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Water suppression in the human brain with hypergeometric RF pulses for single- and multi- voxel MR spectroscopy

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Abstract

Purpose—To develop and investigate a novel water suppression sequence with hypergeometric pulses at 3T.

Methods—Simulations were used to optimize the delays and amplitudes of five hypergeometric prepulses to minimize the residual water over a range of T_1 and B_1 values. Single voxel data with hypergeometric water suppression (HGWS) prepulses were acquired in the centrum semiovale, two parietal regions, and insula of seven subjects, and compared to VAPOR water suppression. MR spectroscopic imaging (MRSI) data using both VAPOR and HGWS prepulses were also collected and compared. Water suppression performance was calculated as the residual water peak height relative to the unsuppressed water peak. MRSI voxel-by-voxel comparison was performed by calculating the ratio between HGWS and VAPOR residual water peaks.

Results—In simulations, HGWS and VAPOR are insensitive to B_1 and water T_1 variations, but with no B_1 variation, HGWS has a lower average residual water fraction (0.0033) than that of VAPOR (0.0092). In single voxel acquisitions, HGWS performs better than VAPOR in all regions with a 2.3–5.7-fold lower residual water. In MRSI acquisitions, HGWS performs on average 2.3-fold better than VAPOR in 98.9% of the voxels.

Conclusion—HGWS provides better water suppression than VAPOR in both single-voxel and multi-voxel acquisitions with a shorter sequence duration.

Introduction

In vivo ^1H magnetic resonance spectroscopy (MRS) and spectroscopic imaging (MRSI) allow for the non-invasive detection of a variety of neurochemicals within the brain. These

endogenous compounds, however, are present in significantly lower concentrations than water, making their detection and quantification difficult without the use of pulse sequences that suppress the water signal. A number of techniques have been developed to separate the metabolite signals from the more abundant water signal, using either specialized acquisition techniques such as metabolite cycling (1), water suppression (2–4) and/or post-processing techniques to filter out the water signal (5). The most commonly used method is the inclusion of a water suppression module to saturate the water signal before spectral acquisition (3, 4).

Most suppression techniques are based on the difference in chemical shift between the water and metabolite signals. One of the simplest and earliest water suppression methods, CHESS (6), used a single, frequency selective, saturation pulse applied to water prior to excitation and acquisition of the free induction decay. Another type of water suppression, referred to as MEGA (7) or BASING (8), uses selective spin-echo dephasing to remove the water signal by applying a selective refocusing pulse in conjunction with bipolar crusher gradients to dephase the water signal while rephrasing the metabolites. Other methods use either saturation or inversion pulses, where the delay after the RF pulse is optimized to minimize the longitudinal magnetization of water based on its T_1 relaxation time (9). Methods such as the WET (3) or VAPOR (4) sequences apply frequency-selective pre-saturation pulses in conjunction with crusher gradients to dephase and consequently suppress the water signal while leaving the magnetization of the metabolites untouched. An important component of these sequences is compensation for variations in the transmitter B_1 field (and/or miscalibrations of the RF flip angle) and a range of water T_1 s, by applying multiple pre-saturation pulses and optimizing their delays and flip angles. The VAPOR sequence (4, 10) uses either seven or eight RF pulses of variable flip angles to make the sequence B_1 and T_1 insensitive. This results in highly effective water suppression and is currently the most commonly used water suppression sequence in single voxel (SV) MRS. A disadvantage of VAPOR, however, is that it has a long duration of ~750 ms which prohibits its use in short TR sequences, for instance fast MRSI (11).

In this article, a new water suppression sequence with one third of the duration of VAPOR is described. This sequence applies five frequency-selective hypergeometric saturation pulses, RF pulses with an asymmetric amplitude waveform that are closely related to the widely used hyperbolic secant pulses, (2, 12–15) at variable flip angles and delays that were optimized to minimize the residual water signal through iterative, numerical simulations over a range of B_1 variations and water T_1 values. The performance of hypergeometric water suppression (HGWS) was compared to VAPOR in vivo for both single voxel and multi-voxel acquisitions.

Methods

Pulse Sequence Design

The HGWS sequence was designed with consideration to both the longitudinal relaxation (T_1) of water, which varies depending on the tissue type (including possible lesions, and cerebrospinal fluid (CSF)), and the inhomogeneity in the RF field which is influenced by both transmit RF coil geometry and loading. To account for the tissue dependence of the

water longitudinal relaxation, the sequence must null the longitudinal magnetization of a large range of T_1 values. In the human brain at 3T, these values range from 800 ms in white matter to 4100 ms in CSF (16–18). In addition, the sequence must be insensitive to RF field variations to avoid flip angle variations which can affect the effectiveness of water suppression sequence.

Amplitude- and frequency-modulated hypergeometric (HG) RF pulses were chosen as the frequency selective pulses (2, 12, 13). Hypergeometric RF pulses can be designed with an asymmetric frequency profile that contains one edge with a transition width significantly narrower than the other edge. Since most of the resonances of interest in the proton spectrum are upfield from water, the pulse can be designed with a sharp cutoff upfield and a broader transition band on the downfield side.

These hypergeometric RF pulses were created using the following pulse modulation functions for the effective field vector components in Eqn. 1 in Rosenfeld et al. (13):

$$\begin{aligned}\omega_x &= \omega_1 = \Omega_0 \frac{\sqrt{z(1-z)}}{az+b} \\ \omega_y &= 0 \\ \omega_z &= \omega - \omega_0 = \frac{cz+d}{az+b} - \omega_0 \quad [1] \\ t &= \ln\left(\frac{z^b}{(1-z)^{a+b}}\right) \\ z &\in [0, 1], t \in [-\infty, \infty]\end{aligned}$$

where ω_x and ω_y is in rad/s. To create a 30 ms hypergeometric pulse with a sufficiently small transition bandwidth (37 Hz) so that no metabolite spins downfield of 4.1 ppm would be affected, the following parameters were used: $a = 4$, $b = 0.5$, $c = -4$, $d = 3.5$, and $\Omega_0 = 8$ ($\omega_{1max} = 0.2$ kHz) and the waveform was sampled to 1172 points with evenly spaced time points. The pulse was truncated at .1% of the peak amplitude to the left of the peak amplitude and at 7.9×10^{-6} % to the right of the peak amplitude.

Hypergeometric pulses were previously used to create a dual-band water and lipid suppression sequence for MR spectroscopic imaging (HGDB) (2). The sequence developed here differs in that it uses single band HG pulses only for water suppression, and does not include a 100 ms delay which was previously used for 8 outer-volume suppression (OVS) pulses. The pulse amplitudes and delays of the new HGWS sequence were optimized using the water suppression portion of the HGDB sequence (2) as starting values. These starting amplitudes and delays were 1.08 μ T/50 ms, 2.54 μ T/35 ms, 1.09 μ T/100 ms, 1.24 μ T/35 ms, and 3.08 μ T/18.5 ms. The optimization searched for the combination of delays and pulse amplitudes that best suppressed the water signal over a range of T_1 and B_1 variations. Both the amplitudes and delays of the new HGWS sequence were optimized using simulated annealing in two dimensions in MATLAB (19) using an analytical predictor of the adiabatic pulse response (12) rather than a full pulse simulation. This optimization covered a range of T_1 values from 500 ms to 3000 ms and a max B_1 range of 200 Hz to 300 Hz (≈ 4.7 to 7.0

μT). The performance of the optimized sequence was then simulated over a range of T_1 values from 500 ms to 5000 ms and a B_1 variance of -25% to 25% of the nominal B_1 strength of $5.18 \mu\text{T}$ (.22 kHz, the point of zero B_1 variance) and compared to a VAPOR water suppression sequence with sinc-Gaussian pulses that had the following flip angles and delays: 90° , 150 ms; 90° , 100 ms; 160.2° , 122 ms; 90° , 105 ms; 160.2° , 102 ms; 90° , 61 ms; 160.2° , 67 ms; and 160.2° , 28.5 ms. The total duration of the VAPOR sequence was 750 ms. Crusher gradients after each RF pulse were also simulated and assumed to perfectly suppress all transverse magnetization. MATLAB was used to perform all computations.

In Vivo Experiments

All experiments were performed on a Philips Achieva 3T scanner using a body coil for transmit and a 32-channel head coil for receive. All subjects underwent a 3D T_1 -weighted MPRAGE scans with 1 mm isotropic resolution which was used to plan MRS scan voxel locations and also in data processing to estimate gray matter (GM), white matter (WM) and CSF content of each voxel by segmenting these images using SPM. Prior to MRS, field homogeneity was adjusted up to 2nd order. No optimization of RF pulses flip angles was performed for the water suppression pulses. HGWS and VAPOR water suppression sequences were added as prepulses to the PRESS sequence and compared in both single voxel experiments and multi voxel experiments. For the VAPOR sequence, crusher gradients with a 10 ms duration were applied after RF pulse 1 – 7 and a crusher gradient with a 5 ms duration was added after the last pulse. These gradients had the following strengths (mT/m) in the x, y, and z direction: (10,0,0), (0,10,0), (0,0,10), (9,0,0), (0,8,0), (0,0,7), (8,0,0), (0,10,10). Crusher gradients with a 3 ms duration were added after each RF pulse in the HGWS sequence with gradient strengths (mT/m) in the x, y, and z direction: (10,0,0), (0,10,0), (0,0,10), (9,0,0), (0,8,0).

Single voxel experiments were performed 7 healthy adults (3 female; age 27 ± 2 years) in $(3 \text{ cm})^3$ voxels in the centrum semiovale (CSO), midline parietal region, and insula with 80 signal averages. An additional single voxel experiment was performed in a $(4.5 \text{ cm})^3$ midline parietal region with 40 signal averages. Additional scan parameters included an echo time of 35 ms, a repetition time of 2 s, a spectral bandwidth of 2 kHz, and 2048 points. Water unsuppressed references were also collected with 8 signal averages and water suppression factors were calculated as the peak height of the residual water peak divided by the peak height of the unsuppressed water signal. To test for differences in water suppression effectiveness between the two methods, two-tailed paired t-tests were performed with statistical significance defined as $p < 0.05$.

Multi voxel experiments were performed in 6 healthy adults (3 female; age 27 ± 2 years) at an echo time of 41 ms and a repetition time of 1.5 s for a total scan time of 14 min and 52 sec. The PRESS sequence used frequency modulated excitation pulses with a peak B_1 of $13.5 \mu\text{T}$ and a bandwidth of 4.26 kHz. One 20 mm thick slice was recorded with a field of view of $180 \times 210 \text{ mm}$ and a volume of interest of $80 \times 100 \text{ mm}$ sampled with a matrix size of 18×21 . This resulted in a nominal in-plane resolution of $10 \times 10 \text{ mm}$ and a voxel size of 2 cm^3 . Corresponding water-unsuppressed reference MRSI scans were also acquired with

the same scan parameters for calculation of water suppression factors. To suppress unwanted signals outside the VOI in the MRSI experiments, four OVS pulses were also applied.

Results

Simulation Results

The optimized sequence with a total duration of 245 ms is shown in Figure 1. This sequence had the following amplitudes and delays: 2.07 μ T/58.2 ms, 2.63 μ T/58.2 ms, 1.9 μ T/36.8 ms, 2.36 μ T/39.1 ms, 5.18 μ T/49.2 ms. Figure 2a shows the simulated absolute residual magnetization as a function of T_1 and B_1 for both the HGWS sequence and the VAPOR sequence. In both sequences, the residual Z-magnetization does not vary substantially as a function T_1 or B_1 except at low T_1 values and large B_1 variations. Consequently, the standard deviation of the residual longitudinal magnetization is similar for both VAPOR and HGWS at 0.0057 and 0.0066 respectively. However, HGWS has better overall water suppression factors than VAPOR over the range of T_1 s and B_1 values simulated; the average residual water suppression fraction is 0.0033 for HGWS and 0.0092 for VAPOR. Figure 2b plots the frequency profile of the HGWS sequence as a function of B_1 and Figure 2c shows a close-up of the frequency profile ~ 200 Hz about the water frequency (0 Hz); it can be seen that the shape of the transition band changes slightly with B_1 (with increasing bandwidth as B_1 increases), however, even at the highest B_1 value, metabolite resonances such as the *myo*-inositol peak at 4.06 ppm will remain unaffected by the HGWS sequence.

The specific absorption rate (SAR) of the PRESS sequence with VAPOR and HGWS prepulses were comparable at 0.20 W/kg and 0.23 W/kg respectively.

Single Voxel Experimental Results

The four brain regions measured contained different amounts of gray and white matter (table 1). HGWS showed significantly better water suppression factors than VAPOR in all four regions ($p < 0.001$) for all subjects (figure 3). The improvement ranged from 2.7-fold better water suppression in the insula to 5.6-fold better water suppression in the large parietal region. Taking tissue composition into consideration (table 1), the HGWS sequence performed best in the regions with more white matter. HGWS performed better for the large parietal voxel and CSO, which have more white matter than the for small parietal region with more gray matter ($p < 0.05$). In addition, the HGWS residual water signal was greater in the gray matter-rich insula than in the large parietal region with $p < 0.01$. These differences in water suppression can be seen qualitatively in the representative water peak from one subject in each of the regions (figure 4). As can be seen in the rightmost panel in figure 4, the different water suppression methods lead to differences in the baseline of the acquired spectra. However, the metabolite peak intensities are equivalent between the two methods, thus demonstrating that the HGWS sequence does not lead to a loss in signal of other compounds upfield from the 4.68 ppm water peak. In particular, it can be seen that the signal intensity of the *myo*-inositol peak at 4.06 ppm which is close to the water peak at 4.68 ppm is preserved, demonstrating that the transition bandwidth of the hypergeometric pulses is sufficiently small.

Multi Voxel Experimental Results

Figure 5, shows the PRESS volume of interest, an overlay of a map of the residual water for both the HGWS and VAPOR sequence as well as the HGWS/VAPOR residual water ratio in each voxel. The blue, green, and orange box indicate 3x3 voxel areas with nine example spectra where the mean HGWS/VAPOR residual water ratio is 0.83, 0.41, and 0.068 respectively. It can be seen that across the volume of interest, the residual water peak is lower in the HGWS sequence than in the VAPOR sequence. This is reflected in the HGWS/VAPOR residual water ratio map where most of the ratios were below 0.8. Figure 6 shows the residual water peaks and spectra from the regions of interest in figure 5. It can be seen that the spectra have equivalent signal intensity indicating that the HGWS sequence does not lead to metabolite signal loss relative to VAPOR, similar to the single voxel experiments. Figure 7a shows a histogram of the HGWS/VAPOR residual water fraction as well as the mean values across the six subjects. It can be seen that the distribution of the residual water fractions for HGWS is skewed towards lower values with the mean residual water fraction 2.3 times lower when using HGWS versus VAPOR. The mean residual water fraction over all the voxels for each subject was 0.0044 for HGWS and 0.0099 for VAPOR and are in agreement with simulation values of 0.0033 and 0.0092 respectively. It can also be seen in figure 7b that across subjects, the HGWS/VAPOR residual water ratio is less than one in 98.9% of the voxels, indicating that the HGWS sequence performs better than the VAPOR sequence in most voxels across subjects. In addition, 80% of the voxels have a HGWS/VAPOR residual water ratio of 0.6 or less. The B_0 inhomogeneity, as calculated by the deviation of the residual water peak frequency from 4.68 ppm, was 4.7 Hz (average) $\pm$ 2.9 Hz (standard deviation).

Discussion

Sufficient water suppression is crucial for both single voxel and multi voxel spectroscopic acquisitions as sub-optimal water suppression can lead to errors in metabolite quantification. In this paper, HGWS, a new method for water suppression, is introduced, and compared to VAPOR, which is currently a very widely used (the 'gold standard') water suppression sequence for in vivo brain spectroscopy. This current study extends on our previous work on dual water and lipid suppression with hypergeometric pulses (HGDB) in the following ways: (a) it builds a new basic RF pulse with a sharper transition bandwidth that does not affect the metabolite spins (b) it removes the lipid suppression portion of the sequence, and re-optimizes it for water suppression only. A limitation of the HGDB sequence is that the inclusion of frequency-selective lipid suppression prepulses can impede detection of compounds with resonances around the frequency of the lipid prepulses such as lactate, alanine, and leucine. In addition, the inclusion of a 100 ms delay within the sequence for the inclusion of lipid OVS pulses limits the sequence from being completely optimized for water suppression. Thus, a sequence optimized for more effective water suppression only is especially useful for single voxel and PRESS-MRSI acquisitions where the region of interest is far from the lipid-rich peri-cranial regions.

Overall, this optimized sequence is robust, of relatively short duration, and performs better than the VAPOR sequence, despite having fewer RF pulses. Simulations demonstrate that

the sequence is relatively insensitive across the range of T_1 and B_1 variations likely to be found in vivo in the human brain at 3T. This was confirmed in experiments in vivo for both single-voxel and multi-voxel measurements. In addition, this sequence is only 245 ms long, a considerably shorter duration than VAPOR which has eight RF pulses and delays resulting in duration of over 700 ms long. This water suppression effectiveness and reduced duration relative to VAPOR makes the sequence especially suited for fast MRSI sequences where insensitivity to B_1 inhomogeneity and minimization of the presaturation sequence duration is necessary. For example, a shorter presaturation sequence would allow for more slices to be incorporated into a pulse repetition time of a multislice MRSI acquisition (2).

Considering the small region from which measurements were acquired, differences in the HGWS water suppression factors in single voxel acquisitions is not likely to be driven by either B_0 or B_1 inhomogeneity, but T_1 differences arising from different tissue types with HGWS performing better in areas with higher ratios of white to gray matter. Unlike single voxel acquisitions, however, differences in residual water fractions in MRSI acquisitions appear to be tissue-independent. In the multi-voxel acquisitions, areas with low and high water suppression effectiveness have a large heterogeneity of different tissue types. Thus, the differences in water suppression effectiveness is likely driven by RF field inhomogeneity. Even with this additional confounding factor, however, HGWS performs better than VAPOR in most voxels across subjects. In the presence of significant B_0 inhomogeneity, HGWS is also expected to perform better than VAPOR. This is due to the flat inversion profile of the HGWS sequence upfield from the resonant frequency of water (4.68 ppm) relative to the VAPOR sequence which uses more selective sinc-Gaussian editing pulses. This would lead to better water suppression in locations with B_0 inhomogeneities that shift water towards higher frequencies.

In this work, the basic water suppression sequence for VAPOR and HGWS were compared without a separate prospective flip angle optimization for the water suppression sequence prior to acquisition. As commonly performed on many scanners, such optimizations result in a scaling of all water suppression pulses by a single correction factor. In principle, this procedure should not be necessary as flip angle calibration on clinical 3T scanners is usually very accurate, however water suppression factors may be improved by ‘tuning’ the flip angles to minimize the water signal according to the tissue/CSF composition of individual voxels. It is likely that the experimental performance of both sequences compared here could have been improved by such an empirical optimization. However, performing this optimization is often very time-consuming, so sequences that give adequate suppression without optimization are preferable.

In summary, a novel water suppression method using five hypergeometric RF pulses and delays is proposed and evaluated. The sequence is significantly shorter than the VAPOR water suppression sequence making it especially suitable for use in fast MRSI sequences, and performs significantly better in vivo for both single voxel and multi voxel acquisitions.

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Figure 1.

(a) Amplitude and frequency modulation functions for the HG pulses, (b) schematic diagram of the full HGWS sequence showing the delays (ms) and amplitudes (μT) of each RF pulse. The total duration of the HGWS water suppression sequence is 245 ms which is significantly shorter than the total duration of 750 ms for VAPOR (not shown).

Figure 2.

(a) Simulated residual water magnetization fraction (see color bar for scale) as a function of T_1 and B_1 for VAPOR (left) and HGWS (right). (b) Calculated residual Z-magnetization as a function of frequency offset using a fixed T_1 value of 1150 ms for a range of B_1 values between + and - 25% deviation from the nominal B_1 . (c) Close-up of the residual Z-magnetization as a function of frequency offset from (b) about the transition region. The spectral positions of water and *myo*-inositol (mI) at 3T are indicated in the figure.

Figure 3.

In vivo single voxel water suppression factors (residual water fraction) calculated as the peak height of the residual water over that of the unsuppressed water averaged across subjects. In all four brain regions (large and small parietal voxels, centrum semiovale (CSO) white matter, and insular cortex), the HGWS sequence gave a significantly ($p < 0.001$) lower residual water fraction than VAPOR.

Figure 4.

Voxel placements of in vivo single voxel acquisitions in all four regions overlaid on T₁-weighted axial and coronal images as well as representative water peaks, and spectra from each location for both HGWS and VAPOR sequences. The residual water from the VAPOR sequence has a visibly higher peak than HGWS while the metabolite spectra are qualitatively equivalent between the two methods, although differences in spectral baselines can be observed, most notably for the large parietal voxel. The residual water peaks are plotted with a vertical scale 10 times that of the metabolite spectra.

Figure 5.

Volume of interest of the in vivo MRSI acquisitions, representative residual water fraction maps, and a representative residual water peak ratio map of HGWS to VAPOR overlaid on a T_1 -weighted axial image. The colored boxes represent 3×3 voxel areas of low (orange), medium (green), and high (blue) HGWS to VAPOR ratios. The average residual water ratios for these areas are below the T_1 -weighted images and are 0.068, 0.41, and 0.83 respectively.

Mean HGWS/VAPOR residual water ratio: 0.068, 0.41, 0.83

Figure 6.

The residual water peaks (left three columns) and metabolite spectra (right three columns) for the regions of interest shown in figure 5. The residual water peaks are plotted with a vertical scale 16 times that of the metabolite spectra. Although the relative HGWS to VAPOR residual water ratio varies significantly, across the volume of interest, the metabolite spectra between the two water suppression methods are qualitatively equivalent.

Figure 7.

(a) Distribution of the residual water fractions in the MRSI acquisitions for both HGWS and VAPOR across subjects. The average residual water fraction for HGWS is 0.0044 which is less than half of the average residual water fraction of 0.0099 for VAPOR. (b) The residual water ratio of HGWS to VAPOR across subjects. Ratios less than one are voxels in which the HGWS sequence performs better than VAPOR. HGWS performs better than VAPOR in 98.9 percent of the voxels.

Table 1
Tissue composition of the four single voxel locations (mean $\pm$ SD)

Tissue composition of all four single voxel regions showing the percentage of white matter (WM), gray matter (GM), and cerebral spinal fluid (CSF) in each voxel. The CSF volume makes up a small fraction of the voxels and do not vary significantly between regions. The small parietal region and insula region have significantly more gray matter and less white matter than the centrum semiovale and large parietal region.

	WM (%)	GM (%)	CSF(%)
Parietal-small	35.3 $\pm$ 3.5	54.1 $\pm$ 3.0	10.7 $\pm$ 4.0
Parietal-large	50.3 $\pm$ 3.5	37.9 $\pm$ 2.0	11.8 $\pm$ 4.3
CSO	73.4 $\pm$ 2.9	21.4 $\pm$ 3.0	5.2 $\pm$ 1.8
Insula	33.5 $\pm$ 4.4	59.2 $\pm$ 1.7	7.3 $\pm$ 3.9