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Elliptical Localization with Pulsed Second-Order Fields (ECLIPSE) for Robust Lipid Suppression in Proton MRSI

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Abstract

Proton MR spectroscopic imaging (MRSI) has great clinical potential for metabolic mapping of the healthy and pathological human brain. Unfortunately, the promise has not yet been fully achieved due to numerous technical challenges related to insufficient spectral quality caused by magnetic field inhomogeneity, insufficient RF transmit power and incomplete lipid suppression. Here a robust, novel method for lipid suppression in ¹H MRSI is presented. The method is based on 2D spatial localization of an elliptical region-of-interest using pulsed second-order spherical harmonics (SH) magnetic fields. A dedicated, high-amplitude second-order SH gradient setup was designed and constructed, containing coils to generate Z₂, X₂Y₂ and XY magnetic fields. Simulations and phantom MRI results are used to demonstrate the principles of the method and illustrate the manifestation of chemical shift displacement. ¹H MRSI on human brain *in vivo* demonstrate high-quality ¹H MRSI with robust suppression of extracranial lipids. The method allows a wide range of inner or outer volume selection or suppression and should find application in MRSI, reduced field-of-view MRI and single-volume MRS.

Graphical Abstract

A novel method for lipid suppression in ¹H MRSI is presented based on spatial localization of an elliptical region-of-interest using pulsed second-order spherical harmonics (SH) magnetic fields. A high-amplitude second-order SH gradient setup was designed and constructed, containing coils to generate Z₂, X₂Y₂ and XY magnetic fields. Simulations and phantom results demonstrate the principles of the method and illustrate the manifestation of chemical shift displacement. ¹H MRSI on human brain *in vivo* demonstrates high-quality ¹H MRSI with robust suppression of extracranial lipids.

Keywords

proton MRSI; lipid suppression; second-order magnetic fields; human brain

INTRODUCTION

Proton MR spectroscopic imaging (MRSI) is a powerful, non-invasive method to map the metabolic profile of the human brain. The intrinsic chemical specificity of MRSI can reveal altered metabolism in regions that would appear normal on standard MRI. MRSI has successfully been used for brain tumor classification and detection of infiltration, planning of radiation therapy and surgery (1–3) and has helped to characterize a range of neurodegenerative diseases such as multiple sclerosis (4–6), Alzheimer’s disease (7,8) and epilepsy (9,10).

Despite its merits and successes, MRSI is not a widespread clinical imaging modality because the method is hampered by a number of technical challenges related to magnetic field B_0 inhomogeneity, limited transmit B_1^+ amplitude and signal contamination from extracranial lipids. Existing lipid suppression methods include inner volume selection (IVS) of a large cuboidal volume based on single-volume MR techniques like STEAM, PRESS or (semi)-LASER (11–14), and outer volume suppression (OVS) of the skull region with up to 12 slice-selective excitation pulses (15,16). The lipid signals can also be reduced with frequency-selective suppression (17), T_1 -based nulling (18), increased k-space coverage (19), post-processing methods (20), RF-based gradients (21,22) and dedicated crusher coils (23). Each lipid suppression method has its own advantages in terms of ease-of-use and robustness and its own disadvantages regarding level of attainable lipid suppression, peak and average RF power deposition and brain coverage (24).

Here we present a novel method for IVS or OVS based on high-amplitude, second-order spherical harmonic (SH) magnetic fields. The method is referred to as ‘elliptical localization using pulsed second-order fields’ or ECLIPSE. Experimental MR images show the principle of elliptical volume selection using Z_2 and X_2Y_2 shim fields, as well as rotation and translation with XY and linear fields, respectively. Proton MRSI of the human brain *in vivo* is performed to demonstrate high-quality lipid suppression at low RF power deposition.

METHODS

MR system

MR measurements were performed on a 4 T MR system consisting of an actively shielded whole-body magnet (Ø 940 mm) interfaced to a Bruker Avance III HD spectrometer, running on Paravision 6 (Bruker Biospin Corporation, Billerica, MA, USA). The gradient system (Ø 670 mm) is capable of switching 30 mT/m in 1100 µs and provides up to third order shimming. RF transmission and reception was achieved with a 16-element Tx/Rx volume coil (ID = 230 mm, OD = 334 mm, length = 300 mm), whereby the 16 Tx-elements were used in a fixed-phase configuration.

Second-order gradient coil design and construction

The gradient coil was constructed on a nylon cylinder (The Plastic Factory, Bridgeport, CT, ID 342 mm, OD 434 mm) with a 46 mm wall thickness and 600 mm length, capable of accommodating the 16-element RF coil. Dimensions of the gradient coil were guided by anatomical measurements using standard MRI scans on three subjects (Fig. 1A). This led to using 145 mm as distance between the edge and center positions of the gradient coil, and an ellipsoidal region-of-interest (ROI) with diameters of 200 mm, 220 mm and 160 mm for the X, Y and Z spatial directions, for the anticipated volume selection covering the head. All magnetic field optimizations involved in gradient coil wire placements were performed over this ROI.

Wire placements for second-order Z2, X2Y2 and XY coils were based on the basic designs of Romeo and Hoult (25) using current loops and arcs, whereby the short length compared to the diameter of the proposed gradient coils demanded a re-optimization of the relative wire placements and currents. Specifically, the wire center positions for all three coils was limited to $[-130..+130]$ mm relative to the coil center in order to ensure a 10 mm wall thickness. Using the spherical harmonics functions $A_{2,0}(2Z^2 - (X^2 + Y^2))$, $A_{2,2}(X^2 - Y^2)$ and $A_{2,-2}XY$ the target field amplitudes were set as $A_{2,0} = 2.5$ Hz/mm², $A_{2,2} = 1.25$ Hz/mm² and $A_{2,-2} = 1.25$ Hz/mm² for a 50 A input current. The wire positions and number of loops were optimized through least-squares minimization, while maintaining the inherent symmetry of the individual coils. Magnetic fields were calculated through numerical integration of the Biot-Savart law. All magnetic field calculations and optimizations were performed in Matlab 8.3 (The Mathworks, Natick, MA, USA).

The wire tracks for the coils were milled with a CNC-controlled (MicroKinetics Corporation, Kennesaw, GA, USA) Bridgeport Series I Vertical Milling Machine (Bridgeport Machines, Inc., Bridgeport, CT, USA). Tracks were 12.7 mm wide, except for the inner two Z2 wire tracks which had a width of 9.5 mm.

The three coils were manually wound from AWG 12 (Ø 2.1 mm) polyurethane-coated copper wire (Bulk Wire, Yorba Linda, CA, USA) and placed within the wire tracks milled in the nylon former. Following placement of six PT100 thermal sensor probes (two per coil, Omega Engineering Inc, Norwalk, CT, USA) the wires were permanently fixed with a two-part epoxy adhesive (Loctite, Henkel Corporation, Rocky Hill, CT, USA). No effort was made to remove air bubbles from the epoxy. The final gradient coils were characterized by

inductances of 859, 182, and 154 μH and resistances of 475, 240 and 238 $\text{m}\Omega$ for the Z2, X2Y2 and XY coils.

Three Techron 7780 gradient amplifiers (AE Techron, Elkhart, IN, USA) drove the coils with 130 V and 100 A, leading to rise times of 661, 140 and 118 μs for the Z2, X2Y2 and XY coils (Fig. 1G). In order to achieve a straightforward temporal alignment with the MR system's linear gradient pulses, the rise time for all three coils was set to the gradient rise time of 1100 μs . Coil currents were controlled with a home-build, multi-channel gradient controller (26).

MR spectroscopic imaging

All MR studies were performed with an adiabatic double-spin-echo sequence (Fig. 2). A 2.0 ms Shinnar-Le Roux excitation pulse ((27), 2.8 kHz bandwidth) selected a 10 mm thick slice in the Z direction. Two 6.0 ms adiabatic full passage pulses (HS2 modulation (28), 3.33 kHz bandwidth) were used for refocusing in the presence of a combination of X, Y, Z, Z2, X2Y2 and XY magnetic fields. The refocusing pulses were surrounded by 3.0 ms 25 mT/m magnetic field crusher gradients to ensure destruction of signal excited by the 180° pulses from remote locations (Fig. 2). MR images were acquired with gradient-echo frequency encoding (100 kHz spectral width) and phase encoding following the final 180° pulse (FOV 210×210 mm, 128×128 matrix). Following a one-time calibration of the gradient coil magnetic field amplitudes, ECLIPSE magnetic fields and offsets were calculated in Matlab 8.3 on a subject-specific MR image. An elliptical ROI was interactively adjusted (center position, two radii and an in-plane rotation angle) to maximize brain inclusion, while simultaneously minimizing extracranial tissues. MR spectroscopic images were acquired with two phase-encoding gradients following the final 180° pulse sampling a circularly restricted k-space (FOV 210×210 mm, 21×21 matrix) for a nominal resolution of 1 mL. All scans were acquired with $\text{TR}/\text{TE} = 1,500/50$ ms leading to an 8.3 min MRSI acquisition time. The minimum allowable TR based on RF power deposition considerations was 850 ms, whereas the minimum possible TE due to RF and gradient pulses was 35 ms. Water suppression was achieved with a seven-pulse VAPOR sequence (29). Magnetic field homogeneity across the MRSI slice was optimized with first- and second order SH shims calculated from a MRI-based B_0 map. MRSI data processing used a separately acquired water MRSI for receiver phase correction, amplitude-weighting and correction of temporal magnetic field variations (30).

Chemical shift displacement

As a fundamental concept in MRI and localized MRS it is well-known that a frequency-selective RF pulse applied during a linear gradient results in the selection of a 1D spatial slice. Different chemical shifts will result in a displacement of the spatial slice, an effect known as the chemical shift displacement artifact (CSDA). For a given slice thickness the CSDA can only be minimized by increasing the RF bandwidth. The ECLIPSE method uses a frequency selective RF pulse during second-order Z2 and X2Y2 magnetic fields, leading to the selection of a 2D elliptical volume (Fig. 3). The slice boundary r (in mm) for a spin with Larmor frequency ν_0 is given by

$$r = \pm \sqrt{\frac{\nu_{\text{RF}} - \nu_0 \pm \text{BW}/2}{G}} \quad (1)$$

where ν_{RF} is the RF transmit frequency, BW is the RF pulse bandwidth (in Hz) and G is the second-order gradient strength (in Hz/mm²). Depending on the RF transmit frequency, Eq. (1) has between zero and four solutions. The most common situations arise when the RF pulse selects two slice boundaries (Fig. 3A and C) for IVS or four slice boundaries (Fig. 3B and D) for OVS. The green ROIs in Figs. 3C and D depict the spatial region selected for on-resonance spins (i.e. $\nu_0 = 0$). The blue and red ROIs depict the spatial region selected for spins that are off-resonance by -500 Hz and $+500$ Hz, respectively, during a positive second-order field gradient. Note that the CSDA during ECLIPSE manifests itself as an increase or decrease of the selected ROI. For most applications it is preferable to execute ECLIPSE with negative second-order fields such that when the green ROI depicts the selected region for lipids, the blue ROI depicts the region for water and most metabolites resonating at higher Larmor frequencies. Note that the CSDA is substantially smaller for OVS than for IVS due to the steeper magnetic field gradient at the edge of the brain. Similar to conventional OVS using linear magnetic field gradients, the absolute CSDA for ECLIPSE is reduced by selecting the narrowest possible slice that still covers the entire skull region. On most subjects an ROI thickness of 20–30 mm would be sufficient.

RESULTS

The calibration of the second-order gradient coil revealed good agreement with the target design field shapes and amplitudes. Z2, X2Y2 and XY gradient coils were calibrated at 5.48, 2.58 and 2.76 Hz/cm²/A field amplitudes with minor linear gradient field imperfections on the order of 10 Hz/cm/A. The linear imperfections were compensated with the system's linear field gradients. Despite the absence of active water or air cooling, no gradient coil temperature increases were observed during coil calibration or ECLIPSE. This is likely due to the low 5 A maximum current during calibration (at 30% duty cycle) and the low duty cycle during ECLIPSE (0.4 % maximum duty cycle). RF transmit B_1^+ and signal-to-noise ratio maps confirmed the absence of RF perturbations arising from the second-order gradient coils. Besides a minor B_0 magnetic field modulation (1.3 Hz/A with a decay constant of 260 ms), no eddy currents were observed for the pulsed second-order SH coils. This is likely due to the large physical separation between the second-order ECLIPSE coils and the magnet cryostat.

Fig. 4 demonstrates the localization capabilities of ECLIPSE. In the presence of a Z2 magnetic field, a frequency-selective RF pulse selects a 2D circle (Fig. 4B). Adding an X2Y2 magnetic field results in the selection of a 2D ellipse (Fig. 4C). The elliptical volume can be rotated (Fig. 4D) and shifted (Fig. 4E) by adding XY and X magnetic fields, respectively. By adjusting the RF pulse center frequency, the outside of the ellipse shown in Fig. 4C can be selected (Fig. 4F). Fig. 4G–I provide an experimental validation of the CSDA during ECLIPSE for an oil/water phantom. When selecting an elliptical volume during a positive second-order field (Fig. 4H) the lower-frequency oil spins appear as a larger ellipse,

in correspondence with Fig. 3C. When the second-order fields are negative the oil ellipse is smaller than the water ellipse (Fig. 4I). A weaker intensity, larger oil ellipse is visible in Fig. 4I due to the presence of multiple oil resonances closer to the water frequency.

Fig. 5 shows ^1H MRSI on the human brain *in vivo* (A–D) without and (E–H) with 2D in-plane localization using ECLIPSE. Without OVS the extracranial lipid signals dominate each MR spectra in the 21×21 MRSI dataset, including spectra well within the brain (Fig. 5D). The MR image acquired with ECLIPSE (Fig. 5E) demonstrates the high-quality elliptical localization similar to that achieved in phantom studies (Fig. 4). The localization performance is confirmed by the ^1H MRSI data (Fig. 5F/G) showing the absence of lipid signals from all voxels while retaining the metabolite signals at full intensity.

DISCUSSION

Here we have presented a novel method for 2D volume selection for lipid suppression in proton MRSI based on frequency-selective RF pulses in the presence of a second-order SH magnetic field. The principle of using second-order SH magnetic fields for spatial localization was first described by Cho and co-workers (31–33) using a dedicated Z2 gradient coil. Unfortunately, the method never moved beyond the proof-of-principle stage. More recent reports have used standard second-order SH shim coils to achieve field-of-view restriction in MRI (34–36). The introduction of multi-coil (MC) shimming (37,38) has provided complex magnetic field shaping that is ideally suited for 2D localization (39,40). However, the relatively small magnetic field strengths generated by SH or MC shim setups become a significant limitation for spectroscopic localization, where a small magnetic field gradient is synonymous with a small RF bandwidth and hence a large CSDA. The success of ECLIPSE for spectroscopic applications therefore rests on the availability of high-amplitude magnetic field gradients. In this study a dedicated, home-build second-order gradient coil was designed and constructed to achieve high-quality ^1H MRSI without lipid contamination. The constructed gradient coil is characterized by a small length-to-diameter ratio of circa 0.82, but was after optimization of the wire positions, able to achieve high magnetic field efficiencies with good fidelity over the ellipsoidal ROI. The availability of commercial, high-powered shim coil inserts (41) should help with the wider dissemination of the ECLIPSE method. The successful demonstration of high-quality lipid suppression with second-order SH fields certainly provides incentive to pursue a high-powered MC setup for improved ROI shaping.

For any gradient-based localization method the CSDA is minimized by increasing the bandwidth of the RF pulses, which requires an increase of the gradient field in order to attain the same ROI. In previous publications the bandwidth was limited by the small magnetic field strength generated by the SH or MC setups (35–38). The high-amplitude SH fields used here has shifted the limitation to the maximum RF amplitude available with a typical human RF coil and amplifier combination. A robust method to further increase the RF pulse bandwidth without increasing the maximum RF amplitude is to employ gradient modulation. The bandwidth of RF pulses used during regular 1D slice selection can be increased ten-fold by employing the principles of gradient offset-independent adiabaticity (GOIA, (42)) or

frequency offset corrected inversion (FOCI, (43)). A similar modulation of the gradient field to achieve an improved RF bandwidth should be suitable for ECLIPSE.

The current ECLIPSE method was implemented with three out of the five second-order SH fields, allowing the selection and rotating of an elliptical ROI within the axial plane. Selection of an elliptical ROI is possible in any sagittal, coronal or oblique orientation by changing the relative contributions of the Z2 and X2Y2 coils. However, the two missing ZX and ZY fields will be required for rotation in a non-axial plane. ECLIPSE with a complete second-order SH coil set will be able to select an elliptical ROI in any single or double-oblique slice orientation.

Applying a frequency-selective RF pulse in the presence of a Z2 magnetic field leads to the selection of a circular ROI for $Z = 0$. However, since the Z2 field diverges for $Z \neq 0$ the selected ROI will increasingly deviate from a circle for larger Z offsets. At an in-plane ROI size suitable for the human head (circa 120×170 mm), ECLIPSE can select a 40 mm slab without significant deviation of the in-plane shape, allowing for 3D MRSI across central areas of the human brain. However, as the brain shape and size changes along the superior-inferior direction, whole-brain OVS is not possible with the current ECLIPSE or any other slice-based OVS method. Whole-brain OVS will therefore have to be based on multiple slab selections or the use of non-SH-based magnetic fields.

The MRI and MRSI results presented here were all based on IVS. While providing T_1 -independent lipid suppression, the slice definition and CSDA are often less optimal than that achieved with OVS (see Fig. 3). Classical OVS based on frequency-selective RF pulses selecting multiple 1D slices is hampered by T_1 relaxation and incomplete signal dephasing in regions selected by overlapping slices (16). The fact that ECLIPSE can achieve 2D localization with a single RF pulse avoids slice overlap, such that ECLIPSE-based OVS can be optimized with respect to T_1 relaxation and B_1^+ magnetic field homogeneity, similar to water suppression methods like WET (44) and VAPOR (29). Work is currently in progress to re-evaluate OVS methods based on ECLIPSE.

The ECLIPSE method has been demonstrated for lipid suppression in MRSI. However, ECLIPSE can also find application in single-volume MRS and reduced field-of-view MRI. For MRS the main advantages would be related to lower SAR and shorter echo-times due to the reduced minimum number of RF pulses. In addition, ECLIPSE can be beneficial in pathologies (tumors, multiple sclerosis lesions) where an elliptical VOI provides improved coverage of the tissue under investigation.

Acknowledgments

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ABBREVIATIONS

CSDA	Chemical shift displacement artifact
ECLIPSE	Elliptical localization with pulsed second-order fields

FOCI	Frequency offset corrected inversion
GOIA	Gradient offset-independent adiabaticity
IVS	Inner volume selection
LASER	Localization by adiabatic spin-echo refocusing
MC	Multi-coil
OVS	Outer volume suppression
PRESS	Point-resolved spectroscopy
SH	Spherical harmonics
STEAM	Stimulated-echo acquisition mode
VAPOR	Variable pulse power and optimized relaxation delays
WET	Water suppression enhanced through T_1 effects

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Figure 1.

Second-order gradient coil design and construction. (A) RF coil and gradient coil former in relation to the human head. The center of the gradient coil windings is placed at 145 mm from the edge as dictated by the empirically measured distance between shoulders and the middle of the brain. Wire patterns for the (B) Z2, (C) X2Y2 and (D) XY coils as optimized over a $200 \times 220 \times 160$ mm diameter ellipsoid (dotted line). The wire positions relative to the gradient center and the number of turns are indicated below and above the gradient former, respectively. The relative current directions are indicated by small arrows. (E) 3D rendering of the Z2 (red), X2Y2 (green) and XY (blue) coils showing the radial separation. (F) Photograph of the gradient coil former towards the end of the milling process. In addition to the fundamental coil element positions, additional tracks are visible to connect the various coil elements (black arrows) and provide return paths (white arrow). All distances are in mm. (G) Gradient driver and amplifier setup and temperature monitoring.

Figure 2.

ECLIPSE pulse sequence for inner volume selection based on an adiabatic double-spin-echo. The 90° excitation pulse selects an axial slice after which the refocusing pulses provide in-plane ROI selection with second-order SH magnetic fields. Small linear magnetic fields are required to compensate first-order SH imperfections in the second-order SH fields or to achieve translation of the elliptical volume. Linear gradients in the X and Y directions are used as TE crushers surrounding the refocusing pulses. For MRI and MRSI applications the sequence is extended with frequency and phase-encoding gradients following the second refocusing pulse (not shown).

Figure 3.

Chemical shift displacement artifact (CSDA) during ECLIPSE. (A, B) Frequency distributions during (A) 78.7 Hz/cm² and (B) 138.9 Hz/cm² second-order magnetic field gradients. The curves shift up and down relative to an on-resonance condition (green) for positive (red, +500 Hz) and negative (blue, -500 Hz) frequency offsets, respectively. For on-resonance spins a frequency selective RF pulse (bandwidth BW = 3.33 kHz) selects a 2 × 60 = 120 mm wide slice for IVS with an offset $\nu_{RF} = -0.5$ kHz (A, green line). OVS with 17.5 mm wide slices centered at ± 68.8 mm is achieved with an offset of 6.66 kHz (B, green line). Off-resonance spins will select wider or narrower slices depending on the chemical shift and the sign of the second-order gradient field. (C) Selection of a 120 × 170 mm ellipse (green, BW = 3.33 kHz, $\nu_{RF} = 2.83$ kHz) for on-resonance spins leads to the selection of 130.2 × 184.4 mm and 108.9 × 154.3 mm ellipses for spins that are off-resonance by -500 Hz and +500 Hz, respectively. (D) Selection of a 120 × 170 mm ID OVS ring (17.5 × 24.8 mm thickness, BW = 3.33 kHz, $\nu_{RF} = 5.0$ kHz) for on-resonance spins leads to the selection of 125.9 × 178.3 mm (16.8 × 23.9 mm thickness) and 113.8 × 161.3 mm (18.2 × 25.8 mm thickness) ID OVS rings for spins that are off-resonance by -500 Hz and +500 Hz, respectively. For both IVS and OVS the blue and red ROIs are swapped in the presence of a negative second-order magnetic field.

Figure 4.

Experimental volume selection using ECLIPSE. (A) Baseline MRI acquired in the absence of magnetic field gradients during the refocusing pulses. (B–F) MR image in the presence of a Z2 magnetic field and additional (C) X2Y2, (D) X2Y2 and XY, (E) X2Y2 and X and (F) X2Y2 magnetic fields. In all cases the gradient strengths were adjusted to select a (B) 80 mm diameter circle or a (C–F) 80×120 mm diameter ellipse. The RF frequency offsets in (B–E) were adjusted to provide IVS, whereas the offset in (F) was adjusted for OVS. (G–I) Experimental demonstration of the CSDA in ECLIPSE on an oil-water phantom. (G) MRI acquired without in-plane volume selection and (H, I) with in-plane selection of an elliptical VOI during (H) negative and (I) positive second-order magnetic fields. A faint larger ring is visible in (I) due to the multiple resonances in vegetable oil leading to a range of chemical shift displacements.

Figure 5.

ECLIPSE MRI and MRSI on human brain *in vivo*. (A) MRI and (B) MRSI without in-plane volume selection show strong extracranial lipid signals that contaminate every voxel, including those from within the brain (red box, spectrum shown in (D)). The 3 × 3 grid as indicated in (A) is extracted from the full 21 × 21 MRSI grid. (C) Metabolic image obtained through (absolute-valued) spectral integration of the 1.8 – 2.2 ppm chemical shift range is dominated by strong extracranial lipid signals. (E) MRI and (F) MRSI in the presence of in-plane selection of a 125 × 170 mm elliptical volume. The extracranial lipid signals are suppressed while retaining the metabolite signals at full intensity. (G) Metabolic image from the 1.8 – 2.2 ppm region provides a NAA spatial distribution map without lipid artifacts. Note that the vertical scale in (G) is 50 times higher than in (C). The metabolic images in (C, G) are not intensity corrected for the receiver sensitivity profiles. (H) ¹H MR spectrum extracted from the identical voxel as shown in (D).