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Impact of Deprivation and Preferential Usage on Functional Connectivity Between Early Visual Cortex and Category-Selective Visual Regions

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ABSTRACT

Human behavior can be remarkably shaped by experience, such as the removal of sensory input. Many studies of conditions such as stroke, limb amputation, and vision loss have examined how removal of input changes brain function. However, an important question yet to be answered is: when input is lost, does the brain change its connectivity to preferentially use some remaining inputs over others? In individuals with healthy vision, the central portion of the retina is preferentially used for everyday visual tasks, due to its ability to discriminate fine details. When central vision is lost in conditions like macular degeneration, peripheral vision must be relied upon for those everyday tasks, with some portions receiving "preferential" usage over others. Using resting-state fMRI collected during total darkness, we examined how deprivation and preferential usage influence the intrinsic functional connectivity of sensory cortex by studying individuals with selective vision loss due to late stages of macular degeneration. Specifically, we examined functional connectivity between category-selective visual areas and the cortical representation of three areas of the retina: the lesioned area, a preferentially used region of the intact retina, and a non-preferentially used region. We found that cortical regions representing spared portions of the peripheral retina, regardless of whether they are preferentially used, exhibit plasticity of intrinsic functional connectivity in macular degeneration. Cortical representations of spared peripheral retinal locations showed stronger connectivity to MT, a region involved in processing motion. These results suggest that the long-term loss of central vision can produce widespread effects throughout spared representations in early visual cortex, regardless of whether those representations are preferentially used. These findings support the idea that connections to visual cortex maintain the capacity for change well after critical periods of visual development.

1 | Introduction

The field of neuroscience has long sought to understand the brain's profound ability to adapt to changes in experience. This ability to adapt is particularly evident in conditions where neural input is lost or altered, such as in cases of stroke (Grefkes and Fink 2014), real and simulated limb amputation (Newbold et al. 2020; Ramachandran and Hirstein 1998; Sparling et al. 2024), as well as deafness and blindness (Merabet et al. 2008). Since the early sensory deprivation experiments of Hubel and Weisel, the visual system in particular has been one of the most well-studied examples of how the brain adapts to the loss of sensory input (Gilbert and Li 2012; Hubel and Wiesel 1962; Hubel and Wiesel 1963). However, while many

Summary

- Portions of early visual cortex representing central versus peripheral vision exhibit different patterns of connectivity to category-selective visual regions.
- When central vision is lost, cortical representations of peripheral vision display stronger functional connections to MT than central representations.
- When central vision is lost, connectivity to regions selective for tasks that involve central vision (FFA and PHA) are not significantly altered.
- These effects do not depend on which locations of peripheral vision are used more.

of these studies have focused specifically on the deprivation aspect of sensory loss, sensory deprivation is often a multifaceted phenomenon that can involve multiple, simultaneous features (Cramer et al. 2011; Liu et al. 2010; Toyoizumi et al. 2014; Turrigiano 1999). While obvious differences can arise when comparing cortex deprived of input to cortex with maintained inputs, it is not necessarily the case that all regions with maintained input exhibit uniform function. For example, in the case of partial vision loss, some cortical regions representing intact vision may receive preferential usage compared to other regions with spared input (Liu et al. 2010). Identifying how regions with preferential usage are different from non-preferred and deprived regions of cortex is necessary for an improved understanding of how the brain changes with experience.

Studying patients with selective sensory impairment, such as central vision loss due to late-stage macular degeneration (MD), can inform our understanding of how the brain adapts to changes in experience (Baker et al. 2005; Baker et al. 2008; Baseler et al. 2011; Burge et al. 2016; Dilks et al. 2009; Masuda et al. 2008; Masuda et al. 2021; Sabbah et al. 2017; Sunness, Liu, and Yantis 2004). In later stages of MD, photoreceptor cells degenerate, forming a lesion in the center of the retina (Zarbin 2004). This results in the deprivation of bottom-up, retinal input to the cortical representation of the lesioned area—the so-called lesion projection zone (LPZ). Due to the lack of central vision, many individuals with MD preferentially use a specific part of their intact peripheral vision, known as the "preferred retinal locus" (PRL), as an oculomotor reference point for everyday visual tasks like recognizing faces (Bullimore, Bailey, and Wacker 1991) and reading (Timberlake et al. 1987). The preferential usage of the PRL makes it functionally distinct from other "un-preferred retinal loci" (URLs), which maintain sensory input to visual cortex, but do not necessarily receive increased use. Due to the precise retinotopy of visual cortex, projections from PRL and URL regions of the retina can be predicted based on anatomy (Benson et al. 2012) and the location of those projections is not thought to change substantially after MD (Baseler et al. 2011). However, little is known about how the cortical representations of the PRL and URL (referred to here as the cPRL and cURL) are differentially altered in response to input deprivation or preferential usage.

Functional connectivity, or the correlation in spontaneous activity between brain regions (Biswal et al. 1995), is a stable and reproducible metric (Gratton et al. 2018), used to assess changing brain function in many contexts, including development (Dosenbach et al. 2010; Fair et al. 2007; Satterthwaite et al. 2013), psychopathology (Fleming, Harnett, and Ressler 2024; Harnett et al. 2024), aging(Andrews-Hanna et al. 2007; Chan et al. 2014; Geerligs et al. 2015; Meunier et al. 2009), during tasks (Cole et al. 2021; Elkhetali et al. 2019), as well as with changes in visual experience (Lewis et al. 2009). Because central and peripheral vision are used differently after central vision loss, this loss offers an opportunity to examine alterations in typical patterns of functional connectivity in visual cortex related to deprivation, preferential usage, and simple maintenance of inputs. Changes in functional connectivity brought on by experience may reflect a history of repeated co-activation of brain regions over time in a Hebbian-like fashion (Harmelech and Malach 2013; Hebb 1949). Previous work shows that functional connectivity in primary visual cortex is retinotopically organized such that regions representing central vision have different functional connectivity patterns from those that represent peripheral vision (Arcaro et al. 2015; Genç et al. 2016; Griffis et al. 2017; Heinzle, Kahnt, and Haynes 2011; Raemaekers et al. 2014; Striem-Amit et al. 2015). These differences are thought to reflect the differential functions of central and peripheral vision. Thus, examining patterns of functional connections in people with central vision loss due to macular degeneration, where peripheral vision must be used for all visual tasks, provides a window to understand plasticity driven by deprivation, maintenance, and preferential usage.

Prior work suggests that functional connections change following vision loss. For example, following the loss of central vision, cortical representations of peripheral vision in early visual cortex exhibit altered patterns of functional connectivity to ventral occipital cortex (Sabbah et al. 2017). This finding is noteworthy given that ventral occipital cortex exhibits different patterns of connectivity to central versus peripheral representations in early visual cortex (Park et al. 2018). These differential patterns of connectivity for central versus peripheral representations likely reflect the ways in which central and peripheral vision are normally used for different types of visual tasks. For example, central vision is typically used more for everyday visual tasks such as recognizing faces. Thus, cortical representations of central vision are more strongly associated with regions with high selectivity for faces, like fusiform face area (FFA) (Levy et al. 2001). On the other hand, there may be specific roles for peripheral vision that are associated with other category-selective regions. For example, human area MT is involved in identifying looming or moving stimuli (Tootell et al. 1995). While motion detection is important throughout the visual field, it is performed particularly well with peripheral vision (Yu et al. 2010).

Visual areas with different central versus peripheral biases likely also exhibit different patterns of connectivity following central vision loss. For example, regions normally biased toward central vision, like fusiform cortex, appear to become more strongly functionally connected to early visual cortical representations of intact, peripheral vision in individuals with central vision loss (Sabbah et al. 2017). However, it remains unclear whether this association is different between regions that receive increased, preferential usage, versus those that maintain input that is not necessarily preferentially used.

Using a recently developed method for precise retinal mapping in individuals with central vision loss (Defenderfer, Demirayak, and Visscher 2021), we directly tested the hypothesis that the organization of visual cortex is dependent not only on deprived versus intact input, but also on the preferential usage of remaining input. Specifically, we examined patterns of functional connectivity in patients with central vision loss (i.e., macular degeneration). We focused on functional connectivity between early visual cortex and higher-order visual regions that exhibit selectivity for specific types of visual stimuli (i.e., fusiform face area (FFA), parahippocampal area (PHA), and middle temporal area (MT)). In doing so, we set out to understand how deprivation, preferred, and non-preferrent usage produce macroscale changes in the intrinsic properties of visual cortex that are likely outcomes of microscale forms of plasticity.

2 | Materials and Methods

2.1 | Participants

Patients were recruited as part of the NIH Connectomes in Human Diseases MD Plasticity project. Inclusion criteria for MD patients included in the current analyses were: (1) Central vision loss in both eyes for a minimum of two years, (2) a clearly-defined preferred retinal locus as determined from a Macular Integrity Assessment (MAIA) microperimetry, (3) visual acuity of 20/100 or worse in their best eye, and (4) having a matched healthy control participant. The larger Connectomes in Human Diseases MD Plasticity project included some participants who did not meet these strict criteria. Retinal microperimetry and a visual acuity assessment were performed in order to verify that each MD participant had significant loss of central vision. Visual acuity was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) test (Ferris et al. 1982). Healthy control participants were matched on the basis of sex, age (matched to an individual participant +/− 5 years), and education level (no high school diploma, high school diploma, some college, college degree, or advanced degree). Control participants were required to have normal or corrected-to-normal vision and be free of ocular disease. Recruitment was conducted through referrals from the UAB Callahan Center for Low Vision, the Retina Specialists of Alabama, and community- advertisements. The data analyzed here includes 11 MD patients (5 males, 6 females, mean age = 56.7 years) and 11 healthy control participants who met the above criteria (Table 1). All methods, including obtaining informed consent, were carried out in accordance with ethical standards under the oversight of the University of Alabama at Birmingham (UAB) Institutional Review Board.

2.2 | MRI Data Acquisition

Functional and structural imaging data were acquired using a 3 T Siemens Magnetom Prisma MRI scanner using protocols based on those of the Human Connectome Project (Glasser et al. 2016). High-resolution 3D anatomical scans were obtained using a 3D-MPRAGE sequence (T1-weighted; repetition time (TR) = 2400 ms; echo time (TE) = 2.22 ms; field of view (FOV(a p,rl,fh)) = 208 × 208 × 144 mm; voxel size = 0.8 mm isotropic; flip angle (FA) = 8°). Scientists collecting the data reviewed image quality during the scan session in accordance with Human Connectome Project protocols (Marcus et al. 2013). Under these guidelines, each scan was given a numerical rating of 1–4 (1 = poor, 2 = fair, 3 = good, 4 = excellent). These ratings were based on overall image crispness, blurriness, motion, and any additional observable artifacts. If the T1w scan received a rating lower than three, the scan was reacquired during the same scan session if time allowed or in one of the subsequent scan sessions for the study. Resting-state functional scans (eyes open) were acquired in total darkness using a Gradient-echo EPI sequence (T2*-weighted, TR = 800 ms, TE = 37 ms, FA = 52°; voxel size = 2.0 × 2.0 × 2.0 mm isotropic; echo spacing = 0.58 ms; mutliband acceleration factor = 8) resulting in 420 volumes per scan. In order to ensure complete darkness, the investigators blocked out all possible sources of light in the room (windows, waveguides, lights on equipment) prior to the start of the resting-state scan. Participants were instructed to relax and keep their eyes open until the scan was complete. An infrared camera system, which does not emit visible light, was used to monitor participants during scanning in order to ensure that their eyes remained open during the scanning session. Each scan lasted 5.6 min and was repeated 8 times for a total duration of 44.8 min of scan time.

2.3 | MRI Data Processing

Raw data MRI data files were first converted into Brain Imaging Data Structure (BIDS) format (Gorgolewski et al. 2016) in order to enable use with open source pre-processing pipelines. Initial first-pass quality control was performed through manual inspection of the data using MRIQC (Esteban et al. 2017). Initial image pre-processing steps were performed with FMRIPrep version 1.2.5 (https://fmriprep.org/) under the default settings (Esteban et al. 2019). For reproducibility of methods, a more detailed description is provided in the Supporting Information. To summarize briefly: BOLD data underwent co-registration to T1w anatomical space, spatiotemporally filtered, slice-time corrected, scrubbed for motion artifacts using the XCP engine workflow (Ciric et al. 2018) with a framewise displacement threshold of 0.5 mm. Data were then converted into fsLR_32k cifti template-space using *Ciftify* (Dickie et al. 2019) and tools from the *HCP Connectome Workbench* (Marcus et al. 2011).

2.4 | Region of Interest Definitions

Regions of interest within the early visual cortex were defined based on atlases of visual regions coupled (described fully in the next paragraph) with maps of the visual field acquired from retinal imaging acquired outside of the MRI scanner (as described in this paragraph). Visual field mapping was performed on a Centervue Macular integrity Assessment (MAIA) device (Centervue, Padova, Italy). The MAIA device uses a confocal scanning laser ophthalmoscope to image the retina in real-time while perimetry is performed using a Goldmann size III white stimulus. During the examination, the MAIA uses a 25 Hz eye tracker to compensate for eye movements and measure fixation. Participants fixate a red annulus and indicate when they detect a light flash with a button push. A 4–2

TABLE 1 | Demographics.

SubID	Group	Age	Sex	Education	Handedness	Visual acuity (ETDRS Snellen)	Match
MDP005	MD	22	M	Associate degree	R	20/125	MDP015
MDP006	MD	50	F	Bachelor's degree	R	20/160	MDP001
MDP008	MD	70	F	Associate degree	L	20/160	MDP035
MDP014	MD	68	M	Master's degree	R	20/400	MDP069
MDP016	MD	55	M	Some college, no degree	R	20/150	MDP026
MDP021	MD	27	M	No diploma, but finished 12th grade	R	20/200	MDP034
MDP022	MD	83	F	Some college, no degree	R	20/100	MDP066
MDP023	MD	35	F	Master's degree	R	20/400	MDP029
MDP050	MD	83	M	Doctoral degree	R	20/125	MDP055
MDP065	MD	61	F	12th grade, high school graduate	R	20/160	MDP120
MDP122	MD	70	F	Bachelor's degree	R	20/400	MDP116
MDP001	HC	48	F	Master's degree	R	20/16	MDP006
MDP015	HC	23	M	Some college but no college degree	R	20/12.5	MDP005
MDP026	HC	57	M	High school graduate	R	20/20	MDP016
MDP029	HC	32	F	Master's degree	R	20/12.5	MDP023
MDP034	HC	24	M	High school graduate	R	20/12.5	MDP021
MDP035	HC	68	F	High school graduate	R	20/16	MDP008
MDP055	HC	81	M	Master's degree	R	20/20	MDP050
MDP066	HC	78	F	Bachelor's or RN degree	R	20/16	MDP022
MDP069	HC	68	M	Doctoral or law degree	R	20/32	MDP014
MDP116	HC	72	F	Some college but no college degree	R	20/25	MDP122
MDP120	HC	59	F	High school degree	Both	20/32	MDP065

staircase strategy was used to determine sensitivity thresholds. This resulted in three pieces of information: a map of the retinal lesion, a map of the retinal locations with spared and lesioned vision, as well as an estimate of the location at which the MD patients tended to primarily fixate (i.e., the preferred retinal locus, PRL). The PRL was defined based on the cloud of fixation locations over time. The center of the PRL was defined as the center of the cloud, and the boundary was defined as the Bivariate contour ellipse area (BCEA) that included 63% of fixation locations (Steinman 1965). In cases where the PRL was located in extremely eccentric areas, the 95% BCEA was used in order to capture enough cortical vertices for each ROI. The boundaries of the retinal lesion were manually drawn from the MAIA output image based on the locations where the participant did not detect light.

The locations of the PRL region and the retinal lesion were mapped to their corresponding regions on the cortical surface in V1, V2, and V3 using an automatic pipeline described elsewhere (Benson and Winawer 2018; Benson et al. 2012; Defenderfer, Demirayak, and Visscher 2021; Defenderfer et al. 2023) based on a previously published retinotopic atlas (Benson and Winawer 2018; Benson et al. 2012; Defenderfer, Demirayak, and Visscher 2021; Defenderfer et al. 2023). This resulted in regions of interest for each MD participant in V1, V2, and V3 for the cortical representation of the PRL (cPRL) and the cortical representation of the lesion (i.e., the "lesion project zone," LPZ). In addition to the cPRL and LPZ regions, we also defined a control region that we refer to here as the cortical representation of the "Un-preferred Retinal Locus" or cURL. This region was defined by identifying a region on the retina outside of the lesion that was: (1) the same eccentricity as the PRL region, (2) as far away from the PRL as possible, and (3) was confirmed to have light sensitivity as measured by the MAIA. The placement of these retinal loci was conducted by a trained expert (M.K.D), automatically mapped to visual cortex, and verified by three investigators with specialization in retinal anatomy (L.L.F, P.D., and K.M.V.). A schematic of

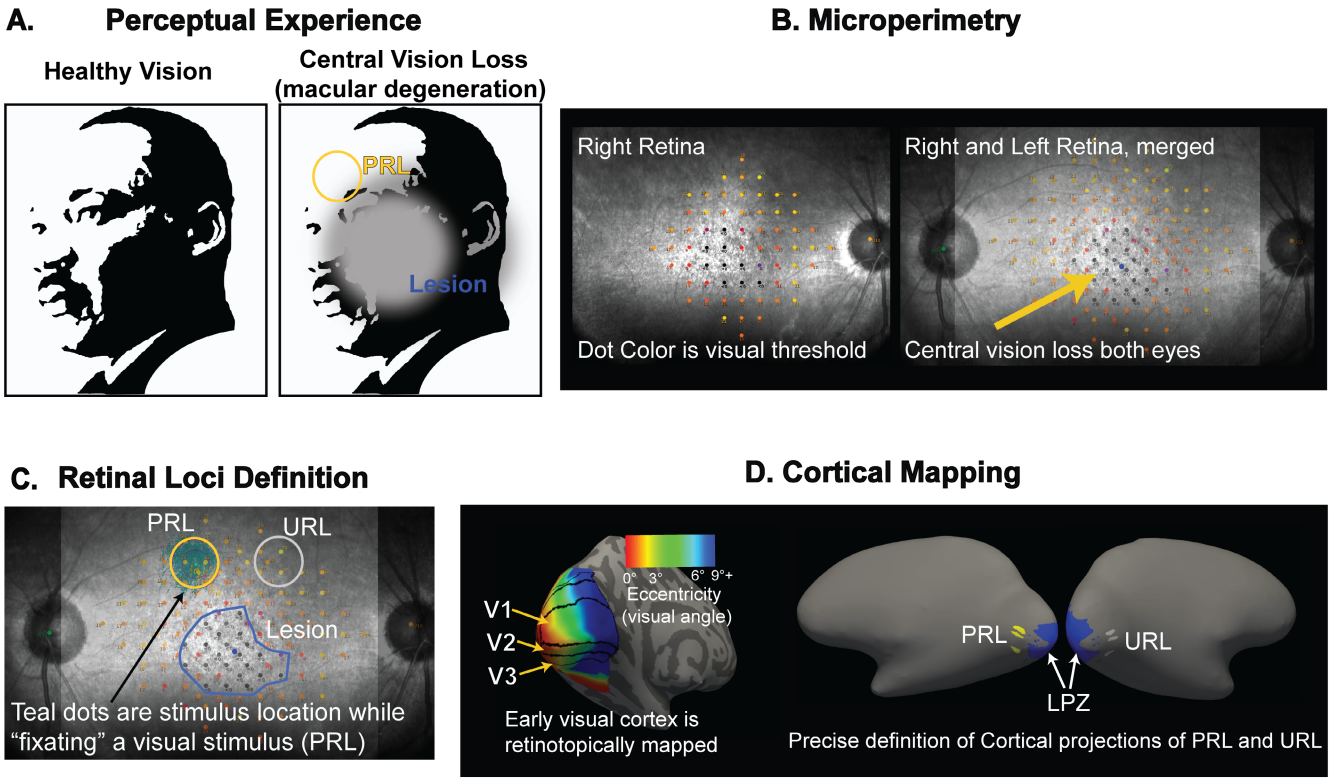

FIGURE 1 | Schematic of early visual cortex ROI Definition. The perceptual experience of individuals with macular degeneration in comparison to healthy vision is shown in (A). In macular degeneration, a lesion forms in the center of the retina, rendering patients unable to see in the center of the visual field (gray patch). Retinal imaging was first conducted using microperimetry separately in both eyes (B). The PRL (preferred retinal locus), URL (un-preferred retinal locus), and lesion are then determined (C). Using this information, a retinotopic atlas of visual cortex is then is used (D—left) to map the cortical representations of these three loci in early visual cortex (V1, V2, V3), shown on the right (D).

this process is summarized in Figure 1. The result of this process is shown for four representative participants is shown in Figure 2. The locations for each participant are shown in Figure S3.

We treated each healthy control participant the same as their matched MD counterpart, placing their cortical ROIs according to the location in retinal space of the lesion, PRL, and URL of their matched MD participant counterpart. These regions were first created on the native cortical surface, and then projected onto the fsLR_32k template in cifti space. In cases where significant group effects were observed for both the cPRL and the cURL, we defined an additional "all peripheral" ROI to examine the generalizability of the effects. This ROI consisted of all regions in early visual cortex (V1, V2, and V3) outside of the lesion project zone. This was done in order to determine whether any observed functional connectivity group differences extended to cortical regions representing all of the remaining, intact portions of the retina.

In addition to the early visual cortex ROIs, we used a previously published cortical atlas (Glasser et al. 2016) to define regions of interest for three category-selective visual regions: fusiform face area, parahippocampal area, and middle temporal area. These regions were selected using the anatomical names described in the Glasser parcellation documentation (See details in Supporting Information).

2.5 | Functional Connectivity Analysis

The average time course of each ROI was extracted from the preprocessed resting-state fMRI data using in-house scripts in MATLAB 2021a (MathWorks, Natick, MA). Functional connectivity was then calculated as the Pearson's correlation between the timecourses of each early visual cortex ROI and those of the category-selective ROIs. Connectivity for each early visual cortex ROI (cPRL, cURL, and LPZ) was first calculated independently at the levels of V1, V2, and V3 and then averaged across levels to generate a single value for each ROI type.

2.6 | Statistical Analysis

The effects of deprivation, preferred usage, and non-preferred usage on functional connectivity were assessed by using two-way, repeated measures analysis of variance (ANOVA) with factors of early visual cortex ROI (LPZ, cPRL, and cURL) and group (MD vs. healthy controls). Here, we applied a "yoked-control" approach, using group as a repeated measures factor due to the fact that each MD participant was matched based on age, sex, and education to a control participant. Each MD participant's individualized regions of interest for LPZ, cPRL, and cURL were applied to their yoked healthy vision control participant. This approach helps control for factors of age,

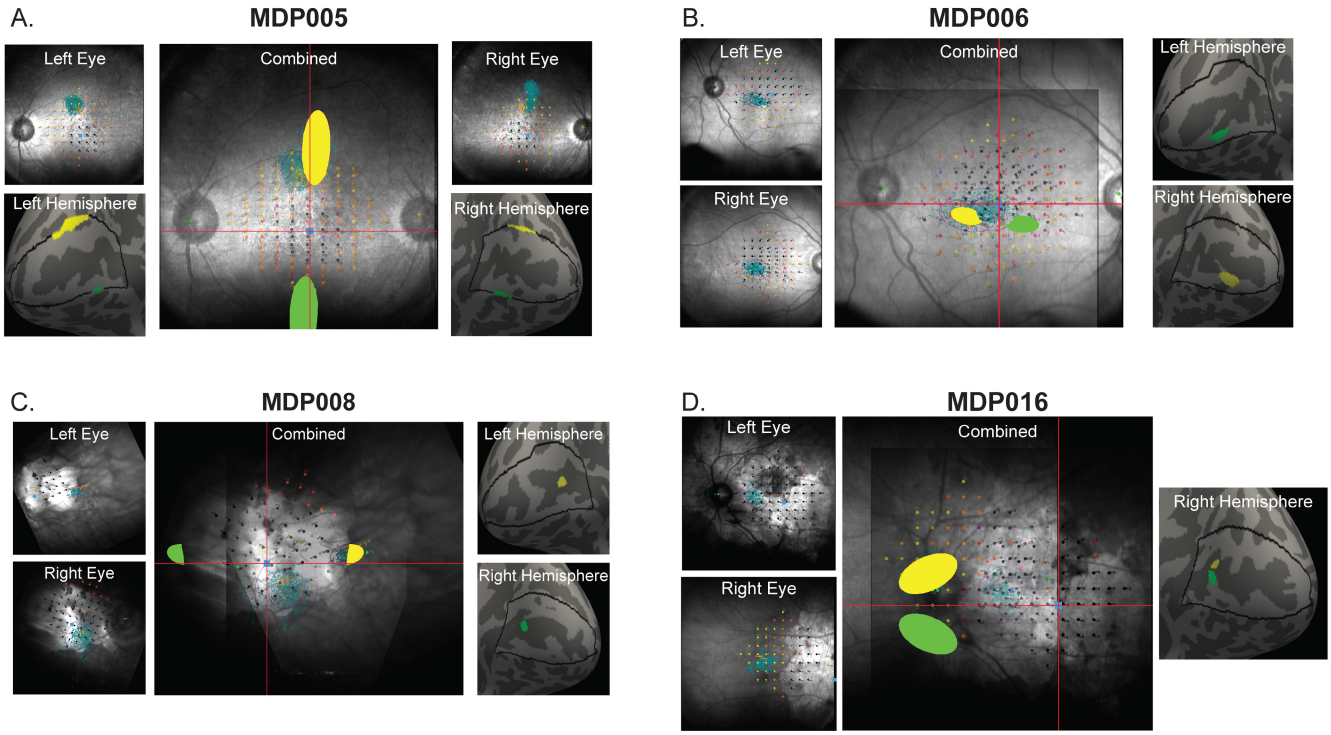

FIGURE 2 | Individual participant retinal images. Retinal images from microperimetry are shown for 4 representative individuals. PRL locations are shown in yellow. URL locations are shown in green. Microperimetry images for left and right eyes are shown in upper corners of each panel. Center images show combined image of left and right retinal images. Mapping onto left and right cortical surfaces are shown in bottom corners of each panel.

sex, and education. Significant results using this approach were followed up with unpaired tests as a validation measure (described in results). In cases where statistical assumptions were not met, Wilcoxon rank sum tests were used as a non-parametric alternative to the ANOVA. This required the calculation of difference scores of cPRL and cURL minus LPZ connectivity, respectively, in order to generate a single value that could be compared between groups. This approach was used to mitigate the fact that there is no *true* non-parametric alternative for a 2-way ANOVA under conditions of unequal variance. Statistical tests were corrected for multiple comparisons using the Bonferroni correction procedure. Statistical analyses were carried out using R version 4.1.3 (R Core Team, 2022) using the rstatix package (version 0.7.0).

3 | Results

3.1 | Functional Connectivity to Fusiform Face Area (FFA)

We first investigated how central vision loss impacts functional connectivity between fusiform face area (Figure 3B), a normally centrally biased visual area, and cortical representations of deprived (LPZ), preferred (cPRL), and non-preferred (cURL) loci on the retina (Figure 3A). A two-way repeated measures ANOVA revealed a statistically significant main effect of early visual cortex ROI (LPZ, cPRL, cURL) on functional connectivity to fusiform face area ($F(2,20) = 78.712$, $p = 3.31e{-}10$). Post hoc *t*-tests with a Bonferroni adjustment revealed that functional connectivity of the LPZ was significantly greater than that of the cPRL and cURL in both MD patients and healthy controls (Figure 3C). No significant effect of group differences were observed, suggesting that functional connectivity patterns between may be maintained following central vision loss.

3.2 | Functional Connectivity to Parahippocampal Area (PHA)

Next, we tested whether central vision loss and increased use of the PRL is related to altered patterns of functional connectivity between early visual cortex and parahippocampal area, a brain region that demonstrates selectivity for scenes (Figure 4). To this, we conducted a two-way, repeated measures ANOVAs with factors of group (MD vs. healthy controls, as a yoked control) and early visual cortex ROI (LPZ, PRL, and URL). The ANOVA results revealed a statistically significant main effect of early visual cortex ROI (LPZ, PRL, URL) on functional connectivity to parahippocampal area ($F(2,20) = 32.70$, $p = 4.96e{-}7$) Post hoc *t*-tests with a Bonferroni adjustment revealed that functional connectivity of the LPZ was significantly greater than that of the PRL and URL in both MD patients and healthy controls.

3.3 | Functional Connectivity to Middle Temporal Area (MT)

We next investigated functional connectivity between the early visual cortex ROIs and area MT (Figure 5). A Levene's test of homogeneity of variances test showed unequal variances connectivity between groups for the cPRL ($F(1,20) = 8.08$, $p = 0.01$)

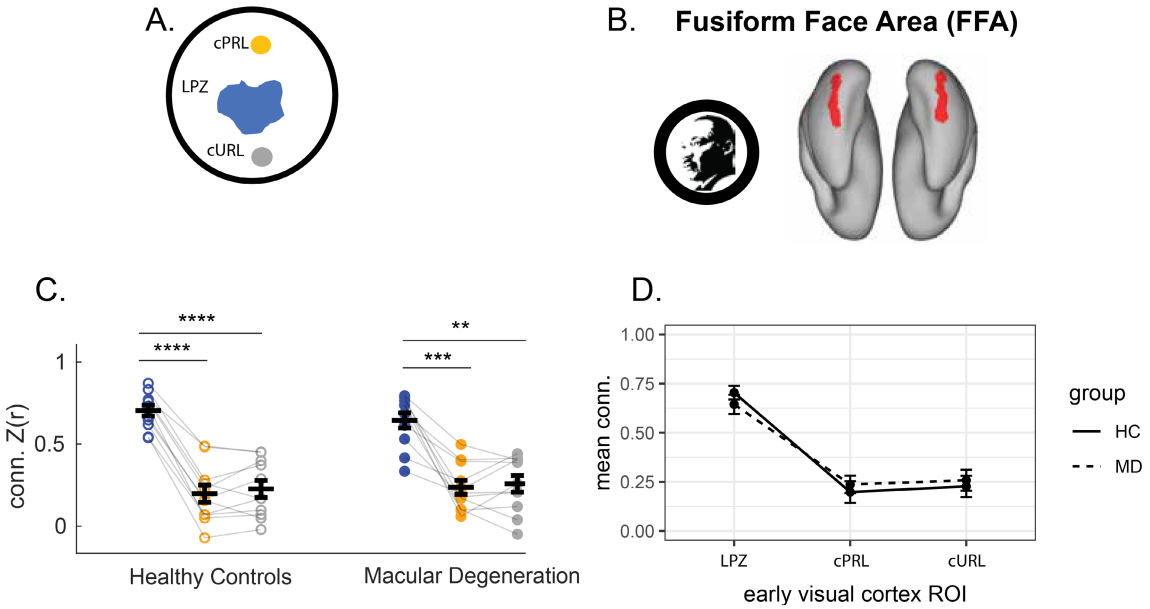

FIGURE 3 | Connectivity to fusiform face area. Panel A shows the corresponding regions in visual space of the three early visual cortex regions of interest: The lesion projection zone (LPZ) in blue, the cortical representation of the preferred retinal locus (cPRL) and the cortical representation of the un-preferred retinal locus (cURL). These regions were defined in early visual cortex using the methods described in Figure 1. Functional connectivity was measured between these regions and fusiform face area (FFA), shown in panel B. Fisher's Z-transformed connectivity values between the three early visual cortex ROIs and FFA are shown for healthy controls (HC) and macular degeneration patients (MD) in panel C (color-coded based on panel A). Connectivity to FFA was significantly higher for the LPZ, relative to the cPRL and cURL, in both groups (C). Group means for each ROI are shown in D. Error bars in both figures represent the standard error of the mean. Stars (*) denote statistical significance levels based on the following conventions: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

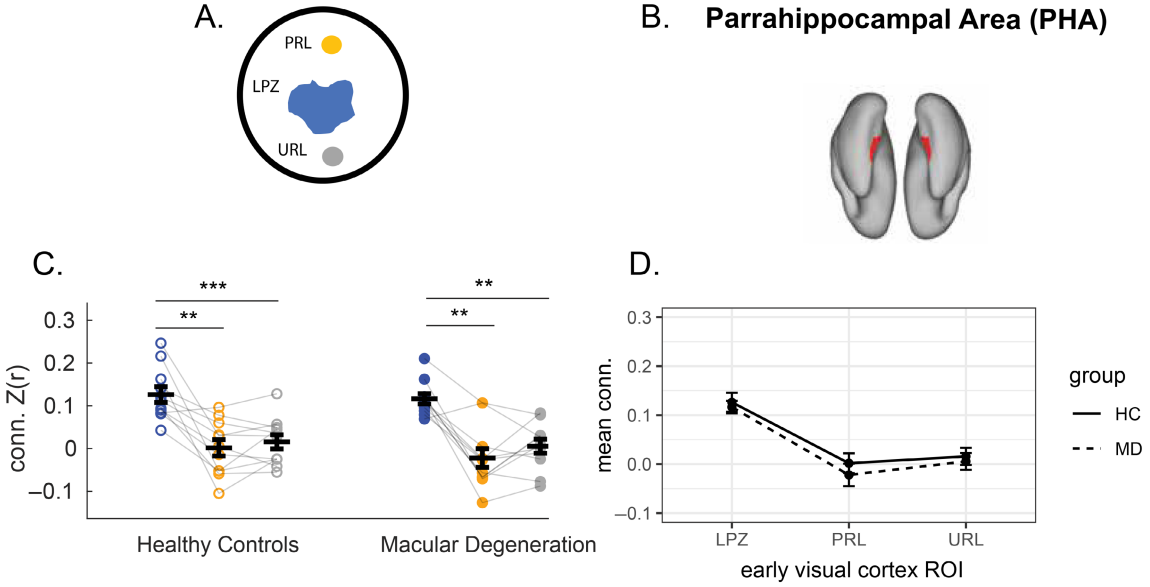

FIGURE 4 | Connectivity to parahippocampal area. Panel A shows the corresponding regions in visual space of the three early visual cortex regions of interest: The lesion projection zone (LPZ) in blue, the cortical representation of the preferred retinal locus (cPRL) and the cortical representation of the un-preferred retinal locus (cURL). These regions were defined in early visual cortex using the methods described in Figure 1. Functional connectivity was measured between these regions and parahippocampal area (PHA), shown in panel B. Fisher's Z-transformed connectivity values between the three early visual cortex ROIs and PHA are shown for healthy controls (HC) and macular degeneration patients (MD) in panel C (color-coded based on panel A). A two-way, repeated measures ANOVA revealed a significant main effect of early visual cortex ROI, such that LPZ connectiviy was higher relative to cortical representations of the PRL and URL in both groups (C). Group means for each ROI are shown in D. Error bars in both figures represent the standard error of the mean. Stars (*) denote statistical significance levels based on the following conventions: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

and the cURL ($F(1,20) = 8.06$, $p = 0.01$). Specifically, MD participants are more homogeneous than controls. Because there is no well-accepted alternative for 2-way ANOVA under unequal variances, we performed a non-parametric Wilcoxon test to separately compare cPRL and cURL connectivity (relative to central, LPZ connectivity) in MD participants versus controls (Figure 6). This required the generation of a single value for MD and control participants, respectively. As a result, we calculated two separate difference scores and performed two independent group comparisons: cPRL minus LPZ connectivity score in MDs versus controls (Figure 6A), and a cURL minus LPZ connectivity score in MDs versus controls (Figure 6B).

Because we observed similar results for the cPRL and cURL difference scores, we employed a combined approach (Figure 6C) by calculating a mean score for the central ROI (LPZ) and subtracted this value from the mean of the peripheral rois (cPRL and cURL). This "peripheral relative to central" value was then compared between the two groups. A Wilcoxon ranked sum test found that peripheral relative to central connectivity to MT was significantly different between groups using both a paired/yoked approach, where each MD participant matched by age, sex, and education to a control (Wilcoxon's $W = 5$, $p = 4.88e{-3}$) and an unpaired approach (Wilcoxon's $W = 27$, $p = 1.40e{-2}$). In healthy controls, peripheral minus central connectivity values were centered around zero (Figure 6A), suggesting very little difference between the ROIs. In MD, this number was a positive value, suggesting that peripheral connectivity to MT was greater than that of central representations (mean = 0.12).

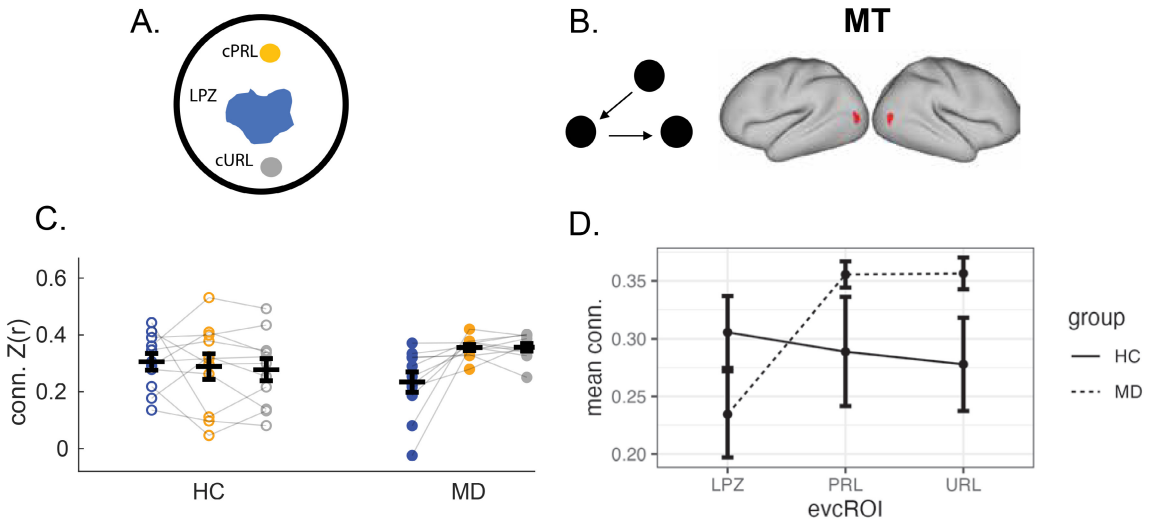

FIGURE 5 | Connectivity to middle temporal area. Panel A shows the corresponding regions in visual space of the three early visual cortex regions of interest: The lesion projection zone (LPZ) in blue, the cortical representation of the preferred retinal locus (cURL). These regions were defined in early visual cortex using the methods described in Figure 1. Functional connectivity was measured these regions and middle temporal area (MT) are shown in panel B for visualization purposes only. Fisher's Z-transformed connectivity values between the three early visual cortex ROIs and MT are shown for healthy controls (HC) and macular degeneration patients (MD) in panel C (color-coded based on panel A). Group means are shown in D.

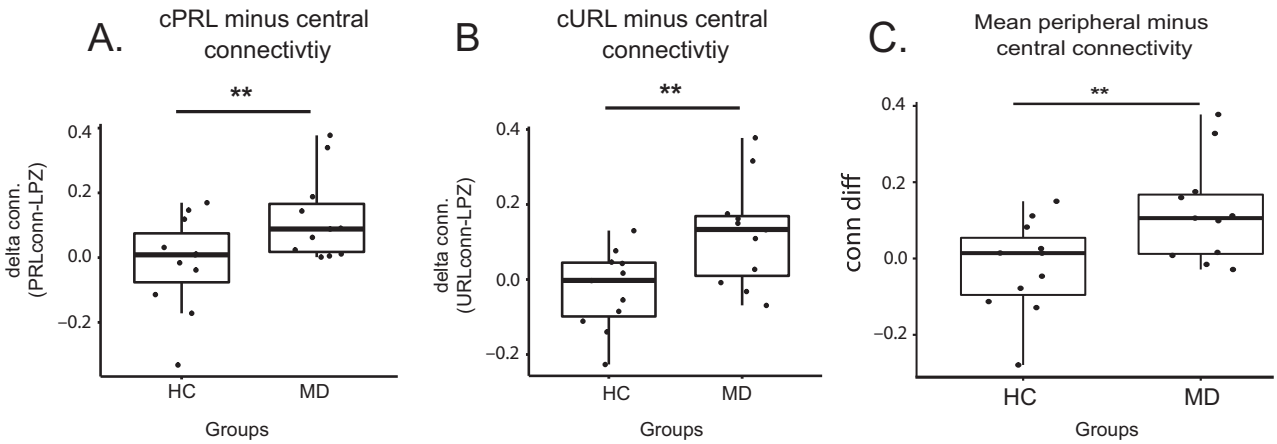

FIGURE 6 | Central versus peripheral connectivity to middle temporal area. Wilcoxon rank sum tests revealed that PRL connectivity (A) and URL connectivity (B) relative to central (LPZ) connectivity were significantly greater in MD participants realtive to healthy vision controls (both $p < 0.01$). Similar results were found when examining the mean of the two perpiheral ROIs (cPRL and cURL) realtive to central (LPZ) connectivity (C). Stars (*) denote statistical significance levels based on the following conventions: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

3.4 | Generalizability of Peripheral Connectivity to MT

The highly similar functional connectivity profiles for the cPRL and the cURL regions suggested the observed increase in peripheral connectivity may not be specific to only the preferentially used portion of peripheral vision. As a result, we tested whether a similar result would be found if we looked at all areas of usable peripheral vision simultaneously (Figure 7). To do this, we created ROIs for each individual subject pair that included all areas of usable vision outside of the lesion projection zone. A Levene's test of homogeneity of variances test showed unequal variances connectivity between groups for the peripheral ROIs (cPRL: $F(1, 20) = 8.08$, $p = 0.01$; cURL: $F(1, 20) = 8.06$, $p = 0.01$). Specifically MD participants were more homogeneous than controls. Similar to described earlier, an "all peripheral relative to central" score was calculated by subtracting LPZ to MT connectivity from "all peripheral" connectivity. A Wilcoxon rank sum test revealed that peripheral (relative to central) connectivity was significantly greater in the MD group compared to controls using both a paired (Wilcoxon's $W = 5$, $p = 9.77e{-3}$) and unpaired approach (Wilcoxon's $W = 27$, $p = 2.81e{-2}$).

4 | Discussion

The overall goal of this investigation was to determine whether deprivation, preferred, and non-preferred usage differentially influence the organization of functional connection patterns in visual cortex. Our findings, using central vision loss as a model, confirm prior evidence demonstrating that early visual cortex exhibits retinotopically specific patterns of functional connectivity to downstream, category-selective visual areas. Additionally, we show that central vision loss is associated with strengthened functional connectivity between cortical representations of peripheral vision and regions involved in motion detection (MT). Interestingly, we found that these changes were present not just for the region of preferred usage, but extended to other regions of usable peripheral vision. Together, these findings suggest that long-term changes in visual experience can produce changes in intrinsic cortical activity, well after the critical period of visual development.

5 | Retinotopic Patterns of Connectivity to FFA and PHA

Category-selective visual areas can exhibit biases toward information from different parts of the visual depending on their function (Brewer et al. 2005; Hasson et al. 2002; Kreichman and Gilaie-Dotan 2024). We observed that compared to peripheral representations in early visual cortex, centrally representing regions exhibited greater functional connectivity to both FFA and PHA. The stronger connectivity of FFA to central representations is consistent with previous work showing that activity in FFA is biased toward information from central vision (Hasson et al. 2002; Kreichman and Gilaie-Dotan 2024; Levy et al. 2001). Here, we replicate this finding by showing in MD patients and healthy controls that the cortical representation of central vision in early visual cortex (the LPZ) was more strongly connected to FFA than peripheral regions (cPRL and cURL). This bias toward central vision information is believed to be due to the high visual acuity required to make out details in faces that convey important information, such as facial expressions, physical facial features, and eye gaze direction (Levy et al. 2001; Slotnick and White 2013). Because individuals with central vision loss must rely on peripheral vision to make out facial features (Mitchell et al. 2018), we initially hypothesized that FFA would exhibit a bias toward peripheral visual information in patients with MD. However, we did not find a statistically significant difference in FFA connectivity between groups. There was considerable between-subject variability, however, and future work will be needed to identify whether this variability may be explained by other factors. An important question is whether brain connectivity, along with the decreased visual acuity inherent in central vision loss, contributes to the known deficits that MD patients commonly experience difficulty with tasks like recognizing faces (Bullimore, Bailey, and Wacker 1991; Mitchell et al. 2018). It may be possible that without strengthened peripheral connectivity, information from the peripheral visual field is not properly transmitted to regions like FFA in a way that would improve visual performance on facial processing tasks. Future studies should explore this question and determine whether the strength of connectivity between FFA and peripheral

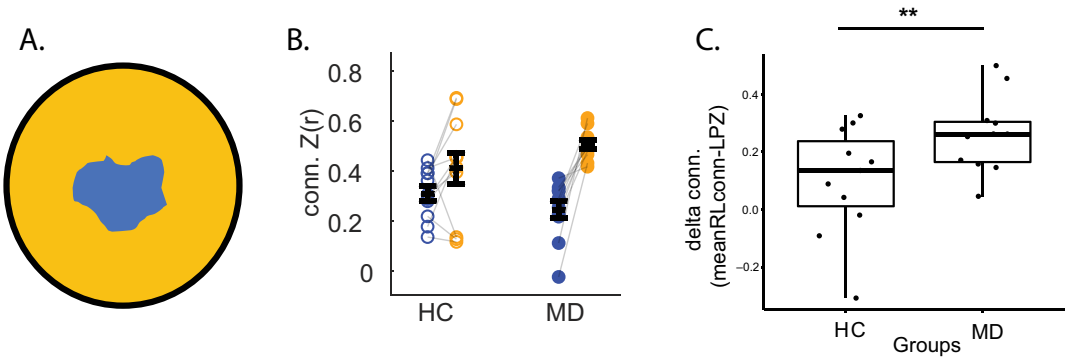

FIGURE 7 | Generalizability of peripheral connectivity difference. Connectivity of all peripheral regions to MT was calculated in order to probe the generalizability of the previous observed effects. Schematic of the all peripheral regions (yellow) and lesion region (blue) are shown (A). Connectivity between each early visual cortex ROI and MT are shown in (B). A direct comparison of "all peripheral" minus LPZ difference scores are also shown (C), revealing greater peripheral relative to central connectivity in MD participants ($p < 0.0.01$). Statistical analysis in (C) was performed using a Wilcoxon rank sum test. Error bars for all figures represent the standard error of the mean. Stars (*) denote statistical significance levels based on the following conventions: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

representation in early visual cortex relate to performance on peripherally presented facial stimuli, and whether this connectivity can be strengthened with intervention.

Another possible reason for the lack of stronger connectivity between cPRL and FFA in patients with MD may be that individuals with central vision loss may be using vision less overall for visual tasks (like facial recognition) that require fine-grain detail. The low resolution of patients' spared vision may not allow individuals to engage in enough everyday facial recognition to produce noticeable changes in connectivity. In future work, it will be important to factor in whether the amount of overall vision use in MD patients is related to the strength of connectivity between peripheral representations and regions like FFA, that are involved in tasks normally performed with central vision.

We found that PHA showed stronger connectivity to the representations of central vision (LPZ) than peripheral vision in both MD patients and controls. This finding was not in the direction of previous work showing PHA may exhibit bias toward peripheral visual information (Baldassano, Fei-Fei, and Beck 2016; Kreichman and Gilaie-Dotan 2024; Levy et al. 2001). However, it should be noted that different subregions of PHA have been shown to have differential patterns of connection to V1 (Baldassano, Fei-Fei, and Beck 2016) and our PHA region was defined as a relatively large swath of cortex, and not defined based on localizers as in some earlier studies. Here, a larger region of interest was used for PHA in an attempt to account for previous reports indicating its high individual variability in location and size (Weiner et al. 2018; Zhen et al. 2017). Future work is needed to probe whether these more subtle relationships between subregions within the parahippocampal area and early visual cortex change following the loss of central vision.

6 | Functional Connectivity to MT

In participants with healthy vision, functional connections between MT and early visual cortex did not significantly differ between central representations (LPZ) and peripheral representations (cPRL and cURL). Patients with central vision loss, but not controls, showed patterns of connectivity that differed based on retinotopy: In patients, there was stronger functional connectivity between MT and representations of peripheral vision than central vision. Importantly, this between-group difference was statistically significant, indicating that the presence of the retinotopic pattern may be a consistent outcome of the experience of central vision loss. Notably, the relative increase in functional connectivity for peripheral vision was not confined to regions within the vicinity of the cPRL and cURL, but extended to the cortical representation of all of the visual periphery.

Our finding of increased connectivity between peripheral representations in early visual cortex and area MT is consistent with previous reports in the literature. For example, prior work in animal models of MD show that central vision loss is associated with increased MT neuronal sensitivity to motion (Hagan et al. 2020), improved motion detection (Burnat et al. 2017), and enhanced velocity discrimination (Burnat et al. 2017). Other work has demonstrated that connections between MT and early visual cortex are modifiable in adulthood and can boost sensitivity to motion (Romei et al. 2016). This raises the question of whether the greater connectivity between peripheral representations and MT in our MD patients is associated with enhanced performance on motion detection tasks. It may be the case that loss of central vision may allow peripheral vision to enhance its connectivity to improve performance on tasks for which peripheral vision is already specialized, as suggested by earlier evidence (Burnat et al. 2017). This is especially relevant given the important role of connections to MT from representations of the far periphery for visual behaviors including orienting, postural and defensive reactions (Palmer and Rosa 2006). Thus, repeated use of spared, peripheral vision in MD patients for these acitivies may selectively lead to enhanced connectivity to areas like MT, which are essential for moving through the world. This would be consistent with previous evidence demonstrating that the function of MT in vision is modifiable by experience (Liu and Pack 2017). Still, future work is needed to determine whether the functional connectivity of MT is related to behavioral performance on motion tasks in MD patients.

Previous work has shown that while other brain regions in the visual network decrease their overall activity level, activity in MT is still maintained after central retinal lesioning (Burnat et al. 2017; Hagan et al. 2020), despite the loss of bottom-up inputs from central vision. This suggests that MT's increased connectivity to peripheral representations in early visual cortex in our data may act homeostatically to maintain a "preferred" level of activity in MT. However, future studies would need to confirm this notion by relating these connections to the activity level of MT using methods like positron emission tomography which could measure absolute (not relative) activity levels.

Understanding the inputs to MT can give insight into why MT connectivity to peripheral representations in early visual cortex increases in patients with central vision loss. The majority of inputs to MT from V1 come from the magnocellular stream, which is known to have cells with relatively large receptive fields and strong sensitivity to motion. However, MT also contains some inputs from the parvocellular stream, which dominate the makeup of ganglion cells in the central retina (Dacey 1993). Removal of input from the fovea, which is dominated by less motion-sensitive parvocellular neurons (Masri, Grünert, and Martin 2020; Yan et al. 2020), may result in a proportional increase of input to V1 from motion-sensitive cells (magnocellular) compared to non-motion-sensitive (parvocellular) cells. Thus, removal of parvocellular input may allow V1 to be more strongly driven by magnocellular inputs, resulting in overall greater functional connectivity of peripheral regions to MT.

7 | Generalizability of Peripheral Connectivity Effects

Interestingly, we found that the effect of increased connectivity between MT and peripheral early visual cortex was present

not only for the area of preferred usage (PRL), but also for un-preferred areas. Furthermore, this effect was maintained when factoring in the cortical representation of all parts of usable peripheral vision. This finding seems logical within the grand scope of PRL usage in MD patients. Prior reports indicate that individuals with MD can use multiple PRLs for different tasks (Crossland, Crabb, and Rubin 2011; Déruaz et al. 2002; Duret, Issenhuth, and Safran 1999; Lei and Schuchard 1997). In our study, PRLs were defined based on microperimetry in each participant's better eye during performance of only one task. Thus, our "un-preferred retinal locations" may include some locations that are preferred during different tasks, and the generalization of the connectivity effects may result from this effect. On the other hand, the connectivity difference was shown to generalize to the cortical representation of the entire spared peripheral visual field. This would not be expected if the increased connectivity were limited to a handful of specific retinal locations. Thus, our data suggest that MT increases connection strength to the cortical representations of all spared vision after central vision loss, regardless of preferential use. This interpretation is consistent with the idea that habitual processing of large peripheral looming stimuli are involved in this shift in connection strength. However, more work is needed to clarify this relationship.

8 | Differences in Variability of Functional Connections to MT

In this analysis, we detected group differences in variability for functional connectivity between peripheral representations in early visual cortex and MT. While comparisons of variability are often used as a measure to test assumptions for statistical analysis, in the case of plasticity, individual variability in functional connectivity can be informative of deeper underlying biology (Mueller et al. 2013). Furthermore, individual variability has been shown to be important in several contexts related to normal development, aging, and brain-related diseases (Hahamy, Behrmann, and Malach 2015; Sele et al. 2021). Notably, previous work suggests that group differences in variability exist when examining individuals with healthy vision versus individuals with congenital blindness. For example, Sen and colleagues (Sen et al. 2022) found that individual variability in the functional connectivity of visual cortex is higher in individuals with congenital blindness compared to individuals with healthy vision. These results suggest that increased use of vision results in more consistent functional connectivity between individuals. In our study, we observed that increased use of peripheral vision similarly leads to more across-subject similarity in connectivity in individuals with MD. This serves as yet another form of evidence toward the importance of visual experience in the establishment of connectivity between brain regions. Moreover, it supports the idea put forth by Sen et al. (2022) that "shared sensory experience enforces consistency across individuals" (Sen et al. 2022). Our results add a new layer to this idea, suggesting that visual experience can influence individual variability in a specific manner when one particular part of the visual field is used more. While these differences in individual variability are interesting, a couple of outstanding questions remain. First, the results shown in the current study only look at individuals who had visual input in the early stages of life. Previous work has shown visual system development in sighted individuals decreases variability compared to congenitally blind individuals (Sen et al. 2022). Our results suggest a possible further refinement of this individual variability in adulthood when individuals increasingly use one section of the visual field. Second, it remains to be fully understood why increased use is related to reduced variability of functional connectivity in visual cortex. One possibility may be activity-dependent changes that are known to drive plasticity related-change in visual cortex (Hubel and Wiesel 1963; Hubel and Wiesel 1970). In the case of central vision loss, increased reliance on peripheral vision likely drives higher-than-normal levels of activity that may alter peripheral representations of visual cortex that look similar across individuals. Such activity may drive activity-dependent gene-expression changes that have been previously shown to play an important role in the plasticity of visual cortex (Tropea et al. 2006). In the present study, our findings highlight an important role of experience in shaping individual differences in the brain that may be related to such changes.

9 | Limitations and Future Directions

This study has a number of limitations that stand as opportunities for future studies. First, this study had the strength of targeting a very specific presentation of macular degeneration (dense central vision loss). However, recruiting this patient population became difficult given that it consisted of elderly adults who were among those most vulnerable during the COVID-19 pandemic. Future work in a larger sample may provide greater statistical power to reveal some effects that were not observable in the present dataset. Second, this study was cross-sectional in nature and did not contain measurements of the progression of macular degeneration and its subsequent neurobiological effects over time. Additionally, this investigation focused specifically on changes in the synchrony of spontaneous activity in visual cortex. It should be noted that spontaneous waves of activity also take place in the retina that could also potentially influence functional connectivity in visual cortex. While we did our best to control for differences in the stimulation of retinal activity by scanning in complete darkness, it is possible that central vision loss may lead to differences in spontaneous retinal activity, and thus downstream patterns of cortical activity. However, our interpretations rely mainly on the effects observed in the cURL and cPRL, where vision is maintained, and this effect should not be present. Thus, while future work in animal models may help understand the influence of spontaneous activity in the pathway of the lesioned retina following sensory loss, these effects should not impact the interpretations we make here. One question not addressed by this study was whether there was an influence of differences in the number of eye movements between patients and controls. Here, an infrared camera was used to qualitatively ensure participant eyes remained open during scanning. While we did not quantify eye movements, existing literature suggests that the effects of eye movements on functional connectivity appear to be minimal, at around 2.5% (Koba et al. 2021). However, future studies are needed to investigate whether eye movement differences between patient populations and typically sighted individuals contribute to differential effects on functional connectivity. Lastly, the

present analysis used an ROI-to-ROI approach to test specific hypotheses about functional connectivity following central vision loss. However, it would also be interesting to determine whether connectivity to other regions, namely between MT and the rest of the brain, are also differentially altered following central vision loss. However, given the limited sample size and need to correct for multiple comparisons, this is beyond the scope of the current study.

10 | Conclusions

In summary, our study sheds light on the impact of preferential usage on patterns of functional connections, specifically in individuals with long-term loss of central vision. Our findings provide strong evidence for the role of brain plasticity well after the critical period of development, demonstrating Hebbian-like plasticity in the connections between early visual cortex and the middle temporal area. Moreover, our results highlight the importance of functional connectivity during rest as a meaningful characteristic of the brain that can be shaped by experience. Overall, this study highlights the remarkable flexibility of the human brain and its capacity for adaptation in response to changes in sensory input, even in older adults with long-term visual impairment. These findings provide new insights into the mechanisms of brain plasticity and have important implications for the development of new approaches for rehabilitation and treatment.

Author Contributions

L.L.F.: conceptualization, formal analysis, investigation, writing – original draft. **M.K.D.:** methodology, investigation. **P.D.:** methodology, investigation. **P.S.:** software, formal analysis. **D.K.D.:** resources, supervision. **K.M.V.:** conceptualization, writing – review and editing, funding acquisition, supervision.

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Ethics Statement

All portions of this study were carried out in accordance with ethical standards under the oversight of the University of Alabama at Birmingham (UAB) Institutional Review Board.

Consent

Informed consent was obtained from all participants prior to study enrollment.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used in this study are freely available at https://www.humanconnectome.org/. Code for automatic mapping of retinal loci is openly available in a Gitlab repository: https://github.com/Visscher-Lab/image-to-surface.

References

Andrews-Hanna, J. R., A. Z. Snyder, J. L. Vincent, et al. 2007. "Disruption of Large-Scale Brain Systems in Advanced Aging." *Neuron* 56: 924–935.

Arcaro, M. J., C. J. Honey, R. E. B. Mruczek, S. Kastner, and U. Hasson. 2015. "Widespread Correlation Patterns of fMRI Signal Across Visual Cortex Reflect Eccentricity Organization." *eLife* 4: e03952.

Baker, C. I., D. D. Dilks, E. Peli, and N. Kanwisher. 2008. "Reorganization of Visual Processing in Macular Degeneration: Replication and Clues About the Role of Foveal Loss." *Vision Research* 48: 1910–1919.

Baker, C. I., E. Peli, N. Knouf, and N. G. Kanwisher. 2005. "Reorganization of Visual Processing in Macular Degeneration." *Journal of Neuroscience* 25: 614–618.

Baldassano, C., L. Fei-Fei, and D. M. Beck. 2016. "Pinpointing the Peripheral Bias in Neural Scene-Processing Networks During Natural Viewing." *Journal of Vision* 16: 9.

Baseler, H. A., A. Gouws, K. V. Haak, et al. 2011. "Large-Scale Remapping of Visual Cortex Is Absent in Adult Humans With Macular Degeneration." *Nature Neuroscience* 14: 649–655.

Benson, N. C., O. H. Butt, R. Datta, P. D. Radoeva, D. H. Brainard, and G. K. Aguirre. 2012. "The Retinotopic Organization of Striate Cortex Is Well Predicted by Surface Topology." *Current Biology* 22: 2081–2085.

Benson, N. C., and J. Winawer. 2018. "Bayesian Analysis of Retinotopic Maps." *eLife* 7: e40224.

Biswal, B., F. Z. Yetkin, V. M. Haughton, and J. S. Hyde. 1995. "Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI." *Magnetic Resonance in Medicine* 34: 537–541.

Brewer, A. A., J. Liu, A. R. Wade, and B. A. Wandell. 2005. "Visual Field Maps and Stimulus Selectivity in Human Ventral Occipital Cortex." *Nature Neuroscience* 8: 1102–1109.

Bullimore, M. A., I. L. Bailey, and R. T. Wacker. 1991. "Face Recognition in Age-Related Maculopathy." *Investigative Ophthalmology & Visual Science* 32: 2020–2029.

Burge, W. K., J. C. Griffis, R. Nenert, et al. 2016. "Cortical Thickness in Human V1 Associated With Central Vision Loss." *Scientific Reports* 6: 23268.

Burnat, K., T.-T. Hu, M. Kossut, U. T. Eysel, and L. Arckens. 2017. "Plasticity Beyond V1: Reinforcement of Motion Perception Upon Binocular Central Retinal Lesions in Adulthood." *Journal of Neuroscience* 37: 8989–8999.

Chan, M. Y., D. C. Park, N. K. Savalia, S. E. Petersen, and G. S. Wig. 2014. "Decreased Segregation of Brain Systems Across the Healthy Adult Lifespan." *Proceedings of the National Academy of Sciences* 111: E4997–E5006.

Ciric, R., A. F. G. Rosen, G. Erus, et al. 2018. "Mitigating Head Motion Artifact in Functional Connectivity MRI." *Nature Protocols* 13: 2801–2826.

Cole, M. W., T. Ito, C. Cocuzza, and R. Sanchez-Romero. 2021. "The Functional Relevance of Task-State Functional Connectivity." *Journal of Neuroscience* 41: 2684–2702.

Cramer, S. C., M. Sur, B. H. Dobkin, et al. 2011. "Harnessing Neuroplasticity for Clinical Applications." *Brain* 134: 1591–1609.

Crossland, M. D., D. P. Crabb, and G. S. Rubin. 2011. "Task-Specific Fixation Behavior in Macular Disease." *Investigative Ophthalmology & Visual Science* 52: 411–416.

Dacey, D. M. 1993. "The Mosaic of Midget Ganglion Cells in the Human Retina." *Journal of Neuroscience* 13: 5334–5355.

Defenderfer, M., P. Demirayak, and K. M. Visscher. 2021. "A Method for Mapping Retinal Images in Early Visual Cortical Areas." *NeuroImage* 245: 118737.

Defenderfer, M. K., P. Demirayak, L. L. Fleming, D. K. DeCarlo, P. Stewart, and K. M. Visscher. 2023. "Cortical Plasticity in Central Vision Loss: Cortical Thickness and Neurite Structure." *Human Brain Mapping* 44: 4120–4135.

Déruaz, A., A. R. Whatham, C. Mermoud, and A. B. Safran. 2002. "Reading With Multiple Preferred Retinal Loci: Implications for Training a More Efficient Reading Strategy." *Vision Research* 42: 2947–2957.

Dickie, E. W., A. Anticevic, D. E. Smith, et al. 2019. "Ciftify: A Framework for Surface-Based Analysis of Legacy MR Acquisitions." *NeuroImage* 197: 818–826.

Dilks, D. D., C. I. Baker, E. Peli, and N. Kanwisher. 2009. "Reorganization of Visual Processing in Macular Degeneration Is Not Specific to the "Preferred Retinal Locus"." *Journal of Neuroscience* 29: 2768–2773.

Dosenbach, N. U. F., B. Nardos, A. L. Cohen, et al. 2010. "Prediction of Individual Brain Maturity Using fMRI." *Science* 329: 1358–1361.

Duret, F., M. Issenhuth, and A. B. Safran. 1999. "Combined Use of Several Preferred Retinal Loci in Patients With Macular Disorders When Reading Single Words." *Vision Research* 39: 873–879.

Elkhetali, A. S., L. L. Fleming, R. J. Vaden, R. Nenert, J. E. Mendle, and K. M. Visscher. 2019. "Background Connectivity Between Frontal and Sensory Cortex Depends on Task State, Independent of Stimulus Modality." *NeuroImage* 184: 790–800.

Esteban, O., D. Birman, M. Schaer, O. O. Koyejo, R. A. Poldrack, and K. J. Gorgolewski. 2017. "MRIQC: Advancing the Automatic Prediction of Image Quality in MRI From Unseen Sites." *PLoS One* 12: e0184661.

Esteban, O., C. J. Markiewicz, R. W. Blair, et al. 2019. "fMRIPrep: A Robust Preprocessing Pipeline for Functional MRI." *Nature Methods* 16: 111–116.

Fair, D. A., N. U. F. Dosenbach, J. A. Church, et al. 2007. "Development of Distinct Control Networks Through Segregation and Integration." *Proceedings of the National Academy of Sciences* 104: 13507–13512.

Ferris, F. L., A. Kassoff, G. H. Bresnick, and I. Bailey. 1982. "New Visual Acuity Charts for Clinical Research." *American Journal of Ophthalmology* 94: 91–96.

Fleming, L. L., N. G. Harnett, and K. J. Ressler. 2024. "Sensory Alterations in Post-Traumatic Stress Disorder." *Current Opinion in Neurobiology* 84: 102821.

Geerligs, L., R. J. Renken, E. Saliasi, N. M. Maurits, and M. M. Lorist. 2015. "A Brain-Wide Study of Age-Related Changes in Functional Connectivity." *Cerebral Cortex* 25: 1987–1999.

Genç, E., M. L. Schölvinck, J. Bergmann, W. Singer, and A. Kohler. 2016. "Functional Connectivity Patterns of Visual Cortex Reflect Its Anatomical Organization." *Cerebral Cortex* 26: 3719–3731.

Gilbert, C. D., and W. Li. 2012. "Adult Visual Cortical Plasticity." *Neuron* 75: 250–264.

Glasser, M. F., T. S. Coalson, E. C. Robinson, et al. 2016. "A Multi-Modal Parcellation of Human Cerebral Cortex." *Nature* 536: 171–178.

Glasser, M. F., S. M. Smith, D. S. Marcus, et al. 2016. "The Human Connectome Project's Neuroimaging Approach." *Nature Neuroscience* 19: 1175–1187.

Gorgolewski, K. J., T. Auer, V. D. Calhoun, et al. 2016. "The Brain Imaging Data Structure, a Format for Organizing and Describing Outputs of Neuroimaging Experiments." *Scientific Data* 3: 160044.

Gratton, C., T. O. Laumann, A. N. Nielsen, et al. 2018. "Functional Brain Networks Are Dominated by Stable Group and Individual Factors, Not Cognitive or Daily Variation." *Neuron* 98: 439–452.e5.

Grefkes, C., and G. R. Fink. 2014. "Connectivity-Based Approaches in Stroke and Recovery of Function." *Lancet Neurology* 13: 206–216.

Griffis, J. C., A. S. Elkhetali, W. K. Burge, et al. 2017. "Retinotopic Patterns of Functional Connectivity Between V1 and Large-Scale Brain Networks During Resting Fixation." *NeuroImage* 146: 1071–1083.

Hagan, M. A., T. A. Chaplin, K. R. Huxlin, M. G. P. Rosa, and L. L. Lui. 2020. "Altered Sensitivity to Motion of Area MT Neurons Following Long-Term V1 Lesions." *Cerebral Cortex* 30: 451–464.

Hahamy, A., M. Behrmann, and R. Malach. 2015. "The Idiosyncratic Brain: Distortion of Spontaneous Connectivity Patterns in Autism Spectrum Disorder." *Nature Neuroscience* 18: 302–309.

Harmelech, T., and R. Malach. 2013. "Neurocognitive Biases and the Patterns of Spontaneous Correlations in the Human Cortex." *Trends in Cognitive Sciences* 17: 606–615.

Harnett, N. G., L. L. Fleming, K. J. Clancy, K. J. Ressler, and I. M. Rosso. 2024. "Affective Visual Circuit Dysfunction in Trauma and Stress-Related Disorders." *Biological Psychiatry*. Published ahead of print, July 10, 2024.

Hasson, U., I. Levy, M. Behrmann, T. Hendler, and R. Malach. 2002. "Eccentricity Bias as an Organizing Principle for Human High-Order Object Areas." *Neuron* 34: 479–490.

Hebb, D. 1949. "The Organization of Behavior."

Heinzle, J., T. Kahnt, and J.-D. Haynes. 2011. "Topographically Specific Functional Connectivity Between Visual Field Maps in the Human Brain." *NeuroImage* 56: 1426–1436.

Hubel, D. H., and T. N. Wiesel. 1962. "Receptive Fields, Binocular Interaction and Functional Architecture in the cat's Visual Cortex." *Journal of Physiology (London)* 160: 106–154.

Hubel, D. H., and T. N. Wiesel. 1963. "Receptive Fields Of Cells In Striate Cortex Of Very Young, Visually Inexperienced Kittens." *Journal of Neurophysiology* 26: 994–1002.

Hubel, D. H., and T. N. Wiesel. 1970. "The Period of Susceptibility to the Physiological Effects of Unilateral Eye Closure in Kittens." *Journal of Physiology (London)* 206: 419–436.

Koba, C., G. Notaro, S. Tamm, G. Nilsonne, and U. Hasson. 2021. "Spontaneous Eye Movements During Eyes-Open Rest Reduce Resting-State-Network Modularity by Increasing Visual-Sensorimotor Connectivity." *Network Neuroscience* 5: 451–476.

Kreichman, O., and S. Gilaie-Dotan. 2024. "Parafoveal Vision Reveals Qualitative Differences Between Fusiform Face Area and Parahippocampal Place Area." *Human Brain Mapping* 45: e26616.

Lei, H., and R. A. Schuchard. 1997. "Using Two Preferred Retinal Loci for Different Lighting Conditions in Patients With Central Scotomas." *Investigative Ophthalmology & Visual Science* 38: 1812–1818.

Levy, I., U. Hasson, G. Avidan, T. Hendler, and R. Malach. 2001. "Center-Periphery Organization of Human Object Areas." *Nature Neuroscience* 4: 533–539.

Lewis, C. M., A. Baldassarre, G. Committeri, G. L. Romani, and M. Corbetta. 2009. "Learning Sculpts the Spontaneous Activity of the Resting Human Brain." *National Academy of Sciences* 106: 17558–17563.

Liu, L. D., and C. C. Pack. 2017. "The Contribution of Area MT to Visual Motion Perception Depends on Training." *Neuron* 95: 436–446.e3.

Liu, T., S.-H. Cheung, R. A. Schuchard, et al. 2010. "Incomplete cortical reorganization in macular degeneration." *Investigative Ophthalmology & Visual Science* 51: 6826–6834.

Marcus, D. S., M. P. Harms, A. Z. Snyder, et al. 2013. "Human Connectome Project Informatics: Quality Control, Database Services, and Data Visualization." *NeuroImage* 80: 202–219.

Marcus, D. S., J. Harwell, T. Olsen, et al. 2011. "Informatics and Data Mining Tools and Strategies for the Human Connectome Project." *Frontiers in Neuroinformatics* 5: 4.

Masri, R. A., U. Grünert, and P. R. Martin. 2020. "Analysis of Parvocellular and Magnocellular Visual Pathways in Human Retina." *Journal of Neuroscience* 40: 8132–8148.

Masuda, Y., S. O. Dumoulin, S. Nakadomari, and B. A. Wandell. 2008. "V1 Projection Zone Signals in Human Macular Degeneration Depend on Task, Not Stimulus." *Cerebral Cortex* 18: 2483–2493.

Masuda, Y., H. Takemura, M. Terao, et al. 2021. "V1 Projection Zone Signals in Human Macular Degeneration Depend on Task Despite Absence of Visual Stimulus." *Current Biology* 31: 406–412.e3.

Merabet, L. B., R. Hamilton, G. Schlaug, et al. 2008. "Rapid and Reversible Recruitment of Early Visual Cortex for Touch." *PLoS One* 3: e3046.

Meunier, D., S. Achard, A. Morcom, and E. Bullmore. 2009. "Age-Related Changes in Modular Organization of Human Brain Functional Networks." *NeuroImage* 44: 715–723.

Mitchell, P., G. Liew, B. Gopinath, and T. Y. Wong. 2018. "Age-Related Macular Degeneration." *Lancet* 392: 1147–1159.

Mueller, S., D. Wang, M. D. Fox, et al. 2013. "Individual Variability in Functional Connectivity Architecture of the Human Brain." *Neuron* 77: 586–595.

Newbold, D. J., T. O. Laumann, C. R. Hoyt, et al. 2020. "Plasticity and Spontaneous Activity Pulses in Disused Human Brain Circuits." *Neuron* 107: 580–589.e6.

Palmer, S. M., and M. G. P. Rosa. 2006. "A Distinct Anatomical Network of Cortical Areas for Analysis of Motion in Far Peripheral Vision." *European Journal of Neuroscience* 24: 2389–2405.

Park, B.-Y., K.-J. Tark, W. M. Shim, and H. Park. 2018. "Functional Connectivity Based Parcellation of Early Visual Cortices." *Human Brain Mapping* 39: 1380–1390.

Raemaekers, M., W. Schellekens, R. J. A. van Wezel, N. Petridou, G. Kristo, and N. F. Ramsey. 2014. "Patterns of Resting State Connectivity in Human Primary Visual Cortical Areas: A 7T fMRI Study." *NeuroImage* 84: 911–921.

Ramachandran, V. S., and W. Hirstein. 1998. "The Perception of Phantom Limbs. The D. O. Hebb Lecture." *Brain: A Journal of Neurology* 121, no. Pt 9: 1603–1630.

Romei, V., E. Chiappini, P. B. Hibbard, and A. Avenanti. 2016. "Empowering Reentrant Projections From V5 to V1 Boosts Sensitivity to Motion." *Current Biology* 26: 2155–2160.

Sabbah, N., N. Sanda, C. N. Authié, et al. 2017. "Reorganization of Early Visual Cortex Functional Connectivity Following Selective Peripheral and Central Visual Loss." *Scientific Reports* 7: 43223.

Satterthwaite, T. D., D. H. Wolf, G. Erus, et al. 2013. "Functional Maturation of the Executive System During Adolescence." *Journal of Neuroscience* 33: 16249–16261.

Sele, S., F. Liem, S. Mérillat, and L. Jäncke. 2021. "Age-Related Decline in the Brain: A Longitudinal Study on Inter-Individual Variability of Cortical Thickness, Area, Volume, and Cognition." *NeuroImage* 240: 118370.

Sen, S., N. N. Khalsa, N. Tong, et al. 2022. "The Role of Visual Experience in Individual Differences of Brain Connectivity." *Journal of Neuroscience* 42: 5070–5084.

Slotnick, S. D., and R. C. White. 2013. "The Fusiform Face Area Responds Equivalently to Faces and Abstract Shapes in the Left and Central Visual Fields." *NeuroImage* 83: 408–417.

Sparling, T., L. Iyer, P. Pasquina, and E. Petrus. 2024. "Cortical Reorganization After Limb Loss: Bridging the Gap Between Basic Science and Clinical Recovery." *Journal of Neuroscience* 44: e1051232024.

Steinman, R. M. 1965. "Effect of Target Size, Luminance, and Color on Monocular Fixation*." *Journal of the Optical Society of America* 55: 1158.

Striem-Amit, E., S. Ovadia-Caro, A. Caramazza, D. S. Margulies, A. Villringer, and A. Amedi. 2015. "Functional Connectivity of Visual Cortex in the Blind Follows Retinotopic Organization Principles." *Brain* 138: 1679–1695.

Sunness, J. S., T. Liu, and S. Yantis. 2004. "Retinotopic Mapping of the Visual Cortex Using Functional Magnetic Resonance Imaging in a Patient With Central Scotomas From Atrophic Macular Degeneration." *Ophthalmology* 111: 1595–1598.

Timberlake, G. T., E. Peli, E. A. Essock, and R. A. Augliere. 1987. "Reading With a Macular Scotoma. II. Retinal Locus for Scanning Text." *Investigative Ophthalmology & Visual Science* 28: 1268–1274.

Tootell, R. B., J. B. Reppas, A. M. Dale, et al. 1995. "Visual Motion Aftereffect in Human Cortical Area MT Revealed by Functional Magnetic Resonance Imaging." *Nature* 375: 139–141.

Toyoizumi, T., M. Kaneko, M. P. Stryker, and K. D. Miller. 2014. "Modeling the Dynamic Interaction of Hebbian and Homeostatic Plasticity." *Neuron* 84: 497–510.

Tropea, D., G. Kreiman, A. Lyckman, et al. 2006. "Gene Expression Changes and Molecular Pathways Mediating Activity-Dependent Plasticity in Visual Cortex." *Nature Neuroscience* 9: 660–668.

Turrigiano, G. G. 1999. "Homeostatic Plasticity in Neuronal Networks: The More Things Change, the More They Stay the Same." *Trends in Neurosciences* 22: 221–227.

Weiner, K. S., M. A. Barnett, N. Witthoft, et al. 2018. "Defining the Most Probable Location of the Parahippocampal Place Area Using Cortex-Based Alignment and Cross-Validation." *NeuroImage* 170: 373–384.

Yan, W., Y.-R. Peng, T. van Zyl, et al. 2020. "Cell Atlas of the Human Fovea and Peripheral Retina." *Scientific Reports* 10: 9802.

Yu, H.-H., R. Verma, Y. Yang, et al. 2010. "Spatial and Temporal Frequency Tuning in Striate Cortex: Functional Uniformity and Specializations Related to Receptive Field Eccentricity." *European Journal of Neuroscience* 31: 1043–1062.

Zarbin, M. A. 2004. "Current Concepts in the Pathogenesis of Age-Related Macular Degeneration." *Archives of Ophthalmology* 122: 598–614.

Zhen, Z., X.-Z. Kong, L. Huang, et al. 2017. "Quantifying the Variability of Scene-Selective Regions: Interindividual, Interhemispheric, and Sex Differences." *Human Brain Mapping* 38: 2260–2275.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.