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Long-term reproducibility of Edinger–Westphal stimulated accommodation in rhesus monkeys

Lin He, Mark Wendt, Adrian Glasser*

College of Optometry, University of Houston, 4901 Calhoun Road, Houston, TX 77204, United States

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ABSTRACT

If longitudinal studies of accommodation or accommodation restoration procedures are undertaken in rhesus monkeys, the methods used to induce and measure accommodation must remain reproducible over the study period. Stimulation of the Edinger–Westphal (EW) nucleus in anesthetized rhesus monkeys is a valuable method to understand various aspects of accommodation. A prior study showed reproducibility of EW-stimulated accommodation over 14 months after chronic electrode implantation. However, reproducibility over a period longer than this has not been investigated and therefore remains unknown. To address this, accommodation stimulation experiments in four eyes of two rhesus monkeys (13.7 and 13.8 years old) were evaluated over a period of 68 months. Carbachol iontophoresis stimulated accommodation was first measured with a Hartinger coincidence refractometer (HCR) two weeks before electrode implantation to determine maximum accommodative amplitudes. EW stimulus-response curves were initially measured with the HCR one month after electrode implantation and then repeated at least six times for each eye in the following 60 months. At 64 months, carbachol iontophoresis induced accommodation was measured again. At 68 months, EW stimulus-response curves were measured with an HCR and photorefraction every week over four consecutive weeks to evaluate the short-term reproducibility over one month. In the four eyes studied, long-term EW-stimulated accommodation decreased by 7.00 D, 3.33 D, 4.63 D, and 2.03 D, whereas carbachol stimulated accommodation increased by 0.18 D–0.49 D over the same time period. The short-term reproducibility of maximum EW-stimulated accommodation (standard deviations) over a period of four weeks at 68 months after electrode implantation was 0.48 D, 0.79 D, 0.55 D and 0.39 D in the four eyes. Since the long-term decrease in EW-stimulated accommodation is not matched by similar decreases in carbachol iontophoresis stimulated accommodation, the decline in accommodation cannot be due to the progression of presbyopia but is likely to result from variability in EW electrode position. Therefore, EW-stimulated accommodation in anesthetized monkeys is not appropriate for long-term longitudinal studies of age-related loss of accommodation or accommodation restoration procedures.

1. Introduction

Rhesus monkeys are an important animal model for human accommodation and presbyopia since they have an accommodative mechanism similar to humans (Glasser et al., 2006; Glasser and Kaufman, 1999) and develop presbyopia with a similar relative age course to humans (Bito et al., 1982; Neider et al., 1990). The long-term reproducibility of accommodation in monkeys is of interest for the possibility of undertaking longitudinal studies of the progression of presbyopia and for understanding the long-term effects of accommodation restoration procedures. Although accommodation in rhesus monkeys decreases over time due to age-related loss, accommodative amplitude could theoretically be preserved with accommodation restoration procedures such as surgical implantation of accommodative intraocular lenses (A-IOL) (Ben-Nun and Alió, 2005; Glasser, 2008; Koopmans et al., 2006; Sheppard et al., 2010), pharmacological softening or femtosecond laser photodisruption of the natural lens (Baradia et al., 2010; Glasser, 2006; Krueger et al., 2001; Myers and Krueger, 1998). Surgical procedures to restore accommodation (Ben-Nun and Alió, 2005; Koopmans et al., 2006; Nishi et al., 1992) may require long-term assessments to evaluate long-term efficacy. Pharmacological or laser interventions may take a long time to show beneficial or deleterious effects and therefore would require long-term assessment of accommodation. Longitudinal studies in rhesus monkeys

* Corresponding author. Tel.: +1 713 743 1876; fax: +1 713 743 2053.
E-mail address: aglasser@uh.edu (A. Glasser).

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would require reproducible stimulation of accommodative responses with little variation due to the methodology so that changes in accommodative amplitude can be clearly attributed to either an age-related loss of accommodation or due to problems or benefits from an accommodation restoration procedure. Further, if longitudinal studies of the progression of presbyopia are to be undertaken in normal monkeys, the variance in the methodology to stimulate and measure accommodation would have to be less than the age-related decline in accommodation for the latter to be detectable.

Accommodation in monkeys can be stimulated pharmacologically or with electrical stimulation of the Edinger–Westphal (EW) nucleus (Crawford et al., 1989; Glasser and Kaufman, 1999; Ostrin and Glasser, 2007; Vilupuru and Glasser, 2002). Topical pharmacological stimulation has been used (Croft et al., 1996; Koeppl et al., 2005; Ostrin and Glasser, 2004), but in monkeys carbachol iontophoresis can take up to 30 min (Wendt and Glasser, 2012) and intravenous pilocarpine up to 90 s (Wendt and Glasser, 2010) to achieve maximum accommodation, and in general only one pharmacologically stimulated response can be achieved per experimental session. Electrical stimulation of the EW-nucleus produces a rapid, naturally occurring accommodative response with very short latencies. Accommodative responses of varied amplitudes can be induced by increasing the stimulus current amplitude until maximum accommodation is achieved (Baumeister et al., 2008; Crawford et al., 1989; Vilupuru and Glasser, 2002). During a single experimental session, tens or even hundreds of accommodative responses can be stimulated (Vilupuru et al., 2005) with a high degree of reproducibility (Baumeister et al., 2008; Glasser et al., 2006; Vilupuru and Glasser, 2002).

Long-term EW-stimulation experiments can be performed by implanting a stimulating electrode in the EW nucleus using a permanent cranial implant. Stability of the electrode over time is critical for achieving reproducible accommodative responses. In a prior study, stimulus-response functions were measured in two eyes of one monkey over 14 months after the implantation of the electrode (Crawford et al., 1989). Means and standard deviations (SD) of maximum accommodation for each of the eyes digitized from the graphs from that study are 14.6 $\pm$ 1.4 D and 15.3 $\pm$ 1.2 D. However, the long-term reproducibility of EW-stimulated accommodation or the short-term reproducibility a long time period after electrode implantation is unknown.

How accommodation is measured can also affect the reproducibility of the accommodation response due to the precision or reliability of the instrument being used. The Hartinger coincidence refractometer (HCR) (Fincham, 1937) and photorefraction are the two most commonly used methods for measuring accommodation in monkeys (Baumeister et al., 2008; Crawford et al., 1989; Croft et al., 1998; He et al., 2012; Ostrin and Glasser, 2005; Vilupuru and Glasser, 2002). Photorefraction is a video-based technique (Bobier and Braddick, 1985; Howland and Howland, 1974; Schaeffel et al., 1987) that allows dynamic measurement of accommodation (Baumeister et al., 2008; Ostrin and Glasser, 2007; Schaeffel et al., 1993; Vilupuru and Glasser, 2002). The HCR is factory calibrated in the hardware while custom-built photorefractors require calibration with trial lenses (Schaeffel et al., 1993; Vilupuru and Glasser, 2002) or using another calibrated instrument such as the HCR to serve as the calibration source (Baumeister et al., 2008; Ostrin and Glasser, 2007; Vilupuru and Glasser, 2002). If repeated calibrations are required another possible source of variation is the calibrations themselves. The repeatability of the two different measurement methods (HCR & photorefraction) and the photorefraction calibration procedures (trial lenses & HCR) in the same monkey eyes is also not known.

In this study, the reproducibility of EW-stimulated accommodation in four eyes from two adult rhesus monkeys was retrospectively investigated over 68 months after electrode implantation. Maximum EW-stimulated accommodation was compared to the amplitudes obtained from carbachol iontophoresis to assess variability versus any age-related loss of accommodation over the same time period. In addition, the short-term reproducibility of EW-stimulated accommodation and the reproducibility of the calibration procedures were prospectively evaluated over a one month period at 68 months after electrode implantation.

2. Methods and materials

2.1. Animal preparation

All experiments were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and in accordance with institutionally approved animal protocols. Two rhesus monkeys (*Macaca mulatta*), #54 and #58 were used aged 13.7 and 13.8 years at the end of the 68 months study period. At the start of the study, the monkeys were binocularly iridectomized (Kaufman and Lütjen-Drecoll, 1975) to avoid strong pupil constriction from pharmacological stimulation. Although the iridectomy does not affect amplitude from EW-stimulation, it does reduce amplitude from carbachol stimulation (Crawford et al., 1990).

The first carbachol iontophoresis (see Section 2.3.1) was performed as described previously (Koretz et al., 1987; Vilupuru and Glasser, 2002; Wendt and Glasser, 2012). Two weeks later, EW electrodes were implanted (Baumeister et al., 2008; Baumeister et al., 2010; Crawford et al., 1989; Vilupuru and Glasser, 2002). The procedure was modified to improve longevity by cementing the electrode in dental acrylic in a stainless steel head cap with feet that were screwed to the skull. One month after the electrodes were implanted, the first EW stimulus response curves were generated for both eyes and measured with the HCR. Multiple subsequent EW-stimulation experiments were performed over 64 months and the data retrospectively analyzed. Carbachol iontophoresis experiments were repeated on one eye of one monkey (#58 OD) at 48 months and on one eye each of the two monkeys (#54 OS and #58 OS) at 64 months after EW electrode implantation. Maximum accommodation was compared to the first carbachol experiment to assess the age-related loss of accommodation. At 68 months after the EW electrode implantations, EW-stimulation experiments were performed once a week for four consecutive weeks and accommodation measured with the HCR and with photorefraction. Both long-term reproducibility over 68 months and short-term reproducibility over a one month period at 68 months were evaluated. Table 1 shows the chronology of the procedures and experiments.

Table 1
History of procedures and experiments on the two monkeys used in the current study.

Procedure/Experiment	#54	#58
	Age (year/month)	Age (year/month)
Iridectomy	6/9	6/11
First carbachol iontophoresis	8/0	8/2
EW electrode implantation	8/0	8/2
First EW stimulus-response curve	8/1	8/3
Intervening carbachol iontophoresis	–	12/2
Latest carbachol iontophoresis	13/4	13/6
EW reproducibility over 1 month	13/8	13/10

2.2. Anesthesia

For each experiment, monkeys were sedated with intramuscular 15 mg/kg ketamine (Phoenix Pharmaceutical, St. Joseph, MO). Initial carbachol experiments were performed under repeated boluses of 10 mg/kg ketamine. In later experiments monkeys were anesthetized with an intravenous bolus of 1.5 mg/kg propofol (PropoFlo, Abbott Laboratories, North Chicago, IL) followed by continuous infusion at 0.5 mg/kg/min. These different anesthesia regimes do not affect carbachol stimulated accommodative amplitudes (Wendt and Glasser, 2012). All EW-stimulation experiments were performed under propofol anesthesia. Vital signs were monitored and body temperature was maintained at 37 °C with a heating pad. The monkey head was held upright and facing forward in a head holder. The eyelids were held open with a speculum and rigid PMMA contact lenses were placed on the corneas. In the repeated experiments over one month at 68 months, care was taken to ensure the same contact lenses were used in each eye.

2.3. Accommodation stimulation and measurement

2.3.1. Carbachol iontophoresis

For each eye of the monkey, carbachol iontophoresis was performed to measure maximum accommodation. Methods for preparation and application have been detailed previously (Wendt and Glasser, 2012). The contact lens was removed, the carbachol administered, and then the contact lens replaced on the cornea. Refraction was measured with an HCR (Carl Zeiss, Jena, Germany) from before and every two minutes after carbachol was given. At every time point, three measurements were taken within 15 s after moving and then realigning the HCR with eyes. Measurements proceeded until no further change in refraction occurred for three consecutive two-minute intervals. The second dose of carbachol was then applied and measurements continued again until no further change was observed.

2.3.2. EW-stimulation

The procedure for EW-stimulation has been described previously (Baumeister et al., 2008; Ostrin and Glasser, 2007; Vilupuru and Glasser, 2002). Accommodation was stimulated with four-second long stimulus trains (frequency: 72 Hz; pulse width: 600 μs), ranging from 0 μA up to a current amplitude sufficient to produce maximum accommodation. For the one-month reproducibility experiments at 68 months after electrode implantation, the same stimulus current amplitudes were used each time. For every stimulus current amplitude, five consecutive stimulus trains were delivered with 4-s inter-stimulus intervals.

For the one-month reproducibility experiments, accommodation was measured with an HCR to generate static stimulus response curves. Following that refraction was recorded continuously using photorefraction at 60 Hz from five seconds before the stimulus train started to 5 s after the stimulus train terminated (Baumeister et al., 2008; Glasser et al., 2006). Photorefraction was calibrated to diopters in two different ways, by: 1) placing trial lenses (0 D–6 D in 1 D step & 8 D) in front of the eyes to defocus the eyes by known amounts and the relationship between trial lens power and photorefraction slope was fitted with a linear regression (Bossong et al., 2009; Choi et al., 2000; Schaeffel et al., 1993; Vilupuru and Glasser, 2002); 2) both Hartinger refraction and photorefraction slopes were measured sequentially for each stimulus current amplitude and a linear regression fit to the HCR-measured refraction versus photorefraction slope data (Vilupuru and Glasser, 2002). The same photorefractor settings were maintained throughout all experiments. For each eye of the two monkeys, reproducibility over the four-week period was determined by calculating the means and SDs over the four consecutive experiments.

3. Results

3.1. Short-term reproducibility of EW-stimulated accommodation at 64 months

Fig. 1 shows photorefraction trial lens (Fig. 1A and B) and Hartinger (Fig. 1C and D) calibrations from four repeated sessions from four eyes of two monkeys. Trial lens calibrated photorefraction intercepts for the calibration functions can affect absolute refraction values, but do not affect accommodation (Schaeffel et al., 1993). To determine how variations in trial-lens calibration functions affect accommodation measurements in each eye, the percentage error in the range of accommodation that results from applying each individual calibration function was calculated. Linear regressions from each calibration function in each eye were used to convert the range of measured photorefraction slope values back to a range of refraction values. The percentage error in this range of refraction values was compared to the 8 D refractions range of trial lens used. For each eye, this yielded four percentage errors in the accommodation measurements. The ranges (minimum to maximum) of these for each eye are: 2.86–6.56% (#54 OD); 0.445–5.26% (#54 OS); 2.72–6.86% (#58 OD); 0.382–2.68% (#58 OS). This gives the error in the photorefraction measured accommodative responses due to the variations in the trial-lens calibrations, so, for example, a 2.68% error for 10 D of accommodation is 9.732 D or 10.268 D.

The HCR and the photorefraction accommodation measurements (calibrated two different ways) yielded three sets of stimulus-response curves (Fig. 2) from four eyes over four weeks.

Maximum accommodation and the means ± SDs and the corresponding stimulus amplitudes are listed in Table 2. For comparison, the SDs from a prior study (Crawford et al., 1989) showing reproducibility over 14 months after electrode implantation were 14.6 ± 1.4 D (OD) and 15.3 ± 1.2 D (OS). The one-month reproducibility in the current study had a mean SD ± SD of 0.55 ± 0.17 D measured with the HCR in four eyes, which is better than the SDs of 1.2–1.4 D from the prior 14-month reproducibility study (Crawford et al., 1989). The SDs of the photorefraction and HCR measurements are comparable, demonstrating similar precision of the two measurement methods.

From the HCR measurements, the mean ± SD baseline refractions were: monkey #54: OD = −0.06 ± 0.25 D; OS = 1.15 ± 0.26 D; monkey #58: OD = 0.16 ± 0.33 D; OS = 0.61 ± 0.24 D. The mean ± SD maximum accommodation for each eye of each monkey was: monkey #54: OD = 3.83 ± 0.62 D; OS = 8.00 ± 0.75 D; monkey #58: OD = 4.75 ± 0.44 D; OS = 6.99 ± 0.41 D. Fig. 3 shows baseline refractions and maximum accommodation from each experiment. Baseline refraction may vary between experiments due to accommodative tonus, eye alignment and contact lens movement (He et al., 2012; Wendt and Glasser, 2012). Day-to-day variations in baseline refractions can also contribute to variations in measured accommodative amplitudes. Since baseline refraction and maximum accommodation did not co-vary across different experimental sessions (Fig. 3), short-term variation of maximum accommodation was not due to variations in baseline refraction.

3.2. Long-term reproducibility of EW-stimulated accommodation

Fig. 4 shows maximum EW and carbachol-stimulated accommodation from multiple experimental sessions over 68 months. All four eyes show a time-dependent decrease in EW-stimulated

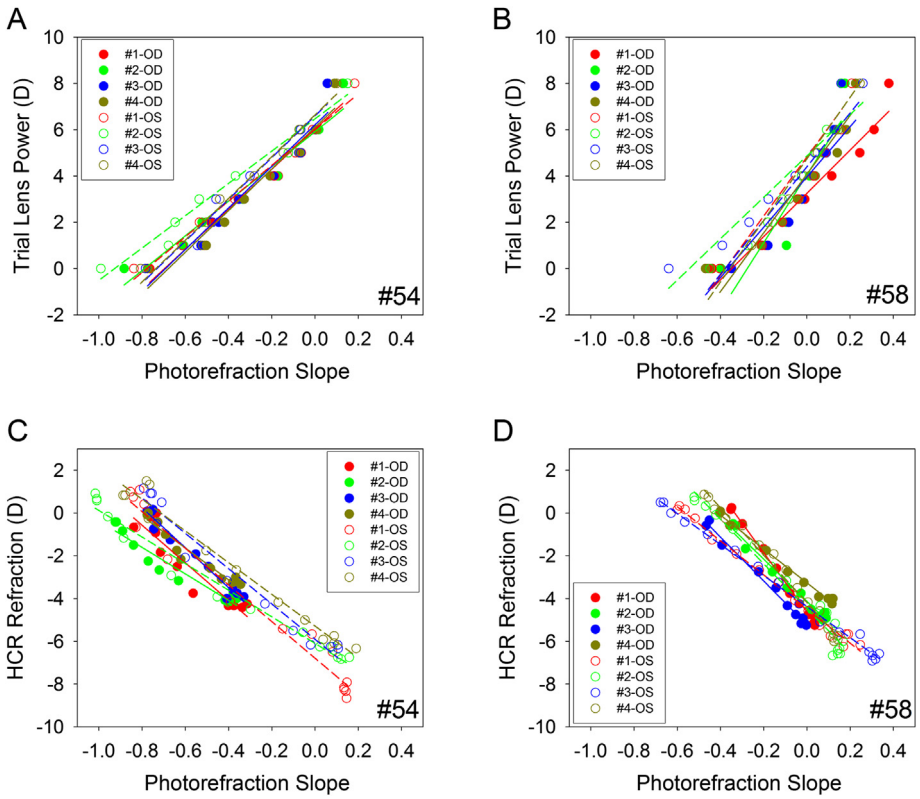

Fig. 1. Photorefraction trial lens calibrations (A & B) and HCR calibrations (C & D) from four experiments over one month from both eyes of monkeys #54 and #58. Filled circles and solid lines represent the right eye while open symbols and dashed lines represent the left eye. Linear regression lines were fit to each eye from each experiment. The trial lens powers ranged from 0 D to 6 D in 1 D step and 8 D. Mean slopes ± SD for trial lens calibrations were: monkey #54: OD = 8.53 ± 0.71; OS = 8.18 ± 1.01; monkey #58: OD = 12.95 ± 1.62; OS = 10.56 ± 1.93. Mean slopes ± SD for the HCR calibrations were: monkey #54: OD = 7.94 ± 1.41; OS = 7.62 ± 1.05; monkey #58: OD = 10.48 ± 2.48; OS = 9.19 ± 1.86.

accommodative amplitude with a greater decrease in the right eyes of both monkeys but no time-dependent decrease from carbachol stimulated accommodation at 68 months in the two eyes tested.

This difference in the change between EW-stimulated and carbachol stimulated accommodation measured using HCR over 68 months is further illustrated in Table 3. Maximum EW-stimulated accommodation decreased by 7.00 D, 3.33 D, 4.63 D and 2.03 D in the four eyes over 68 months. Carbachol stimulated accommodation at 48 and 64 months after electrode implantation in one right eye and two left eyes did not decrease. In addition, the inter-ocular difference in EW stimulated accommodation increased over the 68 months period. The initial inter-ocular difference was 0.50 D and −0.33 D for the two monkeys and the difference increased to 4.17 D and 2.26 D.

4. Discussion

In this study the long-term and short-term reproducibility of EW-stimulated accommodation in rhesus monkeys was evaluated. Both are important if longitudinal studies of accommodation are to be undertaken in the same monkeys. A prior study showed reproducibility of EW-stimulation over 14 months in only one monkey (Crawford et al., 1989). The low SDs of maximum EW-stimulated accommodation measured by HCR from four consecutive experiments over a one month period (Table 2) demonstrate good short-term reproducibility even after long-term electrode implantation. The SDs are smaller than and in some cases half of that in the prior study (Crawford et al., 1989). This one-month reproducibility of EW stimulated accommodation is better than the 0.8 D–2.1 D shown from carbachol iontophoresis induced accommodation over a period of 10–18 months (Wendt and Glasser, 2012). Therefore, even a long time after EW electrode implantation, although the accommodative response amplitudes may have decreased, the short-term reproducibility of EW-stimulated accommodation remains good.

EW-stimulated accommodation was induced and measured over 68 months. The improved electrode implantation techniques used made it possible to retain and use the electrodes for this time-period. However, the EW-stimulated accommodative amplitude decreased, and to a greater extent in one eye than the other, while maximum carbachol iontophoresis stimulated accommodation did not decrease. Although carbachol iontophoresis was only performed in the left eyes of the two monkeys at 64 months, these left eyes were the eyes with the greater EW-stimulated amplitudes. This demonstrated that the decrease in maximum EW-stimulated accommodation is not due to the progression of presbyopia. This conclusion is further supported by the fact that the small inter-ocular differences immediately after electrode implantation (0.5 D and −0.33 D) increased to 4.17 D and 2.26 D by 68 months. Although only two monkeys were included in this study, both show a decrease in EW-stimulated accommodation over 68 months. For EW stimulation to be considered viable for longitudinal studies of accommodation or accommodation restoration procedures, 100% of monkeys would have to retain 100% of their accommodation.

The most likely cause of the decreases in accommodation (up to 7.00 D) over time is the electrode moving from activity of the monkey or tissue ingrowth under the head cap. If the electrode progressively moves to one side from the midline, then the accommodative response will become asymmetric. Instability of dental acrylic-based cranial implants has been suggested to be due

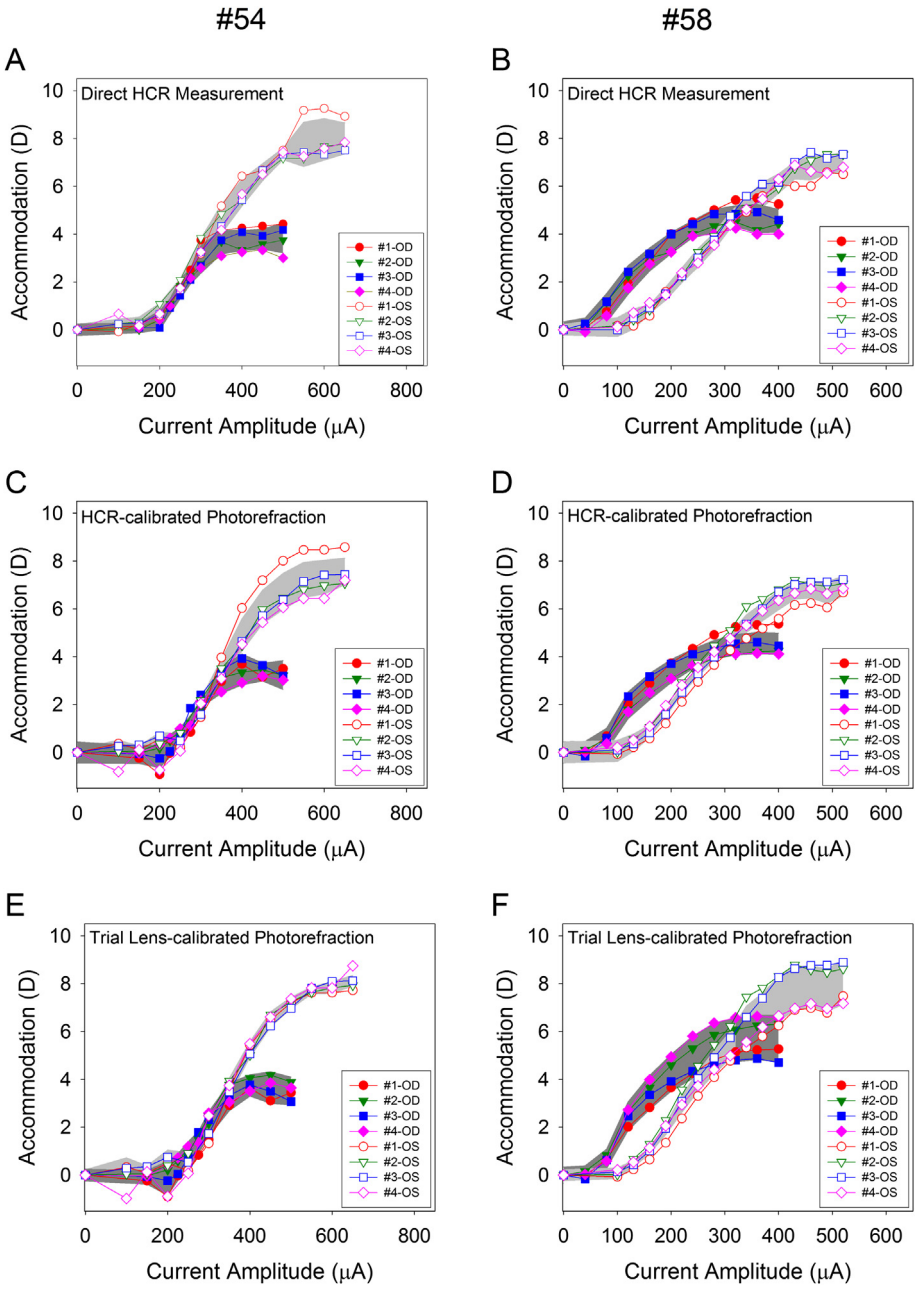

Fig. 2. EW stimulus-response functions from HCR measurement (A & B), HCR-calibrated photorefraction measurement (C & D) and trial lens-calibrated photorefraction measurement (E & F) for the right eyes (filled symbols) and left eyes (open symbols) from four experiments. The gray areas indicate mean ± 1 SD of the four experiment sessions.

to the acrylic not binding well to the skull (Adams et al., 2007). Acrylic-free, biocompatible titanium screws and chambers with feet eventually become integrated into the bone (Adams et al., 2007; Adams et al., 2011). While this may further improve long term viability and stability of indwelling electrodes to improve long-term reproducibility of EW-stimulated accommodation it may still not be sufficient to ensure absolute long-term stability.

Variations of maximum accommodation can be also be caused by the refraction measurement methods and different eye and contact lens positions (Wendt and Glasser, 2012). For photorefraction measurement, since camera and photorefractors settings were kept constant, variations were most likely due to ocular alignment (He et al., 2012). If the measurement axis changes, this can cause differences in fundus brightness which can cause variations in the calibration functions and slopes. If photorefraction calibration functions vary or change over time, this could be a source of variability in the accommodation measurements. Just a single example of a larger than usual variation in the calibration functions as shown in Fig. 1 could account for as much as a 7% error in accommodation measurement. Applying individual calibration functions in each experiment, as they were here can alleviate this source of variability. It is necessary that such sources of variation are known for long-term studies. Although eye and contact lens position could be a source of variation, this should be similar between EW-stimulated accommodation and carbachol stimulated accommodation and between long-term and short-term experiments. Since the SDs from short-term EW-stimulated accommodation are 0.39–0.79 D, the eye and contact lens position are not likely to cause the large variations seen in long-term EW-stimulation.

Table 2
The ranges of maximum accommodation (Max Acc with the means ± SDs) for four consecutive experiments over one month measured with three different methods.

Eye	Week no.	Direct Hartinger measurement	Hartinger-based photorefraction	Trial lens-based photorefraction
		Max acc (D)	Max acc (D)	Max acc (D)
#54 OD	Range	3.33–4.42	3.19–3.93	3.64–4.18
	Mean ± SD	3.92 ± 0.48	3.57 ± 0.31	3.86 ± 0.23
#54 OS	Range	7.50–9.25	7.07–8.58	7.72–8.74
	Mean ± SD	8.08 ± 0.79	7.57 ± 0.69	8.13 ± 0.44
#58 OD	Range	4.25–5.50	4.15–5.37	4.87–6.64
	Mean ± SD	4.79 ± 0.55	4.59 ± 0.55	5.77 ± 0.84
#58 OS	Range	6.58–7.42	6.68–7.23	7.17–8.90
	Mean ± SD	7.05 ± 0.39	6.99 ± 0.27	8.09 ± 0.89

Longitudinal studies of accommodation or of accommodation restoration procedures in monkeys require long-term stability in accommodation stimulation and measurement methods. Some accommodation restoration procedures may require long-term treatments and assessment. If, for example, a pharmacological intervention was proposed to restore 2 D of accommodation over a five-year period, any efficacy due to the treatment could be obscured by variations in EW-stimulated accommodation. Therefore, although EW-stimulated accommodation in anesthetized monkeys has proven valuable, it is not appropriate for longitudinal studies of age-related loss of accommodation or long-term efficacy of accommodation restoration procedures. Pharmacological methods to stimulate accommodation do not have the same issues associated with long-term electrode stability and long-term and short-term reproducibility should be no different. Carbachol iontophoresis or intravenous pilocarpine stimulated accommodation (Wendt and Glasser, 2010, 2012), although not without disadvantages, may be better approaches for longitudinal studies. Intravenous pilocarpine has been shown to produce a similar accommodative response to EW-stimulation (Wendt and Glasser, 2010), but carbachol iontophoresis has been shown to produce a forward shift of the lens that does not occur with EW-stimulated accommodation (Ostrin and Glasser, 2005). Therefore, intravenous pilocarpine may be the most appropriate accommodation stimulation method to use if a natural accommodative response is important to evaluate the particular accommodation restoration strategy being studied.

To the knowledge of the authors, no prior longitudinal studies of accommodation or the progression of presbyopia have been performed in rhesus monkeys. The current study has demonstrated the impracticality of using EW-stimulated accommodation in longitudinal studies in monkeys. While pharmacological stimulated accommodation could be used, the short- and long-term variability in amplitudes seen with carbachol iontophoresis mean that differences less than 2 D would not be detectable (Wendt and Glasser, 2012). Intravenous pilocarpine stimulated accommodation may offer a better alternative (Wendt and Glasser, 2010), but the reproducibility of this method has yet to be determined. Pharmacologically induced accommodation is slow relative to behavioral and EW-stimulated accommodation, so the amplitude could be studied in this way, but not other aspects such as dynamics. Currently, other than EW-stimulation, behaviorally induced accommodation in trained monkeys may offer the only other alternative available for longitudinal studies of the dynamic

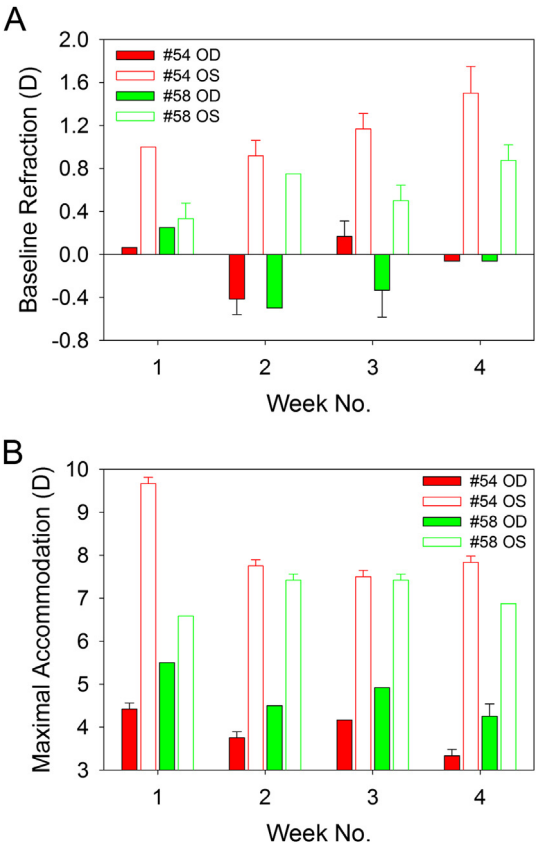

Fig. 3. Baseline refraction (A) and maximum accommodation (B) of all the four eyes in each experiment during the four weeks. Accommodation was calculated as the difference between baseline refraction and the minimum refraction achieved. Filled bars represent the right eyes while open bars represent the left eyes.

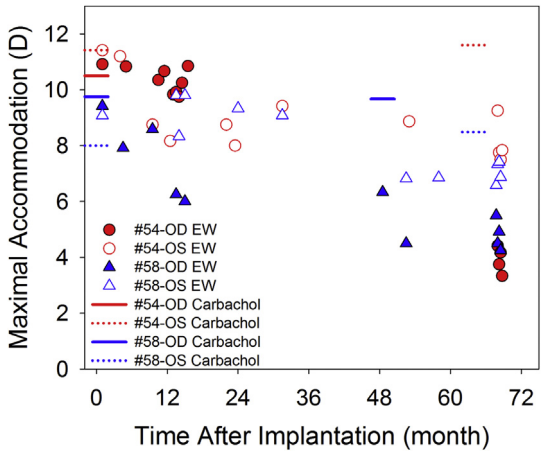

Fig. 4. Maximum accommodation of the four eyes over 68 months after electrode implantation as measured with the HCR. Two monkeys are indicated by different colors (red for #54; blue for #58). Filled (right eye) and open (left eye) symbols are from EW experiments while solid (right eye) and dashed (left eye) lines are from carbachol iontophoresis experiments. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Maximum carbachol and EW-stimulated accommodation (D) during the start (months 0/1) and end (months 64/68) of the 68-month period after EW electrode implantation (month 0) from the four eyes measured using HCR. The dash ('–') associated with the differences indicates the time difference (e.g., '64-0', dark-gray shaded), stimulation method difference (e.g., 'Carbachol–EW', dark-gray shaded) and EW-stimulated inter-ocular difference (e.g., 'OS–OD', light-gray shaded).

	Month	0/1	64/68	Difference (64-0/68-1)
#54-OD	Carbachol	10.50	---	
	EW	10.92	3.92	-7.00
	Difference (carbachol-EW)	-0.42		
#54-OS	Carbachol	11.42	11.60	0.18
	EW	11.42	8.08	-3.33
	Difference (carbachol-EW)	0.00	3.52	
#54 (OS-OD)	Carbachol	0.92	---	
	EW	0.50	4.17	
#58-OD	Carbachol	9.75	---	
	EW	9.42	4.79	-4.63
	Difference (carbachol-EW)	0.33		
#58-OS	Carbachol	8.00	8.49	0.49
	EW	9.08	7.05	-2.03
	Difference (carbachol-EW)	-1.08	1.43	
#58 (OS-OD)	Carbachol	-1.75	---	
	EW	-0.33	2.26	

characteristics of accommodation (Baumeister et al., 2008; Ostrin and Glasser, 2007; Vilupuru and Glasser, 2002), and for studying the longevity of accommodation restoration strategies.

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