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Reorganization of visual processing is related to eccentric viewing in patients with macular degeneration

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Abstract. *Purpose*: Neural evidence exists for cortical reorganization in human visual cortex in response to retinal disease. Macular degeneration (MD) causes the progressive loss of central visual acuity. To cope with this, MD patients often adopt a preferred retinal location (PRL, i.e., a functional retinal area in their periphery used to fixate instead of the damaged fovea). The use of a PRL may foster cortical reorganization.
Methods: We used fMRI to measure brain activity in calcarine sulcus while visually stimulating peripheral visual regions in MD patients and age-matched control participants.
Results: We found that visual stimulation of the PRL in MD patients increased brain activity in cortex normally representing central vision relative to visual stimulation of a peripheral region outside the patients' PRL and relative to stimulation in the periphery of age-matched control participants.
Conclusions: These data directly link cortical reorganization in MD to behavioral adaptations adopted by MD patients. These results not only confirm that large-scale cortical reorganization of visual processing occurs in humans in response to retinal disease, but also relate this reorganization to functional changes in patient behavior.

Keywords: Plasticity, cortical reorganization, functional neuroimaging, fMRI, calcarine sulcus, primary visual cortex, retinal disease

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly – affecting almost 15% of people over the age of 75 (Friedman et al., 2004). By definition, AMD occurs in older adults with symptomatic onset usually occurring at age 50 years or older. However, a similar hereditary disease – juvenile macular degeneration (JMD) or Stargardt's Disease – begins in childhood and affects nearly 1 in 10,000 children (Deutman, 2003). Both forms of macular degeneration (MD) affect the most vital part of the retina (i.e., the fovea and macula, which corresponds to the central 15–20° of the visual field). This region has the highest density of cones, the photoreceptors responsible for high spatial resolution and color vision, and correspondingly produces the highest resolution vision (Riordan-Eva, 1999). Unfortunately for those affected individuals, this high-resolution central region is used for everyday tasks like reading, driving, using computers, and monitoring facial expressions; and thus their ability to perform these tasks is severely limited.

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The key pathophysiological outcome of MD is general degradation of macular function, resulting in a progressive and permanent loss of visual acuity, but not necessarily a complete lack of light perception. Patients often retain a significant degree of visual function in the undamaged, peripheral areas of the retina surrounding the macula.

A primary characteristic of the progression of MD is the formation of a central scotoma, a region of diminished vision within the visual field. Scotomata may cause centrally presented images to appear light, dark, wavy, blurred or even to contain black or gray holes (Arroyo, 2006). As MD progresses, near and far visual activities become quite challenging. For example, parts of words on a printed page falling in central vision may appear distorted or disappear altogether (Cheung & Legge, 2005).

While the rate of functional decline depends on several factors, MD often causes gradual vision loss over a number of years. This continual loss of sight leads to changes in patient behavior, such as ocular movements and visual fixation, as they try to accommodate their declining visual abilities. Once the spatial resolution of the fovea cannot be used to analyze images, a preferred retinal location (PRL) may replace this function. This phenomenon, called *eccentric viewing*, is the only way these patients can learn to continue performing distance and near vision activities (e.g., watching television, reading, etc.) (Noorden & Mackensen, 1962; Timberlake et al., 1987). The location of the PRL depends upon the geographic distribution of the damage to the retina (Sunness et al., 1996), although it tends to develop near the edge of the scotoma in an adjacent functional retinal area (Cheung & Legge, 2005).

Humans rely on vision more than any of the other Aristotelian senses, and more of our brain is devoted to visual perception than all other senses combined (Felleman & Van Essen, 1991). Visual processing is organized topographically in primary visual cortex, with adjacent stimulated locations on the retina activating adjacent areas in primary visual cortex. Input from the fovea and macula is represented on the posterior aspect of calcarine sulcus, projecting to between 15% and 50% of primary visual cortex (i.e., the foveal confluence; McFadzean et al., 2002). Thus, after central scotomata develop, patients with MD are left with a large amount of deafferented visual cortex that previously responded to central visual stimulation.

Affected patients often learn to read and interact with the world by fixating, not with their fovea, but at an eccentric retinal location (i.e., their PRL). These two factors, the unused cortex and the required behavioral adaptation, may be highly conducive to functional cortical reorganization. Functional cortical reorganization, in this sense, refers to changes in neural processing of the deafferented visual cortex (e.g., through selective strengthening of connections with afferented cortex), which may lead to the resumption of neural activity. However, the evidence for functional reorganization of visual cortex thus far has been equivocal.

Investigation of cortical reorganization in response to retinal lesions and other eye impairments has an established literature in both humans and animals. Exploiting the topographic organization of primary visual cortex, research on non-human animals has involved directed lesioning of specific retinal areas to create lesion projection zones of deafferented neurons in the cortex. Results from some of these studies indicate that activity in the lesion projection zone is initially absent after lesioning but begins to resume with time (Calford et al., 2000; Darian-Smith & Gilbert, 1995; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1991; Kaas et al., 1990). This resumed activity is ectopic (i.e., elicited by stimulation from retinal locations outside of the lesion), often resulting from stimulation just outside the lesioned area (Gilbert & Wiesel, 1992; Kaas et al., 1990). Such findings indicate that cortical reorganization may occur by recruiting the deafferented neurons of the lesion projection zone to process input from functional retinal areas.

However, activity in these neurons may not return to normal firing patterns (Heinen & Skavenski, 1991), so their functionality remains unclear. Additionally, other neurophysiological research has not produced clear evidence for cortical reorganization. One experiment reported no evidence for topographic reorganization in non-human primates after monocular retinal lesions (Murakami et al., 1997). Another study conducted a detailed analyses of the columnar structure in primary visual cortex of non-human primates after disruption of monocular vision and showed no anatomical evidence for reorganization, even after 2 years (Horton & Hocking, 1998). These authors also report a similar result in one AMD patient after 4 years. More recently, a functional magnetic resonance imaging (fMRI) study also found no evidence for brain activity in the lesion projection zone in non-human primates (Smirnakis et al., 2005). This technique *has* been criticized (Calford et al., 2005), although fMRI has been used to demonstrate functional cortical reorganization in humans (Baker et al., 2005; Baseler et al., 2002; Morland et al., 2001).

These equivocal findings are reflected in fMRI-based human research as well. In addition to the one pa-

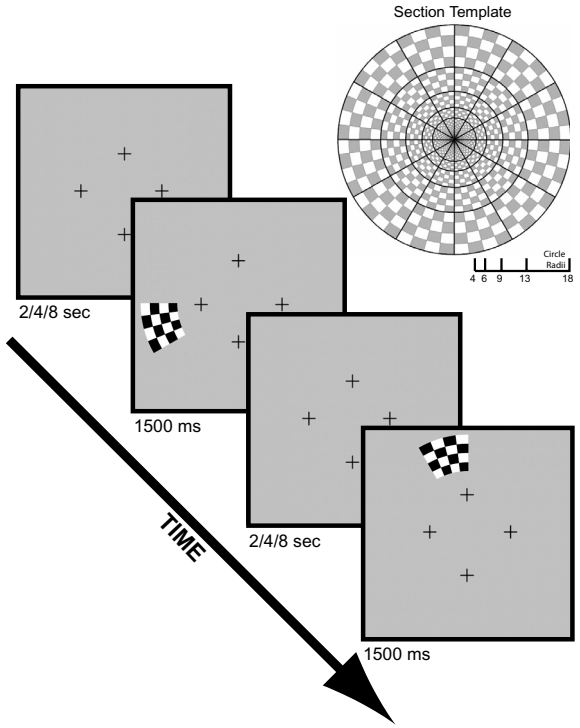

Fig. 1. Schematic of visual display used in the experiment. Participants fixated their eyes on the imaginary intersection of four fixation crosses. Contrast-reversing checkerboard sections (8 Hz) were presented throughout 36° of each participant's visual field. The checkerboard template shown in the upper right appears in gray to highlight the visual sections, but the sections appeared black and white to participants.

tient who did not show evidence for cortical reorganization (Horton & Hocking, 1998), another study reported fMRI evidence (from one patient) against reorganization of visual cortex (Sunness et al., 2004). They used fMRI to investigate the visual cortex of an individual with AMD, who had reported visual loss within the past 3 years. They found an unresponsive area in primary visual cortex corresponding to the location of the scotoma, an indication of the absence of reorganization.

In contrast, other fMRI studies have provided evidence of cortical reorganization in response to foveal lesions, induced by MD and other visual diseases. For example, studies of patients with rod monochromism – a congenital disorder in which the fovea lacks the normal distribution of cones, resulting in a natural foveal lesion – show that they produce brain activity in their lesion projection zone in response to retinal stimulation outside the fovea (Baseler et al., 2002; Morland et al., 2001). These results suggest that functional cortical reorganization occurs in this cortical area. Studies with completely blind patients also show large-scale functional reorganization in visual cortex (Sadato et al., 2002). Finally, recent research also suggests that functional cortical reorganization may indeed occur in MD patients (Baker et al., 2005). Two experiments showed increased fMRI activity in posterior calcarine sulcus of two MD patients, compared to controls, in response to stimuli presented to the periphery, including the PRL.

One reason for the inconsistent results, at least in the human research, may be that functional cortical reorganization occurs for visual stimulation in certain areas of the retina only. Specifically, we propose a functional relationship in MD patients between their PRL and lesion projection zone activity. We tested this hypothesis by using fMRI to measure brain activity in response to visual stimulation along the calcarine sulcus in MD patients and age-matched controls within the MD patients' PRL and within visual regions of the same size and at the same eccentricity outside the patients' PRL (i.e., the nonPRL region). The task procedure is shown in Fig. 1.

Our results demonstrate that the foveal confluence in posterior calcarine sulcus, which is within the lesion projection zone for MD patients with central scotomata, shows significant brain activity to peripheral visual stimulation only within patients' PRLs. No corresponding activity to peripheral stimulation was found in control participants. These results lend substantial support for the hypothesis that there is a close relationship between the PRL and the reorganization of visual processing.

2. Materials and methods

2.1. Participants

Thirteen volunteers participated in this experiment. Six volunteer patients with MD were recruited from the Emory Eye Center. Seven additional age-matched volunteers (controls) were recruited from the Atlanta community. Relevant details about each participant are shown in Table 1. All participants gave their informed consent and were compensated for their performance.

All patients had previously been diagnosed with either AMD or JMD. Control participants were screened to rule out any significant ocular pathology and visual-field defects (e.g., cataracts, glaucoma, or corneal scarring). The eye with best vision was determined for each participant (both patients and controls) using vision charts, testing the lens refraction of participants' glasses, and referral to patient medical charts. Cor-

Table 1
Participant demographics and visual characteristics

Patient control	Disease	Age	Gender	Time since onset	Eye tested	Visual acuity	Farnsworth dichotomous (D-15)	Contrast sensitivity
MD1	AMD	75	Male	R: 3 yrs; L: 3 yrs	Left	20/250	Tritan	0.15
MD2	JMD	63	Male	R: Birth; L: Birth	Left	20/100	Deutan	1.23
MD3	AMD	78	Female	R: 2 yrs; L: 6 yrs	Right	20/100	Normal	1.20
MD4	AMD	72	Male	R: 1 yr; L: 5 yrs	Right	20/200	Tritan	1.05
MD5	AMD	71	Male	R: 5 yrs; L: 5 yrs	Left	20/160	Normal	1.20
MD6	AMD	82	Female	R: $>$ 10 yrs; L: $>$ 10 yrs	Left	20/400	Tritan	1.20
C1		75	Male		Right	20/40	Tritan	1.65
C2		63	Male		Left	20/32	Normal	1.20
C3		78	Female		Right	20/32	Normal	1.50
C4		72	Male		Right	20/20	Normal	1.65
C6a*		82	Male		Right	20/20	Tritan	1.65
C6b*		81	Male		Left	20/25	Normal	1.50

AMD = age-related macular degeneration; JMD = juvenile macular degeneration; C = age-matched control participant
Contrast sensitivity is given in log units where a maximum of 2 indicates majority identification at 1% contrast.
*Data were collected from an extra control participant who was matched to the patient closest in age (MD6).

rected visual acuity in all participants was 20/400 or better in their best eye, which they then used in the experiment. Contrast sensitivity was measured with the Pelli-Robson chart, and color perception was determined with the Farnsworth D-15 color vision test.

2.2. Apparatus

2.2.1. Microperimetry

An MP-1 microperimeter (Nidek Technologies, www.nidek.com) was used to assess retinal function for each participant. This was particularly important for the characterization of the scotomata and presence of a PRL for those patients with MD. The MP-1 combines fundus-based microperimetry (e.g., visual field testing) with color fundus photography, while using biological landmarks to actively track patient fixation during perimetry. The MP-1 first takes an infrared photograph of the retina, which is then digitally registered and matched to the live video of the patient's retina via biological landmarks (e.g., bifurcations in retinal vasculature). Participants were then asked whether they detected stimuli, which were presented serially throughout the visual field. The location of the stimulus array was adjusted 20 times a second to account for eye movements. This tracking system ensured that stimuli were presented accurately to selected retinal areas. More detailed accounts of MP-1 microperimetry testing can be found in (Rohrschneider et al., 2005).

In terms of functional microperimetry, retinal sensitivity is the inverse of the stimulus brightness needed to elicit detection at the prescribed retinal location. Generally, retinal sensitivity is measured in units of dB (dB $= 10 \log_{10} (L_{max}/L_{stim})$, where L_{max} is the maximum stimulus luminance of the instrument and L_{stim} is the luminance of the presented stimulus) to account for the relative capabilities of the machine used for testing. The MP-1 measures retinal sensitivity at each stimuli testing location in dB units, varying from the brightest level, 0 (127 cd/m^2), to the dimmest level, 20 (1.27 cd/m^2). The output from the MP-1 exam includes a retinal sensitivity map, overlaid on a color fundus photograph, which allows for the identification and verification of scotomata, as well as intact retinal areas.

The perimetry exam consisted of a pattern of 76 stimulus locations centered on the fovea and extending peripherally 10° (covering approximately the central 20° of visual field). The testing points were radially arranged with approximately 2° linear spacing between them, with stimuli density decreasing moving peripherally from the fovea. Stimuli used were Goldmann III (white, circular stimuli, approximately 4 mm^2 or 0.47° diameter), presented on a black background (1.27 cd/m^2) for 200 ms. During perimetry testing, stimuli locations were presented randomly and threshold sensitivity of each test point was determined using a 4-2 staircase method (i.e., stimulus intensity level steps up four dB levels (dimmer) when detected and then down two levels (brighter) when not detected, until the threshold is reached). Participants indicated detection of a stimulus by depressing a button on a handheld joystick.

All participants, including MD patients, were instructed to fixate centrally by looking straight ahead and fixating on an imaginary point at the logical intersection of four pericentral fixation targets (red crosses, 1° in extension, 10° spread laterally and superi-

or/inferior). This fixation practice was used to allow for patients with central scotomata to see these peripheral visual targets and use them as a geographic reference to fixate centrally. This method of simulated fixation was used to ensure that a consistent set of testing conditions could be used for both the microperimetry exam and fMRI testing. It should be noted that all participants fixated centrally – not with their PRL – during the microperimetry exam, and during fMRI scanning.

Fixation in MD patients is often less stable than those with normal foveal vision. However, the pericentral fixation method used here has been shown to produce fixation stability similar to that of central fixation in MD patients and is often used as an alternate to central fixation when patients lack foveal vision (Bellmann et al., 2004).

Foveal fixation for control participants, non-central fixation (i.e., PRL) for MD patients, and the ability of MD patients to fixate centrally were confirmed with separate fixation tests. Fixation tests requiring the participant to visually fixate on a single central cross were used to confirm both the location of preferred fixation, as well as relative fixation stability for all patients. The relative location of fixation (e.g., offset from the fovea) was noted as an initial indication of PRL location for MD patients. This was also confirmed with the results of previous patient ophthalmic examination performed at the Emory Eye Center.

PRL location and the function of this retinal area in MD patients was then confirmed with a separate perimetry exam, utilizing an offset 12° pattern of Goldmann III stimuli, centered on the retinal location identified as the PRL during the fixation test. This testing was performed to both confirm fixation stability with the PRL, as well as to profile the retinal sensitivity of the PRL area and determine the relative location/boundaries for the adjacent scotomatous regions.

Scotomatous areas, largely covering the fovea, were identified via visual examination of the fundus photography as well as identification of retinal areas of significantly decreased retinal sensitivity (e.g., 0–2 dB). This was performed using an extension 20° pattern of Goldmann III stimuli, centered on the fovea. This testing was performed to confirm the location, extent, and functional impact (e.g., decreased retinal sensitivity) of scotomata. Additionally, spared regions of peripheral retina were also covered by the testing pattern in order to confirm PRL location, as well as to identify other areas of spared retinal function at similar eccentricities.

Examination of the perimetry results and fundus photographs allowed us to identify both the patients' PRL and additional areas of preserved retina at the same eccentricity as the PRL (i.e., the nonPRL). The retinal sensitivity of these nonPRL regions was matched as closely as possible to the retinal sensitivity of the PRL. These sections are identified by colored boxes in Fig. 2, which depicts the actual microperimetry results reports from the MP-1. These images of each MD patient's retina illustrates the location and extent of their scotoma, which can be examined both visually by examination of the fundus photograph and functionally, in terms of decreased retinal sensitivity.

2.2.2. Magnetic resonance imaging

Images were acquired using a Siemens 3T Trio MR scanner. A standard radio frequency (RF) head coil was used with foam padding to restrict head motion comfortably. An echoplanar sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°) was used to acquire data sensitive to the blood oxygen level dependent signal. Each functional volume contained 33 axial slices of 3.4 mm isotropic voxels. We collected four fMRI runs, which lasted 8:08 min (192 volumes/run) each. A high-resolution 3D MPRAGE (TI = 1100 ms, flip angle = 8°) structural scan (1 mm isotropic voxels) was collected at the end of the fMRI session.

2.3. Procedure

2.3.1. Stimuli

Different sections of each participant's visual field were stimulated with contrast-reversing (8 Hz or 16 reversals/s) checkerboard patterns (mean luminance = 92 cd/m^2). Sixty sections were constructed by dividing a checkerboard template subtending 36° of total visual angle with 5 concentric circles at 4°, 6°, 9°, 13°, and 18° visual angle and 12 radii. The intersection of each radius and circle defined a section. The sections were scaled so that larger stimuli were presented in the periphery of the visual field. Scaling was accomplished by adjusting the diameters of the five concentric circles according to the human cortical magnification factor (Horton & Hoyt, 1991). The following equation was used to calculate the diameter in degrees of visual angle for each of the circles: E(n) = e $^{n/2.76}$-1 (Baseler et al., 1994).

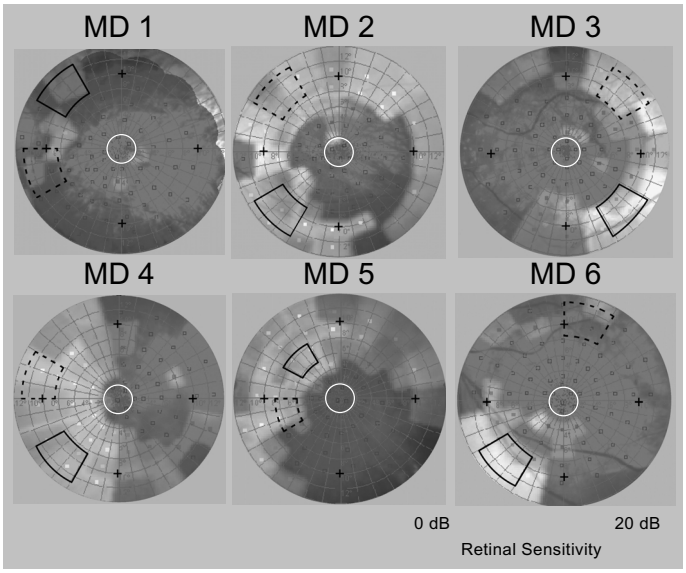

Fig. 2. Microperimetry testing reports, including the fundus photographs and testing results (e.g., testing pattern and retinal sensitivity results) of the tested eye from each MD patient. Retinal sensitivity is depicted by the luminance of the image. The section used to stimulate the PRL is indicated with a solid line. The section used to stimulate the nonPRL region is indicated with a dashed line. The black crosses indicate the 10 fixation stimuli. The white concentric circle indicates 2° of the visual field.

2.3.2. Stimulus presentation

Participants were scanned using only their least visually impaired eye (i.e., the eye possessing the best visual acuity, but still exhibiting MD in the case of the patients; see Table 1). A patch was placed over their other eye. The stimuli were back projected on a screen that participants viewed through a mirror attached to the RF coil. Each participant selected a fixation display with four fixation crosses from among a number of alternatives (viz., red or black crosses, 7, 11, 25, or 30° apart). Participants chose which fixation crosses were most discernable (red or black) and at which eccentricity they could see all the fixation crosses. As expected, MD participants selected fixation stimuli at the larger eccentricities, while all controls were able to see them at 7°.

As during MP-1 examination, participants were then instructed to fixate on the imaginary intersection of these crosses and try to remain fixated on that position during the scanning runs. Eye movements were monitored with a video camera throughout each run. Unfortunately, these videos could not be used to remove trials in which patients made eye movements. Nevertheless, informal monitoring of these videos showed that participants were able to follow directions and remain fixated throughout most trials. This control over eye movements is similar to previous fMRI investigations of these patients (e.g., Baker et al., 2005).

Each fMRI run began with a fixation display. This display remained on screen for the entire run. A contrast-reversing checkerboard section (8 Hz) appeared on screen for 1500 ms. Following the visual stimulation the fixation display remained on screen for a variable inter-stimulus interval of 2 sec on 30 trials, and 4 and 8 sec on 15 trials each, before the next stimulus section appeared. The 60 section stimuli were presented randomly once per run. Thus, the PRL and nonPRL sections were stimulated four times each.

2.3.3. Functional MRI data processing and analyses

Data reconstruction, processing and analyses for each participant were performed using SPM2 (www.fil.ion.ucl.ac.uk/spm). After reconstruction, head-motion artifacts were corrected to the last functional scan with a least squares approach using a six-parameter, rigid-body transformation algorithm (Friston et al., 1995); after which slice acquisition timing differences were corrected.

Data were analyzed using a modified general linear model (Worsley & Friston, 1995). We created design matrices for each participant with the covariates of interest for each section. These covariates were convolved with an idealized hemodynamic response function. A high-pass filter removed frequencies below 0.0078 Hz. Contrast images were computed for each participant for each of the section vs. baseline (i.e., the inter-stimulus interval).

Prior to analysis, patients with MD were age-matched with control participants (see Table 1). Regions-of-interest (ROIs) representing the calcarine sulcus (from occipital pole to the intersection between the calcarine and parietal-occipital sulci) were then created for each participant using anatomical atlases as a guide (Duvernoy, 1991; Talairach & Tournoux, 1988). Each ROI was then divided along the sagittal plane into separate 2 mm coronal slices. Analyses were restricted to the most posterior 20 of these ROI slices because they covered the calcarine sulcus in all participants. β-values were extracted from these ROIs from each participant for subsequent analysis. All analyses were conducted on the data extracted from the ROIs in each participant's native brain space. Each ROI included voxels from both the left and the right hemisphere. Separate analyses conducted for each hemisphere did not affect the results, so the bilateral ROI data are presented here.

3. Results

As shown in Fig. 2, for each patient we identified a section of visual field stimulation that fell within their PRL (identified from fixation testing during microperimetry) and a section of visual field of the same size and at the same eccentricity outside their PRL (i.e., the nonPRL section). Brain activation measures (β-values) were identified for each participant using the contrasts of visual stimulation versus baseline for the four theoretically interesting visual field sections (viz., PRL and nonPRL sections in patients and age-matched control participants). For each control participant we extracted β-values of activity in sections corresponding to the PRL and nonPRL sections identified in their age-matched MD patient.

The retinal sensitivity of the nonPRL regions was matched as closely as possible to the retinal sensitivity of the PRL. The mean retinal sensitivity of MD patient's PRL was 8.8 $\pm$ 5.0 dB. The mean retinal sensitivity for the nonPRL region was 7.2 $\pm$ 5.3 dB. These retinal sensitivities were not significantly different from each other $t(5) = 1.89$, $p > 0.10$. For the age-matched controls, the retinal sensitivity for the PRL and nonPRL sections were also not significantly different from each other (PRL = 14 $\pm$ 4.5 dB; nonPRL = 13.4 $\pm$ 4.9; $t(6) = 0.56$, $p > 0.5$). The difference in retinal sensitivity for the PRL of MD patients and the corresponding region in age-matched controls approached significance: $t(11) = 1.96$, $p < 0.08$.

Mean β-values across the calcarine sulcus ROIs are shown separately for the visual field sections for each participant group in Fig. 3. A 2 $\times$ 2 $\times$ 20 ANOVA, with Group (MD patient and control), Visual Field Section (PRL and nonPRL), and ROI (20 ROIs across the calcarine sulcus) as factors, was used to analyze brain activity. None of the main effects were significant: Group, $F(1,11) = 0.08$, $p = 0.78$; Section, $F(1,11) = 1.71$, $p = 0.22$; and ROI, $F(1,11) = 0.49$, $p = 0.97$. The interaction between group and visual field section was significant: $F(1,11) = 5.92$, $p < 0.05$. The effect on brain activity of visual stimulation to the PRL vs. nonPRL section differed between groups. To investigate the cause of this interaction, we conducted analyses of the simple effect of section within each group. These analyses showed that there was a significant effect of section in the MD patient group: $F(1,11) = 6.49$, $p < 0.05$; but not the control group: $F(1,11) = 0.69$, $p = 0.43$. Thus, as shown in Fig. 3, PRL activity was significantly greater than nonPRL activity for the MD patients but not the control participants.

Of particular theoretical interest in these data is whether MD patients show *more* brain activity in *posterior* calcarine sulcus (i.e., the foveal confluence) in response to visual stimulation of their PRL than in response to stimulation of other visual field sections (e.g., nonPRL), especially compared to age-matched controls. This would demonstrate cortical reorganization in this brain region, which typically lies within the lesion projection zone for the macular scotomata (Dougherty et al., 2003) and has previously shown evidence for cortical reorganization (Baker et al., 2005; Baseler et al., 2002). To investigate this, we combined the five ROIs surrounding the peak of activity in the MD patient PRL group (i.e., the ROI 8mm from the most posterior aspect of the occipital cortex with the two ROIs anterior and posterior to it) and computed the mean activity in this combined region in all four conditions of interest (e.g., patient PRL, patient nonPRL, control PRL, and control nonPRL). We then compared mean activity in the MD patient PRL group with activity in the patient nonPRL and in the control PRL groups using one-tailed t-tests. As shown in Fig. 4, results indicate that brain activity in posterior calcarine sulcus was significantly greater for PRL stimulation in MD patients than for either nonPRL stimulation: $t(5) = 3.76$, $p < 0.01$; or for PRL stimulation in control participants: $t(9) = 2.06$, $p < 0.05$. There was no activity in either visual region for the control participants.

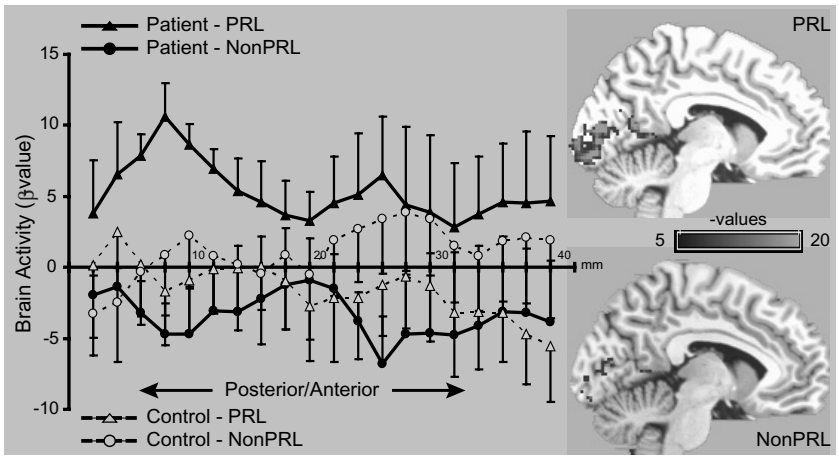

Fig. 3. The line graph depicts mean β-values for visual stimulation in two visual field regions (PRL and nonPRL) for the two groups of participants (MD patients and age-matched controls) from 2 mm regions-of-interest across the extent of calcarine sulcus. These data were extracted from each participant individually. Brain activity across the calcarine sulcus for PRL and nonPRL visual stimulation are also shown for the MD patients on sagittal brain slices ($z = -6$). To display the data in a standard space, the β-values for PRL and nonPRL related activity were first normalized to the Montreal Neurological Institute template brain. Thus, there is a close, but not direct, correspondence between the activation data depicted in the line graph and on the sagittal slices.

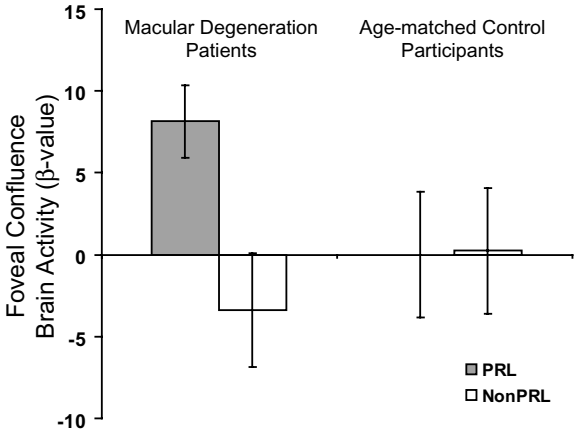

Fig. 4. Mean β-values and standard errors for visual stimulation in two visual field regions (PRL and nonPRL) for the two groups of participants (MD patients and age-matched controls) from the foveal confluence.

4. Discussion

These results show substantial evidence for functionally-related cortical reorganization in human visual cortex. Visual stimulation within the PRL of MD patients produced significantly more brain activity in posterior calcarine sulcus (i.e., the lesion projection zone for the fovea and macula) than did stimulation either to comparable nonPRL visual regions in the patients; or to visual stimulation of regions corresponding to the patient PRL in a group of age-matched control participants. In other words, only the region of the visual field used by patients for eccentric viewing of peripheral stimuli (i.e., the PRL) produced activity in the lesion projection zone corresponding to the scotoma. These results suggest that reorganization of human neural processing in the foveal and macular projection zone is related to the use of a PRL in MD patients and support our hypothesis for a functional relationship between PRL use and cortical reorganization.

Although MD patients are known to have difficulty maintaining stable fixation – especially when not using their PRL (Schuchard et al., 1999), these eye movements are unlikely to have contributed to the results reported here. First, five out of six of our patients were able to remain fixated within 2° during microperimetry, and video monitoring indicated that all patients were able to maintain central fixation throughout most of the fMRI session. Second, we found increased brain activity in posterior calcarine sulcus when visual stimuli fell within each patient's PRL. This is the condition least likely to be contaminated by ancillary eye movements because, on these trials, the stimulus falls within the visual region to which the patients would likely adjust fixation. Therefore, our results are likely caused by a functional reorganization of visual processing within posterior calcarine sulcus, and not an artifact of a failure to maintain central fixation.

4.1. Relationship to existing literature

Our current results provide several new insights to our understanding of visual reorganization in response

to MD. One previous fMRI report did not show evidence for cortical reorganization in patients (Sunness et al., 2004). However, this study investigated only one patient. Additionally, this patient had horseshoe shaped scotomata sparing visual regions at or near the fovea in each eye. This spared macular vision may have inhibited cortical reorganization.

Another study reporting evidence for cortical reorganization in two AMD patients (Baker et al., 2005), showed that stimulation of the PRL of individuals with MD results in activation in deafferented cortical areas that previously represented the macula. Our current results replicate and extend these findings in several ways. First, we replicate the results with six patients. Second, we show that this increased activity emerges only in the foveal confluence and not across the extent of calcarine sulcus. Finally, the previous study only compared activity from PRL stimulation to activity from stimulation of the fovea. Here, we also measure activity in response to peripheral stimulation both inside and outside the PRL. We find that the new functional properties of the deprived visual cortex of MD patients relates only to the PRL and not to more general peripheral stimulation. Thus, our results confirm the existence of functional cortical reorganization in response to MD, localize this reorganization to posterior calcarine sulcus, and demonstrate a relationship between cortical reorganization and the use of a PRL in MD patients.

The relationship demonstrated in this study, via brain activation data, between cortical reorganization and PRL use in patients with MD is consistent with existing behavioral research demonstrating a functional relationship between cognitive processing and PRL use in MD patients. For example, one study found that subsequent PRL location may be related to variability in attentional acuity across a patient's visual field (Altpeter et al., 2000). Another study reported evidence that MD may result in improved processing to peripheral stimuli, though it did not investigate the PRL specifically (Casco et al., 2003). Those authors found that a patient with JMD performed better than age-matched control participants on visual search and lexical decision tasks when the stimuli were presented outside the fovea. Finally, it has also been shown that patients' ability to attend to and use stimuli from multiple sensory channels changes with disease progression (Jacko et al., 2003). In the Jacko et al. study, early-stage AMD patients were least able to make efficient use of multi-modal feedback in a computer-based drag-and-drop task, while patients with more severe cases of retinal impairment were shown to use multi-modal feedback nearly as well as fully-sighted control participants.

4.2. Mechanisms for cortical reorganization

These previous studies demonstrate how cognitive processing changes with MD progression and PRL use. There is growing evidence that these cognitive changes are at least partly the result of reorganization of neural connections (c.f., Das, 1997). Primary visual cortical neurons are arranged in a columnar fashion based on their receptive field properties (Gilbert & Wiesel, 1992), but they also maintain extensive, inter-column horizontal connections (Martin & Whitteridge, 1984). These connections, which normally serve a modulatory role (Hirsch & Gilbert, 1991), may reorganize cortical topography through selective strengthening of connections from afferented cortex. Cortical reorganization may begin almost immediately for neurons in the lesion projection zone resulting in an expansion of receptive field size (Pettet & Gilbert, 1992). In a matter of months, the alteration of receptive fields may lead to permanent physiological change in the arborization of new axons (Darian-Smith & Gilbert, 1994; Obata et al., 1999).

These physiological changes, however, do not preclude cognitive and strategic changes as well. Psychophysical research has shown that covert attention yields improved detection and discrimination thresholds (e.g., Posner et al., 1980) and that attention is subserved by a network of cortical and subcortical brain structures (Corbetta, 1998; Posner & Dehaene, 1994). Research into temporal relationship of these components indicates that feedback pathways exist between extrastriate and striate visual areas. Furthermore, these feedback mechanisms are known to selectively bias neuronal activity in the attended part of the visual field (Martinez et al., 1999). This re-entrant activation from higher cortical areas may be responsible for the improved perceptual performance in spatial attention. For example, a behavioral tendency to attend to a specific part of the visual field may result in the continued modulation of representative neuronal ensembles in V1 and eventually an increased susceptibility to extrastriate feedback. The nature of the reorganization may not solely be a consequence of cortical structure but may also be determined by visual experience, dictated by the behavior of the individual.

Support for this idea comes from a growing body of research using both humans and animals that shows that visual experience and resulting neuronal activity is affected by training and practice (e.g., Kasten et al., 1999). These effects have been observed in both striate (Furmanski et al., 2004; Schiltz et al., 1999), extrastri-

ate (Poldrack, et al., 1998; Yang & Maunsell, 2004), higher-level visual areas (Kobatake et al., 1998; Marshall et al., 2008), and even prefrontal control regions (Marshall et al., 2008; Schumacher et al., 2005). Although Marshall and colleagues employed patients with acquired brain damage rather than visual deafferentation (as reported here), their study demonstrates that the network between early visual areas and higher-order attentional control areas may change with a change in the pattern of visual input. Such findings support the idea that changes in visuo-spatial attention, whether by specified practice, natural adaptation, or both, may yield substantial alterations to activity patterns of the primary visual cortex.

4.3. Lack of signal in non-retinotopically reorganized cortex

One somewhat surprising aspect of our current results is the lack of activity along the extent of calcarine sulcus in the control participants – especially in the anterior calcarine, which normally represents peripheral stimulation (see Fig. 3). There are several possible reasons for this. First, the PRL and nonPRL sections occur throughout the visual field, thus normal retinotopic activity may average out across participants. Most control participants showed some brain activity across anterior calcarine sulcus at the individual level. However, additional analyses showed that foveal stimulation failed to produce significant brain activity in the control participants. One would expect centrally presented contrast-reversing checkerboard sections to elicit visual activity in normally-sighted participants. A lack of such activity may suggest that the visual task used here was not powerful enough to produce an fMRI signal for normal visual responses. Although the 8 Hz contrast-reversing checkerboard pattern used in this experiment has a history of producing retinotopic activation in participants with normal vision (e.g., DeYoe et al., 1996; Engel et al., 1997; Sereno et al., 1995; Slotnick & Yantis, 2003), we stimulated 60 sections of the visual field of each participant. This left us with very few trials stimulating each section. Perhaps this was not enough to elicit significant retinotopic activity for the PRL and nonPRL sections analyzed here.

It is important to note that this lack of normal retinotopic activity in our control participants does not negate the effect found in the MD patients. Rather it reinforces our interpretation. Normal retinotopic activity in the calcarine sulcus averaged to zero across participants, and/or the number of trials presented was not powerful enough to elicit normal retinotopic activity. Yet, the one area of significant activity and relatively low noise (as shown by the size of the standard errors in Fig. 3) was in the posterior calcarine sulcus, for PRL stimulation in MD patients. This suggests that these neurons become active across patients no matter where the PRL is. That is, neurons in the lesion projection zone reorganize to represent the PRL, and thus PRLs from different visual field regions across patients combine to produce significant activity, rather than average away.

5. Conclusions

The current results demonstrate a relationship between PRL use in MD patients and functional reorganization in visual cortex. The directionality of this relationship remains unclear (Cheung & Legge, 2005). It may be that development of a PRL encourages adaptation of neural processing in primary visual cortex (Das, 1997). Alternatively, the potential for reorganization of neurons representing particular visual field regions may drive the development of a PRL in that region (Altpeter et al., 2000). Of course, these effects are not mutually exclusive. Identifying how functional reorganization and PRL development are related will require more research. Nonetheless, our current results offer strong evidence that a connection exists between the functional, cognitive adaptation and the cortical, neuronal reorganization that occurs for patients with MD.

Further studies may help better understand how and why cortical reorganization occurs. This knowledge may enable the development of more effective training paradigms and rehabilitation tools to improve the visual capabilities of individuals with MD and other visual impairments. For example, instituting rehabilitation programs for early-stage MD patients that teach the use of a PRL may help induce and direct cortical reorganization. By leveraging knowledge about how cortical reorganization may develop, which may be related to the temporal progression of the disease and the development of a PRL, one might be able to affect the extent or rate of cortical remapping. However, additional studies of the impact of cortical reorganization on visual function and cognition, in terms of practical activities of everyday living (e.g., reading, discriminating between objects), are also necessary.

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