The Effect of Age and Fixation Instability on Retinotopic Mapping of Primary Visual Cortex

Michael D. Crossland,[1] *Antony B. Morland,*[2] *Mary P. Feely,*[1] *Elisabeth von dem Hagen,*[2,3] *and Gary S. Rubin*[1,4]

Purpose. Functional magnetic resonance imaging (fMRI) experiments determining the retinotopic structure of visual cortex have commonly been performed on young adults, who are assumed to be able to maintain steady fixation throughout the trial duration. The authors quantified the effects of age and fixation stability on the quality of retinotopic maps of primary visual cortex.

Methods. With the use of a 3T fMRI scanner, the authors measured cortical activity in six older and six younger normally sighted participants observing an expanding flickering checkerboard stimulus of 30° diameter. The area of flattened primary visual cortex (V1) showing any blood oxygen level–dependent (BOLD) activity to the visual stimulus and the area responding to the central 3.75° of the stimulus (relating to the central ring of our target) were recorded. Fixation stability was measured while participants observed the same stimuli outside the scanner using an infrared gazetracker.

Results. There were no age-related changes in the area of V1. However, the proportion of V1 active to our visual stimulus was lower for the older observers than for the younger observers (overall activity: 89.8% of V1 area for older observers, 98.6% for younger observers; $P < 0.05$). This effect was more pronounced for the central 3.75° of the target (older subjects, 26.4%; younger subjects, 40.7%; $P < 0.02$). No significant relationship existed between fixation stability and age or the magnitude of activity in the primary visual cortex.

Conclusions. Although the cortical area remains unchanged, healthy older persons show less BOLD activity in V1 than do younger persons. Normal variations in fixation stability do not have a significant effect on the accuracy of experiments to determine the retinotopic structure of the visual cortex. (*Invest Ophthalmol Vis Sci.* 2008;49:3734–3739) DOI:10.1167/iovs.07-1621

From the [1]UCL Institute of Ophthalmology, London, United Kingdom; [2]York Neuroimaging Centre and Department of Psychology, University of York, York, United Kingdom; [3]Medical Research Council Cognition and Brain Sciences Unit, Cambridge, United Kingdom; and [4]NIHR Biomedical Research Centre for Ophthalmology, London, United Kingdom.

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Corresponding author: Michael D. Crossland, UCL Institute of Ophthalmology, 11–43 Bath Street, London EC1V 9EL, UK; m.crossland@ucl.ac.uk.

Since the early 1990s, functional magnetic resonance imaging (fMRI) has become a standard experimental technique for assessing cortical activity in response to visual stimuli in healthy observers.[1–3]

A key development in probing the functional organization of the occipital lobe with fMRI is retinotopic mapping. To perform retinotopic mapping, blood oxygen level–dependent (BOLD) activation is measured using two complementary stimuli. Typically, a rotating wedge-shaped target allows early visual areas to be identified on the basis of localizing representations of the vertical and horizontal meridians, and an expanding ring target is then used to establish the cortical mapping of eccentricity.[4–6]

Although it is known that the number of neurons in primary visual cortex does not decrease with age[7] and that aging causes a decline in the number of photoreceptors, it is thought that neural factors are largely responsible for the age-related decrease in visual acuity.[8–10] Anatomic and histologic studies can determine the number of neurons present, but to determine the activity of these neurons, a functional imaging technique such as fMRI is required. This approach has been used to determine the effects of age on tasks such as saccade control,[11] motor performance,[12] and memory.[13] We used this technique to measure the BOLD response of neurons in V1 to visual stimulation.

Although our primary interest was to evaluate how visual cortical signals change with age, the techniques we used were likely to yield signals that are dependent on fixation stability, which may covary with age.

The effects of poor fixation are likely to be twofold: mapping between stimulus and response may be less accurate, and response amplitude is likely to be diminished.[14] Fixation stability is traditionally measured for short trials (30 seconds or less), whereas observers fixate a discrete cross or point target. In contrast, retinotopic mapping fMRI experiments require subjects to fixate while complex, dynamic stimuli are presented for many minutes. It is known that pericentral fixation targets are less well fixated than centrally presented fixation targets,[15] but fixation stability has not been formally assessed for targets commonly used as fMRI stimuli. Given that fixation stability might vary with time and that fixation has yet to be formally assessed during stimulation of the type and duration routinely used in retinotopic mapping, we set out to record eye movements while retinotopic mapping stimuli were viewed.

In this report, we present measurements of visual cortical responses in two groups of participants with different mean ages. We examine the effects of age and fixation stability on the cortical responses.

Methods

Participants

Twelve control observers with no history of ophthalmologic or neurologic disease were recruited in two groups of six subjects: younger adults (mean age, 25 years; range, 19–38; two males) and older adults (mean age, 76 years; range, 61–86; three males). All subjects had

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corrected visual acuity of 0.1 logMAR (6/7.5; 20/25) and contrast sensitivity of 1.60 log units or better in both eyes. Full eye examinations were performed by an ophthalmologist or an optometrist to exclude any disease.

No participants had contraindications for MRI, as assessed by a detailed questionnaire at recruitment and at the time of each MRI procedure. Briefly, this ensured that no participants had implanted metallic objects, heart disease, epilepsy, diabetes, or claustrophobia and that none could have been pregnant. Informed consent was obtained from all participants before data collection, and the study conformed to the Declaration of Helsinki.

Stimuli

Stimuli were of identical size in the scanner and in the eyetracker. Wedge and ring stimuli were based on a circle with a 30° diameter divided into eight concentric rings, each containing 24 segments of alternating black and white. Each segment of the circle flickered between black and white at 6 Hz. A central black fixation cross of 1° side length was present throughout.

To determine the area of V1, a wedge stimulus was used. This stimulus consisted of one quadrant of the circle being presented at any time, as shown in Figure 1 (top). The visible quadrant rotated clockwise by one segment every 1.5 seconds to complete one revolution every 36 seconds. For eye movement recording performed outside the scanner, this stimulus was presented for 4 minutes to match approximately the duration of the scanning process. For fMRI experiments, seven complete cycles of the stimulus were presented.

Once the location of V1 was defined, a ring stimulus was used to determine the activity within this region. The ring stimulus consisted of three adjacent rings of the circle being presented at one time, starting from the center (Fig. 1, middle) of the circle and moving radially outward by one ring every 4.5 seconds, to return to the center every 36 seconds. Again, this stimulus was displayed for 4 minutes for eye movement recordings and for seven cycles during MRI data acquisition.

For fixation assessment only, a third stimulus was used. This consisted of a black circle 3° in diameter with an 18′ central white detail (Fig. 1, bottom), presented for 10 seconds in each of five positions of gaze. This target is identical to one we have previously used for fixation stability assessment, in common with other groups.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging was performed in a scanner (Trio; Siemens, Erlangen, Germany) at Royal Holloway, University of London. Standard gradient echo planar imaging (EPI) was performed (TR, 3 s; TE, 52 ms; matrix, 64 × 64; FOV, 192 mm) with a 3 × 3 × 3-mm voxel size. Stimuli were viewed through a mirror mounted within the scanner. Subjects were asked to observe the wedge and the ring stimulus for four trials per target. Each trial lasted 252 seconds and consisted of seven stimulus cycles. Breaks could be taken between trials at the participant's request. Where necessary, scanning was performed over two different days. Averaged BOLD responses were derived for each stimulus condition. In addition to the EPI acquisitions, high-resolution (1 × 1 × 1 mm), T1-weighted anatomic imaging was also performed with the modified driven equilibrium Fourier transfer sequence.[16]

Subsequent analysis was performed using routines from the mrVista package (http://white.stanford.edu/software) according to the techniques described by Dougherty.[17] First, gray matter was segmented[18] from the anatomic volume, and a flattened cortical image was produced.[19] Functional acquisitions were motion corrected and then coregistered with the anatomic scan and could thereby be registered with the flattened cortex. Locations of visual areas were identified in the flattened cortical maps by finding phase reversals on the averaged phase map for the *wedge* stimulus using a relatively liberal threshold (of differential over baseline activity) of $P < 0.05$. The boundary of primary visual cortex on the flattened map was determined and used as the region of interest (ROI). Next, the area of BOLD response within this ROI on the flattened averaged phase map for the *ring* stimulus was measured using a more stringent threshold of $P < 0.01$. Note that these datasets are independent. This area was measured and recorded as a proportion of V1 area (defined by the initial identification using re-

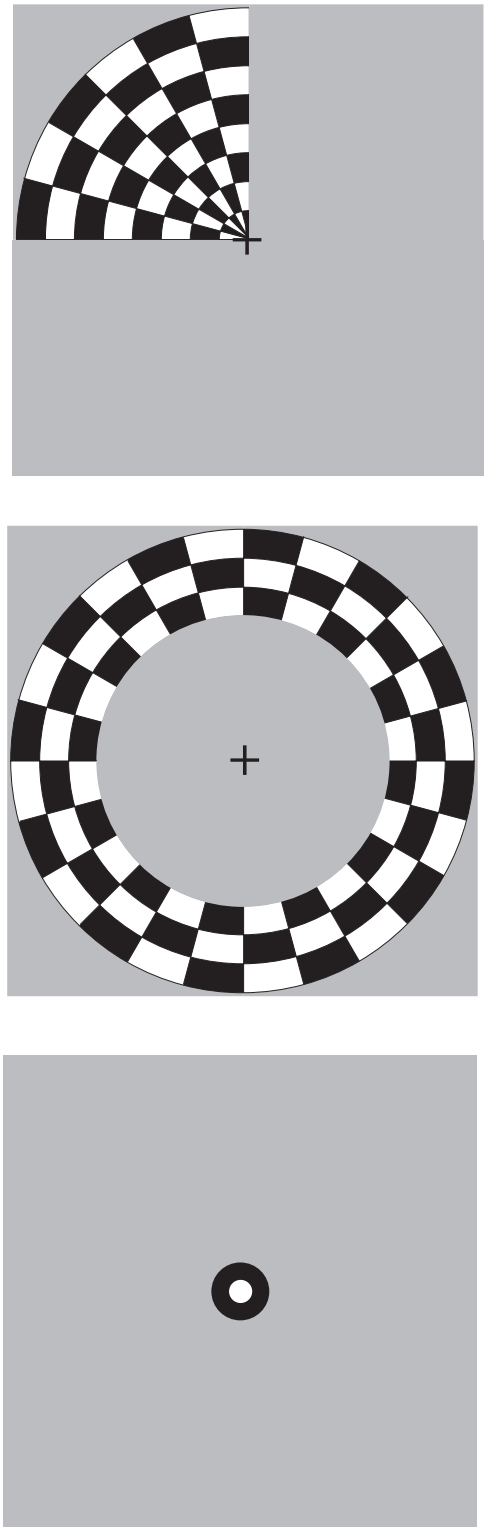

FIGURE 1. Targets used for fixation assessment. *Top*: rotating wedge target. *Middle*: expanding ring target. *Bottom*: point target.

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sponses to wedge stimuli). Supplementary analysis was performed in the same manner for the BOLD response to only the central part of the ring stimulus (subtending 3.75°). Cortical areas were measured in the cortical manifold to avoid area distortions induced by the flattening process.

To correct for hemodynamic changes with age,[20,21] phase delay was retrospectively calculated for the older and the younger subjects by identifying the phase at which reversals occurred. This enabled direct comparison between the stimulus and the cortical response.

Fixation Assessment

Fixation assessment was performed outside the scanner. Subjects observed a 19-inch computer monitor from a distance of 50 cm while wearing appropriate refractive correction. The peak screen luminance was 112 cd/m^2, the resolution was 800 × 600 pixels, and the screen refresh rate was 85 Hz. Subjects were asked to keep their eyes still and to observe the center of each target. They were advised to blink normally.

Eye position was monitored at 250 Hz with an infrared gazetracker (Eyelink I; SensoMotoric Instruments, Teltow, Germany) running Eyelink software (version 2.0.4). This eyetracker consists of two infrared cameras mounted on a headband for observation of the positions of both eyes and a head-mounted camera that corrects for head motion, enabling the system to return a true position of gaze. Calibration was carried out at the start of each session, and drift correction was performed between each block.

Data were analyzed retrospectively using software written in Matlab (Mathworks, Natick, MA). Fixation data for the right eye were analyzed. First, data were cleaned to remove recordings taken for 0.25 seconds before and 0.5 seconds after the start of a blink to remove any vertical positional artifact induced by lid position. For the wedge and ring stimuli, a moving window technique was used to divide the data into sections of 30 seconds in length, starting every second from 0 second to 210 seconds. For each 30-second segment, a bivariate contour ellipse was constructed to encompass 68% of the fixation points. The area of this ellipse was calculated (bivariate contour ellipse area [BCEA]) using the formula $BCEA = 2.28\pi\sigma_H\sigma_V(1 - \rho^2)^{0.5}$, where σ_H and σ_V are the SD of eye position in the horizontal and vertical meridian, respectively, and where ρ is the product-moment correlation between the two position components.[22] The mean BCEA value for these 211 segments was calculated and recorded in minutes of arc^2. Larger BCEA values are associated with larger ellipses of eye position and, hence, poorer fixation stability.

Results

Age

The area of V1, as defined by phase reversals observed in response to wedge stimuli, was the same in older and younger observers (ANOVA: right V1, $F_{(df = 11)} = 0.108$, $P = 0.75$; left V1, $F_{(df = 11)} = 0.127$, $P = 0.73$). However, the proportion of V1 area activated by ring stimuli at a threshold of $P < 0.01$ was significantly lower in older subjects (proportions active: older subjects, 0.898; younger subjects, 0.986; Welch ANOVA: $F = 6.076$, $P < 0.05$). The proportion of V1 activated by rings that occupied the central 3.75° was also significantly smaller in older than in younger participants (proportions active: older subjects, 0.264; younger subjects, 0.407; ANOVA: $F_{(df = 11)} = 7.69$, $P < 0.02$). However, the proportion of V1 activated for eccentricities greater than 3.75° was not significantly different between older and younger observers ($F_{(df = 11)} = 0.82$, $P = 0.21$). Figure 2 shows these data graphically.

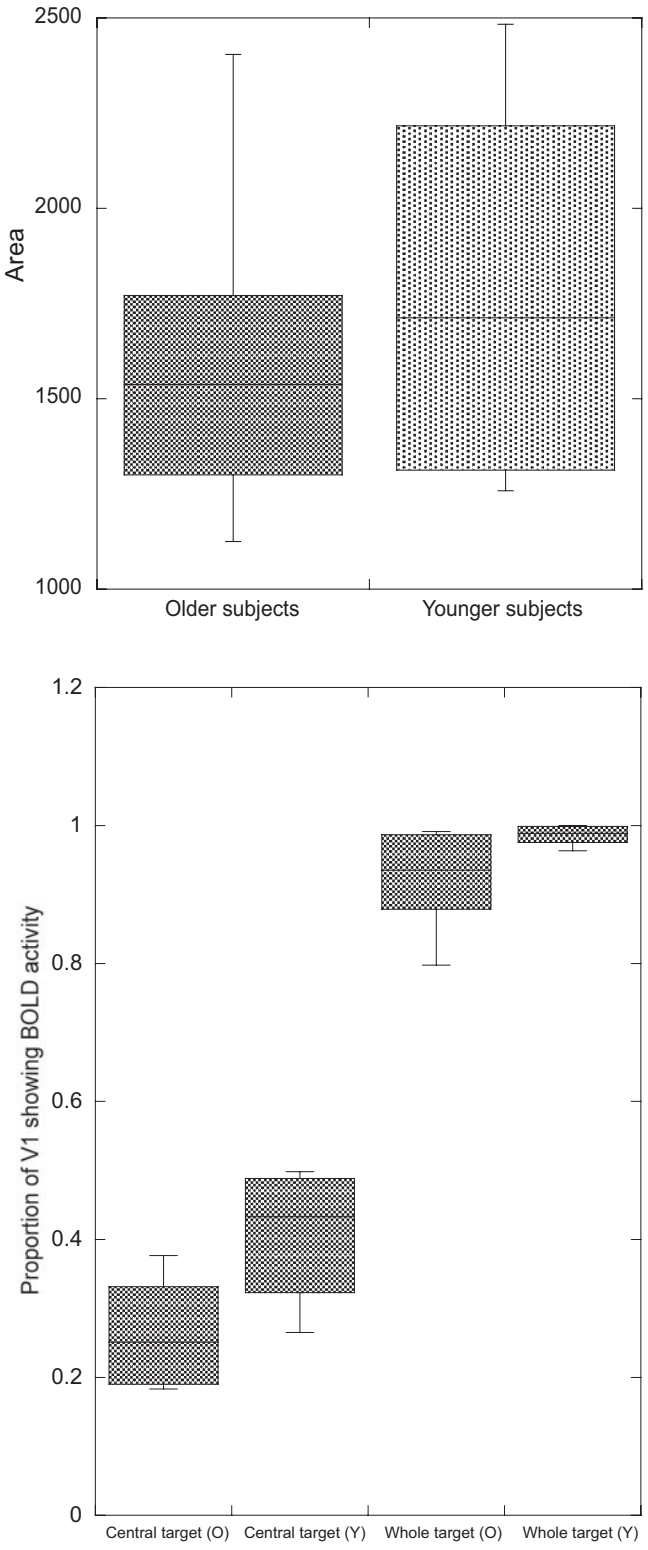

Figure 2. *Top*: size of V1 in older and younger subjects. *Bottom*: proportion of V1 showing activity to (*left*) the central 3.75° of the target and (*right*) the whole target. O, older subjects; Y, younger subjects.

Phase Delay

Analysis of the phase delay in our participants showed that older observers had slower cortical responses, yet this difference was small (phase delay <0.1 radians, or a time delay of 0.58 seconds) and not statistically significant ($P > 0.2$). This delay equates to a reduction in cortical representation of the central 3.75° of no more than 12.5% of the proportion active.

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Fixation Stability

No statistically significant difference in fixation stability was found between the older and the younger subjects (for rings: $t_{(df = 10)} = 0.15$, $P = 0.89$; for wedges: $t_{(df = 10)} = 0.99$, $P = 0.34$). Fixation stability was approximately twice as good for the point target as for the other targets (median BCEA: point target, 2215 minarc^2; ring target, 4215 minarc^2; wedge target, 5849 minarc^2; Wilcoxon signed rank test, $P < 0.01$).

Effect of Prolonged Trial Duration

To determine the effect of the longer trial duration on fixation stability, we compared the fixation stability measurements made for the first 10 seconds of each minute of trial observation. No systematic change was found between any of the values for each trial (repeated-measures ANOVA: Wedge stimulus, $F = 0.42$, $P = 0.67$; ring stimulus, $F = 0.81$, $P = 0.47$).

Fixation Stability and fMRI

No linear relationship was seen between fixation stability and the proportion of V1 activity. Observers with fixation stability poorer than approximately 6000 minarc^2 displayed less activity, but this difference did not reach statistical significance ($F_{(df = 11)} = 2.61$, $P = 0.14$, Fig. 3, top). For our secondary analysis of cortex specifically active to those stimuli within the most central region, there was no significant relationship between fixation stability and cortical activity ($r = -0.25$, $P = 0.43$; Fig. 3, bottom).

Discussion

We have shown that though primary visual cortex size does not change with age, a significantly smaller area of V1 shows BOLD activity on fMRI in healthy older people. The fact that the area of striate cortex does not decrease with age is consistent with previous research,[7,23] and reductions in BOLD activity without corresponding changes in cortical volume have been demonstrated in other areas of the visual and motor systems.[11,12] It has previously been shown that neural deficits are responsible for the poorer vision of older observers,[8–10] and indeed our older subjects did have lower visual acuity and contrast sensitivity than our younger volunteers (mean visual acuity: older observers, −0.03 logMAR; younger observers, −0.19; $P < 0.01$; mean contrast sensitivity: older observers, 1.79 log units; younger observers, 1.95 log units; $P < 0.05$). However, changes in contrast sensitivity are not enough to account for the differences in the cortical activity ($r^2 = 0.11$; $P = 0.35$).

We have considered, by measuring the phase delay for older and younger subjects, the possibility that the reduction in activity is a consequence of general hemodynamic changes with age.[20,21] The size of the effect of phase delay was much smaller than the age-related differences we reported. Further, a change in delay would have had the effect of artificially increasing the representation of the peripheral eccentricities in older participants, which we did not find.

Our paradigm cannot determine whether activity is lower because of changes in the primary visual cortex or changes earlier in the visual system, such as increased light scatter, or a decreased number of retinal ganglion cells[24] or optic nerve fibers.[25] We have reduced the likelihood of our results being related to preneural factors, such as light scatter, by excluding subjects with any lens opacity and ensuring that subjects received optimal refraction for scanning and fixation assessments.

We have also shown that fixation stability is significantly poorer during observation of dynamic stimuli of the type typically used in fMRI experiments than during observation of a discrete point target. Further analysis of our results indicates that this is because of the nature of the stimulus rather than the prolonged period of fixation required for functional imaging of the visual cortex. Our results are consistent with recent findings of a large magnitude of eye motion when control subjects fixated fMRI stimuli.[26] It is perhaps not surprising that fixation stability was poor for these targets given their dynamic and distracting nature. These targets were observed under passive viewing conditions to mimic the stimulus presentation in classical fMRI experiments of the visual system. However, it is not possible to extrapolate these fixation data to fixation behaviors

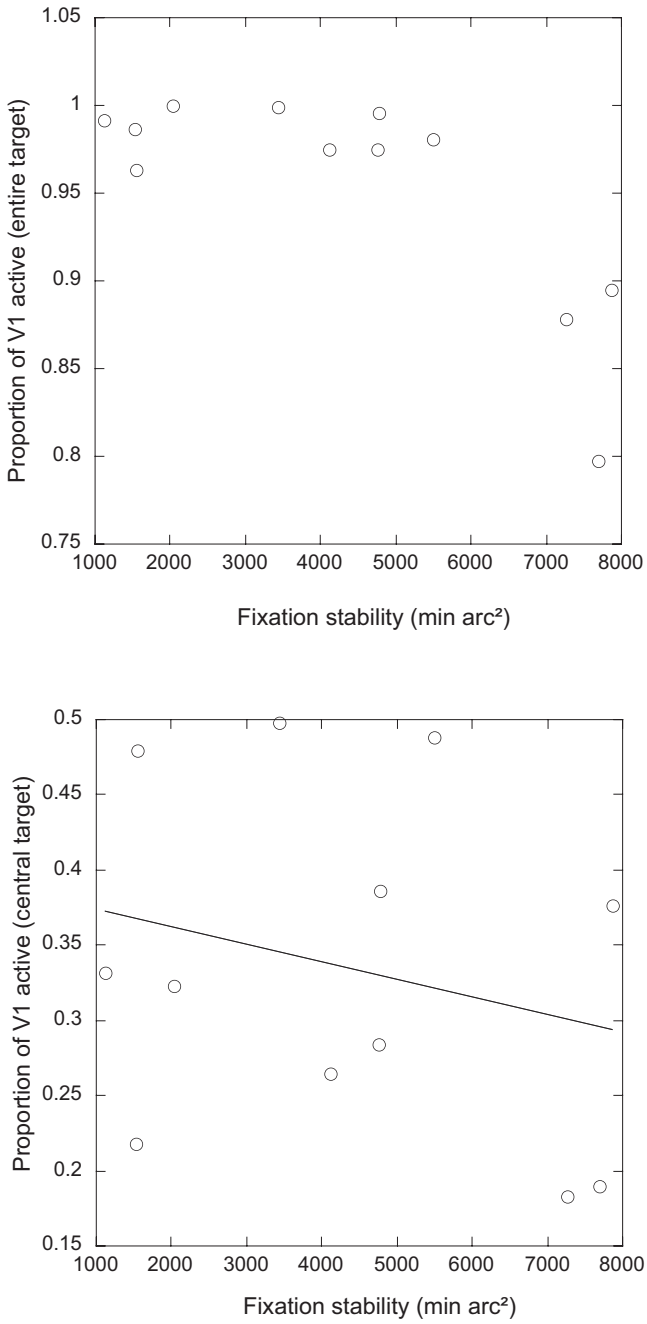

Figure 3. *Top*: relationship between fixation stability for the ring target and the proportion of V1 activity. *Bottom*: relationship between fixation stability for the ring target and the proportion of V1 activity for the central 3.25° of the ring target. Line shows linear regression; $r = -0.25$.

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for a real-world task, such as viewing a natural scene or reading. Although it is generally accepted that the BCEA is an appropriate method of quantifying fixation stability, it does assume that fixations are normally distributed. Small departures from normality have been reported in fixation data.[22] Although we did not formally assess the normality of fixation data in the present study, we did ensure, with the use of a technique we have previously reported,[27] that no data were multimodal.

The quality of the BOLD response in control subjects appeared to be relatively resistant to small changes in fixation stability. Although subjects with poorer fixation stability tended to have smaller areas of V1 showing differential activity to the central region of our ring target, this relationship did not reach statistical significance. Given the large sizes of the targets used, variations in fixation stability between control subjects were relatively small compared with the magnitude of the target.

Cortical reorganization in patients with eye disease is an area of considerable current interest. fMRI is being used to assess retinotopic organization of the visual cortex in patients with conditions causing visual impairment, such as albinism,[28,29] rod monochromatism,[14] amblyopia,[26] glaucoma,[30] and macular degeneration.[31–33] It is known that fixation stability is far poorer for patients with macular degeneration.[15,34,35] To accurately assess the level of cortical reorganization in patients with central scotomas, it is imperative that fixation stability be taken into account.

A limitation of our first analysis, determining the extent of activation within the primary visual cortex, is that the area of V1 was defined by hand using the pattern of phase reversal between striate and extrastriate visual areas. There is a risk that in patients in whom responses are poor, the location of these reversals may be imprecise, introducing some circularity into our results. We attempted to minimize this effect by using different threshold criteria for the identification of V1 and the assessment of active areas. The ROI was defined by ABM, who has considerable experience analyzing flattened cortical maps.

A further limitation of our study design is that fixation stability was measured outside the fMRI scanner and was not measured simultaneously with imaging. Although it is unclear whether fixation stability is poorer in the supine position than in the upright sitting position, it is likely that the rigid head immobilization in the fMRI scanner improves fixation stability because fewer vestibulo-ocular reflex–induced eye movements are present. In a control experiment, we did not find a reduction in fixation stability with scanner noise (determined by recording the sounds of the scanner in operation and measuring fixation stability while listening to this noise, through headphones, at a similar volume). Although the size of our target was carefully matched in the scanner and during our fixation recordings, there might have been small differences in luminance and contrast of the target. In a further control experiment, we found no significant effect on fixation stability of reducing the target luminance (from a maximum of 112 cd/m^2 to a maximum of 1.4 cd/m^2) or contrast (from Weber contrast of 91% to 2.5%). Despite interobserver and intraobserver variability in fixation stability, we do not think it likely that our data were too noisy for a determination of any relationship between fixation stability and fMRI activity. In similar experiments using control observers, we found a marked relationship between fixation stability and reading speed.[34]

Conclusions

In healthy older subjects, the visual cortex shows reduced responses to visual stimulation. Fixation stability is poorer when observing fMRI targets than when viewing a discrete point target, yet this difference is unlikely to have a significant effect on the accuracy of experiments to determine the retinotopic structure of visual areas of the cortex in healthy observers.

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