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Efficiency of electronically monitored amblyopia treatment between 5 and 16 years of age: New insight into declining susceptibility of the visual system ☆

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ABSTRACT

The notion of a limited, early period of plasticity of the visual system has been challenged by more recent research demonstrating functional enhancement even into adulthood. In amblyopia ("lazy eye") it is still unclear to what extent the reduced effect of treatment after early childhood is due to declining plasticity or lower compliance with prescribed patching. The aim of this study was to determine the dose–response relationship and treatment efficiency from acuity gain and electronically recorded patching dose rates, and to infer from these parameters on a facet of age dependence of functional plasticity related to occlusion for amblyopia. The Occlusion Dose Monitor was used to record occlusion in 27 participants with previously untreated strabismic and/or anisometropic amblyopia aged between 5.4 and 15.8 (mean 9.2) years during 4 months of conventional treatment. Group data showed improvement of acuity throughout the age span, but significantly more in patients younger than 7 years despite comparable patching dosages. Treatment efficiency declined with age, with the most pronounced effects before the age of 7 years. Thus, electronic recording allowed this first quantitative insight into occlusion treatment spanning the age range from within to beyond the conventional age for patching. Though demonstrating improvement in over 7 year old patients, it confirmed the importance of early detection and treatment of amblyopia. Treatment efficiency is presented as a tool extending insight into age-dependent functional plasticity of the visual system, and providing a basis for comparisons of effects of patching vs. emerging alternative treatment approaches for amblyopia.

1. Introduction

Amblyopia is a, usually unilateral, impairment of visual functions originating from abnormal visual experience during development. Being induced by strabismus (squint), anisometropia (unequal refractive power of the two eyes) or visual deprivation, it is a frequent cause of visual loss in childhood (Attebo et al., 1998). Occlusion (patching) of the nonamblyopic eye is still the mainstay of treatment (Loudon & Simonsz, 2005; Wong, 2012).

Amblyopia and its treatment have served as natural model situations for studying the susceptibility of the visual system to altered visual input (for reviews see e.g. Daw, 1998; Sireteanu, 2000). Both clinical experience with treatment and extrapolations from animal models (e.g. Hubel & Wiesel, 1970) led to the notion that successful amblyopia treatment is confined to the first 6–8 years of life (Von Noorden & Crawford, 1979). More recently, the concept of a rigid adult visual system lacking plasticity has been challenged (e.g. reviews by Gilbert, 1998; Levi, 2005; Spolidoro et al., 2009). A large number of (sometimes quite controversial) psychophysical, neurophysiological and clinical studies suggested varying degrees of susceptibility to change beyond school entry age (Daw, 1998; Epelbaum et al., 1993; Scheiman et al., 2005; Wandell & Smirnakis, 2009).

Amblyopia treatment lacks standardization concerning not only dosage, but also age limits. This is reflected in textbooks with age limits between "about 8" (Von Noorden & Campos, 2002) and 12 years (Haase & Graef, 2004) and in clinical guidelines (American Academy of Ophthalmology: until 2007 "10 years",

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Table 1
Baseline characteristics of the patients.

Patient no.	Age (years)	Eye	Refraction [D]	Angle of squint (near) [PD]	Initial acuity crowded Landolt [logMAR]	History
1	5.4	RE*	+8.0 −2.0/170°	±0	0.8	Untreated
		LE	+4.75 −0.75/0°		0.2	
2	5.6	RE*	+8.0 −0.5/0°	+10	1.3	Untreated
		LE	+7.75 −0.25/44°		0.5	
3	5.7	RE*	+2.0	+14	1.7	Untreated
		LE	+2.25		0.2	
4	6.0	RE*	+3.0	±0	0.3	Untreated
		LE	+1.0		0.1	
5	6.0	RE	+0.75	±0	0.0	Untreated
		LE*	+6.5 −0.5/160°		1.0	
6	6.0	RE	+5.5	+2	0.1	Untreated
		LE*	+5.25 −0.5/0°		1.0	
7	6.6	RE*	+2.25	+16	0.8	Untreated
		LE	+2.75		0.2	
8	6.9	RE	+2.25 −0.5/140°	+6	−0.1	Untreated
		LE*	+4.75 −1.0/20°		1.0	
9	7.1	RE*	−1.25 +1.25/100°	±0	0.3	Untreated
		LE	−0.25		0.1	
10	7.2	RE	+1.5	±0	−0.1	Untreated
		LE*	+5.25 −0.75/156°		0.7	
11	7.2	RE	0.0	−VD 2	−0.1	Untreated
		LE*	+1.25 −0.75/155°		0.3	
12	7.3	RE*	+6.0 −2.0/170°	Micro	1.0	Untreated
		LE	+5.75 −2.0/180°		0.1	
13	7.7	RE*	+5.5 −1.5/100°	Micro	1.0	Untreated
		LE	0.0		−0.1	
14	8.9	RE*	+3.5 −3.75/175°	±0	0.6	Untreated
		LE	+0.5		0.1	
15	9.0	RE	+0.75 −0.75/0°	+8	−0.1	Untreated (occlusion prescribed at 4–5 yrs., not done)
		LE*	+6.75		1.1	
16	9.1	RE	+2.5	±0	0.1	Untreated
		LE*	+7.0 −3.5/0°		0.4	
17	10.4	RE*	+3.25 −0.75/160°	+35	1.1	Untreated
		LE	+3.25		0.3	
18	10.6	RE*	+2.0 −4.5/175°	±0	0.2	Untreated
		LE	0.0 −0.25/5°		−0.1	
19	11.4	RE	+1.0 −1.0/10°	±0	−0.1	Untreated
		LE*	+6.0 −0.5/175°		0.8	
20	11.6	RE	0.0	±0	−0.1	Untreated
		LE*	+2.0 −1.5/180°		0.3	
21	11.7	RE	+0.5 −0.5/5°	±0	−0.1	Untreated (occlusion prescribed earlier, not done)
		LE*	+1.25 −3.0/0°		0.1	
22	12.1	RE	−0.75 −0.25/62°	Micro	0.1	Untreated
		LE*	0.0		0.8	
23	12.4	RE*	+4.5 −2.5/10°	Micro	0.9	Untreated (occlusion prescribed at 7 yrs., not done)
		LE	+4.0 −2.5/0°		0.0	
24	13.1	RE*	+2.75 −0.25/30°	+6	0.8	Untreated (1 month occlusion at 4–5 yrs. "tried")
		LE	+1.5 −0.25/0°		−0.1	
25	13.6	RE*	+3.0 −1.75/165°	+10	0.6	Untreated (occlusion prescribed earlier, not done)
		LE	0.0 −0.75/5°		0.0	
26	14.3	RE	−0.5 −0.5/171°	±0	0.0	Untreated
		LE*	−1.5 −2.25/6°		0.3	
27	15.8	RE	+1.5 −0.5/60°	+18	−0.1	Untreated
		LE*	+3.75 −0.5/25°		1.7	
Means:	9.2			Means NAE:	0.04	
SD:	3.1			SD NAE:	0.15	
				Means AE:	0.77	
				SD AE:	0.42	

D = diopter, PD = prism diopter. The asterisk marks the amblyopic eye. RE = right eye; LE = left eye; VD = vertical deviation, NAE = nonamblyopic eye; AE = amblyopic eye; SD = standard deviation.

more recently changed to "all children …. regardless of age"; German Ophthalmological Society guideline, 2010: "up to 18 years"). Clinical practice varies accordingly: a questionnaire answered by German and Dutch ophthalmologists and orthoptists yielded upper age limits for the prescription of patching between 4 and 60 years (Fronius et al., 2007), with 20% of the ophthalmologists choosing never to prescribe occlusion treatment beyond the age of 7 years. It is still unclear to what extent less successful treatment in older children and adolescents is due to lower compliance with prescribed treatment or actually to reduced plasticity.

The electronic Occlusion Dose Monitor (ODM) allowed objective monitoring of occlusion treatment (Fielder et al., 1994; Simonsz et al., 1999) as well as the calculation of dose–response relationship, so far mainly in patients of the conventional treatment age between 3 and 8 years (Monitored Occlusion Treatment of Amblyopia Study MOTAS – Stewart et al., 2004b, 2007a; Randomized Occlusion Treatment for Amblyopia Study ROTAS – Stewart et al., 2007b). We demonstrated in a pilot study, including patients with or without previous treatment, that it was feasible to apply occlusion with electronic monitoring between the age of 7 and 16 years (Fronius, Bachert, & Lüchtenberg, 2009). Here we assessed more patients of an extended age range (between 5 and 16 years), all previously untreated, using uniform function tests in the whole group. The aim was to extend knowledge beyond the age investigated by ROTAS and MOTAS into a less studied age range where susceptibility to treatment and thus plasticity is presumably lower (Epelbaum et al., 1993).

We introduced a calculation of treatment efficiency as a measure of a specific aspect of functional plasticity in the human visual system related to amblyopia and patching.

2. Methods

2.1. Participant inclusion and assessment

Participants with strabismic and/or anisometropic amblyopia, between 5 and 16 years of age were included if they were able to accomplish acuity testing with single and crowded Landolt rings. A log minimum angle of resolution (logMAR) acuity difference between the eyes of at least 0.2 after a period of refractive adaptation (wearing glasses for at least 6 weeks before commencing patching, see e.g. Stewart et al., 2004a) was required for inclusion. Patients were not included if they had: other eye disorders; deprivation amblyopia; diminished acuity due to medication, brain damage, or trauma; neurological disorders; spontaneous or easily inducible diplopia; or if the journey to the patient's home was too long for regular visits by researchers for the exchange of the ODM. All patients had a full ophthalmic assessment (including cycloplegic retinoscopy and funduscopy) as well as orthoptic assessment (including angle of strabismus, binocular vision, pattern of fixation determined with the visuscope) before study entry (for details see Fronius, Bachert, & Lüchtenberg, 2009). Prescribed occlusion was usually 6 h/day, unless the treating orthoptists had reasons to deviate from this practice. Visual acuity, scored by line (criterion 4/6 correct), was assessed every 3–5 weeks. Crowded Landolt ring charts with optotype separation 2.6 minarc (Oculus, Wetzlar, Germany) presented at 40 cm distance were used for all patients. Occlusion was recorded using more recent versions of the ODM developed in the Netherlands (Simonsz et al., 1999), which were tested and applied for continuous recording in several previous studies (Awan, Proudlock, & Gottlob, 2005; Chopovska et al., 2005; Fronius, Bachert, & Lüchtenberg, 2009; Fronius et al., 2006; Kracht et al., 2010). Being taped to the occlusion patch, they measure the temperature difference between the patch on the eye and the surroundings. The families also wrote diaries of daily occlusion, so that occlusion times could be completed from the diaries in occasional cases of ODM failure (Fronius, Bachert, & Lüchtenberg, 2009).

The research adhered to "the Code of Ethics of the World Medical Association (Declaration of Helsinki)". The Ethics Committee of the University of Frankfurt approved the study protocol prior to initiation of the study. Written informed consent was obtained from all parents and from participants older than 14 years, and all participants gave assent, prior to inclusion in the study.

2.2. Study participants

Thirty-five patients aged between 5.4 and 15.8 years were recruited from the outpatient clinic of the Pediatric Ophthalmology Department of the University of Frankfurt and several ophthalmologists' offices. Two were not included (one because of comprehension problems, the other because of lack of time of the family). One patient dropped out right after study onset because of parental illness, one lost the ODM immediately and refused to continue participation. Thus, data of 31 patients were recorded. Only previously untreated patients ($n = 27$; mean age 9.2 years ± 3.1)

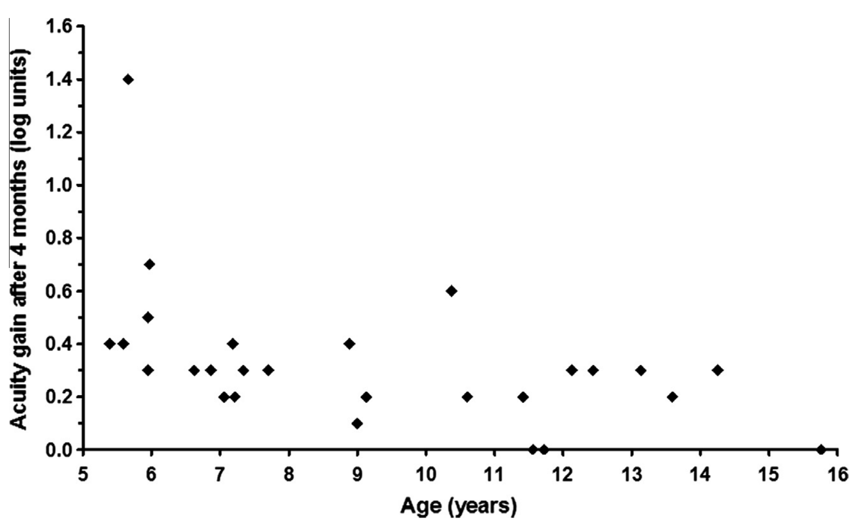

Fig. 1. Relationship between patient age at initiation of occlusion treatment and acuity gains (log units) after 4 months of patching. Linear regression was not an adequate model for these data, therefore no regression line is shown.

Table 2
Electronically recorded occlusion (mean dose rate in h/d ± SD) during the 1st, during the 2nd to 4th months and during the whole 4 months period of treatment.

Group (*n*; mean age ± SD)	1st month	2nd to 4th months	0–4 months
All (*n* = 27; 9.2 ± 3.1)	4.46 ± 1.43	4.07 ± 1.85	4.19 ± 1.63
Age <7 years (*n* = 8; 6.0 ± 0.5)	4.00 ± 1.97	3.47 ± 1.69	3.56 ± 1.68
Age 7–11 years (*n* = 10; 8.4 ± 1.3)	4.46 ± 1.30	4.66 ± 1.73	4.64 ± 1.63
Age >11 years (*n* = 9; 12.9 ± 1.4)	4.88 ± 0.96	3.94 ± 2.10	4.25 ± 1.59

Table 3
Overview of age dependence of dose–response relationship, combined from mathematical modeling data of Stewart et al. (2007a) and our data. In accordance with Stewart et al., the table presents hours of occlusion needed to gain 2 logMAR lines (0.2 log units).

Source of data	Age	Hours occlusion for 2 lines gain (h)
Stewart et al. (2007a)	4 years	170
	6 years	236
Fronius et al.	Mean age 6.0 years	220
	Mean age 8.4 years	490
	Mean age 12.9 years	426

were included in these analyses. Details of their clinical characteristics at the baseline assessment are shown in Table 1. The data of 7 participants, all older than 7 years (nrs. 10, 11, 15, 19 and 25–27), have also been analyzed in our previous pilot study (Fronius, Bachert, & Lüchtenberg, 2009), in which the limited number of participants did not allow the analysis of age dependence of treatment effects, nor did it include patients younger than 7 years or treatment efficiency calculation. The age range overlapping with that of ROTAS/MOTAS was to allow testing for comparability of the procedures.

With logMAR acuities of the amblyopic eyes between 1.7 and 0.1 (interocular differences 1.8–0.2) the group comprised the whole spectrum from severe to mild amblyopia. Eight patients had strabismic amblyopia, 12 anisometropic and 7 combined etiology.

2.3. Data analysis, statistics

To calculate dose–response relationship and treatment efficiency as measures of plasticity, both occlusion recorded by means of the ODM and crowded Landolt ring acuity gains were evaluated after 1 and 4 months of treatment. Some of these data were also analyzed in the context of methodological studies assessing the practicability of continuous electronic recording of occlusion in patients of various ages (Chopovska et al., 2005; Fronius, Bachert, & Lüchtenberg, 2009; Fronius et al., 2006; Kracht et al., 2010). The periods of 1 and 4 months were chosen for the present analysis in order to include the rapid initial changes as well as the time span during which most of the improvement occurs according to previous reports (Kracht et al., 2010; Pediatric Eye Disease Investigator Group, 2003; Stewart et al., 2007b). This is a period during which hardly any changes in prescription are necessary, and during which the majority of the patients may be followed without too many drop-outs. According to ROTAS (Stewart et al., 2007b), the maximal time to reach best acuity was 89 days in children up to 8 years of age. We chose 4 months to allow for possibly more protracted improvement in our older patients.

Treatment efficiency was calculated as: *acuity gain [log units] * 100/recorded occlusion [h] in the same period.* Efficiency values convey the acuity gain per 100 h of administered occlusion during a certain period of treatment.

The following statistical procedures were applied, based on the nature of the data: one-way repeated measures ANOVA by ranks (Friedman test with multiple comparisons by Conover) for

Table 4
Efficiency data (medians, ranges) for the whole sample as well as for the three age groups after 1 and after 4 months of treatment, and results of statistical comparisons (Kruskal–Wallis tests) between groups. Unit for all is log units acuity gain per 100 h occlusion.

Group	After 1 month	After 4 months
All	0.125 (−0.08 to 0.92)	0.05 (0–0.39)
Age <7 years	0.19 (0–0.92)	0.11 (0.04–0.39)
Age 7–11 years	0.13 (0–0.375)	0.05 (0.02–0.10)
Age >11 years	0.07 (−0.08 to 0.24)	0.04 (0–0.12)
Stat.:		
<7 years vs. 7–11 years	$p = 0.422$	$p = 0.051$
<7 years vs. >11 years	$p = 0.094$	$p = 0.014$
7–11 years vs. >11 years	$p = 0.422$	$p = 0.400$

comparison of data between study entry, and 1 and 4 months of occlusion; Wilcoxon matched-pairs test (WMP) for analysis of changes in occlusion dose rate between the two treatment intervals (1st month vs. 2nd to 4th months); one-way ANOVA with multiple Scheffé comparisons, Kruskal–Wallis one-way analysis of variance with multiple Conover–Iman comparisons or Wilcoxon–Mann–Whitney Test (WMW) to compare different groups of patients. Simple regression analysis or Spearman's rank correlation using Edgeworth approximation was applied to study relationships among variables. Multiple regression with backward elimination was used to analyse influencing factors for treatment efficiency. *P*-values < 0.05 were considered statistically significant. All tests were performed using the statistics software package BiAS 10.04© 1989–2013 epsilon-publishing.

3. Results

3.1. Acuity gain

Mean initial, pre-patching acuity of the amblyopic eyes of all patients was 0.77 logMAR ± 0.42, and of the nonamblyopic eyes 0.04 ± 0.15 (see Table 1 for individual values). There was no significant correlation between patient age and initial logMAR values of the amblyopic eyes ($r = -0.12$; $p = 0.54$). LogMAR values improved significantly after 1 month as well as after 4 months of treatment compared to the initial acuity, and also between the 1 and 4 months assessments (all: $p < 0.001$ Friedman test), indicating that the treatment was effective for the patient group during the period analyzed. After 1 month of treatment, all but 7 patients (one 6 years old, the others older than 9 years) showed improved acuity, with a median gain in the whole sample of 0.1 log unit (range −0.1 to 0.9). After 4 months, all but 3 (all over 11 years old) improved at least one line, with a median gain of 0.3 log units (range 0–1.4).

Fig. 1 shows the individual acuity gains after 4 months of patching as a function of age. In spite of some overlap, the data show a tendency toward less improvement with increasing age: zero gain occurred exclusively in patients older than 11 years, and the

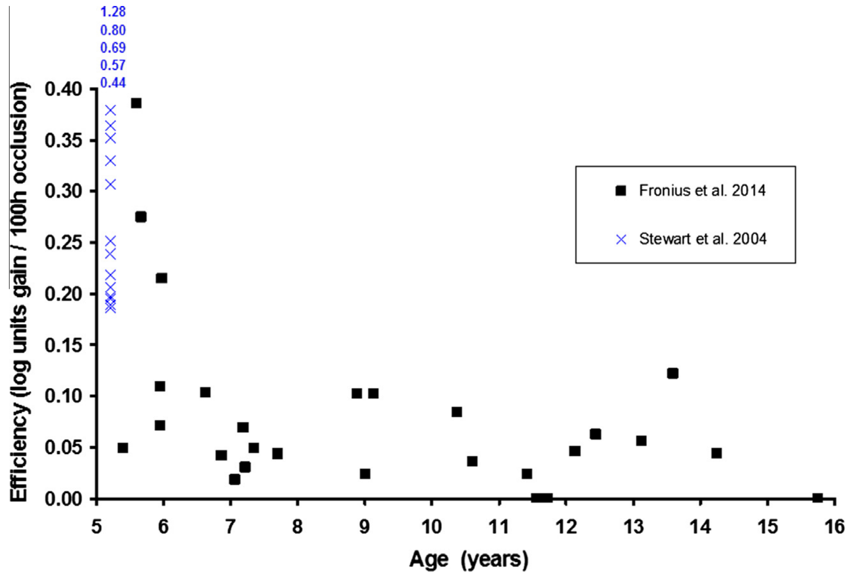

Fig. 2. Relationship between patient age at initiation of treatment and efficiency in acuity gain after 4 months of occlusion of 27 previously untreated patients (black squares). Linear regression between age and logarithmically transformed efficiency data was significant ($r = -0.51$; $p = 0.007$). Crosses and numbers to the left: selected individual efficiency calculated from dose–response data of 3–8 years old patients from the MOTAS study (Stewart et al., 2004b, Fig. 4A; see text 3.3 for details), confirming that efficiency of the magnitude shown by some of our youngest patients (and even much higher, as the numbers are beyond the scale of our ordinate) is not uncommon in this age range.

maximum gain was 0.3 log units in that group. All patients younger than 7 years achieved at least 0.3 log units, and the maximum gain was 1.4 log units in one of the youngest patients.

A simple linear regression model was not adequate for this data because of outliers. Spearman's rank correlation between age and acuity gain after 4 months was significant (rho = −0.58; $p = 0.002$). Kruskal–Wallis one-way analysis of variance revealed significant differences between gains of patients younger than 7 years ($n = 8$; mean age 6.0 ± 0.5; median gain 0.4 log units) and those between 7 and 11 years ($n = 10$; mean age 8.4 ± 1.3; median gain 0.25 log units; $p = 0.043$) as well as those older than 11 years ($n = 9$; mean age 12.9 ± 1.4; median gain 0.2 log units; $p = 0.003$); the difference between the two older age groups was not significant ($p = 0.164$). Initial acuities were not significantly different between any of these three age groups (one-way ANOVA all $p > 0.286$). All age groups comprised patients with and without strabismus (<7 years: 37.5% no strabismus, 62.5% strabismus; 7–11 years: 50% with and without strabismus, respectively; >11 years: 44.4% no strabismus, 55.6% strabismus).

3.2. Electronically recorded occlusion

The question whether the more pronounced acuity gains in the younger patients were attributable to higher occlusion dose rates was analyzed based on the ODM recordings. Following average prescription of 5.44 ± 1.08 h/d, the mean daily received dose rate in the whole group of patients during 4 months of patching was 4.19 ± 1.63 h/d, with individual values extending between 0.75 and 7.99 h/d. Linear regression revealed no significant relationship between age and occlusion dose rate ($r = -0.02$; $p = 0.908$). Table 2 shows all the mean dose rates, of the whole group of patients and then separately for each of the three previously analyzed age groups, separated into the first month, 2nd to 4th months and the whole period of 4 months of treatment.

There were no significant differences in daily dose rates between any of the three age groups during the first month or during the 2nd to 4th month time period (one-way ANOVA, all $p > 0.100$). Although mean occlusion changed slightly between the first and the following 3 months, none of the differences were statistically significant (all $p > 0.100$ WMP). The youngest group occluded on average even slightly less than the other two groups (see Table 2). Thus, the significantly more pronounced acuity gains in the younger patients were not caused by higher occlusion dose rates.

3.3. Dose–response relationship and efficiency of occlusion therapy

After one month of treatment the median *dose–response relationship* was 58.25 h/0.1 log unit acuity gain (range between −124.13 h/0.1 log unit acuity gain in one patient who gained 1 line in the nonamblyopic and lost one in the amblyopic eye, and 186.90 h/0.1 log unit). The median for 4 months of treatment was 169.19 h/0.1 log unit (range 25.90–539.29 h/0.1 log unit).

Table 3 combines our data with those of MOTAS (Stewart et al., 2007a), extending the age range over which dose–response relationship was calculated based on objective recording of occlusion. To be consistent with the article of Stewart and colleagues, dose–response relation is presented in the table as hours of occlusion needed to gain 0.2 log units acuity.

The dose–response relationship becomes more unfavorable with age (see Table 3). At age 6 years, dose–response specified both in our study and MOTAS showed good agreement (220 vs. 236 h/0.2 log units), confirming the comparability of the data. Patients who showed no change in visual acuity (6 during the first month and 3 after 4 months) had to be excluded from this dose–response calculation because of division by zero. Patients excluded from the 4 months calculation were all older than 11 years.

The *treatment efficiency* data (expressed as acuity gain [log units] per 100 h of patching) are shown in Table 4. Efficiency of the whole group ranged between −0.08 and 0.92 after 1 month (median 0.125) and 0–0.39 after 4 months (median 0.05). As to age dependence, after the first month of patching median efficiency decreased from 0.19 in the group of patients aged younger than 7 years to 0.13 in the middle age group and to 0.07 in those older than 11 years, but these differences were not statistically significant at this early stage (see Table 4). After 4 months of treatment, the difference between the youngest (median 0.11) and the oldest age group (median 0.04) was significant ($p = 0.014$).

The ratio between the youngest and oldest age group was 1.9 for dose–response and 2.4 for efficiency.

In a comparison of participants with strabismus ($n = 15$) to those without strabismus ($n = 12$), neither acuity gain nor treatment efficiency were significantly different (all: $p > 0.100$, WMW). Application of multiple regression analysis with backward elimination on the data of the whole group revealed that of the factors analyzed (age, recorded dose rate, initial acuity and presence or absence of strabismus), initial acuity ($p = 0.023$), age ($p = 0.003$) and recorded dose rate ($p = 0.001$) remained as significant independent influencing factors for treatment efficiency after 4 months of patching.

Fig. 2 illustrates the age dependent decline of efficiency over the whole age range of individual patients after 4 months of treatment.

The graph suggests again – despite some overlap – that the age of 7 years seems to mark a change in the susceptibility of the visual system to treatment: efficiency over 0.123 occurred exclusively in patients younger than 7 years, efficiency of less than 0.04 only in those over 7. Fig. 2 also includes for comparison, efficiency data calculated from the inverse of the dose–response values of Stewart et al. (2004b) available in their Fig. 4A in patients between 3 and 8 years (albeit without detailed specification of age). The selected data shown (crosses and numbers to the left side of our Fig. 2) confirm that efficiency of the magnitude found in some of our youngest patients (and even much higher) is not uncommon in this age range.

A linear regression model was not adequate for our efficiency data. Logarithmic transformation of the values according to a procedure taking into consideration zero efficiency (Berry, 1987) yielded a significant ($p = 0.007$; $r = -0.51$) linear regression with age.

4. Discussion

4.1. Evaluation of our data

This study provided the first quantitative account of the age dependent decline of occlusion treatment efficiency between about 5 and 16 years, with the maximal effect occurring before 7 years. The application of the ODM technology supplied interesting insights into the susceptibility of the visual system based on quantified periods of enforced use of the amblyopic eye in a rare group of previously untreated amblyopes. Spanning for the first time an age range from within to beyond the conventional age for patching, this study includes the age range which is within the focus of current alternative treatment approaches (see Section 4.4). The age range of 5–8 years, overlapping with that of previous studies (e.g. Stewart et al., 2004b), confirmed comparability with existing data, rendering the collection of a larger sample of this age unnecessary (see e.g. Table 3). Moreover, our current findings in the mean age group 12.9 years (dose–response 426 h/0.2 log units gain) are consistent with the dimension of the dose–response values from our earlier pilot study (Fronius, Bachert, & Lüchtenberg, 2009) with a small patient sample comprising previously treated and untreated amblyopes of mean age 11.1 years and 468 h/0.2 log units gain. The availability of objective occlusion data allowed the calculation of treatment efficiency, proposed here as an index of age dependent susceptibility of the visual system. It is important to note that patching treatment for amblyopia is a commonly used (Wong, 2012), albeit specific approach to investigate visual system plasticity. We detected a source of bias in the analysis of age dependence of dose–response relationship: patients whose acuity remains unchanged have to be excluded from the calculation because of division by zero. Calculation of efficiency avoids this problem. As our data shows, this was more likely in the older amblyopes (only over 11 year old patients after 4 months of treatment), and may therefore influence assumptions about the magnitude of reduction of plasticity with increasing age. These findings are relevant both in a neuroscientific context and with regard to further optimization of amblyopia treatment. Significant improvement in visual acuity was found not only in the youngest, but also in the older groups after 4 months, confirming that it is worthwhile considering treatment beyond 7 years of age. The significantly more pronounced effects in the youngest age group regarding most findings emphasize the relevance of early detection and urgent treatment of amblyopia. It is important to note that during 4 months of treatment none of the patients reported serious side effects, but exclusion of patients who tend to experience diplopia without much dissociation of the images of the two eyes is advisable.

Both data collection and evaluation were very time-consuming. But the procedure of continuous recording with frequent exchanges of the ODM during home visits by researchers prevented significant drop-out of patients from the study and minimized data loss. Patients older than 7 years (especially previously untreated ones) rarely show up for treatment, and the number of available ODMs was limited (Fronius, 2011; Simonsz, 2012). It was advantageous that the age groups were representative and comparable as to the etiology and severity of amblyopia, and that their actual accomplished mean occlusion was not significantly different. We are aware that the patient sample consisted of selected families accepting the ODM recording, which may influence compliance with treatment and thus outcome. Yet, despite knowledge of monitoring, compliance (calculated as recorded/prescribed dose rate) ranged between 0.17 and 1.65 (mean 0.77) during the period of four months of treatment. It was not the aim of this research to collect compliance data representative for the common clinical population, but to gain insight into dose–response and efficiency as indices for age dependent plasticity. Despite occasional interruptions due to ODM failure, by combining the recordings with patients' diaries (Fronius, Bachert, & Lüchtenberg, 2009), this is so far the most advanced way of continuous monitoring of treatment over several months. As the families were aware of the recording, agreement between ODM data and diaries was usually very good, even if compliance was poor. If agreement was not satisfactory, prompt feedback from the researchers enhanced the quality of the diaries. And of course, patients and their families were not aware if and when an ODM failed to record.

In addition to the factors identified by the multiple regression model as significant for treatment efficiency (age, initial acuity, occlusion dose rates), it cannot be ruled out that some of the variability in the data may be related to different types of activities that the patients engaged in during patching. All were advised to do demanding near work at least part of the time. A PEDIG study (2008) found no significant difference in acuity improvement between near and distance activities during patching.

4.2. Relationship to previous studies

Most previous studies investigating the age dependence of the effect of occlusion treatment for amblyopia had a clinical background, and with a few exceptions (Awan, Proudlock, & Gottlob, 2005; Stewart et al., 2004b, 2007a, 2007b), all lacked objective data of accomplished patching. Epelbaum et al. (1993), in an interesting analysis of the influence of age, reported plasticity close to zero from about 11 years of age. Our four patients aged 12.1–14.3 years who gained 0.3 log units, as well as data by Mohan, Saroha, and Sharma (2004), suggest that the conclusion of Epelbaum and colleagues may have been mislead by lack of knowledge of their patients' compliance. The "rate of responders" (patients achieving at least 0.2 log units improvement) after 4 months of treatment was higher in our patients older than 7 years than in the respective

PEDIG study (Scheiman et al., 2005), probably due to higher prescribed and actually received dose rates in our study.

A large number of studies agree that there is residual plasticity in amblyopes beyond the once assumed age of 6 or 8 years and even into adulthood (Chen, Song, & Wu, 2003), emphasizing either the importance of age (Fulton & Mayer, 1988; Holmes et al., 2011; Rutstein & Fuhr, 1992; Sattler, 1927) or of compliance (Arnold, Armitage, & Limstrom, 2008; Mintz-Hittner & Fernandez, 2000; Park, Hwang, & Ahn, 2004), or the interdependence of the two (Oliver et al., 1986) for successful treatment. In accordance with the MOTAS/ROTAS studies (Stewart et al., 2004b, 2007a, 2007b) and a meta-analysis of the Amblyopia Treatment Studies (ATS, Holmes et al., 2011), we found decreasing susceptibility of the visual system with age to the enforced use of the amblyopic eye. The studies of Stewart et al. (2004b, 2007a, 2007b) covered age groups younger than ours (with some overlap, showing good agreement of results), and collected objective dose rate data allowing the calculation of dose–response relationship of treatment. Although without treatment monitoring, the ATS described a nonlinear relationship between age and improvement, with a difference in responsiveness to treatment between patients younger and older than 7 years of age. Our study confirmed the nonlinear trend as well as significant differences between these age groups, adding novel data on the efficiency of treatment calculated on the basis of objective ODM recordings.

4.3. Considerations about mechanisms

In recent decades, a number of beliefs concerning the time span of maturation (later than assumed) and residual adaptability (more than suspected) of the visual system has had to be revised. Acuity development (especially crowded acuity) seems to continue to some extent until even after the age of 11 years (Haase, 2003; Jeon et al., 2010). Bavelier et al. (2010) and Baroncelli, Maffei, and Sale (2011) have given comprehensive overviews of the current considerations and open questions about the changes governing development and late plasticity. It is still unclear to what extent later improvement is based on unmasking of previously established, but inhibited circuitry via alteration of the excitatory/inhibitory balance, or on the development of new connections after removal of structural "brakes", and how this changes with age. The binocular training applied by Hess, Mansouri, and Thompson (2011) assumes a structurally intact binocular system in amblyopia which needs reduction of inhibitory influence.

Our study adds to the sparsely available data about susceptibility to occlusion treatment during the period of transition from childhood to adolescence. Unfortunately the clinical history of amblyopes is usually not clear enough to allow assumptions about the period of normal development after which amblyogenic factors or amblyopia occurred. Our preliminary prospective data on the development of the depth of interocular suppression during occlusion treatment in amblyopes of this age span suggest that suppression and acuity do not change in parallel (Fronius et al., 2013), making a simple relationship (enhanced acuity due to reduced suppression) unlikely. Refined methods for quantifying the depth of suppression, applicable also in younger children (e.g. Narasimhan, Harrison, & Giaschi, 2012), may enhance understanding of these phenomena.

4.4. Future prospects

After the procedure has been established, age dependent susceptibility of further visual functions with different critical periods (Daw, 1998) may be analyzed in conjunction with quantified intensity of occlusion. Correlations between them may elucidate mechanisms of plasticity of various structures in the visual system. Our data may gain additional importance in the context of various attempts to influence amblyopia with alternative approaches such as perceptual learning (Astle, Webb, & McGraw, 2011; Levi & Li, 2009; Polat, Ma-Naim, & Spierer, 2009), playing video games (Li et al., 2011), various types of binocular training (Hess, Mansouri, & Thompson, 2011; Knox et al., 2012), as well as acupuncture (Zhao et al., 2010), pharmacological enhancement (Campos & Fresina, 2006; Maya Vetencourt et al., 2008), and transcranial magnetic (rTMS, Clavagnier, Thompson, & Hess, 2013; Thompson et al., 2008) or current stimulation (Spiegel et al., 2013a, 2013b), many of which are hardly applicable in young children. Our acuity gain, dose–response and efficiency data may serve as reference for the age dependent effort (e.g. hours of training) necessary to achieve a corresponding effect like with patching.

Findings from studies demonstrating effects of late treatment for amblyopia have already had political implications: in Germany the implementation of pre-school screening for amblyopia/amblyogenic factors by ophthalmologists and orthoptists was turned down with the argument that currently, based on available evidence from studies, it could not be ruled out that amblyopia treatment was equally effective in childhood and in adolescence. In our study treatment efficiency declined significantly with age, suggesting that for the same treatment effect (e.g. acuity gain of 2 lines after 4 months), patients aged between 5 and 7 years had to patch on average around 200 h, those over 7 years more than 400 h, which implies a considerable difference in the feasibility of treatment and associated reduction of quality of life (Pieh et al., 2009). Better availability of ODMs in the future will allow recording of longer periods in larger groups of patients, elucidating more comprehensively effective duration and factors influencing treatment success.

4.5. Conclusion

Electronically recorded occlusion allowed insight into age-dependent efficiency of patching treatment for amblyopia, in previously untreated patients between 5 and 16 years of age. Efficiency is suggested to extend knowledge about declining functional plasticity of the human visual system, and to supply a basis for comparison of effects of patching vs. emerging alternative approaches for amblyopia treatment.

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