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Sequence design and evaluation of the reproducibility of water selective diffusion weighted imaging of the breast at 3T

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Abstract

Diffusion measurements derived from breast MRI can be adversely affected by unwanted signals from abundant fatty tissues if they are not suppressed adequately. To minimize this undesired contribution, we design and optimize a water selective DWI sequence, which relies on spectrally selective excitation on the water resonance, obviating the need for fat suppression. As this method is more complex than standard DWI methods, we also report a test-retest study to evaluate its reproducibility. In this study, a spectrally selective Gaussian pulse on water resonance is combined with a pair of slice selective adiabatic refocusing pulses for water only DWI. Field-map based shimming and manual determination of the center frequency are used for water selection. The selectivity of the excitation pulse is optimized by a spectrally selective spectroscopy sequence based on the same principles. A test-retest study of 10 volunteers in two separate visits is used to evaluate its reproducibility. Our results from all subjects show high quality diffusion weighted images of the breast without fat contamination. Mean ADC values for $b = 0$, 600 s/mm^2 and $b = 50$, 600 s/mm^2 all show good reproducibility as 95% confidence intervals (CI) of the apparent diffusion coefficient values are $4 \times 10^{-5} \text{ mm}^2/\text{s}$ and $5 \times 10^{-5} \text{ mm}^2/\text{s}$ and repeatability values are 1.09×10^{-4} and 1.31×10^{-4} , respectively. In conclusion, water selective DWI is a feasible alternative to standard methods of DWI based on fat suppression. The added complexity of the method does not compromise the reproducibility of diffusion measurements in the breast.

Keywords

apparent diffusion coefficient; reproducibility; breast; spectrally selective

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Introduction

The diffusion of water molecules in biological tissues reflects microscopic properties of cells (1,2). Its role as a contrast mechanism, in addition to proton density and relaxations (T_1 and T_2), has been firmly established in magnetic resonance imaging (MRI) (3,4). Results of diffusion weighted imaging (DWI) can be quantified with apparent diffusion coefficient (ADC) whose clinical value has been demonstrated in the evaluation of cerebral ischemia (5,6) as well as studies of cancer. In particular, the ADC has been shown to indicate cell membrane integrity and tumor cell density (3,7). Measurements of the ADC are valuable for both the diagnosis and monitoring (8-13) of therapy response in cancer. In the diagnostic setting, higher ADC values are frequently seen in benign lesions when compared to malignant lesions (14,15). In the prognostic setting, loss of tumor cells and an increase of the extracellular space induced by neoadjuvant chemotherapy (NAC) or radiation therapy has been linked to higher ADC values during treatment (4). Furthermore, an early increase in ADC in locally advanced breast cancer may be a valuable predictor of positive outcome of NAC (12). Compared to other quantitative imaging methods frequently employed for evaluating breast cancer, such as dynamic contrast enhanced (DCE) MRI, DWI does not require an injection of a contrast agent. In addition, it can be readily implemented on any MRI platform with little or no software modification (2).

Translating DWI from the brain to the body faces significant challenges including respiratory and cardiac motion as well as more heterogeneous distribution of tissues. In the specific application of breast MRI, unwanted signals from abundant fatty tissue can contaminate DWI measurements if not suppressed adequately. This can be particularly troublesome in the context of monitoring treatment response as patients often lose weight in the course of a treatment so significant changes in fatty tissues may occur and potentially contaminate the change of ADC measurement from tumor cells. Despite continued development and optimization of fat suppression techniques (16), residual fat signals can still present ghosting artifacts in diffusion weighted images. This issue is more prominent at 3T (and higher fields) when B_1 variation across a patient's torso compromises the accuracy of the suppression pulses and therefore leads to inhomogeneous fat suppression. In fact, a meeting report sponsored by the National Institutes of Health (NIH) (2) identified this issue and pointed out a solution candidate as "using water excitation as a method for fat suppression". This concept has previously been implemented using binomial pulses (17) in musculoskeletal (MSK) imaging. For breast imaging, DCE-MRI is the first application where water selective excitation was demonstrated to be superior to conventional fat suppression (18). However, since background subtraction is routinely performed for clinical DCE-MRI to remove unenhanced tissue signals including fat, water selective excitation does not seem to be most urgent for clinical DCE-MRI (though, for quantitative DCE-MRI, this will be needed when background subtraction is imperfect due to inconsistent fat suppression, pixel values from enhancing regions may be affected). DWI, as well as other MR modalities such as MR spectroscopy (19,20) and chemical exchange saturation transfer (CEST) (21,22), are often more severely compromised by poor fat suppression that requires better solutions.

Recently, we demonstrated a systematic implementation of water selective excitation for multi-modal MRI and MRS of the breast (23). Instead of relying on spectral spatial excitation pulses, our methods consist of frequency selective excitation for water selection and slice selective refocusing pulses for spatial selection. This common approach to separate spectral and spatial selections was made possible by spin echo (SE) type sequences including SE, turbo spin echo (TSE), and point resolved spectroscopy (PRESS). Very recently, various groups demonstrated spin echo based spectrally selective MRI and MRS in a wide range of areas including ultra high field MRS (24), multi-nuclear MRI (25) and MRS (26). However, none of the existing reports (17,27-29) have addressed a central issue of the general approach of water selective excitation: although it is proven to be superior to conventional fat suppression, it is also more complicated in sequence design and implementation. In this report, we present our sequence design of water selective DWI and a subsequent test-retest study (30) to investigate if the added complexity of this method compromised its reproducibility.

Materials and Methods

Spectrally selective excitation in a single shot DWI sequence was implemented on a 3T whole body scanner with a 16 channel phased array breast coil and 2-channel multi-transmit (Achieva, Philips Healthcare, Best, the Netherlands; Mammotrak, Invivo, Gainesville, FL). Unlike the gradient echo based approach (18), where the only RF pulse was modified to be spectrally *and* spatially selective, the SE based sequence allowed us to design water selective DWI with a frequency selective excitation pulse and slice selective refocusing pulses (Figure 1). Specifically, a Gaussian pulse with a bandwidth (BW) of 213 Hz was combined with one pair of adiabatic full passage (AFP) pulses (31) (5.8 ms duration, 180° and 2.5 kHz BW). As the frequency selective 90° pulse excites water signal in the entire ROI and the slice selective 180° pulses refocus one slice, crushers gradients were increased to remove water signal from outside the slice. The rest of the parameters were: # of slice = 1, TE/TR = 76 ms/1000 ms, slice thickness = 3 mm, FOV = (192 mm)² (FH×AP), resolution = (2 mm)², b-values = 0, 50, 600 s/mm², NSA=10, scan time = 1:41 min. No motion correction was applied. The parameters of the AFP refocusing pulses were determined according to previous applications of such pulses in spectroscopic sequences (32,33). The MRS sequence at 3 T (33) used a duration of 5.0 ms with peak B_1 of 17 μ T. With our peak B_1 of 13.5 μ T, we used the duration of 5.8 ms for this DWI sequence to maintain adiabaticity. A pair of these pulses resulted in a small increase in echo time from 66 ms to 76 ms.

The water selective DWI method designed here depends on accurate shimming and center frequency determination. To achieve this goal consistently, a unilateral, sagittal 3D phase map acquisition (34) was prescribed to cover the breast. The scanner's automatic volume shimming was used for this acquisition that consisted of a 3D fast gradient echo sequence with two echo times of 4.6 ms and 6.9 ms. The other parameters were: FOV = 16 cm³, voxel size = 3 mm³, imaging matrix = 64³, TR = 11 ms, and a total scan time of 29 seconds. The shim optimization procedure was performed numerically using an IDL program (Exelis, Inc., Bolder, CO) for 1st and 2nd order terms combined.

The selectivity of water selective excitation was first optimized with a newly developed spectroscopic method. Specifically, a standard PRESS sequence was modified so that three slice selective refocusing pulses defined a volume and a frequency selective 90° pulse specified a desired spectral region to excite (Figure 2a). (This sequence was denoted 'PRESS with Excitation Restriction', or PRESSER.) This method was initially intended to excite a small spectral window around the Choline (Cho) resonance frequency without relying on water or fat suppression. As we have yet to implement the PRESSER sequence for this application, it was used as a tool to optimize the excitation profile of the excitation pulse in phantom experiments and *in vivo*. The goal, therefore, was to determine optimal duration (and bandwidth) of the 90° pulse to excite all water signals at 4.7 ppm with minimal amount of lipid contamination. A sagittal volume was prescribed to match the coverage of the DWI sequence TE/TR = 61 ms/2 s, NSA = 16, scan time = 34 sec.

Since lipid signals in breast adipose tissues consist of several resonances (0.9 ppm, 1.3 ppm, 2.1 ppm, 2.7 ppm, 4.3 ppm and 5.4 ppm (35)), we performed initial testing using a spectroscopic phantom consisting of a solution of metabolites (N-acetyl aspartate (NAA): 12.5 mM, creatine (Cr): 10 mM, choline (Cho): 3 mM, myoinositol (mI): 7.5 mM, L-glutamic acid (Glu): 12.5 mM, DL-lactic acid (Lac): 5 mM) with spectral peaks between 1.3 ppm and 3.9 ppm. The center frequency of the excitation was placed at the approximate center of the lipid region (2.0 ppm, the frequency location of NAA) while the duration of the pulse was varied from 6 ms to 16 ms in 2 ms increments in phantom experiments. Since the excitation profile of the Gaussian pulse is symmetrical, the subsequent acquisition of the spectral peak of N-acetyl aspartate (NAA) at 2.0 ppm in the presence of residual water at 4.7 ppm was used as an indicator of water selective excitation at 4.7 ppm in the presence of lipid resonances around 2.0 ppm.

All *in vivo* scans were performed with informed consent as required by the institutional review board (IRB) of Vanderbilt University. A single slice was prescribed in the sagittal direction across one breast. Before any measurement proceeded with the shim parameters determined for the sagittal slice, the quality of the shim and center frequency were checked on the scanner console as shown in Figure 3. Specifically, the entire slice was acquired with a standard spectroscopy sequence without any suppression. The spectrum acquired was immediately displayed showing water peak and various fat peaks. The water peak was selected in the spectrum manually by observing the peak amplitudes and comparing the expected peak separations to the frequency markers along the horizontal axis. For example, the water peak at 4.7 ppm and the methyl peak at 0.9 ppm should be separated by 486 Hz at 3T. This can be identified with the frequency markers at 0 Hz and 500 Hz, as shown in Figure 3. When the center frequency was selected manually, a PRESSER spectrum with a 10 ms excitation pulse was acquired in order to compare with a standard PRESS spectrum. This excitation duration confirmed by PRESSER during developmental *in vivo* scans was used to acquire all the subsequent water selective DWI scans in the same fashion.

In summary, this water selective DWI sequence consists of new excitation and refocusing pulses, field map based high order shimming, and manual selection of center frequency. To determine if such added complexity compromised the ability to make reliable measurements in the clinical setting, we performed a test-retest study on 10 volunteers in two separate

visits. Eight subjects returned for their 2nd scan in one or two days while two subjects returned after seven days as permitted by their schedules. In each session, one unilateral breast scan was performed with three b -values (0, 50 and 600 s/mm²) and 10 signal averages. The $b = 0$ images were also used to produce masks to exclude signals from the skin and the chest wall. For each scan, two ADC maps were calculated using b -values of 0, 600 s/mm² and 50, 600 s/mm² using a Matlab script (Mathworks Inc., Natick, MA). A co-registered T_1 -weighted scan was also included to visualize the anatomy.

In order to quantify the results of the water selective excitation, we selected one vertical one-dimensional profile from each T_1 -weighted image and water selective SE image (i.e. DWI sequence with b value = 0) and to identify regions of fat and water. Then, the mean pixel values from the water and fat regions were used to generate apparent ratios of fat to water. As the T_1 - and diffusion weighted sequences have different degrees of T_1 and T_2 weightings, the ratios of proton densities, ρ , of fat and water, acquired by both sequences, were calculated using the signal equation for a standard spin echo sequence:

$$\text{signal}(SE) \sim \rho * \left(1 - e^{-\frac{TR}{T_1}}\right) * \left(e^{-\frac{TE}{T_2}}\right). \quad [1]$$

The values of T_1 and T_2 in Eq. [1] for water and fat in breast tissues were taken from reference (36). The values of TE and TR of the two sequences were used, respectively, in these calculations. As the proton density from water regions is constant, it was used to normalize measurements from fat regions by two sequences. The resulting ratio was used to evaluate the effectiveness of the water selective excitation.

For statistical analysis (37,38), we first computed the differences, d between the two ADC measurements. The distribution of d was tested for its normality using a two-sided Shapiro-Wilk test. A Kendall's tau test was used to estimate the correlation between the magnitude of the differences and overall mean of the two measurements. A Wilcoxon signed-rank test was performed with the original data to test the null hypothesis that the average difference is zero between the two measurements. We then calculated the 95% confidence interval (CI) and repeatability coefficient (r) as described previously (39,40). In addition, we also calculated the intraclass correlation (ICC) for mean ADC values computed using b -values of 0, 600 s/mm² and 50, 600 s/mm².

Results

Figures 2 and 3 demonstrate the phantom and preliminary *in vivo* results we used to optimize the water selective DWI sequence, including excitation profile optimization in Figure 2 and center frequency selection in Figure 3. Figure 2b shows three spectra acquired in a spectroscopy phantom with excitation durations of 6 ms, 10 ms and 14 ms. The resulting excitation ranges are shown by three Gaussian curves with bandwidths of 355 Hz, 213 Hz and 152 Hz, respectively. The phantom experiments show that as the pulse duration increased, a diminishing spectral range was excited at around 2.0 ppm. Specifically, when the duration was 10 ms (BW = 213 Hz), spectral peaks at 3.2, 3.0 and 1.4 ppm were visible while water resonance at 4.7 ppm was adequately excluded. Figure 2c shows two *in vivo* spectra acquired by PRESS and PRESSER from a volume prescribed to match the coverage

of the sagittal DWI sequence. In this comparison, PRESSER acquired a nearly identical water signal with minimal erroneous lipid signals resulting from a dominant resonance at 1.3 ppm. Figure 3 shows a spectrum acquired during the pre-scan of the water selective DWI sequence. Despite expanded spectral peaks resulted from residual B_0 inhomogeneity (~ 200 Hz for water), various fat peaks and the water peak were correctly identified. The spectral location marked by the yellow line on the water peak was chosen as the center frequency of the subsequent water selective acquisitions.

Figures 4, 5 and Table 1 demonstrate the results of the test-retest study to evaluate the reproducibility of the water selective DWI sequence. Figure 4 shows the representative results from two of the 10 subjects enrolled in test-retest DWI study. Each column consists of images from one visit. The 1st row shows the T_1 -weighted images demonstrating two distinct distributions of glandular tissues within adipose tissues. The 2nd row shows the images of the water selective DWI sequence with a b -value of 0. These images were used as the basis for segmentation as water signals from skin, glandular tissues and the chest wall were depicted and separated with high resolution and SNR. The 3rd and 4th rows show ADC maps computed from b -values of 0, 600 s/mm² and 50, 600 s/mm², respectively. The 5th and 6th rows show one dimensional profiles along the lines marked in the 1st (T_1 -weighted) and 2nd (water selective SE) rows. These profiles demonstrate opposite intensity patterns from water and fat regions, showing no chemically shifted fat from nearby regions. Pixel values in water (blue arrows) and fat (green arrows) regions were used to quantify the effectiveness of the water selective excitation. From T_1 -weighted images, the fat to water ratio was 1.2 ± 0.3 ; from water selective DWI, the ratio was 0.12 ± 0.04 . When normalized by water values from water regions in both images, we calculated the water selective method reduced signal intensity in fat regions by $90 \pm 2\%$. This residual signal should be attributed to the water content in fatty tissues (41) as residual fat signal would be chemically shifted in water selective images.

Figure 5 shows measurements from all 10 subjects in a Bland-Altman plot. Mean differences, 95% CI and repeatability ranges are displayed as solid, dotted and dashed lines, respectively. Table 1 shows reproducibility statistics of mean values for ADCs computed from b -values = 0, 600 s/mm² and 50, 600 s/mm². Results of the two-sided Shapiro-Wilk test show p -values of 0.28 and 0.71, indicating normally distributed ADC values. The ICC values were 0.923 and 0.929, respectively. In summary, both the ADC maps and quantitative results demonstrate that the water selective DWI method correctly and reliably produced high quality diffusion measurements from subjects of a wide range of sizes and ages.

Discussion

The selectivity of the water signal by the new DWI method depends on the bandwidth of the excitation pulse and the spectral separations of fat from the water resonance relative to the residual field inhomogeneity. Human adipose tissues consist of resonances at 0.9 ppm, 1.3 ppm, 2.1 ppm, 2.8 ppm and 5.4 ppm (35). With an excitation bandwidth of 213Hz, strong fat signals, except that from the olefinic group “-CH=CH-” at 5.4 ppm, are excluded. The frequency separation between 5.4 ppm and 4.7 ppm at 3 T is approximately 90 Hz, which is

comparable to the line width of water from breast tissue. This is evident in Figure 3 where the fat peak at 5.4 ppm falls within the frequency range of the water signal. Therefore, excluding this fat resonance without compromising water selectivity is not feasible with our method or any fat suppression method at 3 T. In addition, human adipose tissues also contain a non-negligible amount of water (41) so we do not expect zero signal from fat regions (as shown in images and profiles in Figure 4).

A Gaussian pulse was chosen for water selection because of its higher selectivity as it produces no side-lobes in the frequency domain (42). A pair of adiabatic inversion pulses was chosen for refocusing because of their better frequency profiles compared to conventional refocusing pulses. Within their inversion bands, the flip angles are more accurate than conventional pulses if they are maintained above the adiabatic threshold (43). In order to minimize the increased echo time resulted from two refocusing pulses, we chose a pair of analytically optimized adiabatic refocusing pulses first designed by Rosenfeld *et al* (31). Later, numerically optimized adiabatic pulses using the Shinar-LeRoux (SLR) algorithm resulted in similar amplitude and frequency profiles (44). These pulses have shown success recently in magnetic resonance spectroscopic imaging (MRSI) at 7 T (32) and 3 T (33). Their main advantage, compared to conventional hyperbolic secant pulses, is that their peak amplitude and frequency sweep are spread out over the duration of the pulse so they can maintain adiabaticity with lower RF power and shorter duration. Therefore, such pulses are valuable when the echo time needs to be kept as short as possible in applications such as 7 T MRSI or DWI with long diffusion gradients.

Regarding the ADC variations we observed in the test-retest study, we expect the main source to be the difference between slice locations from two visits. The phased array breast coil used in this study is built into a rigid MRI table that is designed to fit subjects of all sizes. As slimmer subjects have considerable room to position themselves in this coil, duplicating the exact slice position and angle in the 2nd visit was difficult. This probably contributed to the ADC variations for the eight subjects that returned in less than two days. For the two subjects that returned after seven days, we observed the two highest variations in mean ADC. Such changes were reported in a recent study to be related to the phase of the menstrual cycle (30). In addition, another potential source of signal variation between the two separate visits lies in the automatic flip angle calibration by the scanner as B_1 inhomogeneity is a known issue for body imaging even at 3 T. In order to minimize this variation, we chose a flip angle of 90° instead of the Ernst angle resulted from the TR. The reason lies in the fact that an excitation pulse of angle α results in transverse magnetization proportional to $\sin(\alpha)$, which presents the smallest derivative when $\alpha = 90^\circ$. Therefore, given the same B_1 variation, a 90° flip angle produces the least amount of variation in signal intensity. When further improvements enable this method for clinical applications, the Ernst angle for the excitation pulse should be used to achieve the maximize SNR.

Most importantly, our method differs from current DWI methods in terms of the non-spatially selective nature of the excitation. This fact eliminates the possibility of multi-slice imaging that is used in conventional DWI methods. Therefore, expanding our method to multi-shot 3D acquisitions with a navigator echo such as Image Reconstruction using Image-space Sampling function (IRIS) (45) is a requirement before the water selective

approach can be efficiently deployed in the clinical setting. In future efforts, after this technique is converted to a 3D method, its reproducibility will be compared to more established methods. In addition, manual procedures for water selection will be automated to make this method more suitable for routine clinical use.

In conclusion, we designed a water selective DWI method for breast imaging. The selectivity was optimized using a similar spectrally selective sequence (PRESSER). Field-map based shimming up to the 2nd order and manual center frequency selection were used to ensure accurate selection of water signal. The added complexity of this approach led us to conduct a quantitative test-retest study of the water selective DWI method with 10 healthy volunteers in two separate visits. These results demonstrated water selective excitation as a feasible alternative to existing methods of fat suppression as the added complexity of the sequence did not compromise the reliability of the diffusion measurements.

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Abbreviations used

MRI	magnetic resonance imaging
DWI	diffusion weighted imaging
CI	confidence interval
ADC	apparent diffusion coefficient
NAC	neoadjuvant chemotherapy
DCE	dynamic contrast enhanced
NIH	national institutes of health
MSK	musculoskeletal
Cho	choline
CEST	chemical exchange saturation transfer
MRS	magnetic resonance spectroscopy
SE	spin echo
TSE	turbo spin echo
PRESS	point resolved spectroscopy
BW	bandwidth
AFP	adiabatic full passage
PRESSER	PRESS with Excitation Restriction
NAA	n-acetyl aspartate

IRB	institutional review board
ICC	intraclass correlation
GRASE	gradient spin echo
SNR	signal-to-noise ratio
SLR	Shinar-LeRoux
MRSI	magnetic resonance spectroscopic imaging
IRIS	image-space sampling function

References

1. Bammer R. Basic principles of diffusion-weighted imaging. *Eur J Radiol.* 2003; 45(3):169–184. [PubMed: 12595101]
2. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJ, Taouli B, Choyke PL. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia.* 2009; 11(2):102–125. [PubMed: 19186405]
3. Charles-Edwards EM, deSouza NM. Diffusion-weighted magnetic resonance imaging and its application to cancer. *Cancer Imaging.* 2006; 6:135–143. [PubMed: 17015238]
4. Belli P, Costantini M, Ierardi C, Bufi E, Amato D, Mule A, Nardone L, Terribile D, Bonomo L. Diffusion-weighted imaging in evaluating the response to neoadjuvant breast cancer treatment. *Breast J.* 2011; 17(6):610–619. [PubMed: 21929557]
5. Beaulieu C, D'Arceuil H, Hedehus M, de Crespigny A, Kastrup A, Moseley ME. Diffusion-weighted magnetic resonance imaging: theory and potential applications to child neurology. *Seminars in pediatric neurology.* 1999; 6(2):87–100. [PubMed: 10404563]
6. Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. *Magn Reson Med.* 1990; 14(2):330–346. [PubMed: 2345513]
7. Glunde K, Jacobs MA, Pathak AP, Artemov D, Bhujwalla ZM. Molecular and functional imaging of breast cancer. *NMR Biomed.* 2009; 22(1):92–103. [PubMed: 18792419]
8. Sharma U, Danishad KK, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. *NMR Biomed.* 2009; 22(1):104–113. [PubMed: 18384182]
9. Hahn SY, Ko EY, Han BK, Shin JH, Ko ES. Role of diffusion-weighted imaging as an adjunct to contrast-enhanced breast MRI in evaluating residual breast cancer following neoadjuvant chemotherapy. *Eur J Radiol.* 2014; 83(2):283–288. [PubMed: 24315957]
10. Richard R, Thomassin I, Chapellier M, Scemama A, de Cremoux P, Varna M, Giacchetti S, Espie M, de Kerviler E, de Bazelaire C. Diffusion-weighted MRI in pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. *Eur Radiol.* 2013; 23(9):2420–2431. [PubMed: 23652844]
11. Atuegwu NC, Arlinghaus LR, Li X, Chakravarthy AB, Abramson VG, Sanders ME, Yankeelov TE. Parameterizing the Logistic Model of Tumor Growth by DW-MRI and DCE-MRI Data to Predict Treatment Response and Changes in Breast Cancer Cellularity during Neoadjuvant Chemotherapy. *Translational oncology.* 2013; 6(3):256–264. [PubMed: 23730404]
12. Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, Meszoely I, Mayer IA, Herman CR, McManus K, Price RR, Gore JC. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. *Magn Reson Imaging.* 2007; 25(1):1–13. [PubMed: 17222711]
13. Manton DJ, Chaturvedi A, Hubbard A, Lind MJ, Lowry M, Maraveyas A, Pickles MD, Tozer DJ, Turnbull LW. Neoadjuvant chemotherapy in breast cancer: early response prediction with

- quantitative MR imaging and spectroscopy. *Br J Cancer*. 2006; 94(3):427–435. [PubMed: 16465174]
14. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, Mahankali S, Gao JH. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging*. 2002; 16(2):172–178. [PubMed: 12203765]
 15. Humphries PD, Sebire NJ, Siegel MJ, Olsen OE. Tumors in pediatric patients at diffusion-weighted MR imaging: apparent diffusion coefficient and tumor cellularity. *Radiology*. 2007; 245(3):848–854. [PubMed: 17951348]
 16. Zhu H, Ouwerkerk R, Barker PB. Dual-band water and lipid suppression for MR spectroscopic imaging at 3 Tesla. *Magn Reson Med*. 2010; 63(6):1486–1492. [PubMed: 20512851]
 17. Thomasson D, Purdy D, Finn JP. Phase-modulated binomial RF pulses for fast spectrally-selective musculoskeletal imaging. *Magn Reson Med*. 1996; 35(4):563–568. [PubMed: 8992207]
 18. Pickles MD, Gibbs P, Bayram E, Buzek J, Zhang ZH, Turnbull LW. A new strategy for consistent uniform fat suppression in breast MR imaging. *Proc Intl Soc Mag Reson Med*. 2012; 20:1488.
 19. Bolan PJ, Nelson MT, Yee D, Garwood M. Imaging in breast cancer: Magnetic resonance spectroscopy. *Breast Cancer Res*. 2005; 7(4):149–152. [PubMed: 15987466]
 20. Meisamy S, Bolan PJ, Baker EH, Bliss RL, Gulbahce E, Everson LI, Nelson MT, Emory TH, Tuttle TM, Yee D, Garwood M. Neoadjuvant chemotherapy of locally advanced breast cancer: predicting response with in vivo $(1)H$ MR spectroscopy--a pilot study at 4 T. *Radiology*. 2004; 233(2):424–431. [PubMed: 15516615]
 21. Zhou J, Zhu H, Lim MC, Blair L, Quinones-Hinojosa A, Messina S, Eberhart CG, Pomper MG, Laterra J, Barker PB, Van Zijl P, Blakeley J. Three-Dimensional Amide Proton Transfer MR Imaging of Gliomas: Initial Experience and Comparison With Gadolinium Enhancement. *J Magn Reson Imaging*. 2013
 22. Zhu H, Jones CK, van Zijl PC, Barker PB, Zhou J. Fast 3D chemical exchange saturation transfer (CEST) imaging of the human brain. *Magn Reson Med*. 2010; 64(3):638–644. [PubMed: 20632402]
 23. Zhu H, Arlinghaus LR, Gore JC, Yankeelov TE. Spectrally selective excitation for improved DWI, APT and MRS of the breast. *ISMRM*. 2013; (21):3376.
 24. Shemesh N, Dumez JN, Frydman L. Longitudinal relaxation enhancement in $1H$ NMR spectroscopy of tissue metabolites via spectrally selective excitation. *Chemistry*. 2013; 19(39):13002–13008. [PubMed: 24038462]
 25. Parasoglou P, Xia D, Regatte RR. Spectrally selective 3D TSE imaging of phosphocreatine in the human calf muscle at 3 T. *Magn Reson Med*. 2013; 69(3):812–817. [PubMed: 22499078]
 26. Josan S, Hurd R, Park JM, Yen YF, Watkins R, Pfefferbaum A, Spielman D, Mayer D. Dynamic metabolic imaging of hyperpolarized $[2-^{13}C]$ pyruvate using spiral chemical shift imaging with alternating spectral band excitation. *Magn Reson Med*. 2013
 27. Hauger O, Dumont E, Chateil JF, Moinard M, Diard F. Water excitation as an alternative to fat saturation in MR imaging: preliminary results in musculoskeletal imaging. *Radiology*. 2002; 224(3):657–663. [PubMed: 12202695]
 28. Kornaat PR, Doornbos J, van der Molen AJ, Kloppenburg M, Nelissen RG, Hogendoorn PC, Bloem JL. Magnetic resonance imaging of knee cartilage using a water selective balanced steady-state free precession sequence. *J Magn Reson Imaging*. 2004; 20(5):850–856. [PubMed: 15503345]
 29. Bieri O, Mamisch TC, Trattnig S, Kraff O, Ladd ME, Scheffler K. Optimized spectrally selective steady-state free precession sequences for cartilage imaging at ultra-high fields. *MAGMA*. 2008; 21(1-2):87–94. [PubMed: 18030512]
 30. O'Flynn EA, Morgan VA, Giles SL, deSouza NM. Diffusion weighted imaging of the normal breast: reproducibility of apparent diffusion coefficient measurements and variation with menstrual cycle and menopausal status. *Eur Radiol*. 2012; 22(7):1512–1518. [PubMed: 22367471]
 31. Rosenfeld D, Zur Y. A new adiabatic inversion pulse. *Magn Reson Med*. 1996; 36(1):124–136. [PubMed: 8795031]
 32. Zhu H, Soher BJ, Ouwerkerk R, Schar M, Barker PB. Spin-echo magnetic resonance spectroscopic imaging at 7 T with frequency-modulated refocusing pulses. *Magn Reson Med*. 2013

33. Gu M, Balchandani P, Sheriff S, Sabati M, Spielman D, Maudsley AA. Short TE Whole Brain MRSI with High-Bandwidth Adiabatic SLR Refocusing and Echo Planar Readout. 2013:3963.
34. Schar M, Kozerke S, Fischer SE, Boesiger P. Cardiac SSFP imaging at 3 Tesla. *Magn Reson Med*. 2004; 51(4):799–806. [PubMed: 15065254]
35. Singer S, Sivaraja M, Souza K, Millis K, Corson JM. ¹H-NMR detectable fatty acyl chain unsaturation in excised leiomyosarcoma correlate with grade and mitotic activity. *J Clin Invest*. 1996; 98(2):244–250. [PubMed: 8755630]
36. Rakow-Penner R, Daniel B, Yu H, Sawyer-Glover A, Glover GH. Relaxation times of breast tissue at 1.5T and 3T measured using IDEAL. *J Magn Reson Imaging*. 2006; 23(1):87–91. [PubMed: 16315211]
37. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Statistical methods in medical research*. 1999; 8(2):135–160. [PubMed: 10501650]
38. Galbraith SM, Lodge MA, Taylor NJ, Rustin GJ, Bentzen S, Stirling JJ, Padhani AR. Reproducibility of dynamic contrast-enhanced MRI in human muscle and tumours: comparison of quantitative and semi-quantitative analysis. *NMR Biomed*. 2002; 15(2):132–142. [PubMed: 11870909]
39. Dula AN, Arlinghaus LR, Dortch RD, Dewey BE, Whisenant JG, Ayers GD, Yankeelov TE, Smith SA. Amide proton transfer imaging of the breast at 3 T: Establishing reproducibility and possible feasibility assessing chemotherapy response. *Magn Reson Med*. 2012
40. Barnes SL, Whisenant JG, Loveless ME, Ayers GD, Yankeelov TE. Assessing the reproducibility of dynamic contrast enhanced magnetic resonance imaging in a murine model of breast cancer. *Magn Reson Med*. 2013; 69(6):1721–1734. [PubMed: 22847762]
41. Baker GL. Human adipose tissue composition and age. *Am J Clin Nutr*. 1969; 22(7):829–835. [PubMed: 5816105]
42. Bauer C, Freeman R, Frenkiel T, Keeler J, Shaka AJ. Gaussian Pulses. *Journal of Magnetic Resonance*. 1984; 58(3):442–457.
43. Garwood M, DelaBarre L. The return of the frequency sweep: designing adiabatic pulses for contemporary NMR. *J Magn Reson*. 2001; 153(2):155–177. [PubMed: 11740891]
44. Balchandani P, Pauly J, Spielman D. Designing adiabatic radio frequency pulses using the Shinnar-Le Roux algorithm. *Magn Reson Med*. 2010; 64(3):843–851. [PubMed: 20806378]
45. Jeong HK, Gore JC, Anderson AW. High-resolution human diffusion tensor imaging using 2-D navigated multishot SENSE EPI at 7 T. *Magn Reson Med*. 2012

Figure 1.

Sequence Diagram of water only DWI. A Gaussian excitation pulse without slice selection is used for water selection. A pair of slice selective adiabatic refocusing pulses [29] was chosen for localization to compensate for the loss of slice selection of the excitation pulse.

Figure 2.

(a) Sequence Diagram of PRESS with Excitation Restriction (PRESSER); (b) Center frequency was placed at 2.0 ppm in a phantom test as we used the amount of excited water to evaluate how spectral selectivity increases with pulse duration. (c) Center frequency was placed on water for *in vivo* confirmation of water selective excitation. The excitation duration of 10 ms (blue) confirmed by PRESSER during phantom and preliminary *in vivo* scans was used to acquire all the subsequent water selective DWI scans in the same fashion.

Figure 3.

Water selection among fat resonances in breast tissue. Peak assignments are confirmed by the agreement between expected and measured peak separations. The spectral location marked by the yellow line on the water peak was chosen manually as the center frequency of the subsequent water selective acquisitions.

Figure 4.

Results of water selective DWI from 2 of ten subjects in 2 visits. The 1st row shows the T₁-weighted MR images. The 2nd row shows the water selective SE image (i.e. image of DWI sequence with b -value = 0). The 3rd and 4th rows show ADC maps of b -values = 0, 600 s/mm² and 50, 600 s/mm². High quality ADC maps were acquired demonstrating two distinct types of distributions of glandular tissues within adipose tissues from both visits. The 5th and 6th rows show intensity profiles sampled at the marked locations in the 1st and 2nd rows. In each profile, pixel values from fat regions (green arrows) and glandular regions (blue arrows) are used to quantify the effectiveness of the water selective excitation.

Figure 5. Bland-Altman plot of mean ADC values of all ten subjects in the test-retest study. The quantitative results demonstrate that the water selective DWI method reliably produced high quality diffusion measurements despite added complexity in sequence design and implementation.

Table 1

Reproducibility Statistics

	ADC mean b = 0, 600	ADC mean b = 50, 600
S-W test (P-value)	0.28	0.71
mean	0.00170	0.00166
mean difference	0.000012	0.000018
Kendall's Tau (Corr. value)	0.24	-0.11
(P- value)	0.38	0.73
Wilcoxin test (P-value)	0.38	0.56
Anova Anaysis: dsd	0.000056	0.000067
CI	0.000041	0.000049
wSD	0.000039	0.000047
wCV	2.30	2.86
r	0.000109	0.000131