Flexible MEGA editing scheme with asymmetric adiabatic pulses applied for $T_2$ measurement of lactate in human brain

Michael Dacko | Thomas Lange

Center for Diagnostic and Therapeutic Radiology, Medical Physics, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

**Correspondence**
Michael Dacko, Medical Physics, Center for Diagnostic and Therapeutic Radiology, Medical Center - University of Freiburg, Killianstrasse 5a, 79106 Freiburg, Germany. Email: michael.dacko@uniklinik-freiburg.de

**Funding information**
Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), Grant/Award Number: LA 3353/2-1 and LA 3353/4-1

**Purpose:** A flexible MEGA editing scheme which decouples the editing efficiency from TE is proposed and the utility of asymmetric adiabatic pulses for this new technique is explored. It is demonstrated that the method enables robust $T_2$ measurement of lactate in healthy human brain.

**Methods:** The proposed variation of the MEGA scheme applies editing pulses in both acquired spectra, ensuring that the difference in J-evolution of the target resonance leads to maximal signal yield in the difference spectrum for arbitrary TE. A MEGA-sLASER sequence is augmented with asymmetric adiabatic editing pulses for enhanced flexibility and immunity to $B_1^+$ miscalibration and inhomogeneities. The technique is validated and optimized for flexible lactate editing via a simple analytical model, numerical simulations and in vitro experiments. The $T_2$ relaxation constant of lactate is determined in vivo via multiple-TE measurements with the proposed method and a dedicated postprocessing and quantification approach.

**Results:** Asymmetric adiabatic editing pulses improve robustness and facilitate efficient J-editing in sequences or protocols with strong timing constraints. Single voxel measurements using the proposed MEGA scheme in the occipital cortex of six healthy subjects yield a relaxation constant of $T_2 = 171 \pm 19$ ms for the methyl resonance of lactate at a field strength of 3T.

**Conclusions:** The proposed MEGA editing scheme allows for novel kinds of J-editing experiments and promises to be an asset to robust $T_2$ measurement of lactate and potentially other J-coupled metabolites in vivo.

**Keywords**
$T_2$, adiabatic editing, human brain, J-editing, lactate, MEGA, MRS

**INTRODUCTION**

J-difference editing based on the (MEsher-GArwood) MEGA\(^1,2\) scheme is an established technique in magnetic resonance spectroscopy (MRS) for detection of J-coupled metabolites which cannot be robustly measured with conventional short-TE methods due to spectral overlap with stronger resonances from other metabolites. Originally proposed...
for GABA editing, this technique has recently been successfully applied to detect other J-coupled metabolites such as ascorbate (vitamin C), β-hydroxybutyrate, glucose, glutathione, lactate (Lac), N-acetylaspartate glutamate, and 2-hydroxyglutarate. Furthermore, extended MEGA schemes for simultaneous detection of two or more J-coupled metabolites have been proposed.11-14

The MEGA editing scheme acts like a filter for uncoupled and other (non-edited) J-coupled spin resonances via subtraction of two acquired spectra, one edited (ON) shot and one unedited (OFF) shot, to obtain a difference (DIFF) spectrum which ideally contains only signal from the edited target resonance and no signal from other resonances in the spectral region of interest. For optimal editing efficiency, TE is typically chosen to maximize the negative in-phase coherence in the OFF spectrum. However, this limits the choice of TE to discrete values dictated by the J-coupling strength and topology of the spin system. For metabolites with simple coupling topologies, these TE settings with optimal editing efficiency can be determined analytically while for other metabolites with more complex coupling networks, numerical simulations can be employed to perform sequence timing optimization based on signal yield or other measures such as the Fisher information matrix. For the weakly coupled AX3 spin system of lactate, analytical calculations yield the following TE settings for optimal editing efficiency: TE = (2n−1)J with J = 7 Hz and n ∈ N. On the other hand, the signal yield of in vivo MRS is strongly affected by T2 decay so that typically only the shortest of these discrete TE settings (e.g., TE = 144 ms for lactate) are applied in practice. Thus, J-editing schemes such as MEGA impose strong restrictions on the sequence timing. In particular for T2 determination where measurements with varying TEs have to be performed, these limitations represent a major drawback.

Apart from sequence timing restrictions, MEGA editing can also be impaired by measurement imperfections arising from the localization scheme and B1 inhomogeneities. For the J-coupled target resonances, spin echo localization suffers from the chemical shift displacement artifact, which gives rise to voxel compartments with different J-evolution and consequently leads to signal loss due to incoherent signal summation. This effect is quite pronounced for detection of weakly coupled spin systems at high field strength (≥3T) and localization schemes such as PRESS, which are based on low-bandwidth refocusing pulses. It should be noted that this signal loss is echo-time dependent and particularly severe for TE settings with maximal in-phase signal inversion, which are used in MEGA editing. The application of broadband adiabatic localization pulses, which strongly reduce the chemical shift displacement, has proved to be a viable remedy for MEGA experiments. Furthermore, the use of gradient-modulated adiabatic pulses allows for a reduction of the deposited energy and enables the realization of even larger bandwidths, thus minimizing chemical displacement and the resulting signal loss. Adiabatic pulses are also beneficial in terms of their immunity against B1 miscalibration and inhomogeneities. While LASER or semi-LASER (sLASER) localization schemes based on such adiabatic pulses are nowadays widely used in MEGA experiments, spectral editing is typically performed with conventional (non-adiabatic) pulses. However, flip angle imperfections due to B1 miscalibration and inhomogeneities can substantially impair the editing efficiency and may result in severe quantification errors if this reduced flip angle is not accounted for in the metabolite basis spectra.

Moser et al have recently applied an asymmetric adiabatic pulse for GABA editing and have demonstrated a reduced susceptibility to B1 miscalibration and inhomogeneities. Compared to conventional low-bandwidth Gaussian editing pulses, asymmetric adiabatic pulses can be realized with a flat-top inversion profile, which makes MEGA editing less sensitive to B0 drifts, for example, arising from scanner instabilities. Due to their beneficial inversion profile with a narrow transition bandwidth, asymmetric adiabatic pulses have also been successfully applied for metabolite cycling as well as for water and fat suppression schemes.

In this work, a flexible MEGA editing scheme that decouples the editing efficiency from TE is proposed for lactate detection. The idea of such an editing scheme has recently been outlined for GABA editing by Near and Kumaragamage. The sensitivity of the proposed method to flip angle imperfections of the editing pulses is assessed and the utility of asymmetric adiabatic pulses for this technique is explored. It is demonstrated that the method enables robust T2 measurements of lactate in healthy human brain.

2 | THEORY

2.1 | MEGA scheme with partial refocusing of J-evolution

The proposed variation of the MEGA scheme enables J-difference editing experiments to be performed at arbitrary TEs (larger than the typically employed optimal TE which is dictated by coupling strength and topology of the spin system), while maintaining maximal editing efficiency and therefore maximal signal yield. This is achieved by employing J-editing for both acquired spectra (denoted as the “POS” and “NEG” shots) so that the J-evolution difference between the two shots leads to a maximal signal yield. It is instructive to illustrate the scheme with Lac, which is a simple weakly coupled AX3 spin system characterized by a doublet situated at 1.31 ppm arising from a methyl group that is J-coupled to a methine proton resonating at 4.10 ppm with a coupling constant of J = 7 Hz.
First, the original MEGA scheme is considered: In the ON shot, a pair of selective editing pulses is applied to invert the methine spin at 4.10 ppm with an inter-pulse separation of $T_{\text{ref}} = \frac{TE}{2} = 144$ ms to completely refocus the J-evolution of the methyl resonance at 1.31 ppm so that it yields a positive in-phase doublet. In the OFF shot, no editing of the methine resonance is performed so that J-evolution gives rise to an inverted negative doublet for the methyl resonance due to $TE = \frac{1}{J}$. In this shot, the editing pulse pair is typically applied in the downfield region at 5.30 ppm to ensure that the water resonance is equally affected in the two shots.

The proposed variation of the MEGA scheme ensures that the methyl resonance appears as a positive doublet in the POS shots and as a negative doublet in the NEG shots for all $TE$ (above a certain threshold $T_{\text{Emin}}$ as discussed below). Thus line shape modulations induced by anti-phase coherences are effectively eliminated. The POS shot is therefore equivalent to the ON shot in the original MEGA scheme and employs $T_{\text{ref}} = \frac{TE}{2}$, but without a restriction on $TE$ (apart from limitations due to the editing pulse duration $T_p$). The NEG shot applies an editing pulse separation of $T_{\text{ref}} = \frac{TE}{2} - \frac{1}{2J}$, which leads to partial J-refocusing and gives rise to a negative doublet for the methyl resonance. Thus, the scheme ensures that J-evolution of the methyl resonance differs by $\frac{1}{J}$ between POS and NEG shots, which maximizes the editing efficiency for Lac. The NEG shot can be regarded as a generalized OFF shot which refocuses a surplus of J-evolution acquired due to a larger echo time $TE > \frac{1}{J}$. An illustration of POS and NEG shots is given in the sequence diagram of Figure 1 (see “Editing schemes—Gaussian”) along with the resulting doublet methyl resonances. Note that the NEG shot requires J-evolution over an interval of at least $\frac{1}{J}$, which imposes a lower limit on $TE$ given by $T_{\text{Emin}} \geq \frac{1}{J} + 2T_p$. In the

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**Figure 1** The sequence diagram is divided into two major parts: the upper part shows rf pulses, slice-selective gradients (gray), and spoiler gradients (black) for spatial localization and the MEGA$^2$ spoiler gradient scheme with G1, G2, G3 (white). The lower part shows various J-editing schemes resulting in a positive or negative Lac methyl doublet resonance (as illustrated in the right panel), corresponding to the POS shot with complete J-refocusing and the NEG shot with partial J-refocusing, respectively. The editing schemes are either realized with (conventional) Gaussian pulses or with asymmetric adiabatic pulses, which allow for different configurations of the editing pairs. The delay $T_{\text{ref}}$ between the editing pulses that is required to achieve the desired J-refocusing effect is indicated in blue.
following, it will be shown that this threshold can be considerably lowered using asymmetric adiabatic pulses.

3 | METHODS

3.1 | Setup and sequence

All experiments were performed on a 3T Prisma MR system (Siemens Healthineers, Germany), using a 64-channel receiver head coil. An in-house single voxel MEGA-sLASER sequence was implemented as shown in Figure 1. Localization is based on two pairs of broadband GOIA-HS84 pulses, with an inversion bandwidth of BW = 20 kHz defined as full width at half maximum, pulse duration $T_p = 5$ ms, gradient modulation factor $g = 0.9$, and $B_1^\text{max} = 17 \mu$T. The MEGA scheme is either realized with a pair of asymmetric adiabatic pulses (for details see Section 3.2) or a pair of conventional Gaussian pulses (for comparison). The sequence user has control over all parameters of the analytically defined adiabatic pulses, which are created at sequence runtime utilizing the C++ Eigen library parameters. Optional time inversion and phase conjugation for each of the adiabatic pulses allow for different pair configurations as described in Section 3.2.2. Along with the adjustable delay $T_{\text{ref}}$ between the MEGA editing pulses (see Figure 1) these settings give control over the extent of refocused J-evolution. Furthermore, gradient spoiler strength and orientation can be adjusted in the protocol. All phantom experiments were performed at room temperature with adjusted editing pulse frequency to account for chemical shift differences to in vivo experiments.

3.2 | Asymmetric adiabatic pulse for J-editing

For a conventional (editing) pulse, $B_1^\pm$ miscalibrations and inhomogeneities cause deviations from the desired flip angle and an overall degradation of the inversion profile. Flip angle errors of the MEGA pulses may lead to reduced editing efficiency and ultimately to erroneous metabolite quantification in MEGA experiments. A rigorous analysis using the product operator formalism was performed and validated by phantom experiments (see Supporting Information Section S1). It shows that imperfect flip angles of MEGA editing pulses lead to TE-dependent signal amplitude and line shape modulations (see Supporting Information Figure S2).

In this work, an asymmetric adiabatic pulse adopted from Hwang et al was used for J-editing. This composite pulse consists of two segments: the first segment is half of a long (hyperbolic secant) HS$_1^1$ modulated pulse producing a narrow transition bandwidth $T_{\text{W,narrow}}$ on one side of the passband while the second segment is half of a short tanh/tan pulse, which is used for fast broadband inversion and produces a wide transition bandwidth $T_{\text{W,wide}}$ on the other side of the passband. The amplitude and frequency modulation functions for the first HS$_1^1$ segment are given for $0 \leq t \leq T_{p,1}$ by

\begin{align*}
\text{AM}_1(t) &= B_1^{\text{max}} \text{sech} \left( \beta \left( 1 - \frac{t}{T_{p,1}} \right)^{1/2} \right), \\
\text{FM}_1(t) &= A_1 \int_0^{T_{p,1}} \text{sech}^2 \left( \beta \left( 1 - \frac{t'}{T_{p,1}} \right)^{1/2} \right) dt',
\end{align*}

where $T_{p,1} = 36$ ms is the duration of this segment, $\beta$ is a truncation factor defined by $\text{sech}(\beta) = 0.01$ and $A_1 / 2 \pi = 100$ Hz determines the frequency sweep and consequently the inversion bandwidth. For a (pulse) carrier frequency of $\omega_c = 0$ Hz, the center of $T_{\text{W,narrow}}$ is located at 100 Hz. In order to minimize spoiling of the edited spectra in MEGA experiments it is desirable the place the center of $T_{\text{W,narrow}}$ close to the edited spin group, for Lac editing in this work the pulse was applied with $\omega_c = \text{ppm}$ (see result Section 4.1 for more details). The modulation functions for $0 \leq t \leq T_{p,2}$ in the second tanh/tan segment are given by

\begin{align*}
\text{AM}_2(t) &= B_1^{\text{max}} \text{tanh} \left( \zeta \left( 1 - \frac{t}{T_{p,2}} \right) \right), \\
\text{FM}_2(t) &= -A_2 \frac{\tan \left( \frac{\kappa t}{T_{p,2}} \right)}{\tan \kappa} \frac{\tan \kappa}{T_{p,2}},
\end{align*}

with $A_2 / 2 \pi = 3.75$ kHz, $T_{p,2} = 4$ ms and the truncation parameters defined by $\zeta = 10$ and $\tan \kappa = 20$, amounting to a total pulse duration of $T_p = T_{p,1} + T_{p,2} = 40$ ms. This particular parameter set was chosen based on Bloch simulations of the inversion profile and validated experimentally in a spherical water phantom where a water suppression profile was obtained by sweeping the carrier frequency $\omega_c$. The $B_1^{\text{max}}$ dependence of the flip angle was investigated by means of Bloch simulations for the asymmetric adiabatic pulse and a Gaussian pulse of equal duration. Based on these simulations, $B_1^{\text{max}} = 8$ $\mu$T was chosen for all further MEGA-sLASER experiments.

3.2.1 | Time evolution of spin isochromats during an adiabatic asymmetric pulse

If the adiabatic condition is fulfilled, the inversion profile of an adiabatic pulse does not depend on the direction of the frequency sweep. Therefore, the frequency sweep of the asymmetric adiabatic editing pulses can be reversed without affecting the editing efficiency. A reversal of the frequency sweep is achieved by time inversion and phase conjugation of the time domain amplitude and frequency modulation.
functions. This changes the evolution of the individual isochromats during the pulse, but does not alter the resulting inversion profile. An asymmetric adiabatic pulse starting with a HS$^2$ segment is called to be in the “LATE” configuration since the long frequency sweep of the HS$^1$ leads to a late inversion of spin isochromats while its counterpart starting with a short tanh/tan segment is called to be in the “EARLY” configuration since it inverts spin isochromats very early in the time course of the pulse. Bloch simulations for both configurations with four isochromats of frequencies $Ω/2π = −100$, 0, 50, and 200 Hz were performed to confirm this qualitative description.

Combining asymmetric adiabatic pulses with different configurations can be exploited in MEGA experiments to reduce or increase the necessary MEGA pulse separation $T_{jref}$ for the desired (partial) J-refocusing effect, that is, an editing pulse pair in the EARLY-LATE configuration will require a smaller $T_{jref}$ than a pair in the LATE-EARLY configuration to realize the same J-refocusing effect. The shortening of $T_{jref}$ for EARLY-LATE and the extension of $T_{jref}$ for LATE-EARLY compared to MEGA schemes with two identical editing pulses will be captured in the timing parameter $Δ_j$ (Figure 1).

### 3.2.2 Effect of different asymmetric adiabatic pulse pair configurations on J-editing

Density matrix simulations of the proposed MEGA scheme using an ideal unselective refocusing pulse sandwiched by a pair or asymmetric adiabatic pulses were performed for $TE = 288$ ms to investigate J-editing of lactate as a function of the MEGA pulse separation $T_{jref}$ for the desired (partial) J-refocusing effect, that is, an editing pulse pair in the EARLY-LATE configuration will require a smaller $T_{jref}$ than a pair in the LATE-EARLY configuration to realize the same J-refocusing effect. The shortening of $T_{jref}$ for EARLY-LATE and the extension of $T_{jref}$ for LATE-EARLY compared to MEGA schemes with two identical editing pulses will be captured in the timing parameter $Δ_j$ (Figure 1).

#### 3.3 $T_2$ determination of lactate in the human brain

To demonstrate its utility, the proposed editing scheme was applied for $T_2$ determination of the Lac methyl doublet resonance at 1.31 ppm in the human brain. It should be noted that apart from wrongly attributed macromolecular resonances also threonine$^{48}$ substantially contributes to the measured Lac signal (see discussion in Section 5.4 and Supporting Information Section 2), which is therefore denoted by Lac$^+$ in the context of in vivo experiments. In vivo measurements were performed on six healthy subjects (age = (31 ± 3) years, one female) with a cubic voxel of 27 mL in the occipital lobe (OCC). A short anatomical scan using a MP-RAGE sequence$^{49}$ was used for planning and tissue segmentation utilizing the FSL-fast routine.$^{50}$ The MRS protocol contained a series of measurements with $TR = 2000$ ms and $TE = 144, 216, 288, 360, 432$ ms with $N = 128, 192, 256, 384, 512$ spectral averages, respectively. The varying number of averages were supposed to compensate for $T_2$-induced SNR reduction. For $TE = 144$ ms the conventional MEGA scheme without J-refocusing (OFF) was used while for all other echo times spectra were acquired with partial J-refocusing (NEG). The POS spectra were acquired with a LATE-LATE configuration and $T_{jref} = TE/2$ while the NEG spectra were measured with a LATE-EARLY configuration in order to enable shorter echo times with a reduced $T_{jref}$. The asymmetric adiabatic pulse pair was applied with $ω_c = 4.6$ ppm so that the spectral region downfield of 3.63 ppm (see Section 4.1) including the water resonance was spoiled by the MEGA crusher scheme, thus providing excellent water suppression. Additional water-unsuppressed reference spectra were acquired for phase and eddy current correction using phase deconvolution.$^{51}$ All in vivo experiments were approved by the institutional review board and written informed consent was obtained from all subjects prior to the examinations.

The quantification of the singlets tNAA of (2.01 ppm), tCr (3.03 ppm), and tCho (3.22 ppm) was performed with LCModel$^{52}$ using the summed spectra (POS + NEG) and simulated basis sets created with the pyGAMMA library$^{46}$ as previously described.$^{19}$ Since LCModel fitting of the DIFF spectra did not yield robust and consistent fitting results of the Lac$^+$ doublet in presence of co-edited macromolecules, a simple in-house fitting routine comparable with $\text{Gannet}^{53}$ was developed. The spectral region around the Lac$^+$ doublet was fitted using a parametric model of a doublet (two Voigt profiles separated by $J = 7$ Hz) for Lac$^+$ and two broader Voigt profiles modeling the co-edited macromolecular resonances MM12 (at 1.21 ppm) and MM14 (at 1.43 ppm).$^{54,55}$ An iterative trust region reflective optimization algorithm from the scipy optimize package$^{56,57}$ was used for fitting. Based on the quantification results, $T_2$ was determined for the Lac$^+$ signal and the singlets of tNAA (2.01 ppm), tCr
(3.03 ppm), tCho (3.22 ppm) by fitting with the mono-exponential decay model $S(TE) = S_0 \exp \left( -TE/T_2 \right)$.

4 | RESULTS

4.1 | Asymmetric adiabatic pulse for J-editing

Amplitude and phase modulation functions of the asymmetric adiabatic pulse are plotted in Figure 2. In the following, the inversion plateau is defined by $BW_{97.5\%}$ as the spectral region satisfying $\left[-1 \leq M_z/M_0 \leq -0.95\right]$ and thus corresponding to an inversion of at least 97.5% of the signal while the inversion bandwidth is defined as $BW_{50\%}$ [33]. The transition bandwidth $TW_{95\%}$ is defined as the spectral region satisfying $\left[-0.95 < M_z/M_0 < 0.95\right]$. Figure 3A shows the simulated inversion profile of the asymmetric adiabatic pulse for the chosen parameter set and a close up of its narrow transition band together with the inversion profile of a Gaussian pulse of equal duration. The asymmetric adiabatic pulse exhibits a broad inversion plateau of $BW_{97.5\%} = 333 \text{ Hz}$ between a narrow transition band with $TW_{95\%} = 36 \text{ Hz}$ and a wide one with $TW_{95\%} = 1612 \text{ Hz}$ while the Gaussian pulse exhibits a slightly narrower transition bandwidth of $TW_{95\%} = 33 \text{ Hz}$ and a much smaller inversion plateau of $BW_{97.5\%} = 7 \text{ Hz}$.

Based on the simulations, a center frequency of $\omega_1 = 4.6 \text{ ppm}$ was chosen for Lac editing with the asymmetric adiabatic pulse. This choice leaves a buffer of 20 Hz between the edited methine group at 4.1 ppm and the transition region starting at 3.94 ppm. Thus immunity to $B_0$ drifts is ensured while retaining the spectral region upfield of 3.64 ppm (Figure 3). The asymmetric adiabatic pulse deposits substantially more energy with $B_{1\text{rms}}^{\text{max}} = 2.9 \mu\text{T}$ than the Gaussian pulse with $B_{1\text{rms}}^{\text{max}} = 0.37 \mu\text{T}$, but less than one of the used GOIA localization pulses with $B_{1\text{rms}}^{\text{max}} = 15.1 \mu\text{T}$ ($B_{1\text{rms}}^{\text{max}}$ is the root mean square (rms) of $B_1(t)$). The comparison between the main pulse characteristics of the two pulses is given in Table 1.

Figure 3B demonstrates very good agreement between the simulated and experimentally measured water suppression profiles of the MEGA scheme equipped with an asymmetric adiabatic pulse pair.

4.1.1 | Immunity against $B_1^+$ miscalibrations and inhomogeneities of asymmetric adiabatic pulses

Figure 4 compares simulated inversion profiles for both asymmetric adiabatic and Gaussian pulses as a function of the applied $B_1^{\text{max}}$. As long as the adiabatic condition is fulfilled (above a threshold of roughly 4 $\mu\text{T}$), the inversion profile of the adiabatic pulse is immune to changes in the applied $B_1^{\text{max}}$ whereas thusse Gaian pulse requires an accurately calibrated rf field $B_{1,\text{cal}}$ since its flip angle scales linearly with the applied $B_1^{\text{max}}$. Based on these simulations, $B_1^{\text{max}} = 8 \mu\text{T}$ was chosen for the asymmetric adiabatic pulse, which still provides a flip angle of $\alpha > 160^\circ$ for 50% of $B_{1,\text{cal}}$. Note that a $B_1^{\text{max}}$ increase beyond this value does not change the flip angle of the asymmetric adiabatic pulse in the narrow transition band (apart from slight broadening of the latter).

4.1.2 | Time evolution of spin isochromats during an adiabatic asymmetric pulse

Figure 5 compares simulated evolutions of $M_z$ during inversion experiments for four isochromats and the resulting final inversion profile produced by an asymmetric adiabatic pulse in EARLY and LATE configuration, respectively. Both configurations give rise to identical inversion profiles. The simulations confirm that $M_z$ inversion is predominantly achieved by the fast frequency sweep of the tanh/tan segment, that is, at the beginning of the pulse for the EARLY configuration and at the end of the pulse for the LATE configuration. It must be noted that for an inversion with an EARLY pulse,
isochromats with lower frequencies are inverted earlier than isochromats with larger frequencies, and vice versa for the LATE configuration.

4.1.3 Effect of different asymmetric adiabatic pulse pair configurations on J-editing

Figure 6A-C show density matrix simulation results of the proposed MEGA scheme with $TE = 288$ ms for three asymmetric adiabatic pulse pair configurations (LATE-LATE, EARLY-LATE, LATE-EARLY). The in-phase signal amplitude of the Lac methyl resonance is plotted as function of the editing pulse separation $T_{\text{ref}}$ and pulse carrier frequency $\omega_c$. On the frequency scale, the graphs consist of three regions with fundamentally different signal evolution: (a) $\omega_c > 4.7$ ppm, (b) $4.7$ ppm $\geq \omega_c \geq 2.3$ ppm, and (c) $\omega_c < 2.3$ ppm. In region (a), neither of the two Lac resonances is affected by the MEGA pulses and consequently a positive Lac doublet is observed. In region (c), both Lac resonances are inverted by the MEGA pulses so that the methyl Lac signal is crushed by the MEGA spoiler gradient scheme. In region (b), selective inversion of the methine resonance is achieved and thus J-editing of the Lac doublet occurs, giving rise to a Lac signal that depends on the MEGA pulse separation $T_{\text{ref}}$. Using the LATE-LATE
**FIGURE 4** Inversion profiles of the applied asymmetric adiabatic pulse (A) and a comparable Gaussian pulse of equal duration (B) as a function of the applied $B_{1}^{\text{max}}$. Red and green contour lines confine the regions for $BW_{97.5\%}$ and $BW_{50\%}$, respectively. The dashed-dotted gray and dotted white contour lines correspond to flip angles of 150° and 120°. The transition bands $TW_{95\%}$ are confined between red and yellow contour lines. A second y-scale on the right side of each plot indicates deviations from the ideal calibration of the rf field.

**FIGURE 5** Inversion profiles (top) and $M_{z}$ evolution (bottom) for experiments with asymmetric adiabatic pulses in the EARLY (A,B) and LATE (C,D) configuration. The evolution is shown for four isochromats with frequencies $\Omega/2\pi = -100, 0, 50,$ and 200 Hz as indicated by correspondingly colored circles in the inversion profiles (A,C)
configuration, partial J-refocusing with $T_{\text{pref}} \approx 72\text{ ms}$ yields a negative doublet (as desired for the NEG shot) while for $T_{\text{pref}} \approx 144\text{ ms}$ full J-refocusing creates a positive doublet (as desired for the POS shot). When using the configuration EARLY-LATE, a shorter $T_{\text{pref}}$ is sufficient to achieve a similar J-refocusing effect while with the configuration
FIGURE 6  (A-C) Density matrix simulation results of a (one-shot) MEGA spin echo experiment with TE=288 ms for three asymmetric adiabatic pulse pair configurations (LATE-LATE, EARLY-LATE, LATE-EARLY). The in-phase signal amplitude of the Lac methyl resonance is plotted as function of the editing pulse separation $T_{jref}$ and the pulse center frequency $\omega_c$. A nonlinear color scheme was applied for illustration of the Lac signal to increase contrast for settings with predominantly negative in-phase magnetization as desired for the NEG shot (bright region) of the proposed MEGA scheme. Two yellow (dotted/dashed) horizontal lines indicate two carrier frequencies $\omega_c$ for which corresponding phantom experiments were performed, the vertical cyan line indicates the optimal $T_{jref}=72$ ms for a conventional LATE-LATE (or EARLY-EARLY) configuration. (D-F) Lac doublet resonances obtained from phantom measurements using the three pulse pair configurations with varying $T_{jref}$ (for visibility only every second spectrum is displayed). (G) Cross sections from the simulation results (A-C) for two pulse carrier frequencies $\omega_c$ as indicated by the yellow (dotted/dashed) horizontal lines, superimposed with results from corresponding phantom experiments. Simulation curves incorporate a shift of 1 ms due to missing localization pulses, which was estimated by additional simulations of the full MEGA-sLASER sequence.

LATE-EARLY, $T_{jref}$ has to be increased accordingly. It should be noted that for the EARLY-LATE and LATE-EARLY configurations the optimal $T_{jref}$ depends on $\omega_c$ (or chemical shift) as previously pointed out in Section 4.1.2. Figure 6D-F show corresponding spectra of the Lac doublet resonance acquired in phantom experiments with an asymmetric adiabatic pulse pair applied at $\omega_c = 4.3$ ppm. The LATE-LATE configuration yields a maximally inverted Lac doublet (as desired in the NEG shot) for $T_{jref} = 72$ ms (Figure 6D). With the EARLY-LATE and LATE-EARLY configurations, this optimal NEG shot setting is shifted toward smaller and larger $T_{jref}$, respectively. In Figure 6G, cross sections from the simulation results (A-C) for the two pulse center frequencies $\omega_c = 4.6$ and 4.3 ppm are superimposed with results from corresponding phantom experiments. It should be noted that the additional spatial localization pulses applied in the phantom experiments give rise to a slightly decelerated J-evolution compared to simulations. This J-evolution delay was verified to be approximately 1 ms with additional simulations and accounted for by a corresponding shift of the simulated data. After this correction, simulations and experiments turn out to be in very good agreement. These results suggest that with the configurations EARLY-LATE and LATE-EARLY, the pulse carrier frequencies $\omega_c = 4.6$ and 4.3 ppm give rise to a $T_{jref}$ change of $\Delta_j = 20$ and 25 ms, respectively. As the $T_2$ measurements of Lac were performed with a carrier frequency of $\omega_c = 4.6$, $T_{jref}$ could be decreased by $\Delta_j = 20$ for NEG shots with optimal Lac signal inversion, thus imposing fewer constraints on the sequence timing and possible TE settings.

When using a LATE-LATE or EARLY-EARLY configuration, $T_{jref}$ of the NEG shot is constrained by the minimal delay between the editing pulse pair: $T_{jref} \geq T_p + \Delta_{LastLoc}$ where $\Delta_{LastLoc}$ is the duration of the last localization pulse and its surrounding spoiler gradients (see sequence diagram in Figure 1). The minimal TE for the LATE-LATE or EARLY-EARLY configuration is therefore given by $T_{Emin}^{(NEG)} = 1/\beta + 2(T_p + \Delta_{LastLoc})$. However, the minimal TE can be reduced or increased by $2\Delta_j$ with the configurations EARLY-LATE or LATE-EARLY, respectively. For $T_p = 40$ ms, $\Delta_j = 20$ ms and $\Delta_{LastLoc} = 9.5$ ms this results in $T_{Emin} = 203$ ms for LATE-EARLY compared to 243 ms for LATE-LATE. On the other hand, if the delay between the editing pulses is insufficient to achieve the desired J-refocusing effect, the EARLY-LATE configurations may be a suitable remedy.

4.2  |  $T_2$ determination of lactate in the human brain

Representative POS, NEG, and DIFF spectra from one subject acquired at multiple TEs for $T_2$ determination in the OCC are shown in Figure 7A-C. The spectral quality was good and consistent across all subjects and spectra with an average FWHM water line width of $LW_{water} = (6.6 \pm 0.6)$ Hz. Note that for $TE = 144$ ms an OFF shot was acquired instead of a NEG shot, which explains the increased signal downfield of 3.6 ppm. The segmentation of the anatomical scans resulted in an average tissue composition of $WM = (48 \pm 2)\%$, $GM = (45 \pm 4)\%$ and $CSF = (6 \pm 2)\%$. Illustrative fitting results of the Lac$^+$ doublet are presented for $TE = 144$ and 288 ms in Figure 7D-E. The spectra exhibit pronounced co-editing of macromolecular resonances MM14 and MM12 (with a potential contribution from $\beta$-hydroxybutyrate$^{4,5,19,58}$). Figure 7F shows the modeled exponential $T_2$ decay of Lac$^+$ for the subject, along with the $T_2$ decay curves for the major singlets of tNAA (2.01 ppm), tCr (3.03 ppm), tCho (3.22 ppm). The Lac$^+$ signal exhibits a slight deviation from mono-exponential decay. Exponential fitting yielded a relaxation constant of $T_2 = 171 \pm 19$ ms for the Lac$^+$ signal at a field strength of 3T. The statistics of the estimated $T_2$ values and concentration ratios are summarized in Table 2.

5  |  DISCUSSION

5.1  |  Summary

This work presents a flexible variation of the MEGA scheme which enables J-difference editing experiments to be performed at arbitrary TEs above a threshold while maintaining optimal editing efficiency. It is further demonstrated that the application of asymmetric adiabatic pulses for J-editing improves robustness and enables more efficient editing in sequences or protocols with strong timing constraints. Finally, the utility of the proposed MEGA scheme equipped with asymmetric adiabatic pulses was demonstrated by $T_2$ measurements of lactate in vivo.
The proposed scheme enables to perform efficient J-editing for arbitrary TE above a certain threshold by decoupling of the optimal editing efficiency from TE, which is usually dictated by the coupling strength and topology of the target metabolite in J-editing experiments. This is achieved by employing J-refocusing in both spectra to obtain a difference in J-evolution which maximizes the signal yield. The scheme was validated for Lac detection by simulations as well as phantom and in vivo experiments. The most obvious application of the scheme is the $T_2$ measurement for weakly coupled spin systems since a superposition of the exponential $T_2$ decay by J-evolution-induced sinusoidal line shape modulations can be avoided. When $T_2$ of J-coupled metabolites is measured with conventional non-editing or MEGA methods, the signal modulation can be accounted for.

### FIGURE 7

Representative spectra from one subject for (A) complete J-refocusing leading to a positive Lac$^+$ doublet (POS shot), (B) partial J-refocusing leading to a negative Lac$^+$ doublet (NEG shot) and (C) the resulting difference spectra (DIFF) acquired at multiple TEs for $T_2$ measurement of Lac$^+$. (D,E) Representative fitting results of the Lac$^+$ doublet resonance (yellow) for TE = 144 and 288 ms. (F) Modeled $T_2$ decay curves for Lac$^+$ as well as the major singlets of tNAA (2.01 ppm), tCr (3.03 ppm), and tCho (3.22 ppm).

### 5.2 MEGA scheme with partial J-refocusing

The proposed scheme enables to perform efficient J-editing for arbitrary TE above a certain threshold by decoupling of the optimal editing efficiency from TE, which is usually dictated by the coupling strength and topology of the target metabolite in J-editing experiments. This is achieved by employing J-refocusing in both spectra to obtain a difference in J-evolution which maximizes the signal yield. The scheme was validated for Lac detection by simulations as well as phantom and in vivo experiments. The most obvious application of the scheme is the $T_2$ measurement for weakly coupled spin systems since a superposition of the exponential $T_2$ decay by J-evolution-induced sinusoidal line shape modulations can be avoided. When $T_2$ of J-coupled metabolites is measured with conventional non-editing or MEGA methods, the signal modulation can be accounted for.
for by either fitting with dedicated metabolite basis spectra\textsuperscript{59-61} or characterization of the J-evolution-induced TE-dependence with phantom experiments.\textsuperscript{62} However, these approaches still suffer from reduced signal yield for certain echo times. Moreover, a modulation function determined with phantom experiments might not be representative for in vivo conditions since chemical shifts and coupling constants often depend on the chemical environment (e.g., pH value or certain ion concentrations), which may give rise to inconsistencies, particularly for longer echo times. Established fitting approaches based on linear combination of metabolite basis spectra usually work well for quantification of non-edited spectra, but often turn out to be less robust for modeling MEGA editing spectra, as was the case in this work. When using the proposed MEGA scheme for $T_2$ measurements, potentially more robust quantification methods based on less complex fitting models may be applied. A viable alternative to the proposed MEGA scheme may be echo time extension with an additional selective refocusing pulse as proposed for GABA editing.\textsuperscript{63} This technique also eliminates the TE dependence of the signal shape, albeit at the expense of an additional (non-adiabatic) pulse, which increases the specific absorption rate (SAR) and susceptibility to $B_0^\perp$ miscalibration and inhomogeneities. The flexible MEGA editing scheme might also be applied for efficient GABA editing at higher TEs, enabling longer editing pulses with improved selectivity for macromolecular-suppressed MEGA editing\textsuperscript{64} without compromising the editing efficiency. Furthermore, the method could be used for TE-averaging\textsuperscript{65} experiments to suppress undesired co-edited resonances of strongly coupled metabolites.

### 5.2 Limitations

The main drawback of the proposed MEGA variant is the loss of spectral information in the NEG shot due to the applied partial J-editing and accompanied spoiling of the inverted spectral region. In contrast, the OFF shot of the original MEGA scheme provides a complete quantifiable spectrum. For Lac editing where the target resonance of the MEGA pulses is at 4.1 ppm, the scheme still enables detection of all other resonances upfield of 3.63 ppm (including the major singlet resonances from tNAA, tCr, and tCho), but for editing of other metabolites this may be more critical. A GABA editing experiment, for instance, would not allow for concomitant NAA quantification. Furthermore, while the proposed scheme is particularly suitable for efficient J-editing at longer TE, the minimal TE that can be used is increased compared to the conventional MEGA scheme. This limitation can be mitigated by reduction of the editing pulse duration or by application of asymmetric adiabatic pulses in the EARLY-LATE configuration, as demonstrated in this work.

### 5.3 Asymmetric adiabatic pulse for J-editing

The two obvious advantages of asymmetric adiabatic pulses for J-editing are their immunity against $B_0^\perp$ miscalibrations and inhomogeneities as well as reduced susceptibility to $B_0^\perp$ frequency drifts due to their larger inversion plateau. In this work, it is shown that they are also useful for reducing sequence timing constraints in J-editing experiments since they enable J-refocusing intervals that are shorter or longer than the inter-pulse delay of the editing pulses. This has already been exploited by Moser et al\textsuperscript{30} who applied an EARLY-LATE configuration in a very timing-constrained MEGA-sLASER sequence to achieve an optimal TE = 69 ms for efficient GABA editing. In this work, a LATE-EARLY configuration was applied in the NEG shot of the proposed MEGA scheme to reduce the minimal TE for $T_2$ measurement of Lac. It should be noted that the configurations EARLY-LATE and LATE-EARLY reintroduce a certain susceptibility to frequency drifts. This effect relies on the chemical shift dispersion of J-evolution when using the EARLY-LATE and LATE-EARLY configurations (see Figure 6A-C). However, it is negligible for typical experimental settings.

#### 5.3.1 Limitations

The application of asymmetric adiabatic pulses for J-editing has two major drawbacks. First, an asymmetric adiabatic pulse deposits considerably more energy than a typically employed conventional Gaussian pulse of equal duration. This issue can be prohibitive, especially at ultra-high field (>3T) and for metabolites which require a short TE for efficient editing such as GABA. However, with the increased flexibility of the proposed MEGA scheme, TE can easily be adapted.

| Metabolite (M) | $T_2$ (ms) | ($M/(tCr)$) TE = 144 ms | ($M/(tCr)$) TE = 0 ms |
|---------------|------------|--------------------------|------------------------|
| tCr at 3.03 ppm | 158 ± 8    | 0.70 ± 0.11               | 1.31 ± 0.09            |
| tNAA at 2.01 ppm | 220 ± 12   | 0.23 ± 0.02               | 0.21 ± 0.02            |
| tCho at 3.2 ppm | 182 ± 7    | 0.12 ± 0.02               | 0.12 ± 0.02            |
| Lac$^+$ at 1.31 ppm | 171 ± 19 | 0.12 ± 0.02               | 0.12 ± 0.02            |

Note: Metabolite concentrations were quantified from the TE = 144 ms acquisitions and extrapolated to TE = 0 ms, using the estimated $T_2$ constants.

### TABLE 2

$T_2$ relaxation constants and metabolite ratios with respect to tCr for Lac$^+$ as well as the singlet resonances of tNAA, tCr, and tCho, as measured in the occipital cortex of six healthy subjects.
to meet $B_1^{\text{max}}$ or SAR restrictions. Alternatively, asymmetric adiabatic editing pulses might be implemented with a MEGA-SPECIAL sequence, which requires fewer localization pulses and is therefore also less timing-constrained than double spin-echo based MEGA methods. Second, the large inversion plateau of the asymmetric adiabatic pulses reduces the susceptibility to $B_0$ drifts but increases macromolecular co-editing. This may lead to erroneous quantification results if not taken into account by the spectral fitting approach, as was done in this work. Furthermore, even TW$_{\text{narrow}}^{\text{95\%}}$ of our asymmetric adiabatic pulse is slightly larger than the transition width of a conventional Gaussian pulse. For robust editing with a narrower transition width, hypergeometric pulses may be a viable alternative.

### 5.4 T$_2$ measurement of Lac$^+$ in human brain

The proposed MEGA scheme was successfully applied for T$_2$ measurements of Lac$^+$ in the occipital cortex of six healthy subjects and yielded T$_2 = 171 \pm 19$ ms. The Lac$^+$ decay curve exhibited a slight deviation from mono-exponential behavior in contrast to the major singlets of tNAA, tCr, and tCho. There are several explanations for this deviation: First, in contrast to the majority of other MRS-detectable metabolites lactate is also present in the extracellular space (eg, in CSP). Intra- and extracellular lactate pools may have (as water) significantly different T$_2$ relaxation constants resulting in a bi-exponential signal decay curve. This hypothesis could be tested by covering a larger range of TEs for the T$_2$ measurements. However, due to the inherently low in vivo concentration of lactate in healthy brain, finding a suitable protocol would be quite challenging. Second, the Lac$^+$ signal contains significant contributions from an overlapping threonine (Thr) resonance at 1.32 ppm, which is coupled to a methine resonance at 4.25 ppm (with J$_{\text{Thr}} = 6.4$ Hz). This Thr methine resonance lies inside the inversion plateau of the asymmetric editing pulse and is therefore strongly co-edited (see Supporting Information Figure S3). Different T$_2$ relaxation constants of Lac and Thr would result in a bi-exponential Lac$^+$ decay. Choi et al. have shown that discrimination between Lac and Thr is possible by the application of very narrow bandwidth (BW$_{\text{50\%}} \leq 15$ Hz) J-editing pulses. Third, spectral overlap with co-edited macromolecular resonances impairs quantification of the Lac$^+$ resonance at 1.31 ppm. Processing the DIFF spectra with LCMODEL led to inconsistent fitting results across TE (and subjects), with a tendency to overestimate the Lac signal for lower TEs. Using a simple in-house fitting routine allowed for more control of the fitting procedure and resulted in more consistent fitting and quantification results. However, perfect distinction of the Lac$^+$ signal from the macromolecular background (in particular the MM14 resonance) turned out to be very challenging. Finally, the slight deviation from exponential decay could also be caused by flip angle imperfections of the editing pulse or anomalous J-modulation due to the four-compartment artifact, which could be strongly reduced with broadband GOIA localization pulses but not entirely eliminated.

The T$_2$ constant of Lac$^+$ determined in this work was within the range of the other measured T$_2$ values for tNAA, tCr, and tCho. There are only very few reports on brain tissue T$_2$ of lactate in the literature. For the same field strength of 3T, a value of 99 ms has been reported by Wyss et al, who have determined the T$_2$ decay of various brain metabolites from JPRESS data quantified with a 2D fitting approach. On the other hand, a much higher value of 240 ms has been measured in brain tumor tissue, using a PRESS sequence with optimized subecho times. A comparison of our results with those values is problematic because of different acquisition and quantification methods as well as different tissue properties of tumor compared to healthy brain.

### 5.5 Conclusion

The proposed MEGA scheme enables more flexible J-editing of lactate and is particularly useful for timing-constrained protocols as required for T$_2$ measurements. The method strongly benefits from asymmetric adiabatic editing pulses in terms of robustness and versatility, and may also be an asset for detection of other weakly coupled metabolites.

### ACKNOWLEDGMENTS

Open access funding enabled and organized by Projekt DEAL.

### ORCID

Michael Dacko
https://orcid.org/0000-0002-9774-8909

Thomas Lange
https://orcid.org/0000-0002-7467-8143

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SUPPORTING INFORMATION
Additional Supporting Information may be found online in the Supporting Information section.

FIGURE S1 A, Sequence diagram for the conventional MEGA scheme with a delay between editing pulses of \( \Delta T = \frac{\Delta T_2}{2} \) leading to a complete J-refocusing. B, variation of the MEGA scheme allowing for partial J-refocusing via a reduced \( \Delta T_{\text{pet}} \). The deviation from the conventional MEGA scheme is expressed with the parameters \( \Delta T_1 \) and \( \Delta T_2 \).

FIGURE S2 A, Influence of the editing flip angle \( \alpha \) on the edited Lac methyl doublet signal for complete J-refocusing leading to positive doublets (POS shots, gray shades) and partial J-refocusing leading to negative doublets (NEG shots, red shades) as derived with the analytical model (see Equations 3 and 4). Superimposed are measurement results obtained with a MEGA-sLASER sequence using complete and partial J-refocusing. The Lac methyl signal was determined as the integral over the spectral interval between 1.1 ppm and 1.5 ppm. B, subset of the measured Lac signals for \( \alpha = 180^\circ \) (black) and \( 120^\circ \) (red), illustrating the line shape modulations due to anti-phase coherence contributions arising from imperfect editing flip angles.

FIGURE S3 Inversion profile (green) of the proposed asymmetric adiabatic pulse (see sections 3.3 and 4.2) and illustration of co-edited metabolites with resonances in the spectral vicinity of the Lac doublet at 1.31 ppm. Macromolecular resonances are displayed as Gaussians.

TABLE S1 Chemical shifts and coupling constants of Lac and metabolites with co-edited resonances in the proximity of the Lac resonance at 1.31 ppm.