Plasticity Beyond V1: Reinforcement of Motion Perception upon Binocular Central Retinal Lesions in Adulthood

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Induction of a central retinal lesion in both eyes of adult mammals is a model for macular degeneration and leads to retinotopic map reorganization in the primary visual cortex (V1). Here we characterized the spatiotemporal dynamics of molecular activity levels in the central and peripheral representation of five higher-order visual areas, V2/18, V3/19, V4/21a, V5/PMLS, area 7, and V1/17, in adult cats with central 10° retinal lesions (both sexes), by means of real-time PCR for the neuronal activity reporter gene *zif268*. The lesions elicited a similar, permanent reduction in activity in the center of the lesion projection zone of area V1/17, V2/18, V3/19, and V4/21a, but not in the motion-driven V5/PMLS, which instead displayed an increase in molecular activity at 3 months postlesion, independent of visual field coordinates. Also area 7 only displayed decreased activity in its LPZ in the first weeks postlesion and increased activities in its periphery from 1 month onward. Therefore we examined the impact of central vision loss on motion perception using random dot kinematograms to test the capacity for form from motion detection based on direction and velocity cues. We revealed that the central retinal lesions either do not impair motion detection or even result in better performance, specifically when motion discrimination was based on velocity discrimination. In conclusion, we propose that central retinal damage leads to enhanced peripheral vision by sensitizing the visual system for motion processing relying on feedback from V5/PMLS and area 7.

Key words: extrastriate cortex; feedback; perceptual recovery; velocity perception; *zif268*

Significance Statement

Central retinal lesions, a model for macular degeneration, result in functional reorganization of the primary visual cortex. Examining the level of cortical reactivation with the molecular activity marker *zif268* revealed reorganization in visual areas outside V1. Retinotopic lesion projection zones typically display an initial depression in *zif268* expression, followed by partial recovery with postlesion time. Only the motion-sensitive area V5/PMLS shows no decrease, and even a significant activity increase at 3 months post-retinal lesion. Behavioral tests of motion perception found no impairment and even better sensitivity to higher random dot stimulus velocities. We demonstrate that the loss of central vision induces functional mobilization of motion-sensitive visual cortex, resulting in enhanced perception of moving stimuli.

Introduction

Extensive research has provided indisputable evidence that the mammalian brain remains plastic throughout life in response to

changes of sensory input (Eysel et al., 1980; Kossut et al., 1988; Kaas et al., 1990; Chino et al., 1992; Gilbert and Wiesel, 1992; Buonomano and Merzenich, 1998; Sammons and Keck, 2015). Induction of matching central retinal lesions in both eyes of highly binocular mammals is an extensively studied animal model for the effects of vision loss as in age-related macular degeneration (AMD) syndrome patients. AMD is one of the leading causes of blindness worldwide. It affects the central retina and damages on average 10% of the central visual field. In AMD patients and animal models, loss of central visual inputs leads to

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retinotopic map reorganization in the primary visual cortex (Gilbert and Li, 2012). Upon instant deactivation of the cortical lesion projection zone (LPZ), due to retinal lesion induction, visual activity recovers during the months following the lesion due to reactivation of neurons from the border of the LPZ inward, as shown electrophysiologically in the form of a topographic map reorganization of the sensory-deprived LPZ of area V1/17 (Kaas et al., 1990; Chino et al., 1992; Gilbert and Wiesel, 1992; Darian-Smith and Gilbert, 1995; Eysel et al., 1999; Giannikopoulos and Eysel, 2006; Abe et al., 2015). The recovery depends on many factors including age at lesion induction, the retinal location and size of the lesion, and becomes incomplete once the lesions exceed 5° of the central visual field (Dreher et al., 2001; Waleszczyk et al., 2003; Hu et al., 2009).

Most of the plasticity research focused on the primary visual cortex (V1) and recognized intra-areal horizontal fibers as the principal anatomical substrate for this type of cortical reorganization (Gilbert and Li, 2012; Sammons and Keck, 2015). Because top-down feedback connections from extrastriate visual areas sculpt V1 receptive visual fields (Angelucci and Bullier, 2003; Gilbert and Sigman, 2007) higher-order areas may have an impact on the plasticity process. We subjected adult cats to binocular central retinal lesions, and analyzed the temporal deactivation and reactivation occurring in visual areas 17, 18, 19, 21a, and posteromedial lateral suprasylvian area (PMLS), the cat homologues of primate cortical areas V1, V2, V3, V4, and V5, respectively (Payne, 1993; Lomber, 2001; but see Connolly et al., 2012). We applied real-time PCR to quantify the expression level of the molecular activity reporter gene *zif268* (Hu et al., 2009). Each visual area showed a significantly lower expression level of *zif268* for its central LPZ compared with peripheral visual field representation, but not V5/PMLS, which exhibited an increase in neuronal activity in central as well as peripheral visual field representations, as registered with *zif268*. The features of V5/PMLS neurons identify PMLS as the motion-sensitive homolog of primate cortical area V5 (MT; Payne, 1993; Villeneuve et al., 2006). To corroborate this result associated with motion perception, we investigated area 7, located at the crown of the suprasylvian gyrus, between area 19 and PMLS. Area 7 receives visually driven input from all areas investigated in this study, but not from V5/PMLS, and direct input from the pulvinar (Olson and Lawler, 1987). This area is motion sensitive (Pigarev and Rodionova, 1998) and strongly visually driven, as shown by metabolic mapping (Vanduffel et al., 1995). The *zif268* signal in area 7 returned to normal levels in the central visual field representation soon after lesioning, and an increase in neural activity was observed in its peripheral visual field representation, just like for area V5/PMLS.

We therefore elaborated the functional relevance of the area 7 and V5/PMLS-specific hyperactivity by behavioral testing of motion perception using random dot kinematograms. We observed that retinal lesions did not impair motion perception, and even enhanced motion detection and velocity discrimination, thereby sensitizing the visual system for motion analysis. Induction of central retinal lesions in adult subjects thus shifts the central-peripheral balance in visual processing, established in the course of development, and removes central dominance over peripheral visual processing.

Materials and Methods

Animals

Experiments were carried in accordance with the European Communities Council Directive of November 24th 1986 (86/609/EEC) and were approved by the Institutional Ethical Committee of KU Leuven (Bel-

gium) and by the First Ethical Commission in Warsaw (Poland). Adult cats used for *zif268* mRNA expression analysis ($n = 15$, 9 males and 6 females) were housed in the Animal Facilities of KU Leuven and exposed to a normal light environment (14 h light/10 h dark) with access to food and water *ad libitum*. Retinal lesioned subjects recovered for different survival times after lesioning: 14 d (14 d, $n = 3$), 1 month (1 m, $n = 3$), 3 months (3 m, $n = 5$) or 8 months (8 m, $n = 3$; Fig. 2, marked in shades of gray). The 14 d time point was chosen as the first experimental condition because previous investigations have shown a maximal molecular response at that time point (Arckens, 2006). A survival time <14 d was not included because of the effect of retinal edema in the first days after the lesions (Eysel et al., 1980; visible as a white rim surrounding the lesion, Fig. 1B, inset). The 8-month time point was chosen because connective changes have so far only been documented for this long survival time (Darian-Smith and Gilbert, 1995). Three extra animals served as controls and received no visual manipulation. Part of the molecular data collected from these animals was published earlier (Hu et al., 2009, 2011).

All cats participating in motion training ($n = 12$, 10 males and 2 females) were raised in the Animal Facilities of the Nencki Institute of Experimental Biology. Training started when the animals were 8 months old. Two cats participating in a pilot study were subjected to lesions after 1 year of motion training (Zapasnik and Burnat, 2013). Control cats (control, $n = 6$) completed motion training in 3 months' time. These same animals were then subjected to binocular central retinal lesions, and, after 14 d of recovery, their motion performance was verified [except for 1 cat; retinal lesion trained cats (RLTrained), $n = 5$]. Retinal lesioned naive cats (RLNaive, $n = 4$) first received retinal lesions and were then trained for 3 months, following the same schedule of motion training as the controls (Timeline of training, Fig. 3A).

Induction of retinal lesions

The homonymous central retinal lesions were induced by photocoagulation (LOG-2 Xenon light photocoagulator, Clinitex) under ketamine/xylazine anesthesia (0.5 ml Ketalar, 0.2 ml Rompun, i.m.). Nictitating membranes were retracted with phenylephrine hydrochloride (5%), and pupils were widened with atropine sulfate (1%). Circular lesions with sharp borders and a $\approx 10^\circ$ diameter were centered over the area centralis, as verified by fundus photography (Fig. 1A,B, insets, prior and postlesion, respectively). This type of lesioning destroys all retinal cell layers (Eysel et al., 1981), and spares optic nerve fibers and retinal ganglion cells encircling the lesion site (Fig. 1B). Starting from the first postlesion day the retinal lesioned cats were observed behaviorally. Behavioral consequences of edema, such as difficulties in depth perception vanished after 4 d postlesion, consistent with Giannikopoulos and Eysel (2006). Regular motion tests started at 14 d postlesion.

Tissue sampling

Before kill, all animals were maintained overnight in total darkness followed by a 45 min light exposure in a well-lit room to induce maximal *zif268* expression in cat visual cortex (Arckens et al., 2000; Hu et al., 2009). All cats were killed with an overdose of pentobarbital (Nembutal, 60 mg/kg, i.v.) under deep ketamine anesthesia (Ketalar, 10 mg/kg, i.m.). Brains were immediately dissected, instantly frozen by immersion in dry ice cooled isopentane (Merck Eurolab) and stored at -80°C . For RNA extraction, coronal sections of 200 μm were cut on a cryostat (Microm HM 500 OM, Microm) and samples of LPZ center (C) and of peripheral visual field representation (P) of the studied regions were dissected.

The anterior–posterior coordinates for tissue sample collection were posterior (P) 5.0, P7.5, P6.5, and anterior (A) 5.0 for area V1/17, V2/18, V3/19, V4/21a, V5/PMLS, and area 7 respectively (Fig. 1C–G). The cat visual cortex map of Rosenquist (1985), complemented with observations for PMLS by Arckens et al. (2000) and Sherk (2010), was used as a guide to guarantee correct retinotopy-driven tissue sampling from all five cat visual areas. To identify the position of the center of the LPZ of these five visual areas *in situ* hybridization for *zif268* was performed on a series of coronal sections of each cat (Fig. 1C–G).

Figure 1. Retinal lesion visualization. **A, B**, Low-power photomicrographs of retinal whole mounts of a control and a 3 month retinal lesion cat, with insets illustrating related fundus photos taken before and after induction of the lesion. White arrows point to the SMI-32-immunolabeled retinal ganglion cell axons, which encircle the area centralis, clear from such fibers, and demarcate raphe. Note the well preserved retinal ganglion cell axons encircling the lesioned, empty zone as visible on the whole-mount preparation (**B**), and the rim of edema encircling the black lesion on the fundus photo taken directly upon lesioning (**B**, inset), which will disappear in ensuing days. **C–F**, Illustration of the LPZ with *in situ* hybridization for *zif268* based on the very low expression level in the central representations of the visual field in areas V1/17, V2/18, V3/19, and V4/21a, at 3 months postlesion (Horsley–Clarke coordinate from posterior (P) 5.0, P7.5, P6.5 to anterior A5). **G**, V5/PMLS and area 7 at A5 Horsley–Clarke coordinate. The C and P boxes indicate the two regions of tissue sampling along the dorsoventral axis for a given frontal brain section/visual area: the retinotopic position of the central (C) and peripheral (P) visual field representations in each of the five visual areas. Scale bars: **A, B**, 1 mm, **C–G**, 2 mm.

Quantitative real-time PCR

All quantitative real-time PCR experiments were performed as described by Cnops et al. (2007) and Hu et al. (2009). The RNA extraction was performed with the Versagene RNA purification kit (Gentra/Biozym) according to the manufacturer's instructions. After biophotometric analysis (Eppendorf, VWR International), RNA samples of identical quantity were reverse transcribed with GeneAmp RNA products con-

taining oligo d(T) primers (Applied Biosystems) at 42°C for 60 min, 99°C for 5 min, and 4°C for 10 min. For the real-time PCR experiments we used specific primers (Eurogentec) and TaqMan probes (Applied Biosystems), which were designed with the Primer Express program (Applied Biosystems), based on the cat sequence of *gapdh* (Forward primer: 5'-tg-gaaagccatcaccatct3'; Reverse primer: 5'-caacatactcagcaccagcatca3'; TaqMan probe: 5'-ccaggagcgagatcccgcca3') or *zif268* (Forward primer: 5'-cttctcgtgctgtaccaa3'; Reverse primer: 5'-gggagaaaaggtgtgtcatgt3'; TaqMan probe: 5'-cagcgctcaacagggtcttcg3'; Hu et al., 2009). cDNAs were subjected to PCR using the ABI Prism 7000 SDS apparatus in a 25 μ l reaction of 1 $\times$ Absolute QPCR Mix (Westburg) with primers at final concentration of 300 nM and probes of 200 nM. Serial dilutions of control cDNA for generating standard curves were run in duplicate for each gene, whereas target samples were run in triplicate on the same well-plate under standard amplification settings (1 $\times$ 50°C for 2 min, 1 $\times$ 95°C for 10 min, 40 $\times$ 95°C for 15 s, and 60°C for 1 min). To compare samples between different runs, we included a reference control in every well-plate. Data were expressed relative to this reference control (Wong and Medrano, 2005). Analysis was performed using ABI Prism 7000 SDS software. The *zif268* quantities were normalized to the endogenous housekeeping gene *gapdh* to account for variability in initial mRNA concentrations and differences in reverse transcription efficiency (Van der Gucht et al., 2003). The relative amount of transcript was quantified by the comparative C_t (cycle threshold) method. To confirm reproducibility, we performed real-time PCR analysis on each cat at least two times.

Verification of the retinal lesions and lesion projection zones

Apart from the fundus photographs taken prior and after lesion induction, retinal whole mounts were prepared for inspection of the retinal ganglion cell and optical nerve integrity in the surround of the lesion (Fig. 1A, B), based on neurofilament protein immunocytochemistry (Burnat et al., 2012). Briefly, after an overnight incubation with the primary antibody (SMI-32; 1/1000), the whole mounts were rinsed and incubated with biotinylated goat anti-mouse IgGs (1/200; 30 min; Dako), followed by incubation in an avidin-biotin-horseradish solution according to the manufacturer's recommendations (Vectastain Elite ABC; Vector Laboratories). The reaction product was visualized as a gray-black precipitate using the glucose oxidase-diaminobenzidine-nickel method (Shu et al., 1988; Van der Gucht et al., 2001, 2007). All dilutions and rinsing steps were made in Tris-buffered saline (0.01 M Tris, 0.9% NaCl, pH 7.6) containing 0.1% Triton X-100. The whole mounts were placed on gelatin-coated slides, dehydrated, cleared with xylene, coverslipped, and viewed through a Leitz DM RBE microscope (Leica Leitz).

The extent of the center of the LPZ was verified in all animals participating in the study using *in situ* hybridization for *zif268*, based on the low *zif268* signal which distinguishes central from peripheral cortical visual field representations, as described previously (Fig. 1C–G; Arckens et al., 2000; Hu et al., 2009). Briefly, a probe complementary to the nucleotides encoding amino acids 2–16 of the rat *zif268* gene (5'-ccgttgctcagcagcatcatctctccagyttrggtagtgc3') was used (Arckens et al., 2000; Van den Bergh et al., 2003; Leysen et al., 2004). After postfixation with 4% paraformaldehyde in PBS (0.1 M, pH 7.4), slide-mounted sections of cat brain were dehydrated and delipidated. Sections were incubated overnight at 38°C with hybridization solution containing the 3'-end terminal transferase 33P-dATP-labeled probes specific for *zif268*. The next day, sections were thoroughly washed with 1 $\times$ standard saline citrate buffer at 43°C, dehydrated, and exposed to an autoradiographic Bio Max film (Kodak). After 3 weeks, the film was developed following standard procedures. For image production from the autoradiograms, a CanoScan LiDE 600F (Canon) was used. Digital files were adjusted for brightness and contrast in Adobe Photoshop. The images were scanned with a HP Precision scan Scanjet 5300C at a resolution of 1200 dpi.

Behavioral training and testing

For control and RLNaive cats the motion discrimination training consisted of four motion tasks with increasing perceptual difficulty, based on Zapasnik and Burnat (2013, Fig. 3A). Visual training started when the animals were 8 months of age. Cats received food as a reward only during training sessions, with *ad libitum* access to water in their home cages.

Body weight was monitored every day before and after training to ensure a healthy condition and kept at 90% of free-feeding body weight. The cats were trained in the two-choice apparatus with a food reward designed after Berkley (Burnat et al., 2005). The animal, enclosed in a box, viewed the stimuli through two translucent response keys 8.7 cm wide and 25 cm high. An occluder between the response keys prevented the animal from seeing the positive (S+) and negative (S−) stimuli together. The viewing distance was 21.5 cm and both stimuli were placed in the center of the response keys. Pressing the response key for S+ provided a semiliquid reward made of mixed canned and dry animal food. Pressing the S− response key was not punished, but prolonged the time interval preceding the next stimulus presentation from 0.5 to 1 s. No correction was allowed. A two-alternative, forced-choice procedure was used in all experiments. Daily sessions consisted of five 20 trial blocks. Percentage of correct responses was calculated for each block. The experiments were performed 5 d per week for 3 months. To speed up the training compared with the previously reported long durations (Burnat et al., 2002, 2005; Zapasnik and Burnat, 2013), we introduced a less-stringent criterion consisting of 70% of correct responses calculated from five best blocks, from 1 training day. Only the two cats of the pilot study were trained for a longer time, following the whole procedure as described before (Zapasnik and Burnat, 2013).

S+ and S− stimuli were displayed simultaneously, with each stimulus being visible behind one of the response keys. The left/right position of the S+ and S− stimuli was randomized. The stimuli were presented on a computer display (refresh rate 120 Hz) with a mean luminance of 38.77 cd/m² against a background of 0.03 cd/m²; measured with a Tektronix J17 photometer. In motion tasks the S+ stimulus was composed of a random dot kinematogram (RDK) consisting of dots moving coherently upward (all at the same speed and direction) which occupied a circular field of 12.3° in diameter. The S− stimulus consisted of a downward moving RDK. The size of dots was 0.19°. Four motion tasks were tested, and the difficulty of the tasks was introduced gradually, as described below in the order of testing.

Global motion detection. The S+ consisted of a RDK with upward moving dots (10 or 50°/s), S− was the identical, but stationary RDK (Fig. 3B).

Fading in direction detection. The S+ consisted of a whole screen upward moving dots (the same as in S+ from the preceding task), S− was identical but stationary. When a cat received 70% of correct responses in the course of 1 d, the stationary dots downward motion was faded in with 10% steps. In total there were 10 downward motion fading steps, as a result at the last step of training all S− dots moved coherently downward. This task was only performed by control and RLNaive cats.

Direction discrimination. The S+ consisted of a RDK with upward moving dots (10 or 50°/s). The S− RDK dots moved downward with the same velocity as S+ dots. In the first level of difficulty the stimuli were presented on the stationary dotted background (Fig. 3G, inset). At increasing levels of difficulty, horizontal motion was added to the stationary background dots. Two background dot velocities were tested, 10 and 50°/s (Fig. 3C).

Form-from-velocity detection (threshold measurement). The S+ remained the same. The S− was no longer a circular RDK, but consisted of background dots moving in the same direction as the dots within S+, but with slower velocity (range from 10 to 40°/s). The velocity of S− dots was adjusted automatically to the cat performance using the staircase method. The S+ was detected on the basis of the velocity difference (Fig. 3D).

Visual acuity testing with sinusoidal gratings. Vertical (S+) and horizontal (S−) gratings with a 50% luminance contrast between dark and light bars were displayed on an equiluminant background. The spatial frequency of both stimuli was gradually increased from the initial 0.13 c/deg level, using the adapting staircase procedure. This procedure was performed only for the two cats participating in the pilot study, and consisted of 1 full training day (120 trials) at the end of the motion training period described in detail by Zapasnik and Burnat (2013), and 14 d, 2 months, and 3 months after retinal lesion induction.

Evaluation of retinal lesion impact upon learned motion tasks. In RL-Trained cats, to avoid impact of learning, the same motion tasks (except

the Fading in Direction Detection task) learned before lesion induction where tested, but only for 2 d a week. Testing days consisted of three tasks, presented in order of perceptual difficulty. Each of the tasks was tested in two blocks consisting of 20 trials. When a cat achieved 90–100% of correct responses in 1 d of testing, the task was not tested anymore, otherwise tasks were repeatedly tested in random order in a course of a 3-month postlesion recovery period.

Statistics

Quantitative real-time PCR analysis. As not all comparisons displayed a normal distribution of data points (Shapiro–Wilk test) within a group and with equal variance between groups and given the number of animals per group, nonparametric statistical tests were performed. The Kruskal–Wallis one-way ANOVA on ranks test was used to analyze data of more than two conditions followed by a Tukey *post hoc* test for all pairwise multiple comparisons. Statistical analyses were performed using Sigma Stat 3.1 (SYSTAT Software).

Behavior. For calculations of standard animal performance, to reduce the daily variability of motivation, the one block with the worst mean percentage of correct responses was excluded and the differences in performance between the groups were calculated using means from the five best blocks. The statistical comparisons were made using the two-level repeated-measures nested one-way ANOVA with *post hoc* Tukey's multiple-comparison test, $p = 0.05$. Days to criterion in the initial Global Motion task, data only from controls and RLNaive were compared and an unpaired *t* test with Welch correction was applied (Fig. 3F). In the Results, we describe only data with significant differences of $p = 0.05$ calculating *F* statistics. Statistical analyses were performed using GraphPad Prism 5 software.

For all tests performed on real-time PCR and behavior data, the probability level (α -level was set to 0.05) of $p = 0.05$ was accepted as statistically significant. All data are presented as mean $\pm$ SE (SD; Figs. 2, 3).

Results

In a first set of experiments, we examined the effect of binocular central retinal lesions on the expression of the molecular activity reporter gene *zif268*. By means of real-time PCR we probed for time- and area-specific changes in the cortical representations of the central and peripheral visual field.

Analysis of *zif268* expression in cat primary visual cortex

In control subjects the central region of area V1/17 displayed significantly lower *zif268* expression than in the peripheral region (Fig. 2A, white bars), confirming previous observations for molecular activity levels in cat primary visual cortex (Hu et al., 2009; Laskowska-Macios et al., 2015b). In cats with retinal lesions (Fig. 2A, gray-black bars), this central-peripheral difference was much more pronounced. The center of the LPZ was clearly characterized by a permanently lower *zif268* expression compared with the peripheral visual field representation ($p < 0.01$, except for 14 d survival time point where $p < 0.05$) or to normal tissue, independent of postlesion survival time ($p < 0.01$). Peripheral area 17 also displayed lower *zif268* levels 14 d and 1 month postlesion (Fig. 2A; $p < 0.01$), followed by a recovery to normal levels from 3 months postlesion onward.

Analysis of *zif268* expression in areas V2/18, V3/19, V4/21a

Parallel analyses of *zif268* expression in the central and peripheral regions of areas V2/18, V3/19, and V4/21a revealed a similar response to the binocular lesions (Fig. 2B–D). Just like in area V1/17, the center of the LPZ of areas V2/18, V3/19, and V4/21a displayed a permanently lower *zif268* expression compared with the periphery ($p < 0.01$) and to normal control tissue ($p < 0.01$) for all, but area V3/19 at 3 months survival ($p < 0.05$).

The peripheral regions of these areas showed a more varied response. Whereas area V2/18 mimicked area 17 by showing de-

Figure 2. Area-specific *zif268* expression profiles in control and retinal lesion cats. Comparison of *zif268* expression levels between central (C) and peripheral (P) visual field representations in each of the six visual areas: (A) area V1/17, (B) area V2/18, (C) area V3/19, (D) area V4/21a, (E) area V5/PMLS (posterior medial lateral suprasylvian area), and (F) area 7. The expression of *zif268* was analyzed in control (white bars) and retinal lesioned (RL; shades of gray and black) cats with a survival time of 14 d, 1 month (1 m), 3 months (3 m), and 8 months (8 m). Note that four examined visual areas (A–D) respond similarly to induction of retinal lesions, but not area V5/PMLS (E) and area 7 (F). V5/PMLS did not exhibit the typical decrease in *zif268* level in either central or peripheral regions at any of the postlesion survival times. Instead, at 3 months area V5/PMLS shows a distinct upregulation of the *zif268* level. Differences in *zif268* expression levels are shown: (1) between control versus the corresponding region of each survival RL time point by symbols above the bars and (2) as a central versus peripheral ratio within each condition by lines plus symbols above pairs of bars (indicated by * $p < 0.01$ and # $p < 0.05$, Tukey *post hoc* test). Results are mean $\pm$ SD. **G, H.** The *zif268* expression in the central (G) and peripheral (H) visual field representation of the same six visual areas in retinal lesion cats as a ratio to the control *zif268* values (value 1 on the vertical axis). Note how for both subregions of PMLS (open square) for none of the postlesion survival times (shown on the horizontal axis) a decrease in *zif268* is detected, but in contrast a marked upregulation of the *zif268* signal at 3 months postlesion only. Area 7 (open circle) also shows quick normalization in the central region and upregulation in the peripheral region.

creased *zif268* levels up to 1 month postlesion (for survival time points: 14 d, $p < 0.01$; 1 month, $p < 0.05$), area 19 did not show any peripheral effects, whereas in area 21a only after 14 d a decrease in *zif268* levels could be discerned compared with normal controls ($p < 0.05$).

Analysis of *zif268* expression in area V5/PMLS

The *zif268* profile of area V5/PMLS as a function of postlesion survival time turned out completely different from all other in-

vestigated visual areas. The *zif268* expression was not significantly altered in the LPZ of area V5/PMLS up to 1 month postlesion (Fig. 2E). At 3 months postlesion a prominent increase in *zif268* signal occurred, which was discernable in the central as well as in the peripheral region of area V5/PMLS ($p < 0.01$). Thus, this elevation of *zif268* mRNA level was present over the entire extent of area V5/PMLS and this response was specifically observed 3 months postlesion, because at 8 months postlesion cats again displayed normal *zif268* levels in both subregions of V5/PMLS (Fig. 2E). This upregulation at 3 months correlates with the time-point of the restoration of normal activity values in the peripheral regions of area 17 and 18 (Fig. 2A, B).

Analysis of *zif268* expression in area 7

In the central region of area 7, only at 14 d postlesion, a downregulation of *zif268* signal was detected ($p < 0.01$). From 1 month postlesion on the *zif268* expression level normalized (Fig. 2F). In contrast, in the peripheral visual field representation, we did not detect any sign of a downregulation, at any postlesion survival time, but instead, similar to area V5/PMLS, from 1 month postlesion on an increase in *zif268* expression was detected (1 month, $p < 0.05$; 3 and 8 months, $p < 0.01$; Fig. 2F).

Comparison of the subregion-specific lesion impact between visual areas

Figure 2, G and H, summarizes the impact of the bilateral central retinal lesions on *zif268* activity in the central and peripheral visual field representations for each examined cortical area as a ratio to the normal *zif268* values. The ratios < 1 in Figure 2G visualize the permanently low *zif268* expression in the center of the LPZ of areas V1/17, V2/18, V3/19, and area V4/21a. For each of the peripheral regions of the same four areas a clearly less pronounced decrease in expression was observed, and only at early postlesion survival times (Fig. 2H). In contrast, the ratios of 2.5 typify the 3 month time point for area V5/PMLS, highlighting the prominent upregulation of the *zif268* expression throughout this area. At earlier time points as well as 8 months postlesion, the *zif268* ratios for both the central and peripheral region of area V5/PMLS were close to one. Also the peripheral visual field representation of area 7, from 1 month postlesion onward, showed a stable upregulation of *zif268* expression, even at 8 months (Fig. 2H), whereas its central region exhibited a *zif268* ratio close to 1, except for the earliest 14 d time point.

In summary, the RL/N ratio evaluation confirms that most visual areas permanently loose normal *zif268* expression similarly

in the very center of the LPZ, except for area V5/PMLS and area 7. Area V5/PMLS clearly exhibits retinotopy-independent hyperactivity specifically at a survival time of 3 months. Because area V5/PMLS is the visual motion V5 homolog in cat, and area 7 has a dominant population of motion-sensitive neurons (Pigarev and Rodionova, 1998), this outcome of the molecular investigations prompted us to look for effects of central retinal lesions, and thus lack of central vision, on motion perception. A pilot study was conducted on two pretrained cats, and instigated further investigations of the impact of retinal lesions on the learning and performance of naive cats for a panel of different motion tasks.

Impact of retinal lesions on pre-learned motion tasks: a pilot study

Third postlesion week

As the only available reports measuring visual performance after retinal lesion concern consequences of either very small binocular lesions (circa 5°; Pasternak et al., 1983) or monocular lesion of increasing diameter (Vandenbussche et al., 1990), we did not know what kind of behavioral deficits to expect. We chose, as a first task, discrimination between a bright and a dark screen with maximal contrast difference. Both cats operated very well in the Berkley box and achieved 85% and 70% of correct responses in this task. Next, a global motion detection task was tested (Fig. 3B; 50°/s). Again, both cats easily mastered this task with 90% and 70% of correct responses.

Up to 6 weeks postlesion

At 4 weeks of recovery, both cats detected global motion with 100% of correct responses. At 5 weeks, for the first time, the Direction Detection task (50°/s, stimuli were presented on the uniform dark background; Fig. 3E) was tested and they performed significantly lower than before lesioning. One day later performance markedly improved, with the highest performance level, even above prelesion performance, reached at 6 weeks postlesion (Fig. 3E).

Later testing and conclusions

From the 7th to 12th week postlesion we tested the response to a battery of stimuli based on decreasing the diameter of the S+ and S− RDKs (from 18 to 4°), the positioning of the RDK (center or randomized) and finally also different dot velocities (10–200°/s). From all of these variations of the Direction Detection task, only the decrease in velocity to 10°/s did impair the performance of the trained lesion cats. Based on these observations we designed the scheme for testing and comparing motion perception in naive cats with and without retinal lesions, as outlined in Materials and Methods.

Finally, visual acuity was measured using stationary sinusoidal gratings. A stable clear drop in performance, independent from time of testing after retinal lesion induction, was determined (from 0.39 and 0.22 c/deg to 0.10 and 0.10, respectively) as previously demonstrated for cats with similar retinal lesions, and in line with the lack of central vision (Vandenbussche et al., 1990).

Motion perception after binocular lesions

Naive lesioned cats versus controls

Before lesion induction the cats were familiarized with the training procedure. After lesion induction, from the beginning of the motion training, it became apparent that the RLNaive cats were very good learners and did not show obvious impairments. In general, RLNaive cats outperformed controls or they performed at a similar level in the motion tasks. In the first Global Motion Detection task (50°/s) RLNaive cats learned to detect motion

responses significantly faster than control animals (Fig. 3F; comparison of days to criterion, $p = 0.03$, $df = 6$).

In the following tasks, Global Motion detection (10°/s), Direction Detection (50 and 10°/s) and Direction Discrimination, RLNaive cats and controls performed equally well. Both groups of cats performed worse for tasks with slower velocity of 10°/s compared with the same tasks with velocity of 50°/s. Interestingly, when the stationary background was added to the Direction Discrimination task with slow velocity of 10°/s, RLNaive cats outperformed controls (Fig. 3G; comparison of the mean correct responses from the first day of training, $p = 0.012$, $F = 7.06$). The Form-from-Velocity Detection task based on figure from background velocity detection again revealed superiority of the RLNaive cats over controls, as they were able to detect figure (RDK) from background motion on the basis of significantly smaller velocity differences than controls (Fig. 3H; comparison of 5 last velocity thresholds for each cat, $p = 0.0001$, $F = 21.86$). When checking for correlations between performance in the different tasks in RLNaive and control cats, we did not find any, except for a strong correlation between achieved enhanced velocity thresholds and a high level of correct responses for the direction discrimination task in RLNaive cats ($r = 0.99$).

Positive effects of retinal lesions on performance in pretrained cats

In general, induction of retinal lesions did not affect prelesion motion performance levels. Yet, we did encounter two tasks with significant improvement in performance for RLTrained cats in relation to their prelesion performance. For the Direction Discrimination task S+ and S− presented on the moving background with high velocity 50°/s ($p = 0.03$) and for the Form-from-Velocity Detection task (Fig. 3H; comparison of the 5 last velocity thresholds achieved prior vs after lesion induction, $p = 0.002$, $F = 10.91$) the trained cats consistently showed a better performance upon lesion induction when compared with their prelesion performance. Thus, comparable to naive cats, performance of trained cats improved after induction of central retinal lesions for the direction discrimination and Form-from-Velocity Detection tasks.

Discussion

We found that the response of areas V5/PMLS and 7 to sudden loss of central vision in adult life is deviating from other visual areas. We demonstrated by means of real-time PCR for the activity reporter gene *zif268* that central retinal lesions have a strong depressive effect on the neuronal activity level in the cortical representation of central vision in primary and most of the higher-order visual areas, followed by gradual reactivation. Only motion areas V5/PMLS and 7 stood out by not showing a decrease in *zif268* mRNA levels but an upregulation. Behavioral testing demonstrated that motion perception is preserved and even enhanced in our AMD model. We showed here for the first time, that retinal lesioned animals were more inclined to learn motion tasks, and irrespectively of pre-lesioned visual experience, they were more sensitive to higher velocities, confirming enhancement of visual processing in regions selectively tuned to high velocities (V5/PMLS; Villeneuve et al., 2006) and related to visual peripheries (Yu et al., 2010).

Intra-areal horizontal connections likely mediate the cortical reorganization

Several studies (Kaas et al., 1990; Arckens et al., 2000; Giannikopoulos and Eysel, 2006) showed before that primary areas V1/17

Figure 3. The reinforcement of motion processing upon retinal lesion induction. **A**, Timeline of training for: pilot study, Control/RLTrained cats, and RLNaive cats. RL, retinal lesion induction, followed by 14 d of recovery period without training. **B–D**, Illustration of the different motion tasks: (**B**) Global Motion Detection task; (**C**) direction discrimination at its most difficult stage, with moving background; easier stages are shown in **E** with empty and in (**G**) stationary background. **D**, Form-from-Velocity Detection task. Arrows denote direction of motion, and dots denote stationary stimuli, loops encircling S+ and S– are drawn for the presentation. Detailed stimuli descriptions are given in the Materials and Methods section. **E**, Pilot study: correct responses (%) from two cats in the Direction Discrimination task. Levels before induction of retinal lesion and in 5 and 6 weeks postlesion (2 measurements, see Materials and Methods). Note the clear recovery of prelesion correct response levels between the 5th and 6th week postlesion. **F–H**, Better performance on motion tasks in retinal lesioned than in control cats; only tasks with significant differences are shown: (**F**) days to criterion during first trained Global Motion Detection task (high velocity, 50°/s). RLNaive cats learned the task faster than controls, $*p = 0.03$. (Figure legend continues.)

and V2/18 undergo topographic map reorganization after the induction of retinal lesions of 10°, with the LPZ not reorganizing completely due to the considerable size of the lesions. In agreement with these findings, we showed here that not only areas V1/17 and V2/18, but also V3/19 and V4/21a share a similar time-dependent *zif268* expression change, with their centers of LPZ also permanently decreased in activity. The comparable timing of the spatiotemporal reactivation of these visual areas indicates that they reorganize simultaneously.

The intra-areal horizontal connections have been proposed before as most probable anatomical candidates steering the topographical reorganization in V1/17 after binocular retinal lesions (Gilbert et al., 1990; Darian-Smith and Gilbert, 1995; Trachtenberg and Stryker, 2001) as cell recordings have shown that the neurons in the reactivated LPZ of V1/17 maintained their original selectivity concerning orientation, direction, and spatial frequency upon reactivation (Chino et al., 1995). Young et al. (2002) reported supporting data for V1/17 and V2/18 after monocular retinal lesion. They concluded that topographic map remodeling for these two visual areas is mediated in an independent manner by the horizontal fibers, because the neurons of both areas retained their initial unique selectivity features. These observations are in favor of the horizontal connections as anatomical substrate of V1/17 and V2/18 reorganization because these fibers connect neuronal cells with similar tuning preferences organized in cortical columns.

The role of input from higher visual areas

Although classical studies have provided evidence that the patches formed by horizontal connections exhibit modular specificity by linking columns of neurons with similar response characteristics, such as preferred orientation (Gilbert and Wiesel, 1989; Callaway and Katz, 1990), there is emerging evidence showing that axon clusters in V1 connect to a variety of different orientation domains, not exclusively similarly tuned (Kisvárdy et al., 1997; Angelucci et al., 2002; Martin et al., 2014). To become active, such differently tuned-organized horizontal connections need to be strengthened, most likely by feedback inputs from higher-order visual areas as proposed by fMRI (Williams et al., 2008) and electrophysiological studies (Galuske et al., 2002).

Motion perception facilitation by central retinal lesions: feedback inputs

The motion-sensitive area V5/PMLS did not display a LPZ, most likely due to the size of RFs, which in cat can far exceed 20° (Djavanian and Harutiunian-Kozak, 1983; Zumbroich et al., 1986). Moreover, our *zif268* data demonstrated a hyperactivity period for this area. Analogously, an fMRI case report of one macaque monkey who developed an AMD condition showed, similar to our findings, specific activation of area V5/MT compared with control subjects (Shao et al., 2013).

We compared V5/PMLS hyperactivity with *zif268* activation to another higher-order visual area, V4/21a, engaged in form processing (Dreher et al., 1993, 1996; Lomber, 2001). The real-

time PCR analysis showed no signs of such hyperactivity. On the contrary, the postlesion effects on the *zif268* expression in V4/21a mirrored those of areas V1/17, V2/18, and V3/19. These results suggest that motion processing is amplified over form processing after central retinal lesions. Our results indeed revealed facilitation of motion perception in naive animals in the first weeks after lesion induction. The timing of the increase of *zif268* expression in central as well as peripheral area V5/PMLS correlates well with the time-point of restoration of normal values of molecular activity in the peripheral region of areas V1/17 and V2/18, suggesting that V5/PMLS might modulate the reorganization of the peripheral part of these areas via feedback inputs. Additionally, the high SDs in the peripheral region of V5/PMLS at 3 months postlesion may be caused by plasticity of peripheral area 17 and 18, as visible by time-dependent *zif268* expression, enhancing reciprocal connections with the peripheral region of V5/PMLS and proceeding with somewhat different speed in each cat.

We are in favor of the feedback hypothesis because neuronal activity in cat V5/PMLS does depend not only upon input from the primary visual cortex, as it receives direct input via the pulvinar complex (Ouellette and Casanova, 2006; Piché et al., 2013) and lesions of primary visual cortex leave response properties of V5/PMLS neurons relatively unchanged (Spear and Baumann, 1979; Guido et al., 1990). Additionally, developmental studies put monkey V5 in a position parallel to V1, as both areas mature in a similar time frame (Bourne and Rosa, 2006) and develop independently (Bottari et al., 2015). Additional evidence for V5 acting independently from V1, comes from blind human subjects where V5 is activated by the motion component in auditory stimuli (Saenz et al., 2008).

Activity restoration of peripheral visual field representation

In contrast to the permanently deprived LPZ center, the peripheral visual field representations of areas V1–V4 exhibited a time-dependent restoration of the prelesion condition. This is most probably due to the fact that the spared peripheral retina is dominated by the motion-sensitive Y-pathway, with V2/18 and V5/PMLS being mostly driven by Y-type inputs (Wang et al., 1997; Vajda et al., 2004). After induction of central retinal lesions the topographic reorganization leads to over-representation of the intact nondeprived peripheral retina, for which the Y-pathway might be the driving force. These findings correspond to previous data at retina level in the context of pattern vision deprivation-induced adaptations to Y-type retinal ganglion cells (Burnat et al., 2012). Based on our cortical development data, it appears that peripheral representations are particularly prompt to plastic rearrangements (Laskowska-Macios et al., 2015a,b; for review, see Burnat, 2015). In line, in deaf subjects the peripheral visual cortex shows stronger sensitivity to visual stimulation, than in normal hearing people (Bavelier et al., 2000; Merabet and Pascual-Leone, 2010). Codina et al. (2017) prove that not only congenital deafness triggers a plastic response within the peripheral visual field, but also extensive training of sign language in normal hearing sign language interpreters does.

Cortical regions that previously received inputs from the fovea become activated by peripheral retinal stimulation from the border of the LPZ inward. fMRI examinations of adult and juvenile macular degeneration (MD) patients also show such plastic change in excitability of the LPZ, which is normally responsive only to foveal stimulation, but in patients is activated by visual peripheries (Baker et al., 2005; Masuda et al., 2008).

MD patients with central retinal lesions often develop an eccentric viewing strategy as substitute for the damaged fovea,

←

(Figure legend continued.) **G**, Correct responses (%) in the Direction Discrimination task with slow velocity (10°/s): RLNaive cats outperformed controls, $*p = 0.012$. **H**, Velocity threshold in the Form-from-Velocity Detection task (dots within S+ circle move with 40°/s velocity, the background velocity adapts to the performance). Control cats reached a significantly lower background velocity threshold, $***p < 0.0001$. Performance of naive before retinal lesion (RLNaive, gray bars), control naive (white bars), and cats trained before retinal lesion induction (RLTrained, hatched bar). Results are mean + SD.

adapting a so-called preferred retinal locus (PRL) where they spontaneously choose to fixate (Cheung and Legge, 2005; Schumacher et al., 2008). Important to our understanding of the plastic mechanisms underlying the recovery after central retinal lesions, most of the MD patients tend to develop a PRL within the lower visual field (Guez et al., 1993), which is involved in motion perception, in contrast to the upper visual field involved in form perception (Zito et al., 2016). Furthermore, the functional importance of processing within the lower visual field is strengthened by attention (He et al., 1996), driven by extrastriate visual cortical areas (Martínez et al., 1999) and it can be even modulated by direct cortical electrical microstimulation of V5/MT in monkeys (Fetsch et al., 2014). Together with the findings showing how sustained attention helps MD patients with solving visual tasks (Altpeter et al., 2000), we suggest that feedback connections are a potential source of reestablishing the visual activity within the border of the LPZ of the different visual areas. Most likely attention-driven feedback can strengthen the bottom-up inputs of peripheral stimuli, as also postulated by fMRI-based data in normally sighted and MD patients (Baker et al., 2005; Masuda et al., 2008; Williams et al., 2008). As shown recently by TMS, application of a protocol that strengthens feedback connections from V5 to V1 leads to motion perception enhancement (Romei et al., 2016). This interpretation also fits with our observations for area 7. Area 7 was recently described to send strong feedback to areas V1/17 and V2/18 (Yang et al., 2016), and to display visual responses enhanced by attention (Pigarev and Rodionova, 1998). V1/17 and V2/18 are the two areas in which the peripheral representations fully recovered by 3 month postlesion, possibly based on the sustained attention-strengthened feedback inputs from area 7.

In conclusion, we have demonstrated that the cortical activity of all primary and higher-order visual areas under investigation is affected by central retinal lesions. Whereas the center of the LPZ of visual areas V1–V4 remained permanently deprived, the peripheral visual field representations exhibited a time-dependent restoration of the prelesion condition. Only area V5/PMLS did not show a LPZ and was characterized by a transient hyperactivity period. We propose that, next to horizontal intracortical connections, also inter-areal feedback connections play a role in the plasticity-mediated cortical reorganization, as we show here for motion perception in the context of central retinal lesions.

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