Dynamics of accommodative fatigue in rhesus monkeys and humans

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Abstract

Changes in accommodative dynamics with repeated accommodation were studied in three anesthetized rhesus monkeys and two conscious humans. Maximum accommodation was centrally stimulated via the Edinger–Westphal nucleus in monkeys with a 4 s on, 4 s off paradigm (4×4) for 17 min, 4×1.5 for 27 min and 2×1 for 16 min. Humans accommodated repeatedly to visual targets (5×5; 5D and 2×2; 6D) for 30 min. In all cases, accommodation was sustained throughout. The anesthetized monkeys showed inter-individual variability in the extent of changes in accommodative dynamics over time while no systematic changes were detected in the human accommodative responses. Little accommodative fatigue was found compared to previous studies which have reported a complete loss of accommodation after 5 min of repeated stimulation in monkeys.
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1. Introduction

Accommodative fatigue can be described as reduced performance of the accommodative system due to prolonged and/or repeated effort (Hasebe, Graf, & Schor, 2001). Prior studies have considered accommodative fatigue as part of visual fatigue following a near vision task (Gur, Ron, & Heicklen-Klein, 1994; Owens & Wolf-Kelly, 1987; Takeda, Ostberg, Fukui, & Iida, 1988). A prolonged, constant near vision task has been shown to produce a myopic shift in resting accommodative tonus (Ostberg, Grandjean, & Viglani, 1982; Owens & Wolf-Kelly, 1987; Schor, Johnson, & Post, 1984). The effects of accommodative fatiguing have also been studied by determining how accommodative fatigue may influence accommodative aftereffect. Accommodative aftereffect is a continued, sustained accommodative tonus after the stimulus to accommodate has been removed or after the accommodative loop has been

opened, for example in darkness. Repetitive accommodative or vergence ramp tracking exercises performed to induce accommodative or vergence fatigue have been shown to reduce accommodative aftereffects (Schor & Tsuetaki, 1987). Accommodative fatigue induced by a repetitive accommodative task using a lens flipper has been shown to reduce tonic accommodation (Hasebe et al., 2001).

Takeda et al. (1988) compared changes in area under the measured accommodative response with the area under the stimulus step function (the ideal response) as a dynamic metric to quantify fatigue following a continuous near vision task. The subject performed near work for 3 h with 3-min breaks during which accommodative responses to step stimuli were recorded. A systematic decline in area under the accommodative response curve was reported. A decrease in this ratio could reflect an overall decrease in the amplitude of the response or a slower onset of the accommodative response (longer latency), but does not distinguish between these possible causes. Repeated stimulation of accommodation for 30 min in humans resulted in a decrease in subjectively measured amplitude of accommodation as estimated

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by the push-up technique (Berens & Sells, 1944). To our knowledge, no studies have systematically examined the changes in dynamic properties of accommodative responses, such as peak velocity, either during or following repeated accommodative tasks. Such studies have, however, been done to understand the nature of vergence fatigue. The vergence system, which is closely related to the accommodative system, showed a decline in peak velocity of response without significant change in main sequence ratio (the ratio of peak velocity divided by response amplitude for each response) following repetitive vergence responses (Yuan & Semmlow, 2000). In that study the authors were able to infer the possible sites of vergence fatigue. Such dynamic analyses of accommodation or vergence provides an opportunity to determine whether fatigue occurs and if so, where the possible origins of this fatigue are.

To study dynamic properties of accommodation it is necessary to elicit and record repeated accommodative responses. Accommodation can be repetitively stimulated in anesthetized rhesus monkeys by electrically stimulating the pre-ganglionic parasympathetic neurons of the Edinger–Westphal (EW) nucleus (Crawford, Terasawa, & Kaufman, 1989; Vilupuru & Glasser, 2002). Previous such studies have used goniovideography to observe the accommodative movements of the lens and ciliary body in iridectomized rhesus monkey eyes with repeated stimulation (Neider, Crawford, Kaufman, & Bito, 1990). They reported that ciliary body movement decreased and finally ceased after 4 min of repetitive EW stimulation in which 2-s long stimulus trains were delivered every 4 s (Neider et al., 1990). Ciliary body movement was observed and recorded to video tape, but no quantitative analysis was performed. However, it is safe to assume that cessation of ciliary body movement implies cessation of accommodation, representing an extreme case of fatiguing of the accommodative system. Another study in rhesus monkeys using goniovideography and Scheimpflug slit-lamp imaging quantified a gradual decline in amplitude of change in ciliary body movement and extent of lens thickening in response to central stimulation of accommodation (Croft et al., 1998). In that study, a gradual decline to about two-thirds the maximum amplitude in accommodative ciliary body and lens movement occurred within 4 min using 2.2-s long stimulus trains with 2-s inter-stimulus intervals.

The aim of the present study was to quantify and characterize the changes in accommodation as a measure of fatigue with repetitive accommodation using basic metrics such as amplitude as well as other more analytical dynamic metrics such as peak velocity. The experiments were undertaken in three anesthetized rhesus monkeys in which accommodation was stimulated via the EW nucleus and in two conscious human subjects accommodating voluntarily to far and near visual targets.

The initial expectation was that repeated stimulation of accommodation in the monkeys would result in a complete and rapid fatigue induced decrease in accommodation within 5 min, as reported previously (Neider et al., 1990). The first stimulation paradigm and duration tested with the first monkey was based on what was believed should have produced complete fatiguing of accommodation. In the past, stimuli to elicit 4-s long accommodative responses followed by 4-s long rest intervals have been used (Vilupuru & Glasser, 2002). After 17 min of stimulation with this paradigm, no overt indications of fatiguing were observed. The stimulus paradigm was then adjusted to increase the frequency of the accommodative responses by reducing the duration of the rest intervals. After a further 27 min of stimulation, accommodation was still sustained, so once again the frequency of the accommodative response was increased further by giving more frequent stimulations and shorter rest intervals. The same paradigms and durations tested on the first monkey were then subsequently repeated with two additional monkeys to allow comparison between the monkeys. Similar paradigms and durations were then also tested in the two conscious human subjects to allow a comparison between the results from anesthetized monkey with conscious humans.

2. Methods

2.1. Subjects

Repeated accommodative responses were stimulated in three anesthetized rhesus monkeys (#4: age 10, #111: age 3.5, #38: age 3.5 years) and in two human subjects (aged 23 and 25 years). Both human subjects were emmetropic and wore no habitual correction. All animal experiments conducted conformed to the ARVO Statement for the use of Animals in Ophthalmic and Vision Research and were performed in accordance with institutionally approved animal protocols. The human subjects research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the human subjects after explanation of the nature and possible risks of the study and the study was performed in accordance with institutionally approved human subjects protocols.

2.2. EW stimulated accommodation in monkeys

The three rhesus monkeys had undergone prior complete iridectomies and surgical implantation of stimulating electrodes in the EW nucleus as described previously (Croft et al., 1998; Glasser & Kaufman, 1999; Kaufman & Lütjen-Drecoll, 1975; Koretz, Bertasso, Neider, True-Gabelt, & Kaufman, 1987; Neider et al., 1990; Vilupuru

& Glasser, 2002). The monkeys were anesthetized (intramuscular 10 mg/kg ketamine and 0.5 mg/kg acepromazine followed by intravenous 15 mg/kg sodium pentobarbital with hourly supplements as required) and placed prone in a head holder with head held upright and facing forward. Convergence eye movements that occur with centrally stimulated accommodation were minimized by passing sutures beneath the medial and lateral rectus muscles (Glasser & Kaufman, 1999; Vilupuru & Glasser, 2002). The eyelids were held open with a lid speculum. Plano, rigid, gas-permeable contact lenses were placed on the corneas to prevent dehydration. Baseline resting refractions were measured with a Hartinger coincidence refractometer (Zeiss, aus JENA) in the two eyes of the monkeys. Repeated accommodative responses were recorded only in one eye of each monkey.

2.3. Stimulation of accommodation: monkeys

For the repeated accommodative stimulations in the monkeys, a stimulus amplitude was chosen to produce the maximum accommodative response available to each eye. A stimulus generator was used to trigger the stimulator with three different stimulation paradigms. Accommodation was stimulated with trains of square-wave pulses 0.6 ms in duration at 71.42 Hz. Current amplitudes for the three monkeys were as follows: #4: 180 μA, #111: 180 μA, #38: 225 μA. These were stimulus amplitudes previously determined, in the same experiment, to produce maximum accommodation.

Three different stimulus paradigms were used. The first was a 4-s long stimulus train with a 4-s long rest interval (i.e., the stimulus pulse train to the EW nucleus was delivered for 4 s to elicit a 4-s long accommodative response followed by a 4-s rest interval) (4×4), presented for about 17 min to produce 128 consecutive accommodative responses. Because that failed to produce overt signs of fatiguing, the stimulus paradigm was adjusted to increase the frequency of the accommodative responses. After a 3-min interval, the second stimulus paradigm was 4-s long stimulus trains with 1.5-s rest intervals (4×1.5), presented for 27 min to produce 295 consecutive accommodative responses. That also failed to produce overt signs of fatiguing, so the stimulus paradigm was again adjusted to further increase the frequency of the accommodative responses. After a 7-min interval, the third stimulus paradigm was 2-s long stimulus trains with 1-s rest intervals (2×1), presented for 16 min to produce 320 consecutive accommodative responses.

2.4. Measurement of accommodation: monkeys

Accommodative responses were measured dynamically with infrared photorefraction as described previ-

ously (Vilupuru & Glasser, 2002; Vilupuru & Glasser, 2003). A custom made photorefractor consisting of a bank of 20 infrared LED's was placed on a knife-edge aperture in front of a 55 mm lens on a CCD camera at a distance of 0.3 m from the monkey eye. This arrangement produces a uniform brightness gradient in the pupil, the slope of which changes systematically with accommodation as the refractive state changes. This video image was recorded onto a video tape for subsequent off-line frame-by-frame analysis. The video signal was fed to a personal computer via a frame grabber board and was analyzed with Optimas image analysis software (Media Cybernetics). A vertical line drawn through the pupil was used to obtain the pupillary brightness profile from the brightness gradient. A regression line was fitted to the pupillary brightness profile, the slope of which corresponds to that particular refractive state (Schaeffel, Wilhelm, & Zrenner, 1993). This slope was converted to refraction using an IR photorefraction calibration curve which was generated at the start of each experiment (Vilupuru & Glasser, 2002). A signal (VSI-Pro: Trans-American International, Inc.) was recorded to the video tape to indicate when the stimulus to the EW nucleus started and terminated. This allowed the stimulus onset, duration and termination to be recorded from the video tape along with the accommodative response.

Twenty responses from each of the 4×4, 4×1.5 and 2×1 paradigms (Fig. 1a–c), at equally spaced intervals over the three stimulation periods were analyzed as described below to determine changes in dynamics of the accommodative responses during EW stimulation.

2.5. Stimulation of accommodation: humans

The accommodative stimulus was presented to the human subjects as described previously (Kasthurirangan, Vilupuru, & Glasser, 2003). Step changes in target vergence were presented to the human subjects observing a distant and near target binocularly through a beam splitter. The distant and near targets were aligned with the right eye by having the subject close the left eye and adjust the beam splitter to get the targets superimposed. This presented defocus cues for accommodative vergence and disparity cues for disparity vergence and some degree of asymmetrical vergence was stimulated along with defocus by aligning the distant and near targets in front of the right eye. The distant and near targets were high contrast black 'H' letter targets printed on white paper and alternatively illuminated with white light emitting diodes (LEDs). The subjects were instructed to fixate and focus on the distant and near targets as they were alternately illuminated and to keep the targets as clear as possible at all times and to accommodate and disaccommodate as quickly as possible following switching of target illumination. Two stimulus
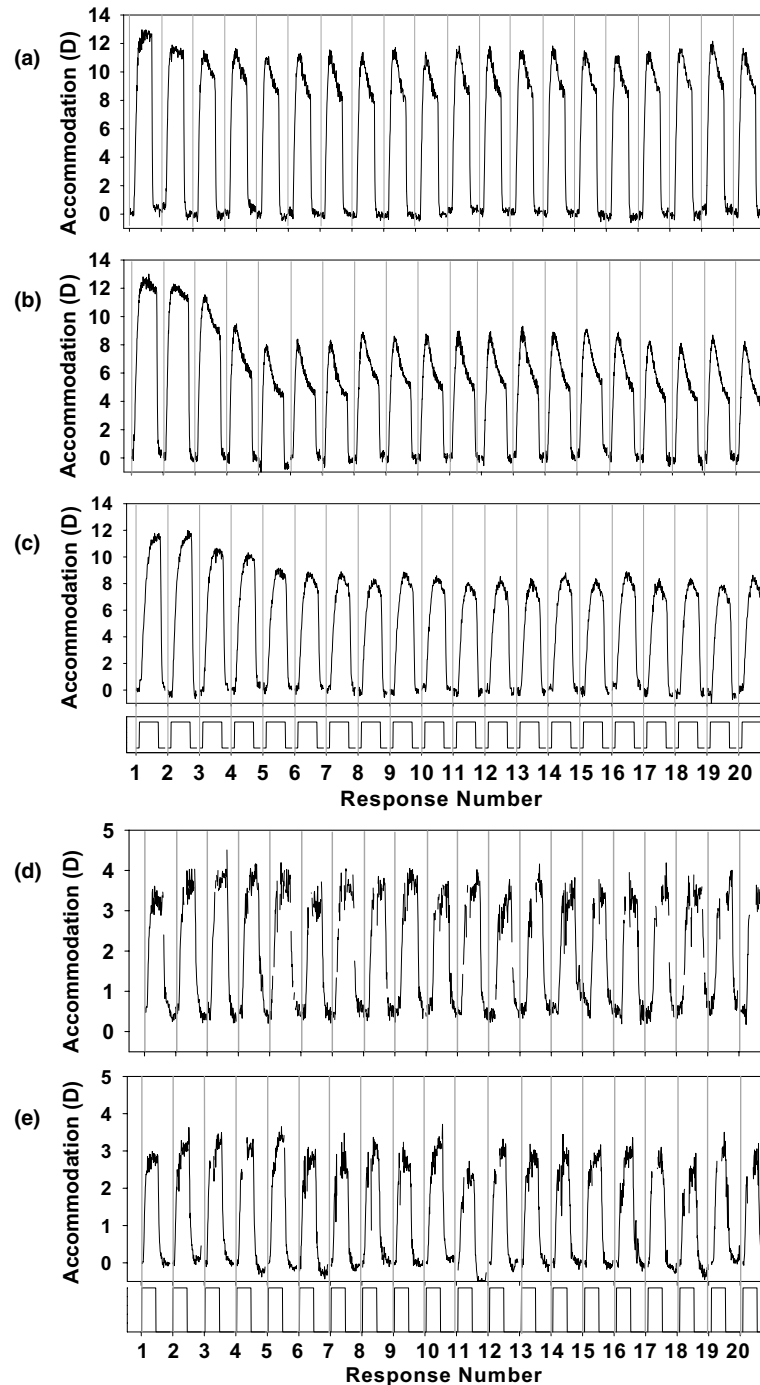
Fig. 1. 20 representative accommodative responses from each of the three stimulation paradigms in one rhesus monkey (#38) (a–c) and 20 representative accommodative responses from two stimulus paradigms in one human (d and e). In the monkeys, 20 responses each at uniform intervals spanning (a) 17 min of 4×4, (b) 27 min of 4×1.5 and (c) 16 min of 2×1 stimulus paradigms were analyzed. In the humans, 20 responses each at uniform intervals spanning 30 min of (d) 5×5 and (e) 2×2 stimulus paradigms were analyzed. The stimulus traces below panels (c) and (e) represent 20 individual stimuli. The time scales and therefore the time point at which each response occurred differs for each of panels (a)–(c). Note that accommodative amplitude does not decline to zero in any of the accommodation fatiguing paradigms used. The change in accommodative maintenance can be seen after about the third response (a and b). The human accommodative responses tend to be more noisy, but are still sustained throughout the 30-min trials (d and e).

paradigms were used. In the first paradigm the distant stimulus was at six meters and the near stimulus was presented at 20 cm (five diopters). The distant and near

targets were alternately illuminated for 5 s each representing a 5-s near accommodative stimulus with a 5-s far stimulus (5×5) (i.e., a 10-s stimulus period with a

0.5 duty cycle), for 30 min to get 180 responses. This relatively conservative paradigm was chosen initially, as it was not anticipated that the subjects would be able to sustain the task for protracted periods. Because the subjects could sustain the task, a more demanding task was subsequently chosen to be more similar to that used with the monkeys. On the following day the subjects were presented with the near stimulus at a distance of 16.7 cm (six diopters). The distance and near targets were alternately illuminated for 2 s each representing a 2-s near accommodative stimulus with a 2-s far stimulus (2×2) (i.e., a 4 s period with a 0.5 duty cycle), for 30 min to get 450 responses. The targets were adjusted in size and presented in real space to maintain a constant angular subtense for the distant and the near targets.

2.6. Measurement of accommodation: humans

The accommodative responses were measured in the human subjects as described previously (Kasthurirangan et al., 2003). Accommodative responses to these step changes were measured dynamically using a PowerRefractor (MultiChannelSystems), an infrared photorefractor. The PowerRefractor dynamically measures refraction, vergence and pupil diameter at 25 Hz (Choi et al., 2000; Kasthurirangan et al., 2003). The video camera of the PowerRefractor was placed at a distance of 1 m and was aligned with the right eye of the subject by means of an infrared beam splitter (in addition to the beam splitter described above for the stimulus presentation) between the distant target and the eye. Changes in refraction during accommodation were measured by the PowerRefractor by monitoring the change in vertical pupillary brightness profile. The slope of the pupillary brightness profile was converted to an absolute refraction measurement by means of individual calibration functions determined at the start of the experiment (Kasthurirangan et al., 2003; Schaeffel et al., 1993). The PowerRefractor dynamically recorded the raw slopes of the pupillary brightness profiles and the times of presentation of the near and far stimuli to a data file. These measured slopes were subsequently converted to refractions during the off-line analysis using the calibration curves.

Twenty responses each from the 5×5 and 2×2 paradigms (Fig. 1d and e), obtained at equally spaced intervals over the entire presentation period were further analyzed to determine changes in dynamics of the human accommodative responses.

2.7. Quantifying the accommodative responses

To further analyze the accommodative responses, functions described previously for monkeys (Vilupuru & Glasser, 2002) and humans (Kasthurirangan et al., 2003) were fit to the accommodative responses and provided excellent fits to the data.

The following metrics were used to further analyze and quantify accommodative responses from the monkey and human data in an attempt to quantify any systematic changes in the accommodative responses with time. These analyses were done only on the subset of the 20 accommodative responses that were extracted for analysis as described above.

(a) *Response amplitude* was used to determine if the amplitude of the accommodative response changed. In the case of the monkeys, response amplitude was determined as the single maximum recorded response directly from the data representing the raw accommodative responses. In the case of the humans, because the responses were more noisy, response amplitude was determined from the functions fitted to the data.

(b) *Accommodative maintenance* was determined for the monkey responses only. The monkey accommodative responses were not always maintained at a constant level throughout each stimulus train (Fig. 1a and b). Accommodative maintenance was determined by subtracting the average of the last ten recorded data points in the accommodative phase of the response (i.e., immediately prior to termination of the stimulus, just prior to the start of the disaccommodative response) from the response amplitude (described above). The monkey responses tend to be more systematic and reliable, thus enabling this analysis to be done. Accommodative maintenance was not analyzed for the human responses because of the considerable variability that is a consistent feature of human accommodative responses.

(c) The *main sequence ratio* has previously been shown to represent a useful metric for dynamics of accommodation (Bahill, Clark, & Stark, 1975; Yuan & Semmlow, 2000). The peak velocity of accommodation and disaccommodation was calculated as the maximum velocity value obtained from the derivatives of the functions fit to the response (Kasthurirangan et al., 2003; Vilupuru & Glasser, 2002).

3. Results

Because the characteristics of the accommodative responses and the changes that occurred with time varied with the individual subjects, the data are not averaged but are presented in "raw" form from each subject to show the individual trends. The main result, namely that accommodative responses continued without cessation,

requires no statistical verification. Because of the non-systematic, individual variations between subjects, a descriptive analysis is presented.

3.1. Rhesus Monkeys

The accommodative responses changed over time, but in different ways in the three monkeys. Accommodative responses did not decline to zero in any of the monkeys with any of the stimulation paradigms (Fig. 1a–c – for monkey #38). No systematic decrease in the amplitude of accommodation was found with continuous stimulation for any of the three stimulus paradigms in monkey #4 (the oldest monkey) but monkeys #111 and #38 did show a systematic decrease in response amplitude for all stimulus paradigms (Fig. 2a–c). Changes in accommodative maintenance with time for each of the three stimulus paradigms for each of the

three monkeys are graphed in Fig. 2d–f. A gradual decrease in the accommodative maintenance was found in the 4×1.5 paradigm for all three monkeys. Monkeys #111 and #38, but not monkey #4, showed a decline in accommodative maintenance for the other two stimulus paradigms (4×4 and 2×1).

Accommodative and disaccommodative main sequence ratios did not change systematically as a function of time for any of the three stimulus paradigms in monkeys #111 and #38 (Fig. 2h,i,k,l). However, in monkey #38 the main sequence ratio first appeared to increase and then decrease for the 4×1.5 paradigm (Fig. 2i, middle trace) and monkey #4 showed a systematic gradual decline in accommodative main sequence ratio for 4×1.5 paradigm (Fig. 2g, middle trace). Monkey #4 did not show a systematic change in accommodative and disaccommodative main sequence ratios for any other stimulus paradigms (Fig. 2g and j).
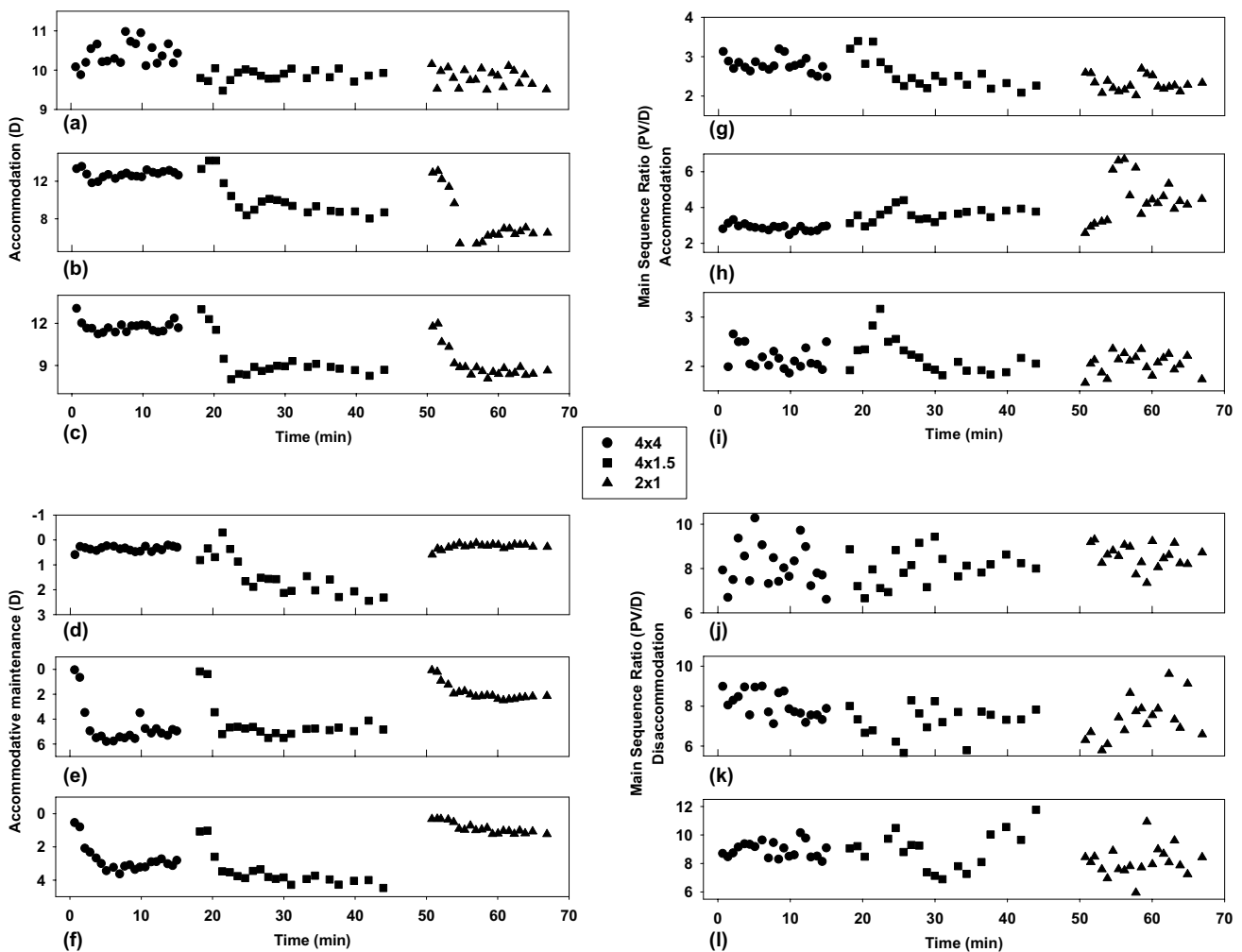

Fig. 2. Response amplitude (a–c), accommodative maintenance (d–f), accommodative main sequence ratio (g–i) and disaccommodative main sequence ratio (j–l) as a function of time with repeated accommodation from the three stimulus paradigms for all three monkeys. In each set of three graphs, the top panel is for monkey #4, middle panel for monkey #111 and bottom panel is for monkey #38.

3.2. Humans

Both subjects were able to reliably track the accommodative stimuli for both paradigms and to elicit reliable accommodative responses throughout the trials. The data shown for one subject (Fig. 1d and e) is representative of the responses from both subjects. This resulted in either 180 consecutive accommodative responses (5×5) or 450 consecutive accommodative responses (2×2) over 30 min. Response amplitude of accommodation did not change systematically during the 30 min for either stimulus paradigm in either subject (Fig. 3a and b). Accommodative and disaccommodative main sequence ratios (Fig. 3c–f) also showed no systematic

change with time following repetitive accommodative response in either of the two subjects. Maintenance of accommodation could not be analyzed for the human responses due to variability.

4. Discussion

This study was undertaken to attempt to quantify changes in dynamic characteristics of the accommodative response during repeated stimulation of accommodation. The study was motivated in part by prior demonstration that repeated stimulation of accommodation in monkeys resulted in complete cessation of
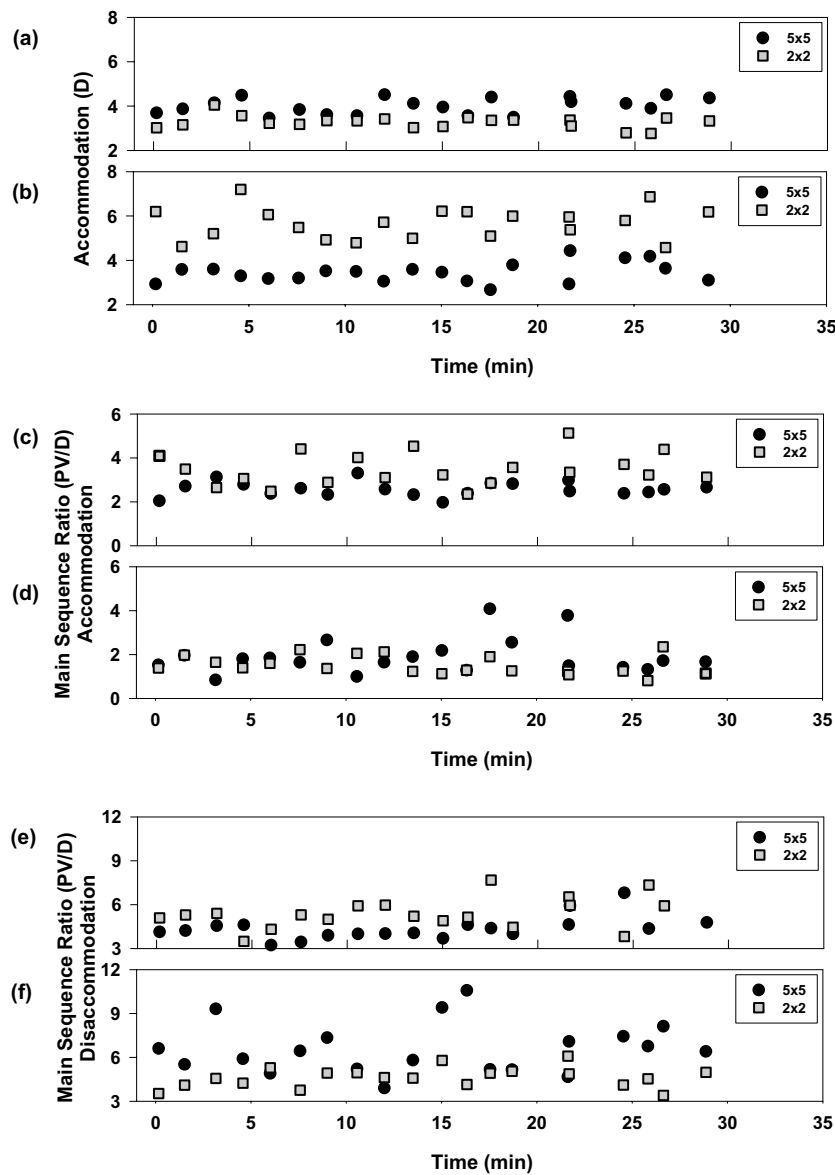

Fig. 3. Changes in response amplitude (a,b) and accommodative (c,d) and disaccommodative (e,f) main sequence ratios with repeated accommodation in 5×5 and 2×2 paradigms from the two human subjects. In each case, data from subject AV is in the top panel and data from subject PB is in the bottom panel.

accommodative ciliary body and lens movements after only 5 min (Neider et al., 1990). We initially set out to test the hypothesis that if repeated stimulation resulted in a decrease in accommodative amplitude it may also result in a change in the dynamics of accommodation perhaps being expressed as a change in main sequence ratio. Repeated accommodative responses induced in the rhesus monkeys with EW stimulation, surprisingly, did not show complete cessation of accommodation as has previously been demonstrated. Despite decreasing the rest interval and increasing the frequency of accommodation to generate a more demanding task, response amplitude did not decrease to zero in any of the three monkeys.

To our knowledge, no prior studies have reported that repeated accommodation produces complete fatigue-induced loss of accommodation in humans. Similar paradigms have been used to study fatiguing effects on vergence, and the results show a decline in peak velocity of vergence (Yuan & Semmlow, 2000), but these studies have not addressed the effects on accommodation. A prior study, however, has shown a decrease in subjective amplitude of accommodation as measured by a push-up test after a period of repeated accommodation (Berens & Sells, 1944). In that study, a target was moved towards the subject at a rate of 2 cm/s until the subject pushed a button indicating blurring of the target, following which the target returned to its original position at the same speed. After a rest period of 2 s the process was repeated. This was continued for 30 min. Subjects participating in that study were patients who reported to the clinic with symptoms of asthenopia and ocular fatigue. In our study, no overt indications of accommodative fatiguing, such as a change in response amplitude or changes in main sequence ratio, were observed when two repeated accommodation stimulation protocols were tested in the normal young human subjects accommodating voluntarily. Fatiguing of accommodation has been reported after a sustained near viewing task when area under the accommodation curve was analyzed from repeated accommodative responses (Takeda et al., 1988). In that study, sustained near viewing was the fatiguing task and repeated accommodation was measured periodically to quantify fatiguing. In the present study, 30 min of repeated accommodation and analysis of the responses were used as both the fatiguing task and the potential metric thereof. The longer, sustained and therefore more demanding near task used by Takeda et al. (1998) could provide an explanation for the differences between the two studies, but the different tasks in the two studies make them difficult to compare directly. Our intent was to present a similar task to conscious humans as we tested in our monkeys and as had previously been shown to produce rapid fatiguing in monkeys.

Based on data reported in prior monkey studies, the expectation was that the repeated stimulus paradigms used would have resulted in complete fatigue-related loss of accommodation in the monkeys and possibly a fatigue-related decrease in amplitude in humans. That this did not occur with centrally stimulated accommodation in the anesthetized monkeys or with voluntary accommodation in the young human subjects unequivocally demonstrates that; (1) the accommodative plant (ciliary muscle of anesthetized monkey and conscious human), (2) the EW neurons and more peripheral accommodative neural pathways of anesthetized monkeys and (3) the entire voluntary accommodative system in conscious humans, are all capable of producing repeated accommodative responses without complete loss of accommodation.

The analysis of the accommodative responses did reveal some indicators of changes in the accommodative responses, perhaps indicating more subtle signs of fatigue than loss of amplitude. There are many possible ways of characterizing fatigue induced alterations in the dynamic accommodative response and a dynamic analysis enables some of these to be examined. Croft et al. (1998) reported fatigue induced loss of accommodation in monkeys. In that study, the velocity of lens thickening during the accommodative phase did not show a decline but velocity of lens thinning during disaccommodation phase did show a significant decrease. "Velocity", as described in that study, was calculated from the linear portion of the rising (accommodation) or falling (disaccommodation) phases of the response and not "peak velocity" as is described in this study. It is therefore not possible to construct the classical main sequence ratios from response velocity as described by Croft et al. (1998).

4.1. Differences between monkey studies

Prior monkey studies showed either complete cessation (Neider et al., 1990) or decrease accommodative movements (Croft et al., 1998) within only 4–5 min, whereas in the present study we found little systematic decrease over extended periods. The surgical procedures and experimental methods are effectively identical between the two research groups (Glasser & Kaufman, 1999). Age of the monkeys is unlikely to be a factor. Two monkeys in this present study (aged 3.5 years) were similar in age to the 4-year-old monkey reported on by Croft et al. (1998). No age is given for the monkey for which fatiguing is reported in the Neider et al. (1990) study, (monkeys in their study ranged in age from 1 to 24 years). The monkey used by Neider et al. (1990) was not likely to have been an old monkey based on the considerable extent of ciliary body accommodative excursion shown. Their monkey may well have been between the 3.5 and 10 years as in the present study. Neider et al. (1990) used a 2-s stimulus followed by 2 s of relaxation (2 × 2 s) and Croft et al. (1998) used a 2.2-s

stimulus with a 2-s relaxation (2.2×2 s). These stimulation paradigms are within the range used in the current study (4×4; 4×1.5 & 2×1 s) and are therefore unlikely to be a factor. It is possible that fatiguing was seen in the two prior studies because of the higher frequency pulse train stimulation or higher current amplitudes used. Both Neider et al. (1990) and Croft et al. (1998) used 100-Hz stimulation and the latter used a 1000-μA current. In the present study 71.42-Hz stimulation (a period of 1.4 ms) with current amplitudes less than 250 μA were used. We used 71.24-Hz stimulation because this is the stimulation frequency we routinely use for our accommodation studies which produce repeatable and reliable dynamic accommodative responses (Ostrin & Glasser, 2004; Vilupuru & Glasser, 2002; Vilupuru & Glasser, 2003). 71.24-Hz stimulation produces a brisk accommodative response of similar amplitude to a 100-Hz stimulus, but with a less dramatic convergence eye movements making dynamic accommodation recordings more reliable (Glasser, unpublished observations). While a 100-Hz stimulus may increase accommodative amplitude for the same stimulus current amplitude, maximum accommodation can still be achieved by simply increasing the stimulus current amplitude. If the different stimulus frequencies is the explanation for the difference, accommodative responses to a 71.24-Hz stimulus may more closely match natural accommodation for the ability to sustain repeated accommodative responses compared to 100-Hz stimulation.

4.2. Changes in accommodative maintenance

Accommodative maintenance, as used here, is the difference between the maximum response amplitude reached and the average amplitude from the last ten data points of the accommodative response. This metric is indicative of how well the accommodative plateau is maintained after maximum accommodation was achieved with EW stimulation. Accommodation was not maintained in any of the three stimulus paradigms in monkeys #111 and #38, whereas in monkey #4 a loss of maintenance was observed only in the 4×1.5 paradigm. The differences between the three monkeys could be due to physiological differences in response characteristics between monkeys or possibly due to differences in the electrode tip position within the EW nucleus.

4.3. Changes in main sequence ratios

To our knowledge no prior study has looked at changes in peak velocities of accommodative response and main sequence ratios during repeated accommodative tasks in humans. Peak velocity of EW stimulated accommodation in anesthetized monkeys has been shown to be linearly related to response amplitude (Vilupuru & Glasser, 2002). In the present study, response

amplitudes did change in the monkeys, therefore the main sequence ratio, as opposed to peak velocity, was used as a dynamic metric to account for a simultaneous decrease in amplitude. The present results, in conjunction with the prior demonstration of a robust EW stimulated main sequence relationship, suggests that, at least in some cases (Fig. 2g, with the 4×1.5 paradigm in monkey #4), fatiguing of accommodation can alter the normally robust main sequence relationship. The vergence system, which is closely related to the accommodative system, showed a decrease in peak velocity of vergence responses with no change in main sequence ratio to step changes in target vergence following a fatiguing task (Yuan & Semmlow, 2000).

A repetitive vergence task causes a decline in peak vergence velocity (Yuan & Semmlow, 2000) along with an associated decrease in response amplitude resulting in a constant main sequence ratio. It is suggested that this is due to a modification of the vergence control system and not due to a change in neuromuscular efficiency. In our experiment, human subjects viewed the far and near targets binocularly and binocular accommodation and vergence responses occurred since they are neuronally coupled with each other and between the two eyes. There was no systematic change in accommodative amplitude or main sequence ratio in either of the two human subjects with time. Because a vergence stimulus was present, it is possible that the vergence accommodative response could have been reduced due to fatiguing in accordance with the results from Yuan and Semmlow (2000). However since there was no systematic decrease in amplitude in the humans it may be that any decrease in vergence accommodative signal may be compensated for by blur driven accommodation to maintain the same overall level of accommodation. In the anesthetized monkey, direct stimulation of the EW neurons means that the higher level accommodative and vergence control centers are not involved. Two of the three rhesus monkeys showed a gradual decline in amplitude of accommodation for all the stimulus paradigms. That some decrease did occur may suggest that the neuromusculature from the EW nucleus to the ciliary muscles in the eye may be prone to some fatigue induced changes with repeated stimulation in some monkeys.

There may be several different types of fatiguing occurring in the monkeys or the humans. We have not attempted to isolate or quantify all possible effects that repeated accommodation may have. For example, there may be a change in resting focus after the task, or there may be a reduced gain of accommodation that could result in a decreased amplitude (e.g., monkey #111 and #38) or reduced velocity (monkey #4). It is possible that fatiguing of vergence and/or differential effects on vergence and accommodation could have resulted. EW stimulated accommodation in the monkeys also

produces convergent eye movements, however, this is due to current spread to the oculomotor nucleus in close proximity to EW, whereas in conscious humans, disparity and blur stimulate vergence. This may have very different effects on vergence fatigue between the anesthetized monkeys and conscious humans. Since the effects of repeated accommodation are different in different monkeys and between the humans and monkeys and between the different paradigms, it is clear that all possible sources of fatiguing are not always present in all subject. Individual variation may play an important factor. In one of the human subjects, for example, a greater lag of accommodation was evident for the 2×2 paradigm with a 6D stimulus than for the 5×5 paradigm with the 5D stimulus (Fig. 3b), whereas the lag was more consistent in the other subject.

This study demonstrates that in monkeys in which accommodation is stimulated via the EW nucleus, accommodation can be elicited repeatedly without a complete loss of accommodation and that repeated stimulation of accommodation did not decrease objectively measured amplitude of accommodation in humans. This provides a possible protocol for future studies where accommodation is repeatedly stimulated to ascertain changes in dynamics under various conditions. For example, it may be of interest to test how various drugs affect the accommodative response (Ostrin, Frishman, & Glasser, 2004; Ostrin & Glasser, 2004) or how the accommodative response is altered by aging and the onset of presbyopia.

5. Conclusions

Anesthetized monkeys and conscious humans can accommodate repeatedly to step stimuli without complete loss of accommodation. The results indicate that accommodative fatigue is stimulus-paradigm and response-criterion dependent, i.e. accommodative fatigue can be expressed quantitatively depending on the fatiguing task and the analysis performed. Both accommodative plant and accommodative control centers may fatigue to a limited extent upon repeated stimulation. In the absence of a complete loss of amplitude, other dynamic metrics of accommodation can demonstrate changes in the accommodative response.

Acknowledgments

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