Spectroscopic Localization by Simultaneous Acquisition of the Double-Spin and Stimulated Echoes

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Abstract

Purpose—To design a proton MR spectroscopy (^1H -MRS) localization sequence that combines the signal-to-noise-ratio (SNR) benefits of Point Resolved Spectroscopy (PRESS) with the high pulse bandwidths, low chemical shift displacements (CSD), low specific absorption rates (SAR), short echo times (TE) and superior radio-frequency transmit field (B_{1+}) immunity of Stimulated Echo Acquisition Mode (STEAM), by simultaneously refocusing and acquiring both the double-spin and stimulated echo coherence pathways from the volume of interest.

Methods—We propose a family of ^1H -MRS sequences comprising three orthogonal spatially-selective pulses with flip angles $90^\circ < \alpha, \beta, \gamma < 128^\circ$. The stimulated and double-spin echo are refocused in-phase simultaneously by altering the pulses' phases, flip angles and timing, as well as the inter-pulse gradient spoiling moments. The $\approx 90^\circ$ nutations of α, β, γ provide STEAM-like advantages (lower SAR, in-plane CSD and TE; greater B_{1+} immunity), but with SNRs comparable with PRESS.

Results—Phantom and in vivo brain experiments show that 83–100% of the PRESS SNR (metabolite-dependent) is achieved at under 75% of the SAR and 66% lower in-plane CSD.

Conclusion—The advantages of STEAM can be augmented with the higher SNR of PRESS by combining the spin and stimulated echoes. Quantification, especially of J-coupled resonances and intermediate and long TEs, must be carefully considered.

Keywords

STRESS; Point resolved spectroscopy (PRESS); Stimulated echo acquisition mode (STEAM); CPMG; spin echo; stimulated echo; coherence pathway; chemical shift displacement (CSD); chemical shift displacement artifact (CSDA)

Introduction

Proton MR spectroscopy (^1H -MRS) requires selective excitation of a volume of interest (VOI) for localization and to prevent aliasing in spectroscopic imaging (^1H -MRSI) (1–5). The two best known and most used VOI excitation modules use three orthogonal spatially-selective pulses: 90° - 180° - 180° Point Resolved Spectroscopy (PRESS) (1); or 90° - 90° - 90°

Stimulated Echo Acquisition Mode (STEAM) (2). The three pulses generate nine transverse coherence pathways: three free induction decays (FID), four spin echoes (SE) and two stimulated echoes (STE) (6,7). Judicious use of gradient spoiling dephases all the pathways that originate from spins outside the VOI, achieving excellent rejection of outer volume contamination (8,9). PRESS and STEAM each refocus a single coherence pathway: the double spin echo (in PRESS) or one of the stimulated echoes (in STEAM), both of which originate only from spins within the VOI.

Per given peak radio-frequency (RF) power and SAR, STEAM's 90° pulses offer several advantages over PRESS's 180° s: (i) lower specific absorption rates (SAR) that allow to reduce the recycle time (TR) to improve the signal-to-noise-ratio (SNR)/unit-time (10); (ii) higher pulse bandwidths, leading to smaller chemical shift displacement (CSD) (11); (iii) shorter echo times (TE), suffering less T_2 and J -coupling losses; and (iv) improved immunity to B_{1+} variations. These, however, come at a cost of half the SNR per scan (9). Since the metabolites' signals are 4–5 orders of magnitude weaker than the water used in MRI, the SNR advantage of PRESS usually make it the method of choice for most ^1H -MRS experiments. The higher CSD in the two 180° pulse directions can be mitigated with high bandwidth refocusing pulses designed using, *e.g.*, optimal control theory (12,13), or the Shinnar-Le Roux algorithm (14), but at a cost of increased SAR, which can become prohibitive trying to keep the same CSD. The spatial B_{1+} variability can be addressed with adiabatic pulses, *e.g.*, SADLOVE (15) or LASER (16–18), but their required double-refocusing prolongs the minimum TE and increases SAR. The longer TE attenuates signals of J -coupled metabolites that often also have short T_2 s, while the higher SAR prolongs the repetition time (TR), thereby reducing the SNR/unit-time.

While both PRESS and STEAM select a single, particular coherence pathway, there are compelling advantages to combining multiple pathways. Indeed, solid and liquid state NMR, pulse sequences such as HNCA, TOCSY-HSQC and MQMAS can combine different pathways for increased sensitivity (19–21), whereas multi-pulse MR imaging sequences refocus multiple coherence pathways to generate contrast and boost sensitivity (22) or to simultaneously obtain maps of several parameters (23). Similarly, refocusing the spin and stimulated echo pathways for efficient T_1 mapping has been suggested recently in the context of echo planar ^1H -MRSI (24).

In this paper we modify the familiar three-pulse ^1H -MRS localization paradigm, by adjusting the three RF pulses' phases, flip angles, timings, and coherence selection gradients, in order to acquire both the double-spin and one of the stimulated echo pathways, a scheme we denote STRESS (STEAM + PRESS). Requiring maximal B_{1+} immunity yields a family of STRESS sequences, parameterized by, the flip angle of the first RF pulse. The B_{1+} immunity is shown to be superior to that of both PRESS and STEAM for most values of α . Results are shown in a phantom and a healthy volunteer at 3 T for the 110° - 108° - 108° member of the STRESS family, which retains 83%–100% of the PRESS SNR (metabolite dependent) at only 75% of its SAR and 33% of its in-plane CSD for equal TE and TR, while also offering a shorter minimum echo time of $TE=27$ ms compared to PRESS's $TE=40$ ms.

Theory

Three pulses having flip angles α , β , γ , will give rise to a total of nine transverse coherence pathways: three free induction decays (FID₁, FID₂, FID₃), four spin echoes (SE₁₂, SE₁₃, SE₂₃, SE₁₂₃) and two stimulated echoes (STE₊, STE₋), as illustrated in Fig. 1 (7). Here, SE_{ij} denotes the coherence excited by the i^{th} pulse and refocused by the j^{th} and SE₁₂₃ refers to the doubly-refocused spin echo (PRESS) pathway. The two distinct STE₊ and STE₋ coherence pathways, sometimes referred to as a stimulated echo and anti-echo, cannot be refocused simultaneously, and only STE₋ is observed in Fig. 1 (25). Only SE₁₂₃ and STE originate solely from within the VOI. All other pathways must be spoiled to achieve localization, by adjusting the inter-pulse spoiler gradients— *e.g.*, those suggested by Moonen *et. al.* (6). Within the VOI, each pathway's amplitude is dependent on α , β , γ , as summarized

in Table 1: SE₁₂₃'s amplitude is proportional to $\sin(\alpha)\sin^2\left(\frac{\beta}{2}\right)\sin^2\left(\frac{\gamma}{2}\right)$, while STE₋'s is proportional to $\frac{1}{2}\sin(\alpha)\sin(\beta)\sin(\gamma)$.

To simultaneously refocus both SE₁₂₃ and STE₋ while dephasing all other pathways, we suggest four changes to the basic three-pulse localization scheme: (i) Set the inter-pulse gradient spoiler moments to a 1:2:1 ratio (Table 1). (ii) Set the delays (center-to-center) to the same 1:2:1 ratio: $\tau=\text{TE}/4$ between the excitation and second pulse, $2\tau=\text{TE}/2$ between the second and third pulses and $\tau=\text{TE}/4$ between the last pulse and acquisition. (iii) Implement a “Carr-Purcell-Meiboom-Gill (CPMG) phase relation”, where the second and third pulses' phases' are incremented by 90° relative to the first. (iv) Modify the flip angles of the three pulses as detailed below and shown in Fig. 2 and Table 2.

Choices (i)–(iii) are best understood by examining the standard CPMG sequence used for T₂ relaxometry (26): $90^\circ_0 - \tau - 180^\circ_{90} - \tau - [\text{echo}] - \tau - 180^\circ_{90} - \tau - [\text{echo}] - \dots$, where only T₂^{*} decay is accumulated between the pulses. If we assume for simplicity that T₂^{*} is caused by a spatially linear B₀-field inhomogeneity, the effect would be analogous to the 1:2:1 gradient-moment ratio suggested in (i) above. The inter-pulse timing modification (ii) assures us SE₁₂₃ and STE₋ refocus at the same time, as can also be gleaned from Fig. 1. The CPMG phase relation (iii) ensures SE₁₂₃ and STE₋ are both in-phase to add constructively (compare Fig. 1a with 1b).

Flip Angle Calibration

Neglecting relaxation, the combined amplitude of SE₁₂₃+STE₋ is

$\sin(\alpha)\sin^2\left(\frac{\beta}{2}\right)\sin^2\left(\frac{\gamma}{2}\right) + \frac{1}{2}\sin(\alpha)\sin(\beta)\sin(\gamma)$. Since the VOI is often square in-plane, we confine ourselves to the $\beta = \gamma$ case, although the results derived below are valid regardless of the VOI's dimensions. In the event of B₁₊ inhomogeneity, we easily compute the signal's dependence on η , the scaling of the B₁ field:

$$S(\eta) = \sin(\eta\alpha) \left[\sin^4\left(\frac{\eta\beta}{2}\right) + \frac{1}{2}\sin^2(\beta\eta) \right]. \quad [1]$$

By demanding maximal immunity to B_{1+} variations at nominal B_{1+} ($\eta=1$),

$$\left(\frac{\partial S}{\partial \eta}\right)_{\eta=1} = 0, \quad [2]$$

one obtains an implicit relation between the flip angles α and β . Numerically solving for β as a function of α given $90^\circ \leq \alpha \leq 128^\circ$, yields a family of STRESS pulse sequences, as shown in Fig. 2. The members of the STRESS family are labeled by α as STRESS- α , and their SNR, relative to PRESS, is also shown in Fig. 2 for a homogeneous B_{1+} field ($\eta=1$). Some specific flip angle values are summarized in Table 2. For $\alpha=90^\circ$, we obtain $\beta=\gamma=180^\circ$ and the flip angles of STRESS-90 coincide with PRESS. As α increases from 90° , decreases sharply from 180° .

The individual (SE_{123} , STE_-) and combined ($SE_{123}+STE_-$) signal strengths are plotted in Fig. 3a–c as a function of the nominal B_{1+} (η) for several members of the STRESS family. For $\alpha=90^\circ$ (Fig. 3a), the signal strength of SE_{123} corresponds to that of PRESS, showing that STRESS- 90° is significantly more robust to B_{1+} variations than PRESS. This is further examined in Fig. 3d which plots the B_{1+} dependence of PRESS, STEAM, STRESS- 90° and STRESS- 105° , showing equivalent or superior performance of STRESS for typical in vivo B_{1+} .

Relaxation Properties of the Signal

The STE_- undergoes T_1 relaxation for $2\tau=TE/2$ between the first and second pulses, while the SE_{123} undergoes T_2 relaxation. The signal at TE will, therefore, be weighted by both pathways:

$$S^{(STRESS)} = S_0 \cdot B_{1-} \cdot \frac{1 - e^{-TR/T_1}}{1 - \cos(\eta\alpha)e^{-TR/T_1}} \cdot \sin(\eta\alpha)e^{-\frac{TE}{2T_2}} \left[\sin^4\left(\frac{\eta\beta}{2}\right)e^{-\frac{TE}{2T_2}} + \frac{1}{2}\sin^2(\beta\eta)e^{-\frac{TE}{2T_1}} \right]. \quad [3]$$

The signal is proportional to S_0 that one would obtain in a simple pulse-acquire experiment; B_{1-} , the receiver profile; and $(1 - e^{-TR/T_1}) \cdot (1 - \cos(\eta\alpha)e^{-TR/T_1})^{-1}$, the dynamic equilibrium weighting-factor. In contrast, the signal in a PRESS experiment would be:

$$S^{(PRESS)} = S_0 \cdot B_{1-} \cdot \frac{1 - e^{-TR/T_1}}{1 - \cos\left(\frac{\eta\pi}{2}\right)e^{-TR/T_1}} \cdot \sin^5\left(\frac{\pi\eta}{2}\right)e^{-\frac{TE}{T_2}}. \quad [4]$$

The differences between Eqs. [3] and [4] must be kept in mind during absolute or ratio quantification. Even if $TR \gg T_1$, the magnitude of the STRESS echo (Eq. [3]) will contain some minor T_1 dependence from the STE_- component; however, for most cases, $TE \ll T_1$, hence $\exp(-TE/2T_1) \approx 1$ with negligible effect on quantification. Moreover, since STE_- only evolves for a time $TE/2$ in the transverse plane, it is less affected by T_2 relaxation compared to the SE_{123} pathway, reducing STRESS's SNR penalty relative to PRESS for $TE > 0$. This can be seen quantitatively from Table 2, which compares the signals in a homogeneous B_{1+} field of PRESS with STRESS for typical metabolite relaxation constants found in-vivo ($T_2=150$ ms, $T_1=1200$ ms). For example, at $TE=40$, PRESS's signal decays to 77% of the

full amplitude (at TE=0), while, *e.g.*, that of STRESS-100 is almost identical at 76%. If 25% B_{1+} inhomogeneity is introduced ($\eta=0.75$), the STRESS-100 SNR even surpasses PRESS by ~20% at TE=40 ms and ~50% at TE=144 ms, although the gain is asymmetrical with η and is smaller for $\eta=1.25$ (since the flip angle optimization, Eq. [2], neglected relaxation). Thus, although the theoretical SNR of PRESS in the absence of relaxation and B_{1+} variation is higher than STRESS for $\alpha>90^\circ$, near parity is expected under realistic conditions at fields ≥ 3 T.

Phase Cycling in STRESS

Phase cycling the pulses' and receiver's phases among different averages is a common technique for providing additional suppression of unwanted coherence pathways (27,28). Phase cycling schemes for PRESS and STEAM cannot be straightforwardly translated to STRESS, since a special phase relationship must be kept between the different pulses to ensure the SE_{123} and STE_- pathways add constructively. One such phase relationship, $\phi_1=0^\circ$, $\phi_2=\phi_3=90^\circ$ (the so-called "CPMG phase relation"), has already been outlined above, where ϕ_i is the phase of the i^{th} pulse ($i=1,2,3$). This, however, is not the only such phase relationship. For example, setting $\phi_1=180^\circ$, $\phi_2=\phi_3=90^\circ$ and consulting Table 1, which lists the phases of the different echoes, we see SE_{123} and STE_- are once more in phase. As long as the phase of SE_{123} and STE_- are kept equal, the above discussion of STRESS's applicability and advantages holds. Motivated by this observation, we suggest four possible phase cycling schemes (outlined in supplemental Table 1 online), which we have labeled C1, C2, C3 and C4. The first scheme, C1, merely alternates the overall phase of the pulse train and eliminates receiver artifacts. The second, C2, suppresses SE_{23} , FID_2 and FID_3 ; this is particularly useful, since SE_{23} and FID_3 are responsible for particularly troublesome artifacts (29), and can also be seen from Table 1 to be the most weakly spoiled pathways in STRESS. The third, C3, suppresses all pathways except FID_1 and DC artifacts. The fourth, C4, suppresses all unwanted coherence pathways, but not DC artifacts.

Different cycles can be combined via nesting (28). However, special care must be taken when nesting different phase cycles: this involves adding their phases modulo 360° , which may not necessarily conserve their special phase relationships. For example, consider two STRESS experiments having $(\phi_1, \phi_2, \phi_3)=(0^\circ, 90^\circ, 90^\circ)$ and $(\phi_1, \phi_2, \phi_3)=(180^\circ, 90^\circ, 90^\circ)$. Although each of these will yield a valid STRESS signal, in which STE_- and SE_{123} are both in phase, the experiment consisting of phases which are the direct sum of both, $(\phi_1, \phi_2, \phi_3)=(180^\circ, 180^\circ, 180^\circ)$, will not and is inadmissible in a phase cycle.

Methods

All experiments were done in a 3 T whole body MR imager (Tim-Trio, Siemens AG, Erlangen Germany), using transmit-receive head-coils capable of producing $24 \mu\text{T}$ (1 kHz) of B_{1+} . In-vivo experiments were done on a 31 year old healthy female volunteer who provided a written institutional review board-approved consent. The machine's reference voltage calibration routines showed high intra-subject repeatability (2% coefficient of variation).

Phantom: Single Voxel

The experiments were carried out on a spherical phantom containing water doped with copper sulfate ($T_1/T_2=660/320$ ms), and metabolite concentrations approximating in vivo human brain: N-Acetyl-L-aspartate (NAA, 12.5 mM, $T_1/T_2=605/465$ ms), choline-chloride (Cho, 3 mM, $T_1/T_2=235/200$ ms), creatine-hydrate (Cr, 10 mM, $T_1/T_2=336/288$ ms), myo-inositol (7.5 mM), L-glutamic acid (12.5 mM) and DL-lactic acid (5.0 mM).

To assess the SNR gains of STRESS-110 (Fig. 4b, $\alpha/\beta/\gamma=110^\circ/108^\circ/108^\circ$) over PRESS (Fig. 4a), as well as investigate the behavior of J-coupled species, a single-voxel experiment was carried out in a $3\times3\times3=27$ cm³ volume in the center of the phantom, shimmed down to 4.5 Hz. The pulses used were all SLR-designed and sinc-like, with peak B_1 of 1.0 kHz: for PRESS, a $T_{90}=3.84$ ms 90° excitation pulse with 3.6 kHz bandwidth (BW) and two $T_{180}=7.68$ ms 180° s of 1 kHz BW; for STRESS, a $T_{110}=3.84$ ms 110° pulse with 3.2 kHz BW and two $T_{108}=3.84$ ms 108° s of 3.15 kHz BW. At 64 averages, 4 dummy scans and $TR=2000$ ms, each acquisition took 2:16 minutes. A receiver BW of ± 1 kHz was used with 2048 complex points. Four different TE values were examined: TE=40 ms (minimum for our PRESS), 60, 100 and 144 ms, representing “short” and “long” TEs. Although TEs as short as 27 ms were possible with STRESS-110, they were not obtained due to lack of comparable PRESS data with TE<40 ms. The 64 averages were apodized using a Gaussian envelope, Fourier transformed and automatically phased using the NAA singlet at 2 ppm.

Note that the STE_z pathway is stored longitudinally for half the TE, making its “true” TE (time spent in the transverse plane) only TE/2. In this paper, “TE” will denote the time between the center of the first excitation pulse and start of acquisition. Some consequences of this difference are further explored in the Discussion.

Phantom: Multi Voxel

To assess the reductions in CSD, STRESS-110 was compared to PRESS using a multi-voxel acquisition. Following an initial localization MRI, a 2D CSI slice was positioned in the phantom’s center and shimmed to 5.0 Hz. TE/TR were 40/1000 ms for both sequences. Rectilinear k-space sampling was employed with a 2D 20×20 acquisition matrix, 20 mm slice thickness, 80×80 mm² VOI and 160×160 mm² FOV, resulting in $8\times8\times20$ mm³=1.28 cc nominal voxels. Total acquisition time, including four initial dummy scans, was 6:46 minutes. An in-house optimized six-pulse 242 ms long frequency-selective water suppression module preceded excitation. Magnetic field drift correction was implemented, as detailed in (30). The transmitter and receiver’s carrier frequencies were centered on the NAA at 2.01 ppm and the signals were each sampled for 1 second at ± 1 Kz BW with 2048 complex points.

Once obtained, the signals from each scan were zero filled to twice their length, arranged in a three dimensional k_x - k_y -t matrix and Fourier transformed over all axes. Automated 0th order phasing was done in each voxel using the NAA peak as a reference. Gaussian apodization was applied in the time domain to improve the SNR. “SNR maps” of the NAA (2.01 ppm), Cho (3.2 ppm) and CH₂ peak of Cr (3.9 ppm) were obtained by dividing their

peak height by the standard deviation of the noise over the metabolite-free 8–10 ppm range in each voxel.

Due to dielectric resonances at 3 T, non-negligible B_{1+} variation were encountered within the VOI. To monitor them and also demonstrate insensitivity of STRESS to them, a 2D Actual Flip Angle imaging sequence was used to obtain B_{1+} maps at an isotropic $5 \times 5 \times 5 \text{ mm}^3$ spatial resolution, with $TR_1/TR_2/TE=20/100/10 \text{ ms}$ for a 3:12 minutes total acquisition time.

In Vivo brain

The experiments were repeated in a healthy, 31 year old female. A localizer was followed by a 5:36 minute 3D MP-RAGE ($256 \times 256 \times 192 \text{ mm}^3$ FOV, 1 mm^3 isotropic). An in-house automatic shim routine then optimized the whole-head B_0 homogeneity in ~5 minutes to 24 Hz (31). This was followed by 2D CSI from a supra-ventricular slice (VOI shim: 17 Hz) for three sequences: using PRESS (TE/TR=40/1000), STRESS-110 (TE/TR=27/1000) and STRESS-110 (TE/TR=40/1000). Shared acquisition parameters were: 16×16 matrix, $140 \times 140 \text{ mm}^2$ FOV, $70 \times 70 \text{ mm}^2$ VOI, 12 mm slice thickness, 0.92 cc nominal voxels, 4 averages for a total 17:08 minutes. As with the phantom, TE=40 ms was the minimum for PRESS, given the amount of spoiling and pulse lengths, while TE=27 ms was the minimum of STRESS-110 and was acquired to compare the SNR gains possible at lower TEs. A 3D flip angle imaging sequence followed to obtain B_{1+} maps for the ^1H -MRSI slice. The entire protocol took 71 minutes. Post processing was identical to the phantom, including the SNR maps. The NAA and Cr singlets at 2.01 and 3.02 ppm were quantified for all three data sets using SITools-FITT spectral fitting software package (32), and the NAA/Cr ratio was calculated for the central $4 \times 4 = 16$ voxels in the VOI, to compare the ratios of the two methods.

Results

Phantom: Single-voxel

Each of the pulses used in the sequence was simulated by solving the Bloch equation without relaxation, and the resulting flip angles were used to calculate the voxel profile as a function of the spatial coordinates (x,y,z) (see supplemental Fig. 1 online). These simulations were also used to verify that the VOI selection gradients were calibrated to yield the same full width at half maximum (FWHM) for both profiles. Note that, at the pulses' in-plane edges, the flip angles α , β or γ vary independently. Along the slice direction the signal dependence is the same for the SE_{123} and STE_- pathways ($\sim \sin(\alpha)$), but note that the STRESS-110 angle α varies from 110° at the voxel's center, through 90° ($\sin(\alpha)$ maximal) and down to 0° , which explains the "horn-like" feature of the STRESS-110 profile seen in supplemental Fig. 1b online. Along the in-plane edges where either β or γ (or both) vary, the relative contributions of the STE_- and SE_{123} pathways will vary as well. Since both T_2 and B_{1+} inhomogeneity affect the SE_{123} more than the STE_- pathway, the STRESS voxel profile is expected to increase in relation to the PRESS's when these are introduced. Indeed, while the total STRESS-110 voxel volume was found to be 85% of the PRESS voxel volume for $\eta = 1$ (supplemental Fig. 1a and 1b online), in the presence 25% B_{1+} inhomogeneity

(supplemental Fig. 1c online) the calculated STRESS-110 voxel volume was 16% higher than the PRESS voxel volume.

The single-voxel spectra of both STRESS-110 and PRESS from the phantom, are overlaid in Fig. 5. These confirm both the theoretical prediction of the STRESS signal, and also confirm that when finite T_2 relaxation is introduced, the STRESS SNR becomes more pronounced, once again in line with the theoretical prediction (Eqs. [3] versus Eq. [4], as well as Table 2).

Of particular interest are the spectral patterns of the homonuclear J-coupled spins: myo-inositol (mI), glutamate (Glu), NAA and lactate (Lac). The STRESS signal is a sum of both a stimulated and spin echo, each of which undergoes different evolution under J-coupling. For short enough TEs ($TE \ll 1/J \sim 140\text{--}200$ ms in-vivo), for which J-coupling evolution is small, the STRESS and PRESS spectral patterns are expected to be very similar. This is true for the Lac and mI resonances up to $TE=60$ ms and for glutamate at $TE=40$ ms. The NAA's methylene group's spectral pattern in the 2.4–2.8 ppm range, however, displays distortions already at $TE=40$ ms.

Note that some distortions of the spectral patterns of J-coupled metabolites are observed in the PRESS spectra due to CSD effects. For example, the Lactate resonance is not completely inverted at $TE=144$ ms (33). In contrast, Lactate's spectral pattern is distorted for STRESS-110 but mostly due to interference between the SE and STE_- pathways.

The B_{1+} maps in the phantom revealed small, $<4\%$, deviations from nominal across the voxel.

Phantom: Multi-voxel

Sample STRESS-110 and PRESS spectra from a column of voxels through the phantom's center are shown in Fig. 6. They readily exhibit two features: (i) slightly lower SNR for STRESS-110; and (ii) greater CSD for PRESS. These are further supported by the SNR maps of NAA, Cho and the CH_2 peak of Cr (0, 150 and 235 Hz off resonance), shown in Fig. 7. The maps show the $\times 3$ fold reduced in-plane CSD for Cho and Cr- CH_2 , estimated using the centers of the one dimensional slice profiles. The results for STRESS-110 were $+4$ and $+6$ mm for Cho and CH_2 -Cr, while for PRESS they were $+12$ mm and $+22$ mm. These are in agreement with the ratio in BWs employed in-plane, which predict a 3-fold decrease in CSD for STRESS-110. Note that all pulses had the same peak B_1 to ensure a fair comparison.

Averaging over the middle 5×5 voxels reveals that the mean STRESS SNR for NAA is 85% that of PRESS, while for Cho it is 86%, in close agreement with the 83% theoretical predictions for STRESS-110 in Table 2. The slight increase can be explained by the finite T_2 s and B_{1+} variations. This is supported by the $\pm 10\%$ variation in the nominal B_{1+} mapped across the slice.

In vivo brain

The same sequences were evaluated in a 2D supra-ventricular slice in the brain of a volunteer, as shown in Fig. 8. The NAA and Cho singlets' SNR for a 16 voxel column is

shown in Fig. 8b and the spectra for PRESS (TE=40 ms) and STRESS-110 (at TE=40 and 27 ms), are shown in Fig. 8c. B_{1+} mapping showed its nominal values to be 0.95 ± 0.09 (mean $\pm$ SD) across the VOI.

Both the spectra and 1D SNR plots confirm the theoretical predictions: (i) the STRESS averaged SNR in the central 4×4 group of voxels is 87%, 94% and 89% that of PRESS for NAA (2 ppm), Cr (3 ppm) and Cho (3.2 ppm), respectively. This agrees with the predictions of Table 2. In particular, the transverse relaxation times of Cr are substantially shorter than NAA's in the brain at 3T, averaging at around 150–200 ms with values as low as 140 ms in the globus pallidus (34,35). For such short T_2 and observed $\sim 10\%$ spatial B_{1+} inhomogeneities, the PRESS and STRESS-110 Cr signals (Eqs. [3] and [4]) are indeed expected to be almost equal. (ii) Greater CSD is observed in PRESS, with Cr and Cho peaks appearing outside the VOI (arrows in Fig. 8c). This artifact is also seen in the 1D SNR map of choline in Fig. 8b, but is too small to be observed in the STRESS data, in agreement with the expected CSDs.

The mean $\pm$ SD of the NAA/Cr ratio, calculated from the spectrally-fitted central $4 \times 4 = 16$ voxels, was 1.54 ± 0.26 for PRESS, 1.47 ± 0.15 for STRESS-110 (both at TE=40 ms) and 1.42 ± 0.13 for STRESS-110 (TE=27 ms). These are in agreement with literature values for healthy adults (36).

Discussion

The two most popular ^1H -MRS localization modules, PRESS and STEAM, are designed to acquire a single coherence pathway while dephasing all others. By acquiring SE_{123} and STE_- simultaneously, one can trade some SNR for significantly reduced TE, CSD and SAR, as well as increased immunity to B_{1+} variations. As shown in vivo for Cr and by Table 2, this SNR loss is expected to be small ($<10\%$), or even be a gain under realistic acquisition conditions at 3 T and up (short T_2 s, substantial B_{1+} inhomogeneities). The 25%-lower SAR of STRESS allows for commensurate TR shortening for higher SNR/unit-time or larger spatial coverage in 3D ^1H -MRSI (10). The STRESS family of sequences should be thought of as a STEAM/PRESS hybrid, parameterized by the flip angle of the first pulse. Unlike STEAM, which can be designed to refocus either STE_- or STE_+ (25), STRESS must refocus STE_- since the spoiling gradients cannot be adjusted to refocus both SE_{123} and STE_+ .

Two practical considerations deserve mention: First, phase encoding in ^1H -MRSI must be applied *after* the third RF pulse, as shown in Fig. 4b. Placing it between the first and second RF pulses would produce mirror images for the STE_- and SE_{123} pathways, since the former inverts the first gradient moment, while the latter does not. Phase encoding after the second pulse would not affect STE_- since it is stored longitudinally between the second and third pulses. Second, the STE_- pathway is re-excited by the third pulse, after which suitable rewinding gradients must be added, much like in STEAM; these must then be balanced for the SE_{123} pathway, by adding identical gradient moments between the second and third pulses, as shown in Fig. 4b.

Simultaneous acquisition of spin and stimulated echoes is inherent to one of the earlier pulse sequences (albeit for a different purpose): the Meiboom-Gill variant (26) of the Carr-Purcell echo train (37), used in NMR and MRI. A recent coherence pathways analysis pinpointed the refocused STEs as the cause of its immunity to B_{1+} variations (38). Interestingly, a “standard” PRESS sequence cannot benefit from this immunity since STE_+ and STE_- are normally spoiled. STRESS does not spoil STE_- and when $\alpha/\beta/\gamma=90^\circ/180^\circ/180^\circ$, it is identical to PRESS, but with added benefit of B_{1+} variation immunity due to the incorporated CPMG phase relation (Fig. 3d).

The Quantification of J-Coupled Resonances

The STRESS signal is the sum of a spin and stimulated echo, each of which evolves differently under the effect of homonuclear J-coupling. Consequently, care must be taken to prevent the two pathways from destructively interfering. This is further complicated by noting the relative amount of each pathway – and, hence, the spectral pattern itself – depends not only on the in-plane angles (β , γ), but also on T_2 , TE and the B_{1+} inhomogeneity (η). While it is common to simulate or acquire a basis set for each metabolite for a given TE, here additional knowledge of T_2 and η is required, which may complicate the quantification procedure.

As TE is reduced significantly below $1/J$ (~125–200 ms for many in-vivo metabolites (39)), the amount of J-coupling evolution diminishes, the two pathways’ spectral patterns increasingly agree, and the quantification of J-coupled resonances becomes simpler and more accurate. This is shown in Fig. 5, where the Lac, mI and Glu peaks of STRESS-110 and PRESS increasingly coincide as TE is reduced. The “threshold” TE will be metabolite dependent, as can be seen for NAA CH_2 group in the 2.4 – 2.8 ppm range, that appear different for the two methods even at TE=40 ms. This makes STRESS a viable option for in-vivo spectroscopy of J-coupled metabolites at short TEs: precisely those which it is designed to attain, and which are often required to boost the low SNR and negate the short T_2 s of these resonances. It should be noted, however, that caution should be applied to metabolite resonances with large enough J (>9 Hz), even at short TEs; these include the NAA’s CH_2 group (2.4–2.8 ppm); some of Glutamate’s and Glutamine’s CH_2 groups (2.0 – 2.4 ppm); and some of myo-Inositol’s CH resonances around ca. 3.5 ppm, among others (39).

Caveats and Possible Pitfalls

The SE_{123} signal remains transverse between the second and third pulses, while STE_- is stored longitudinally for $2\gamma=TE/2$. The two pathways, therefore, differ in their relaxation and evolution during that period, creating a more complex dependency on T_1 , T_2 and B_{1+} inhomogeneity than in STEAM or PRESS, as seen by comparing Eqs. [3] and [4]. Knowledge of T_1 and T_2 is necessary for absolute quantification in either case. However, B_1 dependency in PRESS can be cancelled out by taking metabolite ratios between, *e.g.*, NAA and a reference water scan:

$$\frac{S_{NAA}^{(PRESS)}}{S_{water}^{(PRESS)}} = \frac{S_{0,NAA}}{S_{0,water}} \cdot \frac{1 - E_{1,NAA}}{1 - E_{1,water}} \cdot \frac{e^{-TE/T_{2,NAA}}}{e^{-TE/T_{2,water}}}, \quad [5]$$

with $E_{1,NAA} = e^{-TR/T_{1,NAA}}$, $E_{1,water} = e^{-TR/T_{1,water}}$, and assuming $\cos(\eta\alpha) \approx 0$ for the $\alpha = 90^\circ$ used in PRESS, an excellent approximation for the B_{1+} variations encountered in vivo. In contrast, this B_{1+} dependence remains for STRESS:

$$\frac{S_{NAA}^{(STRESS)}}{S_{water}^{(STRESS)}} = \frac{S_{0,NAA}}{S_{0,water}} \cdot \frac{\frac{1-E_{1,NAA}}{1-\cos(\alpha\eta)E_{1,water}}}{\frac{1-E_{1,water}}{1-\cos(\alpha\eta)E_{1,NAA}}} \cdot \frac{e^{-TE/2T_{2,NAA}} \sin^4\left(\frac{\eta\beta}{2}\right) e^{-TE/2T_{2,NAA} + \frac{1}{2}\sin^2(\beta\eta)}}{e^{-TE/2T_{2,water}} \sin^4\left(\frac{\eta\beta}{2}\right) e^{-TE/2T_{2,water} + \frac{1}{2}\sin^2(\beta\eta)}}, \quad [6]$$

where we approximated $e^{-TE/2T_1} \approx 1$ for NAA and water. Eq.[6] shows that for quantification STRESS requires a B_{1+} map in addition to T_1 and T_2 . Assuming a homogeneous B_{1+} ($\eta=1$) in Eq. [6] introduces an error, E , quantified by the ratio of the actual ($\eta \neq 1$) to assumed ($\eta=1$) signals:

$$E = \left(1 - \frac{S_{NAA}^{(STRESS)}}{S_{water}^{(STRESS)}} \cdot \frac{S_{water,\eta=1}^{(STRESS)}}{S_{NAA,\eta=1}^{(STRESS)}} \right) \cdot 100\%. \quad [7]$$

Its magnitude depends on TR, TE, T_2 and T_1 of the two species, η and β . For example, for STRESS-100 ($\alpha/\beta/\gamma=100^\circ/131^\circ/131^\circ$), TE=40 ms, $T_{2,NAA}=150$ ms, $T_{2,water}=80$ ms, $T_{1,NAA}=1200$ ms, $T_{1,water}=800$ ms, TR=1000 ms and 20% B_{1+} inhomogeneity ($\eta=0.8$), $E=2\%$. E rarely exceeds 5% for these parameters' range in vivo, on par with other confounds in ratio quantification (40).

As T_1 and T_2 relaxation is introduced, the maximum of the signal curve (Eq. [3]) as a function of the B_{1+} inhomogeneity, η , shifts slightly from the nominal B_{1+} , such that Eq. [2] no longer holds. However, the optimal η for the ranges of B_{1+} , T_1 and T_2 in vivo was found to be very close to 1.0, with deviations of only a few percent. Since STRESS already benefits from significant immunity B_{1+} variations, this shift is negligible in practice.

Other sources of artifacts must be kept in mind. For example, a time-dependent resonant frequency drift due to, e.g., eddy currents, will affect the transverse SE_{123} pathway between the second and third pulses, but leave the longitudinal STE_- untouched. Magnets susceptible to eddy currents should, therefore, apply pre-emphasis gradient pulses (41), or use field mapping for quality assurance (42). Our good spectral lineshapes in Figs. 5 and 8 show minimal to nonexistent eddy current effects. Another source of resonance frequency time-dependence is due to the spins' diffusion during spoiling gradients. This loss during a $\tau=10$ ms 10 mT/m spoiler, for pure water ($D \approx 2 \mu m^2/msec$) is

$\exp(-\frac{1}{3}\gamma^2 DG^2 \tau^3) \approx \exp(-10^{-4}) \approx 1$ (43), becoming even more negligible in vivo due to metabolites' lower diffusion coefficients (44). Moonen et. al. modeled the diffusion decay using a pair of Stejskal-Tanner gradient pulses and found that, except for very strong spoiling gradients and long echo times, the diffusion losses of STEAM were negligible (9).

Although STRESS reduces the in-plane nutations considerably, it increases the first pulse's flip angle, α , compared to PRESS and STEAM, leading to increased CSD in that direction and higher SAR. However, since α is kept closer to 90° than 180° , the increases will be small. E.g., using a peak B_1 of 1.0 kHz, the FWHM bandwidth of the SLR-designed first

pulse of the STRESS-110 ($\alpha=110^\circ$) was 3.2 kHz, versus 3.4 kHz of the PRESS SLR 90° , increasing the slice CSD by only 6%. Although the SAR of STRESS's 110° slice selection pulse was 20% higher than that of the 90° used in PRESS, STRESS's total SAR was 25% lower than PRESS in practice.

Conclusions

Simultaneous acquisition of the spin- and stimulated-echo pathways generates a family of sequences, dubbed STRESS, that combine the advantages of STEAM (low SAR, CSD, short TE) with the higher signal intensities normally associated with PRESS and the superior B_{1+} immunity associated with a CPMG train. When $\alpha=90^\circ$, $\beta=\gamma=180^\circ$, STRESS coincides with PRESS, but also properly combines the CPMG phase relation for greater B_{1+} immunity. When $90^\circ < \alpha < 128^\circ$, the sequence sacrifices some of the full spin-echo amplitude for a considerable reduction in SAR and in-plane CSD compared to PRESS. Although the results presented here focused on ^1H -MRSI, STRESS is equally applicable and effective for single-voxel ^1H -MRS. The modification suggested is simple, subtle and incorporate easily into existing PRESS or STEAM sequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Echo formations following three “hard” pulses with $\alpha=63^\circ$, $\beta=\gamma=126^\circ$. Shown is the magnetization’s real (blue, solid) and imaginary (red, dashed) components. No gradients are applied between pulses, with decay exclusively due to T_2^* . The echoes’ magnitudes are shown explicitly for the stimulated echo (STE₋) and doubly-refocused spin echo (SE_{123}). (a) Echo formations with the phases of the pulses all 270° , chosen to excite the magnetization onto the x-axis, using the left-hand rotation rule. Note that STE₋ and SE_{123} are out of phase. (b) Echo formations with phases set to $(270^\circ, 0^\circ, 0^\circ)$, obeying the CPMG phase condition (second and third pulses’ phases advanced 90° compared to the initial excitation). Note how the STE₋ and SE_{123} are both in phase. Furthermore, note that if we set $D_2=2D_1$, as in a CPMG sequence, the STE₋ and SE_{123} pathways would occur at the same time and would cancel out in (a), but add up in (b).

Fig. 2.

Flip angles and signal amplitudes for the STRESS family of sequences (See Table 2 for numerical values). Dashed line: the flip angle of the second and third VOI selection pulses ($\beta=\gamma$), as determined from Eq. [2], is plotted as a function of the flip angle of the first (α). Dotted line: the STRESS signal magnitude (Eq. [1]) at the echo time, as a function of α , neglecting relaxation. Unity signal corresponds to maximal signal intensity obtained using PRESS. A homogeneous B_{1+} field was assumed ($\eta=1$). Note that, as α is increased from 90°, β and γ decrease sharply, decreasing the relative SAR and CSD, but also the available signal intensity.

Fig. 3.

Magnitudes of the SE_{123} (blue, dashed) and STE_- (red, dotted) pathways, and their sum (green, solid), as a function of the B_{1+} (1 indicates no inhomogeneity), for three members of the STRESS family: (a) STRESS-90 ($\alpha/\beta/\gamma=90^\circ/180^\circ/180^\circ$); (b) STRESS-100 ($\alpha/\beta/\gamma=100^\circ/131^\circ/131^\circ$); (c) STRESS-110 ($\alpha/\beta/\gamma=110^\circ/108^\circ/108^\circ$). In all three cases, the combined signal represents the STRESS signal. (d) The signal-behavior of B_{1+} , shown for STRESS-90 (green, solid), STRESS-110 (black, dashed), STEAM (red, dot-dashed) and PRESS (blue, dotted), all scaled to unity to enable a fair visual performance comparison. Of the four,

PRESS is the least robust. STEAM and STRESS-110 are very similar. Note that the STRESS-110 curve is not perfectly symmetrical, although apparent only for very significant, $>45\%$, B_{1+} variation and for higher α -s (not shown). STRESS-90 is the most robust and is, in fact, equivalent to a PRESS with a properly implemented CPMG condition, *i.e.*, an in-phase, unspoiled stimulated echo pathway. Note that the immunity of STRESS family members B_{1+} variations improves as α decreases.

Fig. 4.

Sequences used. (a) A standard PRESS ($90_x^\circ - 180_x^\circ - 180_x^\circ$). Gray gradients represent spoilers, black are slice selection and dashed denote phase encoding. Also used: WS – Water Suppression, ADC – Analog to Digital Conversion. Shown are the spoiler gradient moments, set in the ratio $X:3X:2X$ to ensure all coherence pathways except for SE_{123} are dephased (see Table 1). (b) A “modified” CPMG-PRESS: ($90_x^\circ - 180_y^\circ - 180_y^\circ$), with inter-pulse timings set to $TE/4:TE/2:TE/4 = 1:2:1$. The spoiler gradients’ moments have also been redesigned as $X:2X:X$, which refocus both SE_{123} and STE_- pathways at TE . The constants

R_i ($i=x,y,z$) are the pulse rewinding moments, e.g., for STRESS $R_x=\gamma G_x T_{110}/2$, $R_y=\gamma G_y T_{108}/2$, $R_z=\gamma G_z T_{108}/2$.

Fig. 5. Phantom results: single voxel. Shown are PRESS (blue line) and STRESS-110 spectra (red line) from a $3 \times 3 \times 3 = 27 \text{ cm}^3$ voxel placed at the center of the phantom, shimmed to 4.5 Hz. Four different TEs are shown (40, 60, 100 and 144 ms). Also shown are zoomed-in spectra of the Lac region ($\times 4$ magnification) and the mI-Glu region ($\times 5$ magnification) for improved readability. The spectra are both normalized to the noise rms in a region free of metabolites. For the Cr, Cho and NAA methyl singlets, the numbers represent the ratio between the STRESS and PRESS SNR. These spectra illustrate the following: (i) the STRESS-110 SNR

is approximately 83% that of PRESS for $TE=40\text{ ms} \ll T_2$, in agreement with the theoretical prediction (see, e.g., Table 2). (ii) As $TE \sim T_2$, the SNR of STRESS-110, relative to PRESS, becomes even more pronounced, again as predicted by the theoretical calculations (Table 2). (iii) As TE progresses and approaches $1/J$, the J-coupled spectral patterns become more distorted compared to PRESS, a consequence of summing two pathways (STE_- and SE_{123}) having distinctly different J-coupling evolution.

Fig. 6.

Phantom results: multi-voxel. (a) Placement of phase-encoded acquisition matrix (dotted white lines), and the 100×100 mm² VOI (thick white line). Also outlined in the middle of the VOI are two voxels, shown in greater detail in (b). (b) Sample spectra from two central voxels for STRESS-110 (solid, black) and PRESS (dashed, red), for TE=40 ms, right-shifted by 12 Hz to help visualization. Noise is normalized to the same standard deviation, and both spectra share the same baseline and post-processing parameters. Note that STRESS and PRESS have comparable SNR. The small peak at 2.8 ppm is an artifact of unknown origins

which did not re-appear in subsequent scans. (c) Spectra from the vertical column of voxels (white arrow in (a)), comparing PRESS (left) and STRESS-110 (right), over 1.05 – 3.88 ppm range. Note, again, (i) the comparable SNR; and (ii) the increased CSD of, *e.g.*, choline in PRESS (carrier centered at 2.0 ppm): the Cho peak is shifted by about 2 voxels with respect to the NAA for PRESS, but only about half a voxel for STRESS-110. It should be emphasized that this comparison examines on the in-plane CSD, i.e. PRESS's 180° vs. STRESS-110's 108° pulses. The difference between the two approaches along the slice direction (not shown) is similar, with STRESS's 110° slice-selective pulse having about 6% higher CSD compared to PRESS's 90° pulse (see Discussion).

Fig. 7.

Phantom results: multi-voxel. Shown are SNR maps for NAA, Cho and Cr-CH₂ peaks (0 Hz, 150 Hz and 235 Hz off resonance), illustrating the reduction in the in-plane CSD attainable with STRESS-110 (left). Despite 25% less SAR than PRESS (middle), STRESS-110 CSD is approximately three times smaller than that of PRESS, in accordance with the in-plane pulses' BWs: 1 kHz for the latter, 3.15 kHz for the former. The difference in CSD is also seen in the 1D SNR profiles (right) taken through the set of voxels indicated by the dashed, yellow line, comparing STRESS (blue) with PRESS (red) SNR for each of

the three metabolites. The 1D SNR profiles also show the ~85% signal magnitude of STRESS compared to PRESS.

Fig. 8.

In-vivo results. (a) FOV (red grid) and VOI (white box) placement and CSI encoding grid for a supra-ventricular slice. (b) Plots of the SNR of NAA (top) and the choline resonance (bottom) along a column of voxels (dashed yellow box). The plots illustrate that, for NAA, the SNR of STRESS is on average 87% that of PRESS, while for Cho it is 89%, and 94% for Cr, in good agreement with the theoretical predictions, given the sample's T_2 and average deviation from nominal B_{1+} (Eqs. [3], [4] and Table 2). (c) Sample spectra from that column of voxels, shown for the 1.4 – 4.0 ppm range, illustrating the SNR and spectral

quality of STRESS-110 (at TE=40 ms and 27 ms) compared to PRESS (TE=40 ms). Note the increased in-plane CSD of PRESS, evident by the spatially “shifted” Cho and Cr singlets (arrows) with respect to the NAA at 2.01 ppm (on resonance).

Table 1

Any three pulses of α , β , γ nutation will generate nine transverse coherence pathways: three FIDs (FID_1 , FID_2 , FID_3); four spin echoes (SE_{12} , SE_{13} , SE_{23} , SE_{123}); and two stimulated echoes (STE_+ , STE_-). Here, FID_i stands for the FID created by the i^{th} pulse; SE_{ij} stands for the spin echo excited by the i^{th} pulse and refocused by the j^{th} pulse; and SE_{123} is the doubly refocused spin echo observed in the “standard” PRESS sequence. Each pathway’s amplitude and phase in the VOI is shown (ϕ_i is the phase of the i^{th} pulse; left-hand rotations were assumed). If a gradient having moment k_j is played after the j^{th} pulse, each pathway will experience a total gradient moment shown in the third column. Also shown are three spoiling schemes: “standard” PRESS and STEAM schemes suggested by Moonen *et al.* (6), designed to spoil all coherence pathways but SE_{123} or STE_- , and a “modified” CPMG-like scheme, which refocuses both SE_{123} and one of the stimulated echoes (STE_-). Refocused pathways are shaded.

Pathway's Name	Signal weighting in VOI	Signal Phase	Total Gradient Moment Experienced	PRESS $k_1=(1,1,1)$ $k_2=(2,2,0)$ $k_3=(1,1,-1)$	STEAM $k_1=(1,1,1)$ $k_2=- (4,4,4)$ $k_3=(1,1,1)$	STRESS $k_1=(1,1,1)$ $k_2=(2,2,2)$ $k_3=(1,1,1)$
FID_1	$\sin(\alpha)\cos^2\left(\frac{\beta}{2}\right)\cos^2\left(\frac{\gamma}{2}\right)$	ϕ_1+90°	$k_1+k_2+k_3$	(4,4,0)	(6,6,6)	(4,4,4)
FID_2	$\cos(\alpha)\sin(\beta)\cos^2\left(\frac{\gamma}{2}\right)$	ϕ_2+90°	k_2+k_3	(3,3,-1)	(5,5,5)	(3,3,3)
FID_3	$\cos(\alpha)\cos(\beta)\sin(\gamma)$	ϕ_3+90°	k_3	(1,1,-1)	(1,1,1)	(1,1,1)
SE_{12}	$\sin(\alpha)\sin^2\left(\frac{\beta}{2}\right)\cos^2\left(\frac{\gamma}{2}\right)$	$-\phi_1+2\phi_2-90^\circ$	$-k_1+k_2+k_3$	(2,2,-2)	(4,4,4)	(2,2,2)
SE_{13}	$\sin(\alpha)\cos^2\left(\frac{\beta}{2}\right)\sin^2\left(\frac{\gamma}{2}\right)$	$-\phi_1+2\phi_3-90^\circ$	$-k_1-k_2+k_3$	(-2,-2,-2)	(-4,-4,-4)	(-2,2,2)
SE_{23}	$\cos(\alpha)\sin(\beta)\sin^2\left(\frac{\gamma}{2}\right)$	$-\phi_2+2\phi_3-90^\circ$	$-k_2+k_3$	(-1,-1,-1)	(-3,-3,-3)	(-1,1,1)
SE_{123}	$\sin(\alpha)\sin^2\left(\frac{\beta}{2}\right)\sin^2\left(\frac{\gamma}{2}\right)$	$\phi_1-2\phi_2+2\phi_3+90^\circ$	$k_1-k_2+k_3$	0	(-2,-2,-2)	0
STE_+	$\frac{1}{2}\sin(\alpha)\sin(\beta)\sin(\gamma)$	$\phi_1-\phi_2+\phi_3+90^\circ$	k_1+k_3	(2,2,0)	(2,2,2)	(2,2,2)

Pathway's Name	Signal weighting in VOI	Signal Phase	Total Gradient Moment Experienced	PRESS $k_1=(1,1,1)$ $k_2=(2,2,0)$ $k_3=(1,1,-1)$	STEAM $k_1=(1,1,1)$ $k_2=- (4,4,4)$ $k_3=(1,1,1)$	STRESS $k_1=(1,1,1)$ $k_2=(2,2,2)$ $k_3=(1,1,1)$
STE ₋	$\frac{1}{2}\sin(\alpha)\sin(\beta)\sin(\gamma)$	$-\phi_1+\phi_2+\phi_3-90^\circ$	$-\mathbf{k}_1+\mathbf{k}_3$	$(0, 0, -2)$	0	0

Table 2

Relative signal amplitudes in homogeneous ($\eta=1.0$) and inhomogeneous ($\eta=0.75, 1.25$) B_{1+} field, for different STRESS family members (Eqs. [3] and with $S_0=1$ and $TR=\infty$), with PRESS and STEAM for comparison. Cases for which STRESS equals or exceeds PRESS's SNR are shaded. Three cases are considered: no relaxation, and "typical" in-vivo relaxation parameters with "short" ($TE=40$ ms) and "long" ($TE=144$ ms) echo times. Here, α , β and γ are the flip angles of the first, second and third VOI localization pulses. As α increases, the signal amplitude decreases; on the other hand, β and γ also decrease, reducing the relative SAR and increasing the pulses' BWs (reducing in-plane CSD). Thus, one can trade-off SAR and CSD on the one hand and SNR on the other. The $\alpha>115^\circ$ cases begin performing unfavorably and should be avoided in practice. Note that, when $\alpha=90^\circ$, the STRESS sequence coincides with PRESS, but has the additional B_{1+} immunity of the CPMG condition, making it considerably more robust to B_{1+} inhomogeneities than a regular PRESS (see Fig. 3a). For higher flip angles ($\alpha>90^\circ$), the $\eta=0.75$ and $\eta=1.25$ cases exhibit some asymmetry, due to the fact that the optimal values of β and γ were determined using Eqs. [1] and [2] assuming no relaxation. Also note that, when relaxation is taken into effect, STRESS suffers an even smaller penalty to SNR compared to PRESS, and can sometimes even surpass it, particularly for long TEs, as evident from the table. This is a result of the shorter effective echo time of the stimulated echo pathway.

α (deg.)	$\beta=\gamma$ (deg.)	Signal ($T_1=T_2=\infty$)			Signal ($T_1=1200$ ms, $T_2=150$ ms, $TE=40$ ms)			Signal ($T_1=1200$ ms, $T_2=150$ ms, $TE=144$ ms)		
		$\eta=1$	$\eta=0.75$	$\eta=1.25$	$\eta=1$	$\eta=0.75$	$\eta=1.25$	$\eta=1$	$\eta=0.75$	$\eta=1.25$
90	180	1.0	0.9	0.9	0.77	0.71	0.71	0.38	0.39	0.39
95	144	0.99	0.83	0.88	0.77	0.68	0.67	0.41	0.40	0.34
100	131	0.95	0.79	0.82	0.76	0.65	0.63	0.42	0.40	0.32
105	119	0.90	0.73	0.75	0.73	0.61	0.58	0.42	0.38	0.31
110	108	0.83	0.66	0.66	0.67	0.55	0.52	0.40	0.35	0.29
115	96	0.72	0.57	0.55	0.59	0.48	0.44	0.37	0.31	0.26
120	80	0.57	0.44	0.41	0.48	0.37	0.34	0.30	0.24	0.21
125	62	0.37	0.28	0.25	0.32	0.24	0.21	0.21	0.16	0.13
PRESS:										
90	180	1.0	0.67	0.67	0.77	0.52	0.52	0.38	0.26	0.26
STEAM:										
90	90	0.5	0.39	0.39	0.43	0.34	0.34	0.29	0.23	0.23