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Improved quantification precision of human brain short echo-time ^1H MRS at high magnetic field: A simulation study

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Abstract

Purpose—The gain in quantification precision that can be expected in human brain ^1H MRS at very high field remains a matter of debate. Here we investigate this issue using Monte-Carlo simulations.

Methods—Simulated human brain-like ^1H spectra were fitted repeatedly with different noise realizations using LCModel at B_0 ranging from 1.5T to 11.7T, assuming a linear increase in SNR with B_0 in the time domain, and assuming a linear increase in linewidth with B_0 based on experimental measurements. Average quantification precision (Cramér-Rao Lower Bound, CRLB) was then determined for each metabolite as a function of B_0 .

Results—For singlets, CRLB improved (decreased) by a factor $\sim \sqrt{B_0}$ as B_0 increased, as predicted by theory. For most J -coupled metabolites, CRLBs decreased by a factor ranging from $\sqrt{B_0}$ to B_0 as B_0 increased, reflecting additional gains in quantification precision compared to singlets due to simplification of spectral pattern and reduced overlap.

Conclusion—Quantification precision of ^1H MRS in human brain continues to improve with B_0 up to 11.7T, even though peak SNR in the frequency domain levels off above 3T. In most cases, the gain in quantification precision is higher for J -coupled metabolites than for singlets.

Keywords

^1H magnetic resonance spectroscopy; Human brain; Monte-Carlo simulations; Quantification precision; Cramér-Rao Lower Bounds

INTRODUCTION

Proton magnetic resonance spectroscopy (^1H MRS) allows non-invasive measurement of the concentration of multiple metabolites in the brain in vivo. In principle, high magnetic fields are beneficial for ^1H MRS due to increased signal-to-noise ratio (SNR), increased spectral dispersion and simplification of J -coupled spectral patterns. However, these benefits are mitigated by other factors, such as increased RF power and B_0 shimming requirements. In addition, even with perfect B_0 shimming, the spectral linewidth gets broader at high fields

due to shorter T_2 relaxation times and increased B_0 microsusceptibility effects (1,2). As a result, even with a very short echo-time (T_E) sequence (so that signal loss from T_2 relaxation is minimized), the actual gain in sensitivity and quantification precision of ^1H MRS in human brain at ultra high-field (7T and beyond) is still a matter of debate.

Multiple studies have documented experimental gains in SNR in human brain ^1H MRS with high fields. However the reported gains vary significantly from study to study. Peak SNR in the frequency domain (SNR_{freq} , defined as peak height divided by RMS noise) was shown to increase 23% to 46% at 3T relative to 1.5T (3–5) while another study reported no improvement (6). Another study found a ~80% increase in SNR_{freq} at 4T compared to 1.5T (7). Furthermore a 1:1 linear increase in SNR_{freq} of singlet resonances with B_0 was reported from 1.5T to 7T (8). More recently, a 1.7-fold increase in SNR_{freq} from 3T to 7T (9), and a 1.91-fold increase from 4T to 7T (10) were also reported. Therefore, there is significant variability in the actual sensitivity gains observed at high field. Such variability can be explained in part by the difficulty to match experimental conditions (design and construction of RF coils, B_1 spatial distribution, etc) between different systems at different B_0 field strengths.

Another possible approach to assess potential gains in quantification precision at high field is using simulations. Previous simulations in rodent brain suggested that SNR_{freq} is expected to flatten out as B_0 increases, with little increase ($< 10\%$) in SNR_{freq} of singlet resonances (NAA, Cr) above 10T (11). However, further gains in quantification can reasonably be expected for J -coupled metabolites due to simplification of spectral patterns and reduced overlap at high field (11). Therefore, the improvement in quantification precision for every individual metabolite as B_0 increases remains an open question.

In this context, the goal of the present study was to determine the relationship between quantification precision (estimated by Cramér-Rao Lower Bounds or CRLBs) and B_0 for every brain metabolite present in in vivo ^1H MR spectra. To achieve this goal, we performed Monte-Carlo simulations together with LCModel and simulated ‘brain-like’ spectra at multiple B_0 field strengths.

MATERIAL AND METHODS

Simulations were performed with two main assumptions: (a) the in vivo linewidth increases linearly with B_0 above 1.5T as measured experimentally (1) and (b) the SNR *in the time domain* (SNR_{time}) increases linearly with B_0 (12,13). ‘Brain-like’ ^1H NMR spectra were simulated in Matlab (14), assuming no J -evolution (pulse-acquire sequence analogous to an ultrashort T_E sequence). Nineteen metabolites were included with concentrations similar to those found in human occipital cortex: 0.5 mM alanine (Ala), 1 mM ascorbate (Asc), 2 mM aspartate (Asp), 4 mM creatine (Cr), 1 mM γ -aminobutyric acid (GABA), 1 mM glucose (Glc), 10 mM glutamate (Glu), 2.5 mM glutamine (Gln), 0.5 mM glycerophosphorylcholine (GPC), 1 mM glutathione (GSH), 0.5 mM lactate (Lac), 6 mM *myo*-inositol (Ins), 12 mM N-acetylaspartate (NAA), 1 mM N-acetylaspartylglutamate (NAAG), 4 mM phosphocreatine (PCr), 0.5 mM phosphorylcholine (PCho), 1.5 mM phosphorylethanolamine (PE), 0.25 mM

scyllo-inositol (sIns) and 1.5 mM taurine (Tau). Macromolecules were also simulated and added to the spectrum (see Supplemental Methods for details).

Brain-like spectra were then generated at 6 different magnetic field strengths: 1.5, 3, 4, 7, 9.4 and 11.7T with a spectral linewidth of 2.1, 3.7, 4.9, 8.5, 11.2 and 14.0 Hz respectively. These values were obtained by measuring the linewidth of the tCr peak at 3.03 ppm at 4T, 7T and 9.4T, and subtracting the Cr-PCr chemical shift difference (0.0033 ppm or 0.14 Hz/T). Values at 1.5T, 3T and 11.7T were obtained by linear extrapolation of the fit from 4T to 9.4T. The slope was 1.31 Hz/T and 1.17 Hz/T before and after subtraction of the Cr-PCr chemical shift difference respectively. All metabolites were simulated with the same linewidth, neglecting small differences in linewidth due to different T_2 relaxation times. The resulting simulated spectra (Figure 1) were very similar in appearance to those obtained experimentally in the human brain (1,3,8–10,15).

For Monte-Carlo simulations, Gaussian noise was added to the simulated ^1H NMR spectra, with a noise level inversely proportional to B_0 . The resulting spectra were fitted with LCModel version 6.1-4A (16). This procedure was repeated 50 times with 50 different random noise realizations (sufficient for proper convergence), yielding 50 CRLB values for each metabolite at each B_0 . The quantification precision for each metabolite at a given B_0 was calculated as the average of these 50 CRLB values.

The SNR of the simulated spectra was chosen in order to obtain accurate estimates of the CRLBs at all magnetic fields. If SNR is too low, many low concentration metabolites cannot be reliably fitted. If SNR is too high, estimates of CRLBs for high concentration metabolites are very small ($< 2\%$) and are not precise enough because of rounding in LCModel. Therefore, two simulations were performed. One simulation was performed with ‘low’ SNR (SNR of NAA peak measured in the frequency domain was 25 ± 1 at 4T) to estimate CRLBs for Cr, PCr, Glu, NAA and Ins as well as the sums tCho = PCho+GPC, tCr = Cr+PCr and Glx = Glu+Gln. A second simulation was performed with ‘high’ SNR (SNR of NAA peak in the frequency domain was 100 ± 4 at 4T) to determine CRLBs for all other metabolites.

T_1 effects were neglected because T_1 relaxation times show only modest increases with B_0 (1). For example, assuming a T_R of 5s and an increase in the T_1 of tCr-CH₃ from 1.39s at 1.5T to 1.75s at 9.4T (1) would result in a negligible 3% loss in SNR at 9.4T compared to 1.5T due to T_1 saturation.

RESULTS

SNR_{freq} becomes nearly constant as the B_0 field increases

In our simulated ^1H NMR spectra, both the linewidth (in Hz) and the SNR in the time domain were assumed to increase linearly with B_0 . With those two assumptions, SNR_{freq} of singlets, defined as peak height relative to RMS noise, was found to level off and showed only modest increase above 3–4T (Figure 2). This is explained by the fact that the increase in SNR_{time} is offset by the increase in linewidth. Quantitatively, SNR_{freq} is proportional to SNR_{time}/ ν_{Hz} , where ν_{Hz} is the spectral linewidth in Hz. With our assumptions: SNR_{time}= $C \cdot B_0$ and ν_{Hz} = $D \cdot B_0 + E$ where C, D and E are constants. It follows that SNR_{freq}

is proportional to $C \cdot B_0 / (D \cdot B_0 + E)$. When B_0 increases, then $D \cdot B_0 \gg E$ and SNR_{freq} becomes nearly constant. For example using experimental values for the tCr linewidth at 3.03 ppm, the linewidth of tCr in the human brain (including the small chemical shift difference between Cr and PCr) can be expressed as $\nu_{\text{Hz}} = 1.31B_0 + 0.27$ (1) or in ppm, $\nu_{\text{ppm}} = \nu_{\text{Hz}} / \gamma B_0 = 0.031 + 0.006/B_0$. For $B_0 > 3\text{T}$, the second term becomes negligible ($< 5\%$) resulting in a constant linewidth (in ppm) of ~ 0.031 ppm as well as constant SNR_{freq} . The above formula is valid for tCr, and the constants would be slightly different for other singlets, but NAA shows a similar behavior, with a plateau in SNR_{freq} above 3–4T (Figure 2).

Quantification precision continues to increase with B_0 at very high field—In spite of the fact that SNR_{freq} become nearly constant at very high field, simulations show that the quantification precision (estimated by CRLBs) continues to increase substantially for all metabolites as B_0 increases. Figure 3 shows examples of this improvement for tCr, Glu, Gln and GABA.

To quantify the improvement of CRLBs as a function of B_0 , these plots were fitted with a function in the form $\text{CRLB} \propto B_0^\alpha$ or, in logarithm coordinates, with a linear function $\log(\text{CRLB}) = \alpha \cdot \log(B_0) + C$, with α and C as free parameters. Results show a close linear relationship between $\log(\text{CRLB})$ and $\log(B_0)$ for all metabolites (R^2 ranging from 0.96 to 1 for all metabolites, except $R^2=0.88$ for glucose and $R^2=0.93$ for sIns). The fitted slope ranged from $\alpha=-0.42$ (for glucose) to $\alpha=-1.05$ (for glutamine) (Table 1). A slope value of -1.0 corresponds to $\text{CRLB} \propto 1/B_0$, whereas -0.5 corresponds to $\text{CRLB} \propto 1/\sqrt{B_0}$.

These findings are supported by theory. Indeed, theoretical calculations of CRLB for a singlet predict that, if SNR_{time} and ν_{Hz} both increase linearly with B_0 (i.e constant SNR_{freq}) then the CRLB of the estimated concentration decreases as $1/\sqrt{B_0}$ (17). Our simulation results show that, for metabolites appearing primarily as singlets in the ^1H NMR spectrum, the slope α was close to -0.5 (-0.61 for tCr, -0.51 for tCho and -0.56 for sIns), which is in good agreement with theoretical predictions.

For other metabolites that appear as multiplets with complex J -coupled spectral patterns, such theoretical calculations are generally not possible. However, the increase in quantification precision was higher than for singlets in most cases, with the slope α generally comprised between -0.5 and -1 . Metabolites that showed the highest increase in quantification precision with B_0 were glutamine ($\alpha=-1.05$), glutamate ($\alpha=-0.95$) and GABA ($\alpha=-0.97$). This reflects the simplification of spectral pattern and reduced overlap of these metabolites at high field, whereas they overlap strongly at lower field (Figure 1). Similarly, reduced overlap between the J -coupled resonances of GPC and PCho at high field contributed to higher α values for these two metabolites ($\alpha=-0.92$ for GPC and $\alpha=-0.80$ for PCho). However, we found exceptions to this trend: for Glc ($\alpha=-0.42$), Asp ($\alpha=-0.44$), or Ins ($\alpha=-0.52$), the decrease in CRLBs with B_0 was more modest. Therefore, the actual improvement in quantification precision with B_0 is strongly dependent on the spectral pattern of each metabolite.

The number of metabolites that can be quantified reliably increases with B_0 —

The improvement in quantification precision with B_0 resulted in a steady increase in the number of metabolites that could be quantified reliably, using $\text{CRLB} < 25\%$ as a threshold (Table 2). With the ‘low SNR’ simulation condition, which is typical of in vivo MRS in human brain, five metabolites could be quantified reliably with $\text{CRLB} < 25\%$ (tCr, tCho, NAA, Glx and Ins) at 1.5T, six metabolites (Cr, PCr, tCho, NAA, Glx and Ins) at 3T and up to sixteen metabolites at 11.7T (Table 2). The remaining three metabolites (Asc, Glc and sIns) had CRLBs around 30% at 11.7T. Although this is only valid for those particular SNR conditions, it illustrates how gains in quantification precision translate into increased neurochemical information content.

DISCUSSION

Comparison between human brain and rat brain

In human brain, we show here that both peak SNR in the frequency domain (SNR_{freq}) and the linewidth expressed in ppm (ν_{ppm}) are expected to become nearly constant above 3T. A similar prediction has been made in the rat brain, where the increase in linewidth (in ppm) was shown to become nearly constant at high field (11,18). According to de Graaf and colleagues (11), the linewidth of tCr in rat brain becomes nearly constant above 9.4T and converges to ~ 0.018 ppm (compared with ~ 0.031 ppm in human brain). Interestingly, the B_0 threshold above which ν_{ppm} and SNR_{freq} level off is higher in rat brain (9.4T) than in human brain (3T). This is due to the longer T_2 relaxation times of metabolites and smaller microscopic B_0 inhomogeneity in rat brain compared to the human brain, resulting in smaller metabolites linewidth in the rat brain.

Relevance of assumptions used in simulations

Assumption on SNR—Simulations in the present study assumed a linear 1:1 increase in SNR_{time} with B_0 , based on the expected theoretical gain in intrinsic SNR (13). However, the actual gain in SNR_{time} with B_0 is strongly dependent on experimental factors such as the performance of RF coils used or the spatial distribution of B_1 field. Even if experimental conditions (RF chain, RF coil geometry, etc) are kept nearly identical, the distribution of the B_1 field inevitably changes with B_0 , especially at high field. As such, any increase in SNR_{time} with B_0 measured experimentally in human brain is valid only for a specific coil geometry and voxel location, even if all other experimental conditions are perfectly matched.

For example, a previous study reported a ~ 2 -fold increase in SNR_{freq} at 7T versus 4T (10), in apparent contradiction with the results of the present simulation study, which predicts very little improvement in SNR_{freq} from 4T to 7T. However, a 2-fold increase in SNR_{freq} , together with the reported increase in tCr linewidth from 5.9Hz at 4T to 9.8Hz at 7T, would correspond to a 3.3-fold increase in SNR_{time} for tCr. This experimentally measured factor was much higher than the factor of 1.75 (i.e. $7/4$) assumed in our simulations based on theoretical predictions (12,13). One possible explanation for the higher than expected gain in SNR_{time} measured experimentally is that different RF coils were used at 4T and 7T, with slightly different geometry and design, which could favor the 7T coil. Alternatively, even

when using very similar surface coils at 4T and 7T, a larger portion of the available SNR may be concentrated close to the coil as B_0 increases. Indeed, when comparing images at 4T and 7T in (10), SNR clearly drops more quickly at 7T than at 4T when going away from the coil.

While the assumption of a linear increase of SNR_{time} with B_0 may not hold true in all particular cases, our simulations give useful insight into the gains in quantification precision that can be expected at high field for every metabolite. Simulations make it possible to have a consistent SNR hypothesis across all B_0 values, and therefore identify general trends not easily identified from experimental data due to the difficulty to match experimental conditions at multiple B_0 .

In addition, since CRLBs are inversely proportional to SNR_{time} for a given B_0 (17), results can easily be extrapolated using a different assumption for $\text{SNR}_{\text{time}} = f(B_0)$. For example, if SNR_{time} varied as $B_0^{1.2}$ instead of B_0 , all α coefficients in Table 1 would be simply multiplied by 1.2.

Assumption on very short T_E —Our simulations are valid for very short T_E sequences for which the loss of signal from T_2 relaxation during T_E can be neglected. At high field, however, such losses from T_2 relaxation may become significant. For similar experimental conditions, the minimum T_E tends to increase at high field due to increased power requirements, and T_2 relaxation times become shorter. This is particularly true for MRS sequences on clinical scanners, which are generally not optimized to minimize T_E .

State-of-the-art research sites, in contrast, recognizing that minimizing T_E is critical to harness gains in quantification precision at high-field, have used MRS methodology that keeps relatively short T_E even at 7T and 9.4T (1,9,15). However, even in those studies, loss of signal due to T_2 relaxation may not be completely negligible at high field.

Our results can be extended to take into account the additional loss of signal from T_2 relaxation by taking advantage of the fact that all CRLB values obtained in our simulations are inversely proportional to SNR at each B_0 (17). Therefore, corrected CRLBs can be derived from our initial, uncorrected CRLB values as

$\text{CRLB}_{\text{corr}} = \text{CRLB}_{\text{uncorr}} * \text{SNR}_{\text{uncorr}} / \text{SNR}_{\text{corr}}$ with $\text{CRLB}_{\text{uncorr}}$ proportional to B_0^α and α coefficients given in Table 1. If $\text{SNR}_{\text{uncorr}} / \text{SNR}_{\text{corr}}$ is expressed empirically as B_0^β , then $\text{CRLB}_{\text{corr}}$ is proportional to $B_0^{\alpha+\beta}$ and coefficients α in Table 1 simply need to be corrected by adding the term β .

Values of $T_{E(\text{min})}$ and even T_2 relaxation times depend on the specific sequence used. Therefore, we estimated the signal loss using approximate values of $T_{E(\text{min})}$ and T_2 relaxation times at each B_0 for the two MRS sequences currently being used in our center: STEAM and semi-LASER (19).

For STEAM, coefficients α in Table 1 need to be corrected by adding a term $\beta=0.06$ (average of 0.05 for NAA and 0.07 for tCr) (See Supplemental Data for an example). For semi-LASER, coefficients α in Table 1 need to be corrected by a term $\beta=0.2$ (average of 0.18 for NAA and 0.21 for tCr).

Assumption on optimal shimming and spectral quality—The ^1H NMR spectra used in the current study were simulated assuming perfect B_0 shimming in the human occipital lobe in vivo. Shimming imperfections (i.e. B_0 inhomogeneities that cannot be compensated for by 2nd order shim coils) increase linearly with B_0 , and these imperfections may be significant in areas of the brain other than the occipital lobe and/or in large voxels. Therefore the present study provides the maximum achievable improvement of quantification precision at high field for perfectly shimmed voxels.

It was also assumed that there was no baseline distortion and no lipid contamination due to imperfect outer volume suppression. Achieving such optimal conditions is not always possible experimentally, since spectral quality is strongly dependent on the pulse sequence and B_0 shimming algorithm used, the brain region under investigation, and any movement from the subject.

CRLB as estimator of quantification precision—Finally, it should be kept in mind that CRLBs represent only a lower bound of the experimental error. Nonetheless, CRLBs are generally good estimators of the quantification precision of a given metabolite when spectral noise is the main contributor to experimental error, as is the case when SNR for this metabolite is relatively low. At higher SNR, intra-subject experimental error typically becomes dominated by other experimental factors such as movement.

CONCLUSION

In conclusion, the quantification precision of metabolites is expected to continue to improve in the human brain with field strength up to 11.7T, even though SNR_{freq} does not increase substantially above 3T. The improvement in quantification precision is dependent on the spectral pattern of each metabolite. In general, greater improvement in quantification precision is obtained for J -coupled metabolites than for singlets as B_0 increases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Examples of 'brain-like' simulated ^1H NMR spectra with low SNR (left) and high SNR (right) from 1.5T (top) to 11.7T (bottom) using the linewidth values and the concentrations of metabolites given in the text. For each condition (low SNR or high SNR), spectra are scaled so that the RMS noise is identical at each magnetic field.

Figure 2. SNR_{freq} as a function of B₀ measured as NAA peak intensity relative to RMS noise using both the low and high SNR conditions. Error bars represent SD.

Figure 3. Mean CRLBs for selected metabolites (tCr, Glu, Gln and GABA) obtained from Monte-Carlo simulations. The data are plotted in logarithmic scale. Solid lines represent the best fits. Error bars represent SD of 50 CRLB values obtained from Monte-Carlo simulations. Note that values for tCr and Glu were obtained with the “low SNR” condition and values for Gln and GABA with the “high SNR” condition.

Table 1

Slope (α) and R^2 correlation coefficient obtained after fitting the CRLBs as a function of B_0 using a power regression function i.e. $\sigma \cdot B_0^\alpha$ (equivalent to a linear fit in logarithmic coordinates).

Spin systems	Metabolites	Slope, α	R^2
Mostly singlet	NAA [†]	-0.67	0.94
	Creatine [†]	-0.62	0.96
	Phosphocreatine [†]	-0.57	0.96
	Scyllo-inositol	-0.56	0.93
	Total choline [†]	-0.51	1.00
	Total creatine [†]	-0.61	0.98
<i>J</i> -coupled	Alanine	-0.75	0.98
	Ascorbate	-0.67	0.98
	Aspartate	-0.44	0.96
	Glucose	-0.42	0.88
	GABA	-0.97	1.00
	Glutamate [†]	-0.95	0.99
	Glutamine	-1.05	0.99
	Glutathione	-0.87	0.97
	Glycerophosphorylcholine	-0.92	0.99
	Lactate	-0.72	0.98
	Myo-Inositol [†]	-0.52	0.96
	NAAG	-0.70	1.00
	Phosphethanolamine	-0.87	0.99
	Phosphocholine	-0.80	1.00
	Taurine	-0.78	1.00
	Glutamate + glutamine [†]	-0.86	0.99

[†]The [†] sign indicates values obtained using the “low SNR” condition. The SD for the slope was < 0.1 for all metabolites.

Table 2

List of metabolites that can be quantified reliably with $CRLB < 25\%$ at different B_0 using the 'low SNR' simulation condition. While this result is valid only for this particular SNR condition, it illustrates how gains in quantification precision translate into a higher number of metabolites that can be quantified reliably.

Magnetic Field (T)	1.5	3	4	7	9.4	11.7
Number of metabolites	5	6	8	12	14	16
	Metabolite	CRLB (%)	Metabolite	CRLB (%)	Metabolite	CRLB (%)
	NAA	8	NAA	3	NAA	2
	tCho	18	tCho	11	tCho [†]	6
	Ins	10	Ins	6	Ins	3
	Glx	13	Glx	5	Glx [†]	2
	tCr	7	tCr [†]	4	tCr [†]	2
			Cr	12	Cr	7
			PCr	12	PCr	7
			Glu	5	Glu	2
			Gln	18	Gln	6
			GSH	24	GSH	12
					NAAG	12
					PE	13
					GPC	18
					Tau	14
					GABA	15
					Asp	19
					Lac	22
					PCho	23
					Ala	24

[†] Note that metabolites representing the sum of two other metabolites were not counted when their individual components could be quantified separately. For instance, both Glu and Gln were reliably quantified at 4T such that Glx was not counted. Those metabolites are marked with a [†] sign.