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Quantifying interactions between accommodation and vergence in a binocularly normal population

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Abstract:

Stimulation of the accommodation system results in a response in the vergence system via accommodative vergence cross-link interactions, and stimulation of the vergence system results in an accommodation response via vergence accommodation cross-link interactions. Cross-link interactions are necessary in order to ensure simultaneous responses in the accommodation and vergence systems. The crosslink interactions are represented most comprehensively by the response AC/A (accommodative vergence) and CA/C (vergence accommodation) ratios, although the stimulus AC/A ratio is measured clinically, and the stimulus CA/C ratio is seldom measured in clinical practice. The present study aims to quantify both stimulus and response AC/A and CA/C ratios in a binocularly normal population, and determine the relationship between them. 25 subjects (mean±SD age 21.0±1.9 years) were recruited from the university population. A significant linear relationship was found between the stimulus and response ratios, for both AC/A ($r^2=0.96$, $p<0.001$) and CA/C ratios ($r^2=0.40$, $p<0.05$). Good agreement was found between the stimulus and response AC/A ratios (95% CI -0.06 to 0.24 MA/D). Stimulus and response CA/C ratios are linearly related. Stimulus CA/C ratios were higher than response ratios at low values, and lower than response ratios at high values (95% CI -0.46 to 0.42 D/MA). Agreement between stimulus and response CA/C ratios is poorer than that found for AC/A ratios due to increased variability in vergence responses when viewing the Gaussian blurred target. This study has shown that more work is needed to refine the methodology of CA/C ratio measurement.

1.1 Introduction

During normal binocular vision the accommodation and vergence systems act simultaneously to provide clear bifoveal retinal images which are then unified in the visual cortex to form a single binocular image. The primary stimuli for accommodation and vergence are image blur(Fincham, 1951) and horizontal binocular disparity(Wheatstone, 1838) respectively. The accommodation and vergence systems are coupled to ensure a coordinated near response. These interactive components are quantified by the AC/A and CA/C ratios respectively(Fincham and Walton, 1957),

and ensure that accommodation responses are accompanied by simultaneous vergence eye movements and vice versa, thereby maintaining clear, single vision of objects at all distances (Schor and Kotulak, 1986).

Accommodation and vergence responses are modelled as negative feedback control systems using control systems theory (Campbell and Westheimer, 1960, Schor and Kotulak, 1986, Stark, 1965, Toates, 1970, Toates, 1974). One of the most widely accepted models includes phasic (fast acting) and tonic (slow acting) components, and components representing the interactions between the two systems (Schor and Kotulak, 1986). Schor and Kotulak (1986) presented experimental evidence placing the cross-link interactions after the phasic components of the systems, but before the tonic components, (Schor and Kotulak, 1986). Stimulation of the accommodative vergence cross-link resulted in changes in the tonic vergence component and stimulation of the vergence accommodation cross-link resulted in changes in the tonic accommodation component (Schor and Kotulak, 1986) (Fig 1). The positioning of the cross-links in Schor and Kotulak's model (1986) would mean that vergence adaptation would reduce output of the vergence accommodation cross-link and accommodation adaptation reduces the output of the accommodative vergence cross-link without changing the gain of either cross-link component (Schor and Tsuetaki, 1987). The cross-link components are considered by some to be a fixed characteristic of the oculomotor system (Schor and Kotulak, 1986), which remains stable over time (Bruce et al., 1995, Rainey et al., 1998). Other studies have found that the cross-link ratios can be altered temporarily (Eadie et al., 2000, Judge and Miles, 1985, Schor and Horner, 1989), and this has been attributed to changes in the output of the slow tonic components (Fisher and Ciuffreda, 1990, Schor and Horner, 1989). Some models have found the cross-links are reciprocally related (i.e. the AC/A is equal to $1/CA/C$) (Schor and Kotulak, 1986) (Schor, 1992), although other studies have been unable to replicate this finding (Bruce et al., 1995, Owens, 1980, Owens and Wolf-Kelly, 1987, Rosenfield et al., 1995, Semmlow and Hung, 1981). Other models suggest the cross-links are inversely related (i.e. as the AC/A increases in value the CA/C ratio decreases) (Semmlow and Hung, 1981).

Previous work has shown that patients with binocular vision anomalies often have abnormal AC/A and CA/C ratios (Lara et al., 2001, Porcar and Martinez-Palomera, 1997, Von Noorden, 1996). Abnormal AC/A and CA/C ratios are important diagnostic criteria for both convergence excess and convergence insufficiency (Lara et al., 2001, Porcar and Martinez-Palomera, 1997). It has also been found that patients with convergence excess and convergence insufficiency often exhibit unequal adaptation of vergence and accommodation, which may be the cause of the abnormal AC/A and CA/C ratios (Schor, 1988). Convergence insufficiency patients often exhibit a low AC/A ratio (Daum, 1984), hence if the AC/A and CA/C ratios are reciprocally related, it would be expected that convergence insufficiency patients will have high CA/C ratios (Schor and Horner, 1989), however due to methodological difficulties few studies have examined this possibility (Brautaset and Jennings, 2006). The AC/A ratio has also been used as a predictive measure of treatment outcome (Daum, 1984, Kim et al., 2012). It has been shown that, within a group of convergence insufficiency patients, a lower AC/A ratio decreased the probability of successful orthoptic treatment (Daum, 1984). It has also been shown that normalization of the AC/A ratio in non-refractive accommodative esotropia patients (using bifocals) can be used as a predictor of the success of treatment (Kim et al., 2012).

Clinical assessment of the CA/C ratio is clearly an important measure of binocular function, but is rarely undertaken because of methodological difficulties in opening the accommodation loop whilst measuring vergence eye position precisely (Rosenfield, 2009). Open loop responses are responses unregulated by feedback, closed loop responses are regulated by feedback. In order to gain a fuller understanding of the cross-link interactions both ratios should be assessed clinically. This will become increasingly important as the use of stereoscopic displays increases because studies have shown that unequal accommodation and vergence demands found in 3D displays can temporarily modify the cross-link interactions (Eadie et al., 2000, Miles et al., 1987). It has been suggested that

changes in the cross-link interactions could be responsible for asthenopic symptoms(Hoffman et al., 2008), although the cause of asthenopia experienced whilst viewing 3D displays has yet to be determined(Howarth, 2011, Kooi and Toet, 2004, Speranza, 2006).

The stimulus CA/C ratio compares the vergence accommodation response to the vergence stimulus at each stimulus level. The response CA/C ratio compares the vergence accommodation response to the vergence response at each stimulus level. The response CA/C ratio provides the most accurate measure of this cross-link interaction as the responses of both the accommodation and vergence systems are observed directly(Tsuetaki and Schor, 1987). Of the studies which have examined either the stimulus or the response CA/C ratio in adult populations(Bruce et al., 1995, Hung G.K., 1986, Rosenfield et al., 1995, Tsuetaki and Schor, 1987, Wick and Currie, 1991), only one has compared stimulus and response ratios (Tsuetaki and Schor, 1987). Tsuetaki and Schor(1987) reported good agreement between the stimulus and response CA/C in a small sample of 6 subjects. The accommodation loop was opened using a difference of Gaussian target and the authors suggested this method could be employed to measure the stimulus CA/C in clinical practice (Tsuetaki and Schor, 1987).Other studies have examined only the response CA/C ratio (Bruce et al., 1995, Hung G.K., 1986, Rosenfield et al., 1995) and further work is required to establish the characteristics of the relationship between stimulus and response CA/C ratio in a larger sample.

Many studies which have investigated the CA/C ratio previously have used a difference of Gaussian target (Brautaset and Jennings, 2006, Eadie et al., 2000, Tsuetaki and Schor, 1987, Wick and Currie, 1991). The low spatial frequency characteristics of the difference of Gaussian target allows stimulation of the vergence system whilst the accommodation loop remains open (Tsuetaki and Schor, 1987). Previous investigations have shown that the accuracy of steady state fixation depends on the spatial and temporal properties of the stimulus(Schor and Tyler, 1981). Schor and Tyler (1981) showed that the size of Panum's fusional area can range from approximately 2.5 arcmin for targets high in spatial and temporal frequency (2cpd/5Hz) to >20 arcmin for targets low in spatial and temporal frequency (0.125 cpd/ 0.1Hz), suggesting that vergence responses to low spatial frequency targets (such as difference of Gaussian targets) will be inherently more noisy due to the stimulus characteristics.

The stimulus AC/A ratio compares the accommodative vergence response to the accommodation stimulus at each stimulus level, whereas the response AC/A ratio measures the accommodative vergence response and compares it to the accommodation response at each stimulus level. Clinically the stimulus AC/A ratio is easily obtained, and shows good agreement with response measures of the AC/A ratio (Alpern, 1962, Rainey et al., 1998).The response AC/A ratio provides the most accurate measure of the strength of the interaction between the two systems. Measurement of the response AC/A ratio is time consuming and requires specialist equipment and is rarely undertaken in a clinical setting, therefore a robust clinical measure of the stimulus AC/A ratio is essential as part of a comprehensive assessment of binocular vision. The gradient method has been found to give the most accurate representation of both cross-link interactions (Bhoola, 1995, Sloan et al., 1960).

Several studies have investigated the stimulus and response AC/A ratios concurrently in the same subjects and found that the two measures are well correlated, with the response ratio being 8% to 24% higher than the stimulus ratio (Alpern, 1962, Bhoola, 1995, Gratton and Firth, 2010, Rainey et al., 1998, Rosenfield et al., 1995). The close proportional relationship between the stimulus and response AC/A ratios makes the stimulus AC/A a clinically useful measure of accommodative vergence interaction(Bhoola, 1995).

The response AC/A ratio measured using the gradient method has been found to depend upon target position (Pankhania and Firth, 2011), with response AC/A ratios measured at 3.8m being significantly lower than those measured at 0.33 m (Pankhania and Firth, 2011). The same study also found no correlation between the response AC/A ratios measured using the target at these two distances (Pankhania and Firth, 2011). Another study did find a significant correlation between the AC/A ratio measured at distance and near ($r^2=0.2601$) and found no significant difference between the AC/A ratios measured using a distance or a near target (Jackson and Arnoldi, 2004).

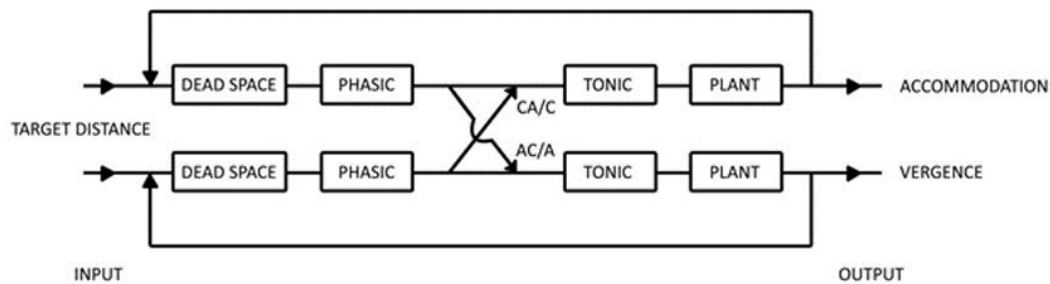


Fig 1. Negative feedback model of the accommodation and vergence system. Phasic, tonic and interactive components of the accommodation and vergence responses are all represented (after Schor and Kotulak, 1986). The Dead space represents depth of focus and Panum's fusional area in the accommodation and vergence systems respectively. The phasic components represent the initial fast component of response of the accommodation and vergence systems. The tonic components represent the sustained response of the accommodation and vergence systems. The plant represents the physiological components of the accommodation and vergence systems.

Previous studies have described the distribution of AC/A and CA/C ratios within binocularly normal adult populations (Table 1). Values in Table 1 and throughout the paper will be quoted in Meter Angles/Diopter for AC/A ratios and in Diopters/Meter Angle for CA/C ratios. 1MA represent the reciprocal of the distance in metres to which the eyes are converged (Fincham and Walton, 1957). Some of these studies are confounded by the effect of age, which causes a decrease in accommodation function, leading to an increase in the response AC/A (Bhoola, 1995, Bruce et al., 1995, Ciuffreda et al., 1997, Fincham and Walton, 1957, Hung G.K., 1986, Rosenfield et al., 1995) and decrease in the response CA/C ratio (Bruce et al., 1995, Rosenfield et al., 1995, Wick and Currie, 1991). In addition, some studies have small subject numbers (Alpern, 1962, Morgan, 1968, Ogle et al., 1967, Tsuetaki and Schor, 1987), and none have quantified the stimulus and response ratios for both AC/A and CA/C within the same population. Studies have also shown that AC/A ratios are elevated in some populations with myopia due to increased accommodative lag, particularly for blur-only stimuli (Gwiazda et al., 1999, Mutti et al., 2000, Rosenfield and Gilmartin, 1987). More work is needed to confirm if refractive error has an effect on the CA/C ratio.

The lack of any substantial comparison between stimulus and response CA/C ratios in the literature hinders a full understanding of the physiological reasons behind binocular vision dysfunction. It is also important that normative values of the stimulus and response CA/C ratios exist so that the binocular response to stereoscopic displays can be accurately quantified and understood. This study aims to provide a comprehensive evaluation of the cross-link interactions in a binocularly normal adult population.

	Number of subjects	Stimulus AC/A ratio	st dev	Response AC/A ratio	st dev	Stimulus CA/C ratio	st dev	Response CA/C ratio	st dev
Bhoola 1995**	23	0.58	0.36	0.72	0.21				
Bruce 1995**	23			0.73	0.25			0.45	0.27
Fisher 1990*	12			0.67	0.06				
Franceschetti 1970	355	0.47	0.20						
Gratton 2011**	16	0.33	0.22	0.41	0.27				
Hung 1986	22			0.55	0.13			0.74	0.28
Jackson 2004	69	0.35 ⁺ /0.38	0.05 ⁺ /0.03						
Morgan 1968	4			0.67	0.33				
Ogle 1967	10			0.72	0.22				
Pankhania 2011	25			0.51 ⁺ /0.78	0.29 ⁺ /0.39				
Rainey 1998	8	0.39	0.17	0.63	0.23				
Rosenfield 1995*	42	0.48	0.15	0.58	0.10			0.68	0.6
Tsuetaki 1987	6					0.27	0.13	0.33	0.13
Wick 1991 ^o	40/6					0.19	0.07	0.50	0.35
Mean of studies where vergence is stated in MA		0.4175	0.185	0.593333	0.213333	0.23	0.1	0.5625	0.34
Mean of all previous studies		0.45	0.22	0.63	0.2	0.23	0.1	0.54	0.33
Present study	25	0.57	0.28	0.66	0.33	0.58	0.15	0.55	0.28

Table 1
Previous work examining the AC/A and CA/C ratios in normal adult populations. AC/A ratios are expressed in MA/D and CA/C ratios are expressed in D/MA . * Converted from prism diopters assuming a 60mm pupillary distance. ^oStimulus CA/C ratio was measured on 40 subjects and response CA/C ratio was measured on 6 subjects. ⁺ Measured using a distant target.

1.2 Materials and Methods

25 subjects (mean±SD age 21.0±1.9 years) were recruited from the student population at Glasgow Caledonian University. To be included in the study subjects had to meet the following criteria; less than 2^Δ of horizontal heterophoria at distance, less than 4^Δ of horizontal heterophoria at near(measured at 33cm) and no vertical heterophoria, as measured using prism cover test and verified using Maddox rod. Stereopsis was required to be a minimum of 55 seconds of arc with the Frisby stereotest. All subjects had normal amplitude of accommodation for their age. Mean spherical equivalent (MSE) refraction ranged between +0.50 to -6.00DS (measured using the Shin-Nippon SRW-5000 with the subject fixating on a spotlight at 5m, and calculated as the mean of ten static measurements). Hyperopic subjects and subjects with more than 0.50D of astigmatism were excluded, subjects with more than 0.50D of anisometropia were also excluded. Hyperopic subjects were excluded, because the authors wanted to ensure that all participating subject's refractive errors were fully compensated to avoid contamination in the accommodation response during AC/A and CA/C measurement due to under or overcorrection. Subjects were fully corrected throughout

the experiment and all subjects had a minimum corrected visual acuity of 6/6 in either eye. The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects prior to participation in the study.

Accommodation was measured in the right eye using the Shin-Nippon SRW-5000 autorefractor (Shin-Nippon Commerce Inc., Tokyo, Japan) in static mode with the average of ten consecutive readings being taken at each stimulus level. In static mode the SRW- 5000 has been found to be accurate to within 0.25D compared to subjective refraction and highly repeatable ($0.04 \pm 0.22D$ MSE) (Mallen et al., 2001). Individual accommodation responses at each stimulus level were removed if they were out-with $\pm 2SD$ of the mean accommodation response.

Eye movements were recorded continuously at a sampling frequency of 100Hz using the Skalar Iris infra-red limbal reflection eye tracker Model 6500 (Cambridge Research Systems., Kent, United Kingdom). Eye tracker resolution was 2 mins of arc under optimal conditions with cross-talk in the order of 10% and linearity to within 3% over a $\pm 30^\circ$ operating range as quoted by the manufacturer (Reulen et al., 1988). The typical noise levels were 19 minutes of arc in each eye in live human recordings (determined from the variability during periods of fixation) this variability also takes into account the physiological stability of each participants oculomotor system. The eye tracker was mounted on a trial frame allowing the inter-pupillary distance (PD) to be altered precisely from 45 to 80mm.

Accommodation and vergence responses were measured concurrently during each trial session. Stimuli for accommodation (lenses) and vergence (prisms) were introduced in a random order. Each session lasted approximately 40 minutes and comprised 4 experimental runs, each separated by 3 minute breaks to avoid fatigue.

For AC/A ratio measurement the target was a high contrast, sharp edged line subtending 13.2 mins of arc in width at a viewing distance of 33cm aligned with the right eye. Open-loop vergence position and closed loop accommodation responses were measured for accommodative stimuli between 1 and 6D presented randomly, in 1D steps, using a series of spherical lenses placed in front of the right eye at a back vertex distance of 12mm. Subjects were asked to inform the examiner if they could not make the target clear at any time, no blurring of the stimulus was reported at any stimulus level. The vergence loop was opened by occluding the left eye.

For CA/C measurement the same line target used during AC/A measurement was modified using Image J software (National Institutes of Health, USA). The target was created by applying a Gaussian blur filter (16 blur sigma radii) to the sharp line target.

A pilot study was carried out on 5 subjects taking 20 static measurements of the accommodation response while the subject viewed the target monocularly at 2 stimulus levels (2D and 4D). The results did not show any significant difference between accommodation responses for the two positions, confirming that the accommodation system was open loop when viewing this target.

The vergence demand was varied randomly from 1 to 6MA of convergence, in 1MA steps, using prismatic lenses placed in front of the left eye whilst the right eye was aligned with the target. To minimize prism adaptation the prisms were presented for no more than 30 seconds and there was a recovery time of 30 seconds between each stimulus. All subjects had sufficient fusional reserves to overcome the 18Δ base out and 6Δ base in demand required at the 33cm working distance. Most subjects also had sufficient fusional reserves to overcome the 12Δ stimulus at near. Not all subjects were able to fuse the full range of vergence stimuli but all subjects completed a minimum of 4 vergence stimulus levels.

Both targets were viewed in free space through a white aperture (height 10cm, width 15cm) attached to the front of the autorefractor. The aperture ensured that the edges of the target were not visible thus minimizing proximal stimulation of the accommodation and vergence systems.

Proximal cues were also minimized as the target remained stationary at a viewing distance of 33cm throughout all measurements.

1.3 Results

Investigations were carried out to examine the relationship between the accommodation stimulus and the accommodation response under monocular conditions at each stimulus level during AC/A measurement (Fig 2). The accommodation response shows typical lags of between 0.75 and 1D, and the lag increased with increasing stimulus values. Investigations were also carried out to examine the relationship between vergence response and vergence stimulus during CA/C measurement (Fig 3). The vergence responses show a lag of between 0.25 and 0.5MA, which is similar across all stimulus levels.

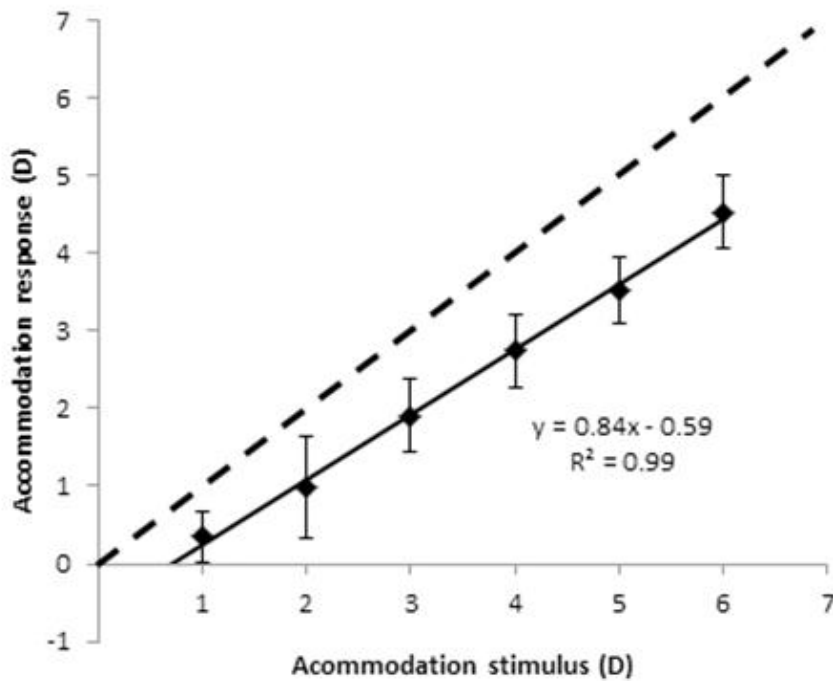


Fig 2. The stimulus response curve for the group mean accommodation data \pm SD at each of the stimulus levels during AC/A measurement. The dashed line represents equal accommodation stimulus and response.

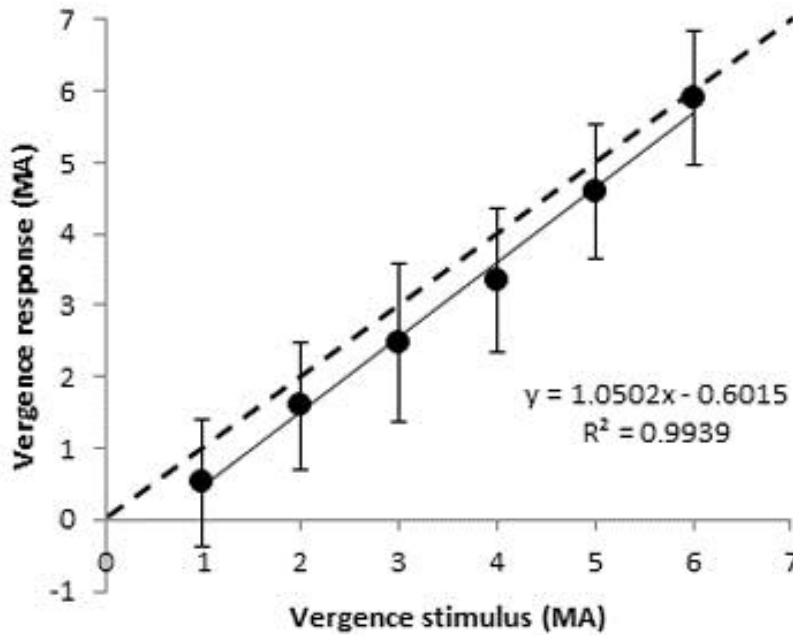


Fig 3. The stimulus response curve for the group mean vergence data \pm SD at each of the stimulus levels during CA/C measurement. The dashed line represents equal vergence stimulus and response.

The distribution of stimulus and response ratios were found to be normal for both AC/A and CA/C measures (Kolomogorov-Smirnov, $p > 0.05$). The group mean \pm SD values for all 4 ratios are shown in Fig 4. The group mean stimulus and response AC/A ratios were not significantly different from each other and the group mean stimulus and response CA/C ratios were not significantly different. Typical data from a number of individual subjects are shown in Fig 5.

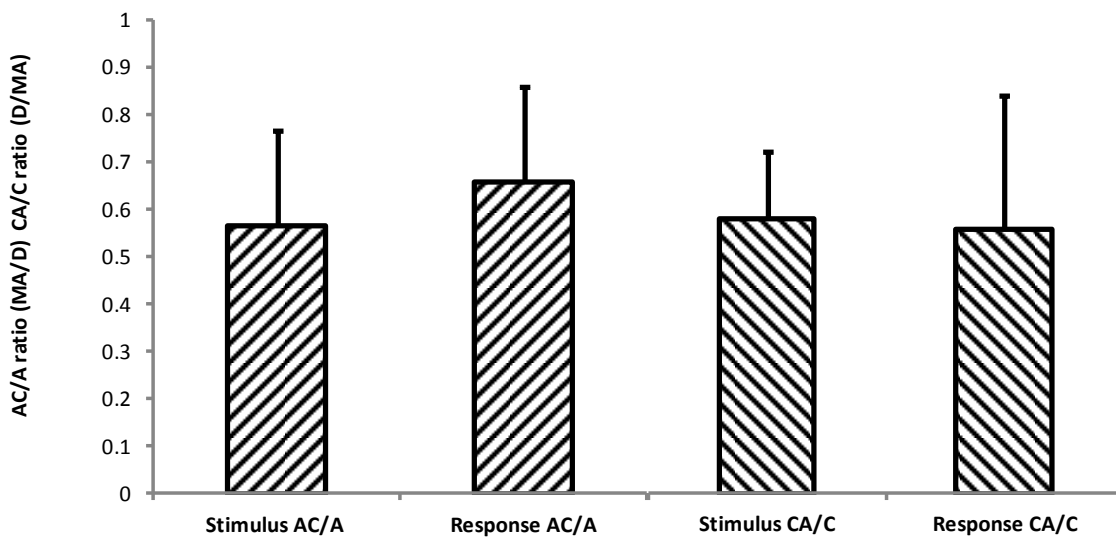


Fig 4. A plot of the group mean stimulus and response cross-link ratios are shown. AC/A values are stated in MA/D and CA/C values are stated in D/MA.

A significant linear relationship existed between stimulus and response AC/A (Fig 6: linear regression, $R^2= 0.96$, $F=587.37$, $df=1,24$, $p<0.001$) where the response AC/A was found to be 16% greater, on average, than the stimulus AC/A ratio. A significant positive linear relationship was also found between the mean of the stimulus and response AC/A ratios, and the difference between stimulus and response AC/A ratios (Fig 7: linear regression, $R^2= 0.42$, $F=16.57$, $df=1,24$, $p<0.01$), such that the difference between stimulus and response increased with increasing value of the ratio albeit within a relatively small range.

A significant linear relationship between stimulus and response CA/C was found (Fig 8: linear regression, $R^2= 0.40$, $F=15.50$, $df=1,24$, $p<0.01$), with the response ratio being 25% greater on average than the stimulus ratio. Furthermore, a significant positive linear relationship was found between the mean of the stimulus and response CA/C ratios, and the difference between stimulus and response CA/C ratios (Fig 9: linear regression, $R^2=0.48$, $F=20.99$, $df=1,24$, $p<0.001$), such that stimulus ratios tend to be higher than response ratios for low ratio values and lower than response ratios at high values, with stimulus and response ratios being equivalent at a value of ≈ 0.6 .

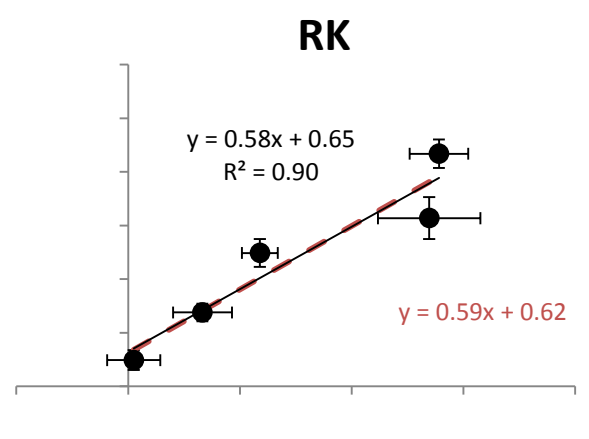
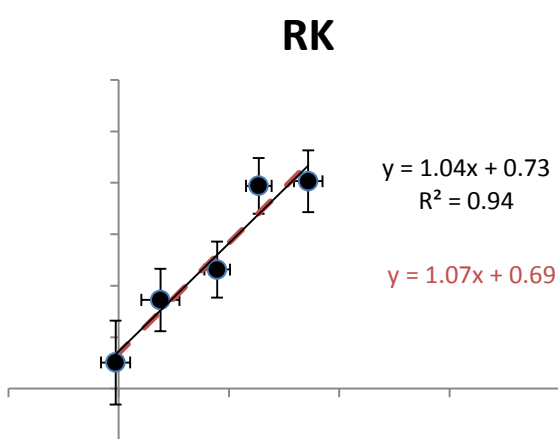
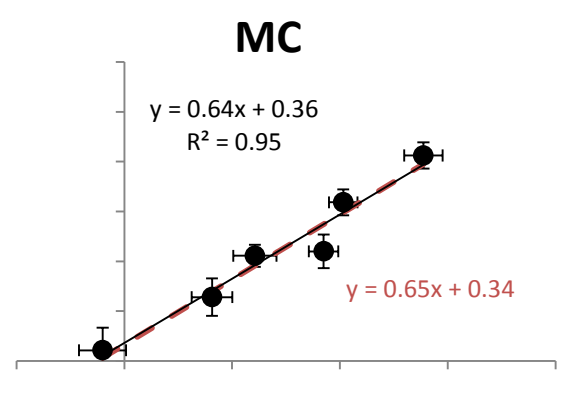
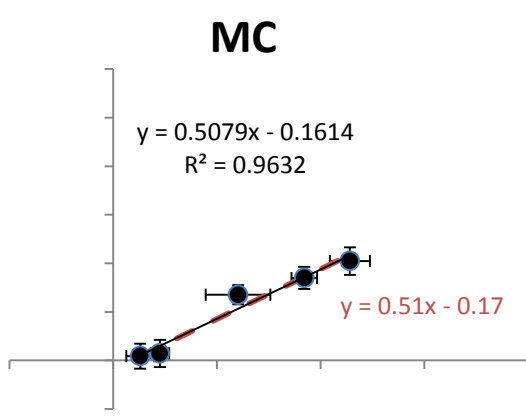
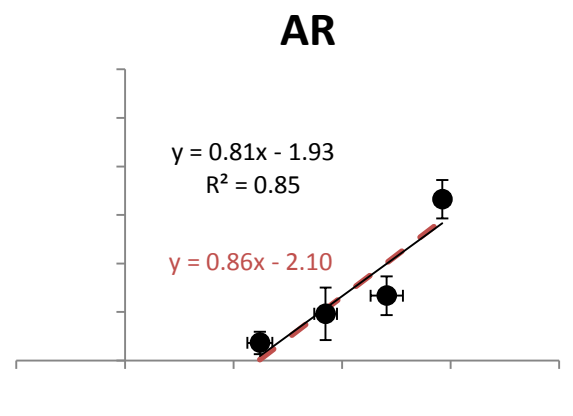
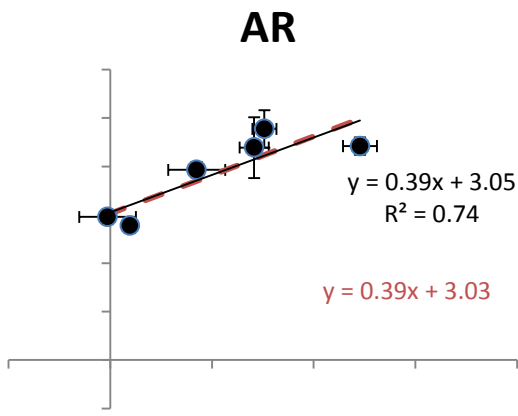
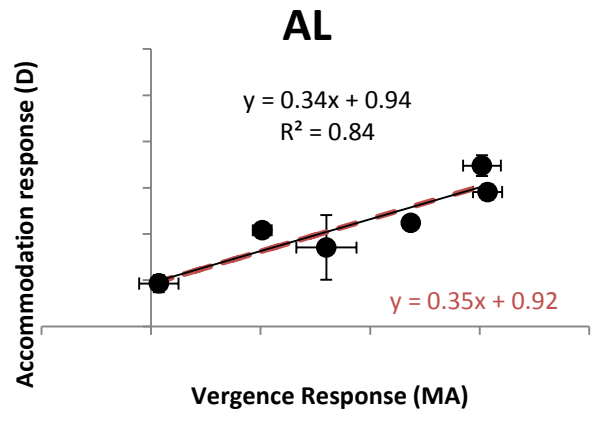
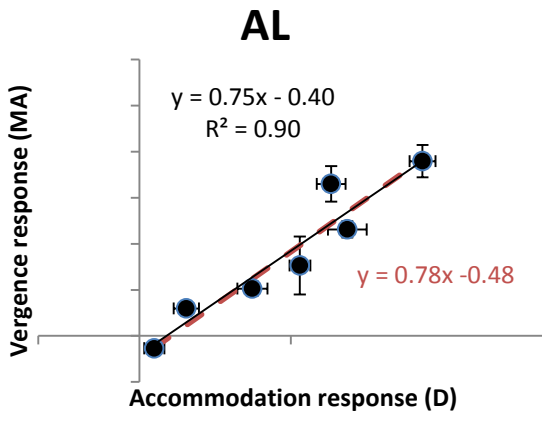


Fig 5. Individual Subject AC/A (on the right) and CA/C ratios (on the left) calculated using the gradient method. Black solid trend line and equation in black represent the least squares linear regression and red broken trend line and equation in red represent the orthogonal linear regression.

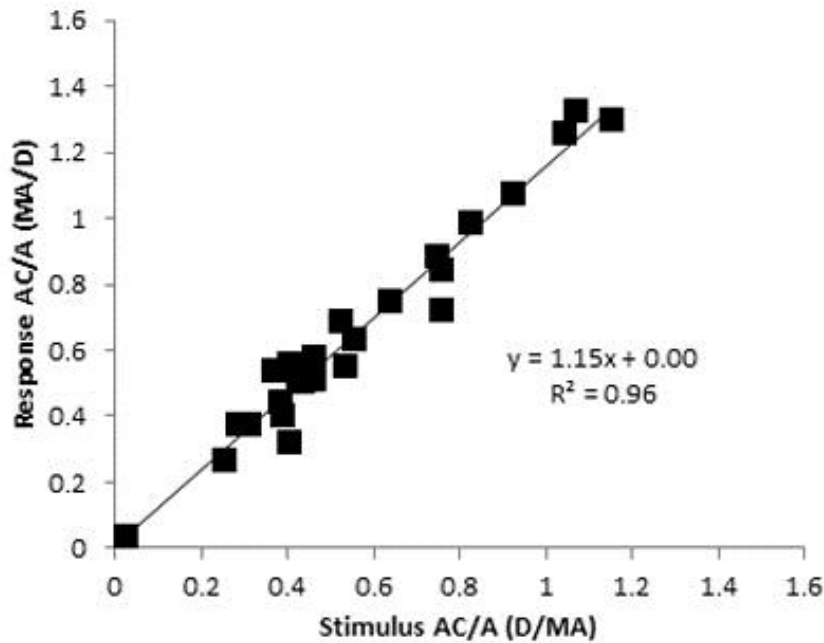


Fig 6. A plot of the stimulus and response AC/A ratios, a significant correlation existed between stimulus and response AC.A ($R^2= 0.96$, $F=587.37$, $df =1,24$, $p<0.001$).

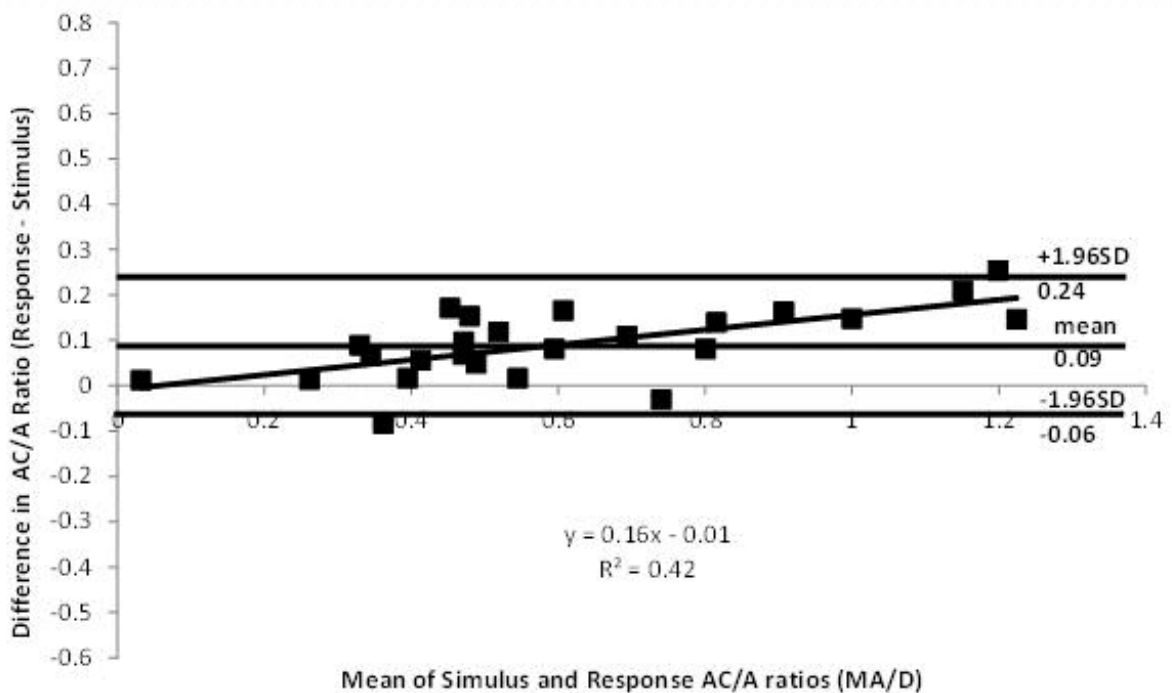


Fig 7. A significant correlation existed between the mean of the stimulus and response AC/A ratios versus the difference between response and stimulus AC/A ($R^2= 0.42$, $F=16.57$, $df =1,24$, $p<0.01$).

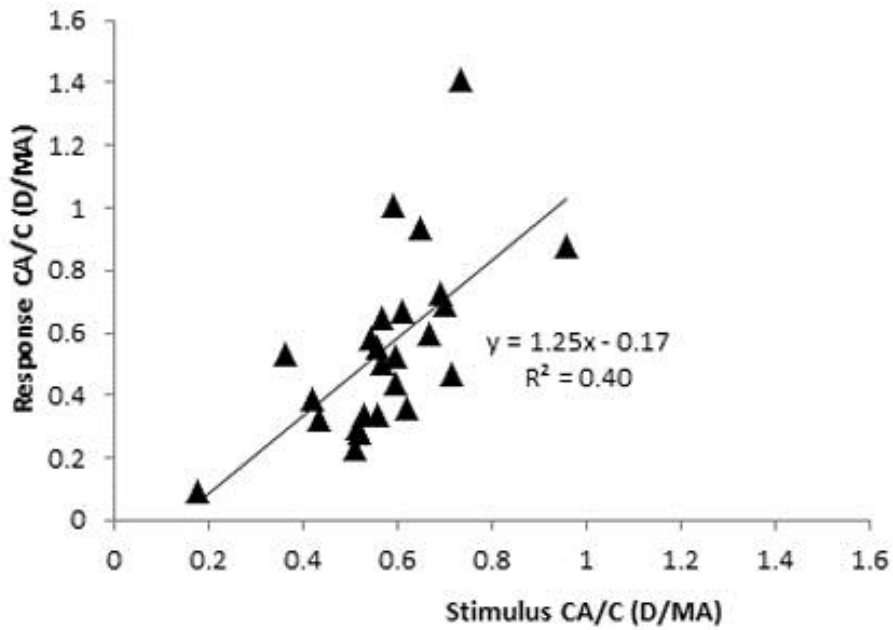


Fig 8. A plot of the stimulus versus response CA/C ratios is shown, a significant correlation existed between stimulus and response CA/C ratios ($R^2= 0.40$, $F=15.50$, $df=1,24$, $p<0.01$).

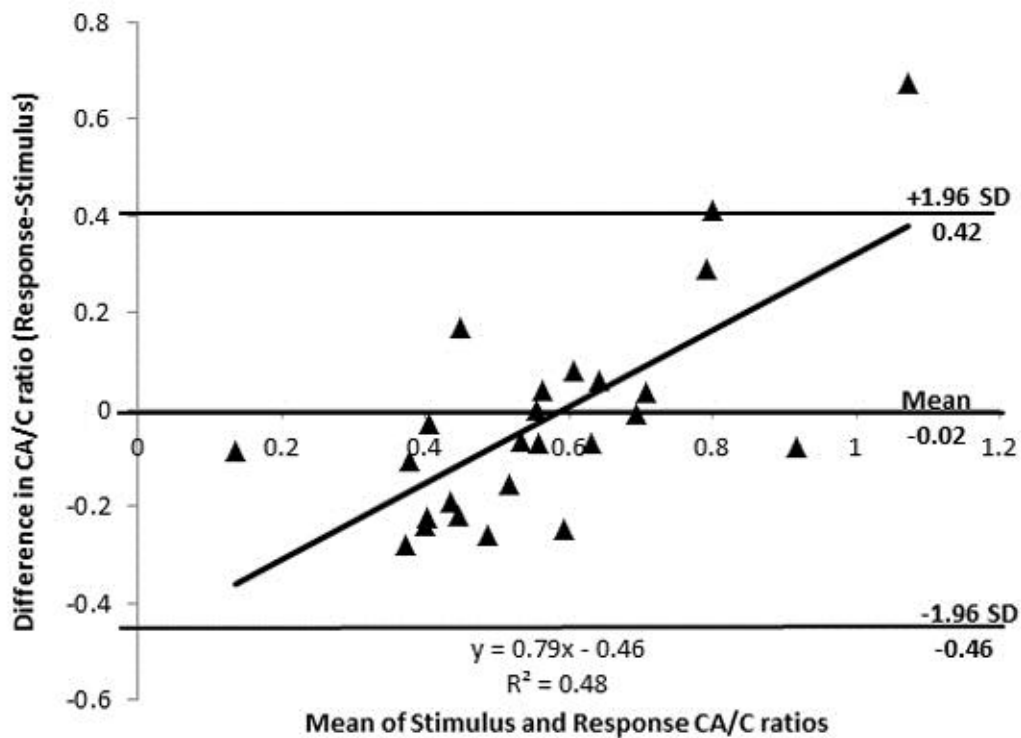


Fig 9. A significant correlation existed between the mean of the stimulus and response CA/C ratios versus the difference between response and stimulus CA/C ($R^2= 0.48$, $F=20.99$, $df =1,24$, $p<0.001$).

No significant relationship was found between the stimulus AC/A and CA/C ratios (Fig 10). A significant negative linear relationship was found between the response AC/A and the response CA/C ratios (Fig 11; linear regression, $R^2=0.24$, $F=7.15$, $df=24$, $p<0.05$). No significant relationship was found between the response CA/C and the reciprocal of the response AC/A.

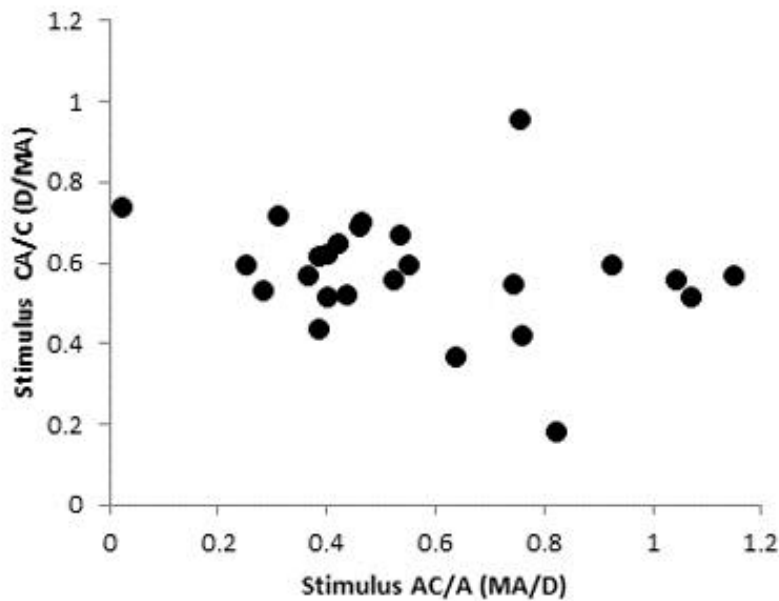


Fig 10. A plot of stimulus AC/A ratio versus the stimulus CA/C ratio, no significant relationship existed between these two parameters.

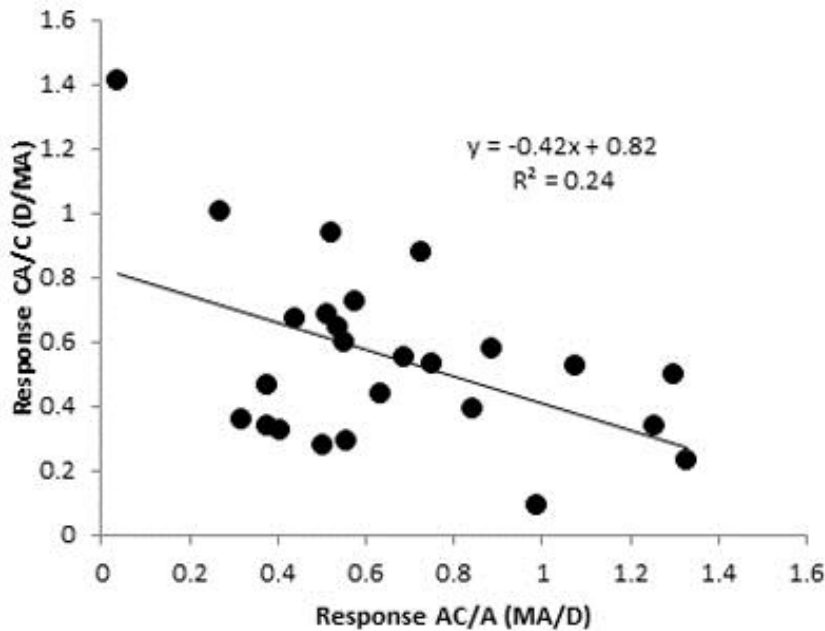


Fig 11. A plot of response AC/A versus response CA/C. A significant negative regression existed between the two ratios ($R^2= 0.24$, $F=7.15$, $df=1,24$, $p<0.05$).

1.4 Discussion

The present study is the first to measure both stimulus and response AC/A and CA/C ratios in a substantially larger sample than any previous studies of visually and binocularly normal, asymptomatic subjects. Previous studies have investigated either stimulus or response ratios but very few have investigated both response AC/A and CA/C in the same cohort (Bruce et al., 1995, Hung G.K., 1986, Rosenfield et al., 1995). This study is also the only study to examine the relationship between the stimulus and response CA/C ratios in a substantial sample providing new insights into the distribution of the CA/C ratio within a binocularly normal population, and the relationship between stimulus and response measures. The larger sample of CA/C ratios gathered in our study also allowed the relationship between the AC/A and CA/C ratios to be examined in greater detail than before.

The group mean response CA/C was 0.55 ± 0.28 D/MA which is very similar to the mean response CA/C from all previous studies (all studies combined mean 0.55 ± 0.33 D/MA, see Table 1).

One study (Schor and Tsuetaki, 1987) found the stimulus and response CA/C ratios to be highly correlated in a small population and felt that the stimulus CA/C ratio was a good representation of the convergence accommodation cross-link interaction. Another study (Wick and Currie, 1991) investigated CA/C ratios and showed that there was no significant difference between accommodation measures by Nott retinoscopy compared to an infra-red optometer when viewing a difference of Gaussian target, suggesting that clinical accommodation measures could be used to calculate the stimulus CA/C accurately (Wick and Currie, 1991). However, response CA/C ratio and stimulus CA/C ratio data were obtained from different populations which does not allow for a direct comparison between the calculated stimulus and response ratios obtained from both methods, and makes it difficult to determine if the clinical method described is robust (Wick and Currie, 1991).

A finding of the present study is the significant linear relationship between stimulus and response CA/C ratios (see Fig 8) ($r^2 = 0.40$), however the agreement (95% CI -0.46 to 0.42 D/MA, see Fig 9) was found to be poorer than the agreement found between stimulus and response AC/A ratios in the present study. Our data shows that the response CA/C ratio is on average 25% larger, although this varies considerably between subjects (from 91% larger to 34% smaller) suggesting that a simple proportional relationship does not adequately quantify the relationship between the two CA/C measures. The only previous comparable study found that the response CA/C ranged from 0 to 40% smaller than the stimulus CA/C in a sample of 6 subjects (Tsuetaki and Schor, 1987). In this study, which measured the relationship between stimulus and response CA/C in a larger sample ($n=25$) we show that the relationship between the two measures is not as strong as has been suggested previously. We feel that due to the larger sample size our data gives a more realistic assessment of the variation in the relationship between the stimulus and response CA/C ratios and shows values to be expected in a normal population.

In addition, although the vergence system produces highly accurate responses (Erkelens et al., 1989a, Erkelens et al., 1989b), the precision of the vergence response is dependent upon the target specifications. The size of Panum's areas is known to depend upon the spatial characteristics of the target, being larger with lower spatial frequency targets (Schor and Tyler, 1981, Tyler, 1975). In the present study a low spatial frequency blurred target was necessary to ensure that the accommodation response was open loop. The size of Panum's area for a target of a given spatial frequency could vary between individuals leading to differences in the vergence response without the appreciation of diplopia. It is known that individual differences exist in vergence response dynamics, such as temporal asymmetries and differing response gains (Tyler et al., 2012). When comparing the stimulus response relationship for accommodation (Fig 2) and vergence measurement (Fig 3), it can be seen that there is a systematic lag of accommodation at all stimulus levels, with low variation between individuals at each stimulus level. However during vergence measurements, although the group mean vergence response is accurate at each stimulus level,

substantial intersubject variability exists. This could explain why the stimulus CA/C ratio is higher than the response ratio in some cases and lower than the response ratio in other cases.

It is interesting to note that the equivalent spatial frequency of the target used in the present study was higher (1 CPD) in comparison to the target in the study of Tsuetaki and Schor(1987) (0.2 CPD). A lower spatial frequency target might be expected to cause more variation in the vergence response, and consequently poorer agreement between stimulus and response CA/C ratio.

Also in the study by Tsuetaki and Schor(1987) a binocular Badal system was used to present the difference of Gaussian target to both eyes, whereas in the current experiment the target was presented in free space. It is possible the Badal system used by Tsuetaki and Schor (1987) led to proximal stimulation of the accommodation and vergence systems which could in turn contaminate the CA/C ratio measurement and result in similar stimulus and response CA/C ratios due to the contribution of the proximal component to both measurements.

Currently the AC/ A ratio is measured clinically as part of the battery of diagnostic binocular vision tests (Bhoola, 1995, Daum, 1984, Kim et al., 2012, Porcar and Martinez-Palomera, 1997, Wybar, 1974)whereas there is no clinically amenable method to measure the CA/C ratio, although several methodologies have been suggested (Tsuetaki and Schor, 1987, Wick and Currie, 1991). Our findings suggest more work is needed to refine the measurement methodology for clinical CA/C ratios due to the degree of variability between the stimulus and response ratio data demonstrated in the present study (See Fig 8).

The relationship between stimulus and response AC/A ratios has been reported previously (Bhoola, 1995, Bruce et al., 1995, Rainey et al., 1998, Rosenfield et al., 1995) although several studies examine a wide range of ages(Bruce et al., 1995, Rosenfield et al., 1995) which confounds the results. Bruce et al (1995) found a higher group mean AC/A ratio than the present study (see Table 1) although the study by Bruce et al (1995) used a distance target for AC/A measurement compared with the near target used in the present study. As has been mentioned previously, the effect of proximal stimulation on the relationship between AC/A ratios obtained at different viewing distances is still unclear(Jackson and Arnoldi, 2004, Pankhania and Firth, 2011), and this makes a direct comparison with the present results difficult. It is well established that voluntary effort can significantly affect oculomotor responses in open-loop conditions. McLin & Schor (1988) showed that voluntary effort primarily drives accommodation and affects convergence secondarily through the AC/A cross-link, while other authors have reported changes in vergence without accommodation(Ogle and Martens, 1957). To ensure consistency between subjects and minimize the effect of voluntary stimulation during AC/A and CA/C measurement subjects were all given the same instructions prior to completing the experiment.

One study did investigate the validity of the gradient stimulus AC/A and considered it to be a valid representation of the response AC/A ratio(Bhoola, 1995),however this study did not investigate the CA/C ratio. It should also be noted that, although the authors of this work use the term validity, no gold standard method of measuring the accommodation-convergence cross-link has been established.

Our study found that the stimulus and response AC/A ratios were linearly related with high correlation ($r^2=0.96$) (see Fig 6). Good agreement was demonstrated between the two measures (-0.06 to 0.24MA/D) as can be seen in Fig 7. Other studies have also found a significant correlation between stimulus and response AC/A ratios with R^2 values of 0.79 and 0.96(Bhoola, 1995, Gratton and Firth, 2010)

The present study shows that the response AC/A is on average 16% greater than the stimulus ratio. Previous studies have found the response AC/A ratio is between 8% and 24% larger than the stimulus ratio(Alpern et al., 1959, Bhoola, 1995, Gratton and Firth, 2010, Rosenfield et al., 1995), which compares well with the current findings. This systematic difference between the stimulus and

response AC/A ratios could be explained by the increased lag at higher accommodation stimulus levels (Fig 2) which would lead to a slight increase in the response AC/A ratio when compared to the stimulus AC/A ratio.

Further analysis of this relationship revealed that the agreement between the stimulus and response AC/A ratios varied with the magnitude of the ratio, with the discrepancy between stimulus and response AC/A increasing at high AC/A values. This tendency has been shown in a previous study which examined the response AC/A and stimulus AC/A using a distant target (Gratton and Firth, 2010).

In clinical practice, it has been proposed that a simple calibration factor could be applied to stimulus AC/A ratio data (Alpern et al., 1959), however the results of this study suggest that this approach may not be wholly accurate. From our data we would suggest that for stimulus AC/A values above 0.9MA/D it should be expected that the response ratio will be more than when calculated using a calibration factor of 1.16 (See Fig 7).

This data set also represents the first substantial sample of stimulus AC/A and stimulus CA/C ratio data gathered from the same population. Analysis of the stimulus AC/A and stimulus CA/C ratio data revealed no significant inverse or reciprocal relationship between the two ratios. This shows that the clinical measures are unrelated and hence in a clinical situation both ratios should be measured.

Lastly the relationship between the response AC/A and response CA/C ratios was determined. An inverse relationship was demonstrated between the response AC/A and CA/C ratios (Fig 10; $R^2 = -0.24$, $F=7.15$, $df=24$, $p<0.05$). However no evidence of a reciprocal relationship between the response AC/A and CA/C ratios was demonstrated, similar to the findings of Rosenfield (Rosenfield et al., 1995). This inverse relationship adds to the body of evidence which suggests two separate neural mechanisms control the accommodative vergence cross-link and the vergence accommodation cross-link (Bruce et al., 1995, Owens, 1980, Rosenfield et al., 1995, Semmlow and Hung, 1981, Wolf et al., 1987). The lack of a reciprocal relationship between the AC/A and CA/C ratios means that measuring only the AC/A ratio, which is common in current clinical practice, does not give a true representation of both cross-link interactions.

1.5 Conclusion

From our findings it can be concluded that the stimulus AC/A ratio shows good agreement with the response AC/A values. However at higher AC/A values larger differences existed between stimulus and response AC/A, and at these values a simple calibration factor may not be a reliable way to convert the stimulus to the response ratio.

The stimulus and response CA/C ratios exhibited a weaker, but significant linear relationship. The agreement between stimulus and response CA/C ratios was poorer than the agreement demonstrated between stimulus and response AC/A ratios in the current data set. More work is needed to refine the methodology of stimulus CA/C measurement to provide a clinically useful measurement.

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