NeuroVision Treatment of Unilateral Amblyopia in Patients Older than 9 Years

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Abstract

Purpose: To investigate the effectiveness of the NeuroVision system, an innovative noninvasive computerized treatment method that uses Gabor patches to stimulate neural connections in the primary visual cortex, for the treatment of amblyopia in patients older than 9 years.

Metohds: Twenty-six patients aged 10 to 59 years with unilateral amblyopia underwent NeuroVision treatment. Best-corrected visual acuity (BCVA) (ETDRS charts), contrast sensitivity (Optec 6500 system), and stereoacuity (Titmus test) were compared before and after visual stimulation training. The presence of strabismus, anisometropia, emmetropia, myopia, or hypermetropia were evaluated against the visual results.

Results: Mean BCVA (logMAR) improved from 0.54 ±0.16 to 0.35 ±0.15 (1.9 lines) ($p=0.004$). Contrast sensitivity improved in all frequencies, with statistically significant differences in the lower ones ($p< 0.05$). Median stereo-acuity improved from 300 to 140 seconds of arc. Patients with strabismus showed greater improvement in BCVA and contrast sensitivity than patients with anisometropia without strabismus. BCVA improved more in patients with emmetropia than in patients with myopia or hypermetropia.

Conclusions: NeuroVision treatment for amblyopia can improve visual performance in older children and adults.

Introduction

Amblyopia is characterized by functional abnormalities in vision,[1-5] including reductions in best corrected visual acuity (BCVA) and contrast sensitivity, in addition to binocular abnormalities, such as impaired stereo-acuity. The reduced vision is attributed to an impairment of the binocular neuronal network within the primary visual cortex.[6] Although itg is considered irreversible after the first decade of life,[7-9] when the developmental maturation of the visual system is completed, several studies have reported an improvement in visual acuity in the amblyopic eye of older patients in whom vision of the better eye was reduced by age-related macular degeneration, cataract, or trauma.[10-15]

NeuroVision™ (NeuroVision Pte Ltd, Singapore) is a novel, noninvasive, patient-specific treatment modality based on the principles of perceptual learning. It is designed to train the neuronal network by stimulating the primitive neuronal populations that are responsible for vision and promoting their spatial interactions.

The individual neurons in the visual cortex function like highly specialized image analyzers or filters, responding only to specific parameters (e.g., orientation, spatial frequency) of a visual image. Visual processing involves their integrated activity, effecting both excitation and inhibition.[16]

The aim of the present study was to evaluate the effectiveness of the NeuroVision system for the treatment of amblyopia in patients older than 9 years.

Patients & Methods

Patients

The study was conducted at the Enaim Laser Refractive Center in Israel. The study group consisted of 26 patients aged 10 to 59 years diagnosed with unilateral amblyopia secondary to strabismus and/or anisometropia, with no ocular disease. None of the patients had diabetes mellitus, epilepsy, migraines, or attention deficit hyperactivity disorder. Each patient or his/her parent/legal guardian signed an

informed consent form prior to enrollment. The study protocol was approved by the local institutional review board.

Clinical Evaluation

On enrollment to the study, patients underwent full medical history evaluation including detailed ophthalmic history with an emphasis on amblyopia-related factors (age at diagnosis, past treatments, family history). This was followed by a comprehensive ocular examination, including evaluation of the anterior and posterior segments, visual acuity with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, and cycloplegic refraction. Ocular movements and ocular alignment for distance and near were assessed by cover, uncover, and alternating cover tests. Contrast sensitivity was measured with the Optec 6500 system (Stereo Optical Co., ILC, Chicago, IL, USA), and stereo-acuity with binocular function were examined with the Worth-4-dot and Titmus stereo-tests (Stereo Optical Co.).

Treatment Procedure

The NeuroVision system employs an interactive, computer-assisted, Internet-based technology. The basic element of visual stimulation is the Gabor patch (Figure 1), which matches the shape and orientation of the primitive receptive fields of the visual cortex and effectively activates them.[17-25] The stimulation-control technique, called lateral masking, involves the display of co-linearly oriented flanking Gabor patches in addition to the target Gabor image.

In the present study, the nonamblyopic eye was occluded during training. The patient, wearing the best optical correction for the amblyopic eye, was initially exposed to two short successive displays of Gabor patches, in a random order on the computer screen and was asked to identify the display that contained the target of Gabor image (Figure 2). An audio feedback system was activated if the patient responded incorrectly. The difficulty of the task was increased in a stepwise manner until the patient reached his or her visual threshold level.

The treatment was applied in 30-minute sessions administered 2-3 times a week. Visual acuity was evaluated at baseline and again after every 10 sessions to monitor progress.

Statistical analysis

To analyze the changes in visual acuity following treatment, logMAR units were used. T test was used to determine the significance of the change in visual parameters before and after treatment, and Pearson correlation test was applied to determine the effect of antiamblyopia patching treatment in childhood and patient age on the response to NeuroVision training. The level of significance was set at $p<0.05$.

Results

The study group consisted of 16 male (61.5%) and 10 female (38.5%) patients with a mean age of 28 ±14.3 years. BCVA in the amblyopic eyes at onset of the study ranged from 0.2-0.7 logMAR (6/9 to 6/45). Mean spherical equivalent was +0.8 D (range -2.65 D - +6.75 D). The amblyopic eye was myopic in 9 patients (34.5%), hypermetropic in 14 (54%), and emmetropic in 3 (11.5%). Eleven patients (42.3%) had anisometropic amblyopia, 8 (30.7%) had strabismic amblyopia, and 7 (27%) had both.

The mean number of NeuroVision sessions was 46, and the average duration of the entire treatment was 3 months.

An improvement in BCVA after treatment was noted in 25 of the 26 amblyopic eyes (96.1%): 20 eyes (76.9%) improved by one or more lines, 9 eyes (34.6%) by two or more lines, and 2 eyes (7.7%) by 5 lines. Mean BCVA (logMAR) increased from 0.54 ±0.16 at baseline to 0.35 ±0.15 (6/24 to 6/15) at the end of treatment; this difference was statistically significant ($p=0.004$) (Figure 3). Interestingly, BCVA in the normal eye improved as well from 0.055 to 0.025 (6/6.6 to 6/6; 0.3 lines).

Median stereo-acuity improved from 300 seconds of arc at baseline (range 40 to 800) to 140 seconds of arc (40 to 400) following treatment (Figure 4).

Contrast sensitivity improved in all frequencies (Figure 5). The improvement in contrast sensitivity in the low frequency scores was statistically significant ($p< 0.05$). Contrast sensitivity also increased in the normal eyes, but to a lesser extent.

Patients who were treated by antiamblyopic patching in childhood (n=14) showed a greater improvement in visual acuity in the amblyopic eye than the patients who were not, but the difference was not statistically significant (1.9 lines of improvement with patch vs. 1.75 without, p=0.7). Younger patients, showed a nonsignificant tendency of greater improvement in visual acuity than older patients (r= -0.144, p=0.4 8).

Outcome of treatment was also compared by the spherical equivalent refraction in the amblyopic eye (Figure 6). Mean age of the hypermetropic group was 30.3 years (n=14); of the myopic group, 30.6 years (n=9); and of the emmetropic group, 16 years (n=3). The emmetropes gained 3.5 lines of vision (0.57 to 0.22 logMAR, p=0.02); the myopes gained 2.3 lines (from 0.58 to 0.35, p=0.0008), and the hypermetropes gained 1.5 lines (from 0.53 to 0.38, p=0.00007).

Mean age of the patients with strabismus (n=8) was 28.4 years. Their mean spherical equivalent was +0.25 D, and 63% (5/8) had been treated by patching in childhood. Mean age of the patients with anisometropia (n=11) was 22.1 years. Their mean spherical equivalent was +1.34 D, and 54% (6/11) had been treated with patching in childhood. NeuroVision treatment was associated with greater improvement in BCVA in the strabismus group (2.3 lines; 0.53 to 0.30 logMAR, p=0.002) than in the anisometropic group (1.5 lines; 0.52 to 0.37 logMAR, p=0.0003) (Figure 7 A,B). The strabismus group also demonstrated better improvement in contrast sensitivity, especially in the low spatial frequencies (Figure 7 C,D).

In our study 10 patients (10/26 - 38%) have reached 1 year follow up. Their visual acuity, contrast sensitivity and stereoacuity were maintained throughout the

whole year, but all the other patients had a shorter follow up time and longer follow up is needed.

Discussion

Amblyopia is defined as a reduction of best corrected visual acuity to 20/30 or less in one eye, or a two-line difference in visual acuity between the two eyes in the absence of any pathology. Studies have established that there is a critical developmental period for amblyopia that probably lasts through more of the first decade of life.[26-28] Its estimated prevalence ranges from 2% to 4%.[5,26]

Amblyopia has traditionally been categorized by the major disorders that may be responsible for its occurrence: strabismic amblyopia, anisometropic amblyopia, and isoametropic amblyopia. Strabismic amblyopia, the most common form, occurs as a consequence of the discrepancy in the images projected to the brain in children with ocular misalignment, and develops in the eye that is consistently deviating. Anisometropic amblyopia occurs as a consequence of the brain's suppression of the blurred retinal image from the more ametropic eye due to an unequal amount of uncorrected refractive error in each eye or due to anisoconia.[5,26] Isoametropic amblyopia develops as a consequence of bilateral visual deprivation due to a very high, but clinically equal, uncorrected refractive error in the two eyes.[5,25] This study included only patients with unilateral amblyopia secondary to strabismus or anisometropia.

NeuroVision technology is based on the assumption that perceptual learning can modify the plasticity of the primitive visual cortex to adapt and retain the changes that have been learned. The stimulus- and task-specificity of perceptual learning[15, 29-31] make it a useful tool for predicting the anatomical site at which learning takes place. Studies have reported an improvement in performance in many visual tasks[15] after NeuroVision training, independent of subject age.[32,33] In adults, changes in spatial interactions have been documented following repetitive

trials with the target-flanker task using Gabor image stimulation.[33] Others reported an increased range of excitatory interactions[18] and reduced short-range inhibitions[22] in normal-sighted subjects, and in monkeys.[34] Further evidence of brain plasticity was provided by studies showing that the visual acuity of the amblyopic eye improves in older adults when vision is reduced in the better eye due to disease or trauma.[10-15]

Treatment of amblyopia in children up to age 9 years consists of prolonged patching or optical degradation of the better eye, which forces the ‘‘lazy eye’’ to function. The efficiency of this practice is negatively correlated with age,[35] and the probability of failure is 7.9 times higher for the 11- to 20-year age group than for 0-3-year group. Although treatment success has been reported in 60% to 70% of children,[35] outcome is difficult to assess because of the various definitions used among studies.[6,8] The results of the present study suggest that NeuroVision treatment can improve visual acuity, contrast sensitivity, and, stereo-acuity in patients more than 9 years old.

Dr. Waring IV and Dr. Durrie[36] treated 26 amblyopic patients who underwent refractive surgery. Half of the patients were subsequently treated by NeuroVision, The other half were a control group and underwent “sham” treatment (eg, a video game) for 2 months. In the NeuroLASIK group, following refractive surgery and NeuroVision, eyes with UCVA worse than 20/20 gained two lines versus 0.45 lines in the control group. One month after LASIK, 75% of the patients in the NeuroLASIK group achieved a UCVA better than 20/20 before undergoing NeuroVision training of their visual cortex. This percentage jumped to 96% after patients completed the NeuroVision portion of the NeuroLASIK treatment.

Our research sample showed an overall improvement in visual acuity of 1.9 lines: 1 line in 77% and 2 or more lines in 34.6% of eyes; 2 eyes (8%) gained 5

lines. The most significant improvement in contrast sensitivity was found in the low frequencies. Median stereo-acuity improved from 300 to 140 seconds of arc. Interestingly, the better eye also showed mild, albeit nonsignificant, improvement in visual acuity and contrast sensitivity. This finding may be explained by cross-linkage of the neuronal interactions that developed during the training period.

10 patients (10/26 - 38%) have reached 1 year follow up. Their visual acuity, contrast sensitivity and stereoacuity were maintained throughout the whole year, longer follow up is needed.

The greater improvement of visual acuity in the emmetropic eyes (3.6 lines) compared to the myopic and hypermetropic eyes might be attributable to the greater likelihood of the visualized images to be focused on the retina during the time of day when the child is alert. Additionally, overall, the younger patients showed a tendency for better visual improvement than the older patients, and the patients with emmetropia were younger than the myopes and hyperopes. It should be point out that, the visual improvement shown by the myopic group was greater than that of the hypermetropic group (2.3 lines compared to 1.5 lines), although both groups had an almost identical mean age (30 years). We suggest that the retinal image may have been clearer to the child’s myopic eye at near whereas in the hypermetropic eye, the image of the visualized object is always focused behind the retina and therefore the retinal image is in constant blur, depending of course on accommodation.

The greater improvement in BCVA and contrast sensitivity observed in the patients with strabismus than in those with anisometropia might be explained by the nearly emmetropic spherical equivalent in the eyes with strabismus (+0.25D) compared with the +1.34 D spherical equivalent in the anisometropic group. Furthermore, a greater percentage of the patients with strabismus had been treated by antiamblyopic patching during childhood (63% compared to 54%), a factor found

to be associated with better post-treatment visual performance in the sample as a whole.

Since one of the limitation & of our study is the fact that we have no control group, our results can be compared to the controlled study by Polat et al[25] which was reported to the FDA. It is a prospective, randomized, masked, controlled clinical study. It enrolls includes 54 patients, between 9 and 55 years old, with unilateral amblyopia secondary to strabismus and/or anisometropia. The BCVA in the amblyopic eyes ranged from 20/30 to 20/100 The treatment group included 44 patients who had NeuroVision treatment: a series of specific sequence with special algorithm that enhance the slimuli .The control group included 10 randomal selcted subjects who had sessions provided in a non-specific sequence with no algorithm. In the treatment group visual acuity improved from 0.42±0.14 Log MAR at the ETDRS chart to 0.17±0.14 Log MAR (2.5 lines) compared to the control group which showed no improvement (0.41±0.12 Log MAR to 0.41±0.12 Log MAR).

Despite the improvement in visual performance, our study leaves several questions unanswered. Would extending the treatment time yield better results? Will it be necessary to repeat this treatment in the future? However, in spite of these questions, the results of the present study support the use of a structured, targeted, visual stimulation system based on Gabor patches in order to improve visual performance in adults with amblyopia.

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Legends to Figures

Figure 1: Gabor patch: The basic element of NeuroVision visual stimulation. It efficiently activates and matches the shape and orientation of the primitive receptive fields in the visual cortex.

Figure 2: Lateral masking. The fundamental stimulation control technique includes colinearly oriented flanking Gabor patches which are displayed in addition to the target Gabor image.

Figure 3: Visual acuity (logMAR) before and after NeurVision treatment in the amblyopic eye. An improvement of 1.9 lines is noted.

Figure 4: Median stereo-acuity in the amblyopic eyes before and after NeuroVision treatment. An improvement of 300 to 140 seconds of arc was noted.

Figure 5: Contrast sensitivity in the amblyopic eyes before and after NeuroVision treatment. A statistically significant increase in the low frequency range is noted.

Figure 6: Visual acuity (logMAR) before and after NeuroVision treatment, divided by the spherical equivalent of the amblyopic eyes in emmetropic (A), myopic eyes (B), and hyperopic eyes (C).
A. The emetropic eye gained an average of 3.5 lines;
B. The myopic eye gained an average of 2.3 lines;
C. The hyperopic eye gained an average of 1.9 lines.

Figure 7: A+B: Visual acuity (logMAR) before and after NeuroVision treatment divbided by subgroups of strabismus (A) and anisometropia (B).

Greater improvement in visual acuity and contrast sensitivity was noted in the strabismus group.

C+D: Contrast sensitivity before and after NeuroVision treatment divided by subgroups of strabismus (C) and nisometropia (D).