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Visual field changes after a rehabilitation intervention: Vision restoration therapy

Jose G. Romano [a,*], Patricia Schulz [b], Sigrid Kenkel [b], David P. Todd [b]

[a] University of Miami, Miller School of Medicine, Miami, Florida, United States
[b] NovaVision, Boca Raton, Florida, United States

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ABSTRACT

Background: The objective of this study was to determine the effect of a visual rehabilitation intervention on visual field defects in a US cohort. Vision Restoration Therapy (VRT) consists of a specific pattern of stimulation that is directed at the border of the blind field.
Methods: This retrospective study evaluated individuals with homonymous visual field defect from retrochiasmatic lesions treated with 6 modules of VRT. Suprathreshold visual field testing of the central 43×32 was obtained at baseline and after each module. The main outcome measures were the change in stimuli detection and the shift in the position of the border of the blind field. The impact of age, time from injury and type of visual field defect were analyzed.
Results: Among 161 patients, the mean absolute improvement in stimuli detection was 12.8%. The average border shift was 4.87. Improvements of ≥3% was noted in 76% of patients. Absolute change in stimulus detection of ≥3% at mid-therapy was associated with a greater final improvement. Age, time from lesion and type of visual field defect did not influence the degree of field expansion.
Conclusions: VRT improves stimulus detection and results in a shift of the position of the border of the blind field as measured on suprathreshold visual field testing. These results support prior reports and support VRT as a useful rehabilitative intervention for a proportion of patients with visual field defects from retrochiasmatic lesions.

1. Introduction

Although visual field defects after brain injury are common [1] until recently rehabilitation interventions were limited to compensatory strategies, including prisms [2] and saccadic training [3]. In the past decade, reports arising mostly from Germany have suggested that a specific pattern of visual stimulation directed to the border between the seeing and the blind field, Vision Restoration Therapy (VRT), can result in expansion of visual fields in those with brain or optic nerve injury [4,5]. However, some controversy has arisen surrounding the methods employed to evaluate the improvement noted with this intervention [6].

The objective of this study was to determine the effects of VRT on visual field testing in a US cohort in order to assess if the European results were reproducible, and to explore the determinant effects of baseline patient characteristics and of test performance parameters on changes in visual field testing.

2. Methods

This retrospective study reviewed the patient characteristics and visual field information of patients treated with VRT in the US prior to December 2005. In order to be eligible for the study, patients had to have a homonymous visual field defect that affected the central 30° of the visual field caused by a retrochiasmatic insult. Inclusion and exclusion criteria to undergo VRT include the ability to detect stimuli presented on a screen, which necessitated a visual acuity better than 20/200; ability to fixate on a central stimulus, with absence of nystagmus in primary gaze position; absence of significant cognitive deficits that would preclude the completion of therapy; absence of progressive ocular disease expected to advance during the course of therapy; and the absence of photosensitive epilepsy. All clinics that offer VRT have received standardized training. This study involved the review and analysis of the database of patients that underwent this intervention; it was reviewed and approved by the Western Institutional Review Board.

Visual field testing was performed binocularly with suprathreshold stimuli that tested the central 43° (horizontal) by 32° (vertical) field in a 25×19 grid, with 475 test points. The distance between the center of each test point was 1.7°. The stimulus size was 9 pixels, stimulus luminance was 129.5 cd/m^2 with a background luminance 5.9 cd/m^2, and the time of stimulus presentation was 150 ms. Stimulus presentation was random in space and time based on a randomization

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[*] Corresponding author. University of Miami Miller School of Medicine, Department of Neurology. 1120 NW 14th Street, Suite 1357. Miami, FL, 33136, United States. Tel.: +1 305 243 9411; fax: +1 305 243 7081.
E-mail address: jromano@med.miami.edu (J.G. Romano).

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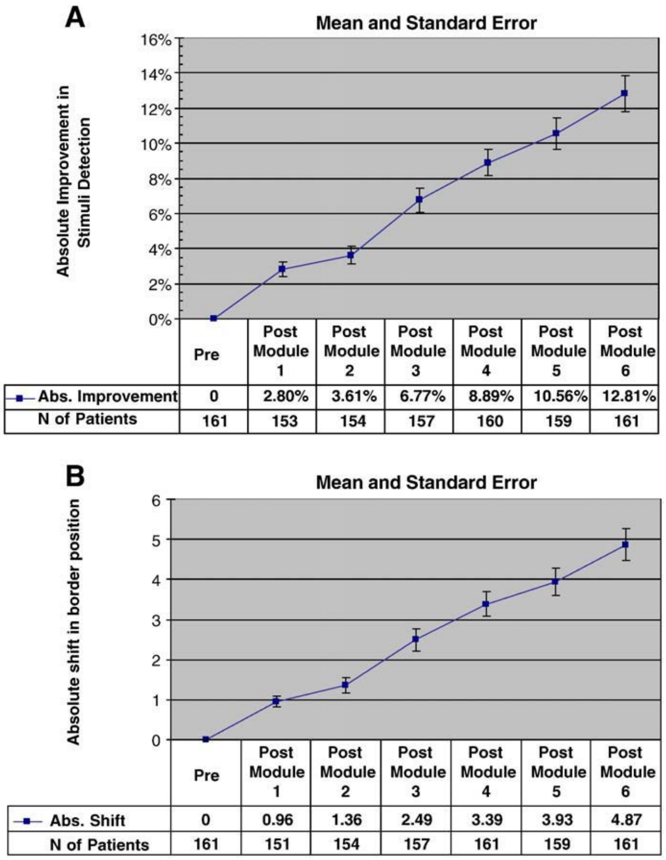

Fig. 1. Time course of improvement in visual field testing during Vision Restoration Therapy. Panel A shows the absolute improvement in stimulus detection over baseline. Panel B represents the absolute shift in the border of the deficit.

paradigm. Fixation was controlled by an isoluminant change in color from green to yellow, or by change in form of a central fixation stimulus. The central fixation target had a luminance of 129.5 cd/m^2, was 9 pixels in size, and had duration of 200 ms. The total number of fixation target changes presented was between 70 and 100 for each diagnostic test. The period of time to respond to an individual stimulus is set to start 150 ms after stimulus presentation and lasts up to 1000 ms after stimulus presentation (in some cases where response times were found to be consistently delayed, the allowable time to respond was increased). If a response occurred before 150 ms or after 1000 ms, that response was classified as a false positive response. This visual field test was repeated 3 times at baseline, and again 3 times after each of 6 modules of therapy. Therefore, patients performed about 21 visual field tests over the course of treatment.

The characteristics of VRT have been previously described [5]. Briefly, the device presents thousands of stimuli to the border of the blind field, while the patient fixates on a central fixation target. After each seen stimulus, patients need to respond by clicking on a button. Therapy evolves over time in that it becomes more challenging, stimuli change from suprathreshold stimuli to near threshold stimuli. Therapy is performed twice daily for 30 min, 6 days a week, for a total of 6 modules; each module takes 4 to 5 weeks to complete.

Baseline data collected included patient age, cause of cerebral insult, time from onset of insult, and type of visual field defect. Visual field defects were classified as complete, incomplete and partial (modified from [7]). A complete homonymous hemianopsia was considered to be present when the homonymous visual field defect respected the vertical meridian, had macular splitting and involved the entire hemifield on the affected side. An incomplete hemianopsia included homonymous defects that respected the vertical meridian, was contiguous from top to bottom of the visual field tested, with or without macular splitting, but spared some visual field in the affected hemifield. A partial visual field defect was not contiguous from top to bottom, and this category included quadrant, sector or scotomatous defects. From the visual field tests performed at baseline and after each module of VRT, the data recorded included the percent of stimuli detected, the shift in the border between the seeing and blind field, the percent of false positive responses, and the percent of fixation point changes detected. The border shift was calculated by averaging the shift from the central vertical meridian to the edge of the blind field at each of the 19 horizontal rows in the visual field grid performed by an automated paradigm. Stimulus detection was expressed as a percentage of stimuli presented in the entire visual field, while the position of the border was defined as the shift from the vertical meridian in the affected hemifield.

The main outcome measure was the absolute change in stimulus detection and the absolute shift in the border between the seeing and the blind field. Responders were defined as those who had an absolute improvement of ≥3% in stimulus detection over baseline; this magnitude of improvement was chosen based on reports showing correlation with functional improvement [8]. Good perimetric test performance was defined as fixation detection ≥95% and false positive rate ≤10%.

Statistical analysis was performed with SPSS. Stimuli detection and border shift pre and post VRT results were analyzed with *t*-tests for paired samples, bivariate Pearson correlations. Impact of performance parameters (fixation accuracy, false positive rate) were explored by Pearson correlation and regression analysis.

3. Results

A total of 161 patients treated at 16 US clinics were included; 58 were female, and the mean age was 58.7 years (range 17 to 89). The mean time from insult to initiation of therapy was 38.4 months (range 1 to 451), with only 4 patients beginning VRT within 3 months, and 15 patients within 6 months of the onset of hemianopsia. The most common cause for the visual defect was stroke (84%), followed by traumatic brain injury (9%) and complications of cranial surgery (3%), and other or unknown causes (4%).

3.1. Stimulus detection and border shift after Vision Restoration Therapy

At the baseline suprathreshold perimetry, the average number of stimuli detected was 57.21%; after therapy this increased to 70.02%, for a 12.8% absolute increase in stimuli detected ($t = 13.032$, $P < 0.001$, CI [10.87%, 14.75%]). At baseline, the border between the seeing and the blind field was situated at a mean of 7.56° from the vertical meridian, and after therapy at 12.43°, representing a 4.87° shift in the border of

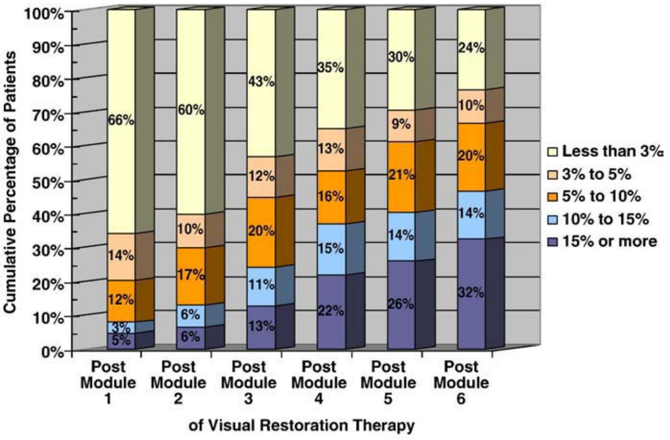

Fig. 2. Cumulative change in absolute stimulus detection change per module of therapy.

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the blind field (t=11.996, P<0.001, CI [4.07°, 5.67°]). Fig. 1 shows the time course of the increase in stimuli detection and the shift in the border. Not all patients improved in a similar manner. Fig. 2 shows the cumulative change over time for stimulus detection. As is illustrated, 76% had at least a 3% absolute improvement in stimulus detection (responders), of which 30% had a ≥3 to 10% increase, and 46% had >10% increase in stimulus detection.

3.2. Effect of baseline demographic factors on visual field change

Table 1 summarizes the effect of baseline factors on the degree of improvement. Age did not appear to correlate with improvement. Although those older than 70 years of age had a slightly lower mean improvement than younger patients (9.9% vs. 13.74%), that difference was not statistically significant. Regarding the time from insult to initiation of therapy, the degree of improvement was similar for all categories, with similar rate of improvement for those with lesions >4 years compared with more recent lesions. The improvement was also similar for all types of visual field defects.

3.3. Early response to therapy and its correlation with final outcome

The pattern of improvement of those who had a significant final improvement in stimulus detection was different from those who improved slightly or did not improve. In an effort to predict during the course of therapy whether early response to VRT would indicate a better final outcome, we divided patients into a group that had a >3% absolute increase in stimulus detection after the 3rd module (i.e. after 3 months of VRT) and compared them with those that had <3%. Those with a >3% increase midway through the treatment course had a significant final absolute improvement in stimulus detection of 18.65%, while the group with <3% absolute increase in stimulus detection after the 3rd module improved by an average of 4.62% by the end of treatment. Regression analysis of improvement at 3 modules as a final predictor of success at the end of therapy revealed an R^2=0.48, SD 0.0902, suggesting that performance after 3 modules predicted 48% of the final outcome. Evaluation of improvement patterns of patients on a case-by-case basis revealed that it is difficult to make individual predictions based on the lack of improvement after 3 modules, as 42% of patients who had not improved by 3 modules had a positive final outcome (>3% increase in stimulus detection) after 6 modules.

3.4. Test performance parameters and their effects on outcome

Two performance factors were evaluated: fixation stimulus detection and false positive rate. Overall, there was excellent fixation detection 96.90%+/−1.26% and low false positives 5.50%+/−2.58% (mean+/−SD) at the final visual field evaluation. The course of these performance parameters is presented in Fig. 3. There was no effect of fixation detection on stimulus detection (Pearson correlation −0.036) but false positives did have a positive correlation (Pearson correlation 0.533, P<0.001). Regression analysis suggested that false positives may explain 28% of the stimulus detection change; fixation performance has negligible effect. Therefore, at least 70% improvement cannot be accounted for by performance parameters.

In order to evaluate the effects of this intervention in those with good test performance parameters, we identified 106 individuals with excellent fixation (≥95%) and low false positives (≤10%). In this group the absolute improvement in stimulus detection was 9.68% and the shift in the border between the seeing and the blind field was 3.76°; of these, 75 individuals (71%) had 3% or greater absolute improvement in stimulus detection (responders). Within the responders there was a 13.29% absolute improvement in stimulus detection and a 5.11° shift in border of blind field. The summary of primary outcome measure for the whole group, those with good performance parameters and for responders within the good test performance group is presented in Table 2.

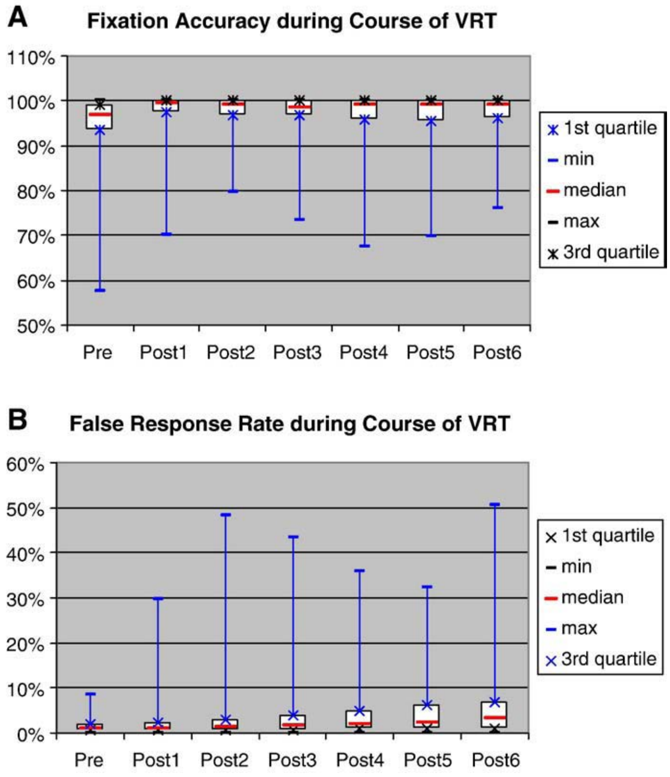

Fig. 3. Time course of visual field performance parameters. The box plot in panel A shows fixation detection and panel B shows false positive rate.

Table 1
Baseline factors and change in stimulus detection

Overall stimulus detection change		N	%
		161	12.81
Age	<50	44	13.92
	50–60	40	13.12
	61–70	38	14.19
	>70*	39	9.90
Time from lesion	<6	15	10.63
	6–12	28	16.32
	13–24	32	11.07
	25–48	31	9.12
	>48*	55	14.71
Type visual field defect	Complete hemi	26	11.04
	Incomplete hemi	85	12.98
	Partial hemi[a,b]	32	11.09

[a] Differences between groups not statistically significant.

[b] In the type of visual field defect, 18 cases had bilateral field involvement and therefore not included in this analysis.

Table 2
Absolute stimulus detection and absolute shift in border position for the whole group, for those with good test performance parameters, and for responders within the good test performance group

	Whole group N=161	Responders ≥3% in whole group N=124	Good test performance N=106	Responders ≥3% with good test performance N=75
Stim. Detection: Absolute Δ	12.81%, t=13.032 P<0.001	16.42%, t=15.226 P<0.001	9.68%, t=9.946 P<0.001	13.29%, t=11.744 P<0.001
Border shift: Absolute Δ	4.87° t=11.996 P<0.001	6.20° t=13.381 P<0.001	3.76° t=8.965 P<0.001	5.11° t=9.772 P<0.001

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4. Discussion

We have shown that in patients with visual field defects from retrochiasmatic insults, VRT results in an increase in stimulus detection and shift in border position on suprathreshold perimetry in 74% of those treated. The average increase in stimulus detection for the group evaluated was 12.8%, and the average shift in the edge of the blind field was 4.87°. Our data did not reveal that demographic factors such as age, time from lesion and type of visual field defect allow a prediction about future success after VRT as the improvement was similar for all categories. In addition, it appears that an increase of >3% in stimulus detection (absolute improvement over baseline) after 3 modules of therapy corresponds to a greater improvement after completion of therapy. This may be an important point for clinicians to consider when evaluating the therapy strategy for those with <3% improvement at 3 modules. However, the lack of improvement after 3 modules does not allow for a precise prediction as some individuals in this group had improvement at the completion of 6 modules of therapy. The reason why some individuals respond, and that this is apparent early on, is as yet unknown. Future studies might be able to identify whether certain lesion size, location, and overall burden of cerebral ischemic disease allows for better patient selection. Finally, the time course of increased stimulus detection appears to be linear for those with significant early response, suggesting that perhaps extending the course of treatment for these individuals may have further benefit.

The data that supports this intervention comes from a number of studies. In a randomized controlled study of 19 cases with retrochiasmatic insults, those treated with VRT had a 3.9% absolute increase in stimulus detection and a 5° shift of the border of the blind field [5]. A second prospective randomized study also studying 19 cases found the same improvement of 3.9% in stimulus detection [9]. A retrospective study of 69 cases reported a 9.9% absolute increase in stimulus detection [10], while a larger retrospective study involving 300 cases also found a 10% change in stimulus accuracy [11]. Other investigators have used alternative repetitive visual stimulation modalities and have documented increased visual perception in animals [12] and humans [13] with visual cortex injury. However, controversy has arisen based on a report of 16 patients treated with VRT [6]. In this study, scanning laser ophthalmoscope microperimetry failed to demonstrate a change in visual fields after therapy. Some editorialists [14] suggested that the changes on suprathreshold perimetry were due to eye movements rather than a true expansion in visual fields. Others argued that the scanning laser ophthalmoscope microperimetry task employed in that study was too difficult to complete but that other visual tasks did improve [8]. In this study we did not have alternative fixation strategies to exclude small eye movements, although the excellent fixation performance argues against eye movements as the main or only cause of the visual field enlargement. This view is supported by other reports that have controlled for fixation with alternative strategies and showed improvement in stimulus detection. An eye tracker study of 15 cases that underwent VRT revealed that patients spent 88.3% of the time within 1° of fixation, and 98.9% of the time within 2° of fixation; these parameters were actually slightly better after VRT compared with baseline, with saccades occurring as frequently into the seeing field as to the blind field [15]. Therefore, the almost 5° shift in the border position observed in the present study is unlikely to result solely from eye movements. A second report employed microperimetry before and after VRT; this perimetric technique presents stimuli directly on the retina using the retinal vessels as a reference in a way that controls for eye movements. That study showed that all 6 patients evaluated had visual field improvement after VRT by microperimetry [16]. Although it is possible that eye movements and false positive responses contribute to a portion of the visual field improvement, as noted in our results, perimetric performance differences account for a minority of the visual field changes.

The present study evaluated the changes in visual field testing with suprathreshold stimuli. Near threshold field testing was not available to us for comparison. However, other studies have compared the suprathreshold perimetry we employed [17], and a 76-point central 30° suprathreshold test (of lesser grid density than the instrument employed in this report) [18,19], and showed comparable accuracy to traditional visual field testing in detecting neuro-ophthalmological disease. Also, previous reports have shown improvement with near threshold testing [5,9,10,15]. Nonetheless, a 16-patient study generated controversy as investigators diverged on the interpretation of the significance of the changes noted in the Automated Tubingen Perimetry [8,20]. One of the reasons for the discrepancy might be methodological differences in the analysis and pre-specified endpoints, but inherent differences in the testing paradigms are also likely to explain differences noted with various perimetric techniques. For example, there is a 6° distance between the center of each test point in a 24-2 or 30-2 Humphrey Visual Field test (Humphrey Field Analyzer II I series, Users Guide, Carl Zeiss, Meditec Inc.; [21]), while this distance is 1.7° in the testing modality employed in this study. Therefore, a 5° shift in the position of the border might not be as apparent with a less dense mapping grid. The improvement of visual fields with microperimetry [16] supports the idea that different perimetric techniques affect the quantification of the visual field change.

The manner by which VRT benefits visual field testing is unclear. Although multiple processes may be involved, and the precise mechanisms remain to be elucidated, it is possible that cortical reorganization may play a role in the detected changes in visual fields. This concept is supported by neuroimaging data: cortical activation changes have been reported after Vision Restoration Therapy on functional MRI [22]; others have shown occipital changes on PET [23], and in BOLD signal with functional MRI in cortically blind individuals after a repetitive visual stimulation task different from VRT [24]. Localized attention may also play a role in improvement of stimulus detection at the border of the hemianopic field [9]. Although cortical activation on neuroimaging does not necessarily equate cortical reorganization, the visual field expansion noted when eye movements were controlled [15,16] supports the notion of cortical reorganization and localized attention as mechanisms responsible for the visual field changes noted after VRT. Regardless of the processes that underlie the visual field changes, it is clear that patients benefit functionally in mobility, collision avoidance, reading, and with specific tasks that require better visual function [10].

The limitations of this study include its retrospective non-controlled nature. In addition, a small percentage of patients started VRT within 6 months from onset of symptoms (9%). Spontaneous improvement may occur early on, mostly in the first 3 months but perhaps as long as within 6 months [25,26]. However, only 4 patients were treated within 3 months and 11 between 3 and 6 months; in addition, the change in stimulus detection was similar for those treated beyond 6 months compared to those treated within 6 months from insult. This suggests that spontaneous improvement is unlikely to explain the visual field changes appreciated with VRT.

Considering these limitations, we believe that this large US cohort of cases treated with VRT enhances the knowledge base of neuro-rehabilitation interventions for those with visual field defects from cerebral insults. We conclude that this intervention results in better stimulus detection and in shift of the position of the border of the blind field as tested by suprathreshold perimetry in a majority of patients with retrochiasmatic insults. We could not identify any baseline factors that allow prediction of response to VRT. Other visual rehabilitation interventions are available [3]. New advances in prism technology may obviate some of the difficulties experienced by previous generation lenses [27], and a small study of optokinetic nystagmus inducing therapy showed improvement in reading speed [28]. VRT adds to the armamentarium that clinicians have at their disposal to help hemianopic patients.

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Conflicts of interest

Jose G. Romano is a member of the Scientific and Medical Advisory Board of NovaVision and provides consulting services for NovaVision under an agreement between the University of Miami and NovaVision. Patricia Schulz and Sigrid Kenkel are currently employed by NovaVision. David P. Todd was employed by NovaVision during the conduct of this study.

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