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Prediction of after-training changes in acuity of amblyopes using the patterned V.E.R.

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Abstract
The Visual Evoked Response (VER) is an electrical response by the brain to visual stimulation. It is one of the evoked potentials used frequently in clinical neurophysiology. It has also begun to offer more and more information to the clinical optometrist. In this paper, we compared the relationship between the VER and Amblyopia. We divided our amblyopia population (5) into two categories, deprivation and non-deprivation (fixation anomaly) amblyopia. We then measured the amplitudes of the VER responses to varied acuity check sizes. Although amplitudes are less reliable than latencies, we averaged the amplitudes over several VER recordings and repeated trials. Then we compared the results of post-visual training VER's with the pre-training VER's. We found that in non-deprivation amblyopia, there was not a significant increase in VER amplitudes after training. However, in the deprivation amblyopes the amplitudes did change after training. Thus, there appears to be an increase in visual cortex cell response after training in the deprivation amblyopia population.

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William M. Ludlam

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PREDICTION OF AFTER-TRAINING CHANGES
IN ACUITY OF AMBLYOPES USING THE
PATTERNED V.E.R.

A SENIOR THESIS
PRESENTED TO
THE FACULTY OF THE COLLEGE OF OPTOMETRY
PACIFIC UNIVERSITY

IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE
DOCTOR OF OPTOMETRY

BY

RANDALL TERRY SCHLEISMAN

DR. WILLIAM M. LUDLAM
ADVISOR

MARCH 1983

Received
3/28/83

William M. Ludlam
Thesis Advisor

A -
ABSTRACT

The Visual Evoked Response (VER) is an electrical response by the brain to visual stimulation. It is one of the evoked potentials used frequently in clinical neurophysiology. It has also begun to offer more and more information to the clinical optometrist. In this paper we compared the relationship between the VER and Amblyopia. We divided our amblyopia population (5) into two categories, deprivation and non-deprivation (fixation anomaly) amblyopia. We then measured the amplitudes of the VER responses to varied acuity check sizes. Although amplitudes are less reliable than latencies, we averaged the amplitudes over several VER recordings and repeated trials. Then we compared the results of post-visual training VER's with the pre-training VER's. We found that in non-deprivation amblyopia, there was not a significant increase in VER amplitudes after training. However, in the deprivation amblyopes the amplitudes did change after training. Thus, there appears to be an increase in visual cortex cell response after training in the deprivation amblyopia population.

We would like to thank the Beta Sigma Kappa fraternity - of which we are both members - for their grant for this study.
One of the most significant discoveries with direct clinical ramifications being researched today is the measurement and assessment of the visually evoked response (VER, VEP, VECP). Because of its noninvasive, objective elicitation coupled with its potential usefulness in a wide array of clinical capacities, it has been grossly overrated in the lay press. However, Sherman\(^1\) states that "the clinical future of evoked potentials can be said, almost without exaggeration, to depend upon only one essential factor. This factor is the degree of reliance which the clinician ascribes to the technique."

The VER is a measure of a cortical response to light that originated at the retina and proceeded along the visual pathway. It is measured from Broadman Area 17. Fully one-third of the visual cortex is concerned with the central 5\(^0\) of the macula.\(^2\) Thus it follows that the VER is essentially a measure of foveal activity and has the potential for determining V.A., refractive error and anomalies affecting the visual pathway and central acuity. Harter and White\(^3\) were the first (1968) to show that there is a relationship between the VER amplitude and the sharpness of contour and size of a patterned stimulus on the retina. Visual acuity has been shown to be monitored by the VER by using patterned stimuli of variable check size.\(^4\) The check size corresponds to different acuity demands. A subtracted component between the patterned and (equal luminance) unpattered stimuli lends a determination as to whether the cortical cells were given enough contrast in order to fire.\(^3,5\)

The VER is a very weak signal of between 3 and 5 u.v. It is readily obscured by neural activity occurring elsewhere. In order to obtain the VER, it is differentially timelocked and allowed to build while the random neural activity cancels itself out.\(^6,7,22\) The VER takes on a two component waveform referred to as an A-B wave. The A component is a negative deflection occurring at between 80 to 100 msec. after the stimulus is presented, while the positive B wave has a latency of between 180 to 200 msec. Thus, the VER\(^8\) is potentially useful in indicating either slowing or attenuation of the visual response as it is transmitted along the visual pathway from the retina to the brain. It takes about 10 msec. for a nervous impulse
to cross a synapse, and there are eight synapses. This is why the A component takes slightly longer than 80 msec. to occur. Thus, any optic nerve disorder, demyelination, or visual tract impairment can be objectively measured by noting the increased latency. The amplitude of the VER has been shown to correlate with visual acuity\textsuperscript{2-6}, binocular vision\textsuperscript{9}, and amblyopia.

This literature review is going to deal with the relationship between the VER and amblyopia. It has been shown very early in the literature\textsuperscript{10} that, by using a patterned stimuli of a given acuity demand, we could then compare this to another patterned stimuli to look for any change in amplitude. Harter and White have shown the greatest amplitude to occur at between 10 and 20 minutes of arc.

When one considers that the visual cortex is composed of "edge detector cells" that fire to specifically oriented signals of good contrast, and that the VER is able to monitor these "findings", the clinician is thus able to alter the patient's VER by the acuity demand or the clarity (refractive error correction). Lombroso, et al.\textsuperscript{10} reported that 50% of their amblyopia subjects had reduced amplitudes to 60' arc check size. Sokol and Bloom\textsuperscript{11}, Yinon, Jakobovitz and Auerbach\textsuperscript{12}, found reduced amplitude responses in all their amblyopes using various small check sizes. Levi\textsuperscript{13}, using 11' checks found that all subjects showed amplitude reduction ranging from 13 to 81% in their amblyopic eyes as compared to their non-amblyopic eyes. These studies compared the responses between the two eyes. More recently\textsuperscript{13,14,15}, researchers have been looking at the VER differences over a range of check sizes and have found diminished or extinguished responses in the amblyopic eye as compared to the normal eye. These amblyopes included strabismic amblyopes with normal foveal fixation, strabismic amblyopes with eccentric fixation and anisometropic (deprivation) amblyopes.

Most all of the studies relating the VER to amblyopia have only dealt with the diagnostic quantification and have not looked at whether the evoked response can be improved after visual training. In an unpublished senior thesis at Pacific University, Gottlieb and Cook\textsuperscript{16} obtained VER's from four amblyopes, proceeded to train and then took a second VER reading before the training was complete (in order to meet the thesis deadline). Although they reported that the ratio between the normal and amblyopic eye's VER did not change significantly after training, they were able to train the
patients to the lower visual acuity level (or beyond) as indicated by the initial VER's in all of the subjects. The important factor here was that the amblyopic population were all fixation-anomaly amblyopes. Ludlam\textsuperscript{6,17} has also found that the initial VER measurement can give an indication as to what the endpoint visual acuity may be after amblyopic visual training. However, this indication is different between fixation anomaly amblyopes and deprivation amblyopes. Ludlam has found that the VER is somewhat more inaccurate with the deprivation (anisometropic)amblyopes than with the eccentric fixation amblyopes. The results tend to be greater than that predicted by the VER. It would then follow that the reason for this inability to predict acuity would be that the amplitude ratio between the amblyopic eye and the non-amblyopic eye would change in the deprivation amblyopia while with the fixation anomaly amblyopia, the ratio would remain constant. This change in the amplitude ratio would approach a more one to one relationship if the amplitudes improve in the amblyopic eye.

Because the VER is a record of cortical edge detector firing, anything which helps to "tune" the edge detectors would elicit higher levels of firing. We cannot differentiate the exact level of cortical cell depression or inhibition because the VER's are "slow mass recordings ... and the VER does not allow localization of the site of visual impairment. These techniques do offer promise in objective assessment of amblyopia, and offer great possibilities for assessment of prognosis"\textsuperscript{13}, however. This "assessment of prognosis" refers to the ability to begin to elicit greater responses from the simple, complex, and hypercomplex cortical edge detectors.

One of the most recent innovations in amblyopic therapy (as well as controversial), that works to "tune" these edge detectors is the Campbell Stripe Therapy approach. When the amblyopic patient's refractive error has been corrected and the poor accommodative response has been taken into account so that the patient can obtain a fairly clear visual input, very positive results have been claimed by Campbell, et al.\textsuperscript{18} and Ludlam\textsuperscript{17} in the treatment of amblyopia. Ludlam has found that acuity is better following training and that this is then reflected in VER responses to smaller check sizes. It can be noted that Ludlam presented twenty-two case studies supporting these suppositions to the 1976 American Academy of Optometry meetings.
We hope to look at two things in this paper. First, following conventional amblyopic training (as well as Campbell Stripe Therapy), does the post-training VER improve in both deprivation and non-deprivation (eccentric fixation) amblyopia? Gottlieb and Cook\(^6\), in their doctoral thesis, found that there did not appear to be any change in VER amplitudes with the non-deprivation amblyopia. We would like to confirm or refute their results, while also determining whether there is a significant improvement in VER amplitudes in deprivation amblyopia as suggested by Ludlam.

INSTRUMENTATION

The VER to be used in this study is the same as that devised by Ludlam and Meyers\(^6\), and followed by Gottlieb and Cook\(^6\). In the Ludlam and Meyers paper is a list of factors (page 170) believed to be necessary for optimal clinical success:

A. Tailoring bandwidth to the frequency spectrum of the VER.
B. Utilization of a slow repetition rate of flashes to avoid interaction of responses to successive flashes.
C. Previewing occipital activity preceding the onset of the flash.
D. Use of a 20-foot refraction distance to avoid proximal effects and a 12° field of view to ensure foveal stimulation despite wandering fixation.
E. The proper type, placement, attachment, and termination of electrodes to enhance signal-to-noise ratio.
F. A reduced number of visual presentations to establish the response for a given dioptric value, thus reducing contamination by subject fatigue and habituation factors.
G. Utilization of a type of response-averaging electronics that minimizes artifactual machine contributions to the reponse.

PROCEDURE

We have obtained five amblyopes from the Pacific University Clinic population. We measured the acuities (whole line and single letter), refractive error, and eccentric fixation using both subjective and objective testing methods. VER's were run on each subject with target check sizes ranging from 9 minutes of arc (20/180) to 1.25 minutes of arc (20/25).

After the first VER measurements were recorded, each subject was trained using the passive and active techniques outlined in Borish's Clinical
Refraction (3rd edition, pp. 1295-1299) along with the Campbell Stripe Therapy. We used the DISCO vision therapy unit with a range between 0.5 cycles/degree to 16.0 cycles/degree which corresponds approximately to between 20/1200 and 20/40. We selected the square wave discs by going two octaves higher than threshold of stripe detection and then working to one octave below threshold. Perceptual, sensory, and motor training were also stressed.

At the end of the research period, visual acuities were measured and VER evaluations were performed. Having completed these steps, we compared the initial VER's to both the results of the treatment and the second VER's for both types of amblyopes.
This acuity level was not initially run on KB
This acuity level was not initially run on AM

This acuity was not run initially on KB, SC
<table>
<thead>
<tr>
<th>RE</th>
<th>Type</th>
<th>Acuity (Whole Line)</th>
<th>Acuity (Single Letters)</th>
<th>VER (Smallest)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before*</td>
<td>After*</td>
<td>Before*</td>
</tr>
<tr>
<td>LB</td>
<td>OD</td>
<td>+4.25 sph</td>
<td>Non-Dep.</td>
<td>20/80</td>
</tr>
<tr>
<td></td>
<td>OS*</td>
<td>+4.25 sph</td>
<td>Non-Dep.</td>
<td>20/80</td>
</tr>
<tr>
<td>AM</td>
<td>OD*</td>
<td>+3.25 -1.50x090</td>
<td>Non-Dep.</td>
<td>20/50</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>+3.00 -1.00x083</td>
<td>Non-Dep.</td>
<td>20/50</td>
</tr>
<tr>
<td>SC</td>
<td>OD*</td>
<td>+4.50 sph</td>
<td>Non-Dep.</td>
<td>20/50</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>+1 sph sph</td>
<td>Non-Dep.</td>
<td>20/50</td>
</tr>
<tr>
<td>KB</td>
<td>OD*</td>
<td>+3.50 -0.75x180</td>
<td>Dep.</td>
<td>20/60</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>+0.25 sph</td>
<td>Dep.</td>
<td>20/60</td>
</tr>
<tr>
<td>JL</td>
<td>OD*</td>
<td>+3.25 sph</td>
<td>Dep.</td>
<td>20/200</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>+0.25 sph</td>
<td>Dep.</td>
<td>20/200</td>
</tr>
</tbody>
</table>

* denotes Amblyopic Eye
TABLE #2
AMPLITUDE RATIOS OF AMBLYOPIC EYE/NON-AMBLYOPIC EYE

<table>
<thead>
<tr>
<th></th>
<th>20/180</th>
<th>20/120</th>
<th>20/90</th>
<th>20/70</th>
<th>20/40</th>
<th>20/30</th>
<th>20/25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
</tr>
<tr>
<td>LB</td>
<td>- 0.52</td>
<td>- 0.83</td>
<td>0.75</td>
<td>0.70</td>
<td>1.11</td>
<td>0.93</td>
<td>0.45</td>
</tr>
<tr>
<td>AM</td>
<td>0.27</td>
<td>0.34</td>
<td>0.43</td>
<td>0.38</td>
<td>0.81</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>SC</td>
<td>- 0.75</td>
<td>1.60</td>
<td>0.58</td>
<td>0.38</td>
<td>0.89</td>
<td>- 1.05</td>
<td>0.87</td>
</tr>
<tr>
<td>KB</td>
<td>- 1.28</td>
<td>0.47</td>
<td>0.48</td>
<td>0.21</td>
<td>0.42</td>
<td>- 0.79</td>
<td>0.51</td>
</tr>
<tr>
<td>JL</td>
<td>0.26</td>
<td>0.47</td>
<td>0.06</td>
<td>0.32</td>
<td>0.00</td>
<td>0.07</td>
<td>0.00</td>
</tr>
</tbody>
</table>

TABLE #3
RATIOS OF B/A

<table>
<thead>
<tr>
<th></th>
<th>20/180</th>
<th>20/120</th>
<th>20/90</th>
<th>20/70</th>
<th>20/40</th>
<th>20/30</th>
<th>20/25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
<td>B/A</td>
</tr>
<tr>
<td>LB</td>
<td>-</td>
<td>-</td>
<td>1.08</td>
<td>1.20</td>
<td>0.95</td>
<td>0.82</td>
<td>1.21</td>
</tr>
<tr>
<td>AM</td>
<td>0.79</td>
<td>1.13</td>
<td>-</td>
<td>0.89</td>
<td>1.51</td>
<td>1.10</td>
<td>-</td>
</tr>
<tr>
<td>SC</td>
<td>-</td>
<td>2.76</td>
<td>0.43</td>
<td>-</td>
<td>0.61</td>
<td>1.08</td>
<td>-</td>
</tr>
<tr>
<td>KB</td>
<td>-</td>
<td>0.98</td>
<td>0.50</td>
<td>-</td>
<td>0.62</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>JL</td>
<td>0.74</td>
<td>0.40</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

- $\bar{x}$ of non-deprivation amblyopes: 0.79 1.95 0.76 1.05 1.02 1.00 1.21 1.11
- $x$ of deprivation amblyopes: 0.74 0.69 0.25 0.00 0.31 0.07 - 0.34

"B" denotes Before Training
"A" denotes After Training
INTERPRETATION OF RESULTS

In our graphs we plot, at each acuity check size that we measured, the relationship between time (weeks) and the ratio between the amplitudes of the amblyopic and non-amblyopic eyes. If the line deflects up or down away from 1.0, this signifies that the ratio of Amblyopic Eye/Non-Amblyopic Eye either increases or decreases respectively. One point that is interesting to note is the variability of amplitudes that manifest themselves on the graphs. Also, at the lower acuity graphs we see that we were unable to elicit a response from JL initially but that with training, minimal but reliable responses are able to be recorded.

In table #1, we outline the visual acuities and refractive errors as well as the lowest check size presented for which a response was elicited. We also differentiate our five amblyopes into deprivation and non-deprivation amblyopes. LB and AM both presented as accommodative esotropes with eccentric fixation. SC, JL, and KB all show anisometropia and amblyopia. It is important to note that SC is being considered as a non-deprivation amblyope rather than a deprivation amblyope even though she shows the anisometropia. The reason for this is that SC had been in training for seven months prior to entering our project. SC was fit with a unilateral contact lens and placed in training. Her visual acuity came down to 20/30. SC discontinued training for two months whereupon the V.A. decreased to 20/50. It was at this point that SC joined our project. Because there were no initial VER's before training, we weren't sure whether the deprivation factor was still causing the amblyopia or whether the poorer acuity (after having attained 20/30 whole line) was a result of an active suppression. After looking at the VER's and her training, as well as the data, she is responding more like the non-deprivation amblyopes and thus has been placed in that category. Refractive error corrections were worn only in the case of LB and SC (part time) at the beginning of training. Contact lenses were prescribed for KB and glasses for AM and JL.

In table #2, we listed the target sizes which we set at 20/180, 20/120, 20/90, 20/70, 20/40, 20/30, and 20/25. For each target size, the difference ratio between the amblyopic eye and the non-amblyopic eye were calculated for both before and after the training. Our initial aim was to run VER's every two to three weeks to map out the progress of training. However, due to the fact that the VER had to be repaired twice (once while the thesis was in progress) and the fact that
we added subjects later on in the program, made this methodology unworkable, especially when one considers the time-frame demands. At this point we decided to run a before and after statistical analysis. This has presented some problems in that not more than one initial VER was run on the subjects. However, it should be noted that because we were still not as comfortable with the VER’s, we spent more time taking more points to establish the exact latencies and amplitudes. What we have done is to average the VERs of late-in-training and after-training to give us a more reliable VER with which to compare to our initial findings. Below this in table #3, we compared the ratio of before/after at each check size to see if there would be any significant improvement in amplitude. We then separated the deprivation from the non-deprivation amblyopes and averaged the overall findings. If the ratio was 1.0, then this obviously would suggest no change in VER amplitudes as a result of amblyopia training. With ratios greater that 1.0, this would imply that VER amplitudes were less after training than before training, thus indicating that training was possibly detrimental. However, if the ratio was less than 1.0, then this implies that amblyopic VER amplitudes were greater after training than before training, thus indicating that the training was beneficial.

Statistically, we used the t-test to evaluate our data. We calculated the findings at the .05 significance level. We divided our patients into non-deprivation and deprivation amblyopes. We used the formula \( \frac{x-u}{\sigma} \). Our findings were: 

- **Non-Deprivation** --- \( \bar{x} = 1.11 \quad \sigma = 0.3711537 \quad 1.11-1.00/0.37 \quad t = 0.296 \)

With a df of 6, we needed 1.94 to reject our \( H_0 \), which would suggest that there is no significant difference at the .05 level. We could not reject \( H_0 \), Therefore there is not a significant difference with the non-deprivation findings.

- **Deprivation** --- \( \bar{x} = 0.34 \quad \sigma = 0.2828231 \quad 0.34-1.00/0.28 \quad t = -2.333 \)

With a df of 5, we need a value of 2.13 to reject \( H_0 \). Since \( t = 2.33 \), we are able to reject \( H_0 \). This means that, at the .05 significance level, our findings are significant, suggesting that the increase in amblyopic amplitude was a result of the amblyopia training.

**CONCLUSION**

The VER is used to assess the physical integrity of the visual pathway.
to the levels of the visual cortex. By placing the recording electrode over Brodmann's Area 17, we are eliciting a response primarily from the foveal (macular) region. Amblyopia is a condition where there does not appear to be any pathological reason for the diminished central acuity. Thus, the VER allows us an opportunity to look at amblyopia and its relationship with the visual pathway up to the level of the visual cortex.

It becomes important for us to differentiate amblyopia into two basic subcategories — deprivation and non-deprivation (fixation anomaly) amblyopia. Hubel and Wiesel and von Noorden et. al. have done much research on visual deprivation in cats and monkeys, and the resultant deprivation amblyopia. They found that the cortical edge detectors (simple, complex, and hypercomplex cells) either did not fire or that their response was attenuated in those animals manifesting deprivation amblyopia.

With regard to the non-deprivation (fixation anomaly) amblyopia, it has been argued that there is not the disruption of the visual pathway at or below the visual cortex, but that this seems to be a higher level mechanism causing the eccentric fixation. Thus, after visual training we would not expect to see the ratio between the VER amplitudes of the amblyopic and non-amblyopic eyes to increase significantly as the subjective visual acuity improves. This, in fact, has been shown to be the case. Gottlieb and Cook, and this study, both find the ratio of before and after training VER amplitudes to not have changed to any significant level.

However, the amplitude ratio did change after training in the deprivation population of our study. This would suggest that maybe the therapy helped to increase the firing rate and efficacy of firing at the cortical level. Although our patient population was small, the numbers generated are significant to the 95% confidence level. Thus, our data suggests that in deprivation amblyopia there appears to be an increase in the amplitude of post-training VER's.
BIBLIOGRAPHY


3. Harter MR, White, CT: Effects of Contour Sharpness and check size on visually evoked cortical potentials. Vision Res. 8(6) 701 - 711, 6/68


