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Test-Retest Analysis with Functional MR of the Activated Area in the Human Visual Cortex

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PURPOSE: To investigate the intersubject and intrasubject variability of the activated area in the visual cortex with functional MR imaging. **METHODS:** Double-section gradient-echo MR images were acquired at 1.5 T in 28 healthy volunteers using the fast low-angle shot (FLASH) technique. Visual stimulation was obtained with light-emitting diode (LED) goggles. Eighteen volunteers were studied twice. The size of the activated areas in the visual cortex and the increase in signal were measured. A reproducibility ratio for size (R_{size}) and for location (R_{overlap}) was calculated on a scale of 0.0 to 1.0. **RESULTS:** Activation was seen in 89% of the subjects. The size of the activated area was widely variable among subjects: mean, $460 \pm 284 \text{ mm}^2$; range, 0 to 1029 mm^2 in the first study in all volunteers. Signal increases ranged from 3.2% to 10.9%, with a mean of $6.6 \pm 1.7\%$. The mean values of intrasubject variability testing were $R_{\text{size}} = 0.83 \pm 0.16$ and $R_{\text{overlap}} = 0.31 \pm 0.11$. **CONCLUSION:** Functional MR imaging with the FLASH technique is useful in identifying certain cortical areas that have quite variable locations among subjects. This study provides reference data for the intrasubject and intersubject variability of the activation pattern of the visual cortex.

Index terms: Magnetic resonance, functional; Magnetic resonance, technique

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Several studies have used blood oxygen level-dependent (BOLD) functional magnetic resonance (MR) imaging to measure human brain activation in the motor (1, 2) or visual (2–6) cortex. Activation in the auditory cortex (7, 8) or in areas activated by higher cognitive functions like speech (9), word generation (10), and working memory (11) has also been measured with BOLD functional MR imaging. Visual paradigms are probably most widely studied, and,

recently, functional MR imaging has revealed borders of multiple visual areas in human subjects (12). However, the structure, size, and even location of the visual cortex differs from person to person (13). In addition, subjects undergoing functional MR imaging can be classified into three groups: those who show consistent activation in the expected area, those who show variable results, and those who show no activation at all.

In one study, three subjects were tested for test-retest reliability using a cognitive paradigm (J. D. Cohen, D. C. Noll, L. Nystrom, "Qualitative and Quantitative Assessment of Test-Retest Reliability of Functional MRI Data," presented at the annual meeting of the Society of Magnetic Resonance and the European Society for Magnetic Resonance in Medicine and Biology, Nice, France, August 1995), and Yetkin et al (14) tested four subjects using a sensory and motor paradigm. We investigated the size and reproducibility of activated areas in the visual cortex in a large group of healthy volunteers.

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Fig 1. Parasagittal scout view shows positioning of the two sections around the calcarine fissure for measuring the visual paradigm.

Subjects and Methods

Studies were done on a 1.5-T MR unit using a standard circularly polarized head coil. Twenty-eight healthy volunteers (15 men and 13 women, 19 to 33 years old) without ocular refraction anomalies, history of vision loss, or color blindness participated in a complete visual stimulation study, and 18 of these subjects were studied a second time after a period of 1 to 3 weeks. Informed consent was obtained after the nature of the procedures had been fully explained.

Subjects were positioned with the standard equipment. First, a localizer scan was made in all three orthogonal directions to verify visually whether the midsagittal plane appeared vertical in the coronal and axial images. Next, T1-weighted sagittal images were acquired to locate the calcarine fissure. For the axial functional MR images, sections were placed parallel on either side of the calcarine fissure (Fig 1) and first-order shimming was performed manually. This procedure of defining the two sections was done by the same investigator in each of the two studies.

The functional MR imaging measurement consisted of a double-section flow-compensated (read direction and through-plane) fast low-angle shot (FLASH) sequence (15) with the following parameters: 91/60/1 (repetition time/echo time/excitations), a flip angle of 15° to reduce inflow effects (16), a section thickness of 5 mm, a field of view of 250 mm, a matrix of 128^2 sinc-interpolated to 256^2 , an intersection gap of 1 mm, an acquisition time of 14 seconds, and a bandwidth of 19 Hz per pixel. Twenty-five images of both sections were acquired in an alternating manner: five during rest, five during visual stimulation, and so on. All subjects underwent the same visual paradigm while wearing modified goggles (Grass Instruments, Quincy, Mass) with two 5×6 light-emitting diode (LED) matrices, one in front of each eye. It was made sure that the goggles fitted each subject well, and all subjects were

instructed to lie completely still throughout the study and to keep their eyes open. During the rest periods, subjects were lying in the dark, since the goggles were turned off and no light from outside could enter the goggles. During the stimulation periods, the goggles were turned on and the visual field of each eye was illuminated with a flashing red light (8 Hz).

All postprocessing was done using the 256^2 images. During postprocessing, images were corrected for possible small movement artifacts with a simplified version of the algorithm described by Woods et al (17), correcting for in-plane translations and using linear interpolation. Stability of the signal of the functional MR images during the examination was verified visually by viewing the signal of an area near the calcarine fissure in time. Signal-to-noise ratio (SNR) was calculated for the gray/white matter in the occipital region with the formula $SNR = 0.655 \times (M_{ave, tissue}/M_{SD, background})$, with $M_{ave, tissue}$ the average of the signal of the gray/white matter and $M_{SD, background}$ the standard deviation of the background signal (18). SNR values had to be high enough so that activation could be detected. Activation was detected with the correlation method (19). A boxcar function with the same on-off period as the stimulus was used as a reference. No delay was used, since acquisition time was longer than the expected hemodynamic response time. Areas in the occipital region were considered activated when the correlation value was 0.5 or higher ($P < .01$ per pixel) and when the areas consisted of at least four connected pixels that were activated. Next, the size of the total activated area in the primary visual cortex and its mean signal increase were measured.

To test for reproducibility, we first considered the size of the activated area in the first (A1) and second (A2) studies for all 18 subjects who were studied twice. As a measure of reproducibility, ratio R_{size} was calculated as $R_{size} = 1 - |A1 - A2|/(A1 + A2)$. This ratio varied between 0.0 (no reproducibility of size) and 1.0 (perfect reproducibility). Second, we considered the location of the activated area in each subject: images of the second study were matched to images of the first study on a pixel-by-pixel basis, with the same algorithm that was used for motion correction. Next, the size of the areas activated in both studies ($A_{overlap}$) were determined and the ratio $R_{overlap} = 2 \times A_{overlap}/(A1 + A2)$ was calculated. This ratio was a measure of the reproducibility of the size and the location of the activation: in case of perfect reproducibility, this ratio was 1.0. A diagram illustrating the method of calculating these two ratios appears in Figure 2.

Results

One subject was unsuccessfully studied because of claustrophobia. In the first study of the remaining 27 subjects, no large motion artifacts were found. The signal was stable and SNR ranged from 95 to 145. Only in two subjects was no reliable activation detected. In these two

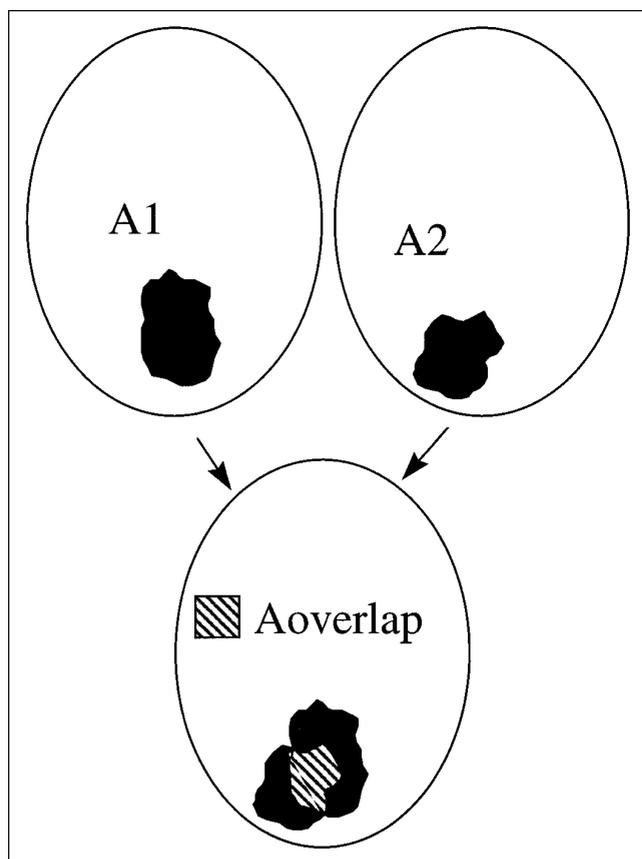


Fig 2. Diagram illustrates the method for calculating the parameter R_{size} , indicating intrasubject reproducibility of measured sizes of activated areas, and of $R_{overlap}$, indicating reproducibility of the size and location of activity. *Upper left* drawing shows the visual area activated in the first study (of size $A1$). *Upper right* drawing shows the result of the second study, with $A2$ the activated area in *black*. R_{size} is given by $1 - |A1 - A2| / (A1 + A2)$. In the *lower image*, the two studies are matched, with the *hatched area* representing the area activated in both studies. $R_{overlap}$ is now calculated with $2 \times A_{overlap} / (A1 + A2)$.

cases, either there was no activation of at least four connected pixels or pixels were artifactually activated outside the region, near the calcarine sulcus, which were indistinguishable from activated pixels inside this region, and all activated pixels were considered to be artificial. Possible explanations include small, undetected stimulus-correlated motion or scanner instability.

Figure 3A is an example of an activation pattern in one section in one subject; Figure 3B plots the signal intensity in this area. The total activated area in the two sections for the 25 subjects who showed activation ranged widely, from 125 to 1029 mm² (mean \pm SD, 496 mm² \pm 262). Not only size but also the signal increase in the activated areas differed: in Figure

4 the size of the activated area is plotted against the signal increase. Signal increases ranged from 3.2% to 10.9% (mean, 6.6% \pm 1.7).

Of the 18 second studies, one had to be excluded owing to technical problems. For the remaining 17 subjects, signal stability and SNR were found to be of the same order as in the first examination and, again, no large motion artifacts were detected. The results from the two subjects who showed no activation in the first study were consistent in the second; that is, no reliable activation was seen. The other 15 subjects showed activation in both studies. The size of the activated areas ranged from 112 to 908 mm² in the second study (mean, 474 mm² \pm 226). We found no significant difference in size of activated areas between the two studies (nonparametric test, $P = .61$). Signal increases in the activated areas ranged from 4.5% to 10.0% (mean, 6.4% \pm 1.7). Figure 5 shows the size of the activated area in the second study plotted against the size in the first study. In cases of perfect reproducibility of measured size, points appear on the line, which has a slope of 1.0 in the graph. Again, one can see that the range in activated areas (ie, intersubject variability) is large.

In testing for location of the activated area, all images from the second study were matched to the images from the first study for each subject. The borders of the images from the first study were marked and overlaid on the borders of the matched images from the second examination. In one subject, images of the first and second study could not be matched correctly because the sections differed too much in orientation owing to a placement error. In the 14 remaining subjects with activation in both studies, the result of the matching procedure was found to be acceptable after visual inspection. These were used for further analysis. For these subjects, areas that were activated in both studies could be distinguished from areas that were activated in either study alone.

Figure 6 shows the activated areas in a subject who showed high reproducibility (Fig 6A) and in a subject who showed less activation and also less reproducibility of the location of the activated area (Fig 6B). Overlapping activated areas (activation in both studies) in the visual cortex were found for all subjects. The size of the overlapping areas of all 14 subjects ranged from 45 to 477 mm² (mean, 162 mm² \pm 120). The overlapping areas exhibited a typical pat-

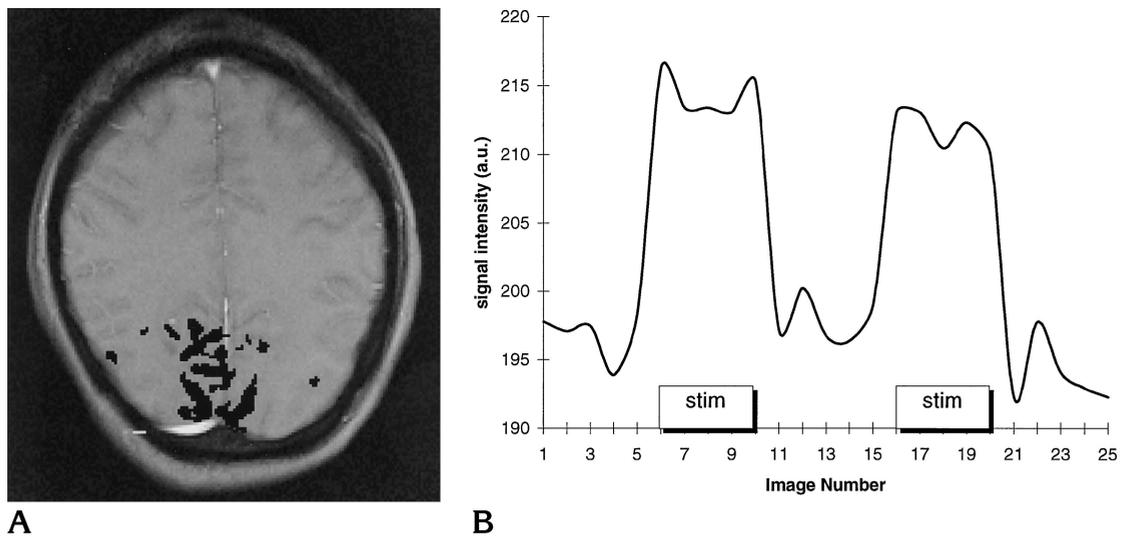


Fig 3. A, Example of the area activated upon visual stimulation (8-Hz flashing LED goggles) superimposed on an anatomic image. Pixels with correlation values higher than 0.5 are seen in black. This subject has a large area of activation in the visual cortex. B, Time course of the signal intensity in the activated area of A. Signal intensity (in arbitrary units) is plotted against image number. The signal goes up and down with the onset and offset of the stimulus. Mean signal increase in this area was 8.6%.

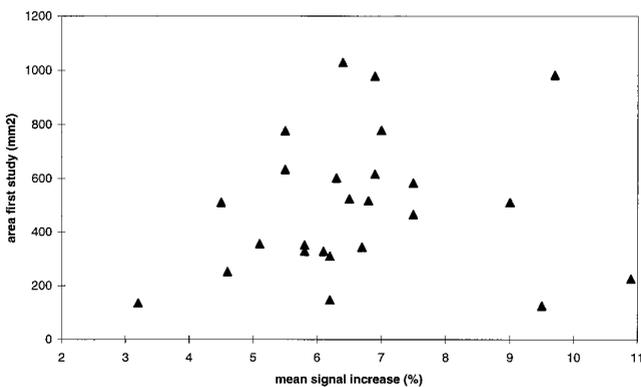


Fig 4. The total size (in mm²) of the activated area (sections 1 and 2) plotted against mean signal increase (in %) of the activated area for all 25 subjects who showed activation in the first study. Note wide range in size and signal increase.

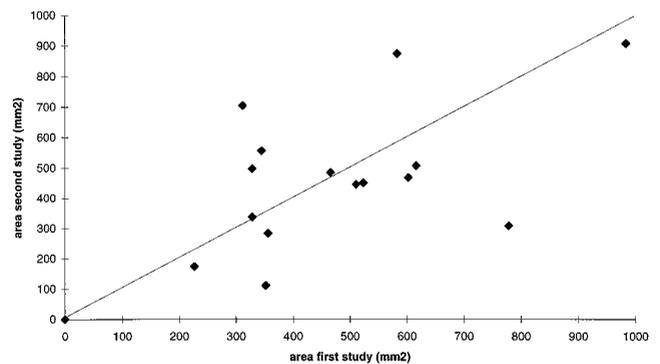


Fig 5. Size of activated area in the second study (in mm²) plotted against size in the first study for the 17 subjects in whom a technically successful second study was obtained. Note that two subjects in each study showed no activation. The slope of the line is equal to 1.0; for subjects with perfectly reproducible sizes, points are on this line.

tern: in general, they formed a “center of pixels” activated in both studies surrounded by pixels that were activated in either study alone. The mean signal increase of overlapping areas was $6.7\% \pm 1.8$ (range, 4.0% to 10.3%); for areas activated in either study, the mean signal increase was $6.2\% \pm 1.2\%$ (range, 3.9% to 8.1%). The difference was not significant ($P = .06$, Wilcoxon’s signed rank test, two-tailed). Further, if we consider areas that were merely significantly activated in one study, we find that this area also showed a small signal increase in

the other study, although no significant activation was detected in that session. These signal increases were observed with all subjects and ranged from 0.30% to 3.20% (mean, $1.61\% \pm 0.75$).

The mean value of R_{size} was 0.83 ± 0.16 (range, 0.48 to 0.98); the mean value of R_{overlap} was 0.31 ± 0.11 (range, 0.15 to 0.50). From the high values of R_{size} it can be seen that reproducibility of the number of activated pixels was high. Yet a number of activated pixels differed in location between the first and second studies, resulting in a lower R_{overlap} .

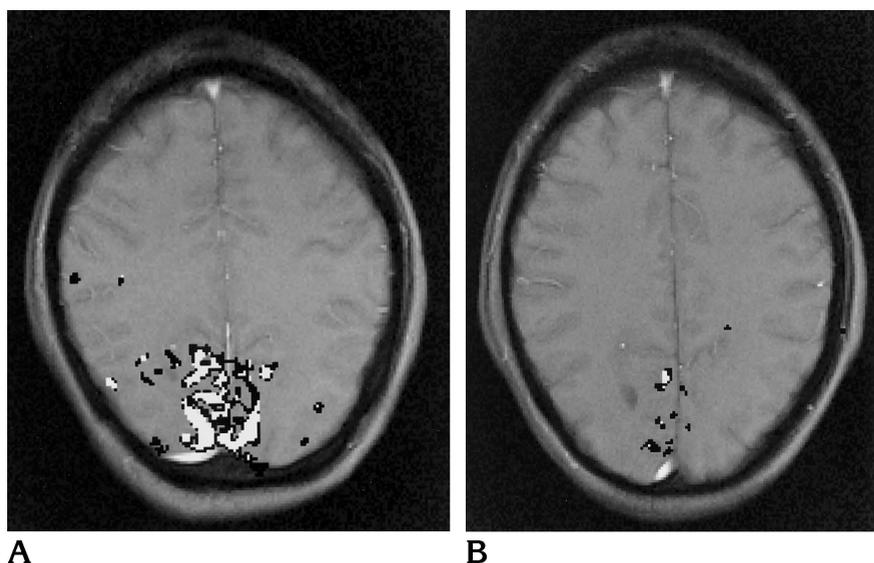


Fig 6. A, Example of high reproducibility: the area that is activated in either of the two studies is shown in *black*; the area that is activated in both studies is shown in *white*. The total size of the area (sections 1 + 2) showing activation in both studies is 477 mm². Total R_{size} is 0.96 and R_{overlap} is 0.50.

B, Example of less activation and less reproducibility than seen in A. The size of the area activated in both studies is 60 mm²; R_{size} is 0.98, and R_{overlap} is 0.18. Note that the reproducibility of the number of activated pixels for this subject is on the same order as that for the subject in A, whereas reproducibility of the location of the activity is much worse.

Discussion

Activated areas were found in 25 (89%) of our 28 subjects. One subject was claustrophobic, and in the remaining two (7%), no activation was found in either session. The size and shape of the activated areas exhibited a large intersubject variability, with activated areas ranging from 125 to 1029 mm², consistent with the notion that the size and location of the visual cortex differ among individuals (13). The mean ratio of reproducibility of sizes of activated areas within subjects was 0.83 ± 0.16 ; for reproducibility of location, the mean ratio was 0.31 ± 0.11 , on a scale of 0.0 to 1.0.

Reproducibility of the location and shape of activated areas displayed overlapping areas in each subject. A test-retest study with a cognitive paradigm (Cohen et al, "Qualitative...") showed areas of activation in the prefrontal cortex as measured with BOLD functional MR imaging. These areas showed local spatial variation across tests. Reliable centers of activation, surrounded by pixels that were active in either study alone, were detected. We also found centers with activation in both studies, surrounded by pixels that were active in only one of the studies. In most subjects, the signal increase was highest in these centers, but the difference in signal increase was not statistically significant.

In the study by Yetkin et al (14), test-retest reliability was studied on a motor and sensory paradigm within a single imaging session. Reproducibility ratios were between 0.39 ± 0.39 and 0.59 ± 0.15 and it was found that higher

correlation values did not improve reproducibility. The ratios that were used in that study have no upper limit: perfect reproducibility would produce infinite ratios. Their technique would give R_{overlap} between 0.44 and 0.54. Further, our study differs from the study of Yetkin et al (14) in three respects. First, our second study was done after an interval of 1 to 3 weeks, introducing more sources of variation, similar to those that may be expected in a clinical setting (repositioning, time of the day, and so on). Second, the visual cortex is known to be a large and complicated structure; reliability studies using different paradigms are likely to give different results. Third, our sample size was larger, providing more reliable statistics.

Our study was aimed at measuring the reproducibility of FLASH functional MR imaging in two sections placed parallel to the calcarine fissure in a situation comparable to a practical clinical setting. The technique we used was limited by the small number of sections measured and therefore could not detect all areas of activation. Moreover, repositioning between the studies introduced possible differences in measured activation patterns. Echo-planar imaging has the advantage of providing very fast acquisitions, thus affording the possibility of measuring multiple sections with increased statistical power. With multisection echo-planar acquisitions and three-dimensional matching procedures, results might be more reproducible. Such studies would prove extremely useful. Since echo-planar imaging requires special hardware, and two-dimensional techniques are more

widely available, we expect that a substantial number of clinical applications using functional MR imaging will be done with single- or double-section FLASH techniques. Further, echo-planar techniques suffer from reduced spatial resolution and image distortion.

The difficulty in explaining intrasubject variation lies in the fact that the sensitivity of the method is not entirely known. In our studies, SNR, motion, and temporal stability were acceptable and cannot explain the observed variation. The influence of another important factor, the position of the sections, was kept to a minimum by defining this location with precision in each examination. Further, the results of Yetkin et al (14) suggest that repositioning may not be the main cause of differences in activation patterns between two studies. Even without repositioning errors (by design), reproducibility in their study was comparable to ours. Within subjects, the number of activated pixels was quite reproducible, but the location of activation differed. Pixels that were activated in one study but not in the other also showed a signal increase in the latter study, indicating that part of the intrasubject variation may be explained by physiological effects.

In conclusion, two-dimensional BOLD functional MR imaging with the FLASH technique is useful in identifying certain cortical areas that have quite variable locations among subjects. Given this variability, the diagnostic implications of a single BOLD functional MR examination using the FLASH technique remain to be determined. The technique might be more suitable for the follow-up of individual patients over time, for which this study provides reference data.

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