggests a central role for the thalamus in the pathology of early MS[1]. Thalamic atrophy has been found before diagnosis and in pediatric MS, but although metabolic changes can precede atrophy and provide pathologic specificity, thalamic MR spectroscopy (MRS) has been done only in patients with advanced disease[1]. The purpose of this study was to investigate thalamic metabolism in early stage relapsing-remitting (RR) MS through quantification of N-acetyl-aspartate (NAA), creatine (Cr), choline (Cho) and myo-inositol (mI). This was done by combining proton MR spectroscopic imaging (^{1}H-MRSI) with segmentation masks of the thalamus and performing a priori experiments on controls' data
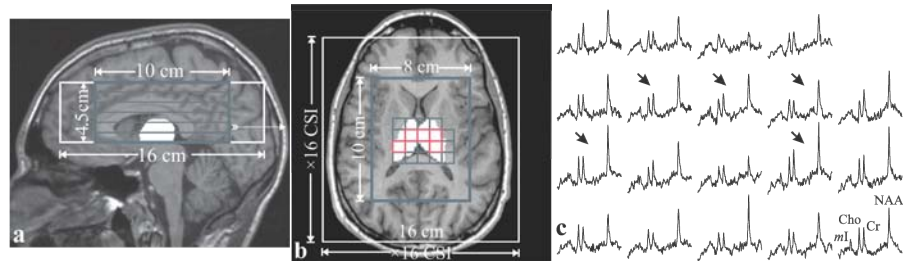

Fig. 1: Sagittal (**a**) and axial (**b**) MP-RAGE overlaid with the ^{1}H-MRSI VOI (navy box) and field-of-view (white lines). The location of **b** is indicated on **a** by an arrow. Spectra (**c**) from all voxels with some thalamic contribution, indicated on (**b**). Note that only voxels with a minimal thalamic fraction of 0.8 (red on (**b**) and denoted with arrowheads on (**c**)) were used in the analyses.

in order to determine the optimal tradeoff between good reproducibility and minimal partial volume. A secondary purpose was to test for thalamic atrophy in order to determine its temporal relationship to the ^{1}H-MRSI findings.

METHODS: 18 patients with clinically definite RR MS and an average disease duration of 32 months were prospectively recruited. They were age- and gender-matched with 10 healthy volunteers. Data from 4 serial scans of these controls (40 scans total) was used to optimize the approach (see below). Note that global metabolism and volumetry was recently reported for this patient and control cohort[2]; for detailed description of the acquisition and post-processing pipeline up to and including spectral fitting please see ref[2]. Measurements were done at 3 T and the ^{1}H-MRSI volume-of-interest (VOI) of $10 \times 8 \times 4.5 = 360$ cm^3 (TE/TR=35/1800 ms, 6 slices, 480 voxels, 0.75 cm^3 each) was placed over the corpus callosum, as shown in **Fig. 1a-b**.
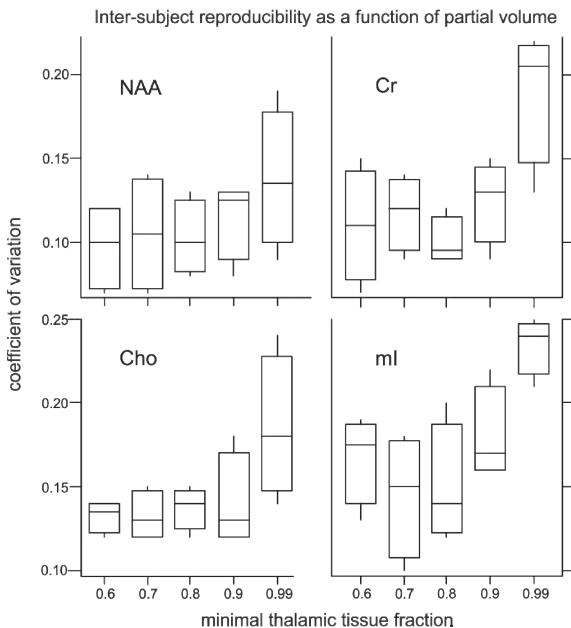

Fig. 2: Box plots of minimal thalamic tissue fraction as a function of reproducibility in controls show an optimal tradeoff between accuracy and precision at 0.8, which yields average CVs of NAA, Cr: 9%, Cho: 12%, mI: 16%, and small (relative to the other data) inter-session variance.

The post-processing considerations and protocol specific to the current study were as follows. The MP-RAGE images were segmented with the Freesurfer image analysis suite to generate thalamic masks. These were extracted in the subjects' native space and co-registered with the ^{1}H-MRSI grid using in-house software. Average concentrations (institutional units/mL) within the mask were calculated by dividing the sum of each metabolite (weighted by the mask fraction in each voxel) by the total mask volume, for those voxels passing a minimal tissue fraction threshold. To determine the threshold which provides the best tradeoff between accuracy and precision we quantified the reproducibility of 5 different thresholds in the 10 controls by determining the inter-subject coefficients of variation (CVs) for each of the 4 serial scans (**Fig. 2**). Reproducibility was to be evaluated by considering (*i*) the mean of the 4 inter-subject CVs (position on the y-axis); and (*ii*) their variability (size of boxplots), representing inter-session variations. Patients were then processed with the threshold selected as optimal, and concentrations in millimolar (mM) were obtained for all subjects using phantom replacement with correction for T_1 and T_2 relaxation time differences between in vitro and in vivo (using published thalamic T_2 values in RR MS). Thalamic fractions in the whole brain, indicative of thalamic atrophy, were obtained by dividing the total mask volume by the intracranial volume. Paired sample Student's t-test was used for the statistical analyses.

RESULTS: In all subjects, an average of 96% of the total thalamic volume was included in the VOI (range: 72%-100%). Based on **Fig. 2**, a minimal threshold of 0.8 was chosen for the spectroscopic analyses (see **Fig. 1c** for an example). An average of 9±2 (mean±standard deviation) voxels per metabolite in controls and 8±2 voxels in patients fulfilled the threshold requirement. The average thalamic tissue fraction in those voxels was 93±1% in both groups. None of the metabolite concentrations were different in comparisons of patients vs controls: NAA: 9.7±1.1 vs 9.6±1.3; Cr: 7.4±1.1 vs 7.2±0.7; Cho: 1.7±0.3 vs 1.7±0.3 and mI: 5.7±0.8 vs 5.7±0.9, all in mM, all $p>0.5$). Nor there was a difference in whole brain thalamic fractions (0.0103 vs 0.0106, $p=0.3$), i.e. no evidence of atrophy.

DISCUSSION AND CONCLUSION: This study was conducted on the basis of evidence suggesting considerable thalamic involvement in MS, including prior to diagnosis[1]. It represents the first report of thalamic metabolism in recently diagnosed patients and its design accounts for partial volume effects. Specifically, similar fractions of thalamus were sampled in all subjects, and by establishing optimal experimental parameters a priori we obtained high accuracy (only ~7% of partial volume) at minimal loss of precision. The finding of normal metabolism in these patients may reflect their very mild disease burden measured both clinically (median EDSS[2]=1) and by conventional imaging (median VOI T_2 lesion load[2]=2.1 cm^3). Indeed, in volumetric studies, thalamic atrophy almost always correlates with T_2 lesion load, suggesting a model where axonal injury propagates via Wallerian degeneration and becomes concentrated in the thalamus because of its extensive WM interconnectivity. The small lesion load and lack of thalamic atrophy in this cohort support the notion of thalamic sparing, which is substantiated by the ^{1}H-MRSI results.

REFERENCES: 1. Minagar et al. The thalamus and multiple sclerosis. Neurology 80:210-219, 2013.
2. Kirov II et al. Serial proton MR spectroscopy of gray and white matter in relapsing-remitting MS. Neurology 80:1-8, 2013.