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Interleaved narrow-band PRESS sequence with adiabatic spatial-spectral refocusing pulses for ^1H MRSI at 7T

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Abstract

Proton magnetic resonance spectroscopic imaging (^1H MRSI) is a useful technique for measuring metabolite levels *in vivo*, with Choline (Cho), Creatine (Cr) and N-Acetyl-Aspartate (NAA) being the most prominent MRS-detectable brain biochemicals. ^1H MRSI at very high fields, such as 7T, offers the advantages of higher SNR and improved spectral resolution. However, major technical challenges associated with high-field systems, such as increased B_1 and B_0 inhomogeneity as well as chemical shift localization (CSL) error, degrade the performance of conventional ^1H MRSI sequences. To address these problems, we have developed a Position Resolved Spectroscopy (PRESS) sequence with adiabatic spatial-spectral (SPSP) refocusing pulses, to acquire multiple narrow spectral bands in an interleaved fashion. The adiabatic SPSP pulses provide magnetization profiles that are largely invariant over the 40% B_1 variation measured across the brain at 7T. Additionally, there is negligible CSL error since the transmit frequency is separately adjusted for each spectral band. *In vivo* ^1H MRSI data was obtained from the brain of a normal volunteer using a standard PRESS sequence and the interleaved narrow-band PRESS sequence with adiabatic refocusing pulses. In comparison with conventional PRESS, this new approach generated high quality spectra from an appreciably larger region of interest and achieved higher overall SNR.

Keywords

adiabatic; high-field; MRSI; B_1 inhomogeneity; 7T; spectral interleaf

2 Introduction

Proton magnetic resonance spectroscopic imaging (^1H -MRSI) offers a non-invasive method for the identification, visualization, and quantification of specific brain biochemical markers and neurotransmitters, the assessment of abnormalities in injured or diseased brain tissue, the longitudinal monitoring of degenerative diseases, and the early evaluation of therapeutic interventions [1-7]. The most prominent *In vivo* ^1H MRS-detectable brain metabolites are N-acetyl aspartate (NAA, found largely in neuronal cell bodies, dendrites, and axons, and hence commonly used as a neuronal marker [8]), choline containing compounds (Cho, largely constituents of phospholipid metabolism and usually interpreted as an indicator of cell membrane synthesis or degradation [9]) and creatine/phosphocreatine (Cr, a measure of high-energy metabolic processes [9]).

Technically, *In vivo* ^1H -MRS of the brain is complicated by many factors, including low signal-to-noise ratio (SNR), large water and lipid resonances, magnetic field inhomogeneities, and overlapping metabolite peaks. The clearly identified need to improve sensitivity and resolution has been a primary driving force behind the development of ultrahigh-field human scanners (e.g., 7T). ^1H MRSI at 7T offers the advantages of increased SNR, which may be used to reduce scan times or improve spatial resolution, and increased peak separation, which results in improved spectral resolution. However, B_1 inhomogeneity, B_0 inhomogeneity and chemical shift localization (CSL) errors significantly limit the performance of high-field *In vivo* human spectroscopic imaging. Approximately 40% B_1 variation was measured across the adult human head in our 7T GE whole body magnet. The conventional Position Resolved Spectroscopy (PRESS) sequence [10] utilizes linear-phase Shinnar-Le Roux (SLR) [11] excitation and refocusing pulses that are sensitive to changes in B_1 . Additionally, CSL error scales with field resulting in significant spatial misregistration between metabolites.

In order to address the issue of B_1 and B_0 inhomogeneity as well as CSL error, we have developed an interleaved narrow-band PRESS sequence with adiabatic spatial-spectral (SPSP) refocusing pulses. The sequence acquires two separate spectral passbands, one for Cho and Cre and a second for NAA, within one TR. Each band is acquired using a linear-phase SPSP 90° pulse followed by two phase-matched narrow-band adiabatic SPSP 180° pulses for volume localization. The sequence has a number of important advantages. First, the 180° refocusing pulses are adiabatic, thus gaining insensitivity to B_1 inhomogeneities. Second, each spectral band has a bandwidth of 285 Hz, making the sequence robust to peak shifts due to the B_0 inhomogeneity. Finally, shifting the center frequency for each narrow-band excitation virtually eliminates chemical shift misregistration errors.

3 Methods

3.1 Overall Pulse Sequence

The overall ^1H MRSI pulse sequence we have developed is shown in Fig. 1 A. One SPSP 90° pulse followed by two adiabatic SPSP 180° pulses with a narrow spectral bandwidth of 285 Hz are used to individually excite a single or a group of closely spaced metabolites in an interleaved fashion. See Fig. 1 B for the RF and gradient waveforms used to excite each interleaved frequency band. Interleaving allows excitation of a large spectral range without an increase in scan time. The sequence works in a manner similar to multi-slice imaging, but with spectral bands instead of slices. An interleaved approach to excite metabolites has been used previously in a different but related context [12]. Using adiabatic SPSP refocusing pulses with a narrow spectral bandwidth centered on the chosen metabolite resonance for a given interleaf allows adiabatic refocusing for a range of B_1 values as well as immunity to B_0 shifts for a given RF peak amplitude limit. A SPSP 90° pulse designed to have the same 2D spatial-spectral profile as the adiabatic SPSP 180° pulses is used for excitation. Since the transmit frequency is set to the center of each interleaved spectral band, there is negligible relative shift between the excited volumes for different metabolites. Thus, this approach provides greater immunity to B_1 and B_0 inhomogeneity, while virtually eliminating chemical shift localization error. What follows is a detailed design of the pulse sequence components.

3.2 Pulse Design

All pulses used in the sequence were spatial-spectral so we could take advantage of the significantly increased spatial bandwidth, and hence reduced chemical shift misregistration, offered by these pulses [13,14]. SPSP pulses have been used previously for spectroscopic imaging at high fields [15]. Since standard SPSP pulses are still susceptible to the significant B_1 variation at 7T, we used adiabatic SPSP 180° pulses [16] to provide some immunity to B_1 variations as well as CSL errors. The two adiabatic refocusing pulses have compensating

nonlinear spectral phase profiles, significantly reducing both the required peak and average RF power [17]. Due to the unavailability of low power, slice-selective adiabatic excitation pulses, a standard SPSP 90° was used.

3.2.1 Adiabatic SPSP 180° Pulse Design—The adiabatic SPSP 180° pulse was designed by first creating a conventional adiabatic sech/tanh [18] pulse using Eqns. 1 and 2 for the amplitude and frequency modulation functions respectively.

$$A(t) = A_0 \text{sech}(\beta t) \quad -T/2 \leq t \leq T/2 \quad (1)$$

$$\Delta\omega(t) = -\mu\beta \tanh(\beta t) \quad -T/2 \leq t \leq T/2 \quad (2)$$

where the maximum B_1 field $A_0 = 11 \mu\text{T}$, the modulation angular frequency $\beta = 300 \text{ rad/s}$, the bandwidth determining dimensionless parameter $\mu = 3.2$, and the pulse duration $T = 24 \text{ ms}$.

The resultant pulse had a spectral bandwidth of 285 Hz which is large enough to account for metabolite shifts of $\pm 0.475 \text{ ppm}$ due to B_0 inhomogeneities at 7T. The pulse was then subsampled with an optimal trade off between sideband distance and minimum slice thickness yielding 50 samples. The spectral sidebands had to be placed at a sufficient distance away from the main passband such that NAA did not get excited in the first acquisition. The final adiabatic SPSP pulse was comprised of 50 conventional small tip-angle subpulses scaled by the sampled values of the adiabatic sech/tanh envelope. The resultant separation between the main passband and sidebands was $\pm 1.9 \text{ kHz}$. The opposing sidebands were located at $\pm 950 \text{ Hz}$. This separation was large enough to prevent erroneous excitation of metabolites meant for the next interleaf. Figure 2 A & B show the magnitude and phase of the final adiabatic SPSP 180° RF pulse. The pulse is played in conjunction with an oscillating gradient waveform.

The adiabaticity of the spatial and spectral magnetization profiles of the pulse was verified through simulations. In Fig. 3 A, the simulated spatial profile is shown for a range of B_1 overdrive factors above adiabatic threshold. If the nominal B_1 is set to be at the adiabatic threshold, the pulse may be overdriven by 60% (i.e. an overdrive factor of 1.6) before reaching the $17 \mu\text{T}$ RF peak amplitude limit for our 7T RF amplifier. An increase in spatial selectivity with increasing B_1 is noticeable in Fig. 3 A. However, if the pulse is overdriven by factors above 2.5, well beyond the the RF peak amplitude limit, there is some degradation in the spatial profile at the center. Figure 3 B shows the main spectral passband of the pulse over the same range of B_1 overdrive factors. The spectral profile stays invariant over a 60% increase in B_1 , at which point the RF amplifier limit is reached. Beyond an overdrive factor of 2.5, there is some variation in passband behavior and increase in stopband ripple.

3.2.2 Linear-Phase SPSP 90° Pulse Design—A linear-phase SPSP 90° pulse was designed to have the same spectral profile as the adiabatic SPSP 180° pulse. Pulse design was similar to the 180° pulse except a linear-phase SLR envelope was used instead of a sech/tanh adiabatic envelope.

3.3 Interleaving

In principle, the sequence could have been designed without interleaves, with one excitation covering the entire spectral range of interest. However, simulations showed that the adiabatic SPSP refocusing pulses reached the $17 \mu\text{T}$ peak RF amplitude limit of our 7T scanner at a spectral bandwidth of approx 500 Hz. For a non-interleaved sequence, this limited spectral passband, combined with the increased spectral separation at 7T would result in metabolite

signal loss due to peaks shifts caused by B_0 inhomogeneity. In addition, operating the pulses at the peak RF amplitude limit leaves insufficient RF power to overdrive the pulses and maintain the adiabatic condition during excitation. Dividing the spectral range of interest into several interleaved narrow bands enables greater immunity to B_0 shifts and B_1 variations without increased scan time. The technique is particularly advantageous for reduction of CSL errors, as the transmit frequency is shifted to the center of each interleaved band, yielding negligible relative spatial shift.

Chemical shift localization error was calculated and compared for conventional PRESS, PRESS using SPSP pulses and the interleaved narrow-band PRESS sequence with adiabatic SPSP refocusing pulses. Figure 4 shows the relative shift between the excited volumes for NAA and Cho for the three sequences. For conventional PRESS, linear-phase SLR pulses with limited spatial bandwidth are used to excite along the in-plane dimension resulting in significant shift between the selected PRESS boxes for NAA and Cho, shown in Fig. 4 A. Typically the 90° excitation pulse is used to localize along at least one of the in-plane dimensions (in Fig. 4 A, the anterior-posterior dimension) resulting in less severe CSL error along that dimension. Figure 4 B shows the significant reduction in CSL error when SPSP pulses, which have higher spatial bandwidth, are used instead of conventional SLR pulses in the PRESS excitation. Figure 4 C shows the nearly coincident excited volumes when an interleaved approach is used. CSL error is mostly but not completely eliminated due to the small spectral separation (0.2 ppm) between the Cho & Cre resonances.

3.4 Final Pulse Sequence Parameters

In our sequence (Fig. 1), volume excitation for each interleaved band was achieved by the SPSP 90° degree pulse followed by two adiabatic SPSP 180° pulses. This was repeated within the same TR and the two echoes acquired were from passbands centered on Cho+Cre and NAA respectively. With a 260 ms readout, both narrow-band acquisitions can easily be interleaved into the 3 s TR window used for the overall sequence timing. A long TR was used to accommodate the long metabolite T_1 's at 7T and to stay within Specific Absorption Rate (SAR) limits. Very Selective Saturation (VSS) pulses [19] were used to diminish signal from subcutaneous fat. A 90 ms echo time was chosen as a compromise between reducing T_2 -induced signal losses and allowing sufficient time for the three SPSP RF pulses. T_2 values at 7T for prominent brain metabolites such as NAA and Cr have been found to be approximately 158 ms and 109 ms, respectively [20]. For these and other metabolites with T_2 's greater than 90 ms at 7T, the spectral and spatial profiles of the pulses used in our sequence should stay fairly constant. In addition, the magnetization is spin-locked during the adiabatic SPSP 180° pulses and, as a result, undergoes $T_{1\rho}$ decay instead of pure T_1 and T_2 decay [21]. As a result, slower effective decay of magnetization can be expected when compared to a conventional PRESS sequence with the same echo time.

Figure 5 shows simulations of the magnetization profiles for the final echo acquired at readout following the three 90° - 180° - 180° pulses. Figure 5 A shows the spatial profile of the final echo for a 0.75 cm slice. The spectral profile for the final echo, showing the main spectral passband with a bandwidth of 285 Hz and sidebands located at ± 1.9 kHz, is shown in Fig. 5 B. Metabolite and water resonance frequencies are depicted for the case of the first interleaved, with the spectral band centered between the closely spaced Cho and Cre resonances. The main passband, sidebands, as well as faint opposing sidebands are visible in the 2D spatial-spectral profile shown in Fig. 5 C. When the main spectral passband is centered between Cho and Cre, the sidebands shown in Fig. 5 B & C do not overlap with the water and NAA resonances ensuring mutual exclusivity of the interleaved spectral bands. Similarly, the Cho, Cre and water resonances are not affected when the main spectral band is centered on NAA. The spatial phase of the profile at the final echo is determined by the spatial subpulses. Linear-phase subpulses

were used for all SPSP pulses, hence, the spatial phase of the final echo is linear. Because the use of a pair of identical adiabatic SPSP 180° pulses results in the refocusing of their nonlinear spectral phase, the spectral phase at the final echo is linear as well. The 2D phase profile of the final echo is depicted in Fig. 5 D. Flat-phase is achieved across the main SPSP passband.

The sequence was tested *In vivo* by exciting a single slice through the brain of a normal volunteer and comparing the results to those obtained using a conventional PRESS sequence. The scans were performed on our 7T scanner (Echospeed whole-body magnet; GE Healthcare, Waukesha, WI, USA) using a standard GE volume head coil. The acquisition parameters for the ^1H MRSI scans were: Slice thickness = 1.5 cm, FOV = 18×18 cm, matrix size = 12×12 (5×5 voxels within the PRESS box), voxel volume = 3.4 cc, TE/TR = 90/3000 ms, NEX = 1 and scan time = 7:10 min. The center frequency for the pulses in the conventional PRESS sequence was -256 Hz or 3.8 ppm. B_1 and B_0 maps of the imaged slice were also obtained.

4 Results

Figure 6 A shows the image of a single slice through the brain of a normal volunteer scanned at 7T. ^1H MRSI data were obtained with a conventional PRESS sequence and the interleaved narrow-band PRESS sequence with adiabatic SPSP refocusing pulses. The PRESS box and spectral grid location for both ^1H MRSI experiments are shown on the image in Fig. 6 A. The measured B_1 map for the same slice, acquired using the double-angle method [22, 23], can be seen in Fig. 6 B. An approximate 40% reduction in B_1 from the center to the periphery of the brain is evident. The B_0 map in Fig. 6 C was obtained after first and second order shimming was used to optimize the B_0 homogeneity (17.75 Hz RMS, 180 Hz peak-to-peak). Changes in B_0 over the region of interest stay well below the width of the spectral band of the SPSP pulses used in our sequence.

The data obtained for the spectral grid location shown in Fig. 6 A, using a conventional PRESS sequence, can be seen in Fig. 6 D. When the same region is excited using the interleaved narrow-band PRESS sequence with adiabatic SPSP refocusing pulses, the spectral grids for Cho, Cre and NAA shown in Fig. 6 E are obtained. The scale was adjusted such that the noise, as determined from the spectral region without peaks, was equivalent for both data sets. Increased spatial coverage is clearly visualized.

In the spectra obtained using the standard PRESS sequence (Fig. 6 D), non-central voxels, especially those in the anterior portion of the grid, have reduced overall signal due to severe B_1 drop-off. This reduction in B_1 is visible in the 2D B_1 profile shown in Fig. 6 B. The interleaved narrow-band sequence provides much more signal in these areas (Fig. 6 E). The SPSP 90° pulse is still not adiabatic and shading due to the B_1 receive profile still exists, so some signal loss due to B_1 inhomogeneity is to be expected. For the standard PRESS sequence (Fig. 6 D), the column of voxels along the left (i.e. patient's left, reader's right) edge of the PRESS box contain almost no NAA signal due to chemical shift localization error. This is considerably improved in the interleaved narrow-band acquisition (Fig. 6 C). See Fig. 4 A and C for the expected shift of the selected NAA volume for the two sequences. Signal variation may also be attributed to biological variation due to tissue type. When all voxels are averaged, the overall signal increase obtained with our sequence, relative to standard PRESS, is approximately 70% for Cho+Cre and 110% for NAA.

It is important to note that to remain under peak RF amplifier limits and within SAR constraints, the 180° refocusing pulses in the conventional PRESS sequence are replaced by 137° pulses. This is the standard GE Healthcare implementation for PRESS sequences at 3T and above, and involves a trade-off between signal amplitude and pulse bandwidth. High bandwidths are needed to reduce chemical shift misregistration errors. The adiabatic SPSP pulses used in the

interleaved narrow-band sequence provide a 180° flip angle while remaining below RF peak amplifier and SAR limits, even when overdriven. As seen in Fig. 4 C, chemical shift localization error is negligible, regardless of the flip angle. Our sequence results in approximately 55% more signal than conventional PRESS at the central voxels due to this difference in flip angle as well as some B_1 inhomogeneity.

5 Discussion and Conclusions

We have designed and implemented a 7T ^1H MRSI sequence that utilizes a SPSP excitation pulse and two narrow-band adiabatic SPSP refocusing pulses to achieve spectral coverage in an interleaved fashion. The sequence provides greater immunity to B_1 and B_0 variations and virtually eliminates chemical shift localization errors. *In vivo* data demonstrate that the interleaved narrow-band adiabatic SPSP sequence provides improved spatial coverage and increased overall SNR in comparison to a conventional PRESS sequence.

The interleaved spectral bands for this sequence are narrow enough to completely suppress water, eliminating the requirement for additional water suppression techniques. Furthermore, because the water resonance is not excited by any of the pulses in the metabolic interleaves, the sequence can easily be extended to incorporate a third spectral band centered at water to provide a signal for absolute quantification. The 3 s TR affords sufficient time to interleave a total of 4 spectral bands without exceeding SAR limits.

The 90° excitation pulse used in the sequence is not adiabatic and will thus induce some imaging shading due to B_1 variations. For example, a $\pm 20\%$ change in B_1 will result in approximately a 5% signal loss. Adiabatic alternatives for this pulse are currently being explored, so that excitation for all spectral bands can be made completely B_1 -insensitive.

Partial fat suppression is also provided by the spectral selectivity of the SPSP pulses. Fat suppression techniques such as inversion recovery may be used with this sequence for further suppression of lipids resonating close to NAA. The sequence is geared toward imaging three of the main metabolites of interest in the brain (Cho, Cre, NAA). A similar sequence with more interleaves and wider passbands may be explored to capture other metabolites of interest.

Another application for this sequence may be multinuclear spectroscopy/spectroscopic imaging, especially for nuclei with spectra that contain a large chemical shift range, such as ^{13}C . Metabolite resonances in the ^{13}C spectrum are separated by many ppm, requiring very high bandwidth pulses to capture all peaks of interest without severe chemical shift localization error. By using an interleaved approach with several spectral bands centered at the metabolites of interest, pulses with narrower bandwidth may be used and chemical shift localization error reduced or even eliminated.

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Figure 1.

(A) Interleaved narrow-band SPSP pulse sequence with first interleaf exciting spectral band 1 (centered between Cho & Cre resonances) and the second exciting spectral band 2 (centered on the NAA resonance). Very Selective Saturation (VSS) pulses are used to spatially saturate signal from subcutaneous fat. Timing parameters for the sequence are: readout duration (TAD) = 260 ms, TE = 90 ms and TR = 3 s. The long TR's required at 7T leave room for the insertion of a third interleaf. Excitation RF and gradient waveforms for each interleaf are shown in (B).

Figure 2.

(A) Magnitude and (B) phase of the 24 ms adiabatic SPSP 180° pulse used for refocusing. The peak B_1 value of the pulse is well below the limit of our 7T RF amplifier, which is 17 μ T.

Figure 3.

Simulated magnetization profiles for the adiabatic SPSP 180° pulse. (A) Spatial profile and (B) central passband of the spectral profile versus B_1 overdrive factor. Pulses can be overdriven by 60% before reaching the peak B_1 limit of the RF amplifier (17 μ T) on our 7T magnet; however, the pulses maintain adiabaticity well beyond that limit.

Figure 4.

Chemical shift localization error at 7T between selected volumes for NAA and Cho when using (A) a conventional PRESS sequence, (B) a PRESS sequence with SPSP 180° pulses and (C) our interleaved narrow-band PRESS sequence with adiabatic SPSP 180° pulses. CSL error is greatly reduced with the use of SPSP pulses and practically eliminated when an interleaved approach is used with adiabatic SPSP pulses for refocusing.

Figure 5.

Simulated magnetization profiles for the final spin echo after the last 180° pulse. (A) Spatial profile, (B) spectral profile showing the main passband as well as the location of the sidebands (± 1.9 kHz). All pulses were designed such that the frequency separation between the main passband and sidebands was large enough not to erroneously excite metabolites designated for the next interleaf. Dashed lines show resonant frequencies for metabolites when the main spectral passband is centered on Cho & Cre. (C) 2D spatial-spectral magnitude profile for pulse, showing selectivity in both space and frequency. The opposed sidebands visible at ± 950 Hz are also located such that there is no spectral interference between interleaves. (D) 2D spatial-spectral phase profile demonstrating that flat phase for the main passband is achieved.

Figure 6.

(A) Water image, (B) B₁ map and (C) B₀ map of a 1.5 mm slice of a normal human brain for which ¹H MRSI data was obtained at 7T. The 5×5 spectral grid within the prescribed PRESS box is shown in (A). The location of the spectral grid is also overlaid on the maps in (B) and (C) to show the expected B₁ and B₀ changes between voxels. The obtained ¹H MRSI data is shown for (D) conventional PRESS and (E) our interleaved narrow-band sequence with adiabatic SPSP refocusing pulses. Greater spatial coverage and overall SNR is achieved with our sequence in comparison to conventional PRESS. Acquisition parameters are: single 1.5 cm slice, 18×18 cm FOV, 12×12 matrix (only central 5×5 portion within PRESS box is shown), 3.4 cc voxels, TE/TR: 90/3000 ms, 1 NEX, 7:10 min scan time.