Magnetic Field Strength Increase Yields Significantly Greater Contrast-to-Noise Ratio Increase: Measured Using BOLD Contrast in the Primary Visual Area[1]

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Rationale and Objective. The advantage of a higher static magnetic field for functional MRI has been advocated; however, the observed advantage varies. The aim of this study was to evaluate the effect of increasing static magnetic field strength on the task-related increase in blood oxygenation level–dependent (BOLD) signal and residual noise with visual stimuli of different frequencies, which may enable better comparisons of results of different MRI scanners.

Materials and Methods. Eight right-handed healthy volunteers were presented checkerboard stimuli flickering at 5 different frequencies up to 8 Hz. Field strengths of 3 T or 1.5 T were used to measure frequency-dependent signal changes in the primary visual area. Regression analysis was performed for the signal increase and the "noise," which was defined by the root mean of squares of the residual signal fluctuation. These values were compared and their relationship was analyzed. Imaging parameters were identical except for the use of a 25% shorter echo time using 3 T.

Results. The frequency-dependent increase in BOLD signal using 3 T was twice that using 1.5 T. In contrast, the ratio of noise values that reflect time-course signal fluctuation (3 T/1.5 T) was only 0.88. There was large individual variance in these values, but the slope and noise values were linearly related using either field strength. The contrast-to-noise ratio using 3 T was 2.3 times higher than that using 1.5 T.

Conclusion. There was a greater-than-linear increase in the contrast-to-noise ratio compared with the increase of field strength, demonstrating an advantage of using higher field strengths in fMRI studies.

Key Words. Functional MRI; magnetic field strength; BOLD contrast; contrast to noise.

Functional MRI (fMRI) is now widely accepted as one of the standard tools for the analysis of human brain func-

tion. Many fMRI experiments use the blood oxygenation level–dependent (BOLD) contrast measurement (1). Using a static magnetic field strength of 1.5 T, the BOLD signal change is usually small (only a few percent), and the ratio of activation signal increase over background signal fluctuation is typically only 3 to 4 (2). Thus, differences in task-related signal changes are often difficult to discern (3). One of the solutions is to use an MR scanner with a higher static magnetic field strength. A model analysis showed that the BOLD signal is proportional to the static magnetic field strength (B_0) for large vessels (diameter $> 8\ \mu$m, venules and veins) and to B_0^2 for

small vessels (diameter $< 8 \mu$m, capillaries) (4). This raises the possibility that use of a higher static magnetic field strength would be advantageous for detecting task-related signal changes in fMRI experiments, particularly at the level of capillaries. Previous studies indicate that the detectability of signal changes increases using higher field strengths, but the results are not consistent. The observed signal differences vary from being almost the same (5), to almost linear (6), and to supralinear (7) with an increase in field strength. Such discrepancies may be due in part to differences in background signal (noise), the definition of the region of interest, and the scan parameters used, such as repetition time (TR), echo time (TE), and flip angle (FA).

Statistical results are a function not only of the magnitude of the comparators (in this case signal change) but also of the variability (in this case fluctuation in background signal, ie, "noise"). In fMRI studies (2,3,5,6,8,9), the ratio of the task-related signal change to background signal fluctuation is called the contrast-to-noise ratio (CNR) and is different from the signal-to-noise ratio (SNR) observed in each single image. The background signal fluctuations are caused by numerous factors, including thermal noise, pulsatile flow of blood and cerebrospinal fluid, changes in blood oxygenation with respiration, and head motion (3,10). Therefore, task-related signal changes and the background signal fluctuations should be evaluated separately and compared to make a reliable inference on the merit of using higher field strength.

In the present study, we adopted a task in which the activation levels changed linearly with the grading of stimuli. Use of a parametric experiment was advantageous because, although absolute signal intensity is not a reliable measure in fMRI, the degree of signal changes observed during graded tasks was mutually scaled and normalized among sessions (at least within the linear portion of the change in signal) and comparison among subjects and setups (including scanners) was possible (2). There is a linear increase in signal in the primary visual areas in response to viewing increasing frequencies of flickering stimulus up to 8 Hz (11) that is suitable for parametric analysis. It allows a measurement of internally referenced gradual signal changes and is less confounded by factors such as subject position, shimming, and scanner calibration at different field magnets (12). To investigate the possible advantages of using higher magnetic field strengths, we measured frequency-dependent response amplitude and its residual errors (noise) in the primary

visual area using 2 different static magnetic field strengths.

MATERIALS AND METHODS

Eight right-handed healthy volunteers (4 men and 4 women, 26.0 ± 3.70 years old) gave written informed consent and participated in the study. This study was approved by the institutional ethical committee. Flickering black-and-white circular checkerboard stimuli were presented at five different frequencies (1, 2, 4, 6, and 8 Hz) generated by CIGAL software (University of Pittsburgh, Pittsburgh, PA) (13), each frequency used in a separate session. The control condition was eye-fixation on a crosshair. In each session, the control (C) screen and flickering stimuli (S) were alternately presented, each for 32 seconds; repeated 3 times; and followed by a last control condition (CSCSCSC). For both measurements, the same video projection setup was used (ELP-7200, Epson, Tokyo, Japan). This setup allowed viewing of stimuli with a visual angle of approximately 32.5 degrees horizontally and 16.7 degrees vertically. Subjects were instructed to give the same level of attention to each part of the experiments.

Data Acquisition

The images were acquired using a 1.5 T or a 3 T scanner (Signa, GE, Milwaukee, WI) with a single-shot gradient echo (GE) echo planar imaging (EPI) sequence. The same design of standard circulatory polarizing head coils was used for both scanners. Common parameters were: TR = 4 seconds, FA = 90°, field of view = 22 cm, matrix size = 64 x 64 in 26 axial planes of 4 mm thickness with a 1-mm gap. This long TR of 4 seconds is typical for a study involving imaging the whole brain, in which activation is dominated by the level of blood oxygenation and vascular enhancement related to inflow effects is minimized (14). TE was 40 ms when using 1.5 T and 30 ms when using 3 T. With an intermission of approximately 30 minutes, the same tasks were performed using a different magnetic field strength. The orders of both task frequencies and field strengths were randomized among subjects. When using 1.5 T, the anatomical images were acquired with a T1-weighted, 3-dimensional, inversion recovery, GE sequence using the following parameters: FA = 15°, TE = 4.2 ms, TR = 30 ms, and inversion time = 300 ms. The matrix size was 256×256 and 124 slices of 1.5 mm thickness were scanned. When using 3 T, the same dimension of anatomical images as when
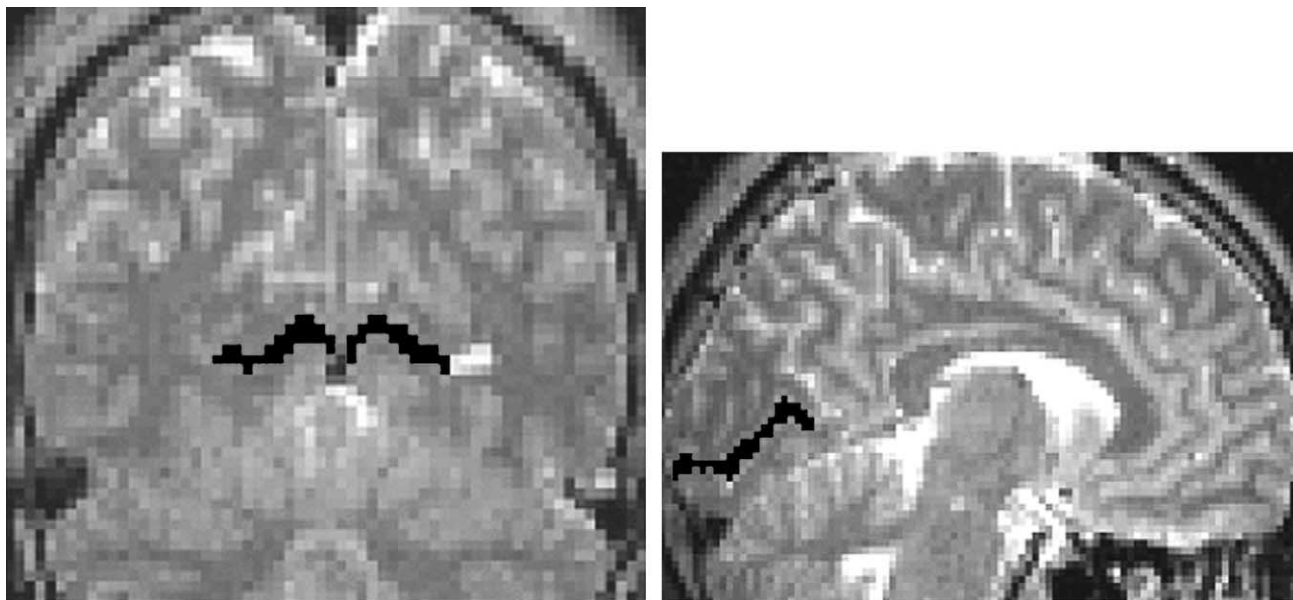
a.   **b.**

Figure 1. An example of the region of interest placed along the calcarine fissure is indicated in black. **(a)** Coronal view. **(b)** Sagittal view.

using 1.5 T was acquired with a T2-weighted, fast spin echo sequence using the following parameters: TR = 6000 ms and TE = 70 ms, although the number of acquired slices was 112.

Data Processing

Data was analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented using Matlab (Mathworks, Sherborn, MA) (15). The first 4 images were discarded to allow stabilization of the magnetization. Functional images were realigned to the first image for movement correction, transformed into a standard stereotaxic space (16) using the least square method (17) using anatomical images that had been coregistered to the referenced EPI images, and smoothed with a 6 mm full width at half maximum (FWHM) Gaussian filter. The anatomical images of the same subjects collected using both field strengths were coregistered and T2-weighted anatomy was used for normalization. Each 32-second checkerboard stimulation block was analyzed separately and the signal changes were estimated after scaling the mean value of time-course signals to 100 for each and every voxel, which yielded 3 sets of response amplitude images (or percent signal change images) for each of 5 stimulus frequencies. Signal fluctuations slower than half of the task frequency were modeled

and removed. Task-related signal changes were averaged over the subsets of voxels at and around the calcarine sulcus (18–21) (Figure 1) with reference to a standard brain atlas (22), because of individual variances in the calcarine anatomy (20,21). These voxels were cross-referenced with the EPI and anatomical images to confirm that they did not lie in a "dark" line that represents a blood vessel (8). Voxels in which the signal decreased at any stimulus frequency using either field strength were excluded and the region of interest that was common to both field strengths was used. A linear regression line for the task-related signal increases plotted against the frequencies was calculated for each subject and the slopes of the lines of all subjects were compared between 1.5 T and 3 T. Residual time-course signal fluctuations after the subtraction of estimated task-related signal change were averaged as root mean of squares, which is referred to as noise in the following.

RESULTS

The average coefficients for linear regression between frequency and signal increase were 0.62 ± 0.13 (mean $\pm$ S.D.) using 1.5 T and 0.75 ± 0.10 using 3 T (Table 1). In all subjects, the significance level of linear fit was

Table 1
The Average of Regression Coefficients

Field strength mean ± S.D.
3T 0.75 ± 0.10
1.5T 0.62 ± 0.13

($P < .05$)

$P < .05$, but there was a significantly better fit using 3 T, shown by a significant difference in the regression coefficients ($P < .003$). The slope of the regression lines was steeper using 3 T. The averages were 0.049 ± 0.033 using 1.5 T and 0.097 ± 0.075 using 3 T (Fig. 2). When these values were viewed individually, they ranged from 0.021 to 0.11 using 1.5 T and from 0.040 to 0.28 using 3 T. Individual ratios of slope values using 3 T compared to those using 1.5 T ranged from 1.1 to 2.9 and the average was 2.0 ± 0.56. In the V1, noise was smaller using 3 T than that using 1.5 T. Noise values ranged from 0.43 to 1.92 using 1.5 T and from 0.42 to 1.97 using 3 T and the averages were 0.93 ± 0.53 and 0.78 ± 0.49, respectively. The ratios of noise values using 3 T to those using 1.5 T ranged from 0.44 to 1.1 and the average was 0.88 ± 0.20.

When the slope values of the regression lines were plotted against noise values, there was a linear relationship between these values using either field strength ($r > 0.95$, Fig. 3). These values ranged from 0.038 to 0.081 and the average was 0.053 ± 0.016 using 1.5 T and from 0.075 to 0.16 and the average was 0.12 ± 0.031 using 3 T. The ratio of slope to noise values yielded a relative CNR, because the slope value was the ratio of signal increase to stimulus frequency. The relative CNR comparing use of 3 T to 1.5 T was 2.3.

DISCUSSION

The results of the present study indicate that there is an advantage to using higher static magnetic field strengths when conducting fMRI experiments involving BOLD contrast analysis. The contrast-to-noise ratio was supralinear with an increase in field strength: CNR increased 15% more than the increase in field strength. Although the task-related signal increase varied from one subject to another with the increased field strength, they were positively correlated with the noise.

In the present study, we defined the region of interest on the primary visual cortex based on the anatomical definition.
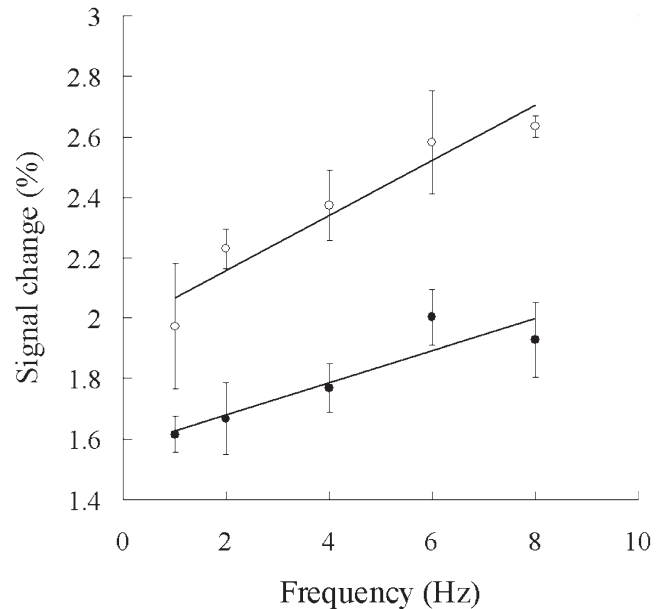

Figure 2. A representative example of the linear relationship between stimulus frequencies and the average percent signal changes using either field strength in a single subject. Closed circles represent data collected using 1.5 T and open circles represent data collected using 3 T. The error bars indicate the standard deviations.

Several previous studies defined their ROI based on areas activated over a certain threshold. Studies that have used the former method (7) reported larger signal increases than studies that used the latter method (5,6) when experiments were performed at higher magnetic field strengths, consistent with the results of the present study. The linear (or less) signal increase observed in studies using the latter method may be due to the fact that 36% (5) to 70% (6) more voxels were included in the average using higher field strengths. When the number of activated voxels increases, the averaged signal increment decreases (5,23). A comparison of signal changes using different field strengths based on the activated voxels may result in underestimation of the signal increase, because voxels with a smaller task-related increment may then exceed a certain threshold upon activation at higher field strengths and be included for averaging. This is especially true when the residual signal fluctuations decrease using higher field strengths.

In the present study, the average ratio of the slope values using 3 T to those using 1.5 T was 2.0, indicating that the signal change increased linearly with the increase in static magnetic field strength. This result, however, is affected by 25% shorter TE value (or transverse relaxation time) for the data collected using 3 T (30 ms) than that using 1.5 T (40 ms). Different TE values were adopted because T_1 and
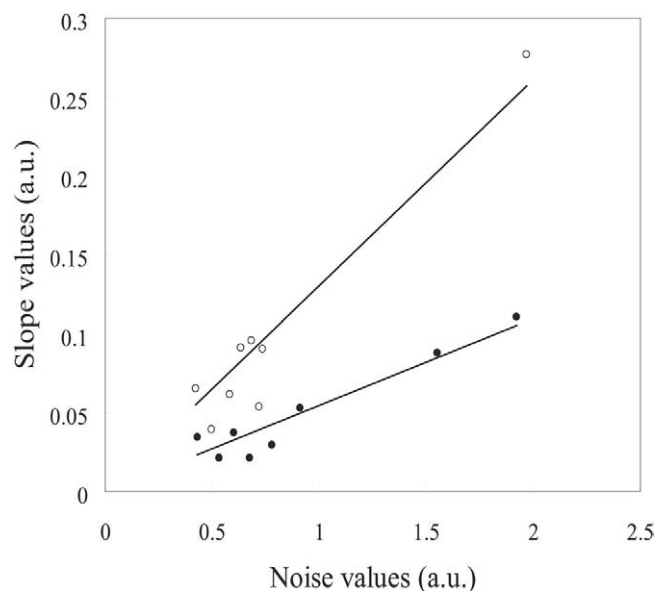
Figure 3. The individual slope values were plotted against RMS values using 1.5 T (closed circles) or 3 T (open circles). There was a linear relationship between slope and RMS values using either field strength ($r > 0.95$).

T_2^* properties are dependent on field strength and scan parameters must be adjusted so that the signal defect (24) and image distortion (25) caused by susceptibility artifact are kept within an acceptable level. To evaluate the signal increases under the same conditions, the change in the apparent transverse relaxation rate (ΔR_2^*) that is independent of TE values should be compared. It can be approximated by the equation:

$$\Delta R_2^* = \Delta S / TE$$

where ΔS is percent signal change by activation (6). In the present study, the slopes of the regression lines can be substituted for ΔS. Thus, the averaged ratio of ΔR_2^* using 3 T to that using 1.5 T was 2.7. This supralinear relationship is equivalent to the result reported by Turner et al (7), who evaluated the activation signal increase from a fixed ROI and adjusted for difference in TE values using 1.5 T or 4 T. Yang et al (6) also compared ΔR_2^* values using 1.5 T or 4 T and found that the increase was almost linear. They extracted signal changes from activated areas above a certain threshold, however, resulting in the averaging of more voxels using 4 T than using 1.5 T. An increase in the number of averaged voxels likely results in an underestimation of percent signal changes, as discussed previously.

There was a significant difference in the regression coefficients between observations using 1.5 T or 3 T in the present study. This difference, however, may not affect the estimation of the regression coefficients. Cohen and DuBois (23) conducted a Monte Carlo experiment and examined the accuracy to which the slope could be measured under a variety of different noise conditions. Their results suggest that even under very noisy conditions, the slope can be determined relatively precisely. In the present study therefore, the differences in the regression coefficients between observations using 1.5 T or 3 T were not considered to have much influence on the accuracy of the regression slope estimations.

When evaluating neuronal activation in fMRI experiments, most methods rely on a statistical measure that compares the degree of signal increase to the underlying baseline signal fluctuation (26). Thus, the amount of signal increase and analysis of the signal fluctuation irrelevant to the task (ie, noise) are both important. In the present study, we found that the average of noise values using 3 T was 12% less than that using 1.5 T. The noise components in BOLD imaging can be divided into non-physiological (σ_0, thermal, and system) and physiological (σ_p) noise (9). The signal and the intrinsic non-physiological noise in each MRI image have been shown to be quadratic and linear to static magnetic field strength, respectively (27). Hence, the noise in each image should be half at 3 T in comparison with 1.5 T, if the signal level is the same. In our analysis, the average time-course signal values were normalized to 100 at both magnetic field strengths, and non-physiological noise should be half at 3 T. However, we observed much less reduction in the total amount of noise in the current study. According to Kruger and Glover (9), the physiological noise is further divided into two components: one is dependent on the BOLD contrast (σ_B) and the other is not (σ_{NB}). Their measurements revealed that 84% of the noise in BOLD imaging was explained by the BOLD contrast-dependent noise (σ_B), which can be calculated as:

$$\sigma_B = c_1 \cdot \Delta S$$

where c_1 is a constant and ΔS is the degree of signal change (9). Therefore, if the task-related signal increase is large, then the increase in noise will also be large, given that σ_B is the predominant component of the total noise. Therefore, the advantage of better signal-to-noise of each image at 3 T was largely impaired by the increase in

physiological noise, resulting in only slight improvement in terms of the total noise level. The results also showed that slope/noise is dependent on the static magnetic field strength (Fig. 3). Because c_1 is equal to $\sigma_B/\Delta S$, the inverse of CNR, slope/noise is equal to relative CNR. The large interindividual variability of signal change and noise may reflect differences in the individual responses and noise characteristics of that particular experiment session. The positive linear relationships among subjects at either field strength, however, indicate that the higher CNR yields an advantage to using higher field strengths for fMRI experiments involving BOLD contrast analysis. The averages of relative CNR (slope/noise) were 0.053 using 1.5 T and 0.12 using 3 T, and the 3 T/1.5 T ratio was 2.3; a greater-than-linear increase. With implementation of the noise reduction methods, especially physiological ones (28–30), the advantage of a higher magnetic field in functional imaging will be more pronounced by further reduction of the noise.

CONCLUSION

Using parametric analysis, we examined internally referenced task-related fMRI signal change and noise using different magnetic field strengths. Using 25% shorter TE to maintain artifacts within acceptable levels, the increase in response amplitude using 3 T in comparison to that using 1.5 T was almost linear to the increase in field strength. Analysis of the increase in noise level, however, showed that the statistical inference was supralinear, confirming the advantage of using higher magnetic field strengths in fMRI studies involving BOLD contrast analysis.

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