ORIGINAL INVESTIGATION

Agreement and Repeatability of Noncycloplegic and Cycloplegic Wavefront-based Autorefraction in Children

Franziska G. Rauscher, PhD,[1,2]* Heike Lange, MSc,[2] Maryam Yahiaoui-Doktor, PhD,[1] Helmut Tegetmeyer, MD,[2] Ina Sterker, MD,[2] Andreas Hinz, PhD,[3] Siegfried Wahl, PhD,[4,5] Peter Wiedemann, MD,[2] Arne Ohlendorf, PhD,[4,5] and Ralf Blendowske, PhD[6]

SIGNIFICANCE: Increasing prevalence of refractive error requires assessment of ametropia as a screening tool in children. If cycloplegia is not an option, knowledge about the increase in uncertainty for wavefront-based autorefraction is needed. The cycloplegic agent as the principal variant presents cross-reference and allows for extraction of the influence of accommodation.

PURPOSE: The purpose of this study was to determine the repeatability, agreement, and propensity to accommodate of cycloplegic (ARc) and noncycloplegic (ARnc) wavefront-based autorefraction (ZEISS i.Profiler plus; Carl Zeiss Vision, Aalen, Germany) in children aged 2 to 15 years.

METHODS: In a clinical setting, three consecutive measurements were feasible for 145 eyes (OD) under both conditions. Data are described by spherical equivalent (M), horizontal or vertical astigmatic component (J0), and oblique astigmatic component (J45). In the case of M, the most positive value of the three measurements was chosen, whereas the mean was applied for astigmatic components.

RESULTS: Regarding agreement, differences for ARc minus ARnc were statistically significant: for M, 0.55 (0.55 D; mean [SD]; $P < .001$), that is, more hyperopic in cycloplegia; for J0, –0.03 (0.11 D; $P = .002$); and for J45, –0.03 D (SD, 0.09 D; $P < .001$). Regarding repeatability, astigmatic components showed excellent repeatability: SD < 0.11 D (ARnc) and SD < 0.09 D (ARc). The repeatability of M was SD = 0.57 D with a 95% interval of 1.49 D (ARnc). Under cycloplegia, this decreased to SD = 0.17 D (ARc) with a 95% interval of 0.50 D. The mean propensity to accommodate was 0.44 D from repeated measurements; in cycloplegia, this was reduced to 0.19 D.

CONCLUSIONS: Wavefront-based refraction measurement results are highly repeatable and precise for astigmatic components. Noncycloplegic measurements of M show a systematic bias of 0.55 D. Cycloplegia reduces the propensity to accommodate by a factor of 2.4; for noncycloplegic repeated measurements, accommodation is controlled to a total interval of 1.49 D (95%). Without cycloplegia, results improve drastically when measurements are repeated.

Optom Vis Sci 2019;96:879–889. doi:10.1097/OPX.0000000000001444
Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Optometry. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

OPEN

Author Affiliations:
[1]Institute for Medical Informatics, Statistics, and Epidemiology, Leipzig University, Leipzig, Germany
[2]Department of Ophthalmology, Leipzig University, Leipzig, Germany
[3]Department of Medical Psychology and Medical Sociology, Leipzig University, Leipzig, Germany
[4]ZEISS Vision Science Lab, Institute for Ophthalmic Research, Eberhard Karls University Tuebingen, Tuebingen, Germany
[5]Carl Zeiss Vision International GmbH, Aalen, Germany
[6]Department of Mathematics and Natural Sciences, University of Applied Sciences, Darmstadt, Germany
*franziska.rauscher@medizin.uni-leipzig.de

The measurement of wavefront aberrations has become a widely used and applicable technology in ophthalmology and vision science over the last decade. Therefore, it is essential to know about the metrological details of these devices used to determine the objective refraction. The focus of the article is measurements in children.

It has been suggested to use wavefront-based autorefraction to determine central refractive errors in pre-school and schoolchildren.[1] Therefore, because screening studies increasingly use such devices,[2–4] it is important to establish repeatability and accuracy of wavefront-based devices.

For data from a typical clinical setting, the feasibility of wavefront-based autorefraction in children is examined first. Second, the agreement between cycloplegic measurements and results under natural conditions are investigated. Noncycloplegic refractions in children, despite their obvious disadvantages, become more frequently used. In most countries of Europe, the application of cycloplegic drops is considered an invasive method. Therefore, ethics councils sometimes refrain from giving permission to more general orientated studies in children to include cycloplegic screening of refractive error. Third, to estimate the short-term repeatability of refraction data under both conditions, repeated measurements in both cases are obtained. From these data, the propensity to accommodate is investigated.

Agreement of noncycloplegic and cycloplegic measurements of autorefraction (abbreviated as ARnc and ARc hereinafter) within one instrument was established only in a few studies; none of them are wavefront-based devices.[5–11] Some method comparison studies of ARc or ARnc measured with wavefront-based devices exist with regard to subjective refraction or retinoscopy,[12–15] including one study on a handheld wavefront-based device in 40 children (age, 5 to 17 years).[12] Therefore, the only data for ARc and ARnc in the same wavefront-based instrument were obtained for a handheld device.

Research studies examining different objective methods investigating repeatability of autorefractor measurements in children have used handheld autorefractors and eccentric photorefractors.[6,16–18] More recently, wavefront-based autorefractors were investigated for repeatability in adults,[13,14,19–23] children,[12,24] and infants.[25] The three studies investigating repeatability for wavefront-based measurements in children are not sufficient to estimate repeatability for a larger age range nor can their data be used as cross-reference for examinations with the tabletop ZEISS i.Profiler plus (Carl Zeiss Vision GmbH, Aalen, Germany) in children: cycloplegic repeatability data were presented for the COAS G200 system, a wavefront-based tabletop design (Wavefront Sciences, Albuquerque, NM), by Martinez et al.[24] in 81 subjects around 12 years of age. Noncycloplegic repeatability in 74 infants was studied for handheld wavefront-based SureSight (Welch Allyn, Skaneateles Falls, NY) by Adams et al.[25] Rosenfield and Ciuffreda[12] investigated repeatability of cycloplegic and noncycloplegic wavefront-based autorefraction for a handheld device in a small group of five subjects (age, 5 to 17 years) for the SVOne (Smart Vision Labs, New York, NY).

Very few data on noncycloplegic and cycloplegic measurements of autorefraction in children within one instrument based on wavefront-based technology exist. Our study expands these data regarding the range of age, range of refractive errors, and the number of participants.

METHODS

This study was approved by the institutional ethics board of the Medical Faculty of Leipzig University. Informed written consent from at least one parent or legal guardian and verbal assent from each child were obtained. The child then was invited to participate in the wavefront-based autorefraction and had the opportunity to opt out at any point in time. Clinical refraction data were examined for all children as part of their routine visit between May and November 2013 at the Paediatric Ophthalmology Section of the Department of Ophthalmology at the University Hospital Leipzig. Routine examination included the assessment of refractive errors by cycloplegic retinoscopy and by using wavefront-based autorefraction before and after application of cycloplegia. The individual performing retinoscopy was not aware of wavefront-based autorefraction results. Cycloplegia was induced by applying 0.5% tropicamide (Mydrum, Bausch & Lomb GmbH, Berlin, Germany) as part of the clinical routine eye examination. Yazdani et al.[26] showed that differences between tropicamide and cyclopentolate are not significant for a 1% solution. Furthermore, the percentage concentration of 0.5% was used successfully in previous studies.[27,28] Nevertheless, this may be considered to be a weak cycloplegic agent. To this end, each eye was checked by the leading ophthalmologist during retinoscopy for absence of fluctuations of the neutral retinoscopic reflex and absence of a light-induced change of pupil diameter. If it were judged that cycloplegia was incomplete, one more dose would be necessary. However, such a case was not observed.

Data were obtained in the following sequence. The measurement protocol prescribed three repeated measurements of noncycloplegic wavefront-based autorefraction. The autorefraction measurement process per eye takes less than 1 minute once the child is situated in front of the machine. Then, one drop of the aforementioned cycloplegic agent was administered into each eye, and after an interval of 10 minutes, a second drop was inserted into each eye. Twenty minutes after the second drop was administered, cycloplegia was examined as described previously. Then, three repeated measurements with wavefront-based autorefraction in cycloplegia were obtained.

One optometrist (HL) performed both autorefractions with the wavefront-based device (ZEISS i.Profiler plus; Carl Zeiss Vision GmbH).[29]

In total, 201 children (106 male and 95 female, aged 2 to 15 years) were examined in the given time frame. Children with a pathological chief complaint and/or abnormalities/diseases of the retina, lens, or cornea were excluded from this clinic-based data set before the current analysis. However, data of subjects with strabismus (if fixation for single-eye measurements was adequate), amblyopia, nystagmus, or anisometropia were allowed to be included into the analysis. Children who had fewer than three measurements under either measurement condition were excluded from the presented analyses. Both eyes were analyzed separately, and according to current practice, only data on one eye (right eyes) are presented in text and tables.

A wavefront aberrometer based on a Hartmann-Shack sensor, the ZEISS i.Profiler plus, was used to measure the outcoming wavefront for each eye of the participant three times. A chin and head rest was used to stabilize the subject's head. The alignment with reference to the measurement instrument was achieved automatically by detecting the pupil center. A fixation target is used to reduce the eye's movement. In case of blinking or a larger decentration of the eye, the measurement is repeated automatically after a few seconds. During the measurement, the subject looks through the optics of the instrument at a projected target (hot air balloon with colored stripes), which undergoes a fogging process to relax accommodation. Then, a series of images are taken with the Hartmann-Shack sensor and combined into one result. This entire process is called one measurement.

The process of presenting the target is divided into three parts: (1) a fogged target is shown in the beginning; (2) the far point of the eye is measured, and the optical distance of the projected target is adjusted accordingly to produce a sharp image; and (3) as a last step, the image of the target is slowly fogged during 3 seconds to deaccommodate the eye. During this deaccommodation process, three internal measurements are obtained. This procedure is considered to minimize accommodation.

The eye's wavefront is measured over the complete pupil, which is detected automatically by the instrument. However, to determine autorefraction data, the internal software reduces the evaluated pupil size to a diameter of 3 mm. In this central region, the second-order Zernike coefficients of the wavefront are determined and converted to equivalent sphere (M) and two astigmatic components, J0 (horizontal/vertical astigmatism) and J45 (oblique astigmatism), as described previously.[30]

To minimize the influence of accommodation, the most positive value of the spherical equivalent (M) is chosen. To emphasize this fact, instead of a mean value, the least negative (myopic) result of the three measurements is applied. The three results for the astigmatic components (J0 and J45), however, are represented by their ordinary mean value.

Statistical Assessment of Repeatability and Agreement

Agreement

For the comparison of noncycloplegic and cycloplegic wavefront-based autorefraction, the method comparison approach by Bland and Altman[31] is applied. Agreement between measurement conditions was assessed by computing the difference between measurements in both conditions, ARc minus ARnc for each subject. These differences are averaged across the group to give the mean difference, termed *bias*. A positive value for the bias signalizes a more myopic result for ARnc, that is, potential accommodation.

Repeatability

The measurements are repeated by the same operator in a time interval of a few minutes. This could be referred to as short-term repeatability; however, the common wording of repeatability is applied.

Two different statistical approaches are used to determine the repeatability for the astigmatic components and the spherical equivalent.

The three measurements for astigmatic components J0 and J45 are represented by their mean value and their spread by the standard deviation. The representative variability of all subjects is then described by the pooled variance (arithmetic mean of individual variances):

$$S_p^2 = \frac{1}{N} \sum_{n=1}^{N} S_n^2$$

This quantity is also known as "within-subject variability" from an analysis of variance, where each subject is treated as a group.[32] By taking the square root of pooled variance, a pooled standard deviation S_p is calculated. The 95% reference interval is estimated by $\pm 1.96 \cdot S_p$.

In case of the spherical equivalent M, the method to evaluate the results is different. Here, the most positive value of the set of three measurements is chosen. The rationale behind this approach is the following. If the status of the eye with the lowest refractive power is considered as zero accommodation, the process of accommodation can change the results only in one direction, namely, increasing the refractive power, leading to more myopic values of the spherical equivalent. In other words, accommodation cannot be negative. Hence, we elect the most positive value of M, or the one with the lowest accommodation. The elected value will be denoted by a tilde, $\tilde{M}$.

The variance of this elected value has to be estimated to access its repeatability. It is assumed that the elected value will deviate from the true one, denoted M, by an unknown amount of accommodation A. Hence,

$$\tilde{M} = M - A$$

where the accommodation A is positive or zero. Only if the accommodation is zero, the desired value M is measured.

An estimate for the probability distribution for the occurrence of accommodation can be extracted from presented repeated measurements in the following way. From the most positive value, the remaining two measurement results are subtracted for each eye:

$$\Delta M_k = \tilde{M} - M_k \quad k = 1, 2$$

They represent the propensity to change the accommodation. These remaining values are pooled for all eyes, and their distribution is taken as an empirical proxy to the propensity to accommodate.

The mean of this distribution describes the offset from zero accommodation (bias). The standard deviation is taken as an estimate for the repeatability.

In addition, an exponential distribution ($\lambda \exp(-\lambda x)$), with only one parameter λ, is fitted to the data. Both the mean and the standard deviation are given by the inverse of the fitting parameter λ. Simplicity and the reasonable shape motivated the heuristic choice of the exponential distribution.

Under cycloplegia, such argument applies to a much lesser extent for measurements as well, where a remaining tonic accommodation does not necessarily guarantee zero accommodation. Having this caveat in mind, information on accommodation behavior during the measurement process presents valuable empirical information, which is available only from repeated measurements.

RESULTS

First, the aspects of feasibility are presented. Noncycloplegic wavefront-based autorefraction was termed *ARnc*, and cycloplegic measurements are referred to as *ARc*. All children in the said time frame were examined. After exclusion of children with aforementioned pathologies, 187 children entered the investigation. Here, nystagmus was present in three subjects with minor severity; amblyopia was present in 16 eyes.

As a first finding, wavefront-based autorefraction was not successfully obtained in 11 young children for the initial ARnc measurement (ages, 1 to 4 years plus a 12-year-old); here the main reasons were anxiousness or an excess of body/head movements during measurement. In these children, ARc was not attempted. In addition, further 15 children have no ARc measurements, as they declined to be examined by cycloplegic autorefraction at the end of their visit; their ages were 3 to 12 years.

Because the wavefront-based measurement was part of the children's routine visit at the Department of Ophthalmology, three measurements were encouraged but not mandatory. For the presented article, children who had fewer than three autorefractor measurements under either measurement condition were excluded from the respective repeatability and agreement analyses. Depending on the attention and cooperation of each child during measurement, for ARnc, fewer than three measurements were obtained in 10 children (ages, 2 years [one child], 3 years [five children], 6 years [two children]), and for ARc, fewer than three measurements were obtained in 16 children (ages, 3 years [three children], 4 years [one child], 5 years [four children], 6 years [three children), 7 years [one child], 8 years [one child], 9 years [one child], 10 years [two children]).

Based on three measurements per eye and measurement technique, the intersection formed the analyzed data set, which consisted of 145 children (ARc: 73 pre-school children; mean [standard deviation] age, 4.9 [1.0] years) and 72 schoolchildren (mean [standard deviation] age, 9.3 [2.2] years). The descriptive results of the mean across the groups are presented in Table 1. The spans of refractive errors are greater than 16 D for M, 3.9 D for J0, and 1.8 D for J45.

Agreement of Wavefront-based Autorefraction

Agreement: Astigmatic Components (J0, J45)

For the comparison of wavefront-based autorefraction without cycloplegia and with cycloplegia, data for the astigmatic components are shown in a Bland-Altman plot; see Fig. 1, where the difference of data for the two conditions along the ordinate is plotted against the mean along the abscissae. The abscissae are scaled identically for both components, rendering a visual impression of the much smaller span of the oblique component J45 in comparison with J0.

A clinically irrelevant bias of –0.026 D (J0) and 0.025 D (J45) was found. The total width of the 95% reference interval is 0.40 D (J0) and 0.33 D (J45). Hence, 95% of all differences for measurements under the two conditions are smaller than 0.4 D. All data points including probable outliers that present the typical clinical situation are shown in Fig. 1; see Table 2 for full results.

TABLE 1. Overview of descriptive statistics regarding noncycloplegic (ARnc) and cycloplegic (ARc) wavefront-based autorefraction

	Measurement condition	ARnc			ARc		
	Refractive error data (D)	*M* (most positive)	J0	J45	*M* (most positive)	J0	J45
All children (n = 145)	Mean	1.38	0.32	–0.02	1.92	0.29	0.01
	SD	2.21	0.55	0.27	2.34	0.53	0.28
	Min	–8.02	–0.79	–0.87	–8.60	–0.82	–0.66
	Max	8.44	3.07	1.04	8.78	2.94	1.22
	ARnc compared with ARc	$P = .04$	$P = .68$	$P = .45$			
Preschool children (2–6 y; n = 73)	Mean	1.51	0.34	–0.02	2.23	0.32	0.02
	SD	1.97	0.51	0.28	1.95	0.50	0.28
	Min	–1.46	–0.79	–0.80	–1.08	–0.82	–0.66
	Max	8.44	1.94	0.98	8.78	1.94	1.18
	ARnc compared with ARc	$P = .02$	$P = .81$	$P = .48$			
Schoolchildren (7–15 y; n = 72)	Mean	1.24	0.29	–0.02	1.61	0.26	0.00
	SD	2.45	0.59	0.26	2.65	0.55	0.27
	Min	–8.02	–0.69	–0.57	–8.60	–0.71	–0.49
	Max	7.12	3.07	1.04	8.08	2.94	1.22
	ARnc compared with ARc	$P = .38$	$P = .72$	$P = .72$			

Refractive error data (right eyes) from three measurements. The most positive was elected for *M*. The astigmatic components J0 and J45 are averages. The upper rows present descriptive statistics for all subjects, the middle rows display descriptive statistics for pre-school children, and the lower rows depict descriptive statistics for schoolchildren. We emphasize the large span (>16 D) of our data for the spherical equivalent. *P* values are provided for the difference between the cycloplegic and noncycloplegic findings.

Most of the differences do not follow from the dissimilarity between measurement conditions (ARc or ARnc) but reflect the repeatability of each method itself. This can be seen from the coefficients of repeatability ($\sqrt{2} \cdot 1.96 \cdot S_p$) for each condition. The results are the following: 0.24 D for J0 and 0.21 D for J45 in cycloplegia and slightly higher values of 0.30 D for J0 and 0.29 D for J45 without cycloplegia; see Table 3 for full results. All differences (less than tenths of a diopter) are clinically irrelevant. Therefore, statistics are omitted.

The results of the analysis of left eye data (not presented) agree with the results obtained for the right eye.

The statistical comparison of agreement (J0, J45) between ARnc and ARc for pre-school (younger than 7 years) children versus schoolchildren showed no statistically significant difference.

Agreement: Spherical Equivalent (M)

The agreement for the spherical equivalent (*M*) can be estimated from the Bland-Altman plot in Fig. 2. As stated previously, the values for the spherical equivalent are determined from the most positive value of three measurements. The ARnc minus ARc difference results in a bias of +0.55 D ($P < .001$). Hence, measurements without cycloplegia are more myopic, as can be expected from the remaining accommodation. The limits of agreement for the differences span an interval of total width of 2.21 D, or 1.10 D to either side of the bias value (bias, 0.55; –0.55 to +1.65); for full results, see Table 2.

Although the Bland-Altman plot focuses on the agreement of final results, the scatterplot in Fig. 3 illustrates the variability as available from repeated measurements. Data points show the most positive measurement result. The bars, extending in negative direction (to the left or downward), represent the range of accommodation with reference to the data point. The inset expands the densely populated region between –1.5 and 2.5 D. Most of the data lie above the bisecting line (not shown), as expected from results being more myopic in the ARnc condition.

Analyses for pre-school versus schoolchildren resulted in no statistically significant differences. As before, results for the left eye (not shown) are nearly identical.

Repeatability of Wavefront-based Autorefraction

Repeatability: Astigmatic Components (J0, J45)

The distributions of the centered coordinates for both astigmatic components J0 and J45 are shown in Fig. 4. The distributions are too leptokurtic to represent a normal distribution. The Jarque-Bera test rejects the null hypothesis that a normal distribution is present, at a level of $P < .001$ for all distributions. This is a typical result for data from a clinical environment because far-lying outliers distort the otherwise normal distribution.

The spreads of the distributions, as described by the pooled standard deviation, are 0.11 D (J0) and 0.08 D (J45) under the ARnc condition and 0.09 D (J0) and 0.08 D (J45) under the ARc condition; see Table 3 for full results. The Ansari-Bradley test rejects the null hypothesis that variances are different at $P = .65$. We therefore conclude that there is no significant effect of cycloplegia on repeatability of astigmatic components. No effect of age groups on repeatability can be seen from our data. The data on the left eye (not shown) are nearly identical.

Repeatability: Equivalent Sphere (M)

To evaluate the repeatability of the spherical equivalent *M*, the standard deviation of the empirical distribution of accommodation

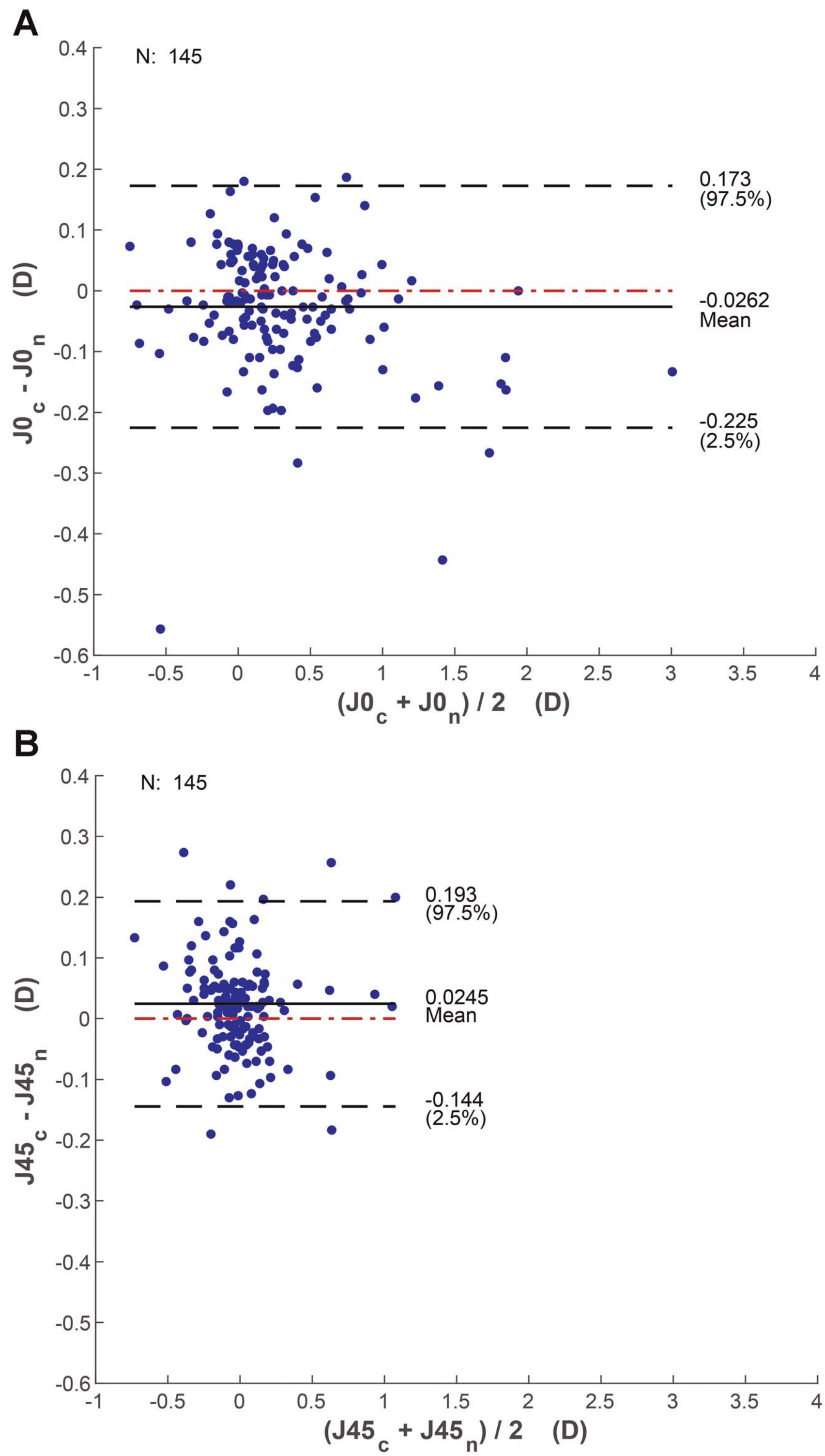

FIGURE 1. Agreement for astigmatic components J0 (top) and J45 (bottom) compared for measurements obtained under the cycloplegic and noncycloplegic conditions. The bias (mean) is marked as a solid black line, and zero difference is included as a red dot-dashed line for orientation purposes. The bias is clinically insignificant for both components. The 95% limits of agreement are shown as dashed black lines. Most of the variability stems from each measurement process itself. The span of values for component J45 is much smaller than that for J0.

is estimated relative to the most positive value measured. Fig. 5 displays the distribution for the two investigated conditions. In addition to the histogram of the probability density, calculated from the empirical data, a fit is added for the exponential distribution. The inverse of the only fit parameter λ equals both the mean value and the standard deviation. There are very few contributions

TABLE 2. Agreement between noncycloplegic (ARnc) and cycloplegic (ARc) measurement conditions for all subjects (n = 145, right eyes) and separated for pre-school children and schoolchildren

	ARc minus ARnc (D), n = 145		
	M	J0	J45
All children	*P* < .001	*P* = .002	*P* < .001
Mean	0.55	–0.03	0.02
SD	0.56	0.11	0.09
2.5 percentile	–0.22	–0.26	–0.13
50 percentile	0.42	0.02	0.02
97.5 percentile	1.84	0.15	0.22
±LoA	1.05	0.16	0.17
Preschool children	*P* < .001	*P* = .13	*P* = .002
Mean	0.72	–0.02	0.03
SD	0.59	0.11	0.09
2.5 percentile	–0.11	–0.28	–0.13
50 percentile	0.56	–0.01	0.04
97.5 percentile	2.22	0.16	0.24
±LoA	1.16	0.22	0.17
Schoolchildren	*P* < .001	*P* = .004	*P* = .10
Mean	0.38	–0.03	0.02
SD	0.48	0.09	0.08
2.5 percentile	–0.30	–0.20	–0.12
50 percentile	0.30	–0.02	0.02
97.5 percentile	1.56	0.14	0.19
±LoA	0.93	0.17	0.16

The computation of ARc minus ARnc for the comparison of agreement of the measurement conditions (all entries are in diopters) showed a statistically significant difference for *M* and for some entries of J0 or J45. However, the computed difference between astigmatic components is clinically insignificant. LoA = limit of agreement.

beyond the limit of 2 D, which are not visible at this scale. Therefore, the abscissa is truncated at 2 D.

As expected, children under the ARc condition do accommodate very little, with a mean (standard deviation) value of 0.185 (0.185) D (confidence interval, 0.17 to 0.21 D). This number is probably an upper limit because the current data represent a typical clinical, not an optimal environment.

Under the ARnc condition, the distribution becomes much broader, and the mean (standard deviation) value increases by a factor of 2.4 to reach a value of 0.448 (0.448) D (confidence interval, 0.40 to 0.50 D). All values are obtained from the fitted distribution. Numbers calculated directly from the empirical distribution agree nicely regarding the mean value for both ARc and ARnc. A higher result is obtained for standard deviation (0.57 D) in the ARnc condition. This difference in standard deviation indicates a deviation from the exponential distribution, most probably due to outliers.

The empirical 95% percentiles are 1.49 D for ARnc and 0.50 D for ARc, which means that the width of the ARc reference interval is a third of the ARnc case; see Table 3 for full results. For the comparison with other data, one has to keep in mind that this width spans the total interval, not only ± the half, as it is commonly used. An effective standard deviation is affiliated by the formula $\mathrm{SD\_eff} = 1.49\,\mathrm{D}/(2{*}1.96) = 0.38\,\mathrm{D}$. This effective standard deviation would reproduce the 95% reference interval limits under the assumption of a normal distribution of data.

It is of interest to investigate which of the three measurements lead to the most positive value. Because in cycloplegia accommodation is substantially reduced, no preference for any of the measurements, or in other words an equal distribution, is expected. This is the actual result: all measurements, independently of the number of repetition, contribute identically with 33% to the most positive value. Under the ARnc condition, the distribution is different, namely, 44, 26, and 30% for the first, second, and third measurements. Therefore, repeated measurements definitely improve the results.

Finally, the propensity to accommodate is compared in a qualitative way. Two measures are considered: (*a*) the differences to the most positive value from the triple measurements and (*b*) the actual accommodation distribution, as determined by the differences between the values for *M* under the ARc and ARnc conditions. Both distributions are shown in Fig. 6. Note that the first blue bar (ARc minus ARnc) includes all contributions from negative values (up to –0.5 D) of accommodation.

The general appearance of both distributions agrees remarkably well. After a substantial decline toward 0.75 D, a slight increase between 1.0 and 1.5 D can be observed. The intrinsic measure from three measurements alone overestimates smaller accommodation and underestimates the width of the distribution.

DISCUSSION

Feasibility

Wavefront-based measurement with the tabletop based ZEISS i.Profiler plus was feasible in this clinic-based setting to determine

TABLE 3. Repeatability of wavefront-based autorefraction results without cycloplegia (ARnc) and in cycloplegia (ARc) for all subjects and separated for pre-school children and schoolchildren under each condition

	ARnc (D)			ARc (D)		
	M	J0	J45	*M*	J0	J45
All children (n = 145)						
SD	0.57	0.11	0.08	0.17	0.09	0.08
95% Total empirical interval	1.49	0.36	0.32	0.68	0.34	0.34
Preschool children (n = 73)						
SD	0.56	0.13	0.10	0.19	0.10	0.09
95% Total empirical interval	1.47	0.41	0.42	0.75	0.43	0.36
Schoolchildren (n = 72)						
SD	0.57	0.07	0.07	0.15	0.07	0.06
95% Total empirical interval	1.61	0.28	0.27	0.56	0.27	0.28

Results for the SD of astigmatic components J0 and J45 are based on three repeated measurements per eye, which are pooled for all eyes. All entries are given in diopters. For the spherical equivalent *M*, the most positive value was elected as a reference, and the spread is one-sided. The reference interval for 95% of all data is provided. In the case of J0 and J45, this is the whole interval for the difference between two measurements. In the case of *M*, it is the whole interval for the range of differences to the most positive value.

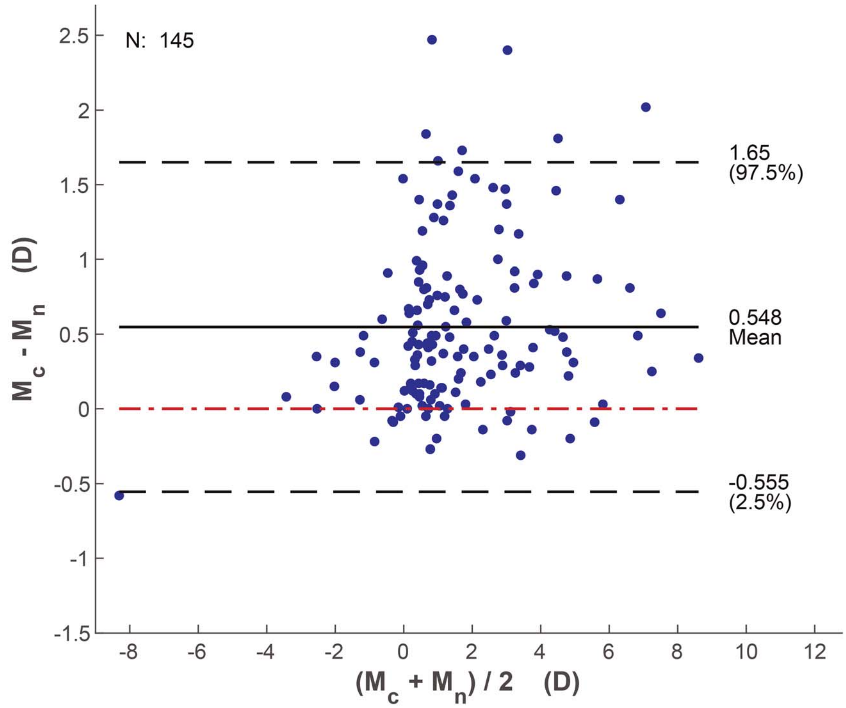

FIGURE 2. Agreement of spherical equivalent (*M*) for the noncycloplegic and cycloplegic conditions. Results are obtained from three repeated measurements, from which the most positive, that is, maximal value, is elected. The bias (mean) of 0.55 D is shown as a solid line. The red line orientates for a value of zero bias. Most of the results lie above zero, indicating more myopic results under the noncycloplegic condition. The 95% limits of agreement are included as dashed lines. The span of data ranges from highly myopic (–8 D) to highly hyperopic (+9 D) subjects.

refraction data in children with repeated measurements. We expect that dropout experienced (22% for analysis based on strictly three measurements) could be reduced significantly by improved explanation to children and parents, time management, and preparations.

Limitations

First, we would like to discuss the limitations of our study regarding cycloplegia. (1) We have to acknowledge that 0.5% of tropicamide is not the recommended standard dose, and it is possible that adequate cycloplegia was not always achieved. Because the application of this dose is a common approach in clinical care in Germany, the data might be of interest for this specific dose, even if the highest degree of cycloplegia may not have been achieved. (2) Because pupil diameter in children is not indicative of accommodation, residual accommodation was assessed—as a proxy—by investigation of the absence of fluctuations of the neutral retinoscopic reflex. We are aware that this is not the standard parameter of examining residual accommodation in children. Furthermore, this assessment of the retinoscopic reflex depends on the experience of the practitioner and contains a subjective component. However, in the given environment, other assessments of accommodation were not possible. (3) From these limitations, one might conclude that application of a stronger agent might lead to different results. We cannot exclude this argument. However, we share the view of Mutti et al.[6] that "the role of cycloplegia may be to inhibit accommodation rather than to paralyze it," as described in the discussion of their publication. Then, relaxing accommodation, for example, by appropriate fogging implemented during refraction, will support to achieve a better estimate of distance correction, which is the desired quantity. This view is supported by the results of Fan et al.[28] They did not find a significant difference for cycloplegic refraction using tropicamide 0.5% compared with using a combination of tropicamide 1.0% and cyclopentolate 1.0% in a group of moderately hyperopic children.[28] Nevertheless, whenever the term cycloplegia is used for our data, it is linked to a nonstandard dose of 0.5% tropicamide.

Agreement of Noncycloplegic and Cycloplegic Data

Data on astigmatism show excellent agreement from a clinical perspective. Furthermore, these data reconfirm convincingly that accommodation is no issue in the case of astigmatic components of refraction data. It was shown before that the mean change in astigmatism with each diopter of accommodation was only 0.036 D.[33] Stability and agreement for both conditions can be explained by the fact that accommodations work equally on both principal meridians of the eye lens. Because astigmatism is based on differences of powers in two meridians, an equal offset to both of them cancels out in the final result. Therefore, cycloplegia does not show different or better results for the astigmatic components.

In the case of the spherical equivalent, however, the situation is different; a bias of 0.55 D was observed. It has to be emphasized that this was found for the wide range from –8 to +9 D of the data, with much more hyperopic than myopic subjects, as can be expected for young subjects (Table 1). A linear regression demonstrated that the best linear fit is represented sufficiently by the bias of 0.55 D (the offset). Thus, the bisecting line is parallel transported to fit the data. A parameter value different from 1 for the slope does not result in statistically significant improvements

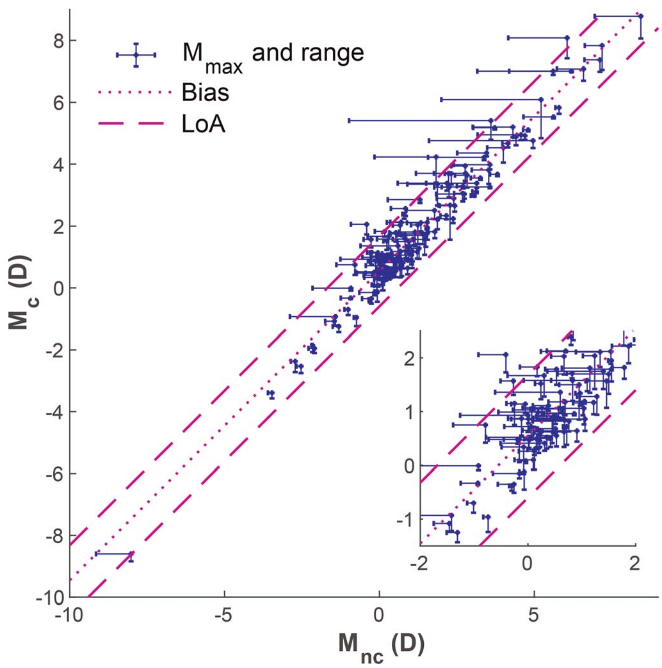

FIGURE 3. Variability of measurements for spherical equivalent (*M*) under the noncycloplegic and cycloplegic conditions. Marked is the most positive value. Bars to the left and to the bottom present the range of the three measurements. The most densely populated region is enlarged in the inset. Nearly all data lie above the bisecting line (not shown), which indicates more myopia for the noncycloplegic measurement condition. A linear regression to the data points results only in a parallel shift of the bisecting line (shown as magenta dotted line). The limits of agreement are shown as dashed magenta lines.

(*P* = .40). Here, the few data points that lie far away from the regression line and have short error bars (like the one at –0.4 and 2.5 D) indicate a stable accommodation during all three measurements. To allow for a connection to the Bland-Altman plot, the limits of agreements by the two dashed lines are added.

Despite using techniques such as fogging to induce deaccommodation, the refraction of hyperopes to date is a delicate matter. That is why cycloplegia dramatically fosters the refraction measurement, especially in children. Only under cycloplegia, the problem of accommodation is controlled, and the refraction procedure is as objective as it can be. In the current data, exactly this effect can be observed. Repeatability is improved under cycloplegic conditions by a factor of 3, most likely due to lack of accommodation, as all other parameters remained constant. Strangely enough, in some studies, the effect of cycloplegia on repeatability is not conclusive; see Rosenfield and Ciuffreda.[12] We cannot explain their results.

For one reason or another, the option of cycloplegia is not always possible. Then, as second best, an autorefraction without cycloplegia has to be considered. Depending on the requirements and purpose of the measurements, the results of the ZEISS i.Profiler plus will serve well. The bias of roughly half a diopter could be corrected for a posteriori by a recalibration of the instrument. However, this does nothing to the variance of the data. That is why repeatability, for example, given as 95% reference interval, is such an important piece of information. Bland and Altman[31] stated that, without knowing the repeatability of methods, it is difficult to compare them in a useful way. In other words, agreement depends on repeatability.

Repeatability

The total reference interval for 95% of all data is 1.4 D for repeatability. This is an astonishingly good result for the total interval, especially if we consider that data were obtained in a typical hospital environment. Systematically high accommodation in the noncycloplegic condition for children can be ruled out by our data. Because accommodation is bounded, more than 84% of the children accommodate less than 1 D (Fig. 6). These data do not leave room for higher systematic accommodation but obviously do not exclude outliers.

This promising result depends largely on repeated measurements, which allow for election of the most positive value; for example, in the current study, only 44% of the first ARnc measurement rendered this result. The quality of measurements can be further enhanced by a sensible operator who can judge the data immediately and improve the refraction result by adding a further measurement. The time span of less than a minute is not at all a time-consuming process, given the advantages linked to it.

Fixation and (de-)accommodation can be a severe obstacle to reliable results without cycloplegia, as can be seen from the findings of Dahlmann-Noor and colleagues,[34] where differences up to 8 D were observed, and only 20% of all difference values fell into in an interval of ±0.50 D. Obviously, the effects depend on the technology applied. In the current approach, an autorefractor was considered, which addresses the problem of accommodation by

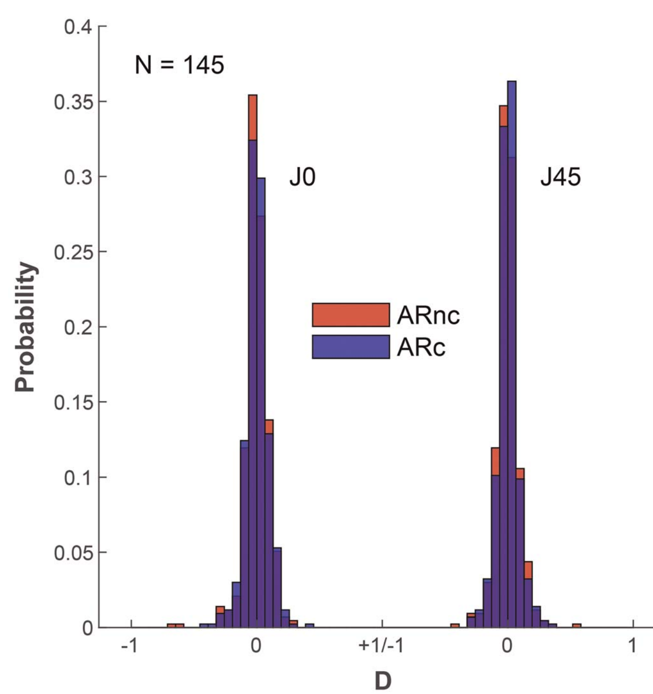

FIGURE 4. The distribution of results for astigmatic components J0 (left) and J45 (right) for the cycloplegic (ARc; blue) and noncycloplegic (ARnc; red) conditions. Shown are differences to the mean (centered coordinates). There is no clinically relevant difference between these results, showing an excellent repeatability of these measurements. Thus, cycloplegia does not influence the repeatability of astigmatic components.

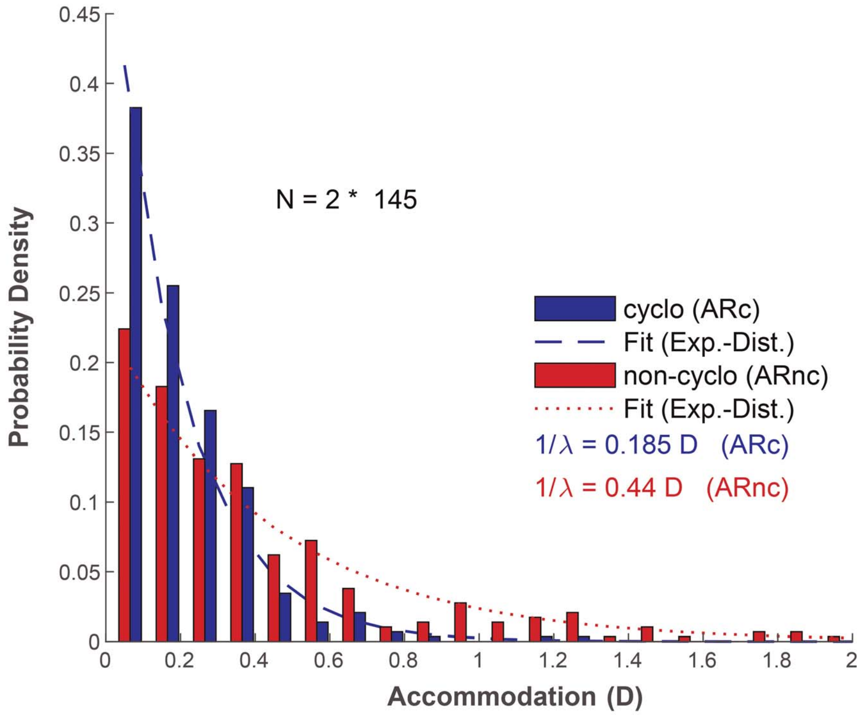

FIGURE 5. Propensity to accommodate under the two conditions—cycloplegic (ARc; blue) and noncycloplegic (ARnc; red)—extracted from the triple of measurements. Clearly, under cycloplegia, accommodation is reduced but not to zero. We fitted an exponential distribution ($\lambda \exp(-\lambda x)$) to the data. The inverse of the parameter λ equals the mean and the SD of the distribution. From these data, we see a 0.44/0.185 = 2.4-fold reduction of the amount and the variability of accommodation in cycloplegia.

fogging the target image. To the best of our knowledge, there are currently no data on the quantitative effect of this procedure in general.

The current study extracted results on the propensity to accommodate in children for the instrument applied. The method might seem as a crude approach. Nevertheless, it has to be considered as a first step to gain quantitative knowledge on how accommodation influences the measurement and eventually how accommodation can be controlled. It would be interesting to compare different instruments regarding the propensity to accommodate and learn about their different strategies to deaccommodate.

Accommodation is a dynamic process in noncycloplegic refraction. A real-time monitoring of the spherical equivalent, for example, on the device display, would be an interesting and yet feasible approach. The most positive value from such an approach would deliver a much better estimate of refraction data in the natural eye. Not only the spherical equivalent but also additional parameters, which are correlated with accommodation, could be monitored continuously. In adults, the change of pupil size and spherical aberration clearly indicate accommodation. However, in children, there is no correlation between pupil size and accommodation.[35] Little is known about the change of spherical aberration with accommodation in children; here, further investigations would be helpful.

In addition, the measurement process itself could be complemented to introduce cognitive deaccommodation, for example, by asking questions. This is a well-known fact in adults.[36] In passing, we mention that this study observed similar effects in children. However, this was not investigated in a systematic way.

Interestingly, only a few other studies carried out a similar setup to the current investigation to facilitate overall comparison when agreement was established based on ARc and ARnc data within one instrument. Two larger studies on non–wavefront-based devices found a bias for ARc minus ARnc for *M* values of 1.18 (1.05 to 1.30) for 6-year-olds and 0.84 (8.81 to 0.87) for 12-year-olds, both on the Canon RK-F1 (Tokyo, Japan),[7] and a bias for *M* of 0.71 for 5- to 10-year-old children was established on the Topcon KR8000 (Tokyo, Japan),[8] the latter data being similar to two earlier studies who found comparable bias in their devices.[5,9]

In line with the current study, there is only one study in children (SVOne)[12] and only one study in adults (COAS),[13] which reported data that would allow for comparison of noncycloplegic and cycloplegic wavefront-based measurements within one device. Salmon and van de Pol[13] kindly agreed to allow to report their agreement data for 28 adults (mean age, 24.7 ± 3.3 years) as part of the current study. Agreement for cycloplegic minus noncycloplegic wavefront-based data in their cohort was 0.56 ± 0.36 D for *M*. Agreement data within one instrument by Salmon and van de Pol on the COAS system therefore presented similar agreement and variability in their adult groups of subjects compared with the children of the current study. It has to be highlighted that their results were obtained for a range of refractive errors that spanned between −1.83 and +0.62 D, whereas the current study investigated children between −8 and +9 D (Table 1).

CONCLUSIONS

Repeatability and agreement of noncycloplegic and cycloplegic wavefront-based autorefraction were analyzed for the first time in

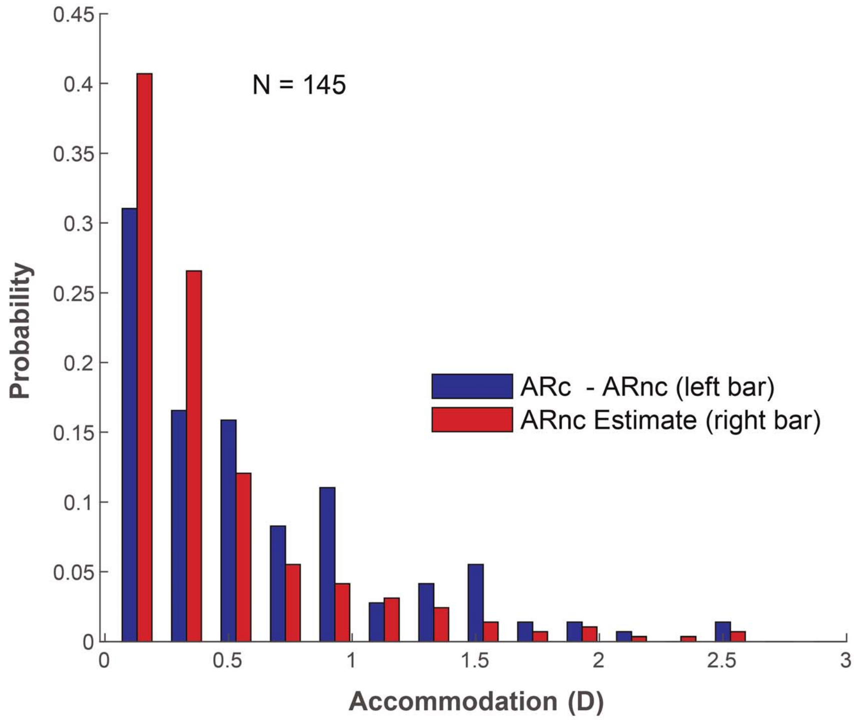

FIGURE 6. Propensity to accommodate, determined by two different ways. First, the differences between the results under the cycloplegic (ARc) and noncycloplegic (ARnc) conditions are shown in blue (first bar includes negative values up to –0.5 D). Second, the results from the three measurements under the ARnc condition alone are presented in red (second bars). The latter method describes the former in a reasonable way. However, lower accommodation values are overestimated, and the width of the distribution is underestimated. Nevertheless, the qualitative agreement is a nontrivial result, made possible by information from repeated measurements.

children of this range of age and refractive errors. Refraction measurements were obtained by ZEISS i.Profiler plus with and without cycloplegia. The agreement and repeatability of astigmatic data are excellent under both conditions. Regarding agreement for the spherical equivalent, ARc presented with higher positive values than did ARnc. The shift can be explained by variations in relaxation of accommodation among subjects when wavefront-based autorefraction was measured without cycloplegia. Agreement and repeatability in children show comparable results with data obtained with wavefront-based devices in adults.

If cycloplegia is not an option, only then can noncycloplegic data be considered. The first strategy is to correct results from ARnc for the bias of roughly half a diopter. This correction scheme does not depend on the individual subject but represents a "one-size-fits-all" approach. However, the most promising strategy, as can be concluded from the current results on the propensity to accommodate, is the repetition of measurements or, even better, a real-time measurement approach with continuous data. Accommodation, as a dynamic process, is best controlled by dynamic means for each individual. From the point of technology, all components are available to realize such a progress.

ARTICLE INFORMATION

Submitted: November 21, 2018

Accepted: August 20, 2019

Funding/Support: Bundesministerium für Bildung und Forschung (031L0026).

Conflict of Interest Disclosure: AO and SW are employees of Carl Zeiss Vision International GmbH; however, none of the authors have any financial or conflicting interests concerning the content of this research, which was conducted following the rules of neutral scientific practice.

Author Contributions and Acknowledgments: Conceptualization: FGR, HT, AH, AO; Data Curation: FGR, HL, IS; Formal Analysis: FGR, HL, MY-D, RB; Funding Acquisition: SW, AO; Investigation: FGR, HL, HT, IS, AO; Methodology: FGR, HL, MY-D, HT, IS, AH, AO, RB; Project Administration: FGR, HL, HT, IS, AO; Resources: FGR, IS, SW, PW, AO; Software: FGR, MY-D, AO, RB; Supervision: FGR, MY-D, AH, PW, AO, RB; Validation: FGR, HT, IS, RB; Visualization: FGR, RB; Writing – Original Draft: FGR, HL, MY-D, HT, AO, RB; Writing – Review & Editing: FGR, MY-D, AH, RB.

FGR and HL contributed equally to this work and are considered co–first authors.

The authors express their sincere gratitude to Professor Thomas O. Salmon, PhD, College of Optometry, Northeastern State University, Tahlequah, OK, for helpful comments on the background of the computations implemented in the current article and for his generous support and collaboration by giving access to the raw data of his 2005 and 2003 articles. The authors are furthermore grateful for important insight gained by discussions with Professor Erin M. Harvey, PhD, Department of Ophthalmology and Vision Science, The University of Arizona, Tucson, AZ, on computations of her cited work within this article. The authors also would like to express their gratitude to Dr. Jonathan Bartlett, PhD, Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, for helpful discussions in preparation of the initial analysis.

REFERENCES

1. Harvey EM, Miller JM, Schwiegerling J. Utility of an Open Field Shack-Hartmann Aberrometer for Measurement of Refractive Error in Infants and Young Children. J AAPOS 2013;17:494–500.

2. Kulp MT, Ying GS, Huang J, et al. Accuracy of Noncycloplegic Retinoscopy, Retinomax Autorefractor, and SureSight Vision Screener for Detecting Significant Refractive Errors. Invest Ophthalmol Vis Sci 2014;55:1378–85.

3. Kemper AR, Keating LM, Jackson JL, et al. Comparison of Monocular Autorefraction to Comprehensive Eye Examinations in Preschool-aged and Younger Children. Arch Pediatr Adolesc Med 2005;159:435–9.

4. Ying GS, Maguire M, Quinn G, et al. ROC Analysis of the Accuracy of Noncycloplegic Retinoscopy, Retinomax Autorefractor, and SureSight Vision Screener for Preschool Vision Screening. Invest Ophthalmol Vis Sci 2011;52: 9658–64.

5. Cordonnier M, Dramaix M. Screening for Refractive Errors in Children: Accuracy of the Hand Held Refractor Retinomax to Screen for Astigmatism. Br J Ophthalmol 1999;83:157–61.

6. Mutti DO, Zadnik K, Egashira S, et al. The Effect of Cycloplegia on Measurement of the Ocular Components. Invest Ophthalmol Vis Sci 1994;35:515–27.

7. Fotedar R, Rochtchina E, Morgan IG, et al. Necessity of Cycloplegia for Assessing Refractive Error in 12-year-old Children: A Population-based Study. Am J Ophthalmol 2007;144:307–9.

8. Fotouhi A, Morgan IG, Iribarren R, et al. Validity of Non-cycloplegic Refraction in the Assessment of Refractive Errors: The Tehran Eye Study. Acta Ophthalmol 2012;90:380–6.

9. Nawrot P, Przekoracka-Krawczyk A, Perz K, et al. Change in Ocular Refraction After Tropicamide Cycloplegia in Preschool Children. Klin Oczna 2012;114:278–81.

10. Sanfilippo PG, Chu BS, Bigault O, et al. What Is the Appropriate Age Cut-off for Cycloplegia in Refraction? Acta Ophthalmol 2014;92:458–62.

11. Hu YY, Wu JF, Lu TL, et al. Effect of Cycloplegia on the Refractive Status of Children: The Shandong Children Eye Study. PLoS One 2015;10:e0117482.

12. Rosenfield M, Ciuffreda KJ. Evaluation of the SVOne Handheld Autorefractor in a Pediatric Population. Optom Vis Sci 2017;94:159–65.

13. Salmon TO, van de Pol C. Evaluation of a Clinical Aberrometer for Lower-order Accuracy and Repeatability, Higher-order Repeatability, and Instrument Myopia. Optometry 2005;76:461–72.

14. Ciuffreda KJ, Rosenfield M. Evaluation of the SVOne: A Handheld, Smartphone-based Autorefractor. Optom Vis Sci 2015;92:1133–9.

15. Salmon TO, West RW, Gasser W, et al. Measurement of Refractive Errors in Young Myopes Using the COAS Shack-Hartmann Aberrometer. Optom Vis Sci 2003;80:6–14.

16. Choi M, Weiss S, Schaeffel F, et al. Laboratory, Clinical, and Kindergarten Test of a New Eccentric Infrared Photorefractor (PowerRefractor). Optom Vis Sci 2000; 77:537–48.

17. Harvey EM, Miller JM, Dobson V, et al. Measurement of Rrefractive Error in Native American Preschoolers: Validity and Reproducibility of Autorefraction. Optom Vis Sci 2000;77:140–9.

18. Harvey EM, Miller JM, Wagner LK, et al. Reproducibility and Accuracy of Measurements with a Hand Held Autorefractor in Children. Br J Ophthalmol 1997;81:941–8.

19. Nissman SA, Tractenberg RE, Saba CM, et al. Accuracy, Repeatability, and Clinical Application of Spherocylindrical Automated Refraction Using Time-based Wavefront Aberrometry Measurements. Ophthalmology 2006;113:577.e1–2.

20. Pesudovs K, Parker KE, Cheng H, et al. The Precision of Wavefront Refraction Compared to Subjective Refraction and Autorefraction. Optom Vis Sci 2007; 84:387–92.

21. Hament WJ, Nabar VA, Nuijts RM. Repeatability and Validity of Zywave Aberrometer Measurements. J Cataract Refract Surg 2002;28:2135–41.

22. Mirshahi A, Bühren J, Gerhardt D, et al. In Vivo and in Vitro Repeatability of Hartmann-Shack Aberrometry. J Cataract Refract Surg 2003;29:2295–301.

23. Mrochen M, Kaemmerer P, Mierdel P, et al. Principle of Tscherning Aberrometry. J Refract Surg 2000;16:S570–1.

24. Martinez AA, Pandian A, Sankaridurg P, et al. Comparison of Aberrometer and Autorefractor Measures of Refractive Error in Children. Optom Vis Sci 2006;83: 811–7.

25. Adams RJ, Dalton SM, Murphy AM, et al. Testing Young Infants with the Welch Allyn Suresight Non-cycloplegic Autorefractor. Ophthalmic Physiol Opt 2002;22:546–51.

26. Yazdani N, Sadeghi R, Momeni-Moghaddam H, et al. Comparison of Cyclopentolate versus Tropicamide Cycloplegia: A Systematic Review and Meta-analysis. J Optom 2018;11:135–43.

27. Hamasaki I, Hasebe S, Ohtsuki H. Cycloplegic Effect of 0.5% Tropicamide and 0.5% Phenylephrine Mixed Eye Drops: Objective Assessment in Japanese Schoolchildren with Myopia. Jpn J Ophthalmol 2007;51:111–5.

28. Fan DS, Rao SK, Ng JS, Yu CB, Lam DS. Comparative Study on the Safety and Efficacy of Different Cycloplegic Agents in Children with Darkly Pigmented Irides. Clin Experiment Ophthalmol 2004;32462–7.

29. Lebow KA, Campbell CE. A Comparison of a Traditional and Wavefront Autorefraction. Optom Vis Sci 2014;91:1191–8.

30. Thibos LN, Wheeler W, Horner D. Power Vectors: An Application of Fourier Analysis to the Description and Statistical Analysis of Refractive Error. Optom Vis Sci 1997;74:367–75.

31. Bland JM, Altman DG. Measuring Agreement in Method Comparison Studies. Stat Methods Med Res 1999;8:135–60.

32. Bartlett JW, Frost C. Reliability, Repeatability and Reproducibility: Analysis of Measurement Errors in Continuous Variables. Ultrasound Obstet Gynecol 2008;31:466–75.

33. Radhakrishnan H, Charman WN. Changes in Astigmatism with Accommodation. Ophthalmic Physiol Opt 2007;27:275–80.

34. Dahlmann-Noor AH, Comyn O, Kostakis V, et al. Plusoptix Vision Screener: The Accuracy and Repeatability of Refractive Measurements Using a New Autorefractor. Br J Ophthalmol 2009;93:346–9.

35. Schaeffel F, Wilhelm H, Zrenner E. Inter-individual Variability in the Dynamics of Natural Accommodation in Humans: Relation to Age and Refractive Errors. J Physiol 1993;461:301–20.

36. Rosenfield M, Ciuffreda KJ. Proximal and Cognitively-induced Accommodation. Ophthalmic Physiol Opt 1990; 10:252–6.