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Multi-vendor standardized sequence for edited magnetic resonance spectroscopy

Muhammad G. Saleh [a,b,*], Daniel Rimbault [c], Mark Mikkelsen [a,b], Georg Oeltzschner [a,b], Anna M. Wang [a,b], Dengrong Jiang [d], Ali Alhamud [c,e], Jamie Near [f], Michael Schär [a], Ralph Noeske [g], James B. Murdoch [h], Lars Ersland [i,j,k], Alexander R. Craven [i,j], Gerard Eric Dwyer [i,j], Eli Renate Grüner [l,m], Li Pan [n], Sinyeob Ahn [n], Richard A.E. Edden [a,b]

[a] Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] F. M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA
[c] Medical Imaging Research Unit, Division of Biomedical Engineering, University of Cape Town, Cape Town, South Africa
[d] Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[e] Department of Nuclear Engineering, University of Tripoli, Tripoli, Libya
[f] Douglas Mental Health University Institute and Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[g] GE Healthcare, Berlin, Germany
[h] Canon Medical Research USA, Mayfield Village, OH, USA
[i] Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway
[j] NORMENT – Norwegian Center for Mental Disorders Research, University of Bergen, Bergen, Norway
[k] Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway
[l] Department of Clinical Radiology, Haukeland University Hospital, Bergen, Norway
[m] Department of Physics and Technology, University of Bergen, Norway
[n] Siemens Healthineers, USA

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ABSTRACT

Spectral editing allows direct measurement of low-concentration metabolites, such as GABA, glutathione (GSH) and lactate (Lac), relevant for understanding brain (patho)physiology. The most widely used spectral editing technique is MEGA-PRESS, which has been diversely implemented across research sites and vendors, resulting in variations in the final resolved edited signal. In this paper, we describe an effort to develop a new universal MEGA-PRESS sequence with HERMES functionality for the major MR vendor platforms with standardized RF pulse shapes, durations, amplitudes and timings.

New RF pulses were generated for the universal sequence. Phantom experiments were conducted on Philips, Siemens, GE and Canon 3 T MRI scanners using 32-channel head coils. In vivo experiments were performed on the same six subjects on Philips and Siemens scanners, and on two additional subjects, one on GE and one on Canon scanners. On each platform, edited MRS experiments were conducted with the vendor-native and universal MEGA-PRESS sequences for GABA (TE = 68 ms) and Lac editing (TE = 140 ms). Additionally, HERMES for GABA and GSH was performed using the universal sequence at TE = 80 ms.

The universal sequence improves inter-vendor similarity of GABA-edited and Lac-edited MEGA-PRESS spectra. The universal HERMES sequence yields both GABA- and GSH-edited spectra with negligible levels of crosstalk on all four platforms, and with strong agreement among vendors for both edited spectra. In vivo GABA+/Cr, Lac/Cr and GSH/Cr ratios showed relatively low variation between scanners using the universal sequence.

In conclusion, phantom and in vivo experiments demonstrate successful implementation of the universal sequence across all four major vendors, allowing editing of several metabolites across a range of TEs.

* Corresponding author. Division of Neuroradiology, Park 359, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21287, USA.
E-mail address: msaleh10@jhmi.edu (M.G. Saleh).

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1. Introduction

Proton (^{1}H) magnetic resonance spectroscopy (MRS) is a non-invasive tool for measuring endogenous metabolite levels in the human brain to investigate healthy and pathological physiology (Bonavita et al., 1999). In vivo ^{1}H MRS is a robust tool for measuring high-concentration metabolites with strong in vivo signals, such as N-acetylaspartate (NAA), creatine (Cr), and choline (Cho). In vivo measurements of low-concentration metabolites, such as the inhibitory neurotransmitter γ-aminobutyric acid (GABA), the antioxidant glutathione (GSH) and the anaerobic product lactate (Lac), are more challenging due to lower signal intensity and substantial signal overlap. Spectral editing addresses this challenge by removing overlapping signals and selectively revealing signals of interest, allowing direct and unambiguous measurements (Harris et al., 2017a). Spectral editing has been used to measure GABA, GSH and Lac in several areas, including Parkinson's disease (Gong et al., 2018), schizophrenia (Shungu, 2012), amyotrophic lateral sclerosis (Foerster et al., 2012; Weiduschat et al., 2014) and hypoxia (Edden et al., 2010).

While arguably the most widely edited metabolite is GABA, there is increasing interest in editing GSH and other metabolites (Rae, 2014; Rae and Williams, 2017). It has recently been shown that more than one metabolite can be edited simultaneously using Hadamard encoding and reconstruction of MEGA-edited spectroscopy (HERMES) (Chan et al., 2016). Different spin systems have different optimal TEs for editing – generally around 70 ms for triplet-like signals and 140 ms for doublet-like signals. In most PRESS sequences (Bottomley, 1987), TE is changed by keeping the first slice-selective echo time (TE1) constant and shifting the second slice-selective refocusing pulse. The time between refocusing pulses is TE/2 (by definition). For effective editing at a range of TEs, the editing pulses must maintain a separation of TE/2 (De Graaf, 2013).

The most widely used spectral editing technique is Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS (Mescher et al., 1998)), largely due to the strengths of PRESS localization and the relative ease of implementation of MEGA editing pulses within the sequence. However, current implementations of MEGA-PRESS are diverse across research sites and vendors, differing in terms of radiofrequency (RF) pulse shapes and pulse sequence timings. Fig. 1 shows four vendor-specific MEGA-PRESS implementations for GABA editing at TE = 68 ms: our own implementation based on the Philips PRESS sequence; the Siemens-distributed Work-In-Progress (WIP) sequence; the GE-distributed WIP sequence; and the Canon WIP sequence. The four sequences differ in the shape and timing of RF pulses used for localization and editing: slice-selective pulses are asymmetric for Philips and Canon, whereas symmetric for Siemens and GE; editing pulses are sinc-Gaussian and positioned TE/2 apart for Philips and GE, and Hanning-filtered Gaussian for Siemens and sinc-Gaussian for Canon (both positioned less than TE/2 apart). Position is altered depending on the bandwidth of editing pulses for the Siemens and Canon WIP sequences. For a given TE, Siemens has the longest TE1 followed by GE, Canon and Philips. These differences in RF pulse shapes and timings can lead to differences in the shape and intensity of the detected GABA signal (Mullins et al., 2014; Edden and Barker, 2007).

Several studies have established the reproducibility of GABA+ (GABA + co-edited macromolecules (MM)) measurements in different regions of the human brain, including parietal, occipital and motor cortex, using either site-specific or vendor-provided MEGA-PRESS sequences. The within-site coefficient of variation (CV) ranges between 5% and 25% depending on the brain region, sequence and acquisition parameters (Near et al., 2014; Bogner et al., 2010; Mikkelsen. et al., 2016; Evans et al., 2010; Saleh et al., 2016a; Shungu et al., 2016; Brix et al., 2017; Geramita et al., 2011). Standardization of methodology is an important endeavor, especially for a somewhat-quantitative methodology such as MRS, substantially enhancing the interpretability of the literature and broadening the scope of application to include large multi-site clinical trials. Initial attempts to quantitatively correct for sequence differences were not entirely successful in improving agreement between platforms (Harris et al., 2017b). A large multi-site study involving diverse implementations of MEGA-PRESS across sites and vendors revealed relatively good agreement (albeit with statistically significant differences) between sites and vendors. This study suggested that approximately 30% of the total variance in the GABA + data was attributed to site- and vendor-level differences in the implementation of MEGA-PRESS (Mikkelsen. et al., 2017).

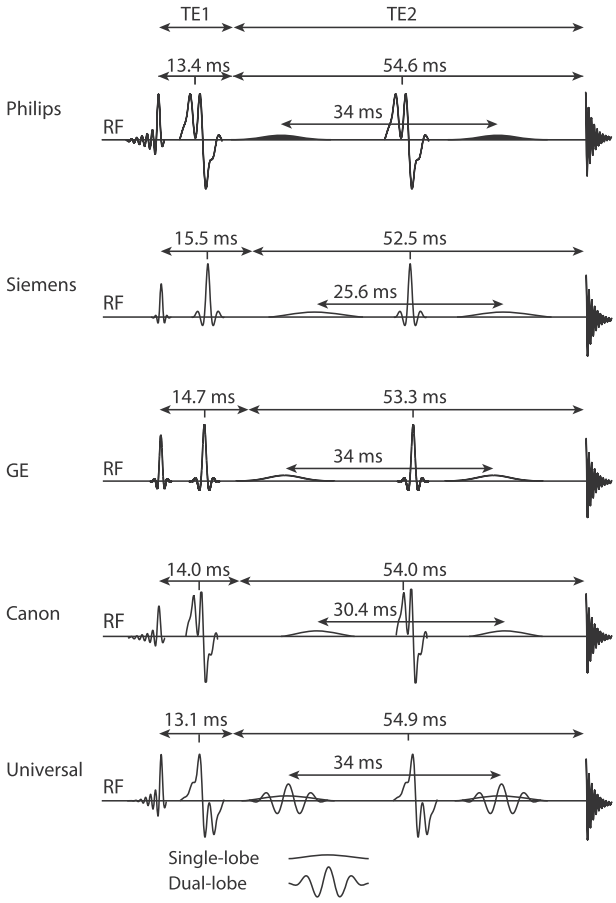

Fig. 1. Pulse sequence diagrams indicating RF pulse shapes and timings for the vendor-native Philips, Siemens, GE and Canon sequences, and the universal sequence at TE = 68 ms. The dual-lobe editing pulse shown on the universal sequence is for the HERMES experiment to simultaneously invert GABA and GSH.

Therefore, in this paper, we report on an effort to develop a universal editing sequence for the major MR vendor platforms with common RF pulse shapes, durations, amplitudes and timings. This universal MEGA-PRESS sequence can be applied at a range of TEs, adjusting the timings of refocusing and editing pulses as required, and has functionality for HERMES editing of GABA and GSH. Since prior implementations all use vendor-proprietary pulse shapes, we have developed a new set of 'open-source' pulse shapes that can be freely implemented on all platforms. We compare the spatial response profiles of the slice-selective RF pulses, then perform edited phantom and in vivo measurements of GABA, GSH and Lac, comparing the original vendor-native implementations with the new (universal) sequence.

2. Materials and methods

Phantom and in vivo experiments were conducted on Philips Achieva (Philips Healthcare, Eindhoven, Netherlands), Siemens MAGNETOM Prisma (Siemens Healthcare, Erlangen, Germany), GE Discovery MR750

(GE Healthcare, Waukesha, WI, USA) and Canon Vantage Galan (Canon Medical Systems, Ōtawara, Japan) 3 T MRI scanners using 32-channel head coils. On each platform, edited MRS experiments were conducted with the vendor-native MEGA-PRESS implementation (our own implementation on Philips; Siemens WIP sequence; the GE WIP sequence; the Canon WIP sequence) as well as the new universal sequence implemented on all four platforms.

2.1. Simulated RF pulse response profiles

The MEGA-PRESS sequence, as shown in Fig. 1, is comprised of three slice-selective pulses for volume localization and two MEGA editing pulses. Either single-band (e.g. Gaussian or sinc-Gaussian) or dual-band (with an additional cosine modulation) editing pulses can be applied. The spatial response profiles associated with the slice-selective RF pulses were simulated using Bloch equations (Simpson et al., 2017), for a nominal voxel width of 3 cm.

When designing a slice-selective pulse, the ideal outcome is a rectangular, or top-hat, profile. This suggests a sinc pulse shape, which is usually filtered further (Gaussian or Hanning) to achieve finite pulse duration. Further optimization is often applied to deliver a high yield of signal within the slice, a narrow transition band, and/or low signal yield outside the slice.

Siemens and GE slice-selective pulse shapes are symmetric. The Philips and Canon sequences use asymmetric minimum-phase excitation pulses (which are very close to an asymmetric sinc-Gaussian) and numerically optimized asymmetric refocusing pulses (Murdoch et al., 1987). As outlined in Table 1 and Table 2, the proprietary slice-selective pulses used in each of the vendor sequences have different RF bandwidths, amplitudes and durations. When calculating the slice-selective gradient that accompanies an RF pulse with a given frequency response, it must be decided where the 'edge' of the ideal voxel is defined as coming. This decision is somewhat arbitrary, often falling at the 'half-maximum' of the slice profile by default, but e.g. Philips choose a more conservative definition, effectively prioritizing low out-of-slice signal over high within-slice signal.

New RF pulses were generated for the universal sequence following an iterative approach (Murdoch et al., 1987). The initial excitation pulse prior to optimization was a sinc-Gaussian function, the product of a center-symmetric Gaussian and an asymmetric sinc. In order to simulate excitation pulse performance, a Bloch simulation was performed, calculating the magnetization after the pulse as a function of frequency offset. For excitation pulses, magnetization evolves under that offset frequency for the latter part of the pulse, but can refocused by a simulated 'rewind' gradient. Optimization of the pulse shape relied upon iterative simulation of the pulse profile, changing the pulse shape to maximize phase-coherent excited signal within the slice (rather than total transverse magnetization as is often the case) and minimizing total transverse magnetization outside of the slice, without constraining the behavior of the transition band between the two regions. The refocusing pulse was optimized along similar lines, based on pulse R2 in reference (Murdoch et al., 1987), including a four-step phase cycle to remove out-of-slice signal that is not refocused. Finally, a symmetrical sinc-Gaussian function was used for the editing pulse without further optimization. These pulses were developed so as to have equivalent performance to current vendor-proprietary pulses and to be freely portable between systems.

Table 1
Parameters of the slice-selective excitation RF pulses.

	Vendor-native			Universal
	Philips	GE	Canon	
Duration (ms)	7.13	3.6	6.0	7.2
Bandwidth (kHz)	2.277	2.367	2.315	2.247
B_{1max} (μT)	13.5	14.2	14.0	13.5
In-slice efficiency (%)	84	86	98	95
Out-of-slice leakage (%)	1	6	8	9

Table 2
Parameters of the slice-selective refocusing RF pulses.

	Vendor-native			Universal
	Philips	GE	Canon	
Duration (ms)	6.19	5.2	5.0	7.0
Bandwidth (kHz)	1.354	1.384	1.619	1.342
B_{1max} (μT)	13.5	17.6	20.9	13.5
In-slice efficiency (%)	88	82	95	88
Out-of-slice leakage (%)	1	6	4	2

Bloch simulations were performed for the vendor-proprietary and new universal pulses. For excitation simulations, the initial magnetization was pure z-magnetization and the excitation was applied about the y-axis. For refocusing, the initial magnetization was pure y-magnetization, and simulations were carried out for rotations about the ±x- and ±y-axes and combined according to the EXORCYCLE phase cycle (Bodenhausen et al., 1977) in order to suppress out-of-slice signal, as would be the case in experiments.

In addition to calculating the spatial response profiles of the pulses, two metrics were calculated for each pulse in order to assess the 'quality' of slice-selection. The in-slice efficiency was calculated as the integral of magnetization (M_x for excitation and M_y for refocusing) within the voxel divided by the total possible in-slice magnetization. The out-of-slice leakage was calculated as the integral of the total transverse magnetization outside of the voxel divided by the ideal voxel integral.

2.2. Phantom experiments

Editing experiments were performed in three phantom types: one containing 10 mM GABA only; one containing 20 mM GSH only; and two brain metabolite phantoms, one with 5 mM Lac and the other with 7.5 mM Lac. The brain phantom with 5 mM Lac ("GE Braino") was used on the Philips, GE and Siemens scanners, while the brain phantom with 7.5 mM Lac was used on the Canon scanner. The MEGA-PRESS experiments were performed using the GABA and brain phantoms, while the HERMES data were obtained from both the GABA and GSH phantoms.

MEGA-PRESS for GABA editing was conducted by applying the editing pulses at 1.9 ppm in ON_{GABA} steps, and at 7.5 ppm in OFF_{GABA} steps. The duration of the editing pulse was 15 ms. Additional scan parameters were as follows: TR/TE = 2000/68 ms; 2048 data points; spectral width = 2 kHz; voxel size = $3 \times 3 \times 3$ cm^3; and 64 transients (32 ON_{GABA} and 32 OFF_{GABA}). MEGA-PRESS for Lac editing was conducted by applying 22-ms editing pulses at 4.1 ppm in ON_{Lac} steps and at 7.5 ppm in OFF_{Lac} steps. The acquisition parameters were the same as for the GABA acquisition except TE = 140 ms.

HERMES (Saleh et al., 2016b) consists of four sub-experiments applying either a dual-lobe editing pulse to both GABA at 1.9 ppm and GSH at 4.56 ppm (A: ON_{GABA}, ON_{GSH}), a single-lobe editing pulse to GABA only (B: ON_{GABA}, OFF_{GSH}), a single-lobe editing pulse to GSH only (C: OFF_{GABA}, ON_{GSH}), or a single-lobe editing pulse at 7.5 ppm (D: OFF_{GABA}, OFF_{GSH}). The Hadamard combination of these sub-experiments results in both GABA-edited (A+B-C-D) and GSH-edited (A-B+C-D) spectra. It is worth noting that the difference spectrum C-D is a classic MEGA-PRESS spectrum for GSH.

The duration of both the single-lobe and dual-lobe editing pulses was 20 ms. The acquisition parameters were the same as for the GABA acquisition except TE = 80 ms. Line broadening of ~3 Hz was applied to phantom data, adjusted for each phantom to give similar final linewidth across platforms. The degree of similarity among vendor-native spectra and among universal spectra acquired on each platform was quantified by means of an intraclass correlation coefficient (ICC) calculated using a two-way mixed-effects model for single measures of absolute agreement (McGraw and Wong, 1996).

The universal sequence was implemented on Philips, GE, Siemens and

Canon systems with the same pulse shapes and timings. In all cases, the first echo time TE1 was 13.1 ms, and the edit pulse spacing was TE/2. The delay between the end of the first (or second) refocusing pulse and the start of the subsequent editing pulse was 2.73 ms for TE 68 ms, 3.23 ms for TE 80 ms, and 17.23 ms for TE 140. On the Canon system, the delays were 3.87 ms for 68 ms and 80 ms TE. Additionally, the Canon HERMES sequence used the same dual-lobe editing pulse for all four sub-experiments, applying the dual-lobe symmetry point at 3.23 ppm (A: ON_{GABA}, ON_{GSH}), 0.57 ppm (B: ON_{GABA}, OFF_{GSH}), 5.89 ppm (C: OFF_{GABA}, ON_{GSH}), and 8.55 ppm (D: OFF_{GABA}, OFF_{GSH}).

2.3. In vivo experiments

Eight adult volunteers (2 females; age: 34 ± 13 years (mean ± SD)) were recruited for the study with approval of the local institutional review board after giving consent to participate. Six subjects were scanned on Philips and Siemens scanners to further compare the universal sequence against the vendor-native sequences. The remaining two subjects, one for GE and one for Canon, were scanned to validate the universal sequence implementation in GE and Canon scanners.

In each subject, MEGA-PRESS was performed for GABA (TE=68 ms as above) and Lac (TE=140 ms as above), using the vendor-native and universal sequences. Additionally, HERMES for GABA and GSH was performed using the universal sequence. Data were acquired from a voxel positioned in mid-cingulate cortex with the same acquisition parameters as the phantom experiments, except the number of transients was increased to 224. The voxel size was 27 ml for TE = 68 ms MEGA-PRESS and TE = 80 ms HERMES experiments, but was increased to 45 ml for the Lac MEGA-PRESS experiment. Interleaved water referencing (Edden et al., 2016) was applied to minimize magnetic field (B_0) drift during data acquisition on the Philips scanner. The duration of each acquisition was approximately 7.5 min.

2.4. Data processing

In vivo data were analyzed using Gannet (Edden et al., 2014). Multi-step frequency-and-phase correction (FPC) was applied to the data to reduce subtraction artifacts (Mikkelsen et al., 2018), followed by a 3-Hz exponential filter and zero padding by a factor of 16. Finally, the fully processed data were subtracted to generate the difference-edited spectra. The GABA-edited signal at 3 ppm was modeled with a Gaussian function with a nonlinear baseline. The GSH-edited signal at 2.95 ppm was modeled with a Gaussian function with a nonlinear baseline. The Lac-edited signal at 1.3 ppm was modeled as in (Edden et al., 2010). Briefly, the model parameters included a Gaussian macromolecule (MM) peak at 1.24 ppm, a Gaussian MM peak at 1.43 ppm and a Gaussian doublet for Lac at 1.3 ppm. Overall fitting of the edited signal was performed by a linear-combination modeling of the Lac and MM signals. The 3 ppm Cr signal from OFF_{GABA}, OFF_{Lac} and OFF_{GSH} was used for quantifying GABA+/Cr, Lac/Cr, and GSH/Cr, respectively. For each subject, the within-subject CV was calculated between the Philips and Siemens data for the vendor-native sequences and for the universal sequence. A paired, two-tailed *t*-test was calculated to determine statistical differences in the CV from the two sequences. A $p < 0.05$ was considered statistically significant. Unless otherwise stated, all metabolite ratios are presented as mean ± SD.

3. Results

3.1. Simulated RF pulse response profiles

The spatial response profiles of the slice-selective excitation and refocusing pulses (Philips, GE, Canon and universal) are overlaid in Fig. 2. The Philips excitation pulse has the narrowest transition bandwidth with a negative overshoot around the edge of the voxel. The GE excitation waveform has the largest transition bandwidth with very little

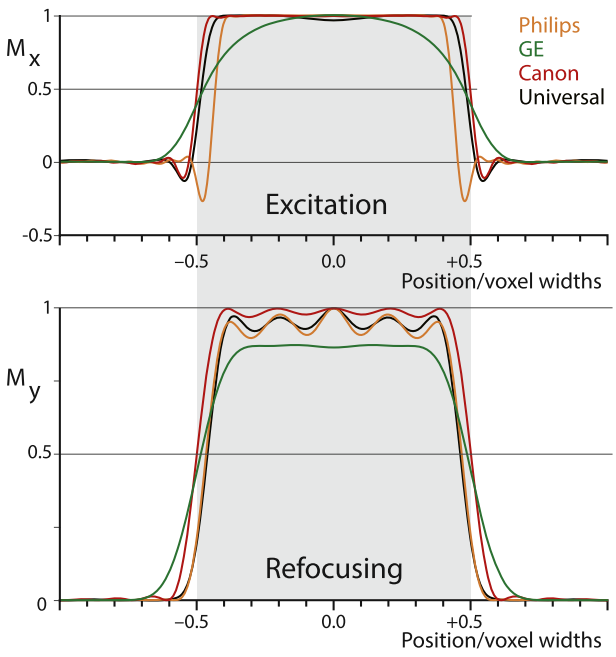

Fig. 2. Spatial response profiles of the slice-selective excitation (top) and refocusing (bottom) pulses from the vendor-native (Philips, GE and Canon) and universal sequences. The response profiles were simulated using Bloch simulations and presented as a function of the voxel width.
Data from one vendor withheld as unpublished proprietary information and due to ongoing optimization of sequence.

overshoot, exciting a relatively large amount of signal outside the prescribed voxel (shaded region). The universal excitation pulse has a slightly reduced flip angle in the middle of the voxel. The Philips and universal refocusing pulses show similar profiles with a steeper transition bandwidth relative to the GE refocusing pulse. The GE refocusing pulse has a nearly flat "top" profile relative to the Philips, Canon and universal refocusing pulses. The GE refocusing pulse has a reduced effective flip angle relative to all other pulses, resulting in lower signal yield within the slice. In more quantitative terms, the two slice quality metrics defined earlier – in-slice efficiency and out-of-slice leakage – are listed for excitation pulses in Table 1, with values for three vendors and the universal pulse. Comparable numbers for refocusing pulses appear in Table 2.

3.2. Phantom experiments

GABA-edited MEGA-PRESS spectra acquired in a GABA phantom using the vendor-native and universal sequences on each vendor platform are overlaid in Fig. 3a. There is greater degree of agreement between the universal sequence spectra (ICC = 0.96, $F = 109.9$, $p < 0.001$) than the vendor-native spectra (ICC = 0.91, $F = 46.9$, $p < 0.001$). Lac-edited MEGA-PRESS spectra acquired in the brain metabolite phantoms using the vendor-native and universal sequences on each vendor platform are also overlaid in Fig. 3a. The lineshape of the edited doublet differs more in the vendor-native spectra (ICC = 0.74, $F = 14.0$, $p < 0.001$) than in the universal spectra (ICC = 0.98, $F = 233.6$, $p < 0.001$). GABA and GSH phantom spectra from the universal HERMES sequence, acquired on each vendor platform, are overlaid in Fig. 3b. The sequence yields both GABA- and GSH-edited spectra with negligible levels of crosstalk on all four platforms, and there is strong agreement among vendors for GABA (ICC = 0.97, $F = 127.4$, $p < 0.001$) and GSH (ICC = 0.99, $F = 883.5$, $p < 0.001$).

3.3. In vivo experiments

GABA-edited MEGA-PRESS, Lac-edited MEGA-PRESS and GABA-/

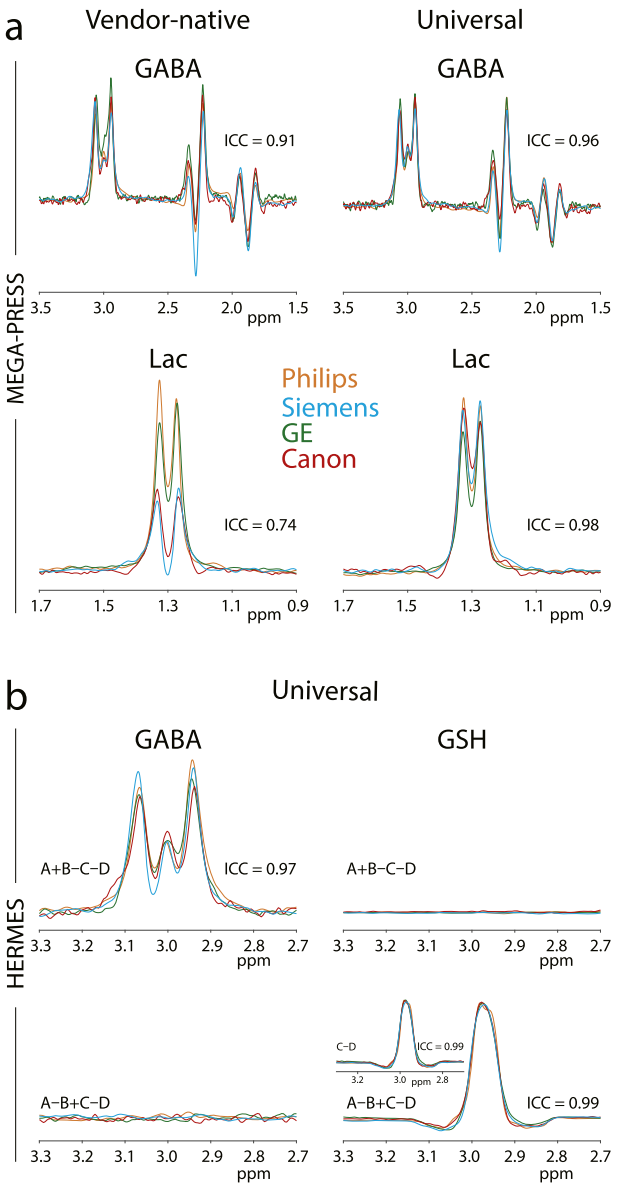

Fig. 3. Phantom experiments. Spectra acquired on the Philips, Siemens, GE and Canon scanners. a) MEGA-PRESS experiment using the GABA phantom (TE = 68 ms) and Lac phantom (TE = 140 ms) from vendor-native sequences (left) and the universal sequence (right). b) Edited spectra from HERMES experiments acquired using the universal sequence, performed in a GABA phantom (left) and a GSH phantom (right). Edited signals from GABA and GSH are seen in different Hadamard combinations as intended, with negligible crosstalk. GSH-edited spectra from the MEGA-PRESS part of the HERMES experiment (Experiment C – Experiment D) overlaid in-line with HERMES GSH-edited spectrum. ICC: intra-class correlation coefficient.

GSH-edited HERMES spectra from the universal sequence acquired in the same subjects on Philips and Siemens scanners are overlaid in Fig. 4. The same spectra acquired in two different subjects on GE and Canon scanners are shown in Fig. 5. As intended, the universal sequence resulted in edited GABA signal at 3 ppm, Lac signal at 1.3 ppm and GSH signal at 2.95 ppm in the respective spectra. Table 3 shows the quantitative measurements of metabolite ratios and average (mean) within-subject variability. Briefly, GABA+/Cr measures from the vendor-native sequences showed larger variation within-subject than the universal sequence (CV: vendor vs. universal = 7% vs 3%, $p < 0.05$). Similarly, Lac/Cr measures from the vendor sequences showed substantially larger variation compared to the universal sequence (CV: vendor vs.

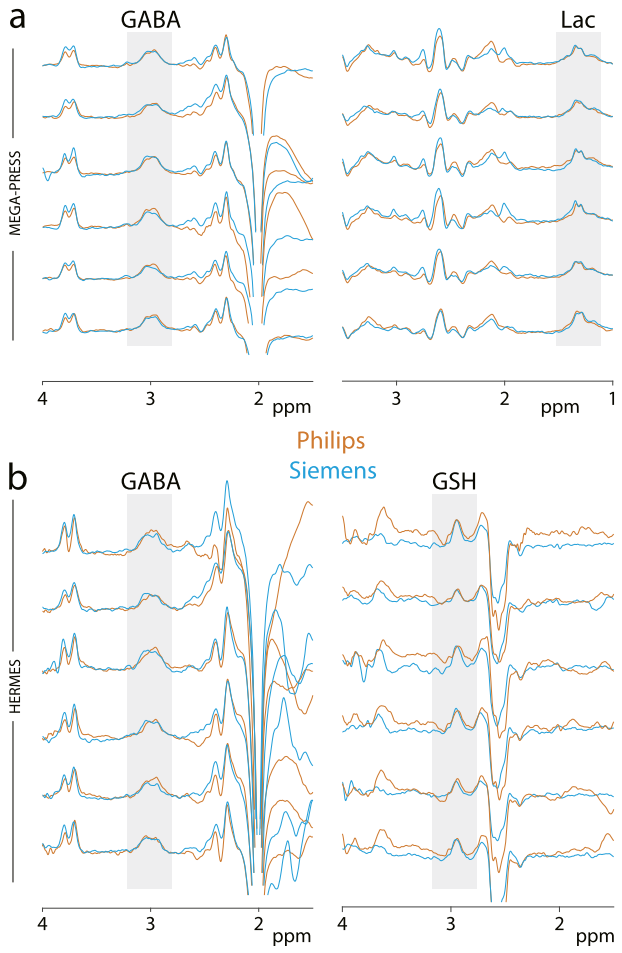

Fig. 4. In vivo experiments using the universal sequence. Spectra acquired on Philips and Siemens scanners are overlaid for each subject. a) MEGA-PRESS GABA (TE = 68 ms) and Lac (TE = 140 ms) spectra. b) GABA- and GSH-edited HERMES spectra.

universal = 41% vs 8%, $p < 0.05$). The GABA+/Cr from the universal HERMES sequence showed similar variation (CV = 3%) to the universal MEGA-PRESS. The HERMES GSH/Cr measures had a CV of 16%.

4. Discussion

This paper has presented a new implementation of the MEGA-PRESS and HERMES MRS sequences that is standardized in terms of the amplitude, duration, shape and timing of RF pulses across the four major vendor platforms. Phantom data indicate that the sequence has been successfully implemented in all cases, and in vivo data from the same subjects on Philips and Siemens systems indicate similar quantitative performance. This sequence standardization reduces inter-sequence differences in multiplet lineshape and amplitude, which should result in reduced inter-scanner variance for multi-site studies. The universal sequence includes simultaneous editing of GABA and GSH with HERMES, allowing excellent separation of the edited signals in half the scan time compared with the sequentially acquired conventional MEGA editing. The universal sequence is available collaboratively to the community for application in future studies.

The slice-selective pulses used in the vendor-native MEGA-PRESS sequences are proprietary and inherited from the base PRESS sequences of each vendor. In common with the Philips and Canon sequences, the universal sequence uses an asymmetric excitation pulse; by having fewer lobes after the main lobe the minimum TE for PRESS is reduced and the maximum duration of editing pulses is increased for MEGA-PRESS. The

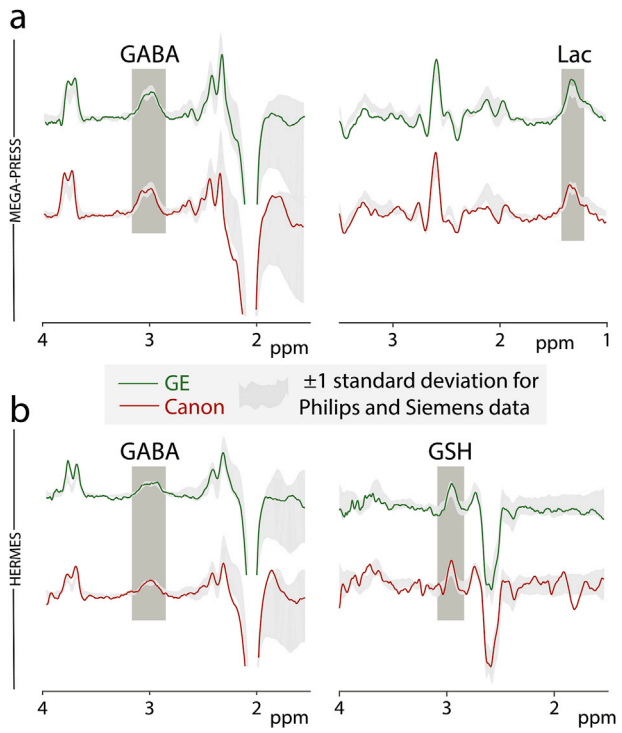

Fig. 5. In vivo experiments using the universal sequence for GE (green) and Canon (red) scanners. Spectra acquired are overlaid on the ± 1SD range (in gray) of the amalgamated Philips and Siemens data (6 subjects). a) MEGA-PRESS GABA-edited (TE = 68 ms) and Lac-edited (TE = 140 ms) spectra. b) GABA- and GSH-edited HERMES spectra.

refocusing pulses are also asymmetric, generating approximately twice the bandwidth as a sinc-Gaussian for a given finite B_{1max}. Simulation of the RF pulses used in the vendor-native sequences highlights some interesting differences. The choice of pulse bandwidth, for a given slice profile, is to an extent arbitrary within the transition band, and involves a trade-off between increased within-slice signal (prioritized by Canon) and reduced out-of-slice signal (prioritized by Philips). The transition bandwidth varies between pulses, depending on the degree of Gaussian character for the pulse and the number of sinc lobes included. These differences in bandwidth definitions result in differences of signal yield of the order of ~10%. Variable refocusing bandwidth between sequences will also result in variable levels of spatially inhomogeneous coupling evolution effects, adding further variance to edited signals (Edden and Barker, 2007). The aim of implementing new RF pulses in this work was to standardize the acquisition across platforms, rather than to improve on the status quo for any given vendor.

Phantom experiments indicate that GABA- and Lac-edited spectra show a substantially improved concordance using the universal MEGA-PRESS sequence compared to the edited spectra from the vendor-native MEGA-PRESS sequences. MEGA-PRESS of GSH, extracted from the HERMES dataset, shows good agreement between vendors. The major differences in the vendor sequences arise from the editing pulse timing behavior as TE changes. For both Siemens and Canon sequences, the editing pulses are less than TE/2 apart for all TEs at a given bandwidth of editing pulse, resulting in imperfect refocusing of coupling evolution in edit-ON scans and a loss of editing efficiency (more pronounced in Lac-edited spectra). Discrepancies do remain between the universal spectra, likely due to hardware and sequence preparation differences. Different vendor scanners operate at slightly different resonant frequencies, altering the degree of strong-coupling behavior the GABA spin system exhibits. Differences in the shimming procedure on each platform alters the linewidth and lineshape achieved in each system (effects that can only partially be addressed by applying different levels of line-broadening). Particularly for the mixed-phase GABA signals at 2.3 ppm and 1.9 ppm, there is a strong interaction between linewidth and signal amplitude. The different B_1 calibration approaches used on each platform will also likely impact the flip angles achieved.

In vivo MEGA-PRESS experiments resulted in GABA- and Lac-edited spectra in all six doubly-scanned subjects using both vendor-native and universal sequences. Similarly, the HERMES experiment yielded GABA- and GSH-edited spectra in the same six subjects. The universal MEGA-PRESS sequence shows modest improvement in the CV of GABA+/Cr and substantial improvement in the CV of Lac/Cr (due to less variable editing efficiency). These improvements in within-subject CV show the importance of standardizing slice-selective and editing pulses, pulse duration and sequence timings. The remaining variance in the universal data includes contributions from voxel positioning changes, subject compliance during MRS scan (Saleh et al., 2016c), and potential physiological variation of metabolite levels (Evans et al., 2010; Floyer-Lea et al., 2006). Although the sample size of our experiment is relatively small (eight subjects), the combination of phantom and in vivo experiments was designed to show the feasibility and successful implementation of the universal sequence in all four vendors.

In this project, several aspects of the universal sequence remain unstandardized across vendors. The B_1 power calibration method is not standardized, likely resulting in differing degrees of variance between subjects and likely in systematic biases between platforms. Small B_1 deviations are generally assumed to impact metabolite and reference signals equally, but this assumption is less true for edited signals than for unedited signals. While the universal sequence employs a fixed RF pattern on each platform, the gradient scheme used for coherence selection is not standardized across platforms, and differences may remain in the extent to which each sequence dephases out-of-slice signals. Gradient-related eddy currents, which can impact editing (Oeltzschner et al., 2018), will differ between vendors and individual scanners. Although adequate B_0 shimming can be achieved on all platforms, variation in the shim quality across vendors can cause differences in the data quality. Volume-localized prospective B_0 drift correction (Edden et al., 2016; Saleh et al., 2016c) improves the fidelity of editing throughout the acquisition. However, it is currently available only in the Philips MR scanner. The water suppression method also differs across vendors (Ogg et al., 1994; Tkáč et al., 1999). Variable suppression of the water signal affects the baseline of the edited spectrum, especially for GSH editing, impacting signal quantification. Finally, the RF phase cycling scheme, which determines the extent to which scan artifacts and signals from

Table 3
Metabolite/Cr ratios and average (mean ± SD) within-subject CVs.

	Vendor-native		Within-subject CV (%)	Universal		Within-subject CV (%)
	Philips	Siemens		Philips	Siemens	
GABA + $_{MP}$	0.114 ± 0.009	0.110 ± 0.006	7 ± 4[a]	0.119 ± 0.007	0.120 ± 0.007	3 ± 2[a]
Lac_{MP}	0.141 ± 0.026	0.097 ± 0.065	41 ± 23[b]	0.138 ± 0.019	0.147 ± 0.019	8 ± 4[b]
GABA + $_{HERMES}$				0.094 ± 0.012	0.094 ± 0.011	3 + 3
GSH_{HERMES}				0.045 ± 0.013	0.051 ± 0.007	16 ± 13

[a] $p < 0.05$: statistically significant difference between the CVs of vendor-native and universal MEGA-PRESS GABA data.
[b] $p < 0.05$: statistically significant difference between the CVs of vendor-native and universal MEGA-PRESS Lac data.

non-PRESS pathways are cancelled, was not specified in this study. Further standardization of these various aspects will enhance spectral quality and agreement between vendors. The PRESS-based universal editing sequence presented can also be improved by implementing sLASER localization (Scheenen et al., 2008; Saleh et al., 2018).

5. Conclusion

Phantom and in vivo experiments demonstrate successful implementation of a universal editing MRS sequence across the four major vendor platforms, allowing editing of a number of metabolites across a range of TEs.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.01.056.

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