

1 **Training in cortically-blind fields confers patient-specific benefit**
2 **against retinal thinning after occipital stroke**

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25 **Abstract**

26 **Purpose:** Damage to the adult primary visual cortex (V1) causes vision loss in the contralateral
27 hemifield, initiating a process of trans-synaptic retrograde degeneration (TRD). Here, we
28 examined retinal correlates of TRD using a new metric to account for global changes in inner
29 retinal thickness, and asked if perceptual training in the intact or blind field impacts its
30 progression.

31 **Methods:** We performed a meta-analysis of optical coherence tomography (OCT) data in 48
32 participants with unilateral V1 stroke and homonymous visual defects, who completed clinical
33 trial NCT03350919. After measuring the thickness of the macular ganglion cell and inner
34 plexiform layers (GCL-IPL), and the peripapillary retinal nerve fiber layer (RNFL), we computed
35 individual laterality indices (LI) at baseline and after ~6 months of daily motion discrimination
36 training in the intact- or blind-field. Increasingly positive LI denoted greater layer thinning in
37 retinal regions affected *versus* unaffected by the cortical damage.

38 **Results:** Pre-training, the affected GCL-IPL and RNFL were thinner than their unaffected
39 counterparts, generating LI values positively correlated with time since stroke. Participants
40 trained in their intact-field exhibited increased $LI_{GCL-IPL}$. Those trained in their blind-field had no
41 significant change in $LI_{GCL-IPL}$. LI_{RNFL} did not change in either group.

42 **Conclusions:** Relative shrinkage of the affected *versus* unaffected macular GCL-IPL can be
43 reliably measured at an individual level and increases with time post-V1 stroke. Relative
44 thinning progressed during intact-field training, but appeared to be halted by training within
45 the blind field, suggesting a potentially neuroprotective effect of this simple behavioral
46 intervention.

48 **Non-standard Abbreviations and Acronyms:**

49 CB – Cortical Blindness

50 OCT – Optical Coherence Tomography

51 LI – Laterality Index

52 dLGN – dorsal lateral geniculate nucleus

53 GCL-IPL – Ganglion Cell Layer-Inner Plexiform Layer

54 RGC – Retinal Ganglion Cell

55 HIS - Hemianopia Intervention Study

56 HVF – Humphrey Visual Field

57 OU – Oculus Uterque (both eyes)

58 OS – Oculus Sinister (left eye)

59 OD – Oculus Dextrus (right eye)

60 SEM – Standard Error Mean

61 PMD – Perimetric Mean Deviation

62 ST_{BF} – Mean Sensitivity of Blind Field

63 TRD – Trans-synaptic Retrograde Degeneration

64

65

66 Introduction

67 Cortical blindness (CB) following unilateral damage to the primary visual cortex (V1) or its
68 immediate afferents presents as a homonymous, contra-lesional visual field defect. Although
69 partial recovery can occur spontaneously in the first few months after damage¹⁻⁴, there are no
70 widely-accepted, validated treatments for the resulting visual defect⁵. Standard of care remains
71 “no intervention”, although occasionally, patients are prescribed compensatory (e.g. saccadic)
72 training or substitution (e.g. prism lenses) therapies⁶⁻⁹. Research also continues to show that
73 visual perceptual training can partially restore vision in CB, measurable by both clinical
74 perimetry and psychophysical tests of visual performance¹⁰⁻²¹.

75 The importance of developing some form of restorative therapy for CB is further
76 highlighted by burgeoning evidence that once patients reach the chronic stage of >6 months
77 post-stroke, visual field defects do not remain completely stable, as was initially thought²².
78 Instead there appears to be progressive worsening of the perimetrically-defined blind field (BF)
79 without intervention^{11,19,22,23}. The most plausible explanation for such deterioration of the BF
80 over time is TRD, which involves the progressive shrinkage and even die-back of neurons in the
81 early visual pathways²⁴⁻³¹. In humans, structural MRI analyses have shown that the optic tract
82 ipsilateral to occipital cortex damage is often reduced in size^{25,29,30,32-35}, as are the thicknesses
83 of the ganglion cell and nerve fiber layers in corresponding regions of the retina in each eye<sup>24,28-
84 32,34,36-45</sup>.

85 Retinal ganglion cells (RGCs) are responsible for pre-processing and ferrying visual
86 information to the rest of the visual system. As such, their loss or dysfunction could significantly
87 threaten the potential to recover visual functions in participants with V1 damage. Specifically,

88 retinal neurons in the therapeutically-targetable retino-geniculate-striate pathways susceptible
89 to trans-synaptic retrograde degeneration (TRD) after occipital stroke. Isolating specific
90 consequences of TRD in retinal regions known to synapse with V1-lesion-projecting neurons in
91 the lateral geniculate nucleus is crucial to better understand the relationship between TRD and
92 visual retraining. Approaches to re-train the visual deficit have been shown to confer
93 perimetrically-computed improvements to CB visual fields^{16,46}. However, most literature has
94 focused on benefits to visual perception resulting from visual retraining, with limited
95 knowledge of the effects of training on anatomical substrates of vision^{16,46}. If visual training
96 strengthens existing circuitry or recruits neuronal neighbors, similar to rehabilitation for motor
97 stroke⁴⁷⁻⁴⁹, this could potentially impact retinal cells that provide input to residual visual
98 pathways. As such, the present study asked two questions: 1) what is the extent and time-
99 course of relative thinning in affected *versus* unaffected inner retinal layers in humans with
100 unilateral occipital strokes, and 2) does the stimulation afforded by visual training impact the
101 progression of inner retinal thinning in such stroke patients? To answer these questions, we
102 performed a meta-analysis of optical coherence tomography (OCT) data collected as part of a
103 recently-completed, multicenter, randomized, double-masked, clinical trial titled the
104 “Hemianopia Intervention Study” (HIS; ClinicalTrials.gov identifier, NCT03350919). The HIS
105 clinical trial design and results have been published in detail⁵⁰, but in brief, the trial involved 2
106 pre-training clinic visits to establish eligibility and measure baseline parameters, a 6-months at-
107 home phase during which training was administered to either the intact field (IF) or BF, and 1
108 post-training clinic visit to evaluate the effect of training. The primary outcome measure for the
109 HIS clinical trial was change in the 24-2 Humphrey perimetric mean deviation (PMD) from

110 baseline, with significant improvements reported for people trained in their BF, and not those
111 trained in their IF.⁵⁰ However, the trial also performed OCT imaging and collected
112 measurements of GCL-IPL and RNFL thicknesses in the affected and unaffected retina of each
113 eye in each participant at each time-point. This rich data set provided us a unique opportunity
114 to both measure the extent of TRD in this patient cohort, and analyze the impact of two
115 different of visual training interventions on TRD progression.

116

117 **Methods**

118 **Participants**

119 The HIS trial (NCT03350919) recruited 48 CB participants (see **Table 1** for demographics) at 3 US
120 academic medical centers: 20 at the University of Rochester's Flaum Eye Institute, 18 at the
121 University of Pennsylvania's Scheie Eye Institute and 8 at the University of Miami's Bascom
122 Palmer Eye Institute. All procedures were approved by the Western Institutional Review Board
123 (WIRB#1181904), adhered to the tenets of the Declaration of Helsinki and all participants gave
124 written, informed consent.

125 Participants were between 21 and 75 years of age, with an MRI-confirmed occipital
126 lesion resulting in unilateral homonymous hemianopia. Additionally, their lesions had to have
127 occurred after the age of 18 and a minimum of 90 days prior to screening. Participants were
128 also required to reliably fixate with both eyes during psychophysical testing and clinical
129 Humphrey perimetry, with fixation losses, false-negative, and false-positive rates during
130 perimetry of <20%. Participants were excluded from the study if they presented with any ocular
131 or neurologic disease that would interfere with training. Concurrent use of any other form of
132 visual therapy, or of medications that would affect training were additional exclusion criteria.

133

134 **HIS clinical trial design and training intervention**

135 As mentioned earlier, the HIS clinical trial⁵⁰ involved 2 pre-training clinic visits, a 6-month at-
136 home training phase and 1 post-training clinic visit. While the primary outcome measure was
137 change in the 24-2 Humphrey PMD from baseline to 6 months post-training, OCT data were
138 also collected at each study visit, followed by computerized psychophysical testing focused on

139 instructing participants to correctly perform the training task. Once enrolled, participants were
140 randomized to 2 training arms: intact field (IF) or blind field (BF) training - in a 1:1 ratio, using a
141 permuted block design stratified by site. Participants randomized to these training groups did
142 not differ in age (BF-trained: 56 ± 12 years, range 32-72 years; IF-trained: 61 ± 9 years, range 45-
143 74 years; unpaired t-test $p = 0.0990$, $CI_{95} = -11.83$ to 1.057) or time since stroke (BF-trained:
144 41 ± 82 months, range 3-373 months; IF-trained: 43 ± 72 months, range 3-338 months; unpaired
145 t-test $p = 0.9096$, $CI_{95} = -50.37$ to 44.98).

146 The training intervention was a 2-alternative, forced-choice (2AFC), direction
147 discrimination task using random dot stimuli presented either inside the BF or at a
148 corresponding location in the IF (**Table 1, Supplementary Materials, Supplementary Fig. S1**).
149 During the home training segment, two participants withdrew and their data are not included
150 herein. The two cohorts trained for a comparable number of days (unpaired t-test $p = 0.3598$,
151 $CI_{95} = -43.82$ to 16.27 ; BF-trained: 101 ± 46 days; IF-trained: 115 ± 51 days).

152 During pre-training, in-clinic assessment, participants received instructions and
153 underwent baseline testing with this task within their intact and blind hemifields, with fixation
154 enforced binocularly using an Eyelink Duo Mobile eye-tracker (SR Research, Mississauga,
155 Ontario, Canada). Training locations were selected at sites where performance first dropped to
156 chance (50% correct) after a 1° lateral shift along the x-axis from the intact into the BF. Using
157 the location where performance first drops to chance as a starting point affords proximity to
158 intact circuitry, enhancing the possibility that training may recruit perilesional $V1^{51}$, and/or
159 induce plasticity and re-integration of residual, damaged circuitry. IF-training locations were
160 selected to be mirror-symmetric to those chosen for training in the BF. CB participants were

161 then sent home to train and were asked to perform 300 trials of the 2AFC task once daily for a
162 minimum of 5 days per week, at their assigned, training location. Participants trained at a single
163 location at a time, either in the IF or BF. Once performance improved sufficiently (at least 10
164 sessions at a threshold $<25^\circ$ with a standard deviation of less than 5°), the location was moved
165 1° laterally away from the vertical meridian. Participant performance as a result of these
166 interventions has been published⁵⁰ and will not be repeated here in detail.

167

168 **Humphrey visual field testing and analysis**

169 Each participant's visual deficit was quantified through Humphrey visual field (HVF) perimetry,
170 which was performed twice in both eyes during each study visit. The University of Rochester
171 and the University of Pennsylvania used a Humphrey Field Analyzer II-i, and the University of
172 Miami used a Humphrey Field Analyzer 3 (Zeiss Humphrey Systems, Atlanta, GA), with all sites
173 using a 24-2 testing pattern. A white, size III stimulus was presented on a background with a
174 luminance of 11.3 cd/m^2 and thresholds were calculated with the Swedish Interactive Threshold
175 Algorithm (SITA-standard). Participants' visual acuity was corrected to 20/20 for testing, and
176 fixation was controlled using the gaze/blind spot automatic settings. The first test was excluded
177 in both eyes to account for potential learning effects. If the second field set was not deemed
178 reliable or could not be completed, the first set was used instead. Participants who did not have
179 complete, reliable pre- and post-training visual fields were excluded from the present HVF
180 analyses($n=5$); an additional two participants failed to complete training and were also
181 removed from our analysis. Two metrics were derived from HVF tests: the perimetric mean
182 deviation (MD) and the average luminance detection sensitivity across the entire blind

183 hemifield of vision. The MD is calculated by the perimeter using an internal, weighted variance
184 from age-defined normal population values, to estimate the amount of vision lost across the
185 measured visual field. In the present study, sensitivity thresholds from the blind hemifield (ST_{BF})
186 were additionally averaged in each eye to capture deficit-specific changes. We then took the
187 monocular MD and ST_{BF} and averaged them to generate a binocular (OU) version of each
188 metric, for pre- and post-training comparisons, in order to compare with binocularly-computed
189 OCT laterality indices.

190

191 **Optical coherence tomography (OCT) procedures and analysis**

192 Retinal OCT was performed using Cirrus HD machines (Carl Zeiss Meditech) at each study site
193 before and after training. A 512×128 Mac Cube scan was used to examine the ganglion cell
194 and inner plexiform layers (GCL-IPL) around the fovea, and 200×200 optic nerve cube scans
195 were used to examine the retinal nerve fiber layer (RNFL). Scans were excluded if they failed to
196 meet signal strength ≥ 7 in each eye.

197 OCT analyses performed as part of the HIS clinical trial⁵⁰ differed from those performed
198 here in several ways. First, they involved group-level comparisons of GCL-IPL and RNFL
199 thickness changes pre- to post-training across affected and unaffected retinal regions,
200 separated by blind field sector and for each eye independently. Here, for the GCL-IPL, we
201 combined the 2 nasal sectors together, and the two temporal sectors together. Furthermore,
202 after reviewing OCT raw data, we excluded 3 HIS participants due to retinal folding or epiretinal
203 membrane/RNFL detachment severe enough to impact layer thickness measurements. In

204 remaining participants, we then computed a laterality index (LI) to account for individual,
205 baseline thickness variances using the following formula:

$$\textit{Laterality Index} = \frac{(\textit{Intact} - \textit{Blind})}{(\textit{Intact} + \textit{Blind})}$$

206 LI was computed for the GCL-IPL using the 2 nasal and 2 temporal sector values of both eyes,
207 excluding superior and inferior sectors that overlapped the vertical meridian (**Fig. 1A**). The nasal
208 and temporal macular segments of each eye corresponding to the blind or intact hemifield
209 were then averaged together according to each participant-specific deficit. For example, a right-
210 sided visual deficit (left-sided occipital lesion) is represented in the nasal sectors of the right eye
211 and the temporal sectors of the left eye (see example in **Fig. 1A**).

212 Computing a laterality for the RNFL regions impacted by the deficit attempted to
213 account for the crossed and uncrossed fibers in corresponding peripapillary sections⁵² (**Fig. 2A**).
214 Superior and inferior peripapillary regions comprised of uncrossed fibers, and nasal
215 peripapillary regions comprised of crossed fibers represent intact or blind hemifields. For
216 example, the same right-sided visual deficit area described above was represented by the
217 superior and inferior RNFL sectors of the left eye as well as the nasal RNFL sector of the right
218 eye (**Fig. 2A**).

219

220 **Statistical Analyses**

221 Paired t-tests were used to assess within-subject differences. For independent sample
222 comparisons, unpaired t-tests were used when contrasting 2 groups. If standard deviations
223 were not the same in each group, Welch's correction was used. Linear regressions were used to

224 model the relationship between explanatory variables and dependent outcomes, with r values
225 and 95% confidence intervals (CI_{95}) for ρ provided, and significance estimated using a t-test.
226

227 **Results**

228 **Baseline retinal layer thicknesses – effects of time since stroke**

229 Prior to intervention, GCL-IPL thicknesses corresponding to the blind or intact hemifields were
230 significantly different from each other, with the affected hemiretina's GCL-IPL being thinner
231 than the unaffected hemiretina's (**Fig.1B**). We then computed LI to factor out possible global
232 retinal phenomena (e.g., aging-related, metabolic, etc.) in order to better isolate lesion-specific
233 degeneration in retinal regions corresponding to perimetrically-defined visual deficits. The $LI_{GCL-IPL}$
234 was positive, averaging 0.056 ± 0.06 , with a range of -0.068 to 0.29. An LI of 0 would indicate
235 no relative thinning of the lesion-projecting compared to the non-lesion projecting part of the
236 retina, while positive LI values denote thinning in retinal areas representing the blind hemifield
237 relative to those representing the intact hemifield. Importantly, the $LI_{GCL-IPL}$ was positively
238 correlated with time since stroke (**Fig. 1C**), with greater thinning of the affected hemiretina
239 GCL-IPL in participants imaged beyond 12 months post-stroke compared to those imaged prior
240 to this timepoint (**Fig. S2A**).

241 A similar pattern of results was obtained for the peripapillary RNFL, which was thinner
242 for segments carrying RGC axons representing the visual field defect compared to those
243 carrying predominantly intact field fibers (**Fig.2B**). As a result, LI_{RNFL} averaged 0.019 ± 0.04 ,
244 ranging from -0.10 to 0.11. Moreover, just like $LI_{GCL-IPL}$, LI_{RNFL} was positively correlated with time
245 since stroke (**Fig. 2C**), with relative thinning most pronounced beyond 12 months post-lesion
246 (**Fig. S2B**). Overall, these data show clear GCL-IPL and RNFL thinning in regions of the retina
247 carrying either RGC somata, dendrites and/or axons representing blind regions of the visual

248 field. They also show greater thinning at later than earlier timepoints, especially >12 months
249 after occipital stroke.

250

251 **Effect of visual training on GC complex thickness**

252 We next asked whether visual training altered signs of TRD at the level of the retina. Here, we
253 analyzed CB patients who completed 6 months of visual training as part of the HIS clinical
254 trial⁵⁰. As previously reported, global direction discrimination training in the perimetrically-
255 defined BF of CB patients elicits improvements not only on the trained task, but also on
256 binocular (OU) Humphrey perimetry^{11,50}. Consistent with this observation, participants trained
257 in their BF exhibited a systematic improvement in OU MD (**Fig. 3A**). To ascertain if the change in
258 MD was driven by the blind hemifield (*versus* improved ability to perform Humphrey perimetry
259 across the entire test area), we also computed OU ST_{BF} change for the blind hemifield. OU ST_{BF}
260 improved significantly following BF training (**Fig. 3B**), contrasting with a lack of significant
261 changes - for both OU MD and ST_{BF} - in the IF-trained cohort (**Fig. 3D, E**). Notably, a strong
262 correlation exists between MD and ST_{BF} in both cohorts, pre- and post-training (**Fig. 3C, F**).

263 Having established a subtle but differential effect of training on perimetry between the
264 two cohorts, we then asked if - and to what degree - the two types of intervention impacted
265 retinal thinning. For LI_{GCL-IPL}, there was a significant overall increase pre- to post-training across
266 all participants (**Fig. 4A**). However, no detectable changes occurred pre- to post-training overall
267 in LI_{RNFL} (**Fig. 4B**). Separating the two interventions, LI_{GCL-IPL} was significantly larger post-training
268 in those who trained in their intact field (**Fig. 5A**), but not in BF-trained participants (**Fig. 5B**).
269 Furthermore, in the IF training group, raw GCL-IPL thicknesses were significantly lower in the

270 post-training affected hemiretina (**Fig. 5C**). Post-training affected GCL-IPL thicknesses also
271 significantly changed from pre-training in the BF training group (**Fig. 5D**). Additionally, a
272 significant difference in magnitude of change in the affected relative to unaffected hemiretinas
273 was present in IF trained participants and, critically, no such difference was found in BF trained
274 participants (**Fig. 5E**). However, we fail to reject the null hypothesis that the pre-post
275 differences of the affected hemiretinas differ by training type (**Fig. 5E**).

276 When assessing the impact of training on the RNFL, no significant change in L_{RNFL} was
277 found in either group pre- to post-training (**Fig. 6A, B**). Similarly, no significant pre-post training
278 differences were observed in either training cohort for raw RNFL thickness (**Fig. 6C, D**).
279 Additionally, when assessing pre-post change, no significant differences were seen between or
280 within training groups (**Fig. 6E**).

281 Consistent with these findings, changes in ST_{BF} and $L_{GCL-IPL}$ were directly [and inversely]
282 correlated in those trained in their blind hemifield (**Fig. 7A**), but not in those trained in their IF
283 (**Fig. 7B**). No significant correlations were observed between changes in ST_{BF} and L_{RNFL} in either
284 training cohort (**Fig. 7C, D**).

285

286

287 **Discussion**

288 The present study asked – for the first time – whether visual stimulation provided by perceptual
289 training alters the progression of retinal ganglion cell layer complex thinning after stroke
290 damage to the occipital cortex in adult humans. First, we confirmed prior reports of relative
291 thinning in the affected *versus* unaffected retinas’ GCL-IPL and RNFL after unilateral V1
292 damage^{28,29,31,32,34,36,39,41,53} using non-invasive OCT imaging. Second, the spread of post-stroke
293 times at participant enrollment allowed us to define a time-course for this thinning. Finally, we
294 now provide evidence that a simple behavioral intervention slows or blocks the progression of
295 relative GCL-IPL thinning whereas comparable stimulation of the intact hemifield of vision fails
296 to do so.

297

298 **Occipital damage causes variable, progressive shrinkage of the GC complex**

299 Our observations showed that the largest, positive deviations from 0 in $L_{\text{GCL-IPL}}$ and L_{RNFL}
300 occurred beyond 12 months post-stroke. While some deviation in $L_{\text{GCL-IPL}}$ (but not L_{RNFL}) was
301 also observed in our earliest participants, there was considerable inter-individual variability
302 which precluded a significance analysis in the present cohort. Large deviations of LI values from
303 0 were previously observed for optic tract volumes using structural magnetic resonance
304 imaging, starting from ~6 months post stroke, albeit also with large inter-individual variability³⁵.
305 This time-course differential makes some sense if one considers that the optic tract contains
306 the distal portions of RGC axons, right before they synapse in the dorsal lateral geniculate
307 nucleus. These distal axons, being closer to the V1 lesion site, might exhibit earlier signs of
308 target loss and degeneration than the cell bodies and dendritic arbors of the parent cells in the

309 retina, but once again, a larger sample size earlier post-stroke would be needed to make this
310 determination from a statistically-valid standpoint.

311 As stated earlier, a positive LI reflects a relative thinning of the lesion-projecting vs.
312 intact-hemisphere-projecting portions of the macular GCL-IPL. This relative thinning could be
313 attributable to shrinking of the RGC soma, cell death, and/or changes in cell branching;
314 similarly, relative thinning in the RNFL could result from RGC axonal loss or shrinkage or
315 both^{24,28,29,32,34,37,40,53-55}. Though past studies show that RGCs are ultimately lost over time after
316 occipital damage^{28,29,31,55,56}, there is also evidence that RGCs change size based on metabolic
317 activity or the beginning stages of apoptosis^{57,58}. As such, slowing or even reversing retinal
318 thinning may be possible if intervention occurs prior to significant cell death.

319 Importantly, both the GCL-IPL and RNFL were previously reported to thin with increasing
320 age in humans⁵⁹, a fact confirmed in the present data set, and is likely related to cell loss and/or
321 shrinkage (**Fig. S3**). However, it is important to note that by computing and tracking changes in
322 LI rather than raw layer thicknesses, we were able to dissociate the impact of the occipital
323 stroke and subsequent training interventions, from this natural trend.

324

325 **Visual training blocks the progression of *relative* GC complex thinning**

326 In spite of initial retinal ganglion cell complex thinning at baseline, participants who trained in
327 their BF for 6 months showed improvements in binocular performance metrics derived from
328 Humphrey perimetry and seemed to avoid the increase in $LI_{GCL-IPL}$ that occurred in participants
329 randomized to train in their IF. While GCL-IPL thickness decreased in both groups, the change in
330 GCL-IPL thickness of the affected relative to the unaffected hemiretina was only significant in

331 the IF-trained participants. Coupled with a failure to reject the null hypothesis in pre- to post-
332 training differences of $LI_{GCL-IPL}$ in the BF-trained group, this suggests a subtle but significant
333 effect of training location on GCL-IPL thinning within a given patient, which is lost when
334 comparing effects across individuals. The inherent variability in OCT layer thickness in small
335 cohorts makes it difficult to compare groups directly. This is further complicated by variability
336 introduced due to time-dependent TRD. In the future, increasing the sample size to increase
337 sensitivity is crucial to better understanding the anatomical underpinnings of visual retraining.
338 This is a difficult endeavor with two critical limitations 1) CB participants with lesions limited to
339 the occipital cortex are rare and challenging to recruit and 2) once recruited, CB participants
340 require time-intensive testing and evaluation. Alleviating these limitations would require
341 expansion of collaborating facilities and personnel, as well as relaxing inclusion and exclusion
342 recruitment criteria, leading to a more heterogenous patient population. However, despite
343 current limitations these within-group comparisons provide novel insights into training-
344 dependent changes within the early visual pathway.

345 These surprising observations suggest first that OCT imaging and our derived LI metric is
346 a sensitive biomarker for assessing the impact of training in post-stroke CB patients. Just as
347 importantly, it also suggests that an intervention which locally stimulates RGCs in a retinal area
348 deprived of several key central targets may benefit the structural integrity of these residual
349 cells. In turn, this may increase the likelihood that these neurons are retained long-term in the
350 residual visual circuitry, perhaps providing the neural substrates of training-induced recovery of
351 visual functions seen deeper into the visual deficit⁵¹. Conversely, training within the intact field
352 locally stimulates circuits that are not directly affected by V1 damage-mediated TRD^{26,29,43}.

353 Though V1 areas of both hemispheres representing visual information along the vertical
354 meridian are connected via callosal axonal projections⁶⁰, notable due to the training locations
355 of these participants, these interhemispheric connections do not appear to provide enough
356 benefit to anterior portion of the visual pathway to be observable at the level of the retina.

357 So, what could underlie the stabilization of $L_{GCL-IPL}$ in BF-trained participants? As
358 mentioned earlier, damaged RGCs undergo changes in their dendritic arbors in the IPL^{61,62} and
359 in supporting cells, such as muller glia^{57,58,63}, which span the entire thickness of the retina.
360 Training in the BF could increase the energy demands of stimulated RGCs, and by consequence,
361 of surrounding supporting cells, in turn causing structural changes manifested as a cell-size
362 increase and/or shrinkage prevention^{36,57}. Changes in surviving RGCs are of course likely
363 occurring in tandem with RGC loss due to retrograde degeneration – a phenomenon on which
364 visual training's effects are unknown.

365 An important question emerging from the present results is whether the stabilization of
366 the $L_{GCL-IPL}$ persists after BF training stops. If this phenomenon relies on increased retinal
367 activity due to training, it is possible that physiological mechanisms of TRD will eventually
368 overcome the benefits gained once training ceases. However, it is also possible that if
369 participants incorporate their regained visual abilities into everyday usage, they could maintain
370 them and sustain their associated circuits.

371 Finally, we saw no significant changes in L_{RNFL} or RNFL thickness in either training
372 cohort, although several factors likely limited our ability to detect such changes with OCT,
373 including the anatomical complexities of the RNFL in different peripapillary zones, the very
374 small volume of the RNFL overall, our relatively small sample size and inter-subject variability.

375 Future studies using larger sample sizes, more detailed analyses and better imaging resolution
376 will be required to rigorously elucidate the impact of training on the RNFL.

377

378 **Conclusion**

379 In conclusion, the present work investigated the impact of a visual training intervention
380 administered either inside the blind or intact field of occipital stroke patients on the
381 progression of TRD at the level of the inner retina. We found that relative thinning in the GCL-
382 IPL and RNFL mirrored a distinct time-course post-stroke previously reported in the literature.
383 Training for ~6 months with a motion discrimination task inside the blind hemifield appeared to
384 block the progression of relative thinning in the ganglion cell complex. In contrast, this relative
385 thinning proceeded unabated when training was administered to the intact field of vision. Our
386 results provide the first evidence of a greater structural benefit in the retina for a behavioral
387 intervention that stimulates circuitry impacted by V1 damage, over one that stimulates the
388 intact circuitry.

389

390

391

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568

569

570 **Figure Legends**

571

572 **Figure 1. A:** Computation of LI for the GCL-IPL using the nasal (N) and temporal (T) sector GCL-
573 IPL (GI) thickness values of both eyes, excluding superior (S) and inferior (I) sectors since they
574 overlapped the vertical meridian. **B:** Plot comparing GCL-IPL thicknesses in the affected or
575 unaffected hemiretinas (*paired t-test*, $CI_{95} = 5.212$ to 10.60 , $t_{42} = 5.921$, $p = <0.0001$). **C:** Plot of
576 $LI_{GCL-IPL}$ against time since stroke (*linear regression*, $R^2 = 0.2703$, $CI_{95}(y\text{-intercept}) = 0.018$ to 0.057 ,
577 $p = 0.0004$).

578

579 **Figure 2. A:** Computation of LI using RNFL thickness values (R) from superior (S) and inferior (I)
580 peripapillary regions comprised of uncrossed fibers, and nasal (N) peripapillary regions
581 comprised of crossed fibers representing intact or blind hemifields. **B:** Plot comparing affected
582 peripapillary RNFL segments carrying RGC axons representing the visual field defect to
583 unaffected carrying predominantly intact field fibers (*paired t-test*, $CI_{95} = 1.046$ to 5.450 , $t_{42} =$
584 2.977 , $p = 0.0048$). **C:** Plot of LI_{RNFL} against time since stroke (*linear regression*, $R^2 = 0.2293$, $CI_{95} =$
585 0.0004 to 0.0217 , $p = 0.0012$).

586

587 **Figure 3. A:** Plot of pre- and post-training OU MD in BF-trained participants (*paired t-test*, CI_{95}
588 $= 0.098$ to 1.2 , $t_{18} = 2.473$, $p = 0.023$, *mean of differences* $= 0.65 \pm 1.15$). **B:** OU ST_{BF} pre- and post-
589 training following BF training (*paired t-test*, $CI_{95} = 0.177$ to 2.258 , $t_{18} = 2.458$, $p = 0.024$, *mean of*
590 *differences* $= 1.22 \pm 2.16$). **C:** Linear regression of MD against ST_{BF} pre-training: $R^2 = 0.9365$, $CI_{95}(y\text{-}$
591 *intercept*) $= -18.28$ to -16.82 ; post-BF training: $p < 0.0001$; $R^2 = 0.9526$, $CI_{95}(y\text{-intercept}) = -18.21$ to -

592 16.84, $p < 0.0001$. **D:** Plot of pre- and post-training OU MD in IF-trained participants (*paired t-*
593 *test*, $CI_{95} = -0.3284$ to 0.6284 , $t_{18} = 0.6587$, $p = 0.5184$, *mean of differences* = 1.5 ± 0.9926). **E:** OU
594 ST_{BF} pre- and post-training following IF training (*paired t-test*, $CI_{95} = -0.1917$ to 0.8655 , $t_{18} =$
595 1.339 , $p = 0.1972$, *mean of differences* = 0.3369 ± 1.097). **F:** Linear regression of MD against ST_{BF}
596 pre-training: $R^2 = 0.963$, $CI_{95}(y\text{-intercept}) = -17.04$ to -15.87 ; post-IF training: $p < 0.0001$; $R^2 = 0.9481$,
597 $CI_{95}(y\text{-intercept}) = -17.67$ to -16.08 , $p < 0.0001$). ns: not statistically significant.

598

599 **Figure 4. A:** Plot of $Ll_{GCL-IPL}$ pre- to post-training for all participants (*paired t-test*, $CI_{95} = 0.005$ to
600 0.019 , $t_{42} = 3.424$, $p = 0.001$). **B:** Plot of Ll_{RNFL} pre- to post-training of all participants (*paired t-*
601 *test*, $CI_{95} = -0.0015$ to 0.01251 , $t_{42} = 1.572$, $p = 0.1234$). ns: not statistically significant.

602

603 **Figure 5. A:** Plot of $Ll_{GCL-IPL}$ pre- to post-training of participants who trained in their IF (*paired t-*
604 *test*, $CI_{95} = 0.003$ to 0.025 , $t_{22} = 2.837$, $p = 0.0096$). **B:** Plot of $Ll_{GCL-IPL}$ pre- to post-training of
605 participants who trained in their BF (*paired t-test*, $CI_{95} = -0.0008$ to 0.0199 , $t_{19} = 1.916$, $p = 0.07$).
606 **C:** Comparisons of unaffected and affected hemiretina GCL-IPL thicknesses, before and after
607 training in the IF (*unaffected pre- vs post-training: paired t-test*, $CI_{95} = -1.017$ to 0.4516 , $p =$
608 0.4332 ; *affected pre- vs post-training: paired t-test*, $CI_{95} = -3.233$ to -1.093 , $p = 0.0004$). **D:**
609 Comparison of unaffected and affected hemiretina GCL-IPL thicknesses, before and after BF
610 training (*unaffected pre- vs post-training: paired t-test*, $CI_{95} = -0.8943$ to 0.4443 , $p = 0.4902$;
611 *affected pre- vs post-training: paired t-test*, $CI_{95} = -2.691$ to -0.0843 , $p = 0.04$). **E:** Comparison of
612 change in GCL-IPL thickness from pre- to post-training in IF or BF-trained participants
613 (*unaffected vs affected hemiretina in IF-trained subjects, paired t-test*, $CI_{95} = 0.2063$ to 3.555 ,

614 $p=0.009$; unaffected vs affected hemiretina in BF-trained subjects, $CI_{95}=-2.601$ to 0.2762 ,
615 $p=0.1071$; unaffected vs unaffected of both training groups, unpaired t-test, $CI_{95}=-0.9176$ to
616 1.033 , $p=0.9056$; affected vs affected of both training groups, unpaired t-test, $CI_{95}=-0.8438$ to
617 2.395 , $p=0.3391$). A: Affected, UA: Unaffected, ns: not statistically significant.

618

619 **Figure 6. A:** Plot of LI_{RNFL} pre- to post-training of participants who trained in their IF (*paired t-*
620 *test, $CI_{95} = -0.003$ to 0.0123 , $t_{22} = 0.7322$, $p = 0.4718$). B:* Plot of LI_{RNFL} pre- to post-training of
621 participants who trained in their BF (*paired t-test, $CI_{95} = -0.0036$ to 0.0197 , $t_{19} = 1.446$, $p =$*
622 *0.1645). C:* Comparison of unaffected and affected RNFL thicknesses, before and after IF
623 training (*unaffected pre- vs post-training: paired t-test, $CI_{95} = -1.860$ to 0.8163 , $p = 0.4274$;*
624 *affected pre- vs post-training: paired t-test, $CI_{95} = -2.796$ to 0.7962 , $p = 0.2606$). D:* Comparison
625 of unaffected and affected RNFL thicknesses, before and after BF training (*unaffected pre- vs*
626 *post-training: paired t-test, $CI_{95} = -1.714$ to 2.414 , $p = 0.7266$; affected pre- vs post-training:*
627 *paired t-test, $CI_{95} = -2.862$ to 0.3951 , $p = 0.1294$). E:* Comparison of change in RNFL thickness
628 from pre- to post-training in IF or BF-trained participants (*unaffected vs affected in IF-trained*
629 *subjects: paired t-test, $CI_{95} = -2.096$ to 1.139 , $p = 0.546$; unaffected vs affected in BF-trained*
630 *subjects: paired t-test, $CI_{95} = -3.627$ to 0.4601 , $p = 0.1213$; unaffected vs unaffected of both*
631 *training groups: unpaired t-test, $CI_{95} = -1.451$ to 3.195 , $p = 0.4529$; affected vs affected of both*
632 *training groups: unpaired t-test, $CI_{95} = -2.614$ to 2.148 , $p = 0.8441$). A: Affected, UA: Unaffected,*

633 ns: not statistically significant.
634

635 **Figure 7. A:** Plot of change in ST_{BF} against $Ll_{GCL-IPL}$ of participants trained in their IF (*linear*
636 *regression, $R^2=0.0307$, $CI_{95}(y\text{-intercept})=-0.3997$ to 0.8511 , $p=0.4727$). **B:** Plot of changes in ST_{BF}
637 and Ll_{RNFL} in IF-trained participants (*linear regression, $R^2=0.001$, $CI_{95}(y\text{-intercept})=-0.3497$ to*
638 *0.766 , $p=0.8857$). **C:** Plot of change in ST_{BF} against $Ll_{GCL-IPL}$ of participants trained in their BF
639 (*linear regression, $R^2=0.2170$, $CI_{95}(y\text{-intercept})=0.6239$ to 2.723 , $p=0.04$). **D:** Plot of changes in
640 ST_{BF} and Ll_{RNFL} in participants training in the BF (*linear regression, $R^2=0.0196$, $CI_{95}(y\text{-$
641 *intercept})=0.0093 to 2.241 , $p=0.5674$).*****

642

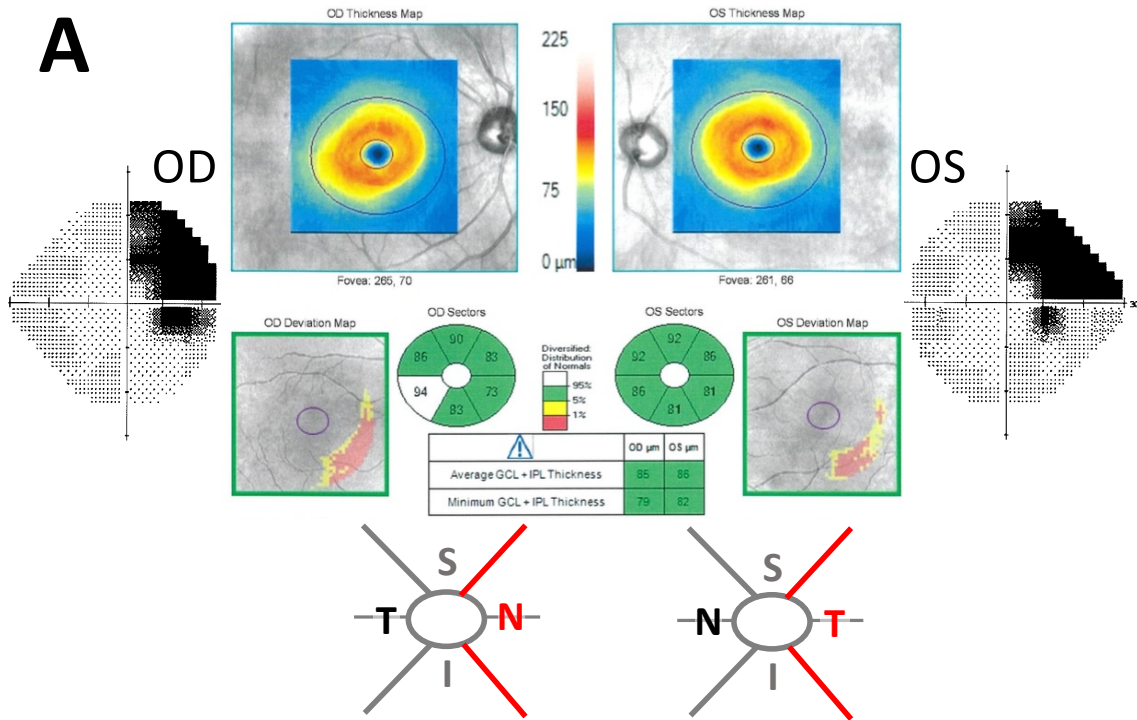
643

644 **Table 1. Participant demographics.** m: male, f: female, R: right, L: left.

Subject code	Sex	Age range (years)	Time since stroke (months)	Affected visual hemifield	Training Group
CB1	m	46-50	32	R	Intact
CB2	f	46-50	13	R	Intact
CB3	m	70-75	20	L	Intact
CB4	m	60-65	61	L	Intact
CB5	m	60-65	43	L	Intact
CB6	m	55-60	105	R	Intact
CB7	f	70-75	338	L	Intact
CB8	m	70-75	10	L	Intact
CB9	m	66-70	6	R	Intact
CB10	m	70-75	4	L	Intact
CB11	m	70-75	58	L	Intact
CB12	f	66-70	16	R	Intact
CB13	f	50-55	24	L	Intact
CB14	m	60-65	130	L	Intact
CB15	m	56-60	13	L	Intact
CB16	m	46-50	63	L	Intact
CB17	m	60-65	8	L	Intact
CB18	f	46-50	15	R	Intact
CB19	m	60-65	20	R	Intact
CB20	m	40-45	5	R	Intact
CB21	m	66-70	3	R	Intact
CB22	m	56-60	4	R	Intact
CB23	m	70-75	6	L	Intact
CB24	m	66-70	60	L	Blind
CB25	f	50-55	38	R	Blind
CB26	f	50-55	18	L	Blind
CB27	m	40-45	15	R	Blind
CB28	m	50-55	373	R	Blind
CB29	m	60-65	5	R	Blind
CB30	m	70-75	47	R	Blind
CB31	m	56-60	8	L	Blind
CB32	m	60-65	47	L	Blind
CB33	m	40-45	11	R	Blind
CB34	m	56-60	4	L	Blind
CB35	f	40-45	10	R	Blind
CB36	m	66-70	105	L	Blind
CB37	m	66-70	36	R	Blind
CB38	m	30-35	5	R	Blind
CB39	f	46-50	5	L	Blind
CB40	f	60-65	3	L	Blind
CB41	m	46-50	14	R	Blind
CB42	m	66-70	3	L	Blind
CB43	m	70-75	6	L	Blind

645

646



$$LI_{\text{GCL-IPL}} = \frac{[(GI_{\text{T_OD}} + GI_{\text{N_OS}})/2] - [(GI_{\text{N_OD}} + GI_{\text{T_OS}})/2]}{[(GI_{\text{T_OD}} + GI_{\text{N_OS}})/2] + [(GI_{\text{N_OD}} + GI_{\text{T_OS}})/2]}$$

(Right deficit)

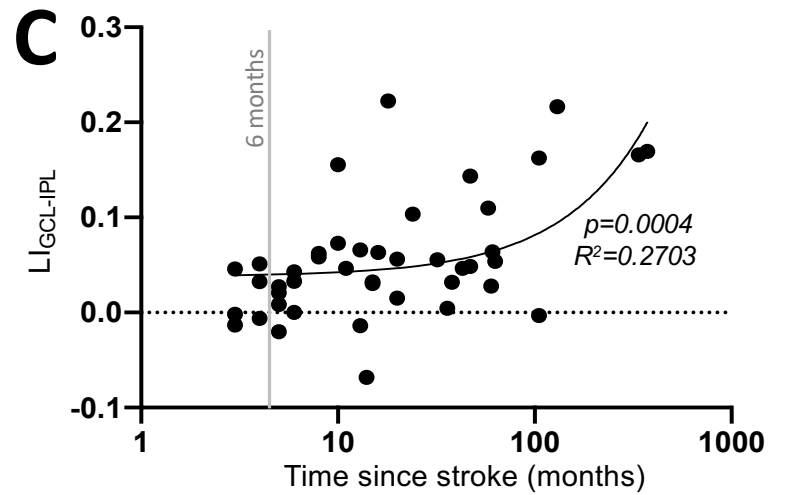
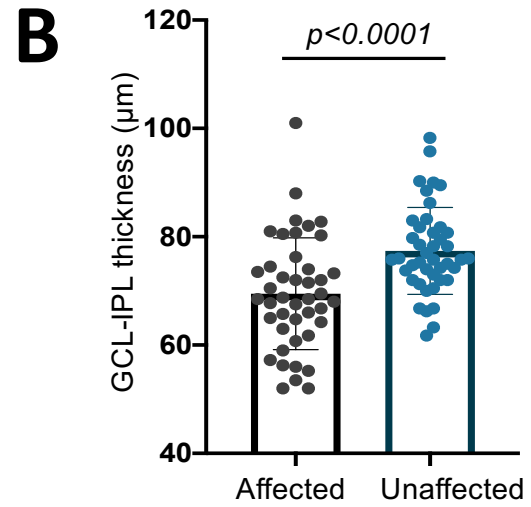


Figure 2

