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RESEARCH ARTICLE

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MASE-sLASER, a short-TE, matched chemical shift displacement error sequence for single-voxel spectroscopy at ultrahigh field

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B_1 inhomogeneity and chemical shift displacement error (CSDE) increase with the main magnetic field strength and are therefore deleterious for magnetic resonance spectroscopy (MRS) at ultrahigh field. A solution is to use adiabatic pulses which operate over a broad range of B_1 and thus are insensitive to B_1 inhomogeneity. Moreover, adiabatic pulses usually have a relatively higher bandwidth, which makes CSDE low to negligible. The use of exclusively adiabatic pulses for single-voxel spectroscopy (SVS) typically brings the disadvantage of a long echo time (TE), but the advantage of a low and matched CSDE. Herein, we took advantage of short-duration, low-power, matched-phase adiabatic spin echo (MASE) pulses to implement a matched CSDE semi-localized by adiabatic selective refocusing (sLASER) sequence capable of attaining short TEs, while CSDE is matched and still comparatively low. We also demonstrate here the feasibility of the direct measurement of the γ-aminobutyric acid (GABA) resonance at 2.28 ppm well separated from the neighboring glutamate resonance at 7 T using the implemented MASE-sLASER sequence at TEs of 68 and 136 ms. The shorter duration of MASE pulses also made it possible to implement a Mescher–Garwood-semi-localized by adiabatic selective refocusing (MEGA-sLASER) (with MASE) sequence with TE = 68 ms for editing GABA at 7 T, the results for which are also shown.

KEYWORDS

MASE, sLASER, MEGA-sLASER, GABA, Single Voxel Spectroscopy, Ultrahigh field, Human brain

Abbreviations used: 3D, three-dimensional; %SD, percentage standard deviation; AC, anterior cingulate; ADC, analog to digital converter; Asp, aspartic acid; Cho, choline; Cr, creatine; CRLB, Cramér–Rao lower bound; CSDE, chemical shift displacement error; DLPFC, dorsolateral prefrontal cortex; FASTESTMAP, fast automatic shim technique using echo-planar signal readout for mapping along projections; FOV, field of view; GABA, γ-aminobutyric acid; Glu, glutamate; Gln, glutamine; Glx, glutamine/glutamate; Gly, glycine; GOIA, gradient offset independent adiabaticity; GPC, glycerophosphocholine; GSH, glutathione; Ins, inositol; LASER, localized by adiabatic selective refocusing; MASE, matched-phase adiabatic spin echo; MC, motor cortex; MEGA-sLASER, Mescher–Garwood-semi-localized by adiabatic selective refocusing; Met., metabolite; mI, myo-inositol; MM, macromolecule; MPRAGE, magnetization-prepared rapid acquisition gradient echo; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamic acid; Occ, occipital cortex; PC, posterior cingulate; PCh, phosphocholine; PCr, phosphocreatine; Prc, precuneus; PRESS, point-resolved spectroscopy; NEX, number of excitations (acquisitions); RF, radiofrequency; Rx, receiver; SADLOVE, single-shot adiabatic localized volume excitation; SAR, specific absorption rate; sLASER, semi-localized by adiabatic selective refocusing; SLR, Shinnar–Le Roux; SNR, signal-to-noise ratio; STEAM, stimulated echo acquisition mode; SVS, single-voxel spectroscopy; tCho, total choline; tCr, total creatine; TE, echo time; TI, inversion time; tNAA, total *N*-acetylaspartate; TR, repetition time; Tx, transmitter; WET, water suppression enhanced through T_1 effects

1 | INTRODUCTION

Magnetic resonance spectroscopy (MRS) at ultrahigh magnetic field strengths benefits from the advantages of increased signal-to-noise ratio (SNR) as well as greater spectral separation between metabolite peaks. However, both B_1 field inhomogeneity and chemical shift displacement error (CSDE) increase at ultrahigh field.[1,2] These problems can be ameliorated by the utilization of adiabatic pulses which operate over a broad range of B_1 field strengths and have a higher spectral bandwidth.[3-6]

Examples are the single-shot adiabatic localized volume excitation (SADLOVE) sequence[7] and localized by adiabatic selective refocusing (LASER) sequence,[4] which use only adiabatic radiofrequency (RF) pulses. This makes these sequences largely immune to B_1 field inhomogeneity, which is an advantage at ultrahigh field. On the other hand, the use of seven RF pulses in SADLOVE and LASER sequences makes them so long that short-echo-time (TE) single-voxel spectroscopy (SVS) acquisition is currently not possible with them at ultrahigh field. As an alternative, the semi-localized adiabatic selective refocusing (sLASER) sequence[8,9] was introduced, which has the advantage of relatively shorter TE, while having the residual disadvantage of sensitivity to B_1 field inhomogeneity along one axis because of the use of a non-adiabatic excitation pulse.

In addition to B_1 field inhomogeneity, another problem in SVS at ultrahigh field is CSDE.[9] This artifact increases linearly with field strength. In order to deal with this issue, high-bandwidth RF pulses are needed. This requirement limits, for example, the use of sinc-like (refocusing) pulses for point-resolved spectroscopy (PRESS) at ultrahigh field because of the need for very high peak voltages to achieve the necessary bandwidth. Here, also, the use of adiabatic pulses with a high bandwidth is a potential solution. For instance, the sLASER sequence benefits from lower CSDE in two refocusing directions because of the use of high-bandwidth adiabatic refocusing pulses.[9] However, the sequence typically still has a larger CSDE in the excitation direction because of the use of a non-adiabatic RF pulse with a lower bandwidth than adiabatic pulses.

Mescher–Garwood-semi-localized by adiabatic selective refocusing (MEGA-sLASER)[10] is currently the most common MRS approach for the measurement of γ-aminobutyric acid (GABA) *in vivo*. Theoretically, the most efficient TE to measure GABA is 68 ms,[11] where the two side-peaks of GABA are refocused (ON mode) and inverted (OFF mode).[12] The requirement for relatively long conventional adiabatic pulses and long editing pulses in the implementation of the MEGA method at ultrahigh field limits the minimum achievable TE to longer than 68 ms. For instance, the MEGA-sLASER sequence was first introduced and implemented as an efficient method to measure GABA at 7 T with TE = 74 ms.[10]

The proton magnetic resonance spectrum of GABA includes three coupled peaks appearing at 1.89, 2.28 and 3.01 ppm *in vivo*.[12] GABA at 3.01 ppm overlaps with the creatine (Cr) singlet peak, and therefore *J* difference editing methods, such as MEGA-sLASER, are currently the most common way to measure this GABA signal. GABA at 2.28 ppm does not entirely overlap with any prominent neighboring metabolite peak; however, it is necessary to distinguish it from the proximal glutamate (Glu) peak at 2.35 ppm. Higher spectral resolution at ultrahigh field therefore provides the possibility of the separation of these two neighboring signals in the acquired spectrum. For instance, Ganji et al.[13] used an optimum PRESS at TE = 92 ms at 7 T to have these two neighboring signals best separated from each other.

Recently, matched-phase adiabatic spin echo (MASE) pulse pairs have been introduced and their application shown in diffusion-weighted imaging.[14] MASE includes a non-adiabatic matched-phase Shinnar–Le Roux (SLR) 90° pulse and an adiabatic SLR 180° pulse, where the SLR 90° pulse is used to compensate for the non-linear phase of the adiabatic SLR 180° pulse across the slice, creating a spin echo without the need for a pair of adiabatic refocusing pulses.[14] This characteristic of MASE can be beneficial at ultrahigh field by reducing possible TE in comparison with a full LASER sequence. A feature of MASE pulses is that they require less power than hyperbolic secant pulses. Consequently, they can operate at shorter duration while having an acceptable bandwidth. These features enable the implementation of the MEGA editing method with TE = 68 ms for the editing of GABA at ultrahigh field, whereas previous editing implementations at 7 T using sLASER-like techniques have been forced to use TEs higher than 68 ms (74 ms[10,15]).

Hence, our aim in this study is to implement a sequence for short-TE, full-intensity SVS with matched and low CSDE in all three directions for general use (MASE-sLASER) and for the editing of GABA with TE = 68 ms [MEGA-sLASER (with MASE)] at 7 T. We also examine the feasibility of the direct measurement of the GABA resonance at 2.28 ppm using the MASE-sLASER sequence.

2 | METHODS

2.1 | Implementation of the sequences

2.1.1 | MASE-sLASER

A short-TE (27 ms) matched CSDE sLASER sequence (MASE-sLASER) (Figure 1) was implemented using MASE for slice selection in one direction and two pairs of MASE SLR refocusing pulses in the two other directions. The slice selection gradient strength of the excitation pulse of MASE was matched with that of the refocusing pulse(s) of MASE. This provided matched slice selection gradient strengths and CSDE in all three directions.

The same MASE RF pulses introduced in Dyvorne et al.[14] were used here. All parameters for the design of these pulses have been described previously.[14]

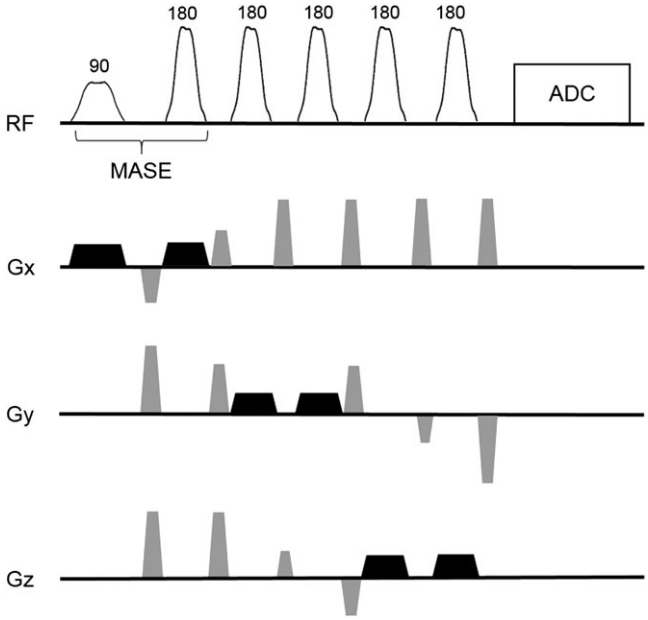

FIGURE 1 MASE-sLASER sequence implemented using MASE and two pairs of MASE adiabatic SLR refocusing pulses for short TE = 27 ms SVS acquisition at 7 T. The MASE pair was used for slice selection in one direction. Two pairs of adiabatic SLR refocusing pulses of MASE were used for slice selection in the two other directions. The implemented MASE-sLASER sequence therefore consists of six RF pulses compared with five RF pulses in sLASER and seven RF pulses in full LASER. Black trapezoids show the slice selection gradients and gray trapezoids represent the spoiler gradients that were used to dephase unwanted echoes. ADC, analog to digital converter

A 3.5-ms SLR excitation pulse with a bandwidth of 5 kHz and a 1.75-ms adiabatic SLR refocusing pulse with a bandwidth of 4.63 kHz were used. Two pairs of the same adiabatic SLR refocusing pulses with a duration of 1.75 ms and a bandwidth of 4.63 kHz were used for slice selection in the two other directions. We used a combination of orthogonal spoiler gradients in the sequence to dephase unwanted echoes. The spoiler gradients have an amplitude of 25 mT/m and their duration varies between 1.2 and 2.6 ms. With this combination of RF pulses, slice selection and spoiler gradients, we implemented an sLASER sequence with a minimum TE of 27 ms and matched CSDE of 1.25 mm/ppm for a voxel size of 20 × 20 × 20 mm^3 (approximately 6%). Four-RF-pulse WET (water suppression enhanced through T_1 effects) water suppression, with less sensitivity to B_1 variations than three-RF-pulse WET water suppression,[16] was used prior to the localization sequence.

2.1.2 | MEGA-sLASER (with MASE) with TE = 68 ms

In this study, we implemented a MEGA-sLASER (with MASE) sequence with TE = 68 ms at 7 T (Figure 2). For the localization part of the sequence, MASE pulses were used. A 5-ms SLR excitation pulse with a bandwidth of 3.52 kHz and a 2.5-ms adiabatic SLR refocusing pulse with a bandwidth of 3.24 kHz were used. Two pairs of the same adiabatic SLR refocusing pulses with a duration of 2.5 ms and a bandwidth of 3.24 kHz were used for slice selection in the two other directions. These pulse durations were sufficient to attain the 68-ms TE, and shorter pulses were not necessary, as CSDE is not an issue in MEGA editing. In addition, a pair of dual-band inversion pulses with a bandwidth of 220 Hz and duration of 11.52 ms was used for MEGA editing and extra water suppression. MEGA-ON and MEGA-OFF modes were interleaved in the sequence as even and odd acquisitions with MEGA pulse excitation centered at 1.9 ppm and 4.7 ppm in the ON mode and 4.7 ppm and 7.5 ppm in the OFF mode. Here, we also used an orthogonal scheme for spoiler gradients with an amplitude of 25 mT/m and durations between 0.8 and 2 ms. The same WET water suppression was used as above.

2.2 | GABA at 2.28 ppm

In preliminary experiments, a putative GABA signal at 2.28 ppm was detected. To authenticate this signal, two sets of experiments were conducted. In the first, the SVS experiment was repeated nine times, in order to examine whether the signal averaged as a 'signal' component rather than as noise. Furthermore, the MASE-sLASER sequence was also used to acquire spectra at TEs of 68 and 136 ms. The GABA signal at 2.28 ppm is a triplet coupled to a partner at 1.89 ppm. Its pattern therefore changes as a function of TE because of the effect of *J*-coupling. The two side-peaks of GABA at 2.28 ppm are in in-phase states at TEs of 68 and 136 ms. The known pattern of the GABA signal at these two TEs was why they were chosen to examine the capability of the MASE-sLASER sequence for the direct measurement of GABA at 2.28 ppm. We also performed simulations to examine the pattern of the GABA triplet at 2.28 ppm and its neighboring Glu multiplet at 2.35 ppm when acquired with the MASE-sLASER and conventional sLASER sequences at TEs of 68 and 136 ms. Two parametric spectral models for GABA and Glu were simulated using the NMRSIM

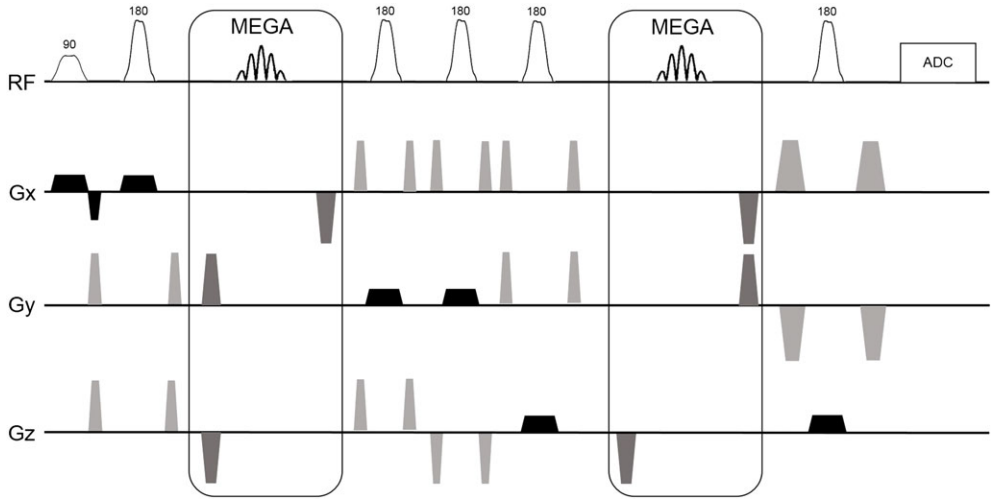

FIGURE 2 MEGA-sLASER (with MASE) sequence implemented using MASE and two pairs of MASE adiabatic SLR refocusing pulses with TE = 68 ms for the editing of GABA at 7 T. MEGA pulses were dual band and were used for the editing of GABA and extra water suppression. Black trapezoids show the slice selection gradients, light gray trapezoids represent the spoiler gradients used to dephase unwanted echoes and dark gray trapezoids represent MEGA editing gradients that were used to suppress residual water signal. ADC, analog to digital converter; RF, radiofrequency

module of the TOPSPIN suite (Version 3.6, Bruker, Rheinstetten, Germany) with the same sequence and scan parameters as for the *in vivo* spectroscopy scan. To compare MASE-sLASER and conventional sLASER, we acquired spectra at TE = 68 ms and TE = 136 ms using MASE-sLASER and conventional sLASER in two separate consecutive acquisitions from the same subject and the same voxel. Matched CSDE for the MASE-sLASER sequence with TE = 68 ms was 1.79 mm/ppm for a voxel size of 20 × 20 × 20 mm^3 (approximately 9%).

There are two groups of glutamine (Gln) peaks positioned between 2.10–2.16 ppm and 2.39–2.50 ppm which are well separated from the GABA peak at 2.28 ppm, which was the reason why Gln was not included in the simulations.

2.3 | Data acquisition

In total, eight healthy subjects (four male; age, 26.5 ± 3.2 years) participated in this study, with approval from the local ethics committee. *In vivo* scans were performed on a 7-T system (Magnetom 7 T, SIEMENS Healthcare GmbH, Erlangen, Germany) with a 32-channel Receiver (Rx) and single-channel Transmitter (Tx) head coil (Nova Medical, New York, NY, USA). An anatomical reference image was acquired using three-dimensional (3D) magnetization-prepared rapid acquisition gradient echo (MPRAGE)[17] [256 slices; slice thickness, 1 mm; repetition time (TR) = 2500 ms; TE = 1.35 ms; inversion time (TI) = 1100 ms; flip angle, 6°; field of view (FOV), 256 × 256 × 256 mm^3; acquisition matrix, 256 × 256; GRAPPA acceleration factor, 2 PE; Ref. lines PE = 48; phase partial Fourier, 6/8; slice partial Fourier, 6/8; scan duration, 298 s]. B_0 shimming was performed using FASTESTMAP (fast automatic shim technique using echo-planar signal readout for mapping along projections).[18]

Single-voxel MRS data were collected from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of two subjects (subjects 1 and 2) using the short-TE MASE-sLASER sequence [TR = 4500 ms; TE = 27 ms; number of excitations (NEX) = 64; scan time, 5:06 min]. Single-voxel MRS data were also collected from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of five subjects (subjects 4–8) using the MEGA-sLASER (with MASE) sequence (TR = 4500 ms; TE = 68 ms; NEX = 64; scan time, 5:06 min).

To show the feasibility of direct measurement of GABA at 2.28 ppm, we acquired nine consecutive MASE-sLASER spectra at TE = 68 ms from a voxel size of 20 × 20 × 20 mm^3 positioned at the medial occipital region of a subject (subject 3) (TR = 4500 ms; TE = 68 ms; NEX = 32; scan time, 2:42 min).

We examined the separation of the 2.28-ppm GABA line from its neighboring 2.35-ppm Glu line at TEs of 68 and 136 ms *in vivo* using the MASE-sLASER and sLASER sequences. Specifically, we collected spectra from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of a subject (subject 5) (TR = 4500 ms; TE = 68 ms; NEX = 64; scan time, 5:06 min for both sequences). Also, we collected spectra using the MASE-sLASER and conventional sLASER sequences from the same voxel size and region of two subjects (subjects 1 and 2) (TR = 4500 ms; TE = 136 ms; NEX = 64; scan time, 5:06 min for both sequences).

The medial occipital region is a benign region for MRS. To compare the performance of the MASE-sLASER sequence and its sensitivity for GABA measurement with the conventional sLASER sequence, we compared the two sequences with the same TE of 38 ms at six different regions of the brain. The reason why we compared the two methods at TE = 38 ms was that this was the minimum TE of the sLASER sequence. We collected spectra from voxels of size 20 × 20 × 20 mm^3 positioned in the anterior cingulate, dorsolateral prefrontal cortex, motor cortex, precuneus, posterior cingulate and occipital cortex. The spectra were acquired using MASE-sLASER and conventional sLASER sequences from

a healthy subject (subject 5) (TR = 4500 ms; TE = 38 ms; NEX = 64; scan time, 5:06 min for both sequences). These regions are representative of those accessible to SVS at 7 T, primarily because of the poor B_0 homogeneity of more inferior regions.

In Table 1, we summarize the application and goal of each acquisition, the subject(s) used for each application and the gender and age of the subjects.

TR in all acquisitions was 4500 ms, which was sufficiently long to avoid specific absorption rate (SAR) limitations. To obtain an estimation of the relative SAR for the two sequences of sLASER and MASE-sLASER, the ratio of $\sum {B_1}^2$ was calculated for a typical reference voltage of 230 V. The $\sum {B_1}^2{}_{\text{MASE-sLASER}}/\sum {B_1}^2{}_{\text{sLASER}}$ ratio calculated in this way was 0.45.

Data were analyzed using LCModel,[19] JMRUI[20] and MATLAB (version. 2016b; Natick, MA, USA).

LCModel software (Version 6.3-1 L; Stephen Provencher, Oakville, ON, Canada)[19] was used to quantify the measured metabolites in this study. The basis set for the LCModel analysis of the short-TE spectra consisted of 21 simulated metabolites. For the MEGA editing method, six edited metabolites of GABA, Glu, Gln, *N*-acetylaspartate (NAA), *N*-acetylaspartylglutamic acid (NAAG) and glutathione (GSH) were included in the basis set. The metabolite concentrations were estimated and the Cramér–Rao lower bound (CRLB) was expressed as the percentage standard deviation (%SD). From 21 simulated metabolites of the short-TE spectra, and six simulated metabolites of the MEGA method, the major metabolites are presented in Tables 2–5. For the absolute quantification of the metabolites presented in Table 2, unsuppressed water spectra were also acquired with MASE-sLASER and sLASER sequences at TE = 38 ms.

To demonstrate the separation of GABA at 2.28 ppm from the neighboring Glu at 2.35 ppm with the MASE-sLASER sequence, we also scanned a brain phantom containing NAA (12 mmol/L), Glu (10 mmol/L), Cr (8 mmol/L), Gln (4 mmol/L), myo-inositol (mI) (5 mmol/L), GABA (2 mmol/L), aspartic acid (Asp) (2 mmol/L) and choline (Cho) (2 mmol/L). The spectra were acquired at TEs of 68 and 136 ms with the same parameters as *in vivo*.

3 | RESULTS

Figure 3 shows the pulse shapes and profiles of the MASE pulses used for excitation in the implementation of the MASE-sLASER sequence and of the conventional SLR pulse used for excitation in the implementation of the sLASER sequence.

In Figure 4, we show a comparison of the CSDE for the MASE-sLASER and sLASER sequences. The CSDE is matched in all three directions and is symmetrical for the MASE-sLASER sequence.

A short TE = 27 ms spectrum acquired from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of a healthy subject, using the MASE-sLASER sequence, is shown in Figure 5. Major observed metabolites are labeled in the spectrum. Another MASE-sLASER spectrum acquired with the same acquisition parameters from another subject is provided in Supporting Information Figure S1.

A MEGA difference spectrum showing GABA+ at 3 ppm and glutamine/glutamate (Glx) at 3.75 ppm, acquired from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of a healthy subject using the MEGA-sLASER (with MASE) sequence, is shown in Figure 6. Four additional MEGA-sLASER (with MASE) spectra acquired with the same acquisition parameters from four subjects are provided in Supporting Information Figure S2.

The absolute concentrations of the major metabolites measured in six different regions of the brain of a healthy subject (subject 5) using sLASER and MASE-sLASER sequences with the same TE = 38 ms, and their corresponding CRLB values, are shown in Table 2. There is good agreement between the absolute concentrations of all metabolites across the two methods; however GSH, GABA and Gln show differences. The results suggest marginal differences between the sensitivity of the two sequences.

TABLE 1 A summary of the applications and goals of each acquisition and which subject(s) were used for which applications

Application	Goal	Subject number	Gender/age (years)
MASE-sLASER (TE = 27 ms)	Demonstrate MASE-sLASER sequence as a short-TE SVS sequence	1 and 2	Two female/25 ± 1.4
Nine consecutive acquisitions with MASE-sLASER (TE = 68 ms)	Show that signal at 2.28 ppm is not noise	3	Male/29
MEGA-sLASER (with MASE) (TE = 68 ms)	Demonstrate MEGA-sLASER (with MASE) sequence at TE = 68 ms	4–8	Three male, two female/26.6 ± 3.8
Comparison between MASE-sLASER and sLASER (TE = 68 ms)	Show feasibility of measuring GABA at 2.28 ppm with MASE-sLASER (TE = 68 ms). Compare with standard sLASER at same TE	5	Male/27
Comparison between MASE-sLASER and sLASER (TE = 136 ms)	Same as above at TE = 136 ms	1 and 2	Two female/25 ± 1.4
Comparison between MASE-sLASER and sLASER in six regions (TE = 38 ms)	Compare spectral quality and absolute concentration over a range of conditions	5	Male/27

MASE, matched-phase adiabatic spin echo; MEGA, Mescher–Garwood; sLASER, semi-localized by adiabatic selective refocusing; SVS, single-voxel spectroscopy; TE, echo time.

TABLE 2 A comparison of the absolute concentrations of the metabolites measured with MASE-sLASER and sLASER sequences at TE = 38 ms from six regions of the brain of a healthy subject (subject 5)

	AC				DLPFC				MC			
	Concentration [mMol/Kg]		CRLB(%)		Concentration [mMol/Kg]		CRLB(%)		Concentration [mMol/Kg]		CRLB(%)	
Metabolite	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER
GSH	**1.48**	**2.37**	**8%**	**5%**	**1.777**	**2.416**	**7%**	**5%**	**1.41**	**2.29**	**10%**	**6%**
NAA	5.95	5.56	2%	2%	7.26	6.76	2%	2%	7.59	7.41	2%	2%
NAAG	0.463	0.647	16%	13%	0.822	0.86	10%	11%	0.924	0.993	10%	10%
mI	5.307	4.36	4%	5%	5.032	4.8	5%	6%	5.16	4.92	5%	6%
GABA	**0.05**	**2.67**	**663%**	**17%**	**0.491**	**2.88**	**80%**	**19%**	**0.277**	**2.44**	**157%**	**23%**
Gln	**0.487**	**2.38**	**23%**	**17%**	**0.447**	**1.293**	**28%**	**33%**	**0.142**	**0.53**	**103%**	**82%**
Glu	9.33	8.2	4%	4%	8.121	6.567	5%	5%	7.42	7.13	6%	5%
Cho+GPC+Pch	1.276	1.36	3%	3%	1.39	1.62	4%	6%	1.35	1.45	4%	3%
Cr + PCr	6.185	6.18	1%	2%	6.262	6.468	2%	2%	6.32	6.78	2%	2%
	Prc				PC				Occ			
	Concentration [mMol/Kg]		CRLB(%)		Concentration [mMol/Kg]		CRLB(%)		Concentration [mMol/Kg]		CRLB(%)	
Metabolite	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER	sLASER	MASE-sLASER
GSH	**1.8**	**2.625**	**6%**	**5%**	**1.76**	**2.29**	**6%**	**7%**	**1.72**	**2.51**	**7%**	**6%**
NAA	7.6	7.2	1%	2%	7.54	7.31	2%	2%	8.04	7.85	1%	2%
NAAG	0.65	0.555	12%	17%	0.72	0.69	12%	17%	0.674	0.584	14%	20%
mI	4.62	4.148	4%	6%	4.65	4.51	5%	7%	4.4	4.075	5%	8%
GABA	**0.967**	**2.296**	**40%**	**22%**	**0.78**	**2.31**	**51%**	**24%**	**1.12**	**1.65**	**38%**	**32%**
Gln	0.591	1.218	23%	33%	0.49	1.43	26%	35%	0.543	0.702	23%	71%
Glu	9.94	8.476	4%	4%	9.92	9.54	5%	4%	8.93	8.904	5%	5%
Cho+GPC+Pch	0.87	0.952	4%	5%	0.94	1.16	4%	5%	0.68	0.664	5%	9%
Cr + PCr	6.55	6.8	1%	2%	6.78	7.26	1%	2%	6.495	7.057	2%	2%

The six brain regions were as follows: AC, anterior cingulate; DLPFC, dorsolateral prefrontal cortex; MC, motor cortex; Prc, precuneus; PC, posterior cingulate; Occ, occipital cortex.

Cho, choline; Cr, creatine; CRLB, Cramér–Rao lower bound; GABA, γ-aminobutyric acid; Gln, glutamine; Glu, glutamate; GPC, glycerophosphocholine; GSH, glutathione; mI, myo-inositol; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamic acid; PCh, phosphocholine; PCr, phosphocreatine.

TABLE 3 A comparison of the concentration of all the metabolites measured with a MASE-sLASER sequence at TE = 27 ms from subjects 1 and 2. The metabolites were quantified with LCModel

MASE-sLASER, TE = 27 ms				
	Subject 1		Subject 2	
Metabolite	Conc. (Met./tNAA)	CRLB	Conc. (Met./tNAA)	CRLB%
GSH	0.332	5%	0.297	6%
NAA	0.929	2%	0.924	2%
NAAG	0.07	19%	0.076	17%
mI	0.758	4%	0.676	4%
GABA	0.49	11%	0.494	11%
Gln	0.269	16%	0.297	13%
Glu	1.257	3%	1.195	3%
Cho + GPC + Pch	0.134	5%	0.145	4%
Cr + PCr	1.03	2%	1.034	2%

Cho, choline; Cr, creatine; CRLB, Cramér–Rao lower bound; GABA, γ-aminobutyric acid; Gln, glutamine; Glu, glutamate; GPC, glycerophosphocholine; GSH, glutathione; Met., metabolite; mI, myo-inositol; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamic acid; PCh, phosphocholine; PCr, phosphocreatine; tNAA, total *N*-acetylaspartate.

TABLE 4 A comparison of the concentrations of the metabolites measured with a MEGA-sLASER (with MASE) sequence at TE = 68 ms from subjects 4–8. The metabolites were quantified with LCModel

MEGA-sLASER [with MASE], TE = 68 ms												
Metabolite	Subject 4 Conc. (Met./tNAA)	CRLB%	Subject 5 Conc. (Met./tNAA)	CRLB%	Subject 6 Conc. (Met./tNAA)	CRLB%	Subject 7 Conc. (Met./tNAA)	CRLB%	Subject 8 Conc. (Met./tNAA)	CRLB%	mean ± std Conc. (Met./tNAA)	CRLB%
GABA	0.112	19%	0.08	25%	0.08	25%	0.102	22%	0.113	18%	0.097 ± 0.016	21.8 ± 3.27%
Gln	0.188	34%	0.08	87%	0.08	87%	0.023	322%	0	999%	0.093 ± 0.069	305.8 ± 403%
Glu	0.961	8%	0.886	9%	0.886	9%	0.96	9%	0.962	6%	0.931 ± 0.041	8.2 ± 1.3%

CRLB, Cramér–Rao lower bound; GABA, γ-aminobutyric acid; Gln, glutamine; Glu, glutamate; Met., metabolite; tNAA, total *N*-acetylaspartate.

TABLE 5 A comparison of the concentration of major metabolites (NAA, tCho and tCr) measured with sLASER and MASE-sLASER sequences in this study, with the results of Ganji et al.,[13] in the medial occipital and medial frontal lobe of the healthy human brain

	Medial Frontal Lobe Concentration (ratio to tNAA)			Medial Occipital Lobe Concentration (ratio to tNAA)		
Metabolite	sLASER	MASE-sLASER	Ganji et al [13]	sLASER	MASE-sLASER	Ganji et al [13]
NAA	0.86	0.87	0.924	0.89	0.95	0.88
tCho	0.18	0.22	0.181	0.11	0.14	0.113
tCr	0.92	1.04	0.82	0.82	0.93	0.755

NAA, *N*-acetylaspartate; tCho, total choline; tCr, total creatine; tNAA, total *N*-acetylaspartate.

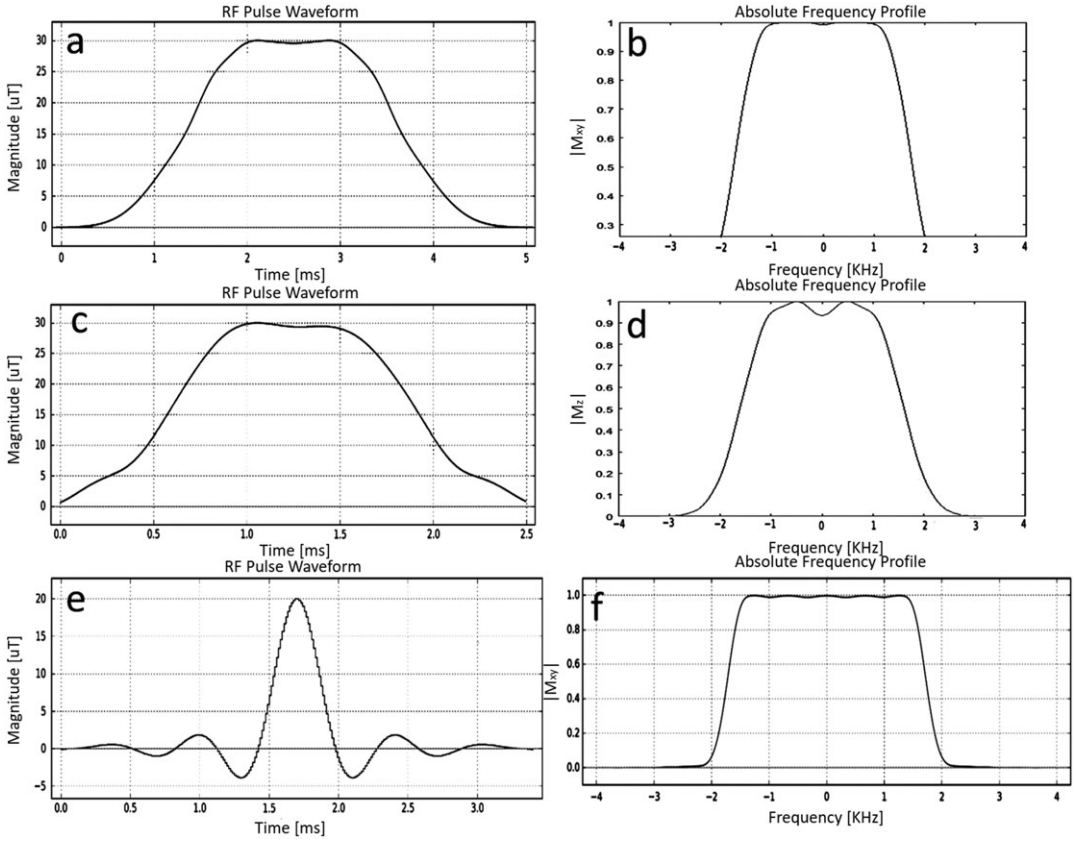

FIGURE 3 Pulse shape and frequency response of the excitation parts of MASE-sLASER and sLASER sequences. The excitation part of the MASE-sLASER sequence consists of a MASE spin echo and the excitation part of sLASER is a conventional SLR pulse. a and b are pulse shape and frequency response of the 90° pulse of MASE. c and d are pulse shape and frequency response of the 180° pulse of MASE. e and f are pulse shape and frequency response of the conventional SLR excitation pulse used in the implementation of the conventional sLASER sequence

Table 3 shows a comparison of the concentrations of the metabolites measured with the MASE-sLASER sequence at TE = 27 ms from subjects 1 and 2. Table 4 shows a comparison of the concentrations of metabolites measured with a MEGA-sLASER (with MASE) sequence at TE = 68 ms from subjects 4–8.

In Table 5, we show a comparison of the concentrations of the major metabolites of NAA, tCho and tCr measured with sLASER and MASE-sLASER at TE = 38 ms in this study, with those reported by Ganji et al.,[13] for the medial frontal lobe and medial occipital lobe. There is good agreement between the quantification of the major metabolites (NAA, tCho and tCr) across the three measurements (sLASER, MASE-sLASER and PRESS[13]).

A notable feature of MASE-sLASER spectra at TEs of 68 and 136 ms is that the signal at 2.28 ppm is well separated from the major neighboring Glu signal at 2.35 ppm. The simulation results for GABA and Glu are shown in Figure 7a, c, e, g. The simulation was performed for these two metabolites and for MASE-sLASER and conventional sLASER sequences at TEs of 68 and 136 ms, TEs at which the pattern of the GABA triplet at 2.28 ppm falls within the real channel. An interesting feature of the simulated spectra is that the resonances of these two molecules centered at 2.28 ppm and 2.35 ppm are in phase relative to each other at TEs of 68 and 136 ms when acquired with the MASE-sLASER sequence

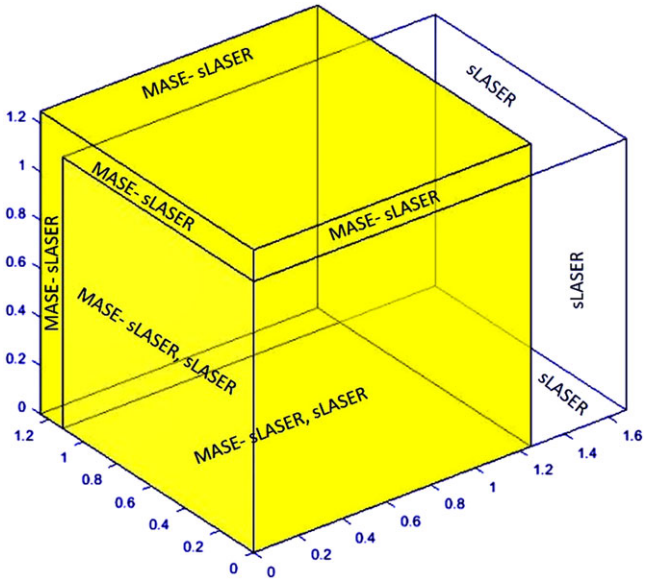

FIGURE 4 CSDE for the implemented short TE MASE-sLASER sequence compared with a conventional sLASER sequence. CSDE for the MASE-sLASER sequence is symmetric in all three directions (yellow). CSDE for the conventional sLASER is not symmetric and is larger in one direction (white). The cubes here do not represent the voxels; they only show the amount of CSDE in three directions in mm/ppm for each sequence

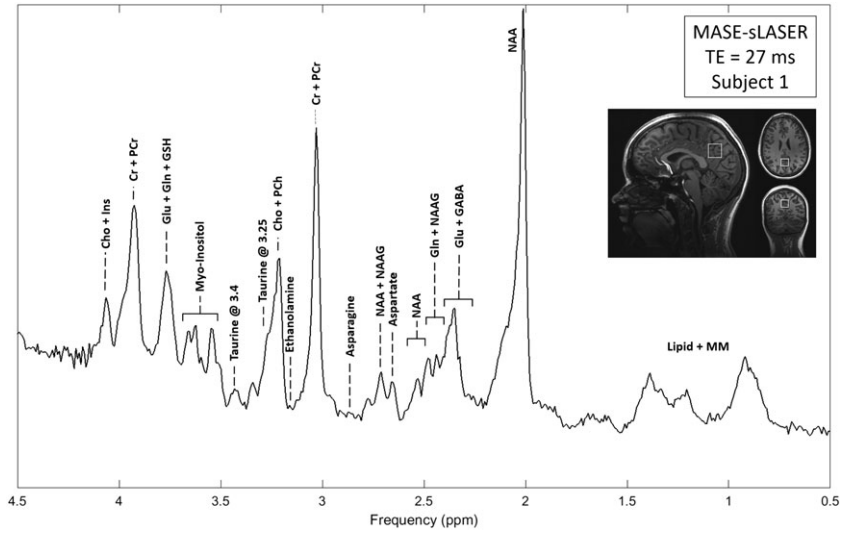

FIGURE 5 Short TE MASE-sLASER single-voxel spectrum acquired from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of the human brain at TE = 27 ms at 7 T. Major observed metabolites are labeled in the spectrum. Cho, choline; Cr, creatine; GABA, γ-aminobutyric acid; Gln, glutamine; Glu, glutamate; GSH, glutathione; Ins, inositol; MM, macromolecule; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamic acid; PCh, phosphocholine; PCr, phosphocreatine

(Figure 7a, e), but not for the conventional sLASER sequence (Figure 7c, g). For MASE-sLASER, the only overlapping sub-peak of Glu with the GABA signal is peak 3 (upfield), which is in phase relative to the coincident GABA resonance at TEs of 68 and 136 ms. As this peak of Glu is very small in comparison with the two other peaks, we conclude that the contribution of Glu to the GABA signal is minimal at these two TEs, and therefore GABA at 2.28 ppm and Glu at 2.35 ppm are well separated when acquired by the MASE-sLASER sequence at these two TEs. However, for conventional sLASER, peak 2 of Glu and peak 1 of GABA overlap at TE = 68 ms (Figure 7c), with peak 2 of Glu being much larger than peak 1 of GABA. Also, peak 3 of Glu overlaps with peak 2 of GABA at this TE. Moreover, peak 2 of Glu and peak 1 of GABA totally overlap at TE = 136 ms (Figure 7g). The simulation results therefore demonstrate a good separation of GABA at 2.28 ppm and Glu at 2.35 ppm when acquired with MASE-sLASER at TEs of 68 and 136 ms, and overlap of these two signals when acquired with the conventional sLASER sequence at the same TEs. *In vivo* results of MASE-sLASER and conventional sLASER acquisitions at TEs of 68 and 136 ms are shown in Figure 7b, d, f, h. While GABA and Glu signals overlap at TE = 68 ms when acquired with the sLASER sequence (Figure 7d), they are well separated when acquired with MASE-sLASER at the same TE (Figure 7b). In addition, although the GABA signal is elevated by the Glu signal at TE = 136 ms when acquired with the sLASER sequence (Figure 7h), it is well separated from Glu when acquired with the MASE-sLASER sequence at the same TE (Figure 7f). Theoretically, the pattern of the GABA triplet at 2.28 ppm should be negative–positive–negative at TE = 68 ms and positive–positive–positive at TE = 136 ms.

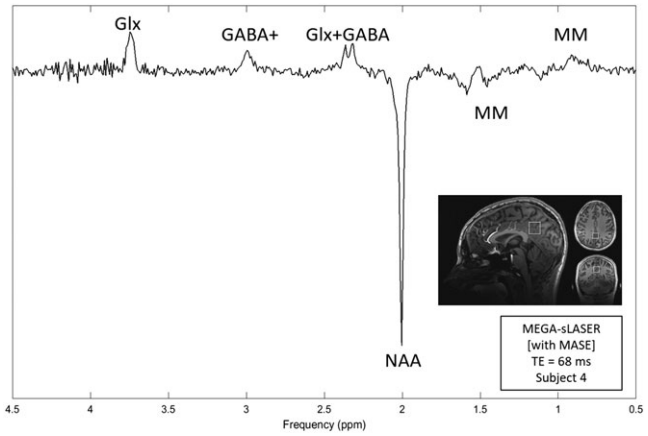

FIGURE 6 MEGA difference spectrum acquired using the MEGA-sLASER (with MASE) sequence implemented with MASE pulses at TE = 68 ms, from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of the brain of a healthy subject at 7 T, showing GABA+ at 3 ppm and Glx at 3.75 ppm. In addition to GABA and Glx, NAA and MM are also coedited in the MEGA edited spectrum

The three sub-peaks of the GABA resonance at 2.28 ppm *in vivo*, measured with the MASE-sLASER sequence and shown in Figure 7b, f, have a negative–positive–negative pattern at 68 ms and a positive–positive–positive pattern at 136 ms as expected theoretically, and match with the simulated patterns shown in Figure 7a, e.

To show that the signal observed at 2.28 ppm arises from GABA, and not noise, we also acquired nine separate consecutive MASE-sLASER datasets from the same voxel at TE = 68 ms. In Figure 8, we show the average of the nine acquisitions in the range 2.1–2.5 ppm which presents GABA at 2.28 ppm separated from the neighbor Glu at 2.35 ppm. The spectra of the nine single acquisitions in the range 2.1–2.5 ppm are given in Supporting Information Figure S3. As a result of the different possible gain settings of these nine acquisitions, we first normalized each of the nine spectra based on the average value of their noise (i.e. equal thermal noise level). After alignment of the spectra based on the NAA peak, the SNR of the 2.28-ppm signal for the separate measurements and for the average were calculated. The averaged SNR was, on average, 3.16 times that of the individual acquisitions, confirming that the observed signal was not noise. The only outlier was the second acquisition which had a comparatively lower SNR than the other eight acquisitions.

The spectra acquired from a brain phantom at TEs of 68 and 136 ms using the MASE-sLASER sequence are shown in Figure 9, demonstrating the separation of GABA from Glu at both TEs.

4 | DISCUSSION

The main advantage of the use of adiabatic SLR refocusing pulses in the implementation of MASE-sLASER sequences is their shorter duration compared with conventional adiabatic pulses. This made it possible to implement the MASE-sLASER sequence with a TE as short as 27 ms, even though we needed two pulses for excitation. Replacing the excitation pulse should yield some reduction in B_1 sensitivity, and we matched CSDE in all three directions.

4.1 | Short-TE MASE-sLASER

The short-TE MASE-sLASER matched CSDE sequence was implemented with minimum TE = 27 ms. As a comparison, the short-TE conventional sLASER sequence at 7 T for SVS of human brain has been implemented previously at TE = 25 ms,[21] TE = 28 ms[15] and TE = 32 ms,[22] Therefore, although our minimum TE is comparable with that of previous implementations, our sequence has the advantage of low and matched CSDE in all three directions which, until now, has been an advantage of full LASER and stimulated echo acquisition mode (STEAM) sequences and not a feature of the sLASER sequence.

4.2 | Comparison with STEAM and standard sLASER

A matched CSDE sequence used for SVS is STEAM. A drawback of this sequence is the halved intensity which is caused by the use of a stimulated echo. To compensate for this disadvantage, STEAM is usually used at ultrashort TE.[23-25] In addition to the mentioned drawback, the RF pulses used in the STEAM sequence are not adiabatic, which makes the sequence sensitive to B_1 inhomogeneity, especially at ultrahigh field. Also, these pulses usually have a lower bandwidth than adiabatic pulses, which makes CSDE relatively larger for this sequence. In comparison, the MASE-sLASER sequence generates a full-intensity echo while keeping the advantage of matched and low

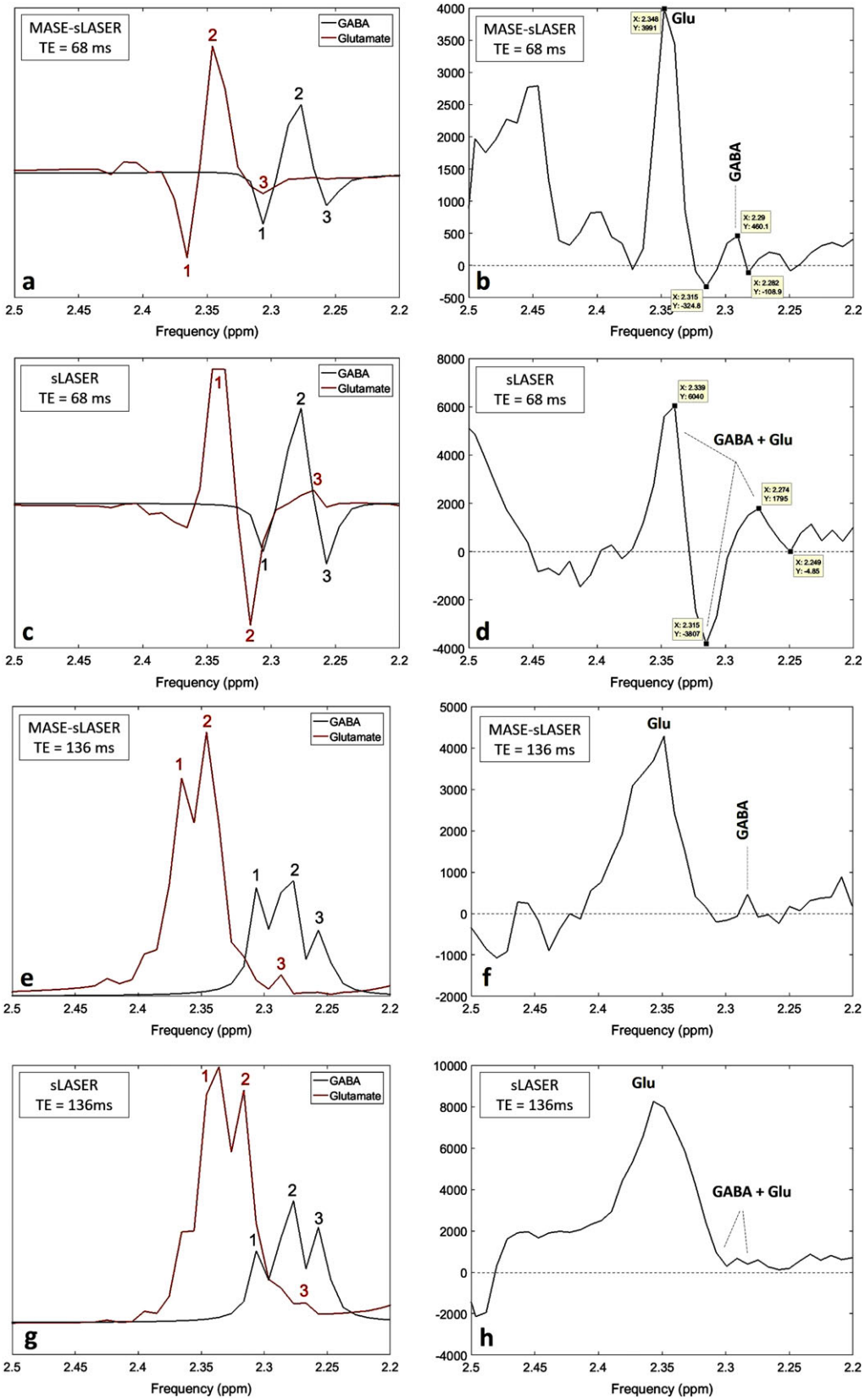

FIGURE 7 Simulation for GABA and glutamate (Glu) at TE = 68 ms for MASE-sLASER (a) and sLASER (c) and at TE = 136 ms for MASE-sLASER (e) and sLASER (g). The major sub-peaks are labeled with numbers 1–3 for each metabolite. The pattern of GABA at 2.28 ppm and Glu at 2.35 ppm, observed *in vivo* at TE = 68 ms acquired with the MASE-sLASER (b) and sLASER (d) sequence, and at TE = 136 ms acquired with the MASE-sLASER (f) and sLASER (h) sequence, is in good agreement with the corresponding simulation results

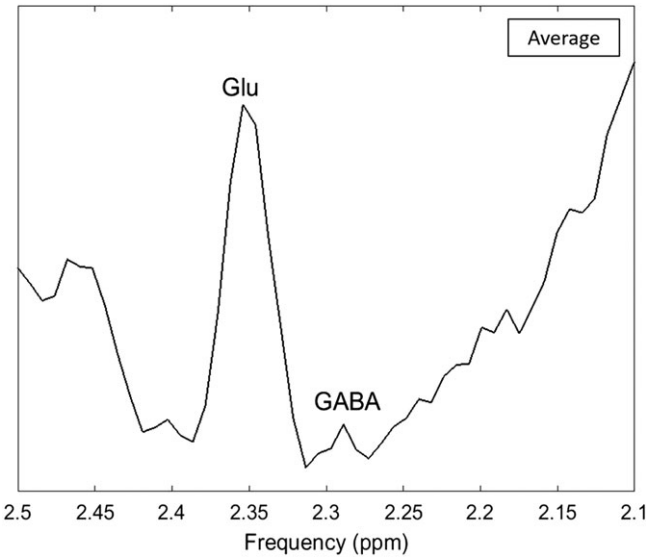

FIGURE 8 Average spectrum of nine consecutive acquisitions acquired from a 20 × 20 × 20-mm^3 voxel positioned at the medial occipital region of a healthy subject (subject 3) using the MASE-sLASER sequence with TE = 68 ms at 7 T. The spectrum is shown in the range 2.1–2.5 ppm. GABA at 2.28 ppm is clearly separated from glutamate (Glu) at 2.35 ppm. The nine individual acquisitions are shown separately in Supporting Information Figure S3

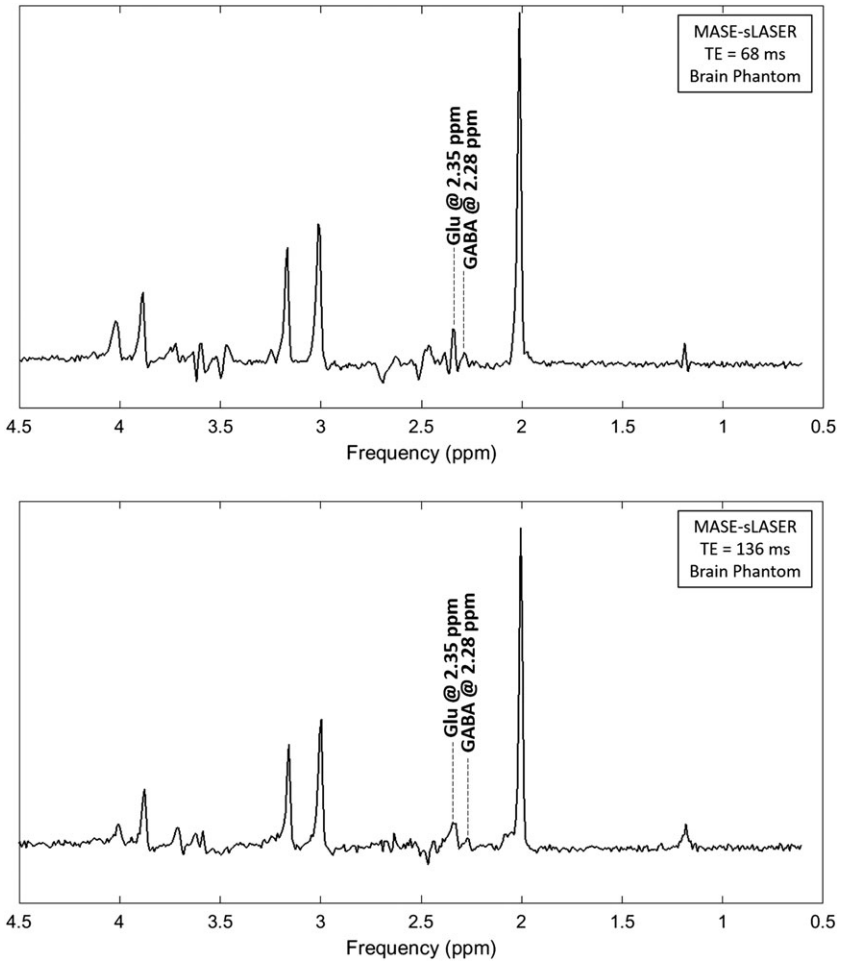

FIGURE 9 Spectra acquired using the MASE-sLASER sequence from a brain phantom at TEs of 68 ms (top) and 136 ms (bottom), showing GABA at 2.28 ppm well separated from Glu at 2.35 ppm

CSDE in all three directions. In addition, the refocusing pulse used in the MASE pair is adiabatic and therefore insensitive to B_1 variations. The non-adiabatic excitation pulse of MASE has been shown to have lower sensitivity to B_1 variations than conventional excitation 90° pulses.[14]

There is a drawback for the application of the standard sLASER sequence at ultrahigh field, which we have compensated for by implementing the MASE-sLASER sequence. The standard sLASER sequence has larger and different CSDE in one direction because of its non-adiabatic excitation pulse with a lower bandwidth than adiabatic pulses. In comparison, MASE-sLASER has low and matched CSDE in all three directions. Indeed, CSDE for our implemented short-TE MASE-sLASER sequence is 1.25 mm/ppm in all three axes for a voxel size of 20 × 20 × 20 mm^3 (6.3%). In comparison, our implemented conventional sLASER sequence for the same voxel size has CSDE of 1.7 mm/ppm in the non-adiabatic excitation direction (8.4%) and CSDE of 1.12 mm/ppm in the adiabatic refocusing directions (5.6%).

4.3 | MEGA-sLASER (with MASE) with TE = 68 ms for editing GABA

The MEGA *J*-difference editing technique for GABA requires fixed TEs of odd multiples of 68 ms. As higher odd multiples of 68 ms are generally considered to be too long because of the loss in sensitivity caused by T_2 relaxation, the optimum TE for editing GABA is 68 ms.[11] With a large number of pulses of relatively long duration, it is not currently possible to implement a full LASER MEGA editing sequence with TE = 68 ms at ultrahigh field. To our knowledge, currently, there is no report of full LASER for editing GABA at ultrahigh field with TE = 68 ms, although gradient offset independent adiabaticity (GOIA)-LASER with TE = 68 ms has been successfully implemented for the measurement of GABA with MRS imaging at 3 T.[26] Although GOIA and MASE pulses are both low power, the major advantage of GOIA pulses relative to MASE pulses is their much higher bandwidth, which makes CSDE negligible, and thus makes GOIA pulses more beneficial than MASE for MRS imaging. For instance, the wide bandwidth of GOIA pulses used in MRS imaging with LASER makes the outer volume suppression of fat unnecessary.[27] However, the implementation of MASE pulses is simpler than that of GOIA pulses, and they can also be used for excitation. Compared with the full LASER sequence, the sLASER sequence offers a shorter TE and therefore has been used to efficiently edit GABA at 7 T.[10] In this study, we present the implementation of the MEGA-sLASER (with MASE) sequence with TE = 68 ms at 7 T as another application of MASE pulses, which is made possible because of the shorter duration of MASE pulses compared with conventional hyperbolic secant pulses. Previously, MEGA-sLASER at 7 T had to be implemented at TEs longer than the optimum value of 68 ms (74 ms[10,15]).

The MEGA editing method implemented here employs two editing inversion pulses that have a narrow bandwidth (220 Hz). These two RF pulses are not adiabatic and therefore B_1 inhomogeneity negatively affects their inversion efficiency. However, the sensitivity of the sequence to variations in the excitation pulse (90°) angle is greater than that to variations in the inversion pulse angle.

In the comparison of the concentrations of metabolites presented in Tables 3 and 4, there is good agreement between the calculated values across the subjects for each method, confirming the reproducibility of the two methods of MASE-sLASER and MEGA-sLASER (with MASE).

In the comparison of the concentrations of the major metabolites presented in Table 5, there is good agreement between the quantification of the major metabolites (NAA, tCho and tCr) across the three methods (sLASER, MASE-sLASER and PRESS[13]).

4.4 | GABA at 2.28 ppm

The contribution of Glu to the GABA signal at 2.28 ppm in simulations is negligible at TEs of 68 and 136 ms when acquired with the MASE-sLASER sequence (Figure 7a, e). However, the simulation results for the conventional sLASER sequence at TEs of 68 and 136 ms demonstrate the overlap of GABA and Glu signals (Figure 7c, g).

We have distinguished GABA at 2.28 ppm from Glu at 2.35 ppm in the spectra acquired with the MASE-sLASER sequence at TEs of 68 and 136 ms, the TEs at which the side-peaks of GABA are in phase because of the effect of *J* evolution. As shown in Figure 7b, f, the GABA signal is clearly separated from Glu at these two TEs. This is in contrast with PRESS acquisitions, where TE = 92 ms was found to be an optimum TE for the good separation of GABA and Glu.[13]

With simulation, it is possible to adjust the timings of the RF pulses, but it is still difficult to separate timing and pulse effects; for example, if we replace the MASE excitation pulse pair with a single SLR pulse, we also need to change the timing of the other pulses. Indeed, there are two main differences between sLASER and MASE-sLASER in terms of sequence elements. The 90° excitation pulse of sLASER is replaced with the MASE pair. In addition to this, the two sequences have different inter-pulse intervals at the same TE. These two factors result in the separation of GABA and Glu with MASE-sLASER, but not with sLASER, at TE = 68 ms. The signal pattern of *J*-coupled metabolites is dependent on the RF pulse scheme and therefore, for sLASER, a TE other than 68 ms could possibly be optimum for the separation of GABA and Glu. However, we have not observed such a separation at the TEs probed in this work. Although a comprehensive search is beyond the scope of this work, we consider it unlikely that such a separation exists at a TE which would also give a good SNR.

For MASE-sLASER specifically, a short TE is not necessarily optimum for the separation of GABA from Glu. At TE = 34 ms, for instance, the GABA resonance at 2.28 ppm is not clearly separated from the neighboring Glu and is not separately visible *in vivo*, as shown in Supporting Information Figure S4. Also, in short-TE spectra acquired at 27 ms, shown in Figures 5 and S1, the GABA peak at 2.28 ppm is not clearly and separately visible.

The main advantages of the MASE-sLASER sequence presented here are the separation of the GABA signal at 2.28 ppm from the neighboring Glu signal at 2.35 ppm and the possibility of implementing MEGA-sLASER (with MASE) with TE = 68 ms to measure GABA at 7 T. The CSDE of the MASE-sLASER sequence is comparable with, but not much less than, that of the conventional sLASER sequence. The improvement in CSDE of the

MASE-sLASER sequence is limited; indeed, the main feature in terms of CSDE is to have a matched CSDE which, until now, had been a feature of a full LASER sequence, but not an sLASER sequence.

4.5 | Limitations

It is worthwhile noting that, as the excitation 90° pulse used in MASE is not adiabatic, the implemented sequence is not full LASER, but sLASER. However, the only non-adiabatic pulse of the MASE sequence (the excitation 90° pulse) has been shown to have a lower sensitivity to B_1 variations than the conventional excitation 90° pulses.[14] Even if the improvement in B_1 insensitivity is marginal, it could have a disproportionate effect on the signal intensity, which is well known to be more strongly affected by imperfections in the excitation than in the refocusing pulses.

A limitation of the MASE-sLASER sequence is the lower bandwidth of MASE pulses compared with hyperbolic secant pulses and GOIA pulses. The bandwidths of the MASE pulses used in the implementation of the MASE-sLASER sequence in this study are in the range of 4.6–5 kHz, which is slightly less than those of the hyperbolic secant pulses used in the implementation of the standard sLASER sequence,[8,9] and much less than those of the GOIA pulses.[27]

5 | CONCLUSION

Short-TE MASE-sLASER is a full-intensity matched CSDE sequence, with a low and matched CSDE in all three directions. Besides, benefiting from the short duration of the MASE pulses, the MEGA-sLASER (with MASE) sequence is implemented here with TE = 68 ms for the measurement of GABA at 7 T. Finally, a characteristic of the spectrum acquired with MASE-sLASER at TE = 68 ms is that the GABA resonance at 2.28 ppm is distinguishable from that of Glu at 2.35 ppm, making direct measurement of this GABA resonance possible with this sequence.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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