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Test-retest reproducibility of neurochemical profiles with short-echo, single voxel MRS at 3T and 7T

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Abstract

Purpose—To determine the test-retest reproducibility of neurochemical concentrations obtained with a highly optimized, short-echo, single voxel proton MRS pulse sequence at 3T and 7T using state-of-the-art hardware.

Methods—A semi-LASER sequence (T_E = 26–28ms) was used to acquire spectra from the posterior cingulate and cerebellum at 3T and 7T from 6 healthy volunteers who were scanned weekly 4 times on both scanners. Spectra were quantified with LCModel.

Results—More neurochemicals were quantified with mean Cramér-Rao lower bounds (CRLB) ≤ 20% at 7T than at 3T despite comparable frequency-domain SNR. While CRLB were lower at 7T ($p < 0.05$), between-session coefficients of variance (CVs) were comparable at the two fields with 64 transients. Five metabolites were quantified with between-session CVs ≤5% at both fields. Analysis of subspectra showed that a minimum achievable CV was reached with a lower number of transients at 7T for multiple metabolites and that between-session CVs were lower at 7T than at 3T with fewer than 64 transients.

Conclusion—State-of-the-art MRS methodology allows excellent reproducibility for many metabolites with 5 minute data averaging on clinical 3T hardware. Sensitivity and resolution advantages at 7T are important for weakly represented metabolites, short acquisitions and small volumes-of-interest.

Keywords

3 Tesla; 7 Tesla, test-retest reproducibility; spectroscopy; coefficient of variation

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INTRODUCTION

In vivo ^{1}H magnetic resonance spectroscopy (MRS) enables non-invasive detection of cellular and metabolic alterations in diseases of the central nervous system and therefore is ideally suited to play a role in the development of diagnostic protocols, preventative strategies, and therapeutic interventions [1]. With increasing availability of high and ultra-high magnetic field scanners comes a need to characterize the benefits of the increased sensitivity and resolution that they provide [2–4]. Systematic investigations of these benefits will facilitate informed choice of field strength for robust clinical applications of the technique.

Clinical applicability of MRS depends upon the test-retest reproducibility in the neurochemical concentrations measured since disease related changes can be detected in individuals only if they are higher than the day-to-day experimental and physiological variability. Test-retest coefficients of variance (CVs) have been reported for many experimental configurations for 3–7 major metabolites, quantified primarily with the standard STEAM and PRESS sequences [5–12]. However the field dependence of test-retest CVs is largely unexplored. In this respect, Cramér-Rao Lower Bound (CRLB) estimates of minimum variance can provide insights. The CRLBs have been shown by simulations [4] and in practice [2,3,7,13] to be lower at higher field, predicting lower test-retest CVs at higher field. However, only a few studies have investigated whether the lower CRLBs indeed translate to lower test-retest CVs at higher field [7,11].

Meanwhile, neurochemical profiles of 10–18 metabolites are increasingly being reported at both 3T [3,14–17] and 7T [3,18–22] using highly optimized, short echo localization sequences such as STEAM, SPECIAL and semi-LASER, which minimize apparent T_2 relaxation and J-coupling evolution that counteract the sensitivity gains, particularly at 7T. Of these, semi-LASER [23,24] was recently shown to provide excellent between-site reproducibility at 3T [14] and 7T [22], documenting its suitability for multi-site trials. In addition, good between-session reproducibility of the sequence was demonstrated for selected VOI at 3T [15] and 7T [22]. However, its limits for test-retest reproducibility of neurochemical profiles and how these compare at 3T vs. 7T remain to be established.

Therefore the goal of this study was to compare test-retest reproducibility of neurochemical profiles obtained with semi-LASER at 3T versus 7T, with state-of-the art hardware at each field. We investigated whether improvements in CRLB at ultra-high vs. high field lead to better test-retest reproducibility, and which metabolites critically need the sensitivity and spectral resolution at 7T to manifest clinically applicable reproducibility. Secondarily, we aimed to determine the number of repeat measurements needed for a robust estimation of test-retest CVs, as between-session test-retest reproducibility investigations typically utilize only one repeat measurement.

The same subjects were scanned at both 3T and 7T using the best hardware available to us and matched software on a clinical platform. We utilized coils that were capable of achieving sufficient B_1 for spectroscopy (with minimal chemical shift displacement) in deep

brain regions at both fields. We focused on two brain regions that are of interest for neurological diseases and that present different levels of technical challenges for MRS: the posterior cingulate, a key node in the default mode network [25], which is affected in a number of neurological and psychiatric disorders [26,27], and the cerebellum, which is affected in multiple movement disorders [28], and is technically more challenging for study by MRS (due to its caudal location in the brain and broader intrinsic linewidths than most other cortical areas).

METHODS

Subjects and study design

Six healthy volunteers (males, 32±8 years) participated in the study after giving written informed consent using procedures approved by the Institutional Review Board: Human Subjects Committee of the University of Minnesota. Volunteers were scanned 4 times at 3T and 4 times at 7T, once weekly for each field strength, except for one subject who was scanned 5 times at 3T and twice at 7T and another subject who was scanned 5 times at 7T.

MR protocol

Studies were performed with a 3T whole-body Siemens Tim Trio and a 7T whole body Siemens MAGNETOM scanner (Siemens Medical Solutions, Erlangen, Germany). At 3T, the standard body RF coil was used for radiofrequency transmission and the 32-channel phased-array Siemens head coil was used for signal reception. At 7T, a 16-channel transceiver array coil [29] allowed B_1^+ shimming as described previously [18]. T_1-weighted MPRAGE images (3T: repetition time (T_R) = 2530ms, echo time (T_E) = 3.65ms, flip angle = 7°, slice thickness = 1mm, 224 slices, field-of-view (FOV) = 256×176 mm^2, matrix size = 256×256; 7T: T_R = 2500ms, T_E = 2.4ms, flip angle = 5°, slice thickness = 1mm, 176 slices, FOV = 232×256 mm^2, matrix size = 232×256) were acquired to position the volume-of-interest (VOI) for MRS. Proton spectra were acquired from the posterior cingulate cortex (PCC, 2.0×2.0×2.0 cm^3) and cerebellar vermis (CBM, 1.0×2.5×2.5 cm^3). Reproducible voxel placement was based on anatomical landmarks: For the PCC, the anterior inferior corner of the voxel was placed at the splenium of the corpus callosum and the anterior superior corner was below the cingulate sulcus. The surfaces, lobes, lobules and fissures of the cerebellum were used for CBM.

After selecting the VOI and B_1^+ shimming at 7T [18], first- and second-order B_0 shims were adjusted in each VOI using FASTMAP (fast, automatic shimming technique by mapping along projections) with echo-planar imaging readout [30]. Next, B_1 levels for localization pulses and water suppression in semi-LASER were adjusted [14]. Metabolite and water reference spectra were acquired using a modified semi-LASER sequence [24] (T_E = 28ms at 3T and 26ms at 7T, T_R = 5s, 64 transients, as described previously [14]. Finally, fully relaxed unsuppressed water signals were acquired at T_E's ranging from 28–4000ms (T_R = 15s) to estimate the cerebrospinal fluid (CSF) contribution to each VOI [31].

Spectral post-processing and quality control (QC)

Single-shot spectra were post-processed in Matlab, including Eddy current correction, removal of shots affected by subject motion, frequency correction using a cross-correlation algorithm and phase correction using a least-square fit algorithm [14], and then averaged. Summed spectra were visually assessed for extraneous coherences and spectra excluded from further analysis if such coherences were noted.

To evaluate the between-session reproducibility of voxel placement, the MPRAGE image from the first session was used as a reference to which images from later sessions were aligned linearly (6 degrees of freedom) together with VOI masks in FSL-FLIRT registration tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT). The proportion of the volume that is shared by at least three of the four VOI masks to the VOI volume was calculated and expressed in percent. This approach was chosen to treat the 4 sessions as 'exchangeable' rather than identifying one of them post-hoc as a 'gold standard' session to which the others should be compared, which may introduce a bias if the reference VOI has poor overlap with the other 3 even if the other 3 VOI overlap well.

Metabolite quantification

Metabolites were quantified using LCModel [32]. The model spectra for alanine (Ala), aspartate (Asp), ascorbate (Asc), glycerophosphocholine (GPC), phosphocholine (PC), creatine (Cr), phosphocreatine (PCr), γ-aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glutathione (GSH), *myo*-inositol (Ins), lactate (Lac), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), phosphoethanolamine (PE), *scyllo*-inositol (sIns) and taurine (Tau) were simulated using density matrix formalism [33] based on previously reported chemical shifts and coupling constants [34,35]. Macromolecule spectra acquired from the occipital cortex of 4–5 volunteers at each field using an inversion recovery technique (TR = 2.5s, inversion time TI = 0.75s at 3T and TR = 2s, TI = 0.69s at 7T) [2] were also included in the basis set. The validity of using a general macromolecule spectrum for fitting spectra from multiple brain regions was recently demonstrated [36,37].

Metabolite concentrations were determined after correcting for tissue water and CSF content, and the T_2 of water in LCModel (version 6.3-0G), as described previously [14]. A water content of 82% was assumed [38]. The % CSF contribution was obtained from a bi-exponential fit of the integrals of water spectra at different T_E values [31]. A water T_2 of 120ms was used at 3T and 87ms at 7T, based on the assumption that the T_2 of water under Carr-Purcell conditions is 1.5× longer than the measured free precession T_2 [14]. Metabolites quantified with CRLB >50% were classified as not detected [39]. Only metabolites quantified with mean CRLB ≤20% were included in the neurochemical profile of each brain region at each field. If the correlation between two metabolites was consistently very high (correlation coefficient <−0.7), their sum was reported [39], e.g. total creatine (tCr, Cr + PCr) and total choline (tCho, GPC + PC).

Statistical analysis

Summaries were calculated per field strength for each region. Spectral quality was quantified by water linewidth and SNR in the frequency domain (SNR_{freq}). Voxel placement

reproducibility was assessed by within-voxel CSF fraction and % voxel overlap between sessions. These quantities were each compared across regions within field strength, and across field strengths within region, using linear mixed models to account for the multiple scans per person. Neurochemical concentrations (summed over 64 transients per scan per subject), and CRLBs of concentrations, were summarized per person using intra-subject means across all scans. Between-session CV of concentration was calculated for the i^{th} subject and m^{th} metabolite across repeat scans as intra-subject sample standard deviation (SD) divided by intra-subject sample mean:

$$\text{intra}-\text{subject}CV=CV_{\text{im}}=s_{\text{im}}/\bar{x}_{\text{im}}.$$

Since some concentrations were excluded according to CRLB criteria (see above), all included concentrations were used in computing these means and SDs. A confidence interval (CI) for each CV_{im} was calculated using the modified McKay approximation [40]. To examine the robustness of the intra-subject CVs to the number of repeat scans, the intra-subject CV and CI calculations were repeated using each person's first 2, then 3 and then 4 scans. For each number of scans used (2, 3, and 4), means across the 6 participants of the intra-subject CVs were calculated:

$$\hat{\mu}_m^{CV}=\frac{1}{6}\sum_{i=1}^{6}CV_{\text{im}};$$

means of the endpoints of the CV_{im} CIs were also calculated. Next, using all scans per person, intra-subject CVs were summarized across people using inter-subject means (as in the above equation) and using inter-subject SDs:

$$\hat{\sigma}_m^{CV}=\sqrt{\frac{1}{5}\sum_{i=1}^{6}(CV_{\text{im}}-\hat{\mu}_m^{CV})^2};$$

similar inter-subject means and SDs were computed for the intra-subject mean CRLBs. Concentrations, CVs and mean CRLBs were compared between field strengths (for each region separately) using paired Wilcoxon tests because of mild non-normality. Lastly, intra-subject between-session CV was separately re-computed five times: including the first 2, 4, 8, 16, and 32 transients from each scan; these were then compared to the original summaries using 64 transients from each scan.

RESULTS

Using an MRS protocol that involved B_0 shimming with FASTMAP, voxel-based B_1 adjustment, localization by semi-LASER [24] and single-shot phase/frequency correction, consistently high quality spectra were obtained in both brain regions at both fields. The high reproducibility of spectral quality and pattern within individuals is demonstrated in Figure 1. Based on QC criteria, 1 spectrum from the cerebellum (of a total of 23 spectra) and 2 spectra from the posterior cingulate (of 23 spectra) at 7T were excluded from further analysis. None of the 25 spectra available for each region at 3T were excluded.

As expected, the PCC spectra had narrower linewidths and better SNR than CBM spectra (Table 1). Frequency domain SNR (SNR_{freq}) was better at 7T for CBM, but not for PCC (Table 1), underlining the importance of the many factors that determine the SNR in addition to field strength, such as coil configurations. Voxel placement consistency was demonstrated both by CSF contribution to each VOI and by between-session voxel overlap (Table 1, $p > 0.05$, 3T vs. 7T).

The quality of spectral quantification is demonstrated in Supporting Figure S1. A larger number of metabolites had mean CRLB $\leq$20% at 7T than at 3T for both VOI (Fig. 2), despite a lower SNR_{freq} for PCC at 7T. Metabolites such as GABA, Lac, PE and NAAG passed the CRLB filter only at 7T, while Glc passed the filter only at 3T for both regions and sIns passed the filter only at 3T for PCC. The concentrations obtained at the two fields were comparable with few exceptions, such as NAA, Glu and Gln, which were estimated at higher levels at 7T likely due differences in the fitted spline baselines (Supporting Fig. S2).

To determine the number of repeat measurements needed for a robust evaluation of intra-subject test-retest reproducibility, between-session CVs were calculated for each of 2, 3 and 4 repeat measurements. Between-session CVs tended to be underestimated for most metabolites with only 2 scans, although the mean CVs were similar with 2, 3 and 4 measurements (Fig. 3, top). On the other hand, the robustness of the intra-subject CV estimates increased substantially (inter-subject means of the intra-subject CI widths decreased substantially) from 2 to 3 repeat scans, while the improvement from 3 to 4 scans was smaller (Fig. 3, bottom).

Mean CRLBs were lower at 7T than at 3T for almost all metabolites while between-session CVs were comparable at the two fields (Fig. 2). Trends for lower CVs at 7T were detected for Glu, Gln and GSH in CBM. Therefore, while the CRLB provided a rough estimate of test-retest reproducibility, they did not fully reflect the true *relative* reproducibility at the 2 field strengths. Notably, NAA, tCr, tCho, Ins and Glu were quantified with between-session CVs of $\leq$5% even at 3T. To investigate whether with the very high spectral quality we have reached a physiological threshold upon which reproducibility cannot be further improved, we analyzed between-session CVs of subspectra. Namely, we summed the first 2, 4, 8, 16 and 32 shots of all spectra and thereby evaluated the between-session reproducibility of spectra with varying SNR at each field (Fig. 4). This analysis showed that the between-session CVs were indeed lower with shorter acquisitions at 7T than at 3T for most metabolites in PCC. For example, the between-session CVs had already leveled off at 2–4 shots for NAA, at 8 shots for tCr and tCho and at 16 shots for Ins at 7 T, while they continuously improved with increasing acquisition duration, i.e. increasing SNR, at 3T. In CBM, mean between-session CVs for Glu, Gln and GSH were lower at 7T vs. 3T across acquisition times.

DISCUSSION

Here we examined the test-retest reproducibility of neurochemical profiles using state-of-the-art MRS methodology at high (3T) and ultra-high (7T) field with an unprecedented number of retests. We demonstrated excellent reproducibility with standard clinical 3T

hardware and a FASTMAP + semi-LASER based MRS protocol. We further showed that more neurochemicals are detected reliably at 7T vs. 3T even when SNR_{freq} was lower at 7T. Importantly, the reproducibility advantages of 7T were realized primarily for coupled metabolites such as Glu, Gln and GSH, and for experimental conditions with low SNR. We further showed that the CRLB and test-retest reproducibility do not necessarily improve together.

Sequences such as semi-LASER are increasingly utilized at high field primarily because they minimize chemical shift displacement, which is a major drawback of the standard full intensity sequence PRESS at high field. While these sequences are not standard, they are available as work-in-progress packages on major clinical scanner platforms. Hence the assessment of their within-person reproducibility is critical for their utility in longitudinal clinical applications. To accomplish this, we focused on two clinically relevant VOI. Better linewidths and SNR were obtained for PCC than CBM, because CBM has more microscopic heterogeneities and is located further away from the receive coils. Still, the MRS protocol used here provided spectra with excellent SNR and linewidths with ~5 minute data averaging from both brain regions at both fields (Fig. 1, Table 1). Importantly we aimed at a practical field comparison here, using matched software and the best hardware available to us to consistently achieve sufficient B_1 at both fields because of the challenges to perfectly match hardware for a strict field comparison. Indeed these challenges have resulted in a wide range of reported SNR improvements at ultra-high vs. high field [4]. Note however that despite the differences in coil configurations at the two field strengths, the relationship between the SNR_{freq} at 3T vs. 7T corresponded well with theoretical predictions for the CBM. Namely, a ~22% increase in SNR_{freq} is expected at 7T vs. 3T for this voxel (SNR_{freq} is proportional to SNR_{time}/Δ_{Hz}, where Δ_{Hz} is the spectral linewidth in Hz. Since theory predicts a linear dependence of SNR_{time} on B_0 [41], $SNR_{freq} \sim B_0/\Delta_{Hz}$), i.e. the increase in SNR_{time} is largely offset by the increase in linewidth. The observed 11% increase in SNR_{freq} (Table 1) is close to the theoretical prediction; hence observations for this VOI are generalizable for 3T vs. 7T comparisons. In addition, the conclusions on test-retest repeatability were the same for the two VOI, further supporting the generalizability of the findings.

The SNR_{freq} was lower at 7T for PCC, likely because the 32 channel receive array at 3T provided superior sensitivity relative to the 16 channel T/R array for peripheral VOI such as the PCC. Hence, SNR improvements at 7T vs. 3T can vary widely depending on the RF coil characteristics and the relative location of the VOI to the receive coils. Importantly, CRLB were lower at 7T for both VOI, leading to more metabolites being quantified with mean CRLB $\leq$20% (Fig. 2) despite the loss in SNR_{freq} in PCC, and therefore are likely due to the resolution enhancement at 7T. Note that Kreis recently cautioned against quality filtering based on relative CRLBs (in %), and laid out cases where such filtering can lead to biased concentrations in cohort data and wrong conclusions in group comparisons [42]. Here we used the 20% CRLB threshold to identify the neurochemicals that were most reliably quantified [39] at each field rather than for group comparisons, consistent with the recommendation to utilize the relative CRLB to define which metabolites should be evaluated at all [42]. Also note that all metabolites that were quantified with mean CRLB $\leq$

20% were also quantified with CRLB < 50% in the *majority* of the spectra, thereby avoiding biases in metabolite selection for reporting.

The extent of improvement in CRLB at 7T vs. 3T differed substantially among neurochemicals, as also shown previously [2,8,11,13]. Namely, the greatest improvements were observed for J-coupled metabolites such as Glu, Gln, GSH and GABA (Fig. 2) due to increased spectral dispersion at 7T, fully consistent with recent simulations [4]. Glc is a known exception to this trend [2] and is more reliably quantified at 3T because of a simpler spectral pattern. Despite these improvements we also noted that more spectra were excluded from analysis at 7T due to unwanted coherences, which were encountered in a larger fraction of spectra likely because of less consistent performance of OVS pulses due to B_1 inhomogeneities at 7T.

We also investigated the extent to which a single retest is sufficient to provide a robust estimate of between-session CVs. We found that mean CVs were similar with 2, 3 and 4 measurements, with only small trends upon increasing the number of retest measurements (Fig. 3). This was because skewness and outliers were absent from the current dataset. Skewness or outliers could cause large changes in the CV or confidence interval estimates when including one or two more data points in the CV calculation. Our analysis showed that 3 repeat measurements instead of 2 can substantially improve the robustness of the estimate for datasets without skewness/outliers.

The between-session CVs observed here (Fig. 2) were lower than almost all prior reports of MRS reproducibility [5–12,43], except for a recent 3T study [17]. Notably, that study utilized the same 32 channel RF coil on the same clinical 3T platform with a non-standard sequence and also investigated reproducibility for a VOI in the PCC. The mean between-session CVs for PCC were lower for multiple metabolites (NAA, tCr, tCho, Ins, Glu) in our study vs. the Wijtenburg et al. study [17], while they were the same (Gln) or higher for others (Asp, GSH). While there were multiple methodological differences between the two studies, including the pulse sequences used and LCModel basis sets (e.g. we included experimentally acquired macromolecule spectra), together these studies demonstrate the advantages of utilizing optimized MRS methodology on standard clinical 3T hardware for improved reproducibility of neurochemical profile quantification. Note however that when using semi-LASER for clinical cohort comparisons, age [44], disease [45], metabolite [46] and region [47] associated variance in T_2 needs to be considered at the TEs achievable with the sequence. In addition to optimized MRS methodology, reproducible voxel placement (Table 1) was clearly also an important factor in the high reproducibility in metabolite concentrations. Note that the approach we chose to report voxel overlap (fraction shared by at least 3 VOI) was appropriate since the voxel was not placed based on a reference session (e.g. session #1). Also note that the reproducibility of metabolite concentrations may be further improved by automating VOI placement using atlas-based approaches.

Importantly, lower CRLBs did not necessarily translate to lower CVs at 7T (Fig. 2). However, the sample size was only 6 for the pairwise comparison of CVs at 3T vs. 7T, therefore notable differences in mean CVs of Glu, Gln and GSH at 3T vs. 7T remained as trends. Analysis of sub-spectra with a reduced number of scans demonstrated that we

reached a minimum achievable CV threshold with a lower number of transients than 64 at 7T for multiple metabolites and that test-retest CVs are indeed lower at 7T than at 3T with shorter acquisitions (Fig. 4).

CONCLUSION

We conclude that the decision regarding which field to utilize for reproducible neurochemical quantification depends on the neurochemical of interest, the spatial resolution needed for the clinical question at hand, and the scanning time that is appropriate for the experiment. For typical sized VOI, e.g ~6 mL and larger as utilized here, state-of-the-art MRS methodology allows excellent reproducibility for many metabolites with 5 minute data averaging on clinical 3T hardware. Sensitivity and resolution advantages at 7T become important for coupled metabolites such as Gln, GABA, GSH and NAAG, short acquisitions and small VOI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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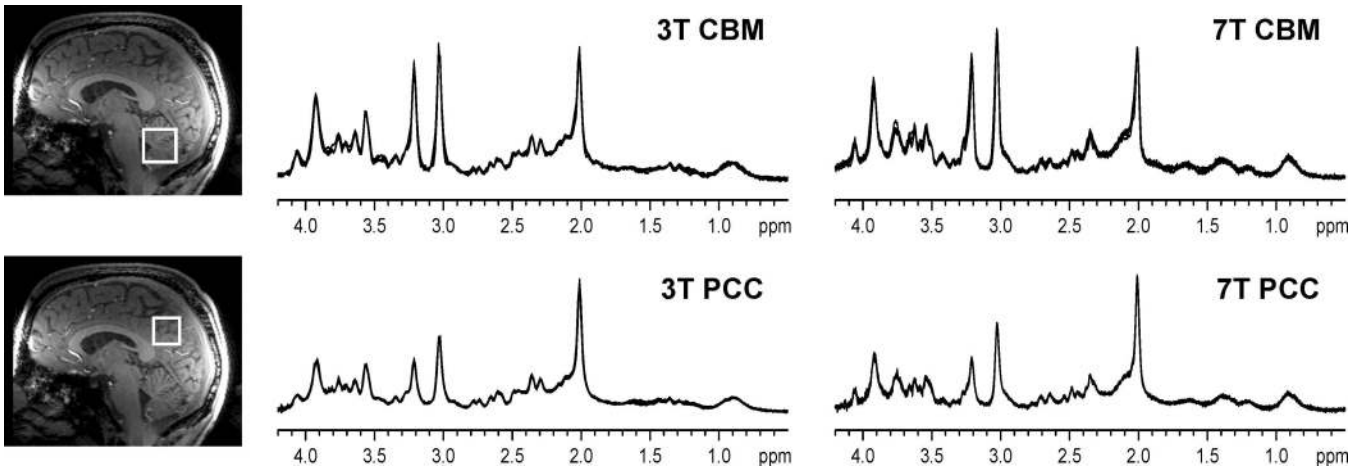

Figure 1. Reproducibility of spectral quality and pattern

All spectra obtained in one subject are shown (semi-LASER, T_E = 28ms at 3T and 26ms at 7T, T_R = 5s, 64 transients), with the 4 spectra obtained per brain region/field overlaid in each panel. The voxel locations are shown on the T_1-weighted images acquired at 3T. Spectra were apodized with linebroadening (1 Hz) and Gaussian multiplication (σ = 0.12 s) for display purposes. PCC: posterior cingulate cortex, CBM: cerebellar vermis.

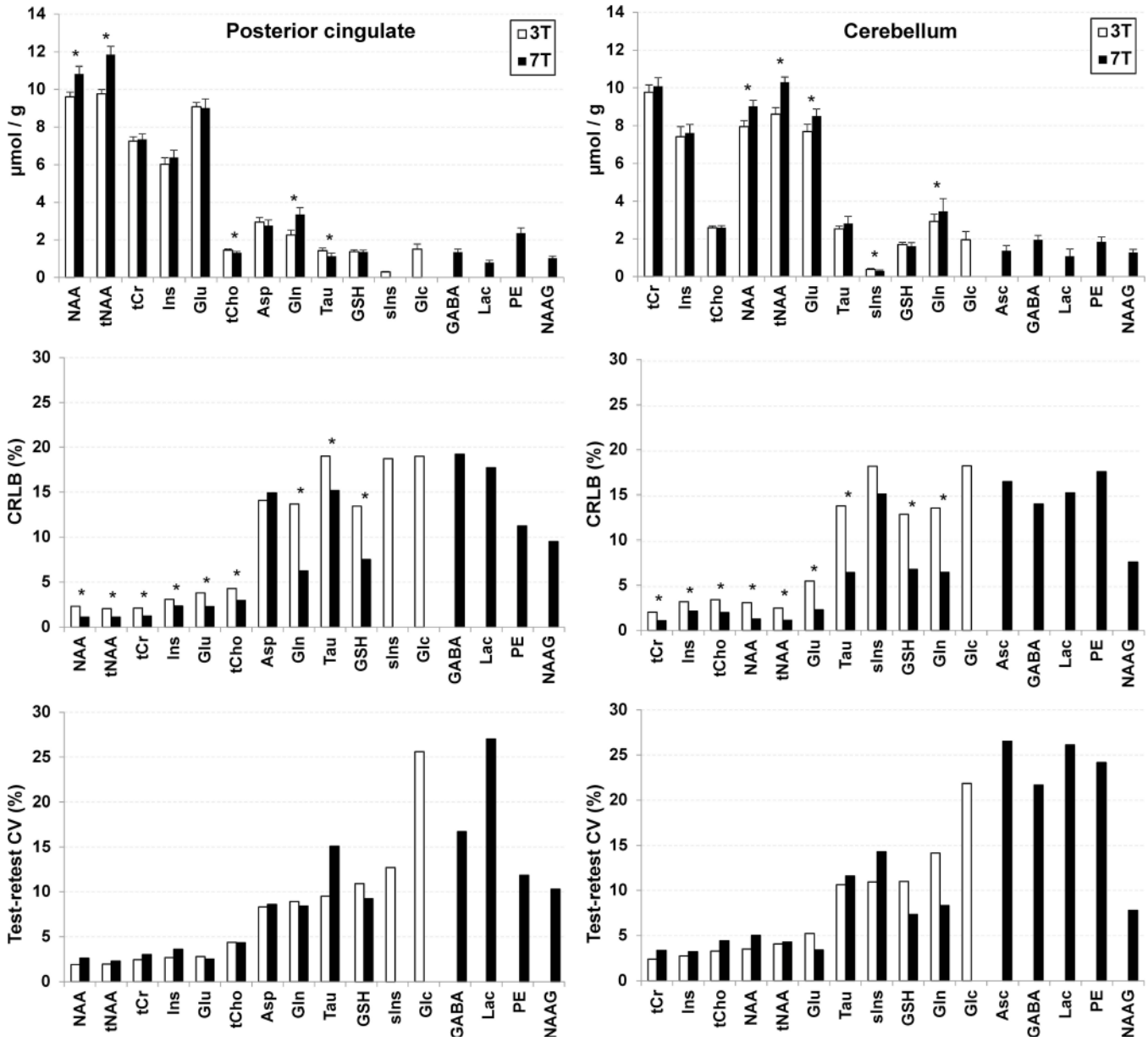

Figure 2. Mean metabolite concentrations, Cramér-Rao lower bounds (CRLB) and between-session CVs obtained with semi-LASER (T_E = 28ms at 3T and 26ms at 7T, T_R = 5s, 64 transients) in the two brain regions at both field strengths

Only metabolites with mean CRLB ≤20% are shown. Error bars represent inter-subject SD of intra-subject means. Means include all scans of each subject, i.e. up to 5 scans at each field strength. * $p < 0.05$, 3T vs. 7T.

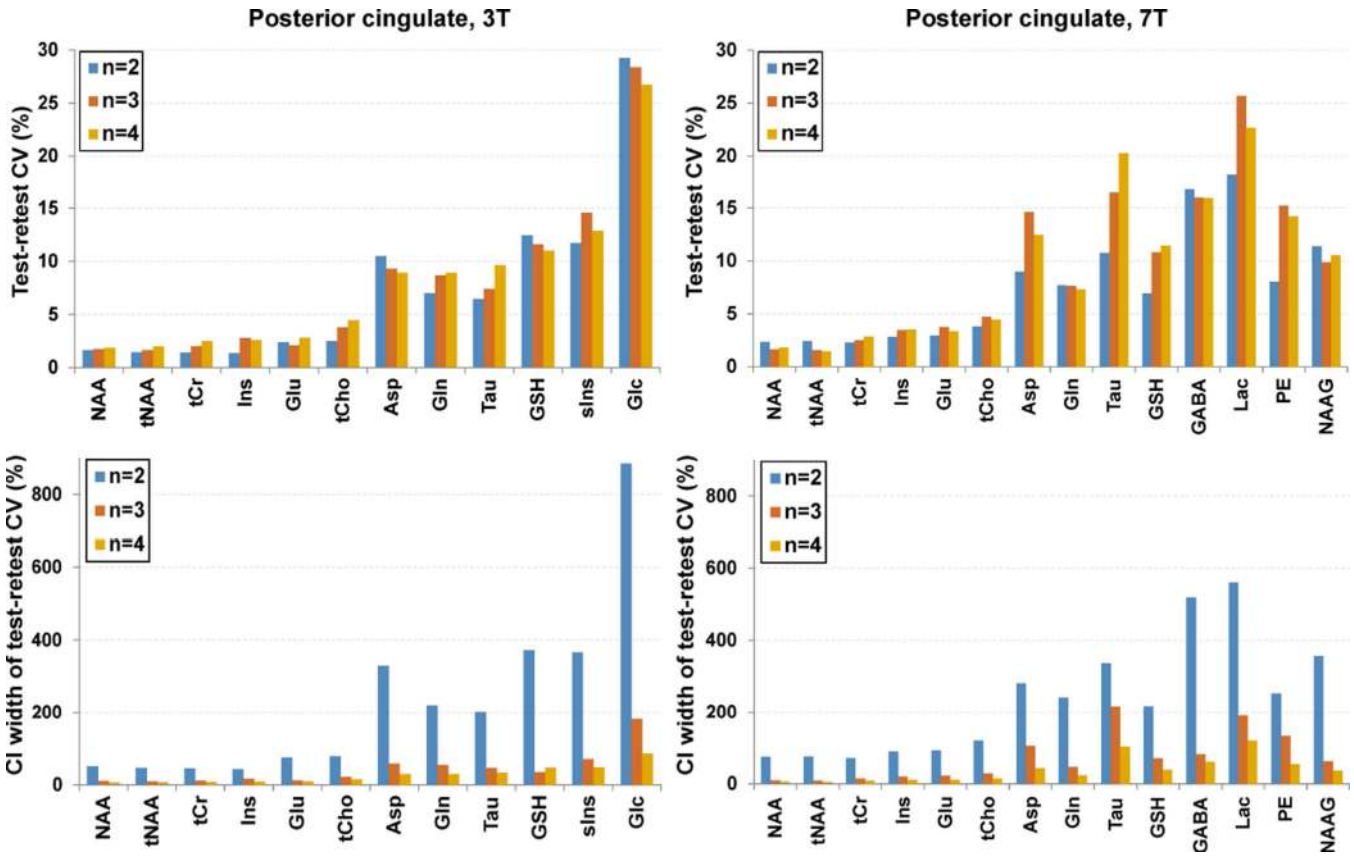

Figure 3. Mean between-session CVs (SD/mean, top row) and inter-subject means of the intra-subject confidence interval widths for between-session CVs (bottom row) for posterior cingulate neurochemical profiles, obtained with 2, 3 or 4 repeat scans

Similar results were obtained for the CBM (not shown)

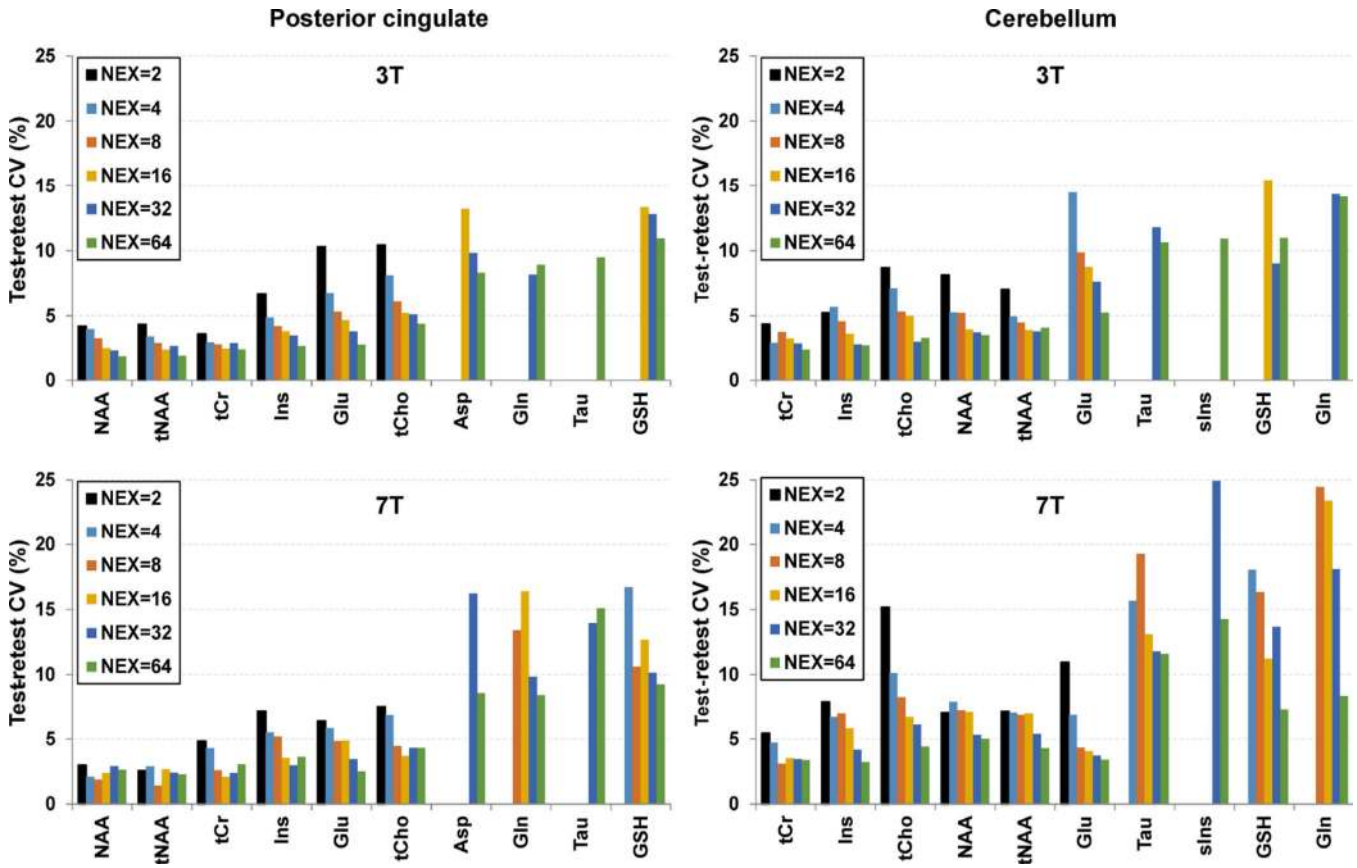

Figure 4. Mean between-session CVs obtained by averaging the first 2, 4, 8, 16, 32 and 64 transients (NEX) of spectra from the two brain regions and field strengths

Only metabolites that passed the CRLB reliability criteria are shown, e.g. weakly represented metabolites such as Asp, Gln, Tau and GSH are not reliably quantified in spectra with 2 transients.

Table 1

Spectroscopic parameters measured in two brain regions and two fields.

	3T		*7T*	
	PCC	**CBM**	**PCC**	**CBM**
Number of spectra (N)	25	25	21	22
Water linewidth (Hz)	6.6 ± 0.4	7.5 ± 0.9 **	12.1 ± 1.0	14.3 ± 1.2 **
SNR_{freq} [a]	234 ± 57	127 ± 29 **	181 ± 28 *	141 ± 21 *, **
CSF fraction (%)	6.1 ± 2.5	7.6 ± 3.3	5.5 ± 1.6	7.8 ± 2.6
Voxel overlap (%) [b]	91 ± 5	90 ± 2	88 ± 5	90 ± 4

Values given are inter-subject mean ± inter-subject standard deviation of the intra-subject means.
PCC: posterior cingulate cortex; CBM: cerebellar vermis.

[a] SNR was measured in the frequency domain (defined as peak height divided by root mean square noise) based on tNAA in non-apodized spectra.

[b] Fraction of total voxel volume that is shared in at least three of the four scanning sessions

* $p < 0.01$, 3T vs. 7T (within region)

** $p < 0.001$, PCC vs. CBM (within field)