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LABORATORY INVESTIGATIONS

Reproducibility of Visual Activation in Functional Magnetic Resonance Imaging at Very High Field Strength (4 Tesla)

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Purpose: The reproducibility of functional magnetic resonance imaging (fMRI) has been studied on 1.5 Tesla (T) (high field strength) scanners. We report the reproducibility of visual activation in fMRI at 4 T (very high field strength).

Methods: Five healthy subjects were scanned twice in the same session with a 4 T scanner during binocular flashing visual stimulation. The activated areas during the first and second acquisition were compared.

Results: Activation of the visual cortex was observed in all subjects and activation of lateral geniculate nucleus was also detected in four subjects. The ratio of overlapping activated voxels in the first and second acquisition was 0.81 ± 0.05.

Conclusions: Reproducibility of visual activation using fMRI at 4 T was found to be acceptable, and the results from 4T scanners show a reliability similar to those at 1.5 T. **Jpn J Ophthalmol 2001;45:1–4**

Key Words: 4 Tesla, functional magnetic resonance imaging, lateral geniculate nucleus, visual activation, visual cortex.

Introduction

The reproducibility of functional magnetic resonance imaging (fMRI) has been investigated using 1.5 Tesla (T) MR units,[1–5] and these studies have shown reasonably good reproducibility of fMRI activation at 1.5 T. High magnetic field scanners, especially those at 4 T, have also been used in fMRI studies,[6] as well as in early studies on blood oxygenation level-dependent (BOLD) contrast.[7] The contribution of the BOLD effects to the apparent transverse relaxation rate was found to be proportional to the squared magnetic field strength for the small vessels and proportional to the magnetic field strength for the large vessels.[8] Also, the signal to ratio (SNR) and signal intensity changes were much larger at 4 T than at 1.5 T.[9–12] Therefore, fMRI at 4 T is ideal for functional mapping of the brain. However, geometric distortion in fMRI images is also thought to be proportional to the magnetic field strength, and image artifacts are more severe at 4 T due to a stronger susceptibility and chemical shift artifacts. Because multiple factors influence the BOLD signal, the reproducibility of fMRI activation at 4 T may differ from that at 1.5 T. Therefore, before this technique is used in research fields and clinical settings, the reproducibility of fMRI at 4 T should be measured.

Recently, the reproducibility of fMRI during a finger-opposition task was explored using a 4 T scanner;[13] however, the reproducibility of visual activation in fMRI at 4 T has not been evaluated. The aim of this study was to determine the reproducibility in fMRI at 4 T during binocular visual stimulation.

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Materials and Methods

Subjects and Data Acquisition

Five healthy volunteers (3 men and 2 women), ranging in age from 25 to 58 years, gave informed consent and participated in this study. Approval of the consent and protocol for this study was given by the Committee on Studies Involving Human Beings of the University of Pennsylvania. No subjects had a history of neurologic or ophthalmologic disease.

All studies were performed with a 4-T Signa scanner (General Electric Medical Systems, Milwaukee, WI, USA) with a quadrature head coil. Three-dimensional axial images were acquired covering the whole brain for anatomic images (28 slices; 5-mm thickness). Subsequently, we selected a volume that covered the occipital lobe for functional image acquisition. Functional images were obtained using a gradient-echo echo-planar image (EPI) sequence (TR = 2000 milliseconds; TE = 28 milliseconds; matrix size = 40×64; field of view = 150×240 mm^2; 21 slices; 5-mm thickness) after data for distortion correction were collected. The first 20 seconds of EPI data (10 scans) were discarded to remove the magnetic saturation effects.

Binocular full-field visual stimulation was provided by light-emitting diode goggles (S10VSB; Grass Instruments, Quincy, MA, USA). Subjects wore the flashing goggles and were instructed to keep their eyes open. During the "rest" condition, the light-emitting diodes were turned off for 20 seconds (10 scans). During the "task" condition, the light-emitting diodes flashed at a rate of 8 Hz for 20 seconds (10 scans). The task condition alternated with the rest condition, and the cycle was repeated six times resulting in the acquisition of 120 scans during 4 minutes. This acquisition was repeated twice without taking the subject out of the scanner in order to evaluate the reproducibility.

Data Analysis

Data analyses were performed on UNIX workstations. IDL (Interactive Data Language, Boulder, CO, USA) and SPM96 (Wellcome Department of Cognitive Neurology, London, UK) were used for data analysis. The first 10 scans were discarded before transferring the data from the scanner to the workstations. Distortion correction files were used to correct geometric distortion in the EPI images caused by residual magnetic field inhomogeneity and this information was applied for the two EPI data sets of each subject.

The anterior commissure (AC) was determined and the origin for the EPI images was set on the superior edge of the AC. The EPI scans were realigned to the first scan of the second study. The data were smoothed using an $8 \times 8 \times 10$-mm full width at half maximum Gaussian kernel. A delayed box-car by 6 seconds was used. Global normalization, a high pass filter, and temporal smoothing were used. The *t*-statistics were calculated for each voxel and converted to SPM.[2] Peak Z-values within the visual cortex and lateral geniculate nucleus (LGN) were recorded. For the comparison of the area of activation, the height threshold was set at $Z > 4.5$ so that the threshold approximately corresponded to $P < .05$ after the correction for multiple comparisons in each subject. The ratios for the size of activation (the smaller of the number of activated voxels divided by the average of the number of two studies) and for the common area of activation (the common voxels for the two studies divided by the average of the activated voxels of the two studies), "R_{size}" and "$R_{overlap}$" in references 4 and 5, were calculated for each subject in IDL. In both measurements, a value of 1.0 indicates that the activated areas for the repeated studies matched perfectly (perfect reproducibility), and the value of 0.0 indicates that there was no overlapped area for the two studies (no reproducibility). Those measurements were also performed at $Z > 3.5$ and $Z > 5.5$ to determine the dependence of the thresholds on the reproducibility.

Results

Each subject's motion did not exceed 1 mm for any of the x, y, z-directions. Robust activation was observed in the visual cortex bilaterally in all subjects (Figure 1). Four subjects showed activation in the LGN; however, the oldest volunteer (58 years old) did not show the activation (Table 1, subject 2). Also, activation in the LGN was not found in the second scan of another older subject {subject 1). The ratio for the size of activation ("R_{size}") ranged from 0.88 to 0.97 (average 0.93). The ratio for the common area of the first and second studies ("$R_{overlap}$") ranged from 0.72 to 0.86 (average 0.81) (Table 2). The measurements with the other thresholds showed similar results (average $R_{size} = 0.93 \pm 0.04$, 0.90 ± 0.05; average $R_{overlap} = 0.81 \pm 0.04$, 0.76 ± 0.08; for $Z > 3.5$ and $Z > 5.5$, respectively).

Discussion

Because the task-induced changes of fMRI at the high magnetic field (4 T) are larger than at the lower

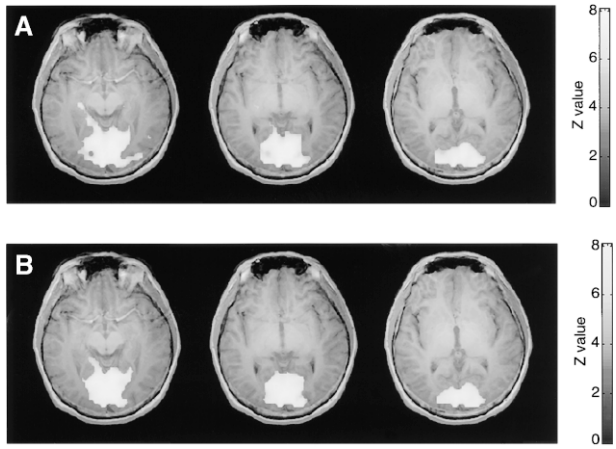

Figure 1. Reproducibility of visual activation of functional magnetic resonance imagin at 4 Tesla. Supra-threshold ($P < .05$, corrected) areas are displayed on corresponding transverse anatomic images of a single subject. (**A**) First study, (**B**) second study.

field, they should be easily detectable at 4 T.[12] In addition, the contrast-to-noise ratio of fMRI experiments has been found to be linearly dependent on magnetic field strength in cortical grey matter but not in the vein regions.[9] Therefore, fMRI at the high field strength is desirable for measuring cortical activity. Although it is difficult to exclude the large vessel effect in this study because of the relatively low spatial resolution, it is likely that the activation area in our study included more grey matter regions than the activated area measured with a conventional 1.5 T scanner.

One major advantage of fMRI at a high field strength is that it allows high spatial resolution images with high SNR. Thus, a small structure, such as the ocular dominance column in the primary visual cortex, has been demonstrated using fMRI at 4 T.[14,15] Although the optimal voxel size may be dependent on the paradigm and the instrument, reduced partial volume effect can provide such high resolution images with increased signal change despite the smaller voxel size.[16] The voxel size in our study is a standard one for EPI fMRI studies at 1.5 T, but it should have provided us with better SNR at the expense of the spatial resolution, given the high magnetic field strength. Additionally, the acquisition with thicker slices yields greater brain volume,[17] which is desirable for fMRI experiments.

Moser and colleagues[3] demonstrated that both SNR and reproducibility reached the maximum at a flip angle of 30° when they applied varying flip angles in their fMRI experiments at 1.5 T. Their study suggested that SNR affects the reproducibility of fMRI. Although direct comparison cannot be made between 1.5 T and 4 T because of the differences of the acquisition sequence and coils, the reproducibility reported here seems to be almost equal to those reported in the literature at 1.5 T.[5] Therefore, this study shows the reproducibility is almost saturated at 1.5 T and is never perfect (the value of 1.0 for "R_{size}" and "$R_{overlap}$") even at 4 T. To increase the reproducibility of fMRI further, it may be necessary to con-

Table 1. Amplitude of Visual Activation

Subject No.	Peak Z Score in Visual Cortex		Peak Z Score in Lateral Geniculate Nucleus*			
			First Study		Second Study	
	First Study	Second Study	R	L	R	L
1	8.62	8.21	5.50	5.62	—	—
2	7.28	6.80	—	—	—	—
3	8.07	8.28	5.25	6.50	4.22	4.76
4	7.82	7.83	4.51	4.05	4.67	4.22
5	7.87	7.71	3.68	3.80	4.06	4.90

*—: Activation was not detected.

Table 2. Reproducibility of Area of Activation

Subject No.	Supra-threshold area ($z > 4.5$) (voxels)			R_{size}*	$R_{overlap}$†
	First Study	Second Study	Overlap		
1	561	450	407	0.89	0.81
2	461	427	319	0.96	0.72
3	1677	1468	1293	0.93	0.82
4	1021	961	851	0.97	0.86
5	980	768	724	0.88	0.83
Average				0.93	0.81

*R_{size}: Smaller of number of suprathreshold voxels divided by average of number of suprathreshold voxels of two studies.

†$R_{overlap}$: Number of common suprathreshold voxels for two studies divided by average of number of suprathreshold voxels of two studies.

trol the subject's alertness or attention even during the simple sensory stimulation.[18]

The activation of LGN was not consistently detected in one subject and was not found in a second subject. These volunteers were the older ones in the group. Because the signal change in the visual cortex during visual stimulation decreases with age,[19] it is likely that age also decreases signal changes within the LGN, so that no activation was observed in the older volunteers. A previous report of fMRI at 4 T demonstrated that the activation of the LGN was not detected in one hemisphere of some volunteers.[20] In addition, the failure in this study to show activity of LGN in 2 subjects may be partly due to the small size of the LGN and the relatively large voxel size. Therefore, the ideal imaging conditions that show LGN activation remain to be determined.

In conclusion, the reproducibility of visual activation with fMRI at 4 T was found to be acceptable. These results suggest that if there is a change which is larger than 20% (either increase or decrease) in the overlap of active voxels, eg, over time, or a difference between groups, we will be able to detect this by using this method. Although activation of the visual cortex was robust and was always found in all subjects, activation of the LGN was not as consistent. It is necessary to consider these variations in activation in the design and interpretation of future experiments as well as in clinical applications.

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