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Change in visual acuity and retinal structures following Repository Corticotropin Injection (RCI) therapy in patients with acute demyelinating optic neuritis: Improvement in low contrast visual acuity in both affected and contralateral eyes in a single-armed open-label study

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ABSTRACT

Background: Current treatments after an episode of optic neuritis have limited success protecting the retinal nerves and restoring visual function.
Objective: To assess the effectiveness of Repository Corticotropin Injection (RCI) after the onset of optic neuritis.
Methods: Twenty-four adults were treated with RCI within 2 weeks of symptom onset. Seven exams over 400 days measured low- and high-contrast visual acuity (LCVA and HCVA) and spectral domain optical coherence tomography of the retinal structures. Differences between and among affected and contralateral eyes were assessed using linear mixed models.
Results: HCVA improved in the affected eye over the study (36.2 letters to 52.5), and LCVA improved in both the affected eye (1.8 letters to 6.8) and the contralateral eye (8.3 letters to 11.7). These functional improvements occurred concurrent to a thinning in the papillomacular bundle and the ganglion cell, inner plexiform, and retinal nerve fiber layers, while the inner nuclear, outer plexiform, outer nuclear, and photoreceptor layers thickened.
Conclusion: The eyes affected by the ON and treated with RCI improved in both LCVA and HCVA, and unexpectedly LCVA improved in the contralateral eye as well. This functional improvement was mirrored by structural changes in the retina. This study lays the groundwork for future studies to explore potential neuroprotective and neuro-restorative effects of RCI.

1. Introduction

Acute optic neuritis (ON), inflammatory demyelination of the optic nerve, results in rapid loss of visual acuity in the affected eye [1]. ON is closely associated with multiple sclerosis (MS), and up to 50% of MS patients first present with ON [1,2]. While the classic patient experiences spontaneous recovery of much of the high contrast visual loss within 6 months, deficits in vision are still apparent through a variety of measures, especially low contrast visual acuity (LCVA) [3]. The structural sequelae of an event of ON episode are detectable through spectral domain optical coherence tomography (SD-OCT) [4] with these images demonstrating a 20% loss of the retinal nerve fiber layer (RNFL) thickness and ganglion cell thickness, and these structural changes can lead to cortical reorganization shortly after the ON event [5].

The immediate therapeutic goals for patients experiencing ON are twofold: [1] preservation of visual acuity and visual fields [6] and [2] preservation of the structure of the optic nerve and retina, a concept termed "neuro-protection." [7] It has been hypothesized that the cells of the retina and the axons of the optic nerve may also suffer damage during the course of remitting relapsing and progressive MS, even in the absence of a clinical event of ON [8], making the need for neuroprotection more acute.

Current therapies are lacking with respect to both goals. While novel treatments for ON are currently in various stages of clinical trials [9], Treatment for ON is typically intravenous methylprednisolone (IVMP) for 3–5 days, the same treatment protocol often used for acute relapses of MS [10] through protocols developed after the Optic Neuritis Treatment Trial (ONTT) [11]. However, systemic reviews [12] and our own imaging studies have found no evidence that IVMP treatment can limit axonal loss or retinal ganglion cell loss. In addition,

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no therapy exists to improve the deficit in LCVA after an event of optic neuritis, and no therapy has been found to affect LCVA in the clinically unaffected contralateral eye. More broadly, no therapies exist to treat any of the clinically recognized residual defects of MS relapses, with the exception of improvement in the 25-ft walk following 6-aminopyridine therapy [13]. Sodium channel inhibitors have demonstrated some early promise at promoting neuroprotection, but these therapies have not been able to show a structure-function relationship where the putative neuroprotection was associated with improvement in visual function [14].

Repository Corticotropin Injection (RCI) treatment is an alternative therapy approved by health care authorities for acute ON. When delivered through Acthar Gel, RCI is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH1-39) analogs and other pituitary peptides [15], including α-melanocyte stimulating hormones (α-MSH, Mallinckrodt data on file). These peptides are thought to influence the central nervous system through their effects on the G-coupled melanocortin receptor system. The melanocortin system has been associated with anti-inflammatory responses that themselves have been associated with potentially protective responses in patients with MS and other central nervous system disorders [16,17]. RCI stimulates corticosteroid production, and is an agonist for all five melanocortin receptors [18], while other melanocortins do not bind to MC2R [16].

While in recent years RCI has been less commonly used than IVMP, RCI may have pharmacological properties not found with IVMP, which may be relevant to neuroprotection and to recovery of neurological and visual function. Of particular interest is the mode of action of RCI in g-protein coupled melanocortin receptors (MCRS). MCRs are present within the central nervous system, including glial cells and in the retina. The MC5R receptor binds to RCI, while not binding to either alpha-methylprednisolone or prednisolone.

Until recently, *in vivo* demonstration of neuro-protection and neuro-recovery has been elusive in the afferent visual system. Recent advances in spectral domain (SD-OCT) have greatly improved the precision and reproducibility to quantify the thickness and volume of all layers of the retina [19], providing a structural metric to validate neuro-protection [20].

Based upon the ability to identify the clinical onset of optic neuritis, and the non-invasive, non-contact, painless and accurate technology of SD-OCT, this open label single-arm study examined patients with acute optic neuritis who were treated with RCI shortly after the onset of their symptoms. Visual acuity and SD-OCT measurements were examined longitudinally to gather evidence for or against neuro-protection and neuro-recovery and regeneration in both the clinically affected eye as well as the clinically unaffected eye.

2. Materials and methods

2.1. Patient population

Twenty-five patients whose history and presentation were consistent with acute unilateral demyelinating optic neuritis were enrolled. Prospective patients were identified if they presented to the Wills Eye Hospital Neuro-Ophthalmology Service at Thomas Jefferson University within 14 days of the onset of visual symptoms. All patients were older than 18 years of age and provided written informed consent.

Patients were included if they had a prior diagnosis of relapsing remitting MS and excluded if they had a prior diagnosis of secondary progressive MS, or primary progressive MS, or prior diagnoses of systemic lupus erythematosus, mixed connective tissue disease, vasculitis, sarcoidosis, or neuro-myelitis optica. During the study, one patient was eventually diagnosed with a non-arteritic ischemic optic neuropathy (NAION) at a relatively young age and was excluded from the final analyses.

The Wills Eye Hospital Institutional Review Board approved the study with the institutional review board review number 13–350.

2.2. Treatment and ophthalmologic exams

At the time of enrollment, all participants were treated with subcutaneous RCI gel for 5 days of with 80 IU, followed by 10 days at 40 IU.

The study participants underwent ophthalmologic exams seven times over the course of the study: at baseline, 4–7 days after the initiation of RCI, 6–10 days after the completion of RCI, and then 1, 3, 6 months, and 1 year after the completion of RCI. During these examinations, patients' best corrected visual acuity was measured in both eyes. LCVA was quantified by the number of ETDRS Sloan low-contrast sensitivity 1.25% total letters correct, HCVA contrast visual acuity (HCVA) was quantified by the number of ETDRS high-contrast total letters identified correctly. The visual acuity measurements followed the refraction, lighting, and test administration protocols used at our institution for phase 2, 3, and 4 clinical trials.

Over the course of the study, three participants experienced severe adverse events: an allergic reaction requiring Benadryl after the seventh dose of RCI gel; a diagnosis of breast cancer unrelated to the treatment; and a MS relapse. Three additional participants experienced non-severe adverse events: a posterior vitreous detachment with retinal tear (unrelated to treatment); spots in vision, subjective change in hearing, and nausea lasting 3 min after last dose of RCI; and hand numbness (likely related to underlying MS).

2.3. Imaging

At each examination, patients underwent SD-OCT imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany), software version 5.3.2 to measure the thickness and volume of the peripapillary retinal nerve fiber layer (RNFL) [21]. Scans were repeated three times and only high quality (Q values > 20) scans were included. For the peripapillary retinal fiber layer, the software measured twelve sections: average thickness, superior quadrant, temporal quadrant inferior quadrant, nasal quadrant, temporal superior, temporal, temporal inferior, nasal inferior, nasal, nasal superior, and the papillo-macular bundle.

In addition to total macular volume, the following retinal layers were measured: ganglion cells, inner plexiform, inner nuclear, outer plexiform, and outer nuclear. Within each of the layers, the software quantified the thickness for following sections: foveal, temporal inner, superior inner, nasal inner, inferior inner, temporal outer, superior outer, nasal outer, and inferior outer, as well as one measurement of the total volume for that layer. Certified ophthalmic photographers masked to the patients' clinical status adjusted segmentation results manually only when algorithm errors occurred.

2.4. Statistical methods

We estimated whether the eye affected by the ON and treated with RCI differed from the contralateral unaffected eyes with respect to HCVA, LCVA and SD-OCT at the time of symptom onset, and 400 days after the onset of symptoms, and also whether the rate of change of these three traits differed between the affected and contralateral eyes. These analyses were implemented with linear mixed models that controlled for within-patient similarities and correlated measures over time, assuming a linear rate of change.

In order to identify deviations from a linear rate of change, trajectories of BCVA and the SD-OCT measurements were plotted using ggplot2 [22] in R version 3.4.0 [23], and a loess-smoothed [24] non-parametric average of the measurement was superimposed over the individual trajectories.

2.5. Data availability

De-identified data are available in Supplemental Data File 1 (to be provided upon acceptance).

Table 1
Characteristics of the study sample.

N (number of participants)	24
% Female	66.7
Mean age (sd)	35.3 (11.0)
Mean days from onset to first treatment (sd)	5.9 (5.4)
Median days from onset to first treatment (range)	6 (2–13)

3. Results

The demographic characteristics of the twenty-four participants are found in Table 1. The average time from the onset of symptoms to the first treatment was 6 days.

3.1. Best corrected visual acuity

For HCVA, the affected eye demonstrated significantly worse high contrast visual acuity at the time of symptom onset (Fig. 1A and Table 2), with 36.2 letters correct compared to 54.3 in the contralateral eye. The affected/treated eye improved in HCVA with an average of 1.2 letters of improvement over a month with the majority of improvement concentrated in the first 75 days after symptom onset. By the end of the study, the HCVA of the affected eye was still less than the contralateral eye (52.5 letters correct compared to 57.3), this difference was no longer statistically significant at the $p < .05$ level.

For low contrast visual acuity, on average, both the affected/treated eye and the contralateral eye improved over the course of the study (Fig. 1B and Table 2). Fig. 1 suggests that the improvement in the contralateral eye occurs over the 400 days of observation. The affected eye appears to improve rapidly in the first 50 days of the study, and then continues to improve at a slower pace for the rest of the observation period.

For the entire study cohort at the time of symptom onset, the average LCVA of the affected eye is 1.8 letters correct (Table 2), which is significantly less than the 8.3 letters correct in the contralateral eye. By the end of the study, the LCVA of the affected eye is below that of the clinically unaffected eye, but the gap between the affected and contralateral eye decreased (6.8 letters correct compared to 11.7).

3.2. Retinal structures

Fig. 2 displays the trajectories of the total macular volume of both the affected and contralateral eyes, while Table 3 contains the estimates of these values at the time of onset and 400 days after onset, as well as the estimates of how they change through time. The macular volume of the affected eyes was slightly smaller than the contralateral eye at the beginning of the study (8.653 mm^3 compared to 8.706 mm^3) but was significantly less by the end of the study (8.184 mm^3 compared to 8.649 mm^3).

While the overall macular volume decreased over the study period in the affected eye, two patterns emerged in the trajectories of the volumes of each of the retinal layers.

The first trajectory pattern is characterized by a decrease in volume in the affected eye occurring in the first 100 days after onset; after this decrease, the volume of the layer remained roughly steady for the rest of the study. The volumes of the ganglion cell layer (Fig. 3A) and inner plexiform layer (Fig. 3B), and the thicknesses of the retinal nerve fiber layer (Fig. 3C) and the PMB (Fig. 3D) also demonstrate this pattern.

The second trajectory is characterized by an increased thickness immediately after onset that peaked approximately 50 days after onset and subsides by 100 days after onset. The inner nuclear layer (Fig. 4A), outer plexiform layer (Fig. 4B), outer nuclear layer (Fig. 4C), and

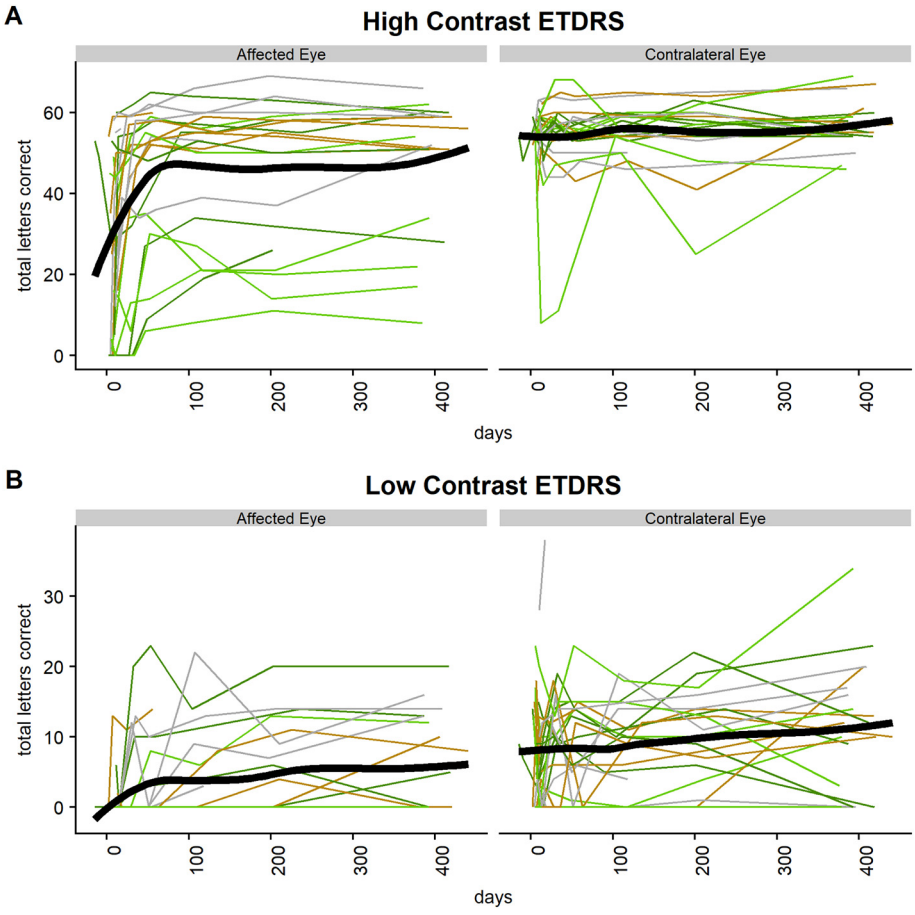

Fig. 1. High and low-contrast best corrected visual acuity.
Individual (green) and average (black) trajectories of visual acuity over the study period for both the affected (left hand side) and contralateral eye (right hand side). High contrast visual acuity is shown at the top (A) and low contrast visual acuity at the bottom (B). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Estimated total letters correct for low-contrast BCVA at time of onset, and day 400, and estimated rates of change in letters correct per month.

	Contralateral eye	Affected eye	*p* for difference
High-contrast BCVA			
Total letters correct at onset (se)	54.3 (2.4)	36.2 (2.4)	< .0001*
Total letters correct/month (se)	0.23 (0.22)	1.22 (0.22)	.0029*
Total letters correct at onset + 400 days (se)	57.3 (3.1)	52.5 (3.1)	.2699
Low-contrast BCVA			
Total letters correct at onset (se)	8.3 (1.0)	1.8 (1.0)	< .0001*
Total letters correct/month (se)	0.26 (0.10)	0.38 (0.10)	.5861
Total letters correct at onset + 400 days (se)	11.7 (1.3)	6.8 (1.3)	.0018*

* *p*-Value < .05.

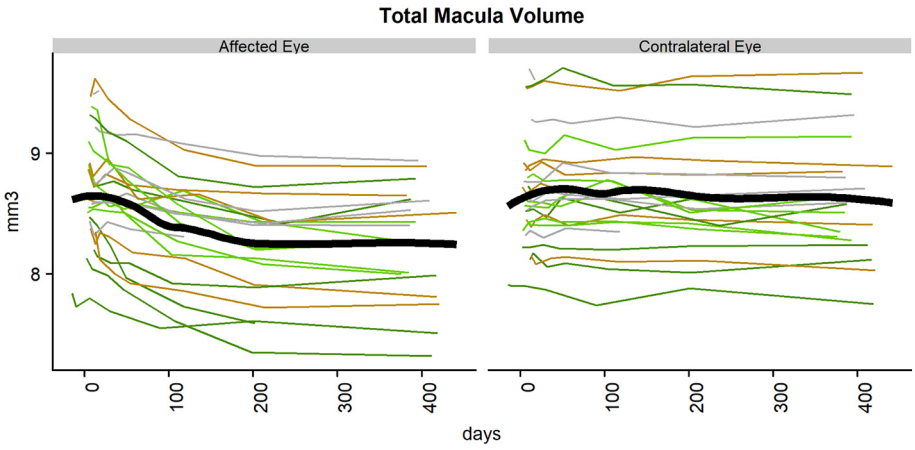

Fig. 2. SD-OCT of Total Macular Volume. Individual (green) and average (black) trajectories of macula volume over the study period for both the affected (left hand side) and contralateral eye (right hand side). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Estimated total macular volume and estimated rates of change in total macular volume over the study.

	Contralateral eye	Affected eye	*p* for difference
mm^3 at onset (se)	8.706 (0.092)	8.653 (0.092)	.0408*
mm^3/month (se)	−0.00428 (0.00288)	−0.03517 (0.00288)	< .0001*
mm^3 at onset + 400 days (se)	8.649 (0.096)	8.184 (0.096)	< .0001*

* *p*-Value < .05.

photoreceptor layer (Fig. 4D) demonstrate this behavior.

For the sake of brevity, the full results of the thicknesses sub-components (the fovea, temporal inner, superior inner, nasal inner, inferior inner, temporal outer, superior outer, nasal outer, and inferior outer) can be found in the supplemental data. The sub-components largely followed the same substantive trends established by the overall volume of that retinal structure.

3.3. Responders in the affected eye

Given that some participants improved in LCVA in their affected eye during the study, we undertook a *post hoc* examination of the baseline characteristics of these participants to identify possible prospective markers of successful response to treatment. Study participants whose affected eye's LCVA at visit seven exceeded the study-wide average (6.8 letters study wide average, seven participants who exceeded this average) were compared to those whose LCVA was below this average.

Table 4 (top) compares the baseline characteristics of the participants whose affected eye ultimately was above average to the participants whose affected eye was below average. The small sample size limited the ability to find statistically significant differences between the groups, but the responders were more likely to be female, younger, and had a slightly longer period between onset and first treatment, although none of these differences are statistically significant. The responders also had more letters correct in both HCVA and LCVA at baseline in their affected eye, although, again, the difference was not statistically significant.

Table 4 (bottom) compares the baseline OCT measurements of the RNFL and GCL (temporal quadrant only) of the affected eye between the improvers and the non-improvers in the affected eye. While in general the improvers began with slightly thicker RNFL and GCL structures (except for the PMB), none of the differences were statistically significant.

3.4. Improvers in the contralateral eye

Unexpectedly, the low contrast visual acuity trajectories of the study participants suggested that some participants improved in their contralateral eye (Fig. 1B). To investigate this observation, we defined "improvers" in the contralateral eye as participants whose LCVA in their contralateral eye at visit seven was at least 7 letters greater than their LCVA at baseline. To better understand this population the average visual acuity and SD-OCT characteristics at baseline were compared between the improvers and the participants who did not improve their contralateral eye vision over the study period. Seven participants demonstrated improvement in the LCVA of their contralateral eye between the time of onset and the end of the study.

Table 5 compares the baseline visual acuity in the contralateral eye of the participants whose contralateral eye improved over the course of the study with those whose contralateral eye did not improve and

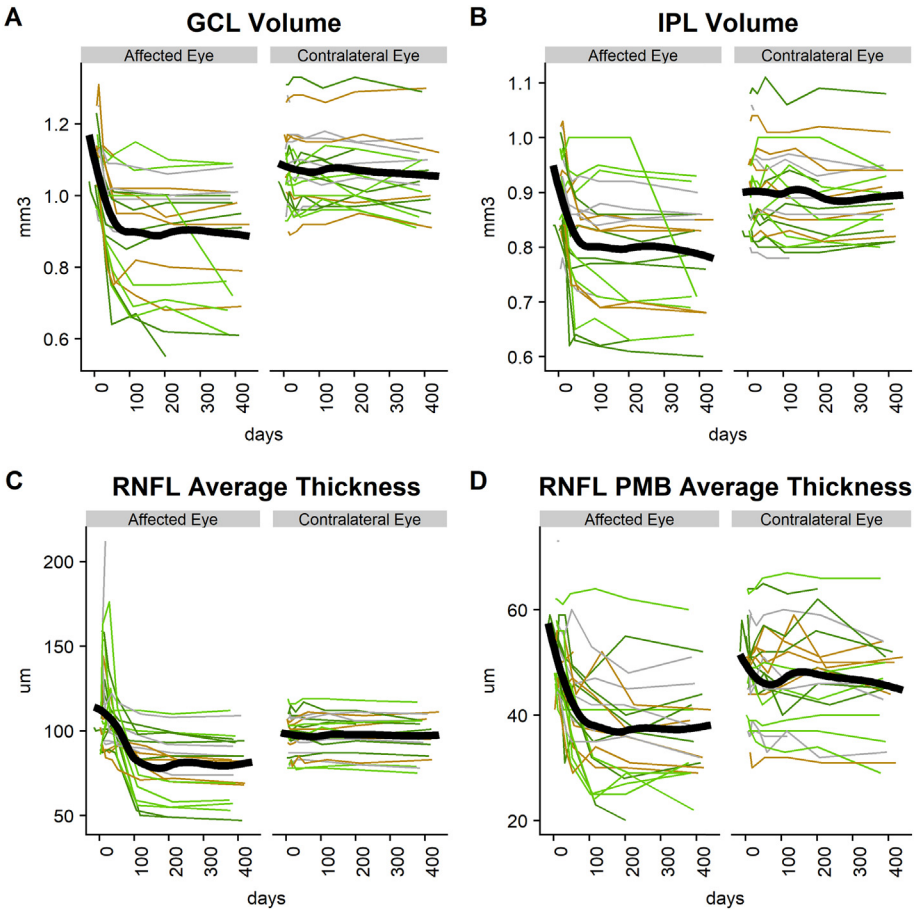

Fig. 3. SD-OCT of the GCL (total volume), IPL (total volume), and RNFL average thickness and PMB average thickness.
Individual (green) and average (black) trajectories of macular structures over the study period for both the affected (left hand side) and contralateral eye (right hand side) in the GCL (A), IPL (B), RNFL (C), and PMB (D). These first set of macular structures all show a thinning over the first 100 days after symptom onset in the affected eye. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

compares the thicknesses of the RNFL between the two groups. No statistically significant differences are seen in either comparison.

4. Discussion and conclusions

This report follows 24 patients with acute unilateral demyelinating optic neuritis treated with RCI within the first 2 weeks of symptom onset. The patients were followed for more than 1 year after the onset of their symptoms and longitudinal changes in HCVA and LCVA and the structure of the retinal were tracked in both the affected and contralateral eyes.

In terms of visual function RCI treatment was associated with an improvement in LCVA in their affected eye by approximately five letters over the course of the follow-up. The improvement began immediately after symptom onset and slowed between 50 and 100 days after symptom onset. The HCVA also improved over the course of the study in the affected eye. While not fully powered to examine this association, no patient characteristics were able to identify those who responded to treatment and those who did not, although high contrast visual acuity was stronger in the responders ($p > .05$); future studies may be designed to better understand whether those with better vision at the time of ON onset may respond more favorably to RCI therapy.

In terms of the structures of the retina, these findings mirror our recent work in vision loss in patients with Lebers Hereditary Optic Neuropathy (LHON) [25]. In this work, we also found that the retinal structures undergo one of two characteristic trajectories after ON: the GCL, IPL, and RNFL thinned for the first 100 days after the onset of symptoms, then remained relatively stable for the remainder of the study period; while in contrast, the INL, OPL, ONL, and photoreceptor layer demonstrated increased thickness after onset, that largely subsiding by 100 days after onset, although typically not fully returning to pre-onset levels. The similarity of the two responses across the two diseases may suggest a possible a shared compensatory mechanism that is a response to the decrease in the inner retinal layers.

Intriguingly, during this study, we observed the improvement in LCVA in the clinically unaffected eye. While larger studies would be needed to confirm this finding, this observation may provide the first level of evidence for neuro-recovery after an optic neuritis episode. This difference between the baseline and last observation LCVA at seven letters represents a clinically significant change [26], and also exceeds the baseline variability in this study. Delay in the latencies of visual evoked responses in clinically unaffected eyes of a patient with acute optic neuritis has been recognized for decades [27]; however, this study is the first to observe LCVA improvement following RCI treatment.

Should additional studies continue to show a positive influence of RCI treatment, additional work will need to be done to understand the mechanism though which RCI is achieving these changes. Previous studies have shown that α-MSH and ACTH can accumulate along the area postrema and penetrate brain parenchyma [28], and α-MSH can suppress inflammation and induce regulatory T-cells [29]. Future work should probe whether these aspects of RCI are responsible for the structure-function relationship described in this current work.

This study generates hypotheses that should be pursued in future work that could expand upon the findings. Next steps should include larger studies with placebo arms and sufficient power to control for multiple comparisons. Such studies would allow investigators to more confidently determine whether any improvements seen in visual acuity are associated with RCI treatment, and be better powered to understand which patients may be more likely to be responsive to this therapy. Additional studies should also focus on additional domains in which RCI treatment may be able to improve multiple sclerosis outcomes, including visual evoked potentials, motor function, and cognitive

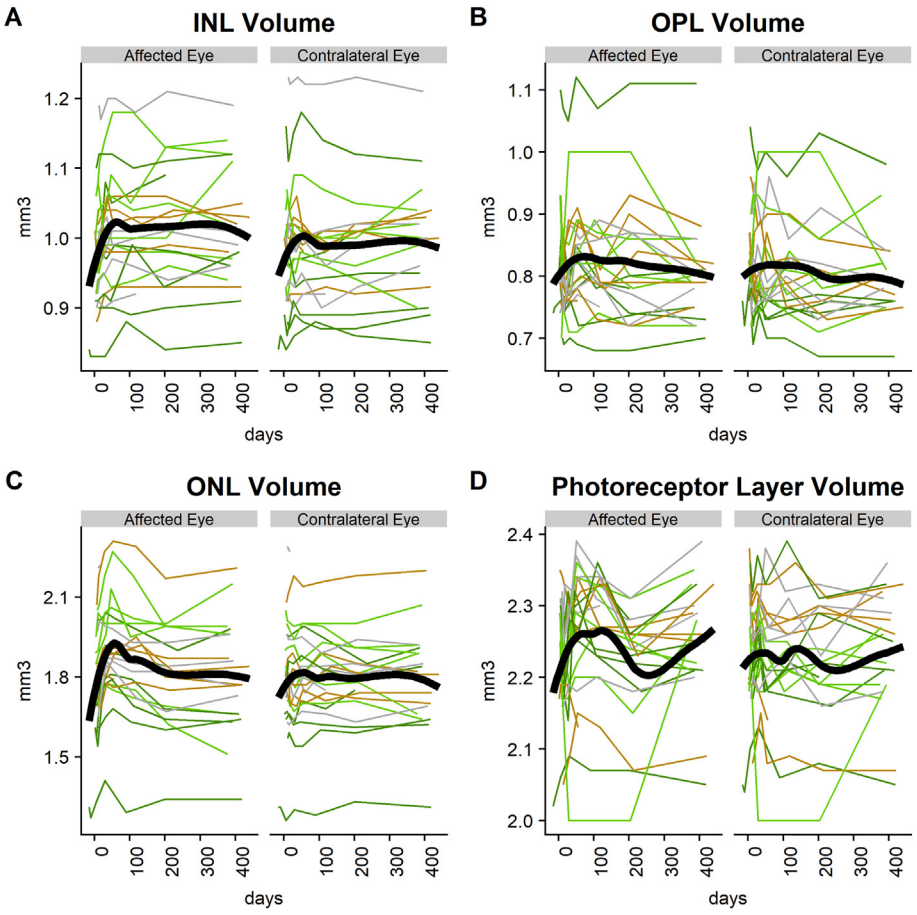

Fig. 4. SD-OCT of the volumes of the INL, OPL, ONL, and photoreceptor layer.
Individual (green) and average (black) trajectories of macular structures over the study period for both the affected (left hand side) and contralateral eye (right hand side) in the INL (A), OPL (B), ONL (C), and photoreceptor layer (D). These second set of macular structures all show a thickening over the first 50 days after symptom onset in the affected eye, followed by a thinning that plateaus around day 100. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

impairment, as these have also demonstrated less than satisfactory improvement following IVMP treatment. Similarly, future studies could include magnetic resonance imaging to identify patients who were most likely to go on to transition to a multiple sclerosis diagnosis in the near future, to better characterize the treated patient population. Of particular interest is whether RCI treatment would have a beneficial effect upon patients who have had a suboptimal improvement in LCVA 1 year following an event of optic neuritis, a time point at which spontaneous

Table 4
Comparison of demographic characteristics, baseline visual acuity, and RNFL and GCL thicknesses in affected eye by affected eye response status.

	Non-responders	Responders	*p* for difference
	n = 16	*n* = 8	
Demographics			
% Female	58.33	87.50	.3700
Mean age	39.42	33.88	.2550
Days from onset to first treatment	6.08	7.88	.1851
Baseline visual acuity in affected eye			
High-contrast BCVA letters correct	20.83	29.50	.4156
Low-contrast BCVA letters correct	0.17	0.75	.4703
RNFL and GCL thickness			
Optic nerve RNFL average thickness	106.83	116.00	.3594
Optic nerve RNFL quadrant superior	137.08	157.50	.2722
Optic nerve RNFL quadrant temporal	65.67	68.75	.5490
Optic nerve RNFL quadrant inferior	143.50	152.50	.5472
Optic nerve RNFL quadrant nasal	81.17	85.62	.6826
Optic nerve RNFL temporal superior	149.08	169.50	.2857
Optic nerve RNFL temporal	65.67	68.75	.5490
Optic nerve RNFL temporal inferior	153.75	160.50	.6176
Optic nerve RNFL nasal inferior	133.08	144.50	.5769
Optic nerve RNFL nasal	81.17	85.62	.6826
Optic nerve RNFL nasal superior	124.92	145.38	.4038
Optic nerve RNFL papillo macular bundle	50.83	49.38	.5342
GCL temporal inner	45.00	47.38	.2062
GCL temporal outer	35.42	38.12	.1503

Characteristics were compared between the two response groups using *t*-tests (*percent female*, *age*, *retinal structures*) and chi-squared statistics (*days from onset* and *number letters correct*).

Table 5
Comparison of demographic characteristics, baseline visual acuity, and RNFL and GCL thicknesses in contralateral eye by contralateral eye improvement status.

	Non-improvers	Improvers	*p* for difference
	n = 17	*n* = 7	
Baseline visual acuity in contralateral eye			
High-contrast BCVA letters correct	55.23	54.71	.8775
Low-contrast BCVA letters correct	8.62	8.71	.9801
RNFL and GCL thickness			
Optic nerve RNFL average thickness	95.77	99.29	.5675
Optic nerve RNFL quadrant superior	120.62	127.71	.5228
Optic nerve RNFL quadrant temporal	64.00	56.14	.0853
Optic nerve RNFL quandrant inferior	127.77	131.86	.6254
Optic nerve RNFL quadrant nasal	70.62	81.86	.1271
Optic nerve RNFL temporal superior	133.08	128.43	.6728
Optic nerve RNFL temporal	64.00	56.14	.0853
Optic nerve RNFL temporal inferior	140.00	133.00	.4756
Optic nerve RNFL nasal inferior	115.77	131.14	.1688
Optic nerve RNFL nasal	70.62	81.86	.1271
Optic nerve RNFL nasal superior	107.92	127.14	.2214
Optic nerve RNFL papillo macular bundle	49.46	43.57	.0773
GCL temporal inner	46.62	44.43	.4897
GCL temporal outer	36.62	35.86	.7490

recovery rarely, if ever, occurs.

Declaration of competing interest

Dr. Sergott is a paid consultant for Mallinckrodt participating in both advisory boards and the speakers' bureau. This clinical research study was funded by an investigator initiated grant from Mallinckrodt who also supplied the study medication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116505.

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