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Visual cortex organization in a macaque monkey with macular degeneration

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Abstract

The visual field is retinotopically represented in early visual areas. It has been suggested that when adult primary visual cortex (V1) is deprived of normal retinal input it is capable of large-scale reorganization, with neurons inside the lesion projection zone (LPZ) being visually driven by inputs from intact retinal regions. Early functional magnetic resonance imaging (fMRI) studies in humans with macular degeneration (MD) report > 1 cm spread of activity inside the LPZ border, whereas recent results report no shift of the LPZ border. Here, we used fMRI population receptive field measurements to study, for the first time, the visual cortex organization of one macaque monkey with MD and to compare it with normal controls. Our results showed that the border of the V1 LPZ remained stable, suggesting that the deafferented area V1 zone of the MD animal has limited capacity for reorganization. Interestingly the pRF size of non-deafferented V1 voxels increased slightly (~20% on average), although this effect appears weaker than that in previous single-unit recording reports. Area V2 also showed limited reorganization. Remarkably, area V5/MT of the MD animal showed extensive activation compared to controls stimulated over the part of the visual field that was spared in the MD animal. Furthermore, population receptive field size distributions differed markedly in area V5/MT of the MD animal. Taken together, these results suggest that V5/MT has a higher potential for reorganization after MD than earlier visual cortex.

Keywords

Plasticity; Reorganization; fMRI; V1; MT

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Introduction

Early visual areas have a topographically precise, retinotopic, representation of the visual field (Van Essen & Maunsell, 1983; Tootell *et al.*, 1988; Brewer *et al.*, 2002; Gattass *et al.*, 2005; Wandell *et al.*, 2007). These maps remain stable over time in healthy adults but are thought to be plastic following injury of the visual pathways (Kaas *et al.*, 1990; Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Chino *et al.*, 1995; Morland *et al.*, 2001; Baker, 2005; Giannikopoulos, 2006; Baker *et al.*, 2008; Schumacher *et al.*, 2008; Dilks *et al.*, 2009; Levin *et al.*, 2010). Understanding the capacity of the visual system for reorganization following injury is an important step in the long-term effort to design treatments aimed at enhancing the ability of the visual system to recover after injury.

The term ‘reorganization’ is difficult to define precisely and has sometimes been used loosely in the literature. To avoid confusion here, we adopt similar conventions as Wandell & Smirnakis (2009) and use the term reorganization to refer to changes that occur over a long period of time and generally require the generation of new anatomical connections or, at least, a permanent change of strength in existing connections. This is in contrast to adaptive processes, which typically operate over a shorter time scale, tracking changes in input statistics. We note that the time scales over which reorganization versus adaptive processes operate overlap, and it is often difficult from functional magnetic resonance imaging (fMRI) to draw a sharp distinction between the two.

Several groups have studied the capacity of the visual cortex for reorganization following retinal lesions, producing controversial results. The majority of electrophysiology studies after homonymous retinal lesions in adult cats and macaques reported that area V1 exhibits a considerable degree of plasticity into adulthood (Kaas *et al.*, 1990; Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Giannikopoulos, 2006; Gilbert & Li, 2012). However, other studies using cytochrome oxidase (Horton & Hocking, 1998), electrophysiology (Murakami *et al.*, 1997) and fMRI (Smirnakis *et al.*, 2005) have suggested that post-lesion responses inside the V1 lesion projection zone (LPZ) are weak or absent.

Several groups have moved beyond experimentally induced retinal lesions to study visual cortex reorganization in a human retinal disease state called macular degeneration (MD). MD is a common cause of human visual impairment, and typically damages the central retina, gradually eliminating the normal retinal input to a large, central, region of the visual cortex. Several fMRI studies have suggested that human primary visual cortex, deprived of its normal retinal input by MD, undergoes large-scale reorganization spanning centimetres of cortical space (Baker, 2005; Baker *et al.*, 2008; Schumacher *et al.*, 2008; Dilks *et al.*, 2009). In contrast, the initial report (Sunnness *et al.*, 2004) found large-scale reorganization in V1 to be absent. The largest human fMRI study surveying MD patients to date (Baseler *et al.*, 2011) has also reported a lack of large-scale reorganization in V1. Wandell & Smirnakis (2009) recently reviewed some of these results in human and animal literature, pointing out that there are numerous inconsistencies still waiting to be resolved.

One difficulty is comparing results from the animal literature, which study cortical reorganization following experimentally induced retinal lesions, with results from the human literature studying subjects with MD. Acute retinal lesions are not necessarily equivalent to lesions induced by a chronic process such as MD. A study of visual cortex reorganization in animals suffering from MD can help bridge this gap. Here we use fMRI population receptive field measurements (Dumoulin & Wandell, 2008) to study cortical reorganization in a macaque monkey suffering from a chronic MD condition approximating human juvenile MD. We compare our results with both the human fMRI and the macaque fMRI and electrophysiology literature.

Materials and methods

Subjects

A male monkey with a binocular central retinal lesion of $\sim 10^\circ$ (left eye) and $\sim 11^\circ$ (right eye) radius due to juvenile MD, weighing 9 kg (Dominik Fischer *et al.*, 2012), and two healthy adult monkeys (C1 and C2), one male and one female, weighing 9 and 6 kg respectively, were used for these experiments. All sessions were performed with great care to ensure the well-being of the animals, were approved by the local authorities (Regierungspraesidium) and were in full compliance with the guidelines of the European Community (EUVD 86/609/EEC) for the care and use of laboratory animals.

The monkeys were anesthetized during the fMRI experiments. Details of the anesthesia protocol have been given previously (Logothetis *et al.*, 1999). Briefly, the animals were premedicated with glycopyrolate [0.01 mg/kg, intramuscular (IM)] and ketamine (15 mg/kg, IM), and then deep anesthesia was induced with fentanyl (3 μ g/kg), thiopental (5 mg/kg) and succinyl chloride (3 mg/kg). Anesthesia was maintained with remifentanyl (0.5–2 μ g/kg/min) under paralysis with mivacurium chloride (3–6 mg/kg/h) to ensure the suppression of eye movements. Heart rate and blood oxygen saturation were monitored continuously with a pulse-oxymeter. Body temperature was kept constant at 37–38° Celsius.

Stimuli

Visual stimuli were displayed at a resolution of 800×600 pixels with a 60-Hz frame rate, using a custom-made fibre-optic projection system with mean luminance of ~ 100 cd/m². Stimuli were centred on the approximate location of the fovea (centre of the lesion) by using a modified fundus camera (Zeiss RC250). Animal eyes were fitted with appropriate contact lenses to ensure the stimulus remained in focus. Monocular stimuli were presented in the left eye for the MD animal and the controls. The field of view was 30° horizontal $\times$ 23° vertical visual angle. The stimulus consisted of a bar aperture with a width of 2° and a length equal to the field of view moving by 1° per volume acquisition (6 s) passing over a rotating polar checkerboard sequentially in four different directions (top-to-bottom, left-to-right, bottom-to-top and right-to-left). The bars were presented continuously with no gap. The same moving bar stimuli were presented to the MD monkey and to the healthy controls. Outside the bar aperture an isoluminant gray background was presented. One important control condition involved presenting the same moving bar stimuli to healthy animals while occluding the central part of the visual field with a black [RGB=(0 0 0)] disk of 10° radius. We refer to this as the ‘artificial scotoma’ (AS) condition and it was designed *a priori* (before the fMRI experiments) to match the size of the lesion in the left eye of the MD animal, which was used for fMRI imaging. This control allowed us to probe whether changes observed in the fMRI signal pattern in area V1 could potentially represent a short-term effect induced because of the absence of central visual stimulation, as opposed to long-term cortical reorganization. As we reported earlier (Dominik Fischer *et al.*, 2012), the radius of MD lesion inside which the inner nuclear layer thickness is destroyed is 9.6° (2.23 mm). The size of the artificial scotoma was taken to extend 0.4° further, corresponding to the point at the MD lesion border where $>75\%$ of the thickness of the inner retina has been destroyed. Note that inner nuclear layer thickness returns to normal at 11.2° , so the full extent of the ‘soft’ border, i.e. the region of the border where the lesion is incomplete and may therefore transmit some information to the cortex, ranged from 9.6° to 11.2° (i.e. size of the lesion border is 1.6°).

Data acquisition

fMRI experiments were performed on a 4.7-T vertical scanner (Bruker Biospec, Bruker Biospin GmbH, Ettlingen, Germany). Multislice fMRI was performed by the use of eight

segmented gradient-recalled echo-planar imaging (EPI). Volumes of 17 slices of $1 \times 1 \times 2 \text{ mm}^3$ were collected, each with a field of view (FOV) of $128 \times 128 \text{ mm}$ on a 128×128 matrix and 2-mm slice thickness, flip angle (FA) 40° , echo time (TE) 20 ms and a repetition time (TR) of 750 ms per segment resulting in a volume acquisition time of 6 s. For anatomical measurements we used a FLASH sequence with the same FOV $128 \times 128 \text{ mm}^2$, matrix 256×256 , slice thickness 2 mm, FA 70° , TE 10 ms and TR 2000 ms. A high-resolution 3-D-MDEFT anatomical scan with an isotropic resolution of 0.5 mm was acquired for co-registration with the FLASH and EPI images. For more details on the fMRI methods see Logothetis *et al.* (1999); Keliris *et al.* (2007). Each fMRI scan included two repetitions of the stimuli (204 volumes per scan) and we acquired 5-7 scans per session.

Data analysis

The expected V1 LPZ of the retinal lesion was calculated from the ^{14}C -2-deoxy-d-glucose staining retinotopic organization maps (Tootell *et al.*, 1988), and from electrophysiological cortical magnification measurements [$M_1(r) = 13r^{-1.22}$; Van Essen *et al.*, 1984, or $M_2(r) = 15.7(r + 1.62)^{-1}$; LeVay *et al.*, 1985], where r is the eccentricity from the centre of the visual field, and M is the magnification factor in $\text{mm}/^\circ$. By integrating the magnification factor equation, the radius D from eccentricity l to eccentricity E can be calculated. Cortical distance in the fovea (from 0° to 1° eccentricity) was estimated using a different equation, more accurate for the central visual field: $D_f(r) = 7\ln(r + 0.33)$ (Dow *et al.*, 1985).

fMRI data were reconstructed and imported into a MATLAB-based toolbox (mrVista; <http://white.stanford.edu/software/>) (Amano *et al.*, 2009; Levin *et al.*, 2010). The gray-white matter boundary was manually segmented using itkGray from the high-resolution 3-D-MDEFT anatomical images, and 3-D cortical surface and flat mesh models were created and realigned with the functional data by using mrMesh/mrVista (Wandell *et al.*, 2000). Data were analyzed by using the voxel-based population receptive field (pRF) analysis method described by Dumoulin & Wandell (2008). We note that the pRF represents the sum response of a large population of neurons within a voxel and it is dependent on the size and the position scatter of the individual receptive fields (see also Haak *et al.*, 2012). Briefly, the activity of each voxel was fitted to a two-dimensional Gaussian function with three parameters (the visual field spatial coordinates x, y reflecting the centre of the pRF and the SD reflecting the pRF size). Explained variance (EV) maps (the fraction of the time series that can be explained by the model) were drawn in order to estimate the noise level and set the threshold. We set the threshold of the EV fraction to be 0.15 for the MD and first control monkey as in previous studies (Levin *et al.*, 2010; Baseler *et al.*, 2011). The noise level of the second control monkey was found to be slightly higher (Fig. 3) and we chose the threshold to be 0.2 (2 SD above the mean of the EV level of a selected non-visually responsive region of interest). After the pRF model fitting, for each voxel above the threshold we got the estimated position of the centre and the size of the pRF. Three types of retinotopic maps were then plotted: the eccentricity map, the polar angle map and the pRF size map. Visual areas were defined by horizontal and vertical meridians of the angle maps and were found to respect anatomical boundaries.

Results

Characterization of the retinal lesion

The MD monkey was identified in the colony of the Max Planck Institute for Biological Cybernetics, Tuebingen, Germany, after an fMRI experiment that showed absence of activation in the occipital gyrus. The animal was subsequently examined ophthalmologically and diagnosed to have a chronic MD condition that approximates human juvenile MD (Dominik Fischer *et al.*, 2012). Optical coherence tomography (OCT) and multifocal

electroretinogram (ERG) were used to characterize the retinal lesion of the MD monkey (Fig. 1). Figure 1a shows the retinal thickness map calculated from the OCT of the MD and one control monkey; ERG results are superimposed. The total retinal thickness is markedly reduced in the MD monkey compared with the control. The retina of the left eye of the MD animal is greatly thinned in a central region of 2.23 mm radius, representing a large central visual field scotoma with a soft border, where the inner retina is between completely destroyed and normal (see Figs 3 and 5d in Dominik Fischer *et al.*, 2012). We measured that this yields a near-symmetric visual field loss of 9.6° radius on average with a soft border of 1.6° (Dominik Fischer *et al.*, 2012; see also Drasdo & Fowler, 1974). Furthermore, multifocal ERG responses were markedly reduced within the scotoma of the MD animal in contrast to the control. Figure 1b shows the optical coherence tomography of the layers of the foveal retina of the MD and the control monkey. The photoreceptor layer of the retina of the MD animal is relatively preserved while the retinal nerve fibre, ganglion cell layer, inner plexiform and inner nuclear layers are destroyed. This was confirmed by retinal histology post-mortem. A detailed account of the retinal pathology of this animal is described elsewhere (Dominik Fischer *et al.*, 2012). Behavioural data from the MD animal confirmed the existence of the central scotoma, but unfortunately the animal had to be killed for health reasons unrelated to this experiment before the entire scotoma border could be mapped in detail behaviourally. We stress that this does not affect our analysis here, as the anatomical borders of the retinal lesion and how they correspond to the visual field have been measured precisely by ophthalmoscopy and confirmed by histology (Dominik Fischer *et al.*, 2012). Specifically, no spared islands were found inside the area of the retinal lesion, and the extent of the lesion border was confirmed histologically.

Visual modulation: extent of the retinal lesion projection zone

Visual cortical responses were measured during anesthetized fMRI for both the MD and two control animals (see Materials and Methods). Note that the normal central (~10° radius) retinal input is eliminated in the MD animal.

Statistical parametric maps (SPMs) of visual cortical activity were estimated from the blood oxygenation level dependent (BOLD) responses and were overlaid on the reconstructed gray–white matter surface meshes of each animal. Figure 2a and b presents two snapshots of such SPMs overlaid onto the right hemisphere of the MD animal. As shown in Fig. 2b the operculum of the MD animal is devoid of any statistically significant activation, in contrast to the control animal (Fig. 2c). We used the isotropic pRF model to estimate the centre and size of the receptive field voxel by voxel by fitting the model to the responses elicited at each voxel from the moving bar stimulus (Fig. 2a). Figure 2a illustrates the optimal pRF of a voxel in peripheral V1, outside the LPZ, showing that the corresponding, predicted, BOLD time series (blue line) matches very well with the measured averaged BOLD time series (black line). As demonstrated by the small subpanels over the time-course in Fig. 2a, whenever the stimulus passed over the estimated receptive field location (small top panels, Fig. 2a) a peak response appeared in the time series. On the other hand, the BOLD time series of voxels lying within the LPZ were not modulated by the stimulus at any location, remaining at baseline levels (Fig. 2b). For such voxels, the pRF model does not explain a significant proportion of the BOLD time series variance, indicating that the voxel does not get significantly modulated by the stimulus.

In an attempt to gain further insight about the extent of the retinal lesion projection zone in the visual cortex of the MD animal, we compared the EV SPMs of the MD and two control animals with a 10° radius AS (C1AS and C2AS) on the unfolded cortical surfaces (see Materials and Methods). It is important to note that for this comparison to be fair we selected monkeys whose brain size was similar to the MD animal. Specifically, for the first control the average distance from fovea to the calcarine fissure was the same as in the MD

animal, and for the second control 1mm larger. Maps of the MD and control animals are shown in Fig. 3.

Given that the shape of the retinal scotoma is approximately symmetric, the extent of the LPZ can be quantified by measuring the average distance from foveal V1 to the border of the LPZ, and then comparing this with the distance estimated from systematic electrophysiological experiments on the same species. We estimated the cortical distances from fovea to 10° eccentricity in macaque using previous reports to range from 33 mm (Tootell *et al.*, 1988) to 33.2 mm (Van Essen *et al.*, 1984; Dow *et al.*, 1985) and 33.1mm (Dow *et al.*, 1985; LeVay *et al.*, 1985). The cortical distances between the fovea and the border of the V1 LPZ for the MD monkey and the border of the artificial scotoma projection zone (ASPZ) for the two control monkeys were measured at various polar angles, and found to be within the range 32–34 mm (samples along the horizontal meridians are shown in Fig. 3); this is also consistent with the distances estimated from the literature. Importantly, across the border of the LPZ (or the ASPZ) the fraction of EV rises sharply (Fig. 3a, c and e). The result is that the LPZ or ASPZ border does not shift much due to the choice of threshold, and the size of the LPZ and ASPZ does not change much as a result of a reasonable threshold choice. To investigate this further we plotted how the fraction of EV in area V1 changes as a function of eccentricity. For both the MD and the control animals with AS, EV changes rapidly, as shown by the steep slopes of the curves (Fig. 3b, d and f). The boundaries of the LPZ and ASPZ borders are illustrated by the dashed and dotted lines for the MD monkey and two control monkeys with AS, respectively. Compared with the control monkeys, the V1 LPZ border of the MD monkey spreads ~ 0.5° further towards the scotoma (8.5°–9° eccentricity, corresponding to ~0.5mm on the cortical surface). This difference could be explained by taking into account that the extent of the absolute retinal lesion (inner nuclear layer thickness ~0) was 9.6° vs. the 10° AS, and suggests that even the part of the soft lesion border with 75% inner nuclear layer damage can activate area V1. Alternatively, this could represent a minimal change of the V1 LPZ border by ~0.5mm. Overall, our results suggest that the V1 LPZ border does not shift by more than 1mm. Voxel histograms of the fraction of EV were similar inside the V1 LPZ and the ASPZ, were commensurate with histograms obtained from non-visually responsive regions, and were well separated from histograms obtained outside the LPZ (ASPZ). Area V2 showed similar trends as V1 (Fig. 3b and d), suggesting that the border of the LPZ in area V2 also did not shift appreciably in this situation.

Retinotopic representation

Although our results argue against a shift of the V1 LPZ border, the size and retinotopic location of the pRFs in the non-deafferented peripheral areas could still change as a result of chronic loss of input. We first compared the locations of the pRFs by plotting the retinotopic angle and eccentricity maps on the visual cortex. Figure 4 shows the thresholded maps of the MD animal and two controls with and without AS and projected on the unfolded and flattened white–grey matter surface. The eccentricity map of the MD monkey showed a similar concentric structure in early visual areas as the maps of the controls. In addition, the positions of the horizontal and vertical meridian which can be seen in the angular maps matched the known anatomical boundaries between areas. Furthermore, there was no obvious distortion in the angular maps of the MD monkey outside the region of the LPZ and the retinotopic structure of non-deafferented early visual cortex remained unchanged.

In contrast to early visual areas V1 ($N=1584, 1499, 1395$ significantly activated voxels, counted on anatomical scans, for MD, C1AS and C2AS respectively) and V2 ($N= 1417, 1324, 1268$), area V5/MT of the MD monkey showed more extensive activation than the control monkeys with AS ($N=561, 152, 162$). The area of V5/MT that was activated in the MD monkey was similar to the extent of V5/MT activity seen in the control monkeys under

full visual field stimulation ($N=612, 722$). These suggest that marked reorganization occurred in area V5/MT of the MD monkey. Nonspecific changes in signal-to-noise ratios (SNR), defined here as the mean intensity of the voxel divided by the SD over time, cannot explain these observations because the SNRs among the scans for the MD and control monkeys were similar in area V1 (1.9, 1.9, 1.9; median logarithm of SNRs for MD, C1 and C2 respectively), V2 (1.9, 2.0, 1.8) and V5/MT (1.9, 1.9, 1.8). Other extrastriate areas (e.g. area V3/V3A) also appear to be upregulated in the MD animal (see Figs 3 and 4), but more data would be needed to make a definite statement here.

pRF size analysis

An important piece of information provided by the pRF method is the pRF size. The pRF size map for the MD and control monkeys are presented in Fig. 4 bottom panels overlaid on the flattened cortical mesh. pRF sizes in area V5/MT were smaller for the MD animal than the controls with a 10° AS. The change in pRF size together with the expansion of the activated area in V5/MT of the MD monkey provide converging evidence for substantial reorganization in this area.

Importantly, the pRF features of controls stimulated under the AS condition remained unchanged compared with normal (no artificial scotoma) visual stimulation conditions outside the ASPZ in areas V1, V2 and V5/MT (Fig. 5), in agreement with previous reports (Baseler *et al.*, 2011; Haak *et al.*, 2012).

In order to quantitatively measure the changes that occur in the receptive field maps between the MD and control monkeys with AS, we measured pRF centre and size distributions in different visual areas (Fig. 6a and Fig. 7a). As the shape of the retinal lesion of the MD monkey was nearly circular, the borders of the LPZ in visual cortical areas were nearly isoeccentric, and the pRF centre distributions could be characterized by plotting the histogram of voxels within different eccentricity bins.

Assuming reorganization happens, one would expect that neurons close to the border of the LPZ should respond to input from the intact retina located adjacent to the lesion. In this case, the number of voxels with receptive fields at eccentricities near and a little beyond the eccentricity of the LPZ border would increase. This was not what we found in area V1; instead, the distribution of the voxels as a function of eccentricity followed a similar pattern for both the MD and the control monkeys with AS (Fig. 6a, left panel). Looking at Fig 6a one might think it possible that there is a slight difference in the histogram profiles around eccentricities 10-12°, but this could be accounted for by the tapered nature of the MD lesion border ($\sim 1.6^\circ$) and cannot be regarded as definite.

In contrast, the pRF size distribution in area V1 of the MD monkey was clearly shifted towards larger pRF sizes (Fig. 6a, right panel). We plotted the pRF size as a function of eccentricity in V1 of the MD and control monkeys with AS. Our results illustrate that pRF size in area V1 of the MD animal increased linearly with eccentricity as in the controls, and that the pRF sizes in the MD animal were larger than the controls with AS for all eccentricities (Fig. 6b). This result cannot be explained by 'ectopic' voxels located inside the LPZ but suggests a rather systematic expansion in pRF sizes close to but outside the LPZ border. Although there is a trend for the effect to be smaller at higher eccentricities (Fig. 6b) this nevertheless suggests that pRF expansion extends to voxels which are considerably distant (~ 3 -5mm) from the LPZ border, towards normal non-deafferented cortex.

pRF sizes in area V2 remained similar in the MD animal and in the controls with the AS (Fig. 6c), and the LPZ border was not found to be shifted (Fig. 3b, d and f), suggesting limited reorganization in area V2 similarly to V1.

Remarkably, the number of visually modulated voxels in area V5/MT of the MD monkey was similar with that of the control animal under full-field stimulation but much higher than the control with an AS (Fig. 7a, see also Fig. 4). This suggests that visually driven activity occurs in most voxels of area V5/MT in the MD animal, but only in a fraction of the area V5/MT voxels in the controls with an AS. Specifically, there were more voxels activated as well as a larger fraction of voxels with small pRF sizes in the MD animal. The number of voxels activated in V5/MT of the two control animals under the AS condition was very small and therefore a direct comparison with the MD was very noisy. Alternatively, we plotted the pRF size as a function of eccentricity in area V5/MT of the MD and compared it with the control monkeys with full-field stimulation (note that as we show in Fig. 5 there was no significant difference between the pRF sizes in controls and controls with AS). Our results illustrate that the pRF sizes in area V5/MT of the MD animal increased linearly with eccentricity as in the controls (Fig. 7b). Importantly, the pRF sizes in the MD animal were smaller than the controls for all eccentricities.

Discussion

Several studies have reported substantial reorganization in the primary visual cortex of cat and monkey following retinal lesions (Kaas *et al.*, 1990; Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Giannikopoulos, 2006) while others have reported minimal, if any, changes (Murakami *et al.*, 1997; Horton & Hocking, 1998; Smirnakis *et al.*, 2005). Similarly, several human fMRI studies in MD patients have suggested that human primary visual cortex undergoes large-scale reorganization (Baker, 2005; Baker *et al.*, 2008; Schumacher *et al.*, 2008; Dilks *et al.*, 2009), but others claim the reverse (Sunnness *et al.*, 2004; Baseler *et al.*, 2011) or qualify the reported reorganization as being dependent on top-down feedback (Masuda *et al.*, 2008). Recently, Wandell & Smirnakis (2009) reviewed the capacity of the primary visual cortex for reorganization following retinal lesions, underscoring the existence of multiple points of controversy.

One reason for some of the differences noted in the literature may be that human studies involve subjects with MD while animal studies involve induced retinal lesions. Here we were given the opportunity to study a macaque with MD that was identified in the colony of the Max Planck Institute for Biological Cybernetics. We used fMRI to measure population receptive field characteristics in the monkey suffering from MD and made direct comparisons with results obtained from healthy macaques with similar area V1 size, which were presented with partially occluded central visual field stimuli that simulated the MD visual field deficit (this is referred to as the AS stimulation condition).

We found no significant shift of the LPZ border, suggesting no large-scale remapping occurs in area V1 of the MD animal. This is in contrast to previous reports (Kaas *et al.*, 1990; Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Chino *et al.*, 1995; Giannikopoulos, 2006) which reported the existence of ectopic receptive fields inside the LPZ and over a large range of distances up to 5 mm. The position of the LPZ border in the MD animal was within ~0.5mm of the position of the 10° AS projection zone border obtained from control animals (Fig. 3). Even the observed ~0.5mm shift can be explained without having to resort to cortical reorganization: As the 'hard' border of the MD lesion was 9.6°, the difference between LPZ and ASPZ borders can be fully explained if the tapering part of the retinal lesion border is capable of transmitting functional information to area V1. These results are in agreement with a previous study in macaque monkeys following retinal lesions induced by laser photocoagulation (Smirnakis *et al.*, 2005) and with recent fMRI results in human MD patients (Baseler *et al.*, 2011). In contrast to Baseler *et al.* (2011; note the differences in preparation and species), we found that there were very few voxels with significant visual modulation inside the V1 LPZ of the MD monkey or inside the ASPZ of the control

monkeys (Fig. 3). The sampling rates in V1 LPZ were 0.7%, 1.2% and 1.8% for the MD, C1AS and C2AS respectively. Visual inspection of the pRFs inside the LPZ/ASPZ that had the highest EV revealed that they were noisy and not representative. This difference might reflect the differences in the AS mask luminance. In our experiments, the AS mask luminance was set to black [RGB=(0 0 0)], in comparison with some previous studies using grey background luminance (Baseler *et al.*, 2011; Haak *et al.*, 2012). Other factors (such as anesthesia) might also play a role.

A possible explanation for the differences between studies reporting large-scale reorganization (Baker, 2005; Baker *et al.*, 2008; Schumacher *et al.*, 2008) and other studies including ours (Sunness *et al.*, 2004; Baseler *et al.*, 2011) that do not, might be the employment of a behavioural task; subjects in studies reporting large-scale reorganization typically performed a one-back memory task (Baker, 2005). A recent report demonstrated visual responsiveness inside the V1 LPZ of MD patients only when the subject performed a stimulus-related judgment as opposed to passive viewing (Masuda *et al.*, 2008). They proposed that responses inside the LPZ are driven by feedback from extrastriate visual cortex elicited by the demands of the stimulus-related judgment task (Masuda *et al.*, 2008). Feedback signals from extrastriate cortex (e.g. V5/MT) can influence V1 (Zeki & Shipp, 1988; Angelucci *et al.*, 2002; Harrison *et al.*, 2007). It would have been desirable to measure the cortical response and pRF features while the MD monkey performed a stimulus-related judgment task, compared to the experiments under anesthesia. Unfortunately, this turned out to be impossible because the animal had to be killed for reasons unrelated to these experiments.

The distribution of pRF centres as a function of eccentricity outside the LPZ (ASPZ) was roughly similar between the MD animal and controls with the AS (Fig. 6a, left panel). However, we found that pRF sizes in the non-deafferented V1 region, i.e. outside the LPZ border, were on average ~20% larger in the MD monkey. pRF size measurements reflect both the receptive field size of individual units inside a voxel and their scatter. The neuronal receptive field and scatter have been reported to co-vary (Hubel & Wiesel, 1974). A recent study by Haak *et al.* (2012) investigated how the pRFs change under AS conditions presented to human subjects and found that pRFs near the border of the AS tend to increase in size (see also Wandell & Smirnakis, 2009). They speculate that the removal of input for voxels inside and near the border of the AS is likely to preferably affect the neurons with small RFs while neurons with larger RFs can still be stimulated by locations outside the AS biasing thus the pRF measurements to larger values. The 20% increase in pRF size we measured is likely to reflect at least partially a similar mechanism. Alternatively, single-neuron RFs could indeed become larger but this effect is potentially overestimated in the pRF measurements. Although the enlargement of pRFs qualitatively agrees with prior electrophysiology studies reporting single- and multi-unit receptive field increases near the border of the lesion projection zone (Gilbert & Wiesel, 1992), it is quantitatively very different: Gilbert & Wiesel (1992) reported a several-fold receptive field size increase over a period of 2 months, whereas the increase we saw is much less pronounced. The ~20% increase in pRF size we report here is more in agreement with other reports (Chino *et al.*, 1995), and could potentially be explained by changes in the balance between excitation and inhibition (Hubel & Wiesel, 1959; Cavanaugh, 2002) induced by deafferentiation. For example, inhibitory inputs arising inside the LPZ may be weakened by deafferentiation (Hendry & Jones, 1986; Rosier *et al.*, 1995; Arckens *et al.*, 1998; Wade & Rowland, 2010), releasing from inhibition units lying outside the LPZ border. pRFs corresponding to voxels lying outside the LPZ would then increase in size. This hypothesis is supported by the observation that the increase in pRF size was greater close to the LPZ border than at higher eccentricities (Fig. 6b). pRF size might also change as a result of altered top-down feedback

to area V1 from higher areas. This explanation is less likely, however, as our experiments were performed under anesthesia.

Area V2 also showed limited reorganization indicated by the stable V2 LPZ border (Fig. 3), and similar pRF sizes outside the V2 LPZ in the MD animal and in controls with the AS (Fig. 6c).

The more striking finding in our study was the large extent of activation seen in area V5/MT of the MD monkey in comparison with control monkeys stimulated with the AS. Earlier reports suggested that functional responses and inter-hemispheric connectivity of human area MT appeared to be relatively unaffected by long periods of deprivation of structured visual input (Fine *et al.*, 2003; Levin *et al.*, 2010). To the best of our knowledge, V5/MT upregulation in subjects with MD has not been reported before, though it is suggested by figures presented in several studies (Baker, 2005; Baker *et al.*, 2008; see fig. 3 in these references). Analysis of the distribution of pRF centre locations in area V5/MT of the MD versus the control animals revealed that many more voxels in area V5/MT of the MD animal respond to inputs from intact, peripheral retina. Some of these voxels are probably from inside the LPZ given that the size of V5/MT activated in the MD animal (both in number of voxels and anatomically) was similar to the extent of V5/MT activity seen in the control animals under full visual field stimulation and much larger than the activity in controls with AS. Neurons in area V5/MT normally have large, overlapping receptive fields receiving inputs from multiple units with smaller receptive fields in area V1 (Hubel & Wiesel, 1974; Albright & Desimone, 1987). Following central V1 deafferentation many V5/MT cells lose only part of their input, preserving the connections that lie outside the area V1 LPZ. These connections are likely to be weak initially, explaining why areas V5/MT of control monkeys are poorly activated under the AS condition (Fig. 4). Over time, however, the surviving connections apparently get strengthened and become capable of driving the significant, though ectopic, extent of visual modulation we observed in area V5/MT of the MD animal (Fig. 7a). This hypothesis is consistent with the fact that area V5/MT pRF sizes in the MD monkey are on average smaller than in controls under the AS condition. One way this may come about is if, over time, deafferented regions of area V5/MT become capable of being visually modulated by stimuli presented outside the retinal lesion but these reorganized, ectopic, pRFs never return to their original size. The relatively slow, chronic progression of MD probably contributes to the large-scale reorganization that is observed.

In summary, our results in this macaque subject with MD suggest that area V1 shows at best limited reorganization: (i) the LPZ border did not shift, and (ii) only a modest, 20% on average, pRF size change was observed outside the LPZ border. Area V2 also shows limited reorganization. In contrast, extrastriate area V5/MT shows considerably more capacity for reorganization: visually modulated ectopic pRFs in the MD animal cover a cortical area much larger than expected from AS controls. Area V5/MT could therefore potentially serve as the source of relatively strong feedback inside the area V1 LPZ.

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Abbreviations

AS	artificial scotoma
ASPZ	artificial scotoma projection zone
BOLD	blood oxygenation level-dependent
ERG	electroretinogram
EV	explained variance
fMRI	functional magnetic resonance imaging
LPZ	lesion projection zone
MD	macular degeneration
OCT	optical coherence tomography
pRF	population receptive field

Fig. 1.

The pathophysiology of the retinal lesion of the MD monkey. (a) Interpolated OCT retinal thickness maps of MD and one control monkey. The multifocal ERG results are superimposed on the retinal thickness maps. The retina of the MD animal is greatly thinned in a central region of 2.2 mm radius and yields a visual field loss of 9.6° radius. (b) OCT of the MD (right) and the control monkey retina (left) from the foveal rim towards the foveal pit (indicated by the white arrows in a). GCL, ganglion cell layer; IRL, inner retinal layer; ORL, outer retinal layer; RPE, retinal pigment epithelium. Panels a and b were reproduced from parts of figs 3 and 7 in Dominik Fischer et al., 2012.

Fig. 2.

Comparing BOLD responses from the MD animal and one control monkey. (a) PRF size map obtained with the bar stimuli overlaid on the inflated gray-white matter surface of the posterior right hemisphere of the MD macaque. The estimated pRF and time series for one selected voxel in the non-deafferented V1 are illustrated. The predicted time series shown in blue matches very well with the actual average BOLD time series in black. Insets on top show the position of the bars that generated the BOLD signal peaks shown below. (b) Average BOLD time series of a voxel inside the deafferented part of the MD monkey V1. Note that there is no significant modulation by the visual stimulus at this position. This results in a large area devoid of visually driven activity in central V1 of the MD monkey that corresponds to the lesion projection zone of the retinal lesion (see Fig. 3). This can be contrasted with (c) the PRF size map on the operculum of a control monkey.

Fig. 3.

Fraction of EV in the visual cortex of the MD monkey versus two controls under the AS condition. (a) Unfolded flat map of the early visual cortex of the right hemisphere of the MD animal. The operculum of the monkey is outlined by the calcarine sulcus (CS), the lunate sulcus (LuS) and the inferior occipital sulcus (IoS). The cortical distance between fovea (yellow star) and the LPZ border in V1 is ~33 mm for both the MD monkey and for the control monkeys with a 10° radius AS (c and e), which agrees well with the retinotopically projected cortical distance derived from the extent of the retinal lesion (see text). (b) Percentage EV as a function of eccentricity in V1 (red lines) and V2 (green lines) for the MD monkey and (d and f) control monkeys under the AS condition. The boundaries of the LPZ border (MD monkey) are illustrated by the dashed lines and of the ASPZ border (control monkey under the AS condition) by the dotted lines.

Fig. 4.

Retinotopic maps derived via population receptive field analysis. Angular, eccentricity and pRF size maps of the MD monkey and two control monkeys with and without AS. The positions of several visual areas and major gyri and sulci are labeled: occipital gyrus (OG), lunate sulcus (LuS), superior temporal sulcus (STS), calcarine (CS), inferior occipital sulcus (IOS) and angular gyrus (AnG). There is no obvious distortion in the retinotopic maps of the MD monkey in the non-deafferented regions of the early visual areas. Note, however, that the situation is different for area V5/MT. (i) The spatial extent of visually driven activation of the V5/MT complex in the MD animal (left column) is much larger than that observed in the control with the AS (middle column) and approximates the extent of V5/MT activation seen in the control animal under full field stimulation (right column). (ii) V5/MT activity in the MD animal arises from voxels whose pRF centres have phase values that correspond to the region of the intact retina (blue/cyan color, left column eccentricity map). Most of these pRFs appear to be ectopic, as they correspond to regions of area V5/MT that would ordinarily be activated by pRFs centred at different eccentricities (compare with eccentricity map, right column).

Fig. 5.

Scatter plots of pRF size versus eccentricity in voxels of control monkeys with and without artificial scotoma. (a) Area V1, (b) area V2 and (c) area V5/MT. pRF size estimates outside the ASPZ for the AS condition are similar to the controls under full-field stimulation.

Fig. 6. Population receptive field analysis in area V1. (a) Distribution of the pRF centres as a function of eccentricity (left panel) and size (right panel) in the MD monkey and in control monkeys with AS. The distribution of pRF centres as a function of eccentricity away from the area V1 LPZ border are similar between the MD animal and the AS control, though a slight ($1\text{--}2^\circ$) shift towards slightly higher eccentricities cannot be excluded for pRFs lying right outside the LPZ border (see also Discussion). A more pronounced change is seen when examining pRF sizes. The distribution of pRF sizes is clearly shifted towards larger values in the MD animal (right panels). (b) pRF size in area V1 as a function of eccentricity for the MD animal and two control monkeys under the AS condition. The slopes (S) of the functions are labelled. PRF size in area V1 of the MD animal increased linearly with eccentricity as in the AS controls, but remained larger than the controls for all eccentricities examined ($\sim 9\text{--}14^\circ$). The slope of the curves is different so that the size difference gap decreases with increasing eccentricity, i.e. as one moves away from the border of the LPZ. (c) pRF size in area V2 as a function of eccentricity for the MD animal and two control monkeys under the AS condition.

Fig. 7. pRF analysis in area V5/MT. (a) Distribution of the pRF centres as a function of eccentricity (left panel) and size (right panel) in the MD monkey and in control monkeys with AS. Note that the number of visually modulated voxels in area V5/MT of the MD monkey is much higher than in the AS control (see also Fig. 4). There is also a larger fraction of voxels with small pRF sizes in the MD animal. (b) pRF size in area V1 as a function of eccentricity for the MD animal and two control monkeys. Note that as the number of voxels activated in V5/MT under the AS condition in the two control animals was very small we have used the controls under full-field stimulation for the comparison.