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Visual acuity increase in meridional amblyopia by exercises with moving gratings as compared to stationary gratings

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ABSTRACT

The aim of the present work was to investigate the effect of a novel therapy based on pleoptic exercises combined with standard occlusion in patients with meridional amblyopia. The exercising system itself, termed focal ambient visual acuity stimulation (FAVAS), consists of sinusoidally modulated circular gratings, which were implemented as a background pattern in computer games binding the children's attention. For the assessment of therapeutic effects, we tested for the development of best-corrected visual acuity (BCVA) in patients trained with a gaming field background of moving gratings (Moving) compared to patients treated with stationary gratings (Stationary). Patients with amblyopia (caused by strabismus, refraction, or both) and astigmatism were randomly allocated to two groups, all of whom received a standard occlusion regimen. In combination with occlusion, using a crossover design, the first group (Moving-Stationary group) was alternately exercised for 10 days with a series of Moving followed by 10 days with Stationary and the second group (Stationary-Moving group) vice versa. The treatment-dependent training effect on BCVA was measured with respect to the alignment of the least vs. the most ametropic meridian in both groups. BCVA was examined using a meridionally direction-sensitive visual test inventory, and we estimated the monocular BCVA in all patients along four meridians: 0°, 45°, 90°, and 135° before and after Moving as compared to Stationary treatments. The Moving-Stationary group consisted of 17 children (34 eyes) aged 10 to 13 (average 11.6 ± 0.3) years. The Stationary-Moving group consisted of 20 children (40 eyes) aged 9 to 14 (average 12.5 ± 0.4). In both groups, visual acuity increased significantly only with Moving combined with occlusion. Thereby, the visual acuity (logMAR) along different meridians showed a statistically significant improvement induced by Moving if testing was coincident with alignment of the directional optical characters close to the most ametropic meridian in the Moving-Stationary group (0.73 ± 0.32 to 0.41 ± 0.22, $p < 0.01$) and also in the Stationary-Moving group (0.48 ± 0.27 to 0.33 ± 0.18, $p < 0.01$). Significant improvement was also induced by Moving if tested in alignment with the perpendicular orientation close to the least ametropic meridian, although with a smaller amount, in the Moving-Stationary group (0.49 ± 0.23 to 0.37 ± 0.21, $p < 0.01$) as well as in the Stationary-Moving group (0.33 ± 0.18 to 0.28 ± 0.16, $p < 0.01$). After Stationary combined with occlusion, however, there was no statistically significant improvement, regardless of the meridian. Visual training of patients with meridional amblyopia by a series of online exercises using attention-binding computer games which contained moving gratings as a background stimulus (Moving) resulted in a statistically significant improvement in visual acuity in the most refractive meridian, and to a lesser extent, in the least refractive meridian. No statistically significant improvement was achieved after the respective exercising series in the sham condition with stationary gratings (Stationary).

Introduction

Amblyopia is one of the most common ophthalmological disorders in young patients, with a prevalence of 5%–6%.[1] While affected children who are not treated timely in childhood have an impact on their daily activities and future job selection when they grow up, they also have an increased risk of severe trauma for the better eye[2] and an increased chance of bilateral visual impairment later in life.[3] Since

Sattler[4] re-introduced the method of occlusion into the practice of applied strabology, that is, the patching of the fellow sound eye, it has been indisputably accepted as the gold standard of modern amblyopia therapy. Early initiation of occlusion and adherence to it persistently are two important factors that influence the effectiveness of this treatment. It has been shown that delayed diagnosis and treatment results in poor outcomes.[5]

However, although therapeutic strategies such as patching have been established in clinical practice for a long time, their success has been limited, with a certain rate of patients being resistant to therapy or not reaching normal visual acuity.[6] Therefore, pleoptics, as a system of visual exercises and stimulation methods in support of the standard occlusion procedure, was developed as a complementary treatment for amblyopia.[7–11] Although the concept of pleoptics has been well-known and established for many decades, this approach is complicated and time-consuming and requires well-trained specialists; therefore, pleoptics requires an insupportably high expenditure of face-to-face therapy hours for patients and medical staff.

Recently, a paradigm shift in the therapeutic approach has been aimed not only at occluding the better eye, but also at stimulating the amblyopic eye in line with the pleoptic tradition. This is achieved with the aid of computer games, behind which a therapeutic stimulation concept is implemented, which makes it possible for patients to carry out pleoptic training online at home in combination with gold-standard occlusion. Notably, a therapeutic software-based visual stimulation system for the complementary treatment of amblyopia was developed two decades ago[12–16] by an interdisciplinary team of ophthalmologic clinics at Dresden University (Theo Seiler), the Department of Psychology (Uwe Kämpf), the Faculty of Informatics (Wilfried Mascolus), and scientific partners (UKE Hamburg, Wolfgang Haase). It was shown that such visual stimulation training is of value as a complementary method in general (first-line therapy)[12] as well as for the treatment of therapy-resistant cases (second-line therapy).[14] With this in mind, we have chosen a variation close to the standard crossover design as a method of investigation for the present trial, as will be explained in more detail later (cf. the following section).

The above-mentioned software-implemented exercises for visual training are based on specially designed *focal ambient visual acuity stimulation* (FAVAS). In the foreground of the screen, a *focal* computer game requires visual fixation performance and adherence from children. Thus, gaming activity serves only for attention binding, which has been previously proven to be a decisive compliance factor for the success of visual training exercises
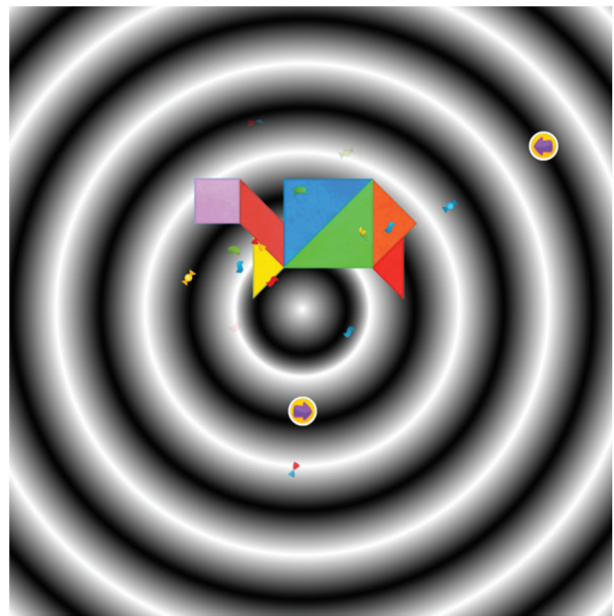

Figure 1. Example of FAVAS circular gratings in the background and game for maintaining attention in the foreground. The background of our games is removed and replaced with circular gratings moving outwards and stimulating the periphery of the retina. The stimulation was performed at a spatial frequency of 0.3 cyc/deg with the temporal frequency of 1 cyc/sec, resulting in an angular velocity of 3.33 deg/sec.

(Figure 1). Simultaneously, *ambient* stimulation is provided in the game's background by a driftingly moving sinusoidally contrast-modulated grating pattern with constant spatial and temporal frequencies. Owing to such periodicity, the moving-grating stimulus is assumed to induce resonance within and between the filter systems of band-pass selective neuronal transmission channels.

This is relevant because, in amblyopia, the transmission quality of the *focal* (parvocellular) visual system, which seems to predominantly filter the frequency-modulated neuronal correlates of form perception, appears to be more impaired than that of the complementary *ambient* (magnocellular) system for the transmission of spectrally filtered neuronal motion correlates (cf. our discussion section of this paper for more details). Thus, at the surface, amblyopic vision disorder manifests itself as a focal dysfunction of the form channels of high spatial vs. low temporal frequency resolution.[18] A comparatively less disorder appears to be observed in the function of ambient motion channels with low spatial versus high temporal frequency resolution.[19] In light of this, our approach

of FAVAS is designed to affect the disturbed focal (parvocellular) form-perception channels not directly but rather collaterally using the cooperative interplay with ambient (magnocellular) motion-perception channels.[12–14]

Additional reasons for this may also be derived from recent neurophysiological experiments in murine deprivation amblyopia.[20,21] These findings suggest the origins of bandwidth-selective acuity degradation, probably due to visual field reorganization after amblyopia-driven changes in the balance of ocular dominance (OD), rooted in a certain interaction between thalamic (LGN) and visuo-cortical (V1) processing levels; regaining OD plasticity could eventually be addressed by FAVAS treatment.

Objectives

Founding our approach on focal-ambient cooperative synergy is crucial for FAVAS, in view of that independently and different from our approach presented above, the reference to visual filter channels had already been the topic of a very early proposal of supportive amblyopia treatment using frequency-bandwidth selective grating stimulation. The so-called CAM-stimulator was developed by the British physiologist Fergus Campbell and his team in Cambridge.[8] Their results were later controversially discussed in view of placebo-controlled trials [22–25,27] and because of these unsuccessful replication studies, this attempt was empirically evaluated as a failure.

However, the Cambridge stimulator aimed at a direct stimulation of form channels (high spatial and low temporal frequency bandpass filtering), thus omitting the possible synergy of the motion channels (low spatial and high temporal frequency bandpass filtering). Its grating stimulus extremely slowly turned clockwise around the center of stimulation, that is, in a nearly stationary or steady-state manner, only once per minute around its axis. Accordingly, the possible effect of the CAM stimulator was presumably solely constrained by the proposed influence of spatial frequency selectivity alone; therefore, there was no significant contribution from the temporal frequency modulation of the stimulus to be expected. Accordingly, we ask here the question of whether this is a critical feature which might have been a probable reason for the failure of Campbell's approach, which was shown as a result of the above-cited placebo-controlled studies.

In light of this, the main objective of the present investigation was to evaluate the training effects of verum stimulation with moving gratings (*Moving*) as compared to sham stimulation with stationary gratings (*Stationary*). Thus, our envisaged primary outcome consisted of the investigation of such possibly differing influences between both types of visual exercises in combination with a standard occlusion treatment *lege artis* on the development of visual acuity.

In our reported trial, we used FAVAS driftingly moving outwards circular gratings as compared to stationary circular gratings (cf. Figure 1). This is advantageous with respect to the scope of a now to be presented second issue of our investigation, since, by such circular arrangement, we are able to reach all the ocular meridians with a comparable degree of impact. As has been recently found, over 90% of amblyopic patients show considerable astigmatism of more than 0.5D,[28] that is, imposing a very general challenge for any treatment. Consequently, meridional amblyopia often arises under such astigmatic conditions due to the long-term developmental consequences of the refractive difference between the differentially affected meridians. In patients with complex visual disorders, it may occur in combination with other varieties of functional weakness, such as dysbinocular, anisometropic, or obscuration-related forms, and can also significantly contribute to the reduction of visual performance in conditions of ocular fundus pathology. In view of this, the question arises whether meridional amblyopia may be successfully treated by the combined effect of occlusion and FAVAS.

In the present trial, however, this question cannot be directly investigated as another primary endpoint, since relevant outcomes might only be detected on the basis of a post hoc meridional specification of differential influences of exercising with *Moving* versus *Stationary* per se. Therefore, conceived as our secondary endpoint, we asked for possible differences between the most-

ametropic and least-ametropic meridians in their responses to the evenly addressing them circular gratings of FAVAS visual exercises.

Our hypothesis: *Moving* combined with attention-binding computer games in combination with occlusion might be more effective in the most ametropic meridian than in the least ametropic meridian when treating children with meridional amblyopia. A comparable effect cannot be expected for the sham condition of *Stationary* combined with computer gaming and occlusion.

According to our objectives, we aimed, in sum, at the following endpoints. Primary endpoint: best corrected visual acuity (BCVA) significantly increased after 10 days of exercising with *Moving* but not after 10 days of *Stationary*. Secondary endpoint, being embedded in the outcome of the primary endpoint: BCVA significantly increased in the most ametropic meridian but probably not as much in the least ametropic meridian. No changes to the specification of the expected primary and secondary endpoints after the trial commenced were introduced in the above-described a priori design.

Patients and methods

Patients

This prospective study adhered to the Declaration of Helsinki and was approved by the local ethics committee (05/2015, trial registration DRKS00022791). The study was conducted at a single center. Informed consent was obtained from the patients' legal guardians to participate in the present investigation, as well as to publish the results of this research work.

Eligibility criteria for participants were as follows: sex of the children (both male and female), age range between 9 and 14 years, and type of amblyopia. As a criterion for the impact, we referred to the BCVA <0.8 in each amblyopic eye measured by single optical characters. Patients suffering from amblyopia ex anopsia with astigmatism were chosen, which is in line with our partial goal of examining the effects of meridional amblyopia. Patients who did not meet the visual acuity criteria or had a history of

strabismus surgery were excluded from the study. No important changes to the eligibility criteria were adopted after trial commencement.

Refraction determination was performed using retinoscopy in all patients. Best-corrected glasses were then prescribed and worn during visual exercises.

The random allocation sequence was implemented by a statistician at the Kharkevitch Institute. The method used to generate the random allocation sequence was to grant a comparable variance to both groups by chance. A random sequence was implemented using a probabilistically allocated crossover design. Eligible patients were randomized into two groups, which approximately corresponded to each other in terms of age composition and type of ophthalmologic disorder of their visual acuity, that is, the expression of their respective amblyopia. The patients were allocated to either group in full randomization at a 1:1 ratio without any restrictions, such as blocking. The participants were assigned to interventions by the medical study supervisor, Mrs. Rychkova.

The first group (*Moving-Stationary* group) consisted of 17 children (34 eyes) aged 10 to 13 (average 11.6 ± 0.3) years. Their mean refractive correction was 4.48 ± 3.58 D absolute sphere with −2.39 ± 1.47 D cylinder by 85,23 ± 76,25 deg for the OD and 4,44 ± 3,86 D absolute sphere with −2,29 ± 1,89 D cylinder by 117,82 ± 70,02 deg for the OS. Of these, six patients had myopic astigmatism, nine patients had hypermetropic astigmatism, and two had mixed astigmatism. Refractive amblyopia (only against the background of astigmatism) was found in four patients, in combination with dysbinocular amblyopia (against the background of strabismus) in four patients, and in combination with a pathology of the eye background in seven patients (four were additionally diagnosed with secondary strabismus). Two patients with artiphakia had a combination of refractive and obscuration-related amblyopia.

The second group (*Stationary-Moving* group) consisted of 20 children (40 eyes) aged 9 to 14 (average 12.5 ± 0.4) years. Their mean refractive correction was 5.57 ± 4.59 D absolute sphere with −1.82 ± 0.92 D cylinder by 72.2 ± 76.24 deg for the

Table 1. Patients' characteristics.

Age	Range	9–14
	Mean	11.2 ± 0.4
Sex	Male	27
	Female	10
Amblyopic eye	Left	37
	Right	37
Type of amblyopia	Strabism	36
	Refraction	10
	Both	10

OD and 5.75 ± 4.79 D absolute sphere with −1.65 ± 0.99 D cylinder by 98.25 ± 79.80 deg for the OS. Of these, 12 patients had myopic astigmatism, seven had hypermetropic astigmatism, and one had mixed astigmatism. Refractive amblyopia (only against the background of astigmatism) was found in three patients, in combination with dysbinocular amblyopia (against the background of strabismus) in 12 patients and in combination with a pathology of the eye background in six patients (in five of them, a secondary strabismus was additionally diagnosed).

Table 1 summarizes the main baseline demographic and clinical characteristics of both groups.

All trial participants were patients of a vision training center specializing in the treatment of pediatric eye diseases. Their selection for the present study was based on the criterion that they had been newly admitted to the center and had not received any amblyopia treatment in the previous 2 years. Before that, they were intermittently occluded by local ophthalmologists between the ages of 4 and 6 years. They completed the visual exercises of the study under the direct supervision of the orthoptist-trained pedagogical staff of the vision training center, who also monitored compliance under the supervision of their senior ophthalmologist.

Methods

The present study was planned and performed as a placebo-controlled, double-blind, randomized crossover trial. According to the prospective design of our study, the variation in the stimulus parameters explored was limited to the above-mentioned parametric conditions that proved effective in previous research.[12–14]

Based on these previous studies, we assumed that the initial combination of FAVAS with occlusion as a first-line therapy might increase the best-corrected visual acuity by at least two lines over 10 days. For the comparison between *Moving* and *Stationary*, we used a slightly modified version of crossover design to additionally prove the possible superiority of first-line therapy application of FAVAS in support of occlusion over a second-line therapy in its application. In light of this, it must be admitted that no washout effect between the crossed over training phases can be expected here, as is the case in a traditional crossover setting. This is because FAVAS exercises combined with occlusion are intended to induce a permanent gain of visual function, which persists for a long time and does not decay to zero after the end of training. Therefore, the carry-over effect of the occlusion should not be excluded from the design. Rather, it is well accepted because we do not compare two kinds of mono interventions but rather combined interventions: visual exercises with *Moving* or with *Stationary*, both combined with occlusion. Accordingly, we analyzed the relative differences in accumulated combined effects between both groups with no extensive intermediate washout pausing between phases with different conditions of exercising rather than absolute effects starting from zero after a long intermittent period of washout.

For both groups, online vision training (Caterna Vision GmbH, Potsdam, Germany; Amblyocation GmbH, Liebstadt, Germany) was applied in crossover according to two modifications. The verum training program included a circular outward-moving grating, before which computer games took place during stimulation (*Moving*). Stimulation was conducted at a spatial frequency of 0.3 cyc/deg with a temporal frequency of 1 cyc/s, resulting in an angular velocity of 3.33 deg/sec. The sham training program contained the same grating, with the only difference being the exposure in a stationary (i.e., non-moving) state of presentation (*Stationary*). In both cases, the children played computer games in the foreground of screenplay, which served to bind attention in front of the stimulating grating in the background. The patients

were trained twice a day for 20 min each session. In parallel, the patients received a standard occlusion regimen *lege artis*.

With respect to the conditions described above, our investigation was planned according to a two-group crossover design (Figure 2): The first group of patients (*Moving-Stationary* group) initially completed 10 days with 10 min per eye using *Moving*. After a 1-week break, the same patients continued their exercises for 10 days, with 10 min per eye, using *Stationary*. In contrast, the second group of patients (*Stationary-Moving* group) initially completed 10 days with 10 min per eye using *Stationary*. After a break of 1 week, the same patients continued their exercises for 10 days with 10 min per eye, using *Moving*.

In accordance with our objectives, we examined our patients with regard to their BCVA using a meridionally direction-sensitive visual test inventory developed at the Kharkevich Institute for Information Transmission Problems.[29] Therefore, we estimated the monocular corrected visual acuity in all patients along four meridians: 0°, 45°, 90°, and 135°. These visual examinations were performed before and after the respective 10-days-of-treatment series.

Results

As a result, we plotted the mean BCVA in logMAR units for both groups of patients as a baseline before the beginning of treatment (day 0), after the initial 10 days of training series until crossover (day 10), and after the following 10 days of training series (day 20) separately for the *Moving-Stationary* group (Figure 3) and the *Stationary-Moving* group (Figure 4). Different graphs show data plots for logMAR close to the most ametropic meridian versus the least ametropic meridian. The graphically presented results are summarized in their numerical representations (Table 2 and Table 3).

For both groups, the BCVA increased significantly only within 10 days, including a series of exercises with *Moving* combined with occlusion. Therefore, the BCVA (logMAR) along different meridians showed a statistically significant improvement induced by *Moving* coincident with an alignment of the directional optical characters close to the most ametropic meridian in the *Moving-Stationary* group (0.73 ± 0.32 to 0.41 ± 0.22, $p < 0.01$, t-test) and also in the *Stationary-Moving* group (0.48 ± 0.27 to 0.33 ± 0.18, $p < 0.01$, t-test). Significant improvement was induced by *Moving* also in alignment with the perpendicular orientation close to the least ametropic meridian, although with a smaller amount, in the *Moving-Stationary* group (0.49 ± 0.23 to 0.37 ± 0.21, $p < 0.01$, t-test) as well as in the *Stationary-Moving* group (0.33 ± 0.18 to 0.28 ± 0.16, $p < 0.01$, t-test). After exercising with *Stationary* combined with occlusion, however, no statistically significant improvement was found, regardless of the meridian (0.41 ± 0.24 to 0.39 ± 0.24 in the *Moving-Stationary*
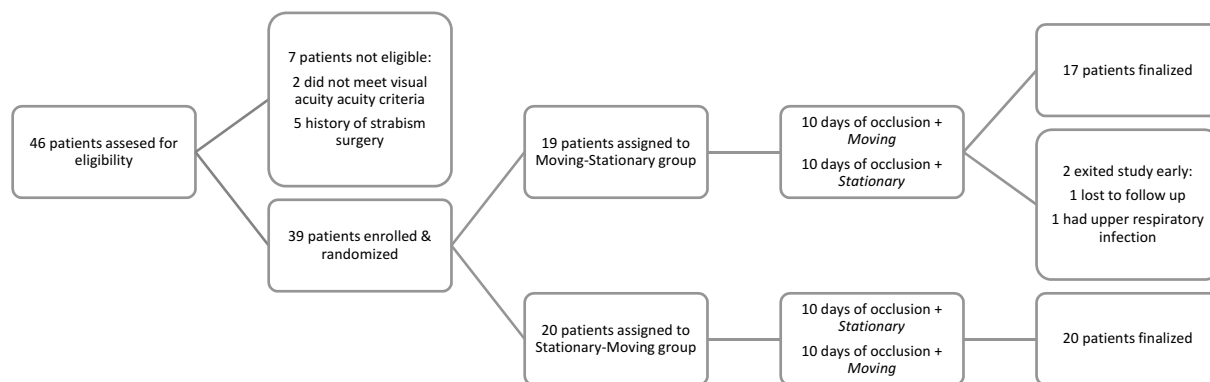
Figure 2. Flowchart showing trial flow and patients' allocation over trial conditions. Forty-six patients were assessed for eligibility, and seven patients which did not satisfy the visual acuity criteria or with a history of strabismus surgery were excluded. From 39 patients, 19 were randomized to *Moving-Stationary* group and 20 to *Stationary-Moving* group. After 10 days of *Moving* followed by 10 days of *Stationary*, 17 patients finalized the trial. Vice versa, 20 patients finalized the trial. At the beginning, after 10 days and after 20 days, BCVA was assessed.
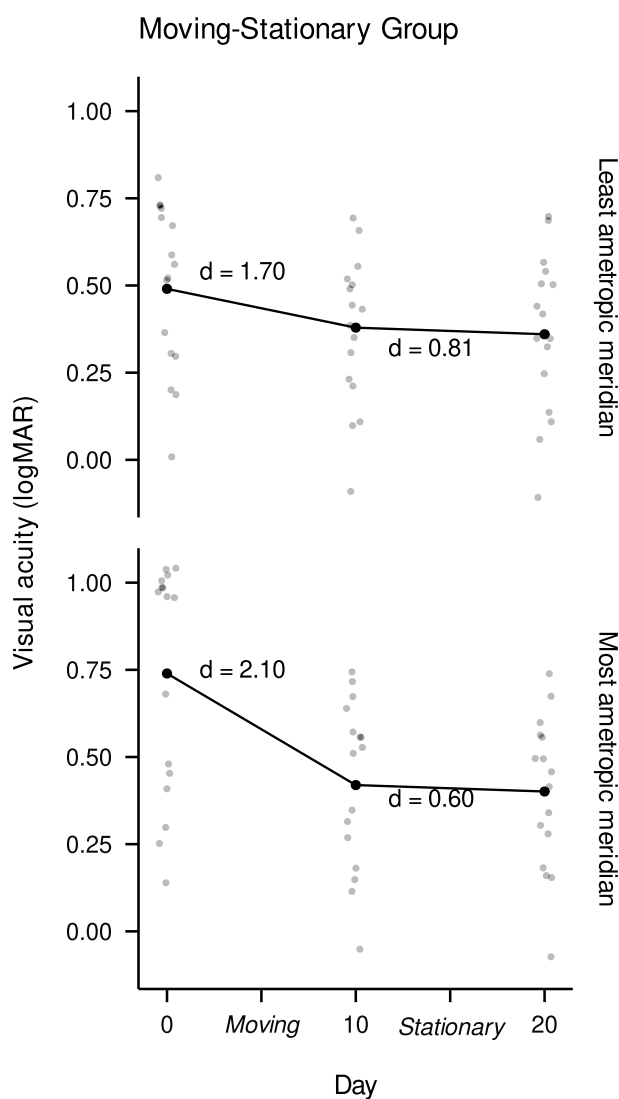
Moving-Stationary Group

Figure 3. The mean BCVA results (logMAR) of the least ametropic meridian versus the most ametropic meridian for the *Moving-Stationary* group at training days 0, 10, and 20. FAVAS intervention with *Moving* was given between days 0 to 10 and with *Stationary* between days 10 to 20. Presented is also an effect-size given by Cohen's d. Highest effect-size and significance revealed by paired Student *t*-test is found for *Moving*, being more imminent in most ametropic meridian as compared to least ametropic meridian. No significance is found for *Stationary*, regardless of meridian.

Stationary-Moving Group

Figure 4. The mean BCVA results (logMAR) of the least ametropic meridian versus the most ametropic meridian for the *Stationary-Moving* group at training days 0, 10, and 20. FAVAS intervention with *Stationary* was given between days 0 to 10 and with *Moving* between days 10 to 20. Presented is also the effect-size given by Cohen's d. Highest effect-size and significance revealed by paired Student *t*-test is found for *Moving* being more imminent in the most ametropic meridian as compared to the least ametropic meridian. No significance is found for *Stationary*, regardless of meridian.

group for the most ametropic meridian and 0.36 ± 0.22 to 0.34 ± 0.22 for the least ametropic meridian; 0.53 ± 0.30 to 0.50 ± 0.29 in the *Stationary-Moving* group for the most ametropic meridian and 0.39 ± 0.24 to 0.36 ± 0.22 for the least ametropic meridian).

Absolute effect sizes were calculated for our significant binary outcomes. Cohen's d = 2.10 for the most ametropic meridian in the *Moving-*
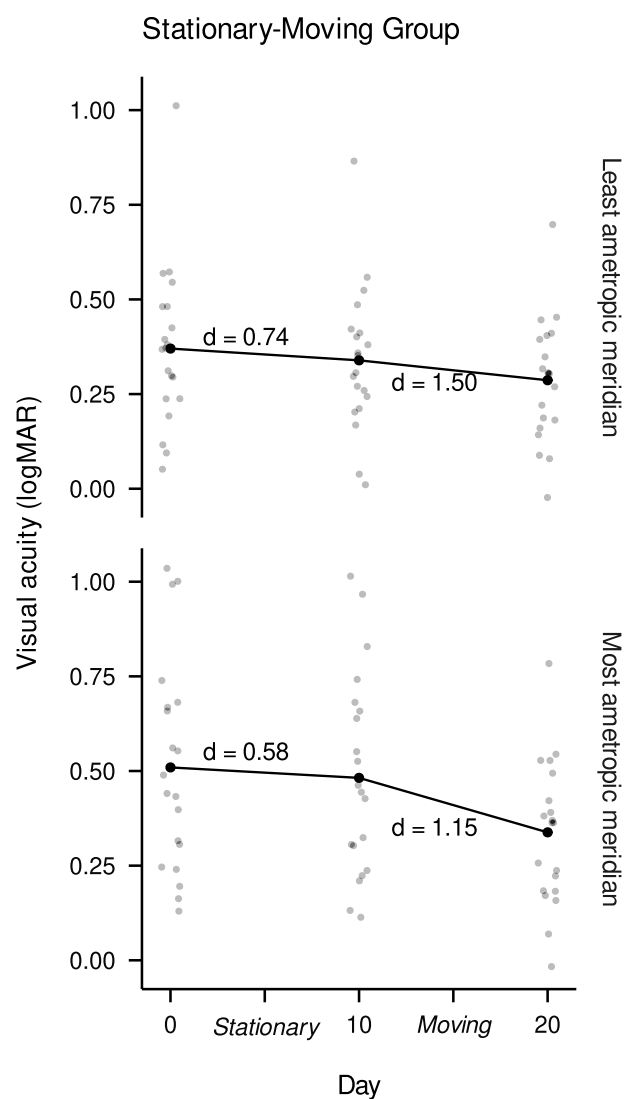
Stationary group with *Moving* vs. Cohen's d = 0.60 with *Stationary*. With the least ametropic meridian, Cohen's d = 1.70 for the *Moving-Stationary* group with *Moving* vs. Cohen's d = 0.81 with *Stationary*.

Cohen's d = 0.58 for the most ametropic meridian for the *Stationary-Moving* group with *Stationary* vs. Cohen's d = 1.15 with *Moving*. Cohen's d = 0.74 for the least

Table 2. Mean BCVA in logMAR and effect-size Cohen's d on days 0, 10, and 20 for *Moving-Stationary* group of patients. Significance revealed by paired Student *t*-test is marked by a double asterisk (*p* < 0.01) and effect-size is estimated by Cohen's d.

Mean BCVA (logMAR)	before treatment (day 0)	after 10 days of treatment with *Moving* (day 10)	after another 10 days of treatment with *Stationary* (day 20)
Most ametropic meridian	0.73 ± 0.32	0.41 ± 0.22 ** Cohen's d=2.10 95% CI [1.19, 2.99]	0.40 ± 0.22 Cohen's d=0.60 95% CI [0.05, 1.14]
Least ametropic meridian	0.49 ± 0.23	0.37 ± 0.21 ** Cohen's d=1.70 95% CI [0.90, 2.48]	0.36 ± 0.21 Cohen's d=0.81 95% CI [0.21, 1.38]

Table 3. Mean BCVA in logMAR and effect-size Cohen's d on days 0, 10, and 20 for *Stationary-Moving* group of patients. Significance revealed by paired Student t-test is marked by a double asterisk (p<0.01) and effect-size is estimated by Cohen's d.

Mean BCVA (logMAR)	before treatment (day 0)	after 10 days of treatment with *Stationary* (day 10)	after another 10 days of treatment with *Moving* (day 20)
Most ametropic meridian	0.50 ± 0.28	0.48 ± 0.27 Cohen's d=0.58 95% CI [0.09, 1.06]	0.33 ± 0.18 ** Cohen's d=1.15 95% CI [0.56, 1.72]
Least ametropic meridian	0.37 ± 0.21	0.33 ± 0.18 Cohen's d=0.74 95% CI [0.23, 1.24]	0.28 ± 0.16 ** Cohen's d=1.50 95% CI [0.84, 2.15]

ametropic meridian for the *Stationary-Moving* group with *Stationary* vs. Cohen's d = 1.50 with *Moving*.

Discussion

The present results show that approximately two lines of BCVA increased after 10 days of exercising 20 min twice a day with *Moving* gratings combined with occlusion, as compared to *Stationary* gratings. Significant effects were achieved to a greater extent in the most ametropic meridians of patients with meridional amblyopia and to a lesser extent in the least ametropic meridians. Thus, our attention-binding computer games with *Moving* combined with occlusion are shown to be more effective than combining occlusion and attention-binding games with *Stationary* in the presented as well as in the reported earlier trials[12–16] and are therefore promising to overcome some shortcomings of stand-alone occlusion therapy per se.

The greater effect size of this result in the *Moving-Stationary* group than in the *Stationary-Moving* group in crossover seems to indicate that an initial combination therapy of occlusion and FAVAS as a first-line therapy might be superior to a second-line therapy. Therefore, our conclusion

from the present results, which we suggest not to be limited exclusively to patients suffering from meridional amblyopia, is that FAVAS in combination with occlusion might be recommended to be applied not only later on for the treatment of therapy-resistant cases, but also for all cases of initial amblyopia treatment as early as possible.

This is both significant, since there has been a lively debate as to whether, in the therapeutic value of FAVAS, the computer games *per se* or the stimulating background with moving sinusoidal gratings were the main reasons for the visual improvement and whether FAVAS should only be used for cases of therapy-resistant amblyopia or whether it should also be initially prescribed from the early beginning as a treatment to newly identified patients from the outset. However, regarding the experimental critiques addressed at these issues by Bau et al,[30] the occlusion scheme used in the trial conditions of these authors was adopted directly from Campbell's[8] original proposal to occlude only within the practice period of visual exercise alone (minimal occlusion). However, our objective was to combine FAVAS therapy with a full occlusion scheme *lege artis*.

Undisputedly, the results of our present trial strongly demonstrate that computer-gaming activities alone cannot be the main reason for the treatment-induced vision enhancement in addition to occlusion because the visual acuity gain was only obtained in our *Moving* condition, but not in our *Stationary* condition, which is similar to Campbell's[8] approach.

This is further underlined by the fact that the maximal gains selectively addressed the most ametropic meridians and less addressed the least ametropic ones. Nevertheless, these effects are not limited to the specificities of meridional amblyopia alone, since a comparable gain was shown in the earlier FAVAS trials with other forms of refractive and strabismic amblyopia.[12–14]

Considering the significant effects of moving versus stationary stimulus gratings in comparison to the results of Campbell et al,[8] it must be further premised that the prototype for our design of the computer-based FAVAS background stimulation was not inspired by the Cambridge Stimulator discussed above *per se*, but rather by the mechanical repetitive-grating arrangement proposed by Haase[31] and Osterloh.[32] This arrangement was originally derived from a visuo-motor and/or visuo-sensor pleoptic stimulation approach, which had been previously developed by Otto and Stangler.[11] Initially, the latter authors described and confirmed in their further related research a beneficial effect of moving light stripe application on the fixation stability of amblyopic eyes.[10,32,33] Additionally, Haase[31] and Osterloh[32] found amplification of this effect using, instead of single bars, a whole grating of repetitively displayed slightly blurred sideward-moving light stripes as a background stimulus in a fixation task.

According to our hypothesis[13,14] the enhanced treatment effect caused by the spatio-temporal periodicity of such a grating stimulus itself is supposed to be achieved as a result of the way the induced optomotoric and optosensoric stimulus effects mutually interact. This is possibly because of synergy in the filter characteristics of the two interacting systems of different sensory transmission channels.[34,35] We already mentioned in the Introduction section that these channels were shown to correspond, roughly speaking, to the neuronal correlates of *focal* processing of visually perceived form and configurative detail (sustained channels, parvocellular system) versus the *ambient* processing of motion and rapid change (transient channels, magnocellular system). The filters of each of these channels are selectively tuned to a narrow band of spatial frequencies.[36,37] Associated each, as has been found in later research, with an appropriate temporal frequency range, both are constrained to one another in reciprocal, that is, inversely counterbalanced synergy.[38,39]

This interdependence is supposed to bear on non-linear coupling in the synchronization of brain functioning by means of so-called neuronal synfire-chains.[40,41] According to this view, the drifting light stripe stimulation under spatial and temporal periodicity of a limited frequency bandwidth (which also characterizes spiral patterns, e.g., those of earlier pleoptic centrophor exercises by Bangerter[7] und Cüppers[9]) is applied to the disturbed synfire-chain system dynamics as an externally organizing order parameter. Thus, it is expected to support regaining the internal temporal coherence of normally highly ordered cortical processing loops, which were shown to be desynchronized in amblyopia.[42–44]

Therefore, in addition to the originally reported fixation-stabilizing optomotor effect of the pleoptic light stripe stimulation[10,11,32,33] we assume repeated stripes[31,32] in the drifting sinusoidal grating to further induce another useful effect, that is, of optosensoric resonance in complementary banks of bandwidth selective filters of form vs. motion channels owing to their cooperatively intertwined modes of visual processing.[17,26] According to our hypothesis, the internal cortical synchronization in brain areas addressed by the focal macular form channels of the central retina is probably externally supported, that is, via resonant phase coupling to oscillations from brain areas addressed by ambient motion channels in the peripheral retina.[13,14]

Another treatment sharing some common theoretical fundamentals with the spatial-frequency approach of Campbell`s as well as to our proposed stimulation has been developed and verified in placebo-controlled trials by Polat et al.[45] In their "perceptual-learning" training, high-contrast ambient grating stimuli in a collineated arrangement of Gabor patches are used as peripheral flankers, inducing focal detection enhancement of low-contrast central Gabor patches of common spatial frequency. Related studies

have demonstrated the considerable efficacy of such training for improving contrast sensitivity and visual acuity in adult amblyopic patients. Unfortunately, unlike Campbells and our approaches, Polat's training is based on a detection task with respect to the presented Gabor low-contrast grating macular stimulus, which might be easily coped with by adults but might be tedious to children.

Nevertheless, similar to our approaches, Polat's training is also based on the assumption of an ambient frequency-selective cooperative effect of peripheral retinal stimulation on central retinal low-level focal visual processing. However, similar to Campbell and differing from our proposed stimulus arrangement, in Polat's setting, the peripheral influence on central vision was mediated by stationary rather than moving stimuli; thus, a solitary influence of spatial frequency on visual learning in their conditions may only be predicted; therefore, such of temporal frequency is certainly excluded.

Finally, our study has certain limitations to consider. The total duration of active stimulation was 20 days, which was justified by the fact that the children had to visit the therapy center daily for the sake of a supervised examination. However, since the strongest increase in visual acuity occurs at the beginning of treatment, the results are considered clinically representative of a therapy cycle duration of 90 days, which we prefer in the sense of greater sustainability. Furthermore, our findings suggest that the combination therapy (FAVAS plus occlusion), which shows success in severe astigmatism, might be even more successful in less severe astigmatism.[46,47]

The vision improvement we observed underlines the value of FAVAS in treating amblyopia in combination with occlusion, where the results seem to suggest that first-line use is superior to second-line use. We hope that combination therapy of FAVAS and occlusion will be useful in future clinical practice.

Disclosure statement

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References

1. Elflein HM, Fresenius S, Lamparter J, et al. The prevalence of amblyopia in Germany: data from the prospective, population-based Gutenberg health study. *Dtsch Arztebl Int*. 2015;112(19):338–344. doi:10.3238/arztebl.2015.0338. PMID: 26043421; PMCID: PMC4458790.

2. Maurer D, McKee SP. Classification and diversity of amblyopia. *Vis Neurosci*. 2018;35:E012. doi:10.1017/S0952523817000190.

3. Van Leeuwen R, Eijkemans MJ, Vingerling JR, Hofman A, de Jong PT, Simonsz HJ. Risk of bilateral visual impairment in persons with amblyopia: the Rotterdam study. *Br J Ophthalmol*. 2007;91 (11):1450–1451. doi:10.1136/bjo.2006.113670.

4. Sattler CH. Erfahrungen über die Beseitigung der Amblyopie und die Wiederherstellung des binokularen Sehaktes bei Schielenden [Experience on the elimination of amblyopia and restoration of binocular vision in strabismus patients]. *Z Augenheilk*. 1927;63:19–124.

5. Birch EE. Amblyopia and binocular vision. *Prog Retin Eye Res*. 2013;33:67–84. doi:10.1016/j.preteyeres.2012.11.001.

6. Awan M, Proudlock FA, Grosvenor D, Choudhuri I, Sarvanananthan N, Gottlob I. An audit of the outcome of amblyopia treatment: a retrospective analysis of 322 children. *Br J Ophthalmol*. 2010;94(8):1007–1011. doi:10.1136/bjo.2008.154674.

7. Bangerter A. *Amblyopiebehandlung [Amblyopia Treatment]*. Basel: Karger; 1953.

8. Campbell FW, Hess RF, Watson PG, Banks R. Preliminary results of a physiologically based treatment of amblyopia. *Br J Ophthalmol*. 1978;62(11):748–755. doi:10.1136/bjo.62.11.748.

9. Cüppers C Grenzen und Möglichkeiten der pleoptischen Therapie [Limits and possibilities of pleoptic therapy]. Travemünde: Tagung der Nord-West-Deutschen Augenärzte. In Schielbehandlung: Einführungs- und Fortbildungsvorträge. Wiesbaden; 1960:39–97.

10. Otto J, Rabethge G. Über die optomotorische Amblyopiebehandlung [About optomotor amblyopia treatment]. In: Freigang M., Hrsg, ed. *Arbeitskreis Schielen*. Vol. 12. Nürnberg: Kaden. 1980:74–80. https://www.bielschowsky.de/docs/Schielbehandlung/Schielbehandlung-Band-12-1980.pdf

11. Otto J, Stangler E. Wirkung optomotorischer Reize auf Fixationsort und Auflösungsvermögen amblyoper Augen mit exzentrischer Fixation [Effect of optomotor stimuli on fixation location and resolving power of amblyopic eyes with eccentric fixation]. *Ophthalmologica*. 1969;157:135–141.

12. Kämpf U, Muchamedjarow F, Seiler T. Supportive amblyopia treatment by means of computer games with background stimulation; a placebo-controlled pilot study of 10 days. *Klin Monbl Augenheilkd*. 2001;218(4):243–250. doi:10.1055/s-2001-14921.

13. Kämpf U, Mascolus W, Muchamedjarow F, Shamshinowa A, Kaschenko T. Coherence induction via phase conjugate adaptive resonance coupling: computer-generated sinusoidal grating patterns as a background stimulus in amblyopia treatment. *J Psychophysiology*. 2006;20(2):149. doi:10.1027/0269-8803.20.2.102.

14. Kämpf U, Shamshinova A, Kaschtschenko T, Mascolus W, Pillunat L, Haase W. Long-Term application of computer-based pleoptics in home therapy: selected results of a prospective multicenter study. *Strabismus*. 2008;16(4):149–158. doi:10.1080/09273970802451125.

15. Kurze U, Ludwig D, Kämpf U, Muchamedjarow F, Mascolus W. Therapie, Prophylaxe und Nachsorge von Amblyopien: Basissoftware zur Visusstimulation und Videogames zur Aufmerksamkeitsbindung [Therapy, prophylaxis and follow-up of amblyopia: basic software for visual stimulation and videogames for attention retention. In: Schorr A. (Hg), ed. *Experimentelle Psychologie: 38. Tagung Experimentell Arbeitender Psychologen, Eichstätt*. Vol. 180. Düsseldorf: Pabst Science Publishers; April, 1996:1–4.

16. Muchamedjarow F, Kämpf U, Mascolus W. Visusstimulation mit sinusoidal moduliert oszillierenden Gittern: Eine neue computergestützte Methode zur Nachsorge von Amblyopie [Visual-acuity stimulation with sinusoidally modulated oscillating gratings: a new computer-assisted method for the follow-up of amblyopia]. Beitrag auf der 6. Tagung der Bielschowsky-Gesellschaft für Schielforschung in Gießen, 29.-31. August Klin Mbl Augenheilk. 1997;211:5.

17. Hess RF, Burr DC, Campbell FW. A preliminary investigation of neural function and dysfunction in amblyopia—iii. Co-operative activity of the amblyopic channels. *Vision Res*. 1980;20(9):757–782. doi:10.1016/0042-6989(80)90005-X.

18. Hess RF, Howell ER. The threshold contrast sensitivity function in strabismic amblyopia: evidence for a two-type classification. *Vis Res*. 1977;17(9):1049–1055. doi:10.1016/0042-6989(77)90009-8.

19. Rentschler I, Hilz R, Brettel H. Amblyopic abnormality involves neural mechanisms concerned with movement processing. *Invest Ophthalmol Vis Sci*. 1981;20:695–700.

20. Seignette K, Levelt CN. Amblyopia: the thalamus is a no-go area for visual acuity. *Curr Biol*. 2018;28(12):R709–R712. doi:10.1016/j.cub.2018.04.081.

21. Stephany CÉ, Ma X, Dorton HM, et al. Distinct circuits for recovery of eye dominance and acuity in murine amblyopia. *Curr Biol*. 2018;28(12):1914–1923.e5. doi:10.1016/j.cub.2018.04.055.

22. Haaf E, Boergen KP, Rentschler I. Erste Ergebnisse mit dem Amblyopiegerät nach Campbell [First results with the Campbell amblyopia device]. In: Freigang M., Hrsg, ed. *Arbeitskreis Schielen*. Vol. 12. Nürnberg: Kaden; 1980:63–66. https://www.bielschowsky.de/docs/Schielbehandlung/Schielbehandlung-Band-12-1980.pdf

23. Koskela PU. Contrast sensitivity in amblyopia. 1. Changes during CAM treatment. *Acta Ophthalmol (Copenh)*. 1986;64(3):344–351. doi:10.1111/j.1755-3768.1986.tb06931.x.

24. Koskela PU. Contrast sensitivity in amblyopia. II. Changes during pleoptic treatment. *Acta Ophthalmol (Copenh)*. 1986;64(5):563–569. doi:10.1111/j.1755-3768.1986.tb06974.x.

25. Linke B. Erfahrungen der Amblyopiebehandlung mit dem Campbell-Stimulator [Experience of amblyopia treatment with the Campbell stimulator]. In: Freigang M., Hrsg, ed. *Arbeitskreis Schielen*. Vol. 12. Nürnberg: Kaden; 1980:67–73. https://www.bielschowsky.de/docs/Schielbehandlung/Schielbehandlung-Band-12-1980.pdf

26. McCana F, Cuthbert A, Lovegrove W. Contrast and phase processing in amblyopia. *Vis Res*. 1986;26(5):781–789. doi:10.1016/0042-6989(86)90093-3.

27. Mehdorn E, Mattheus S, Schuppe A, Klein U, Kommerell G. Amblyopiebehandlung mit dem Cambridge-Stimulator: Eine kontrollierte Studie [Amblyopia treatment with the Cambridge stimulator: a controlled study]. In: Freigang M., Hrsg, ed. *Arbeitskreis Schielen*. Vol. 12. Nürnberg: Kaden; 1980:61–62. https://www.bielschowsky.de/docs/Schielbehandlung/Schielbehandlung-Band-12-1980.pdf

28. Xiao X, Liu WM, Zhao WX, Wang Y, Zhang YJ. Prevalence of astigmatism in 2023 children with amblyopia. *Zhongguo Dang Dai Er Ke Za Zhi*. 2011;13(6):462–465. Chinese. PMID: 21672418.

29. Rozhkova G, Lebedev D, Gracheva M, Rychkova S. Optimal optotype structure for monitoring visual acuity. Proceedings of the Latvian Academy of Sciences. Section B. Natural, Exact, and Applied Sciences; 2014;71:327–338. 10.1515/prolas-2017-0057

30. Bau V, Rose K, Pollack K, Spoerl E, Pillunat LE. Effectivity of an occlusion-supporting PC-based visual training programme by horizontal drifting sinus gratings in children

with amblyopia. *Klin Monbl Augenheilkd.* 2012;229 (10):979–986. German. doi:10.1055/s-0032-1315308. Epub 2012 Oct 24. PMID: 23096142.

31. Haase W. Wert und Unwert der Occlusionstherapie im Rahmen der Schielbehandlung [Value and unvalue of occlusion therapy in the context of Squint treatment]. *Münch Med Wochenschr.* 1978;120:99–102.

32. Osterloh J. *Beeinflussung von Fixation und Fernvisus amblyoper Augen durch optomotorische Reize [Influence of optomotor stimuli on fixation and distant visual acuity of amblyopic eyes]* [dissertation Fachbereich Medizin]. Universität Hamburg; 1972.

33. Stangler E. Ist das Visumeter für die Amblyopi ebehandlung geeignet? [Is the Visumeter suitable for amblyopia treatment?]. *Klin Monbl Augenheilkd.* 1974;164:563–566.

34. Breitmeyer BG, Ganz L. Implications of sustained and transient channels for theories of visual pattern masking, saccadic suppression, and information processing. *Psychol Rev.* 1976;83(1):1–36. doi:10.1037/0033-295X.83.1.1.

35. Kulikowski JJ, Tolhurst DJ. Psychophysical evidence for sustained and transient detectors in human vision. *J Physiol.* 1973;232(1):149–162. doi:10.1113/jphysiol.1973.sp010261.

36. Blakemore C, Campbell FW. On the existence of neurons in the human visual system selectively sensitive to the orientation and size of retinal images. *J Physiol.* 1969;203 (1):237–260. doi:10.1113/jphysiol.1969.sp008862.

37. Campbell FW, Robson JG. Applications of Fourier analysis to visibility of gratings. *J Physiol.* 1968;197 (3):551–566. doi:10.1113/jphysiol.1968.sp008574.

38. Kelly DH. Retinal inhomogeneity. I. Spatiotemporal contrast sensitivity. *J Opt Soc Am A.* 1984;1(1):107–113. doi:10.1364/JOSAA.1.000107.

39. Kelly DH. Retinal inhomogeneity. II. Spatial summation. *J Opt Soc Am A.* 1984;1(1):114–119. doi:10.1364/JOSAA.1.000114.

40. Abeles M. Role of the cortical neuron: integrator or coincidence detector? *Isr J Med Sci.* 1982;18:83–92.

41. Abeles M, Bergman H, Margalit E, Vaadia E. Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. *J Neurophysiol.* 1993;70 (4):1629–1638. doi:10.1152/jn.1993.70.4.1629.

42. Fries P, Roelfsema PR, Engel AK, König P, Singer W. Synchronized gamma frequency oscillations correlate with perception during binocular rivalry in awake squinting cats. *Soc Neurosci Abstr.* 1996;22:282.

43. König P, Engel AK, Löwel S, Singer W. Squint affects the synchronization of oscillatory responses in cat visual cortex. *Eur J Neurosci.* 1993;5(5):501–508. doi:10.1111/j.1460-9568.1993.tb00516.x.

44. Roelfsema PR, König P, Engel AK, Sireteanu R, Singer W. Reduced synchronization in the visual cortex of cats with strabismic amblyopia. *Eur J Neurosci.* 1994;6:1645–1655.

45. Polat U, Ma-Naim T, Belkin M, Sagi D. Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci USA.* 2004;101(17):6692–6697. doi:10.1073/pnas.0401200101.

46. Choi SK, Chang JW. Higher order aberration and astigmatism in children with hyperopic amblyopia. *Korean J Ophthalmol KJO.* 2016;30(1):53–59. doi:10.3341/kjo.2016.30.1.53.

47. Hussein MA, Coats DK, Muthialu A, Cohen E, Paysse EA. Risk factors for treatment failure of anisometropic amblyopia. *J Aapos.* 2004;8(5):429–434. doi:10.1016/j.jaapos.2003.09.005.