GABA Editing With Macromolecule Suppression Using an Improved MEGA-SPECIAL Sequence

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Purpose: The most common γ-aminobutyric-acid (GABA) editing approach, MEGA-PRESS, uses J-editing to measure GABA distinct from larger overlapping metabolites, but suffers contamination from coedited macromolecules (MMs) comprising 40 to 60% of the observed signal. MEGA-SPECIAL is an alternative method with better MM suppression, but is not widely used primarily because of its relatively poor spatial localization. Our goal was to develop an improved MM-suppressed GABA editing sequence at 3 Tesla.

Methods: We modified a single-voxel MEGA-SPECIAL sequence with an oscillating readout gradient for improved spatial localization, and used very selective 30-ms editing pulses for improved suppression of coedited MMs.

Results: Simulation and in vivo experiments confirmed excellent MM suppression, insensitive to the range of B_0 frequency drifts typically encountered in vivo. Both intersubject and intrasubject studies showed that MMs, when suppressed by the improved MEGA-SPECIAL method, contributed approximately 40% to the corresponding MEGA-PRESS measurements. From the intersubject study, the coefficient of variation for GABA+/Cre (MEGA-PRESS) was 11.2% versus 7% for GABA/Cre (improved MEGA-SPECIAL), demonstrating significantly reduced variance ($P = 0.005$), likely coming from coedited MMs.

Conclusions: This improved MEGA-SPECIAL sequence provides unbiased GABA measurements with reduced variance as compared with conventional MEGA-PRESS. This approach is also relatively insensitive to the range of B_0 drifts typically observed in in vivo human studies. **Magn Reson Med 79:41–47, 2018.**

Key words: GABA; MRS; MEGA-PRESS; MEGA-SPECIAL; macromolecule suppression

INTRODUCTION

In vivo measurement of the human brain's primary inhibitory neurotransmitter, γ-aminobutyric-acid (GABA), using proton magnetic resonance spectroscopy (MRS), offers valuable information for understanding brain function in health and disease (1–12). Because of its low concentration, complicated spectrum, and overlap with other larger metabolite resonances at 3 Tesla (T), detecting GABA is difficult with conventional single-voxel MRS techniques such as PRESS and STEAM (13,14). The most widely used sequence for in vivo GABA detection is MEGA-point-resolved spectroscopy (MEGA-PRESS), a J-difference editing approach in which spectral editing pulses are sequentially applied to the GABA C3 resonance at 1.9 ppm for the "editing on" case, and at 7.5 ppm (symmetric to the water resonance at 4.7 ppm) for the "editing off" case (15). Subtraction of the two spectra yields a 3-ppm GABA signal as a result of J-coupling between the 1.9- and 3-ppm GABA peaks. Based on the GABA J-coupling constant, maximum signal is achieved using an echo time (TE) of 68 ms (16,17).

Contamination from coedited macromolecules (MMs) is the primary limitation for interpreting MEGA-PRESS GABA measurements. Finite echo times limit the duration (and therefore spectral selectivity) of the editing pulses, resulting in partial excitation of MM components at 1.7 ppm that, like GABA, have J-coupled partners at 3.0 ppm (18). Indeed, the first reported in vivo ^{1}H MRS GABA studies recognized that 40 to 60% of the detected 3-ppm J-edited peak is not from GABA, but rather macromolecules exhibiting similar J-coupling patterns (19). For many published ^{1}H MRS GABA studies, MM contamination is either ignored or assumed invariant across groups or treatments (5), and this limitation is recognized by reporting results as GABA+ = (GABA+MM). However, more detailed studies of brain MM resonances imply that this is a problematic approach (20–22). Most troubling is the finding that MM contamination is variable across individuals and contributes a significant portion to the observed MEGA-PRESS GABA+ signal variance (23). Regional MM differences have been reported (24), whereas findings with respect to age dependence are inconsistent (25). Using magnetization transfer methods, metabolite-nulled spectra showed a 38% higher gray versus white matter MM baseline (26), and MRS-derived differences were found by Hoffman et al (24) but not by Snoussi (27).

Several techniques that combine GABA editing with MM suppression have been proposed; however, none are widely used. Direct measurement of MMs via a second metabolite-suppressed acquisition doubles the already long scan time (5), for which none of the additional scan

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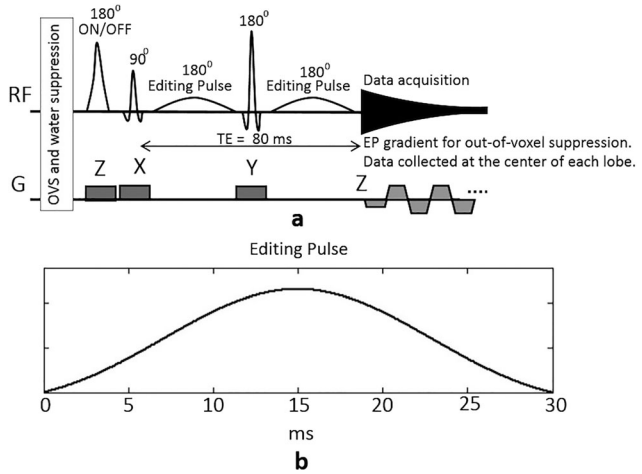

FIG. 1. (**a**) Schematic of the proposed improved MEGA-SPECIAL sequence for GABA editing with MM suppression. An EP readout gradient is used for out-of-voxel artifact suppression. The data points are only acquired at the center of each readout lobe. (**b**) The waveform of the 30-ms Gaussian-weighted sinc editing pulse.

time is used to improve the GABA signal-to-noise ratio (SNR). An alternative, called "symmetric" or "MM-suppressed" MEGA-PRESS, uses inversion pulses placed symmetrically about the 1.7-ppm MM signal to suppress these unwanted resonances with the compromise of the edited GABA signal (5). Editing efficiency and MM suppression can be further improved using longer spectral editing pulses. However, a 68-ms echo time limits the maximum length of the editing pulses in a double spin-echo MEGA-PRESS sequence to approximately 16 ms (28). Edden et al showed that at 3 T the edited GABA signal at 3 ppm is relatively insensitive to modest increases in echo time, and proposed 80-ms TE to allow 20-ms editing pulses for improved selectivity (5). However, symmetric MEGA-PRESS, which relies on the assumption that the macromolecule resonances have chemical shifts symmetrical around 1.7 ppm and are thus equally affected by both editing pulses (29), is highly sensitive to variations in the scanner frequency with drifts of more than or equal to 1 Hz/min, which is common after gradient intensive scans such as fMRI (30). Thus, a 10-min GABA editing sequence, as part of a standard brain imaging protocol, could easily experience center frequency drifts on the order of ± 10 Hz, resulting in unreliable MM suppression. Indeed, Mikkelsen et al found that GABA+ measurements were only weakly correlated with GABA signals acquired with symmetric MEGA-PRESS, an effect attributed to either sensitivity to frequency drifts or interindividual MM variability (28). Recently, prospective frequency corrections using interleaved water referencing have been suggested to help correct such B_0 frequency drifts (31).

An alternative approach uses the MEGA-spin-echo-full-intensity-acquired-localized (MEGA-SPECIAL) spectroscopy technique, which replaces the double spin-echo PRESS acquisition with a single spin-echo acquisition in combination with a preceding slice-selective inversion pulse. This allows for longer, more selective editing pulses, which in turn reduces MM signal contamination (32,33). Unfortunately, MEGA-SPECIAL localization along the inversion direction is relatively poor, as this 1D image-selected in vivo spectroscopy (ISIS) approach is susceptible to subtraction artifacts from out-of-voxel signals (34,35). Furthermore, MM-suppressed spectroscopic imaging of GABA has yet to be achieved (18,36), and conventional single-voxel MEGA-PRESS remains the current method of choice. Indeed, Mullins et al, in a recent MEGA-PRESS review paper (16), stated that "This widespread failure to account for MM ... stands as the greatest single limitation of this area to date and should be acknowledged as such."

Here, we propose to address this concern using an improved MEGA-SPECIAL J-editing pulse sequence, with an echo-planar (EP) readout gradient to improve spatial localization in the ISIS direction and very selective editing pulses to improve MM suppression.

METHODS

The improved MEGA-SPECIAL pulse sequence, shown in Figure 1a, was implemented on a 3T GE MR750 scanner (Waukesha, WI, USA) with a 32-channel Nova receive head coil. GE standard CHESS water suppression and slice-selective outer-volume-suppression pre-excitation RF pulses were used in the sequence. An adiabatic hyperbolic secant inversion pulse with a bandwidth of 5000 Hz was used for the 1D ISIS localization in the z direction. A 3.6-ms slice-selective 90° radiofrequency (RF) pulse with a bandwidth of 2366 Hz was used for excitation, while a 180° 5.2-ms slice-selective RF pulse with a bandwidth of 1384 Hz was used for refocusing. With 1.5-ms crusher gradients surrounding the refocusing RF pulse, two 30-ms Gaussian weighed sinc pulses, shown in Figure 1b, were incorporated into the 80-ms TE sequence and applied at 1.9 and 7.5 ppm for GABA editing.

To suppress the unwanted out-of-voxel signals in the ISIS direction, an EP readout gradient was added. The data sampling rate and corresponding spectral bandwidth were kept unchanged from that of a standard spectroscopic gradient-free readout, with the acquisition of each data point set to occur at the center of each gradient lobe (crossings of the z-axis in k-space), and the EP gradient strength was determined by the prescribed voxel thickness in the ISIS (z) direction. This readout gradient can be seen as an EP version of the spectroscopic imaging acquisition mode (SIAM) method for out-of-voxel artifact suppression (37,38), a 1D implementation of the sensitive point method (39), or a proton EP spectroscopic imaging acquisition for which only data from the central slice are reconstructed (40).

Specifically, this approach exploits the scanner's built-in digital low-pass filter. In contrast to conventional EP spectroscopic imaging, in which a high-bandwidth receiver filter is used and localization is achieved in the EP direction via postprocessing, a narrow-bandwidth low-pass filter as would be used for a conventional spectroscopic readout in the absence of the EP gradient is retained. This narrow-bandwidth low-pass filter suppresses all out-of-slice signals, which resonate outside of the filter bandwidth. For iso-center voxels, the EP gradients cause out-of-slice signals to resonate beyond the cut-off frequency of the receiver's low-pass filter. To accommodate differences in the low-pass-filter passband,

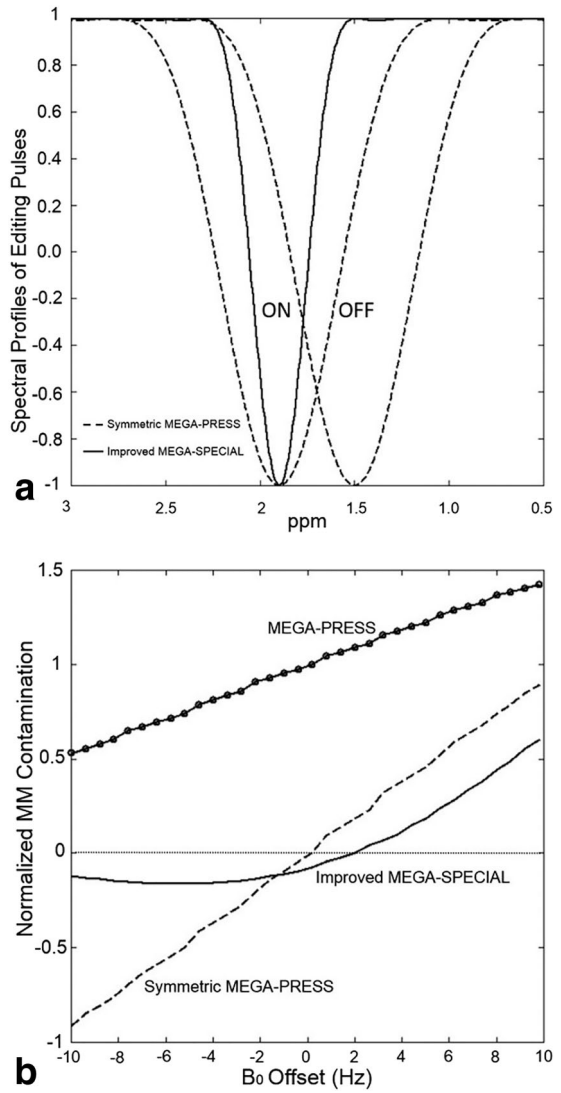

FIG. 2. (**a**) Simulated spectral profiles of the 14-ms 180° editing pulse for MEGA-PRESS and symmetric MEGA-PRESS and 30-ms 180° editing pulse for the improved MEGA-SPECIAL. The editing pulses are centered at 1.9/1.5 ppm for the on/off cases for symmetric MEGA-PRESS, and at 1.9/7.5 ppm for MEGA-PRESS and the improved MEGA-SPECIAL. (**b**) Simulated coedited MM using the MEGA-PRESS, symmetric MEGA-PRESS, and the improved MEGA-SPECIAL under ± 10-Hz B_0 frequency drift. All coedited MMs were normalized to that using MEGA-PRESS on resonance.

EP gradient–selected slice, and the RF-selected slice profile, the EP gradient amplitude is set to provide a slice slightly larger (10%) than the corresponding RF-selected slice in the ISIS (z) direction. For voxels out of the isocenter slice, demodulation of the acquired signal with the frequency determined by the gradient amplitude and the distance from the voxel center to the gradient isocenter is needed. In practice, this can be achieved by dynamically providing the receiver with a demodulating frequency calculated from the same waveform as the EP gradient. This approach also works for oblique voxels, as the EP gradient is played in the logical ISIS (z) direction, and thus rotation corresponding to the voxel orientation is applied to obtain the gradient waveforms in all three physical directions. For this application, each FID was acquired with 1024 data points at an acquisition bandwidth of 2500 Hz (ie, 0.4-ms dwell time), resulting in a 409.6-ms readout. Accordingly, there were 1024 EP gradient lobes for each readout with a 0.4-ms duration of each lobe.

Data reconstruction is therefore identical to that for data acquired without the oscillatory EP gradient readout. The net effect of this additional oscillatory readout gradient is to provide additional localization in the z direction to complement that provided by the (often imperfect) ISIS localization in the original MEGA-SPECIAL approach. Because a four-cycle acquisition (A (inversion off, editing off); B (inversion on, editing off); C (inversion off, editing on); and D (inversion on, editing on)) was used, localized free induction decays (FIDs) with editing off and editing on were first obtained from A-B and C-D, respectively (32). Localized FIDs from each individual coil were phase-corrected frame by frame using the dominant signal of residual water before averaging and coil combination (41,42). Fourier transform was then applied after the 4-Hz-line broadening. Finally, spectrum with editing on was subtracted from that with editing off to obtain the localized GABA-edited spectrum.

To evaluate the sensitivity of the MM suppression to B_0 inhomogeneities, we simulated the residual MM signal from (1) MEGA-PRESS, (2) symmetric MEGA-PRESS, and (3) the improved MEGA-SPECIAL. The MMs were modeled as J-coupled peaks at 1.7 and 3.0 ppm with a 4-Hz linewidth. The MEGA-PRESS and symmetric MEGA-PRESS used 14-ms 180° Gaussian-weighed sinc editing pulses as compared with 30-ms 180° Gaussian-weighted sinc editing pulses for the improved MEGA-SPECIAL. Residual MM signals were computed for ±10 Hz B_0 frequency drift. Ideal hard RF pulses were assumed for the spatial excitation and refocusing RF pulses.

The effects of the oscillatory readout gradient were next assessed by comparing in vivo data from an occipital lobe voxel of a healthy adult acquired with and without the EP gradient. To best visualize out-of-voxel signals, which would normally fold into the final spectrum, 16 phase encodes were applied in the ISIS (z) direction, and a total of 256 transients were acquired with TE/repetition time (TR) = 80/2000 ms.

Finally, GABA measurements with the new improved MEGA-SPECIAL sequence were directly compared with those obtained using conventional MEGA-PRESS in intra- and inter-subject repeatability and variability studies. For the intrasubject study, data were collected from the same healthy subject in five sessions (with subject removal and repositioning performed between scans). The intersubject study consisted of data from 10 healthy subjects. All in vivo data were acquired in a period of 2 months, and all human studies were approved by the local institution review board with informed consent obtained from each participant. The editing pulses for MEGA-PRESS were 14-ms 180° Gaussian-weighed sinc pulses applied at 1.9/7.5 ppm with TE/TR = 68 ms/2 s, respectively. The editing pulses for the improved MEGA-SPECIAL were 30-ms Gaussian-weighed sinc pulses applied at 1.9/7.5ppm with TE/TR = 80 ms/2 s, respectively. The GABA editing was performed on a 30 x 30 x 30 mm voxel in the occipital lobe.

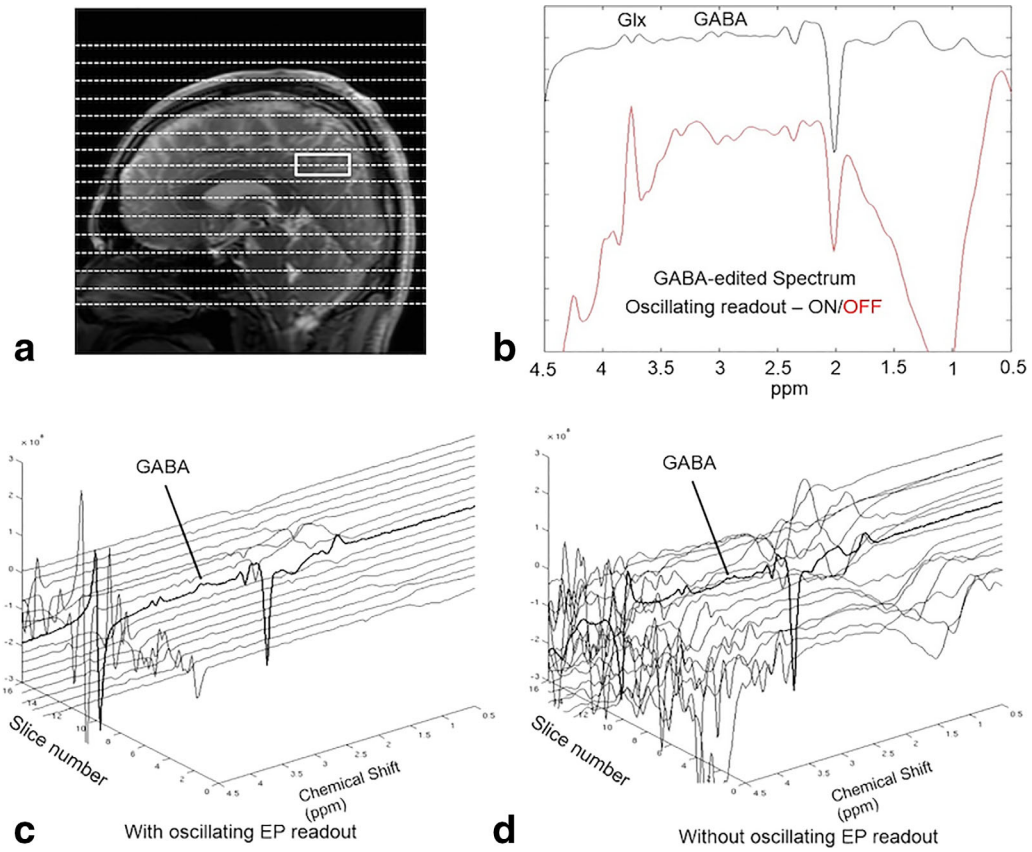

FIG. 3. Beneficial effects of an oscillating readout gradient. (**a**) MRI image showing selected single voxel. (**b**) improved MEGA-SPECIAL spectra with/without the addition of an oscillatory z-readout gradient for suppression of OVS signals (along the z-axis) that adversely contribute to single-voxel spectra. The OVS signals are visualized by adding z-phase encoding (16 slices), and stack plots of the edited spectra from each slice with (**c**) and without (**d**) the oscillating readout gradient show the achievable artifact reduction. The spectrum from slice centered on the excited voxel is highlighted in bold. In addition to using x-, y-, and z-selective RF pulses to define the targeted voxel, all spectra were acquired using conventional slice-selective OVS MRS suppression pulses, demonstrating the added level of suppression achievable with an oscillatory readout gradient. Parameters: editing at 1.7/7.5 ppm, TE/TR = 80/2000 ms, 256 transients, 8.5-min acquisition.

For both MEGA-PRESS and the improved MEGA-SPECIAL, 256 transients were acquired with a scan time of 8 min 40 s. The GABA levels were estimated by integrating the edited peak from 2.85 to 3.15 ppm, and referenced to Cre for quantification.

RESULTS

Figure 2a shows simulated spectral profiles of the 14-ms 180° Gaussian-weighed sinc editing pulse for conventional MEGA-PRESS (and symmetric MEGA-PRESS) and 30-ms 180° Gaussian-weighed sinc editing pulse for the improved MEGA-SPECIAL. The editing pulses are centered at 1.9/1.5 ppm for the on/off cases for symmetric MEGA-PRESS and at 1.9/7.5 ppm for MEGA-PRESS and the improved MEGA-SPECIAL. The transition bandwidths, measured from 5 to 95% transition for the 14- and 30-ms editing pulses, were 73 and 32 Hz, respectively. Simulated coedited MM signals in the presence of a ±10-Hz B_0 frequency drift for MEGA-PRESS, symmetric MEGA-PRESS, and the improved MEGA-SPECIAL are shown in Figure 2b. The MM levels were normalized to 1.0 for on-resonance MEGA-PRESS. Compared with MEGA-PRESS, symmetric MEGA-PRESS achieves perfect MM suppression on-resonance, but is highly sensitive to B_0 frequency drifts, as its on and off cases are affected by B_0 frequency drifts in opposite directions. In contrast, the improved MEGA-SPECIAL has substantial MM suppression (8% of MM contamination as obtained using on-resonance MEGA-PRESS), and is less sensitive to B_0 frequency shifts as compared with symmetric MEGA-PRESS.

The out-of-voxel artifact suppression using the oscillating readout gradient is demonstrated in Figure 3. By adding phase encoding in the ISIS (z) direction (16 steps), out-of-voxel signals can be visualized in the stack plots of the edited spectra from each slice with (Fig. 3c) and without (Fig. 3d) the oscillating readout gradient. Sum spectra, as would be obtained by a conventional single-voxel acquisition without additional z-phase encoding, are shown in Figure 3b. In addition to using x-, y-, and z-selective RF pulses to define the targeted voxel, all spectra were acquired using conventional slice-selective outer-volume-suppression (OVS) pulses. Such OVS pulses are typically sufficient for most ^{1}H MRS applications, but the small residual signals can be important for highly SNR-sensitive acquisitions such as GABA editing. As shown in Figure 3d, without oscillating readout

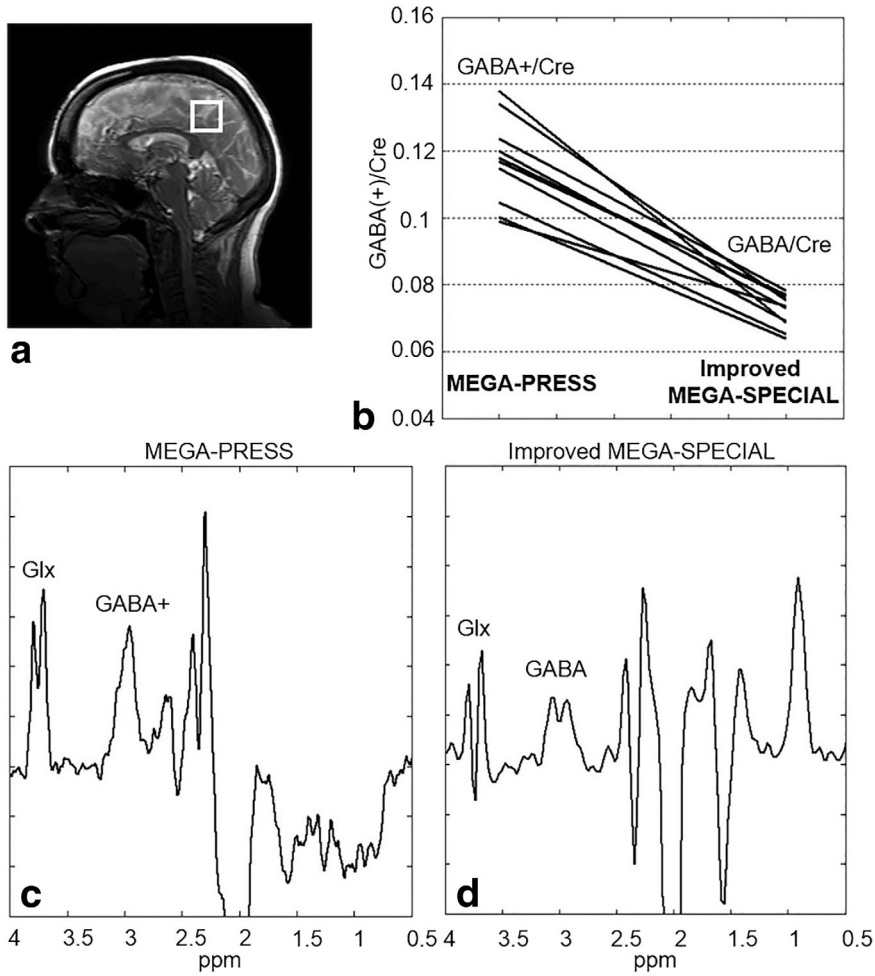

FIG. 4. Intersubject variability study comparing MEGA-PRESS GABA+ versus improved MEGA-SPECIAL GABA estimates from (**a**) a 27-cc voxel in the occipital lobe of normal adults (n = 10). (**b**) GABA measurements were quantified relative to the creatine (Cre) signal. GABA+/Cre = 0.12 ± 0.013 (mean ± standard deviation) and GABA/Cre = 0.07 ± 0.005. Acquisition parameters: 256 transients, 8.5-min acquisition. The coefficient of variation for GABA+/Cre was 11.2%, compared with 7% for GABA/Cre. (**c**) Representative edited spectrum using MEGA-PRESS and (**d**) representative edited spectrum using the improved MEGA-SPECIAL.

gradient, significant water and lipids signals exist in the out-of-voxel slices, affecting the baseline of nonlocalized edited spectrum.

Figure 4 shows results from an intersubject variability study comparing MEGA-PRESS and the improved MEGA-SPECIAL for 10 healthy adult subjects. All GABA measurements were quantified relative to the creatine (Cre) signal. The mean ± standard deviation of GABA+/Cre was 0.12 ± 0.013 using MEGA-PRESS as compared with 0.07 ± 0.005 for GABA/Cre obtained with the improved MEGA-SPECIAL. The coefficient of variation for GABA+/Cre was 11.2% compared with 7% for GABA/Cre. Furthermore, the variance of the GABA/Cre measurements using the improved MEGA-SPECIAL was significantly less than that for GABA+/Cre measurements using MEGA-PRESS (f-test: $f(9,9) = 6.72$, $P = 0.005$). Based on the relative means, MMs contributed approximately 38% to the MEGA-PRESS measurements.

Five edited spectra using the improved MEGA-SPECIAL from the intrasubject repeatability study are shown in Figure 5. The summary statistics were as follows: MEGA-PRESS GABA+/Cre = 0.11 ± 0.007 (mean ± standard deviation) and the improved MEGA-SPECIAL GABA/Cre = 0.07 ± 0.004. The coefficient of variation was 6% for both the GABA+/Cre and GABA/Cre estimates. The estimated MMs contribution to the MEGA-PRESS measurements was 40%.

DISCUSSION

Compared with MEGA-PRESS, the 1D ISIS-based MEGA-SPECIAL sequence has the advantage of using only a single spin echo, thus allowing significantly longer editing pulses. This advantage, however, comes with the drawback of the out-of-voxel signal artifacts in the ISIS direction, as a result of imperfect subtraction. If not suppressed, these signals can greatly compromise the quality of the edited spectra, significantly hampering visualization and quantification of the edited GABA peak. Using the low-pass filter on the scanner's data acquisition board, the out-of-voxel signals in the ISIS direction can be suppressed by acquiring data with a train of EP readout gradient lobes. The amplitude and length of the EP gradient lobes are set according to the acquisition bandwidth and the slice thickness in the ISIS direction, whereas the number of EP gradient lobes are determined by the number of data points acquired for each FID. In practice, eddy currents can cause imperfect gradient lobes. As a result, precise timing is required to ensure that the acquisition of each data point occurs at the z-axis crossing of the k-space. For this application on the GE 750 scanner, the built-in low-pass filter averages 100 data points for each 0.4-ms gradient lobe, effectively suppressing the out-of-voxel signals in the ISIS direction. Compared with the conventional data acquisition without the oscillating EP gradient, this artifact-suppression module maintains the

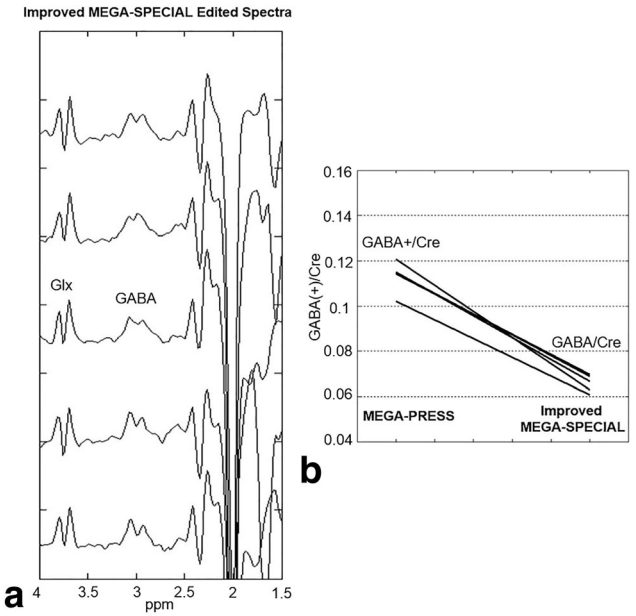

FIG. 5. Intrasubject repeatability. (**a**) GABA-edited improved MEGA-SPECIAL spectra from a 27-cc voxel in the occipital lobe of a normal volunteer scanned five times (with subject removal from scanner followed by repositioning repeated after each scan). Acquisition parameters: 256 transients, 8.5-min acquisition. (**b**) Summary data comparing MEGA-PRESS GABA+/Cre = 0.11 ± 0.007 (mean ± standard deviation) versus improved MEGA-SPECIAL GABA/Cre = 0.07 ± 0.004. The coefficient of variation was 6% for both the GABA+/Cre and GABA/Cre estimates.

same FID data formats and thus requires no changes to the reconstruction and postprocessing routine.

With MEGA-PRESS, MM suppression can be achieved by placing the editing pulse at 1.9 and 1.5 ppm, symmetric to the MM resonance at 1.7 ppm (29). Although effective, MM suppression using this method is highly sensitive to center frequency variations. As center frequency temporal drifts on the order of 5 to 10 Hz are common during a 10-min scan, insufficient and unreliable MM suppression can occur (30). By using very selective editing pulses with the improved MEGA-SPECIAL sequence, coedited MM signals are reduced at the stop band of the editing pulse, decreasing sensitivity to such B_0 drifts. However, even with the selectivity of the 30-ms editing pulses, coediting at 1.7 ppm cannot be completely avoided. In this simulation, MM signal is modeled as a single J-coupled spin pair at 1.7 and 3 ppm. With the very selective editing pulses applied at 1.9 ppm and ±10-Hz B_0 frequency drift, the flip angle at 1.7 ppm can be well below 180°. At such flip angles, the center of the 3-ppm peaks for the editing on is significantly lower than that for the editing off. The coedited 3-ppm peak, obtained by subtracting the editing-off spectrum from the editing-on spectrum, can therefore have a negative peak area as shown in Figure 2b. Nevertheless, over the entire ±10-Hz B_0 frequency drift, coedited MM signal using the improved MEGA-SPECIAL is significantly less strong than using the MEGA-PRESS. On the other hand, because the editing pulse is very selective, GABA editing efficiency is more sensitive to B_0 drift than using less-selective editing pulses. However, even with ± 10-Hz B_0 frequency drift, the very selective editing pulses achieve over 85% inversion of the 1.9-ppm GABA spins, while simultaneously suppressing significantly more MM than those using conventional or symmetrical MEGA-PRESS. Although only single-voxel data are presented in this study, the B_0-frequency-drift insensitivity of the improved MEGA-SPECIAL may make it a good choice for multivoxel studies, in which both spatial and temporal B_0 variations are even more problematic.

Cho and Cre subtraction errors are typically manifested as residual peaks at 3.2 and 3.0 ppm, respectively. Although any residual 3.0-ppm Cr cannot be distinguished from 3.0-ppm edited-GABA signal, we observed no residual peak at 3.2 ppm in any of our data, suggesting that such subtraction artifacts were minimal in these studies.

In our comparison studies, a MEGA-PRESS sequence with TE = 68 ms and 14-ms editing pulses was chosen as a result of the widespread use of these parameters. A TE = 80 ms MEGA-PRESS implementation would likely yield MM suppression intermediate between the improved MEGA-SPECIAL and TE = 68 ms MEGA-PRESS.

For both intrasubject and intersubject repeatability studies, the mean of the GABA/Cre (improved MEGA-SPECIAL) were approximately 40% less than the GABA+/Cre (MEGA-PRESS), demonstrating significant MM suppression achieved using the improved MEGA-SPECIAL sequence. The coefficient of variation for the GABA+/Cre (MEGA-PRESS) and GABA/Cre (improved MEGA-SPECIAL) were both 6% for the intrasubject repeatability study, whereas they were 11.2 versus 7%, respectively, for the intersubject repeatability study. Variations of coedited MMs across subjects likely cause a higher coefficient of variation for the GABA+/Cre (MEGA-PRESS) in the intersubject repeatability study than that in the intrasubject repeatability study. Hence, in contrast to the intrasubject data, the significant reduction of the coefficient of variation in the intersubject study using the improved MEGA-SPECIAL compared with MEGA-PRESS likely arises from MM suppression and the corresponding elimination of MM differences across subjects as a source of variance.

CONCLUSIONS

In this work, we propose a new ^{1}H-MRS editing pulse sequence, improved MEGA-SPECIAL, which provides GABA measurements with MM suppression that are insensitive to the B_0 temporal drifts seen in typical in vivo human brain studies. The method extends the previously proposed MEGA-SPECIAL method via the addition of an EP readout gradient to suppress out-of-voxel artifacts. In vivo 3T data demonstrated reduced spectral baseline artifacts, and both intra- and intersubject studies demonstrated MM-suppressed GABA measurements with less variance than using conventional MEGA-PRESS.

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