Reorganization of Visual Processing in Age-Related Macular Degeneration Depends on Foveal Loss

Daniel D Dilks, Emory University
Joshua B. Julian, University of Pennsylvania
Eli Peli, Harvard Medical School
Nancy Kanwisher, Massachusetts Institute of Technology

Journal Title: Optometry and Vision Science
Volume: Volume 91, Number 8
Publisher: Lippincott, Williams & Wilkins | 2014-08, Pages e199-e206
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1097/OPX.0000000000000325
Permanent URL: https://pid.emory.edu/ark:/25593/txtvm

Final published version: http://dx.doi.org/10.1097/OPX.0000000000000325

Copyright information:
(C) 2014 American Academy of Optometry

Accessed December 29, 2019 8:35 AM EST
Reorganization of Visual Processing in Macular Degeneration Depends on Foveal Loss

Daniel D. Dilks, PhD, Joshua B. Julian, BS, Eli Peli, MSc, OD, FAAO, and Nancy Kanwisher, PhD
Department of Psychology, Emory University, Atlanta, Georgia (DDD), Department of Psychology, University of Pennsylvania, Philadelphia, Pennsylvania (JBJ), Schepens Eye Research Institute, Massachusetts Eye & Ear, Harvard Medical School, Boston, Massachusetts (EP), and McGovern Institute for Brain Research, MIT, Cambridge, Massachusetts (NK)

Abstract

Purpose—When individuals with central vision loss due to macular degeneration (MD) view stimuli in the periphery, most of them activate the region of retinotopic cortex normally activated only by foveal stimuli – a process often referred to as ‘reorganization’. Why do some show this reorganization of visual processing whereas others do not? We reported previously that six individuals with complete bilateral loss of central vision showed such reorganization, while two with bilateral central vision loss but with foveal sparing did not, and we hypothesized that the effect occurs only after complete bilateral loss of foveal vision. Here we conduct a stronger test of the dependence of reorganization of visual processing in MD on complete loss of foveal function, by bringing back one (called MD6) of the two participants who previously did not show reorganization, and who showed foveal sparing. MD6 has now lost all foveal function, and we predicted that if large-scale reorganization of visual processing in MD individuals depends on complete loss of foveal input, then we will now see such reorganization in this individual.

Methods—MD6 and two normally sighted controls were scanned. Stimuli were gray-scale photographs of objects presented at either the fovea or at a peripheral retinal location (i.e., the MD participant’s preferred retinal locus – PRL, or the control participants’ matched peripheral location).

Results—In MD6, visual stimulation at the PRL significantly activated not only the expected “peripheral” retinotopic cortex, but also the deprived “foveal” cortex. Crucially, MD6 exhibited no such large-scale reorganization five years earlier when she had some foveal sparing. By contrast, in the control participants, stimulation at the matched peripheral location produced significant activation in peripheral retinotopic cortex only.

Conclusions—We conclude that complete loss of foveal function may be a necessary condition for large-scale reorganization of visual processing in individuals with MD.

Corresponding author: Daniel D. Dilks, Emory University, Department of Psychology, 36 Eagle Row, Room 469, Atlanta, GA 30332, dilks@emory.edu.
The authors have no conflicts of interest.
Several functional magnetic resonance imaging (fMRI) studies\textsuperscript{1–5} have shown that following the loss of foveal input, and consequent loss of bottom-up input to ‘foveal’ cortex due to macular degeneration (MD), the deprived region of cortex that would normally be responsive only to foveal visual stimuli responds to visual stimuli presented to peripheral retina. However, not all individuals with MD exhibit such extensive changes in activation of retinotopic cortex – what is often referred to as ‘reorganization’ of visual processing. Why do some MD individuals show such reorganization while others do not? One of the above studies\textsuperscript{1} reported that such activation of deprived foveal cortex by peripheral stimuli is only observed when MD individuals perform a task, not during passive viewing (see also\textsuperscript{6}). However, task dependence cannot explain the variability in occurrence of reorganization across MD individuals because some MD participants who were engaged in a task while scanning still do not show reorganization.\textsuperscript{3}

A second possibility is that time since onset, age since onset, or the diagnosis of MD determine whether reorganization occurs. However, as reported in a previous paper\textsuperscript{3}, while we found evidence for reorganization in three individuals with MD, we found no such evidence in two others, and the time since onset, age since onset, and diagnosis varied widely across these participants. For example, there were some MD participants with a long time since onset of MD who showed reorganization and others with similarly long time since onset of MD who did not, so time since onset cannot be the only factor contributing to such reorganization. What was consistent across the participants who exhibited reorganization was complete loss of foveal input, while the two MD individuals who did not show such reorganization had foveal sparing, leading to the hypothesis tested in this paper.

More specifically, Baker and colleagues\textsuperscript{3} found no evidence for large-scale reorganization of visual processing in two individuals with extensive bilateral macular lesions but with foveal sparing (i.e., intact vision in the central two degrees of the visual field), and hypothesized that such reorganization of visual processing occurs only in the complete absence of functional foveal vision. Here we scanned one of the MD individuals who originally had foveal sparing and exhibited no large-scale reorganization, but now has lost all foveal function bilaterally. We predicted that if large-scale reorganization of visual processing in MD individuals depends on complete foveal vision loss, then we will now see large-scale reorganization in this individual.

Note that extensive changes in activation of retinotopic cortex found in MD could be due to disinhibition of pre-existing long-range horizontal connections within early visual cortex\textsuperscript{7}, growth of new horizontal connections\textsuperscript{8}, or unmasking of intracortical feedback to early visual areas from higher visual areas. Here (and in our past papers) we follow standard usage established by previous numerous authors (e.g.,\textsuperscript{9–11}) in which the term “reorganization” refers to the observed changes in activation of topographically mapped cortex after deprivation without implying any particular underlying mechanism. One
group6,12 follows a different usage in which “reorganization” refers to structural change in particular. We prefer the more standard usage that does not commit to a particular mechanism, because in fact the underlying mechanism/s are currently unknown in humans.

**METHODS**

**Participants**

MD6 (as previously reported in Baker et al., 2008) and two normally sighted control participants were scanned for this paper. All participants provided informed consent in accordance with the Committee on the Use of Human Subjects at the Massachusetts Institute of Technology. Further, MD6 was carefully tested behaviorally to determine 1) visual field loss, including testing for any residual foveal function, 2) location of her ‘preferred retinal locus’ (PRL)13, and 3) fixation stability14. At the time of scanning for this paper, MD6 had large bilateral scotomata with complete loss of foveal function (i.e., no functional vision within the central two degrees of the visual field) as measured behaviorally. However, while MD6 had no functional vision in the fovea proper, she still had a sliver of residual vision inside the macular lesion but outside the fovea (at least 5 degrees from the fovea); henceforth, referred to as the ‘parafoveal sliver of vision’ (Figure 1, row 1, column 1). By contrast, five years earlier she had large bilateral central scotomata, but with some preserved foveal function due to sparing of the central two degrees of her visual field (Figure 1, row 3, column 1). Thus, her fovea proper (central two degrees of the visual field) was partially preserved five years earlier, but is completely blind now.

**Behavioral Testing**

**Retinal Imaging and Perimetry**—A Nidek MP-1 retinal microperimeter (Nidek Technologies, Vigonza, Italy) was used to map the location of the PRL and fovea, and to measure the stability of fixation at the PRL for MD6. The retinal image tracker of the MP-1 recorded the participant’s eye movement during 30s fixation trials. This procedure provided a cluster of 750 samples of the location of the fixation cross on the retina (25 samples per second).

Foveal location was determined using the Nidek fixation image and data file. An experimenter manually marked with a cursor a series of points along the optic disk margin. A custom Matlab program was used to fit an ellipse to the set of points15, and find the center of the optic disc. The position of the fovea was computed to be at 15.3° temporally and 1.5° below the center of the optic disk. The latter values were averages of the values determined for normally-sighted observers16,17. Next, the distance from the computed foveal position to the average position of the fixation points was computed to derive the eccentricity of the PRL.

**Visual Field Plotting**—To document visual field loss, measurements were conducted using a custom computerized central perimetry system18 and performed by a technician with extensive experience (i.e., about 9-years-experience). Specifically, a rear projection screen was used to present a uniform background of luminance 97 cd/m² and square target stimuli luminance 0.28 cd/m² (Minolta LS-110 spot photometer). Each eye was tested separately.
For the perimetry testing, MD6 was instructed to maintain fixation using her PRL on a fixation cross at the center of the screen while a 19mm (~1 degree) target was moved across the screen using a mouse. In an exploration phase (aided by the MP-1 measurements, discussed above), MD6 was asked to report whenever a target moving from peripheral to central vision (toward the scotoma) disappeared, establishing a rough boundary of the scotoma. When the scotomatous area was located, the target was placed inside the scotoma and moved from central to peripheral vision in different directions (kinetic perimetry). The target was presented manually, and therefore at variable speeds, aiming to keep the central field loss measurements at about 1 degree/second. The point of first seeing the target as indicated (again by key press) by the participant was used to determine both a more precise boundary of the scotoma and the location of the residual sliver of vision. Once a more precise edge of the scotoma and the sliver of residual vision were mapped, targets were presented in random positions within the scotoma to not only confirm the location, but to determine the extent, of the residual sliver of vision. Static (seen/unseen) perimetry was also conducted in the MP-1, and it confirmed the location of the scotoma found with the custom perimeter described here.

**Two-interval Forced Choice Testing**—We further tested for complete loss of foveal function by using a 2-interval forced choice (2IFC) psychophysical test. MD6 fixated using her PRL on a fixation target. Each trial contained two temporal intervals, and a 1 cycle/degree horizontal (sine phase) Gabor patch (1 degree in SD, 90% contrast) was presented within a 4 degree square in one of those intervals. Testing was conducted at the computed foveal location and the PRL and in other points along the line connecting these two locations. The participant indicated the interval with the Gabor patch, guessing when she was unsure. To avoid light scatter to functioning portions of the retina, the average luminance of the test patches was identical to the background. MD6 performed 50 trials with stimuli at each testing position.

**Functional Imaging**

Stimuli were gray-scale photographs of objects (e.g., airplane, chair, watch) presented at either the fovea or at a peripheral retinal location (i.e., the MD participant’s PRL, or the control subject’s matched peripheral location). The images in our main study were the same size (5 × 5 degrees) for both locations, and for MD6 and the control participants, and were identical in size to those used when we scanned MD6 five years earlier (Baker et al., 2008). However, we also conducted a control scanning session using smaller stimuli (2 × 2 degrees), ensuring that the foveally presented stimuli were presented to MD6’s fovea, not in her parafoveal sliver of vision, to confirm complete loss of foveal vision.

MD6 (and her two matched controls) completed 4 runs per scan of a simple blocked-design experiment. In each run, participants viewed blocks of images (12 blocks of 16 seconds each), 6 blocks presented at each of the two tested positions, randomly chosen. Five blocks of 16 seconds of only a fixation cross (referred to as fixation baseline) were interleaved throughout the stimulus blocks (i.e., one at the beginning and end of each run, plus three more between every 3 consecutive stimulus blocks). In each stimulus block, 20 images were presented for 500 ms each, with a 300 ms inter-stimulus interval. Participants performed a
one-back task, responding via a button box every time they saw a consecutive repetition of the same object image. A one-back task was used here, and in many of our prior studies, to ensure participants are paying attention. However, due to programming issues, the accuracy data on the one-back task was not saved during the scan. That said, we are confident that MD6 was on task because we monitored her performance in real time, which we typically do for all experiments. Specifically, we are able to monitor whether a participant is on task because when he/she presses a button (i.e., for a repeat image in this study), the experimenter hears a beep in the control room. In MD6’s case, we knew she was on task and generally accurate because we could see that the beeping coincided with the repetitions. Further, the expected activation observed in the region of cortex corresponding to the PRL location (arrow in Figure 1, row 1, column 2) confirms that MD6 was paying attention to the stimuli.

All parameters were identical to five years earlier except: i) five years earlier MD6 viewed 8 more blocks of stimuli at each position (thus 24 total blocks per condition in the current study compared to 32 total blocks per condition in the previous one), and the two stimuli positions were presented in separate runs due to the size of the screen at the time, and ii) MD6 was scanned twice for the current study. Note that this year, even with fewer blocks of stimuli compared to the previous study, we find evidence for reorganization of visual processing. Moreover, both in this study and the one five years earlier, we found the expected activation in the region of PRL cortex to stimuli presented at the PRL, revealing that in both studies we had the power to detect neural activation.

Similar to five years earlier, the left eye of MD6 and the control participants was tested, while the right eye was patched. MD6 was instructed to maintain fixation on a cross at the PRL location, whereas matched controls fixated on a cross using their fovea. All stimuli were presented to identical retinal positions between MD6 and her controls.

Participants were scanned on a 3.0 T Siemens Trio scanner at the A. A. Martinos Imaging Center at the McGovern Institute, MIT, Cambridge, MA. Scanning parameters were identical to those used in Baker et al. (2008): Functional images were acquired with a Siemens 12-channel phased-array head-coil and gradient echo single shot echo planar imaging sequence (22 slices, 2 × 2 × 2 mm, 0.2 mm inter-slice gap, TR = 2 s, TE = 30ms), and slices were oriented approximately perpendicular to the calcarine sulcus. High-resolution anatomical images were also acquired for each participant for reconstruction of the cortical surface. During scanning, eye movements were monitored in MD6 using an ISCAN ETL400 eye tracker (ISCAN, Inc., Woburn, MA).

Functional imaging data were analyzed using Freesurfer and FS-FAST software (http://surfer.nmr.mgh.harvard.edu/). Prior to statistical analysis, images were motion-corrected and smoothed (3 mm FWHM Gaussian kernel). Activations (stimulus conditions > fixation baseline) were visualized on the flattened cortical surface. To measure the magnitude of response at the occipital pole (the region of cortex responding to foveal stimulation, a region of interest (ROI) was defined for both hemispheres of all participants based on anatomical criteria. Specifically, ROIs were drawn at the posterior end of the calcarine sulcus with a surface area in each hemisphere of ~200mm² (154mm² for MD6; 153mm² for
control 1; 18 mm² for control 2). Since the ROIs were defined based on the individual anatomy, there was some variation in the precise shape and size of the individual ROIs. For MD6, the same ROIs were used here as in Baker et al. (2008), and because the PRL is on or very near the vertical meridian we again investigated activation in the ROI for each hemisphere, as done 5 years earlier. Activations in occipital pole ROIs to stimuli in different locations were compared with planned t-tests.

RESULTS

Retinal Data

MD6 had large bilateral central scotomata and complete loss of foveal function (i.e., no functional vision within the central two degrees of the visual field) as measured by perimetry. MD6 has a sliver of residual vision within her scotoma (in the left visual field), at least 5 degrees away from the fovea, which we refer to as the ‘parafoveal sliver of vision’ (Figure 1, row 1, column 1). Note that five years earlier the perimetry did not pick up this parafoveal sliver of vision because at that time other more central sparing was evident and this area was not extensively tested as in the most recent perimetry. The 2IFC testing confirmed at the current time the complete loss of foveal function, and showed that MD6 was detecting at chance level stimuli presented at the former foveal location (45% correct with the right eye and 40% with the left eye; 95% CIs [0.30, 0.58] and [0.26, 0.54], respectively), but was well above chance for stimuli presented at the PRL (70% for the right eye and 75% for the left eye; 95% CIs [0.58, 0.82] and [0.63, 0.87], respectively). Note, that small eye movements could move the stimuli presented at the PRL onto non-seeing retina resulting in misses in detection even at the PRL presentations. These findings are in sharp contrast to those reported in Baker et al. (2008) where MD6 had large bilateral central scotomata, but with measurable sparing of central retina and residual foveal function measured by perimetry (Figure 1, row 3, column 1; see also Figure 5 in Baker et al., 2005). (Since MD6 had residual foveal function as measured by perimetry five years earlier, 2IFC was not performed at that time.) MD6 had a clear, stable PRL outside the scotoma (80% of sample fixations were within 4°), consistent with her PRL fixation stability measured five years earlier (Baker et al., 2008). Also consistent with five years earlier, the distance of the PRL from the fovea was approximately 18 degrees, and located close to or on the vertical midline in the visual field.

fMRI Data

In MD6, visual stimulation at the PRL compared with the blank screen baseline produced responses at the occipital pole corresponding to the fovea (white outline in Figure 1, row 1, column 2), revealing large-scale reorganization of visual processing. No evidence of such large-scale reorganization was observed in MD6 five years earlier (white outline in Figure 1, row 3, column 2). As expected, visual activation was also observed in regions of cortex corresponding to the PRL location and in object-selective cortex (arrow in Figure 1, row 1, column 2). In contrast, in the control participant, stimulation at the retinal location corresponding to MD6’s PRL produced significant activation in respective peripheral retinotopic cortex and object-selective cortex only (arrow in Figure 1, row 2, column 2); no activation was observed at the occipital pole (white outline in Figure 1, row 2, column 2).
To measure the magnitude of activation at the occipital pole, the average activation within an independently defined ROI was calculated for MD6 and her control participant. The occipital pole ROI was defined based on anatomical considerations alone without reference to the patterns of activation observed (see Materials and Methods, Functional imaging section). For MD6, there was significant activation in the occipital pole ROI to stimuli presented at the PRL compared with the fixation baseline in both the left and right hemispheres (both p’s <0.01) (Figure 1, row 1, column 3). Note that this activation was not due to MD6 “sneaking a peak” at the PRL stimuli with her parafoveal sliver of vision, as she was able to maintain stable fixation over the entire course of the scan (100% of her fixations were within 3.5°) (Figure 2). In contrast, in the control participant (Figure 1, row 2, column 3) no significant responses above baseline were found in the occipital pole ROI in either hemisphere to stimuli presented at the PRL (both p’s >0.10).

As expected the control participant showed significant activation in the occipital pole ROI to stimuli presented at the fovea (both p’s <0.001). In MD6 too, significant activation in the occipital pole ROI was found for stimuli presented at the fovea compared with fixation in both the left and right hemispheres (both p’s <0.05) (Figure 1, row 1, column 3), presumably because the lower left corner of the stimulus was presented within MD6’s parafoveal sliver of vision.

To confirm that the response at the occipital pole ROI to foveally presented stimuli in MD6 was due to the stimuli being presented in her parafoveal sliver of vision (rather than preserved central foveal function), we scanned MD6 a second time using smaller stimuli, presented at the fovea only, that did not extend into the parafoveal sliver of vision (see Materials and Methods, Functional imaging section), and again measured the magnitude of activation at the occipital pole to stimuli presented at PRL and foveal locations. As before, MD6 exhibited significant activation in the occipital pole ROI to stimuli presented at the PRL compared with the fixation baseline in both the left and right hemispheres (both p’s <0.0001) (Figure 3, row 1), replicating the large-scale reorganization reported in the above experiment. Critically, however, no significant activation in the occipital pole ROI to stimuli presented at the fovea compared with fixation was found in either hemisphere (both p’s >0.20) when we used smaller stimuli, confirming complete loss of foveal vision (Figure 3, row 1). By contrast, in the control participant, we found no significant responses above baseline in the occipital pole ROI to stimuli presented at the PRL (in fact, the response in the occipital pole ROI was significantly below baseline in both hemispheres, both p’s <0.10), but significant activation in the occipital pole ROIs to stimuli presented at the fovea (both p’s <0.001) (Figure 3, row 2).

Thus, following the complete loss of foveal input, the deprived region of cortex that would normally be responsive only to foveal visual stimuli responds to peripheral visual stimuli. Crucially, this same individual exhibited no such large-scale reorganization of visual processing five years earlier when she had some foveal sparing (also see Figure 5 in Baker et al., 2008).
DISCUSSION

We scanned an individual with MD who had some foveal sparing and exhibited no large-scale reorganization of visual processing five years earlier, but who has now lost all foveal function. This individual now shows large-scale reorganization of visual processing, supporting our hypothesis that such large-scale reorganization is dependent on complete bilateral loss of foveal input.

Our finding that large-scale reorganization of visual processing depends on complete foveal vision loss raises the possibility that some previously published failures to find any evidence for large-scale reorganization in MD arose because of some degree of foveal sparing.\textsuperscript{23} That said we cannot rule out the possibility of more subtle reorganization close to the representation of the scotoma border in the Sunness et al. patient or in MD6 with foveal sparing five years earlier. The cortical representation of the scotoma is very difficult to localize, and the precise representation of the border impossible to identify reliably based on the location of visual field loss. Thus, while reorganization of visual processing may not be large enough to produce activation of the entire occipital pole by stimuli presented at the PRL, some local reorganization on the representation of the scotoma border may occur. Nonetheless, MD6 now exhibits large-scale reorganization after complete foveal loss compared to no evidence for such reorganization 5 years earlier before complete loss of foveal vision.

Further, our finding of large-scale reorganization after complete foveal vision loss in MD6 (i.e., after 5 years) provides an upper bound on the necessary time for such reorganization to occur; however, it is possible that such cortical change might happen much more quickly. Determining the time course of functional reorganization can provide important constraints on the underlying neural mechanisms. In another study,\textsuperscript{24} we approached this question using a novel paradigm to chart the time course of cortical change following deprivation in normal adult humans. Specifically, we patched one eye in normal observers, thus depriving the cortical region corresponding to the other eye’s blind spot, and tested for perceptual distortions (a marker for functional reorganization) by probing, at various intervals after the onset of patching, for perceived elongation of shapes presented adjacent to the deprived location. We found that significant elongation occurred around the blind spot within \textit{seconds} of patching, indicating very rapid “reorganization”, and implicating unmasking of pre-existing connections (e.g., horizontal connections in early visual cortex or feedback connections to early visual cortex) as the underlying mechanism of such rapid change, rather than the growth of new connections\textsuperscript{25, 26}. Future research will ask whether this very rapid change reflects the same underlying mechanism as changes in cortex after 5 years as shown in MD6. Such rapid unmasking may not account for the full effect seen in MD individuals, and additional longer-term, possibly structural changes might also occur.

Finally, our finding that large-scale reorganization of visual processing depends on complete foveal vision loss dovetails with our recent finding that activation of formerly foveal cortex in MD individuals with complete foveal vision loss is \textit{not} specific to stimulation of the PRL, but also occurs when stimuli are presented to an iso-eccentric peripheral retinal location\textsuperscript{2}. From that result, we concluded that deprived foveal cortex comes to respond to peripheral...
stimuli because the foveal region gets no bottom-up input of its own, leading it to take input from any cortex responsive to the peripheral stimuli regardless of the behavioral significance of the PRL. Note that MD6 had a clear, stable PRL both now and five years ago, yet the existence of the PRL five years earlier was not sufficient to produce large-scale functional reorganization. Instead, MD6 exhibited large-scale reorganization of visual processing only after complete foveal vision loss, providing further evidence that large-scale functional reorganization is not dependent on the adoption of a PRL, but rather complete foveal vision loss.

Just as we saw in MD6 that the loss of input in the relevant cortical location (i.e., foveal cortex) had to be total in order for large-scale reorganization of visual processing to occur in that cortical location, we speculate that large-scale reorganization in other parts of the visual field depend on complete loss of input to that particular location. For example, in a stroke patient (BL) with optic radiation damage that completely deprived the upper left visual field only, we found reorganization of primary visual cortex representing the upper left visual field.27 Similarly, reorganization of primary visual cortex has been reported in adult cats and monkeys following extensive retinal lesions that were parafoveally, sparing central vision (e.g., 9, 28, 29). Thus, perhaps what drives reorganization of visual processing then is the “denseness” of the scotoma per se; that is, large-scale reorganization of foveal cortex requires complete loss of foveal input, while large-scale reorganization of peripheral cortex requires complete loss of the relevant peripheral retina. This speculation requires eventual clarification of how big an area of total loss is sufficient for reorganization of visual processing to occur arises.

The reorganization of visual processing reported here and in other individuals with MD in previous reports raises a fundamental question for cognitive neuroscience, one that has been scarcely investigated previously: How does cortical change affect perception? What does the MD individual see when a stimulus is presented at the PRL? In Dilks et al. (2007), we reported that stroke patient BL experiences perceptual distortion as a consequence of cortical reorganization: a square presented in the lower LVF was perceived as a rectangle extending into the blind upper LVF, providing the first evidence that we know of that reorganization of adult primary visual cortex affects visual perception. Current research is asking whether similar distortions are present in individuals with MD. Such a result would strengthen the evidence that perceptual distortions are a consequence of cortical reorganization.

How does the reorganization of visual processing arise? One possible mechanism is the disinhibition of pre-existing long-range horizontal connections within early visual cortex.7, 9 A second potential mechanism for reorganization involves the growth of new horizontal connections, rather than the unmasking of existing connections. Finally, a third possible source of reorganization could be the unmasking of intracortical feedback to early visual cortex from higher visual areas. At this time our data cannot distinguish between these three alternatives, and no other experiments in humans or animals have definitively pinpointed the respective contributions of horizontal and feedback connections in cortical reorganization.
It was recently reported that activation of the foveal cortex by peripheral stimuli was observed only when participants were performing a task.\(^1\) This observation was taken to indicate that activation of the foveal cortex by peripheral stimuli reflects unmasking of feedback connections from extrastriate visual cortex (Mechanism 3 above). However, modulation of activity by a task does not provide strong support for a solely top-down mechanism of reorganization, because it is well established that bottom-up visual responses can be modulated by attention. Modulation by task provides evidence for a top-down component, but it is not clear if this top-down influence differs from the standard attentional modulation of bottom-up visual responses observed in participants with full-field vision. Thus, the mechanism of reorganization remains an open question for future research.

In conclusion, this work supports the hypothesis that large-scale reorganization of visual processing (i.e., activation of foveal cortex by peripheral stimuli) occurs only after complete loss of functional foveal vision in MD. Future work should explore both the mechanisms underlying this reorganization and its functional significance.

**Acknowledgments**

We express our sincere thanks to MD6. We would also like to thank the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research, MIT, Cambridge, MA. This work was supported in part by NIH grants EY016559 and EY13455 (NK), and EY05957 (EP).

**References**


SYNOPSIS

When individuals with macular degeneration (MD) view stimuli in the periphery, most of them activate visual cortex normally activated only by foveal stimuli. Why do some show this reorganization of visual processing whereas others do not? Here we test the hypothesis that reorganization in MD is dependent on complete loss of foveal input by bringing back an MD individual who was previously scanned, did not show reorganization, and had some spared foveal function. This individual now has complete loss of foveal function and now also shows reorganization, providing the first evidence for at least one necessary condition for reorganization of visual processing in individuals with MD.
Figure 1.
Visual field (Column 1) and fMRI results (Column 2) from MD6, before (Row 3) and after (Row 1) complete loss of foveal vision (Row 1). fMRI results for a matched control are also shown (Row 2). Column 3. Bar charts showing percent signal change (from fixation baseline) in the independently defined Occipital pole ROI (white outlines on the statistical maps) in response to stimuli presented at the PRL and fovea locations, labeled accordingly, in the left (blue bars) and right (red bars) hemispheres for MD6 and her matched control.
Figure 2.
Eyetracking results from MD6 while inside the scanner. The plus indicates the fixation point (PRL), the boxes indicate the position and size of the PRL and foveally presented stimuli, and the colored pixels depict where MD6 was fixating. In this plot, we averaged pupil position every 50ms and removed 240ms intervals around the times when the participant blinked.
Figure 3.
fMRI data from a second experiment from MD6, after complete loss of foveal vision, and another matched control. All other details are identical to Figure 1.