Longitudinal inter- and intra-individual human brain metabolic quantification with proton MR spectroscopy at 3T

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INTRODUCTION: Proton MR spectroscopy (^{1}H-MRS) is used to add metabolic specificity to the high morphological sensitivity of clinical MRI, both in research and clinical applications. Monitoring disease progression with ^{1}H-MRS requires knowledge of the metabolites' normal cross-sectional and longitudinal variation. Single-voxel and multi-voxel ^{1}H-MRS studies report *inter*- and *intra*-individual coefficients of variation (CVs) as low as 3% to over 20% at 1.5 T, but only a handful quantify them at the higher, 3 T, clinical field. Moreover, none to our knowledge have examined these variations serially for more than a few months. In addition, given the diffuse nature of most neurological disorders the small, ‹10%, brain coverage of single- voxel or two-dimensional (2D) multivoxel ^{1}H-MRS may: *(i)* not represent global tissue status; *(ii)* be dominated by instrumental noise; *(iii)* be influenced by partial volume in the same exam; *(iv)* be confounded by volume-of-interest (VOI) misregistration in serial studies.

To reduce the contribution of repositioning and instrumental noise, we summed the phased and frequency-aligned spectra from all 480 voxels of a 3D ^{1}H-MRS acquisition over a 360 cm^3 VOI (~30% of the human brain) in post-processing. Whole-VOI summation yields a single average spectrum that is relevant to diffuse brain disorders yet with the substantial signal-to-noise ratio (SNR) improvement that is essential for reproducibility, at minimal cost in spectral resolution and repositioning errors. Our two goals, consequently, were to establish the normal brain's cross-sectional (*inter*-) and longitudinal (*intra*-subject) variations of *N*-acetyl-aspartate (NAA), creatine (Cr), choline (Cho) and *myo*-inositol (*m*I). Towards this end we applied annual test-retest 3D ^{1}H-MRS in the brain of ten healthy subjects over a period of three years at the current "high" clinical magnetic field strength of 3 T.

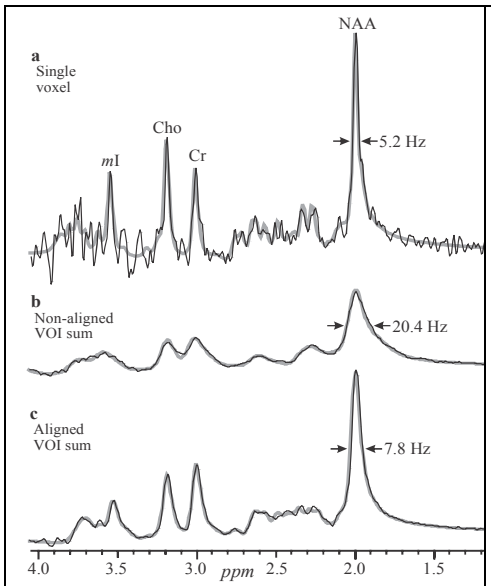
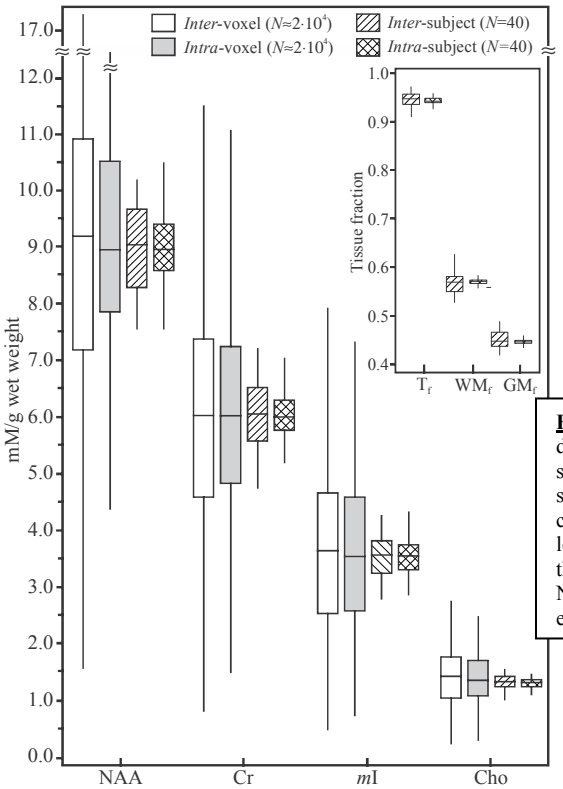


Figure 1: Real part of ^{1}H spectra (black lines) superimposed with their fitted model functions (gray lines).
a: Spectrum from a single 0.75 cm^3 voxel.
b: Non-aligned sum of all 480 spectra in the VOI (equivalent to a 360 cm^3 single-voxel acquisition). Note the better SNR compared with (**a**), but ×2.5 fold degraded linewidth.
c: Same as (**b**), but with spectral alignment prior to summation, resulting in ×2.5 better spectral resolution *and* SNR compared with (**b**).

METHODS: Ten healthy volunteers (7 women, 3 men) 24 to 43 (mean 30) years old were scanned. A $10_{AP}\times8_{LR}\times4.5_{IS}$ = 360 cm^3 VOI centered on the corpus callosum excited with *TE*/*TR* = 35/1800 ms PRESS in 3 sequentially-acquired slabs each with 2nd order Hadamard-encoding in the IS direction. A $16_{AP}\times16_{LR}\times 4.5_{IS}$ cm^3 field of view containing the VOI was partitioned into 480 $1.0_{AP}\times1.0_{LR}\times 0.75_{IS}$ = 0.75 cm^3 voxels with $16_{AP}\times16_{LR}$ 2D chemical-shift imaging matrix. Two ^{1}H-MRS averages were obtained.



All 480 spectra were summed to obtain one global VOI spectrum per subject, representing a $480^{½}$≈22 fold increase in the SNR. Alignment of spectra before summation exploited better B_0 homogeneity across small voxels and thus retained their narrow linewidths in the sum (**Fig. 1**). Improved SNR and resolution allowed for accurate fitting (SITools software) and peak-area quantification (phantom replacement method). To correct for atrophy, metabolite concentrations were divided by the subject's tissue volume fraction (tissue-volume/VOI-volume, segmented with SPM). The *inter*- and *intra*-subject CVs were estimated by dividing the standard deviation (SD) of the within-subject variance by the overall mean (over subjects and time points). The *inter*-voxel CVs were estimated by dividing the SD of the within-voxel variance over time points of the same subject by the overall mean. For the *intra*-voxel CVs, the two averages within a session were processed separately and the SD of the within-voxel variance of all 480 spectra in a subject was divided by the overall mean. Sample sizes needed to detect rates of annual change, as well as the sensitivities to metabolic changes, were also derived.

Figure 2: Main plot: Box plots of the NAA, Cr, Cho and *m*I absolute concentrations distributions for **single voxels**: within-voxel variance from all scans (*inter*-voxel), within-session variance (*intra*-voxel, shaded); and the **summed spectra**: single time points across all subjects (*inter*-subject, right-hatched) and all time points of the same subject (*intra*-subject, cross-hatched). Note the dramatic, ×4 to ×7 fold, improvement in both cross-sectional and longitudinal reproducibility of the sums compared with the single voxels. Insert: Box plots of the GM, WM and tissue fractions (GM_f, WM_f and T_f) distributions in the VOIs of all subjects. Note the narrow distribution, indicating the minimal GM/WM/CSF partial volume repositioning error of the proposed approach.

RESULTS: The means of the four time points were 8.9, 5.9, 1.4 and 3.7 mM. The *inter*-subject NAA, Cr, Cho and *m*I CVs: 8.7%, 10.2%, 10.7% and 11.8%, were higher than the *intra*-subjects': 6.6%, 6.8%, 6.8% and 10%. The much higher respective inter- (38%, 42%, 47% and 49%) and intra-voxel (35%, 44%, 55% and 62%) CVs reflect the improved reproducibility of the VOI sums, consequence of the high SNR (**Fig. 2**).

CONCLUSION: The CVs of the *inter*- and *intra*-subject measurements of the proposed ^{1}H-MRS approach are shown to be on the order of 9-12% and 7-10%, respectively. These indicate good cross-sectional and longitudinal reproducibility of a method suitable for detection of subtle metabolic changes occurring diffusely in a large (~0.4 L) brain volume. Given the over 10% metabolic changes reported in several diffuse brain pathologies, the proposed method may be capable of identifying statistically significant changes with one measurement in a single individual, performance unlikely to be realized with (much) smaller VOIs, whether they are acquired in single voxel or multi-dimensional ^{1}H-MRS.