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***In Vitro* and *In Vivo* Studies of ^{17}O NMR Sensitivity at 9.4 and 16.4 Tesla**

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Abstract

In vivo ^{17}O magnetic resonance spectroscopy (MRS) has been successfully applied for imaging the cerebral metabolic rate of oxygen consumption (CMRO_2) through the detection of metabolically produced H_2^{17}O from the inhaled ^{17}O -labeled oxygen in animals at high field. In this study, we compared the ^{17}O sensitivity for detecting natural abundance H_2^{17}O signals from a phantom solution and rat brains at 9.4 and 16.4 Tesla. The ^{17}O signal-to-noise ratio (SNR) measured at 16.4T was 2.9- and 2.7~2.8-fold higher than that at 9.4T for the phantom and rat brain studies, respectively. Similarly, three-dimensional ^{17}O MRS imaging data showed a more than 2.7-fold higher SNR in the central rat brain region at 16.4T than that at 9.4T. The substantial ^{17}O SNR gain at ultrahigh field significantly improved the reliability for imaging CMRO_2 , and will provide an opportunity for *in vivo* assessment of altered oxidative metabolism associated with brain functions and neurological diseases.

Keywords

In vivo ^{17}O MRS; CMRO_2 ; SNR; sensitivity; high field

INTRODUCTION

The rate of oxygen utilization in the mitochondrial respiratory chain serves as an important index of the cellular metabolic status. However, the lack of non-destructive and robust *in vivo* imaging approaches for the investigation of cellular oxidative metabolism has limited our understanding of the mechanism underlying metabolic alteration between normal and diseased tissues. Although ^{15}O positron emission tomography (PET) has been the standard imaging modality for the measurements of oxygen consumption rate for more than 20 years, its application has been limited to research because of the complex experimental procedures, data interpretation and compartmental modeling requirement (1,2). In contrast, ^{17}O magnetic resonance spectroscopy/imaging (MRS/I) provides the specificity by direct detection of the dynamics of metabolic H_2^{17}O production from the reduction of ^{17}O -labeled oxygen molecules ($^{17}\text{O}_2$) but without confounding signal from $^{17}\text{O}_2$, thus, allows more straightforward measurement and quantification of the cellular oxygen consumption rate *in vivo* (3).

Recently, *in vivo* ^{17}O MRS approaches for the measurement of the cerebral metabolic rate of oxygen consumption (CMRO_2) (4–11) and the myocardial oxygen consumption rate (MVO_2) (12–14) have been developed in animals and human subjects. In comparison with the indirect detection of H_2^{17}O via ^{17}O -induced changes in the proton $T_{1\rho}$ or T_2 , the

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direct ^{17}O MRS/I has the advantages of being highly specific to the tissue H_2^{17}O and the availability of using natural abundance H_2^{17}O signal as an internal reference for quantification of tissue H_2^{17}O concentration. In addition, the direct ^{17}O MRS/I detection approach may avoid the challenges encountered by the indirect method, i.e., the complicated quantification of H_2^{17}O concentration due to the sensitivity of the proton relaxation time to biochemical and physiological changes in tissues, such as pH (15). However, the efforts of direct monitoring and imaging the accumulation rate of H_2^{17}O during an inhalation of $^{17}\text{O}_2$ have been suffered from the low sensitivity of ^{17}O detection because of its low gyromagnetic ratio and low H_2^{17}O content in nature.

It is known that the optimal signal-to-noise ratio (SNR) for the detection of magnetic resonance signal depends on magnetic field strength (B_0), longitudinal relaxation time (T_1), T_2^* and the RF coil quality factor (Q) according to the following relationship:

$$\text{SNR} \propto B_0^\beta \sqrt{\frac{QT_2^*}{T_1}} \quad [1]$$

where, the constant β was suggested to be close to the value of $7/4 \sim 2$ for ^{17}O spins (16,17). Obviously, increasing B_0 is one efficient way to improve the SNR. Two previous studies have compared the *in vitro* and *in vivo* ^{17}O sensitivity between 4.7T and 9.4T, and between 4.7T and 11T, respectively (16,17), suggesting great advantages of high field. The unique NMR properties of ^{17}O , i.e., the independence of ^{17}O relaxation times (T_1 and T_2) on the field strength (16,17) and extremely short T_1 for more signal averaging, also contribute to a large gain of ^{17}O detection sensitivity at high/ultrahigh field (3).

In this study, ^{17}O sensitivity was measured and compared using the natural abundance H_2^{17}O signals in a phantom solution and rat brains at 9.4T and 16.4T, without and with spatial localization, to quantify the possible SNR gain for *in vivo* ^{17}O MRS/I application using the newly developed large-bore animal scanner with ultrahigh field strength of 16.4T.

MATERIALS and METHODS

Phantom and Animal Preparation

A 6-mm-diameter glass sphere filled with natural abundance ^{17}O distilled water was prepared for all phantom studies at 9.4T and 16.4T. For *in vivo* studies, following the initial induction with 5% isoflurane and oral intubation, male Sprague Dawley rats (250~300 g body weight) were anesthetized with 2% (v/v) isoflurane in a mixture of O_2 and N_2O gases (~2:3) during surgery and experiment. To monitor physiological parameters and obtain blood samples, the femoral artery and vein were catheterized during the surgery. Rectal temperature was maintained at $37 \pm 1^\circ\text{C}$ using heated circulating water. Blood gases were sampled for monitoring physiological conditions. The arterial blood pressure and heart rate were monitored during the experiment. The animals were maintained under physiological conditions during all the measurements.

Ten rats (five for each field strength) were used in this study to measure the global and localized SNR at both fields from the natural abundance brain H_2^{17}O signals. One $^{17}\text{O}_2$ inhalation experiment was performed on another rat under alpha-chloralose anesthesia (20) at 16.4T and using ^{17}O -labeled O_2 (74.8% enrichment, ISOTEC) with N_2O gases (~2:3) to imaging and quantify CMRO_2 from the metabolically generated H_2^{17}O signal in the brain. During the sequential acquisitions of localized ^{17}O MRS imaging, the respiration gas was switched from the normal gas mixture with $^{16}\text{O}_2$ to the ^{17}O -labeled oxygen gas mixture. After 2.75 minutes of $^{17}\text{O}_2$ inhalation, the gas line was switched back to the normal gas mixture for ~15 minutes until the completion of data acquisition.

All animal surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Minnesota.

***In vitro* and *In vivo* ^{17}O MRS Imaging**

All measurements were performed on either a 9.4T/31cm or a 16.4T/26cm horizontal bore magnet (MagneX Scientific) interfaced to VNMRJ consoles (Varian, CA). For *in vitro* studies, one ^{17}O radiofrequency (RF) probe consisting of an oval shaped (18mm×13mm) surface coil was designed and constructed. Its resonance frequency can be tuned to either 54.25 MHz for 9.4T or 94.65 MHz for 16.4T application. The glass sphere phantom was fixed on the RF probe for all phantom studies at both fields. For *in vivo* studies, two passively decoupled dual-coil RF probes with identical geometry were constructed and placed over the rat brain to obtain optimum *in vivo* sensitivity for both 9.4T and 16.4T experiments. Each RF probe included an oval shaped single-loop ^{17}O surface-coil (10mm×20mm) for acquiring *in vivo* ^{17}O MRS/MRSI and a butterfly shaped ^1H surface-coil for shimming and acquiring anatomical images.

A single-pulse-acquire sequence was applied to obtain the optimal ^{17}O SNR with a nominal 90° RF excitation pulse and following acquisition parameters: 20 kHz spectral width (SW), 1024 number of points (NP) for each FID, 50 ms repetition time (TR) with the number of signal averages (NT)=128 for phantom measurements and NT=512, 128 or 16 for *in vivo* studies. The spatial localization of ^{17}O MRS was achieved by using the three-dimensional (3D) Fourier series window MRS imaging technique (11,18–20) with 15 ms TR, 0.41 ms echo time (TE), 512 NP, 20 kHz SW, 928 total NT, 9×9×5 3D phase encodes and 30×30×30 mm³ field of view (FOV).

For the $^{17}\text{O}_2$ inhalation experiment at 16.4T, an identical set of 3D ^{17}O MRS imaging acquisition parameters as previously reported for rat brain applications at 9.4T (20) was used in this study. The FIDs were processed by exponential filtering with a line broadening of 100 Hz to enhance the SNR, followed by Fourier transformation.

The ^{17}O sensitivity was evaluated using the SNR of H_2^{17}O resonance peak calculated by dividing peak intensity by the standard deviation of the noise. In addition to the SNR gain at higher field, the relative fluctuation of ^{17}O signals among repeated measurements at a given magnetic field is also an important factor for the evaluation of dynamic studies using direct ^{17}O MRS/I approaches. Therefore, the relative fluctuation of ^{17}O signals was also assessed by the variance from both the phantom and rat brain measurements by computing the standard deviation of the global natural abundance H_2^{17}O signals from 10 repetitions of data acquisition at 9.4T and 16.4T. All results presented in this study were shown as mean ± standard deviation.

RESULTS

Table 1 summarizes the SNR and measurement variance results of global ^{17}O signals measured in the rat brain and phantom at 9.4T and 16.4T. The average ^{17}O SNR at 16.4T was 2.9- and 2.7~2.8-fold higher than that at 9.4T for the phantom and rat brain studies, respectively. In contrast, the ^{17}O signal variance was 2–4-fold smaller at 16.4T than 9.4T. The overall results clearly demonstrate excellent sensitivity and small variance (i.e. high signal stability) at both fields for obtaining the ^{17}O signals of natural abundance H_2^{17}O from either the phantom or rat brains. Nevertheless, the 16.4T scanner offers striking improvements of several folds in both sensitivity and stability.

The 1D ^{17}O SNR profiles along an axis parallel to the RF coil plane obtained from the central slices of 3D ^{17}O MRS images in rat brains at both 9.4T and 16.4T were

demonstrated in Fig. 1a. As shown in Fig. 1b, significantly improved ^{17}O sensitivity, i.e., an averaged more than 2.5-fold SNR gain was observed from the natural abundance H_2^{17}O in the rat brain at 16.4T compared to that at 9.4T. Similarly, the 2D ^{17}O MRS images of natural abundance H_2^{17}O in the rat brain taken from the central slices of 3D ^{17}O MRS imaging data also indicated a more than 2.7-fold higher SNR in the central brain voxels at 16.4T than that at 9.4T (Fig. 2).

The large sensitivity improvement at ultrahigh field indicated the potential of ^{17}O MRS imaging for the quantification of regional CMRO_2 from detecting the dynamic changes of the metabolic H_2^{17}O in small animal brains during a short inhalation of $^{17}\text{O}_2$. Figure 3a shows the stacked plots of H_2^{17}O spectra from one representative voxel with the voxel size of ~ 0.1 ml, located near the center of the ^{17}O RF coil-sensitive region inside the rat brain before, during and after a 2.75-minute inhalation of $^{17}\text{O}_2$. The time course of ^{17}O signal intensity of brain H_2^{17}O in the representative rat shows three distinct phases: constant baseline (from natural abundance H_2^{17}O); approximately linear increasing during $^{17}\text{O}_2$ inhalation; and decreasing exponentially after the cessation of inhalation until reaching a new steady state. Figure 3a also illustrates the excellent sensitivity and small variance of the brain ^{17}O signal measurements, which were important for detecting the dynamic change of the metabolic H_2^{17}O content in the rat brain during and after $^{17}\text{O}_2$ inhalation. The linear fitting of the metabolic H_2^{17}O concentration change in the same voxel during $^{17}\text{O}_2$ inhalation was shown in Fig. 3b. Based on the simplified quantification model (20,21), the CMRO_2 value in this particular voxel was calculated with linear regression method ($=2.1 \mu\text{mol/g/min}$), which was consistent with those reported in the previous studies under the same physiological condition (11,20).

As a further proof of the independent ^{17}O relaxation times on the field strength, we measured T_1 value of natural abundance H_2^{17}O in the rat brain at fully relaxed condition using the inversion recovery pulse sequence at 16.4T. The *in vivo* T_2^* value of natural abundance H_2^{17}O was also evaluated from the line width, i.e., full width at half maximum ($\Delta\nu_{1/2}$), of the H_2^{17}O resonance peak without line broadening. As a result, the measured T_1 (5.3 ± 0.4 ms), $\Delta\nu_{1/2}$ (174 ± 5 Hz) and calculated T_2^* (1.83 ± 0.05 ms) values for rat brains at 16.4T were consistent with those previously reported at 11T, 9.4T and 4.7T (16,17).

DISCUSSION and CONCLUSION

In the present study, we examined the *in vitro* and *in vivo* ^{17}O sensitivity at two high field strengths. The results demonstrate an approximated 2.5~2.9-fold SNR gain at 16.4T compared to 9.4T for the phantom and rat brain studies, which indicated an approximated square power ($\beta=2$) dependence of ^{17}O SNR on B_0 . This finding of quadratic SNR gain over the field strength was consistent with the previous studies (16,17,22) and close to the theoretical prediction of 7/4 (23). Also shown in Table 1, a smaller measurement variance (2~4-fold reduction) was obtained at 16.4T as compared with that of 9.4T indicated an improved signal stability at 16.4T. All of these improvements suggest the significant advantage provided by high/ultrahigh magnetic fields, and more reliable measurements of CMRO_2 are expected from the direct detection of small dynamic changes of metabolically generated H_2^{17}O signal during a brief $^{17}\text{O}_2$ inhalation at high/ultrahigh magnetic fields.

Compare to the 9.4T, a larger error in inter-subject measurements at 16.4T were observed (see Figure 1a and Table 1). Two possible explanations for this observation: a larger SNR variation among different subjects measured at 16.4T; and the non-uniform sensitivity profile for detecting the ^{17}O NMR signal due to inhomogeneous RF (B_1) field of the surface coil applied in this study. Therefore, the measured ^{17}O signal and SNR were sensitive to a number of factors such as the relative position between the sample and RF coil, sample

loading factor, RF coil tuning and matching performance etc. Nevertheless, both SNR and the variance between repeated measurements were much improved at 16.4T than that at 9.4T, which are most crucial for *in vivo* ^{17}O MR application.

Interestingly, the results summarized in Table 1 also indicate that the variance was inversely proportional to $\sqrt{NT}$ at both 9.4T and 16.4T. This observation was consistent with a positive linear relationship between SNR and $\sqrt{NT}$ (see Table 1). They collectively suggest an inverse relationship between variance and SNR, and the white noise is the dominant noise source of the *in vivo* ^{17}O MRS signal measured in the rat brain.

The measured ^{17}O T_1 and T_2^* values for the natural abundance H_2^{17}O in the rat brain were similar between 16.4T and 9.4T, which provide further evidence of the independence of ^{17}O relaxation times on the field strength. Moreover, the short ^{17}O T_1 value makes it possible for much faster data acquisition and more signal averages, and consequently, contributes to the improvement of SNR per unit of sampling time, which is essential for the success of CMRO₂ measurement and quantification. Owing to the unique field independent ^{17}O relaxivity, Eq. [1] can be further simplified to Eq. [2],

$$\text{SNR} \approx k \cdot B_0^\beta \quad [2]$$

where k is a constant. Figure 4 displays the relationship between the relative ^{17}O SNR, which was the SNR of the rat brain normalized to the SNR value measured at 9.4T, and the field strength (B_0) across a wide range up to 16.4T. The relative SNR value of 2.75 at 16.4T was obtained in the present study (averaged from the 2.7 and 2.8 values listed in Table 1). The relative SNR value of 0.238 at 4.7T was obtained from a previous rat brain study (17). The zero SNR value at zero field strength was based on the NMR principle/theory. The solid line in Fig. 4 is the fitting curve according to the function expressed by Eq. [2]. The regression results $k=0.015$ and $\beta=1.9$ for a wide field strength range from zero to 16.4T. The high β power value suggests that compared to *in vivo* ^1H , ^{31}P and ^{13}C MRS, the *in vivo* ^{17}O MRS can benefit the most from the sensitivity gain at high/ultrahigh field.

In conclusion, the significant SNR improvements achievable at 16.4T could benefit the 3D CMRO₂ imaging based on the ^{17}O MRS/I methods, which should provide an opportunity for detecting altered oxidative metabolism associated with brain function and neurological diseases with improved spatial and temporal resolutions.

Acknowledgments

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References

1. Mintun MA, Raichle ME, Martin WR, Herscovitch P. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J Nucl Med.* 1984; 25:177–187. [PubMed: 6610032]
2. Peterson LR, Gropler RJ. Radionuclide imaging of myocardial metabolism. *Circ Cardiovasc Imaging.* 2010; 3:211–222. [PubMed: 20233863]
3. Zhu XH, Chen W. In vivo oxygen-17 NMR for imaging brain oxygen metabolism at high field. *Progress in NMR Spectroscopy.* 2011; 59:319–335.
4. Mateescu, GD.; LaManna, JC.; Lust, DW.; Mars, L.; Tseng, J. Oxygen-17 magnetic resonance: in vivo determination of nascent mitochondrial water in animals breathing ^{17}O -enriched air. *Proceedings of the 1st Annual Meeting of SMRM; San Francisco, California, USA.* 1991. p. 1031

5. Pekar J, Ligeti L, Ruttner Z, Lyon RC, Sinnwell TM, van Gelderen P, Fiat D, Moonen CT, McLaughlin AC. In vivo measurement of cerebral oxygen consumption and blood flow using ^{17}O magnetic resonance imaging. *Magn Reson Med*. 1991; 21:313–319. [PubMed: 1745131]
6. Arai T, Mori K, Nakao S, Watanabe K, Kito K, Aoki M, Mori H, Morikawa S, Inubushi T. In vivo oxygen-17 nuclear magnetic resonance for the estimation of cerebral blood flow and oxygen consumption. *Biochem Biophys Res Commun*. 1991; 179:954–961. [PubMed: 1898415]
7. Atkinson IC, Thulborn KR. Feasibility of mapping the tissue mass corrected bioscale of cerebral metabolic rate of oxygen consumption using 17-oxygen and 23-sodium MR imaging in a human brain at 9.4 T. *Neuroimage*. 2010; 51:723–733. [PubMed: 20188194]
8. Fiat D, Ligeti L, Lyon RC, Ruttner Z, Pekar J, Moonen CT, McLaughlin AC. In vivo ^{17}O NMR study of rat brain during $^{17}\text{O}_2$ inhalation. *Magn Reson Med*. 1992; 24:370–374. [PubMed: 1569875]
9. Mellon EA, Beesam RS, Baumgardner JE, Borthakur A, Witschey WR 2nd, Reddy R. Estimation of the regional cerebral metabolic rate of oxygen consumption with proton detected ^{17}O MRI during precision $^{17}\text{O}_2$ inhalation in swine. *J Neurosci Methods*. 2009; 179:29–39. [PubMed: 19428508]
10. Tailor DR, Baumgardner JE, Regatte RR, Leigh JS, Reddy R. Proton MRI of metabolically produced H_2^{17}O using an efficient $^{17}\text{O}_2$ delivery system. *Neuroimage*. 2004; 22:611–618. [PubMed: 15193589]
11. Zhu XH, Zhang Y, Tian RX, Lei H, Zhang N, Zhang X, Merkle H, Ugurbil K, Chen W. Development of ^{17}O NMR approach for fast imaging of cerebral metabolic rate of oxygen in rat brain at high field. *Proc Natl Acad Sci U S A*. 2002; 99:13194–13199. [PubMed: 12242341]
12. McCommis KS, He X, Abendschein DR, Gupte PM, Gropler RJ, Zheng J. Cardiac ^{17}O MRI: toward direct quantification of myocardial oxygen consumption. *Magn Reson Med*. 2010; 63:1442–1447. [PubMed: 20512845]
13. Rogers, WJ.; Gupte, PM.; Piccione, EA.; Kramer, CM.; Vido, DA.; Reichek, N. T_2 imaging using $\text{O}-17$ for detection of viability in myocardial infarction. *Proceedings of the 7th Annual Meeting of ISMRM*; Philadelphia, Pennsylvania, USA. 1999. p. 309
14. Zhu, XH.; Zhang, Y.; Chen, W. In vivo ^{17}O MRS imaging for assessing myocardial oxygen metabolism in rat heart at 9.4 T. *Proceedings of the 18th Annual Meeting of ISMRM*; Stockholm, Sweden. 2010. p. 172
15. Zhu XH, Zhang N, Zhang Y, Zhang X, Ugurbil K, Chen W. In vivo ^{17}O NMR approaches for brain study at high field. *NMR Biomed*. 2005; 18:83–103. [PubMed: 15770611]
16. Thelwall, PE.; Blackband, SJ.; Chen, W. Field dependence of ^{17}O T_1 , T_2 and SNR - in vitro and in vivo studies at 4.7, 11 and 17.6 Tesla. *Proceedings of the 11th Annual Meeting of ISMRM*; Toronto, Ontario, Canada. 2003. p. 504
17. Zhu XH, Merkle H, Kwag JH, Ugurbil K, Chen W. ^{17}O relaxation time and NMR sensitivity of cerebral water and their field dependence. *Magn Reson Med*. 2001; 45:543–549. [PubMed: 11283979]
18. Garwood M, Schleich T, Bendall MR, Pegg DT. Improved Fourier-Series Windows for Localization in In vivo Nmr-Spectroscopy. *Journal of Magnetic Resonance*. 1985; 65:510–515.
19. Hendrich K, Hu XP, Menon RS, Merkle H, Camarata P, Heros R, Ugurbil K. Spectroscopic Imaging of Circular Voxels with a 2-Dimensional Fourier-Series Window Technique. *Journal of Magnetic Resonance Series B*. 1994; 105:225–232. [PubMed: 7850168]
20. Zhu XH, Zhang Y, Zhang N, Ugurbil K, Chen W. Noninvasive and three-dimensional imaging of CMRO_2 in rats at 9.4 T: reproducibility test and normothermia/hypothermia comparison study. *J Cereb Blood Flow Metab*. 2007; 27:1225–1234. [PubMed: 17133228]
21. Zhang N, Zhu XH, Lei H, Ugurbil K, Chen W. Simplified methods for calculating cerebral metabolic rate of oxygen based on ^{17}O magnetic resonance spectroscopic imaging measurement during a short $^{17}\text{O}_2$ inhalation. *J Cereb Blood Flow Metab*. 2004; 24:840–848. [PubMed: 15362714]
22. Wen H, Chesnick AS, Balaban RS. The Design and Test of a New Volume Coil for High-Field Imaging. *Magnetic Resonance in Medicine*. 1994; 32:492–498. [PubMed: 7997115]
23. Hoult DI, Richards RE. Signal-to-Noise Ratio of Nuclear Magnetic-Resonance Experiment. *Journal of Magnetic Resonance*. 1976; 24:71–85.

Figure 1. One-dimensional ^{17}O SNR profiles along an axis parallel to the RF coil plane obtained from the central slides of 3D ^{17}O MRS imaging in rat brains at 9.4T and 16.4T, respectively (a), and their SNR comparison (b). The vertical dashed lines present the anatomical edges of the rat brain.

Figure 2. Representative anatomical image and the corresponding 2D ^{17}O spectral image of natural abundance H_2^{17}O of the rat brain obtained at 9.4T and 16.4T, respectively (a). The spectra of central brain voxel acquired at 9.4T and 16.4T were shown in (b) for comparison.

Figure 3.

Stacked plots of brain H_2^{17}O spectra from a representative voxel (~ 0.1 ml voxel size and located near the center of ^{17}O coil-sensitive region inside the rat brain) of 3D ^{17}O MRS imaging data acquired before, during and after 2.75 minutes $^{17}\text{O}_2$ inhalation in a rat brain at 16.4T (**a**), and the linear fitting of the metabolic H_2^{17}O concentration in this voxel during the $^{17}\text{O}_2$ inhalation for determining the CMRO_2 value (**b**).

Figure 4. Field dependence of the relative ^{17}O SNR measured in the rat brain and normalized to the SNR value measured at 9.4. The solid line shows the fitting curve according to Eq. [2], covering the field strength from zero to 16.4T.

Table 1¹⁷O SNR and signal stability comparisons between 9.4T and 16.4T (n=5)

	Sphere Phantom (NT=128)	Rat Brain (NT=16)	Rat Brain (NT=128)	Rat Brain (NT=512)
SNR_{9.4T}	36.8±3.5	35.6±2.1	97.5±10.4	197.1±21.8
SNR_{16.4T}	108.4±11.3	96.4±8.8	269.2±28.9	531.3±51.9
SNR_{16.4T}/SNR_{9.4T}	2.9	2.7	2.8	2.7
Variance at 9.4T	2.19%	2.16%	0.90%	0.47%
Variance at 16.4T	0.53%	1.01%	0.33%	0.14%