BEHAVIOURAL CORRELATES OF OCULAR ACCOMMODATION AND THE AUTONOMIC NERVOUS SYSTEM

LEON NICHOLAS DAVIES
Doctor of Philosophy

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Summary

The binding issue of this thesis was the examination of workload, induced by retinotopic and spatiotopic stimuli, on both the oculomotor and cardiovascular systems together with investigating the covariation between the two systems – the 'eye-heart' link. Further, the influence of refractive error on ocular accommodation and cardiovascular function was assessed.

A clinical evaluation was undertaken to assess the newly available open-view infrared Shin-Nippon NVision-K 5001 optometer, its benefit being the capability to measure through pupils ≥ 2.3 mm. Measurements of refractive error taken with the NVision-K were found to be both accurate (Difference in Mean Spherical Equivalent: 0.14 ± 0.35 D; $p = 0.67$) and repeatable when compared to non-cycloplegic subjective refraction. Due to technical difficulties, however, the NVision-K could not be used for the purpose of the thesis, as such, measures of accommodation were taken using the continuously recording Shin-Nippon SRW-5000 open-view infrared optometer, coupled with a piezo-electric finger pulse transducer to measure pulse. Heart rate variability (HRV) was spectrally analysed to determine the systemic sympathetic and parasympathetic components of the autonomic nervous system (ANS).

A large sample ($n = 60$), cross-sectional study showed late-onset myopes (LOMs) display less accurate responses when compared to other refractive groups at high accommodative demand levels (3.0 D and 4.0 D). Tonic accommodation (TA) was highest in the hypermetropes, followed by emmetropes and early-onset myopes while the LOM subjects demonstrated statistically significant lower levels of TA. The root-mean-square (RMS) value of the accommodative response was shown to amplify with increased levels of accommodative demand. Changes in refractive error only became significant between groups at higher demand levels (3.0 D and 4.0 D) with the LOMs showing the largest magnification in oscillations. Examination of the stimulus-response cross-over point with the unit ratio line and TA showed a correlation between the two ($r = 0.45$, $p = 0.001$), where TA is approximately twice the dioptric value of the stimulus-response cross-over point.

Investigation of the relationship between ocular accommodation and systemic ANS function demonstrated covariation between the systems. Subjects with a faster heart rate (lower heart period) tended to have a higher TA value ($r = -0.27$, $p < 0.05$). Further, an increase in accommodative demand accompanies a faster heart rate. The influence of refractive error on the cardiovascular response to changes in accommodative demand, however, was equivocal. Examination of the microfluctuations of accommodation demonstrated a correlation between the temporal frequency location of the accommodative high frequency component (HFC) and the arterial pulse frequency. The correlation was present at a range of accommodative demands from 0.0 D to 4.0 D and in all four refractive groups, suggesting that the HFC was augmented by physiological factors.

Examination of the effect of visual cognition on ocular accommodation and the ANS confirmed that increasing levels of cognition affect the accommodative mechanism. The accommodative response shifted away from the subject at both near and far. This shift in accommodative response accompanied a decay in the systemic parasympathetic innervation to the heart. Differences between refractive groups also existed with LOMs showing less accurate responses compared to emmetropes. This disparity, however, appeared to be augmented by the systemic sympathetic nervous system.

The investigations discussed explored the role of oculomotor and cardiovascular function in workload environments, providing evidence for a behavioural link between the cardiovascular and oculomotor systems.

Key words: Accommodation, autonomic nervous system, heart rate variability, refractive error, cognition.

In dedication to my grandmother

Mrs Irene Batty

1918 - 1993

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisors, Dr James Wolffsohn and Professor Bernard Gilmartin for their help, support and guidance over the last three years.

Thanks also to the Engineering and Physical Sciences Research Council (EPSRC) and BAe Systems Limited, UK, for the award of a three-year CASE scholarship to support my postgraduate studies.

I would like to extend my warmest thanks to the staff and students at Aston University for their support and endurance when sitting for many of my experiments. In particular, I would like to thank my friend and colleague Miss Hannah Bartlett for her support and collaboration on many additional studies.

Special thanks go to Dr Edward Mallen for his continuing friendship, advice, encouragement and technical support.

Finally, I am eternally indebted to my parents and Rachel, without whom none of this would be possible.

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CHAPTER 1

OCULAR ACCOMMODATION

1.1 General introduction

The accommodative system of the human eye is a complex and perplexing mechanism, encompassing a number of sensory, neuromuscular and biophysical processes (Mordi and Ciuffreda, 1998; Chen *et al.*, 2003; Seidel *et al.*, 2003). Its major function is to facilitate the viewing of objects at various dioptric distances from the eye and is primarily driven and controlled by the retinal blur element of a visual stimulus (Ong and Ciuffreda, 1997). Due to its many facets, accommodation or non-optimal accommodation has been associated with a number of optical (retinotopic) and non-optical (spatiotopic) phenomena: headaches (Morgan, 1944); blurred vision with cognitive effort (Kruger, 1977a; 1977b) and over-accommodation (Mandelbaum, 1960). The remit and aim of this thesis was, to investigate the subtleties of ocular accommodation (e.g. microfluctuations) and its control with respect to the systemic autonomic nervous system (e.g. cardiovascular function); the purpose being to correlate oculomotor and cardiovascular function with real-world applications (e.g. visual workload).

Practically, such research might reveal the source of inter- and intra-subject differences in the oculomotor resting states. These findings may prove important to the understanding of the oculomotor and autonomic aetiology of late-onset myopia; strengthened if autonomic correlates can distinguish between refractive groups (i.e. emmetropes and late-onset myopes). Furthermore, the relationship between the autonomic system, accommodative parameters and workload conditions could provide evidence that mental demands on the visual system can influence visual performance and accommodative accuracy. It is important for industries that are involved with the man-machine interface, such as the aerospace industry, to more fully understand the effects of workload on the visual system. Additionally, there is the potential for the visual system to provide objective measures of task workload which would be invaluable in human factors research.

This chapter reviews the literature covering the plethora of topics associated with the oculomotor, cardiovascular and autonomic nervous systems, and describes their anatomy, function, components and interactions paying particular attention to the areas pertinent to this thesis.

1.2 Anatomical structures of ocular accommodation

In order to understand fully the various theories and components associated with and used in accommodation, the anatomy of the eye related to its focusing ability must be considered. The key structures utilised in the accommodation process are described below.

1.2.1 The crystalline lens

The crystalline lens is a transparent, biconvex structure located behind the iris and in front of the vitreous body, with the radius of its anterior surface (~ 8 to 14 mm) greater than that of its posterior surface (~ 4.5 to 7.5 mm). The lens is suspended from the surrounding ciliary body by the zonular fibres, which are attached to the equator of the lens. The diameter of the lens is approximately 9-10 mm with a thickness of 3.6 mm in its unaccommodated state (Millodot, 1997). The lens serves the double purpose of supplying the balance of the eye's refractive power (~ 1/3 of total power) and providing a mechanism for altering the focal length of the eye. As accommodation is induced, both surfaces of the lens (especially anterior) assume a more steeply curved form (Popiolek-Masajada and Kasprzak, 2002); moreover, the centre thickness increases and the anterior pole of the lens surface moves forward, leading to a progressive reduction in anterior chamber depth with increasing magnitude of accommodation. The posterior pole remains stationary due to the resistance of the vitreous humour posteriorly and the zonular plexus anteriorly (Kaufman, 1992).

The lens is a highly complex structure constructed in a number of layers (Cook *et al.*, 1994). Consequently, in a Scheimpflug image (Figure 1.1), bands of discontinuity can be observed (Koretz *et al.*, 1994). This layered appearance is a consequence of the continuous cell growth of the lens throughout life, ultimately resulting in increased convexity of the lens (Dubbelman *et al.*, 2003). The innermost biconvex section, called the nucleus, is easily distinguished from the surrounding cortical section. The highly elastic outer layer of the lens is termed the capsule. The refractive index of the lens varies from pole to pole, such that in the centre of the nucleus the refractive index reaches a maximum value of 1.41 with a gradual reduction towards the poles and a refractive index value of 1.385 (Bennett and Rabbetts, 1998). The gradient refractive index through the lens is thought to lessen the spherical aberration of the eye (Bennett and Rabbetts, 1998). The change in internal structures of the lens during accommodation has been measured in four studies (Patnaik, 1967; Brown, 1973; Koretz *et al.*, 1997; Dubbelman *et al.*, 2003). The data suggest that the increase in lens thickness is attributed to an increase in the lens nucleus, while the thickness of the cortex remains unchanged.

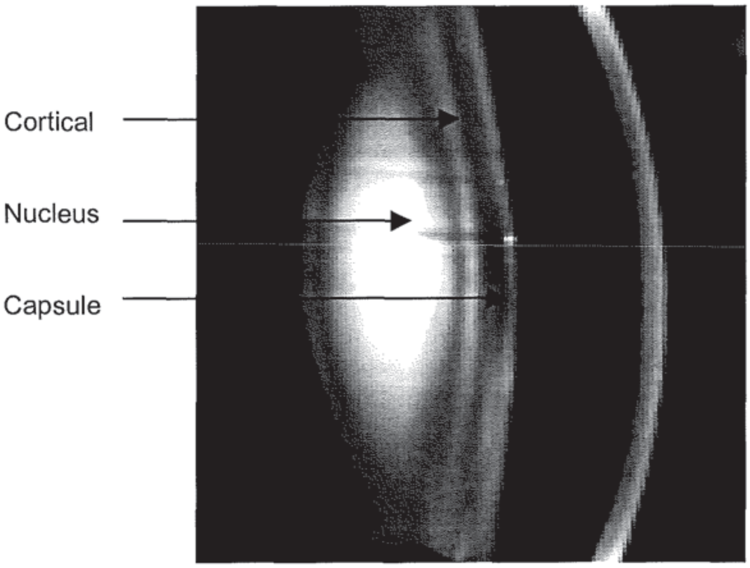

Figure 1.1 Scheimpflug image of a human crystalline lens showing the bands of discontinuity (courtesy of Marcher Enterprises Ltd).

The increase in lens substance throughout life raises the paradoxical feature where the decrease in radius of curvature of the crystalline lens with age does not result in the eye becoming more myopic; the 'lens paradox' (Dubbelman and van der Heijde, 2001). Studies have proposed that there is a compensatory mechanism leading to a concurrent decrease in refractive index of the crystalline lens as neither axial length nor corneal curvature show significant changes with age (Pierscionek and Chan, 1989; Smith *et al.*, 1992; Dubbelman and van der Heijde, 2001). Interestingly, new methods of assessing axial length *in vivo* (Santodomingo-Rubido *et al.*, 2002; Tehrani *et al.*, 2003) may provide fresh evidence as to the correlation between age and axial length, particularly in incipient presbyopic individuals.

1.2.2 The zonules of Zinn

The crystalline lens is suspended by the zonules, consisting of a series of radially arranged fibres connecting the ciliary processes to the lens capsule. These are divided into three sub-groups; two sets are attached both anterior and posterior to the capsule with the third attached to the equator of the crystalline lens (Snell and Lemp, 1998).

1.2.3 The ciliary body

The ciliary body is part of the uvea situated anterior to the ora serrata and extending to the root of the iris where it is attached to the scleral spur. If considered as a whole, the ciliary body is a complete annulus of smooth muscle that runs around the inside of the anterior sclera. It comprises the ciliary muscle, the ciliary processes and is roughly triangular in sagittal section.

The ciliary muscle is a complex, atypical smooth muscle, and serves multiple functions (Kaufman, 1992). During accommodation, the ciliary muscle contracts, the meridional fibres pull the choroid and ciliary body forward, and the circular fibres, acting as a sphincter, move the ciliary body inward (Snell and Lemp, 1998). Morgan (1944) reported that on sympathetic nerve stimulation, astigmatism (with-the-rule) increases. This was attributed to the 4 quadrants of the ciliary muscle being innervated by the 4 branches of the long ciliary nerve. This segmental innervation also occurs in the iris such that the pupil dilates unevenly when the four nerves are stimulated separately.

The ciliary muscle also has an important role in the outflow of aqueous humour. The ciliary muscle, trabecular meshwork and Schlemm's canal are intimately connected. On accommodation and contraction of the ciliary muscle, the fenestrations in the meshwork widen and the canal opens facilitating aqueous humour outflow. As such, intra-ocular pressure (IOP) reduces during accommodation (Whiteacre and Stein, 1993).

Initial findings of a link between accommodation and IOP were reported by Armaly and Burian (1958) where a fall in IOP was demonstrated following sustained accommodation in a group of 7 subjects. Intraocular pressure was measured with a Mueller electronic tonometer while the contralateral eye observed a Landolt ring at 25 cm (4.0 D). To vary the accommodative demand, a supplementary +4.00 DS lens was added, thus providing an accommodative stimulus of 0.0 D. On average, IOP fell by approximately 3.5 mmHg. Armaly and Burian postulated that the fall in IOP may be a consequence of increased aqueous outflow, a reduction in aqueous production or a reduction in intraocular blood volume during accommodation.

Later, Armaly and Rubin found that four dioptres of accommodation sustained for one minute produced a mean reduction of 2.91 mmHg in five patients between 20 and 25 years of age, and a mean reduction of 0.69 mmHg in five patients aged 45 to 55 years (Armaly and Rubin, 1961). Prolonged accommodation for up to six minutes produced reductions in IOP of 4.54 mmHg in the younger group and 2.30 mmHg in the older group. Following relaxation of accommodation, the effects of the accommodation on the IOP dissipated after 10 minutes in most subjects. In a small number, however, the post-accommodation IOP never returned to the pre-accommodation level within the 10 minute period.

More recently, Mauger *et al.* (1984) confirmed a reduction of IOP on accommodation. Accommodation of 1.5 D and 4.0 D for 30 seconds reduced the mean IOP as measured by Goldmann applanation tonometry by a mean of 1.15 mmHg and 1.32 mmHg respectively. Interestingly, a further 3 minutes only reduced the IOP by 1.00 mmHg for the 1.5 D stimulus and 1.06 mmHg for the 4.0 D stimulus.

1.3 Historical aspects of accommodation

Ideas and theories used to develop knowledge of ocular accommodation have evolved over the last 300 years. As such, a full discourse of topics is too extensive for this thesis; however, the key historical events have been assimilated here outlining the foundations of accommodation research.

The word accommodation is of comparatively recent origin and was first introduced by Burrow in 1841 (cited by Gilmartin *et al.*, 1992). The accommodative mechanism, however, interested scientists much earlier. In 1677, Descartes (cited by Fincham, 1937) gave a description of the means by which the eye is enabled to see objects at different distances. Duke-Elder (1970) recounts how Descartes proposed that fibres by which the lens is suspended bring about the change in focus. In 1816 the French physiologist, François Magendie, discovered that unlike other optical systems, the eye had the facility to bring objects situated at different distances to a single focus-plane. Furthermore, Jacques Sturm (1845) concluded from the astigmatic nature of the ocular refractive surfaces, clear vision was made possible, in the absence of a mechanism of adjustment, so long as the retina lay between the two focal planes (cited by Duke-Elder, 1970).

After many proposed accommodative mechanisms, it was the eminent experimentalist Thomas Young (1801) who stated that the crystalline lens was responsible for accommodation. As little was understood about the ciliary muscle, Young incorrectly concluded that the lens itself was muscular. The discovery of the catoptric properties of the eye by Purkinje in 1823 provided a more accurate method of observing changes in accommodation. It was not, however, until the work of Langenbeck (1849) that this connection was made. Cramer (1851) developed the proposal demonstrating that the changes in the crystalline lens were caused by muscular activity. This muscular activity was later proven by the experiments on cats, ape and man by Hensen and Völckers (1868) (cited by Duke-Elder, 1970).

In 1855 Helmholtz stated a new theory suggesting that the power of the lens increases in accommodation. Here, as the ciliary muscle contracts the tension on the zonules relaxes and the convexity of the lens increases. Duke-Elder (1970) recounts that much protestation followed from Tscherning (1909) who disapproved of the theory and proposed contradictory statements. It was the researchers Gullstrand (1909) and Fincham (1925) who stated that the lens capsule and ciliary muscle facilitated accommodation. Fincham (1951) later added that accommodation is initiated by retinal blur at the site of the fovea; this Helmholtzian-type hypothesis is still generally believed to be responsible for ocular accommodation. Hennessey and Leibowitz (1971), however, investigated the effect of peripheral stimulation on accommodation, finding peripheral visual field stimuli can also induce significant changes in accommodation.

In recent years, Schachar and co-workers have proposed an alternative mechanism of accommodation stating that, during ciliary muscle contraction, tension in the equatorial lens zonules increases with a concurrent relaxation of the anterior and posterior lens zonules (Schachar, 1992; Schachar and Anderson, 1995). Although Schachar has published extensive mathematical models and experimental evidence supporting this mechanism (Schachar *et al.*, 1993a; 1993b; 1994), the theory is still not widely accepted.

1.4 Neurophysiology of ocular accommodation

Fundamentally, the nature of the retinal image governs the afferent accommodative pathway (Campbell, 1954). When retinal cone cells are stimulated by defocus, a summated blur signal is transmitted through the magnocellular layer of the lateral geniculate nucleus

(LGN) to visual cortex area 17. The signal is then passed onto the parieto-temporal areas for further processing and dissemination (Ohtsuka *et al.*, 1988). Once at the midbrain, the signal moves to the oculomotor nucleus complex/Edinger-Westphal nucleus where a motor command is generated (Judge and Cummings, 1986; Jumblatt, 1999). Efferent accommodative pathways involve the oculomotor nerve (III cranial nerve), the ciliary ganglion and the short ciliary nerve culminating in the innervation of the ciliary muscle resulting in the accommodative response (Judge and Flitcroft, 1999).

1.5 Autonomic control of accommodation

Several studies have shown that the ciliary muscle of the human eye is innervated by the antagonistic action of the autonomic nervous system (Cogan, 1937; Morgan, 1944; Toates, 1972; Leibowitz and Owens, 1975a, b; Gilmartin, 1986; Gilmartin *et al.*, 1992; Gilmartin 1998). Fundamentally, the autonomic nervous system is composed of two main branches; primarily the parasympathetic branch supplemented by the sympathetic branch (Gilmartin *et al.*, 1992). Parasympathetic innervation of the ciliary muscle is facilitated by the neurotransmitter acetylcholine on muscarinic receptors. Activation of the parasympathetic system increases the accommodative response, whereas suppression of the system leads to a decrease in accommodation. The sympathetic input is mediated by noradrenaline on adrenoceptors, which can be further divided into two sub-groups (Table 1.1). Its action is inhibitory in nature such that activation leads to 'negative accommodation' (Morgan, 1944).

ANS BRANCH	NEURO-TRANSMITTER	RECEPTOR	RECEPTOR SUBTYPE(S)	FUNCTION WHEN STIMULATED
Parasympathetic (cholinergic)	Acetylcholine	Muscarinic	M_1 M_2 M_3 M_4	- Constriction of ciliary muscle - Pupil constriction
Sympathetic (adrenergic)	Noradrenaline	β	β-1	- Secretion of aqueous humour
			β-2	- Relaxation of ciliary muscle
		α	α-1	- Pupil dilation - Inhibition of accommodation

Table 1.1 Summary of ANS branch function in relation to ocular accommodation.

Cogan (1937) reported that parasympathetic innervation of the ciliary muscle induced accommodation for near targets, whilst the sympathetic input was responsible for accommodation for distant objects. Such a dual innervation system, in the absence of an accommodative stimulus, would adopt an intermediate dioptric value. Morgan (1944) established that 'negative accommodation' on distant objects could result from the stimulation of the sympathetic nervous system in rabbits, cats, dogs and monkeys. Later, Törnqvist (1966) postulated that accommodation on distant objects might be a consequence of sympathetic innervation of inhibitory beta-receptors, found in the ciliary muscle in monkeys. Furthermore, Gilmartin (1986) hypothesised that sympathetic forces are relatively small, slow and inhibitory. This was supported by the work of Gilmartin and Bullimore (1987) who suggested sympathetic innervation to the ciliary muscle is unlikely to be involved in the rapid accommodative response focusing on distant objects, as the level of the sympathetically mediated response is small, unless amplified by substantial simultaneous parasympathetic activity.

Hitherto, much evidence regarding the autonomic control of accommodation has been collated by measuring accommodative responses to pharmacological manipulation of the autonomic nervous system (Gilmartin, 1986; Bullimore and Gilmartin, 1987a; Gilmartin and Bullimore 1987; Bullimore and Gilmartin 1988; Rosenfield *et al.*, 1990; Gilmartin and Winfield, 1995). For example, Gilmartin and Hogan (1985) demonstrated that the parasympathetic innervation to the ciliary muscle is the primary candidate responsible for accommodation. A topical antimuscarinic drug (tropicamide, 0.5%) produced a hyperopic shift in accommodation, therefore indicating that parasympathetic innervation is largely responsible for positive/inward accommodation. The parasympathetic response has also been found to be very rapid (1-2 seconds) when the oculomotor nerve is stimulated in monkeys (Törnqvist, 1967).

A detailed and comprehensive review of sympathetic innervation of the ciliary muscle was compiled by Gilmartin (1986). Many previous investigations were conducted more that 50 years ago to reveal the functional role of the sympathetic (adrenergic) system. In the 1960s, Göran Törnqvist was instrumental in the genesis of sympathetic innervation theories. He reported that stimulation of the pre-ganglionic cervical sympathetic nerves of monkeys produced a negative accommodative effect (Törnqvist, 1966). He also noted that non-selective β-blockers (e.g. propranolol) negated this negative accommodation response. The results showed that a β-adrenergic inhibitory mechanism exists in the ciliary smooth muscle. A further study by Törnqvist in 1967 illustrated that this negative sympathetic response was slow, reaching a maximal effect after 10-40 seconds, far too slow to have any impact on the viewing of normal visual environment (Törnqvist, 1967).

Rosenfield and co-workers investigated the influence of alpha-adrenergic agents on tonic accommodation (Rosenfield *et al.*, 1990). They established that the instillation of an alpha-1 adrenergic agonist (e.g. phenyephrine, 2.5%) or a non-selective alpha antagonist (e.g. thymoxamine, 0.5%) does not produce a significant change in tonic accommodation.

Given the common understanding that the purpose of the nervous system is that of adaptation and reaction to the surrounding environment – 'fight or flight' – it is surprising to find that very few investigations have centred on the ramifications of behavioural manipulations (both optical and non-optical) on the autonomic and oculomotor systems. As such, by simultaneously monitoring oculomotor and systemic cardiovascular (autonomic) function, the relative contribution of the parasympathetic and sympathetic systems can be analysed non-invasively during accommodative and cognitive tasks.

1.6 Components of accommodation

In 1956, Gordon Heath described the now classic components of accommodation: convergence accommodation; proximal accommodation; reflex accommodation and tonic accommodation (Heath, 1956).

1.6.1 Convergence accommodation

The accommodative response is a component of the near triad: accommodation; convergence and pupil miosis. This synkinesis is due to the neural connection between the systems. As such, all vergence movements are accompanied by an accommodative change (Ong and Ciuffreda, 1997). The magnitude of the resultant accommodative response will be dependent on the subject's CA/C ratio. Consequently, the greater the CA/C ratio, the larger the accommodative response will be. However, in order to elicit an adequate increase in the accommodative response, the subject must view the target in open-loop conditions (see section 1.7.2). Fincham and Walton (1957) illustrated this phenomenon by comparing the accommodative response to a converging target in open- and closed-loop scenarios (see Figure 1.2).

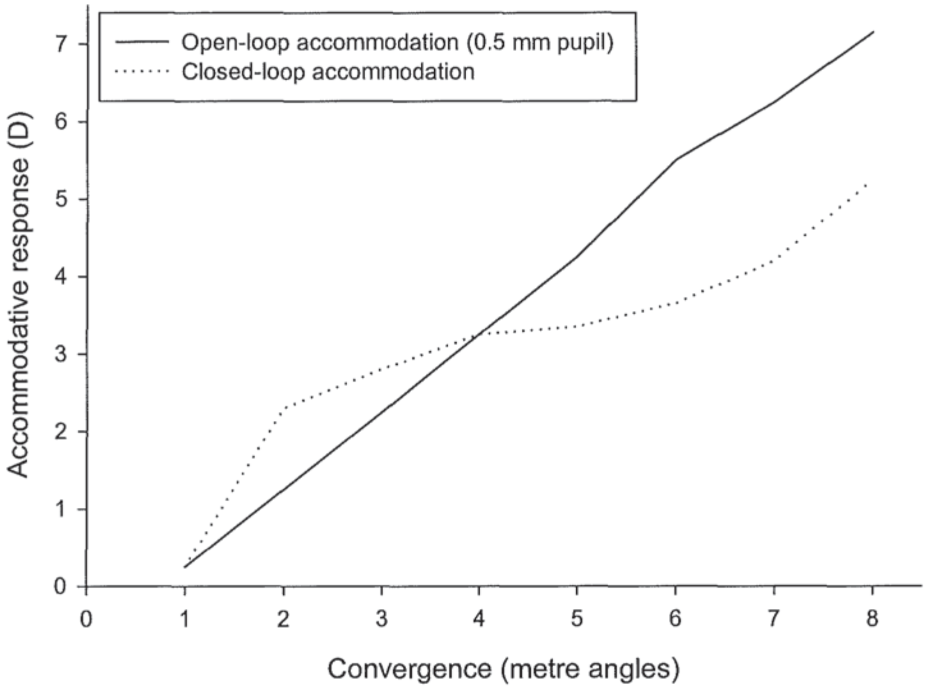

Figure 1.2 Accommodative response as a function of convergence in open- and closed-loop conditions (after Fincham and Walton, 1957).

1.6.2 Proximal accommodation

Here the accommodative response is induced by the prior knowledge of the apparent or perceived proximity of a target. The response is manifest in a variety of scenarios: by presenting a near object; while using a closed-view optometer (instrument myopia); or by the subject thinking near or far. In addition, the accommodative response may also be conditioned by the knowledge of surroundings and their proximity to the subject (i.e. surround propinquity; Rosenfield and Ciuffreda, 1991).

1.6.3 Reflex accommodation

The reflex accommodative response refers to the adjustment of the refractive state of the eye in response to a blurred stimulus, thus maintaining the optimum retinal image quality. Heath (1956) proposed that reflex accommodation was the only component to be initiated by the quality of the visual stimulus.

1.6.4 Tonic accommodation

Inappropriate levels of accommodation are a continual problem in the world of optics. Rev. N. Maskelyne (1789), the Astronomer Royal, first reported night or low-luminance myopia finding that astronomical observations at night were facilitated by the use of negative lenses. Intuitively, one would assume that given no visual stimulus, the eye would relax to focus at infinity as proposed by Helmholtz (1855); however, this is not the case. The resting state of the eye is achieved when there is no definitive object of regard (Kaufman, 1992), referred to as tonic accommodation (TA). It was Thomas Weber (1855; cited by Rosenfield *et al.*, 1993) who first suggested that the eye focused at an intermediate distance when at complete rest. Subsequent work supports this hypothesis and demonstrates that, in the absence of an appropriate visual stimulus, accommodation assumes an intermediate dioptric position (Leibowitz and Owens, 1978; Gilmartin 1986; Rosenfield *et al.*, 1993; Rosenfield *et al.*, 1994).

Leibowitz and Owens (1978) concluded that the eye assumes an individually determined intermediate focus whenever variations in accommodation produce no change in the quality of the retinal image. The individual differences of tonic levels of accommodation are large (Rosenfield *et al.*, 1993). The tonic resting position of accommodation, typical mean value of accommodation is given as 0.65 ± 0.38 D (Rosenfield *et al.*, 1993; Rosenfield *et al.*, 1994), varies greatly between individuals, and has been shown to vary between refractive groups (see Chapter 3).

Research into the functional consequences of this disparity is extensive (Leibowitz and Owens, 1975a,b; Bullimore *et al.*, 1986; Rosenfield *et al.*, 1993; Rosenfield, 1989). Less is understood, however, about the physiological source of the inter-subject variations of TA (Tyrrell *et al.*, 2000). If TA is tenuously connected to refractive error and has inter-subject variability, what factors dictate the level of TA? As the autonomic nervous system is involved in the control of both the oculomotor and cardiovascular systems, one could hypothesise that this connection could be illustrated by behavioural similarities across the two systems. Indeed, Tyrrell and co-workers have not only shown that behavioural connections exist between oculomotor and cardiovascular systems, but also that they covary (Tyrrell *et al.*, 1994). Subjects, who exhibited oculomotor shifts to a near task, also experienced significant linear decreases in heart inter-beat intervals (increased heart rate) as recorded by electrocardiography. A near visual task, therefore, can influence cardiovascular behaviour. Furthermore, an acute reduction in the parasympathetic innervation to the heart, accompanies the oculomotor shifts that are induced by near visual work. Thus, dark focus tended to be nearer during sympathetic dominance of the heart than during parasympathetic dominance (Tyrrell *et al.*, 2000).

A further intriguing phenomenon is depicted in the work of Johnson (1976). Here, both visual acuity and the accommodative response were measured for targets presented over a range of distances and luminances. His data showed that, for all luminance levels, optimal visual acuity was obtained at a distance corresponding to the subjects' dark focus. Moreover, the decline in acuity with reduced luminance became greater as the stimulus distance departed from the dark focus, suggesting that focusing errors increased progressively as stimulation was reduced. Consequently, targets positioned at the dark focus plane (tonic level) are focused accurately regardless of stimulus quality, whereas the accuracy of accommodation for targets displaced from the tonic level in either direction is proportional to the quality of the stimulus.

1.6.4a Alternative terminology

Although the idiom tonic accommodation will be used throughout this thesis to describe the open-loop accommodative response, other terms have also been used to describe the intermediate position of the accommodative response.

'Dark focus' has been used extensively as an alternative to tonic accommodation (Adams and McBrien, 1993; Woessner and Jiang, 1993). The term however is a misnomer, implying an active feedback process. With a subject in total darkness, one would assume that no active focusing could occur. Furthermore, tonic accommodation need not be measured in total darkness.

Studies often use the term resting state of accommodation, however, the expression suggests that this is the point at which the accommodative system exhibits minimum physiological activity. In studies that consider accommodative microfluctuations (Niwa and Tokoro, 1998) this is evidently not the case.

ABIAS, a bioengineering term, is also sometimes used when describing models of accommodation (Hung *et al.*, 1996; Flitcroft, 1998, 1999; Charman, 1999), but its use has been limited.

1.7 Accommodation measurement

In order to assess and quantify the myriad of responses produced by the accommodative system, one must first understand how the accommodative response can be measured. Accommodation can be quantified under open- or closed-loop conditions.

1.7.1 Closed-loop methods

Closed-loop conditions occur in real-world environments. An active feedback mechanism controls the level of accommodation keeping the object of regard in sharp focus. The obvious drawback to closed-loop measurements of accommodation has been documented in various studies (Winn *et al.*, 1991; Rosenfield and Ciuffreda, 1990). For example, under closed-loop conditions any variation in accommodative response alters the degree of retinal blur and thereby provides a secondary stimulus to blur-driven accommodation. Even so, Iwasaki (1993) argued that accommodative changes should be investigated under closed-loop conditions when considering problems that arise due to specific visual tasks. The second and more versatile method (open-loop accommodation) involves removing all optical stimuli that modify accommodation.

1.7.2 Open-loop methods

An important point in many previous investigations has been the use of the open-loop accommodative response (Miller, 1978a,b; Bullimore and Gilmartin, 1989; Rosenfield and Ciuffreda, 1991; Winn *et al.*, 1991). In order to measure TA, it is necessary to open the accommodative loop removing the blur feedback mechanism such that the level of accommodative response is independent of the retinal image quality.

1.7.2a Dark focus

The simplest way of removing visual stimuli is to place the subject in total darkness, thus eliminating blur, vergence, and proximal stimuli to accommodation. Non-optical factors such as auditory signals (Cornsweet and Crane, 1973), personality (Gawron, 1983) and surround propinquity (Chiu and Rosenfield, 1994) however, can influence the resulting level of accommodation (see section 1.12). Consequently, even in total darkness, the accommodative response may not be totally stimulus-free.

1.7.2b Pinholes

Viewing a target through a pinhole (typically 0.5 mm) leads to an increase in depth-of-focus to a level that renders the blur-stimulus to accommodation ineffective (Rosenfield *et al.*, 1993). Numerous investigations have adopted this procedure to open the accommodative loop and measure TA (Ciuffreda *et al.*, 1999; Lee *et al.*, 1999; Strang *et al.*, 2000).

Ward and Charman (1985; 1987) measured the monocular accommodative responses to various stimuli (0.0 to 4.5 D) using a Canon R-1 infra-red autorefractor with four different artificial pupil sizes (0.5, 0.75, 1.0 and 3.0 mm). The data showed that a 0.5 mm diameter or less pinhole produces open-loop accommodation over a stimulus range of 0.0 to 4.5 D.

Some studies, however, have reported that the use of a pinhole can induce proximal accommodation when viewing a near target with prior knowledge of the target distance (Rosenfield and Gilmartin, 1990; Rosenfield and Ciuffreda, 1990; Winn *et al.*, 1991). It is therefore imperative that sufficient target distances are used in order to reduce the proximally induced response.

1.7.2c Ganzfeld (Empty field)

The use of an empty field or Ganzfeld is an alternative method that can be used to open the accommodative loop (Schor *et al.*, 1986; Wolffsohn *et al.*, 2001a). For this technique to work effectively there must not be any stimuli to either blur-driven or proximally induced accommodation. Thus illumination variations must be eradicated and the field must be void of any surface or textural imperfections (Rosenfield *et al.*, 1993). However, this is very difficult to set-up and various methods have been employed to produce a Ganzfeld. For example Schor and co-workers used a bright empty field produced by an opal glass diffuser (Schor *et al.*, 1986), whereas Wolffsohn and colleagues created their empty field by filling a room with theatrical dry ice (smoke; Wolffsohn *et al.*, 2001a).

Bullimore and Gilmartin (1989) found no statistically significant difference between values of TA recorded in a Ganzfeld compared with a darkroom, a finding consistent with that of Westheimer (1957) and Leibowitz and Owens (1978).

1.7.2d Difference of Gaussian targets

A fourth method employed to open the accommodative loop requires a Difference of Gaussian (DoG) target (see Chapter 2 and Appendix 1). A DoG is a one-dimensional target which resembles a bright blurred vertical bar surrounded by a dark vertical bar on either side. A DoG target is produced by subtracting a broad Gaussian function from a narrow one (Kotulak and Schor, 1987).

Kotulak and Schor (1987) measured the steady-state monocular accommodative response using this technique. They assessed the response to different DoG spatial frequencies. The DoGs were presented at a range of distances (between 0.0 and 5.0 D). Kotulak and Schor found that the accommodative response to low spatial frequency DoGs tended to be independent of target vergence. Thus the image was not a blur-driven target for the accommodative mechanism. Furthermore, at these spatial frequencies (~0.1 $cdeg^{-1}$) the accommodative response approximated the dark focus response for most subjects.

In a subsequent study, Tseuetaki and Schor (1987) proposed the potential use of a DoG and dynamic (Nott) retinoscopy in the clinical evaluation of TA. Here, the accommodative loop was opened with a low frequency (0.2 $cdeg^{-1}$) DoG as the target. Tsuetaki and Schor found that the results were comparable to those found when using a pinhole Maxwellian view. Rosner and Rosner (1990) adopted and developed this method by comparing the TA measures found with near retinoscopy and Nott retinoscopy (with a 0.2 $cdeg^{-1}$ DoG target) on a group of 6- to 14-year old children. Their results were inconclusive. They did, however, conclude that the TA values measured by the DoG method were consistent with previously published data, in that TA was highest among hyperopes and lowest among myopes (Rosner and Rosner, 1989).

1.8 Steady-state accommodation

Under closed-loop conditions the accommodative system responds in a generalised pattern with variations in accommodative load (the accommodative stimulus-response function). The error in the accommodative response is greatest at the extremes of the accommodative range. The accommodative stimulus-response function is a description of the relationship between the stimulus to accommodation and the resultant accommodative response over a range of accommodative values. It comprises 4 regions: (1) an initial non-linear region; (2) a linear region; (3) a transitional accommodative saturation region; and (4) a fully saturated pseudo-presbyopic region (see Figure 1.3). As the retinal image is progressively degraded, the gradient of the linear region becomes flatter (Rosenfield *et al.*, 1993). The linear portion of the stimulus-response curve is affected by numerous factors including target luminance (Johnson, 1976), spatial frequency (Tucker and Charman, 1987), pupil size (Ward and Charman, 1985, 1987), blurred targets (Heath, 1956), refractive error (McBrien and Millodot, 1986b) and age (Simonelli, 1983).

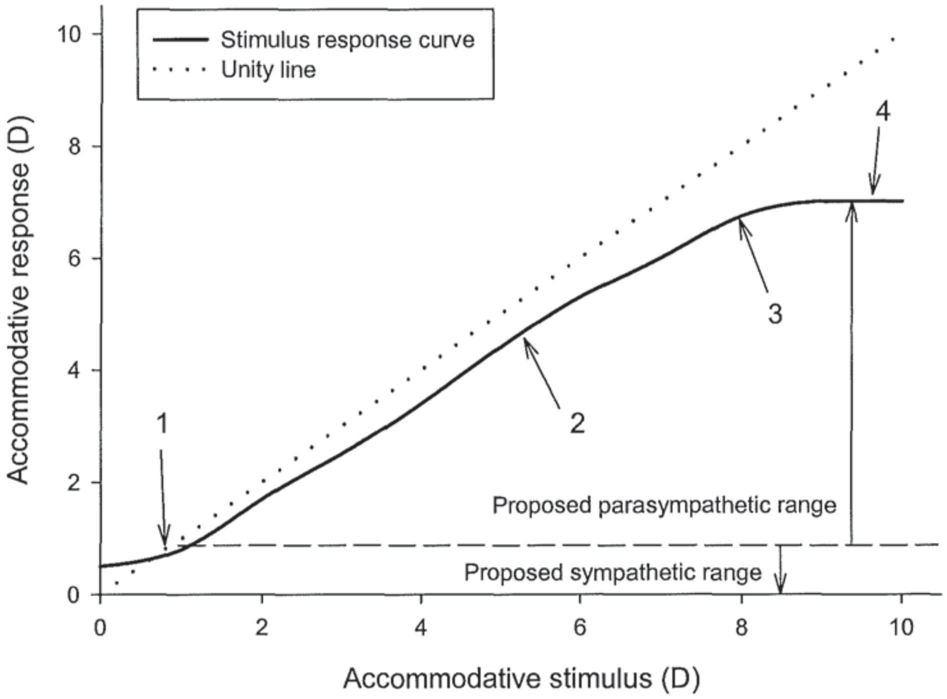

Figure 1.3 A typical human accommodative stimulus response curve (after Bennett and Rabbetts, 1998).

An issue that has raised a strong debate centres on the point at which the stimulus-response curve crosses the unity line (Rosenfield and Gilmartin, 1998). Along this virtual line, the magnitude of the accommodative response is equal to the stimulus to accommodation. A number of researchers have hypothesised that the crossover value of accommodative response is equal to the subject's tonic level of accommodation (Charman, 1982; Ramsdale and Charman, 1989). Other investigations have dismissed these suggestions stating that there is little direct evidence to support the hypotheses (Ciuffreda *et al.*, 1984; Ong *et al.*, 1993). An investigation showing the link between accommodative demand and the cardiovascular response using new methods of heart rate variability analysis (Tyrrell *et al.*, 2000) could expose the effect of the autonomic nervous system on accommodation.

1.9 Accommodative stability

Various studies have examined the temporal stability of tonic accommodation over both short- (Mershon and Amerson, 1980; Krumholz *et al.*, 1986) and long-term (Miller, 1978a; Owens and Higgins, 1983) intervals.

Miller (1978a) concluded that over a period of 2-3 weeks, dark focus did not vary greatly in most subjects (n = 21). He observed a high level of stability, with 13 subjects showing variability in TA < 1.0 D. Intra-subject ranges varied from 0.08-2.92 D with a mean range of 1.07 D over that period. A similar study, investigated the stability of the dark focus of accommodation using a Badal laser optometer (n = 30) (Heron *et al.*, 1981). The results showed that the dark focus position of accommodation was highly stable with the interval between test and retest varying between 3 and 23 weeks (mean 12 weeks). A correlation coefficient of $r = 0.69$ ($p < 0.05$) was found. Diurnal variations in tonic (dark focus) accommodation were also examined by Krumholtz and co-workers using a Hartinger coincidence optometer (Krumholz *et al.*, 1986). Again the results complemented those of previous investigations demonstrating the robustness and stability of tonic accommodation under naturally occurring viewing conditions during the course of a day. However in total darkness, the mean tonic level increasingly fluctuated with time.

1.10 Accommodative microfluctuations

Collins (1937) first detected rapid fluctuations in the accommodative response while using an infrared optometer. Since then, with the advent of new measurement techniques, various investigations have quantified the fluctuations (Charman and Heron, 1988; Winn and Gilmartin, 1992; van der Heijde *et al.*, 1996). The components of the microfluctuations can be measured in two ways: the root-mean-square (RMS) and power spectral density. The RMS is the standard deviation of the response whereas the power spectrum is produced by a fast Fourier transform (FFT).

Campbell, Robson and Westheimer (1959) showed that, using a continuously recording infrared optometer (Campbell and Robson, 1959), accommodative microfluctuations consist of two principal temporal frequencies in the power spectra; a low frequency component (LFC < 0.5 Hz) and a high frequency component (around 2 Hz). However, there is reported variation in the HFC frequency band, for example, Strang and co-workers reported 1.3 Hz < HFC < 2.5 Hz (Strang *et al.*, 1994). The microfluctuations are produced by a combination of noise (respiration and arterial pulse) and neurological control (Collins *et al.*, 1995). The latter is reported to be associated with the LFC (Winn and Gilmartin, 1992; Gray *et al.*, 1993b).

The mechanism by which the arterial pulse augments the HFC is thought to take place via two systems. Firstly, it is thought that choroidal blood flow leads to a pulsatile change in blood volume in the choroid and ciliary muscle thus producing accommodative microfluctuations (Strang *et al.*, 1994). However, this theory does not differentiate between the dynamic fluctuation caused by the choroid or the ciliary muscle. Indeed, an investigation using ultrasonography to observe the steady-state accommodative response illustrated (using spectral analysis) that the axial length of a human eye has its own HFC around 1.35 Hz whereas no HFC fluctuations were present in the crystalline lens or the anterior chamber depth (van der Heijde *et al.*, 1996). This would suggest that the choroid alone is responsible for the HFC. Secondly, the IOP pulse could produce small lens movements that could contribute to the microfluctuations in the overall power of the eye. Again taking the data from van der Heijde and co-workers no HFC was detected in either lens thickness or anterior chamber depth.

If the HFC in accommodation is caused by or linked to arterial pulse, it is puzzling to find that macaque monkeys, which have considerable higher pulse rates than humans, have HF fluctuations of a similar frequency to humans (again centred around 2 Hz; Judge and Flitcroft, 1999). Indeed, fluctuations over and above 2 Hz in humans would suggest clinical tachycardia.

In their review of the literature, Charman and Heron (1988) recount various investigations that have reported that the HFC is pupil dependent as a result of the increased variation in wavefront of the peripheral regions of the lens. Winn and co-workers, however, conducted a series of experiments to investigate the nature and aetiology of the microfluctuations finding that, in their subjects ($n = 5$), the form of the power spectra of the fluctuations was found to be similar for central and peripheral lenticular zones (Winn *et al.*, 1990a). Thus the HFCs are a consistent feature of microfluctuations in central and peripheral zones of the crystalline lens.

It has been proposed that accommodative microfluctuations operate by a continuous trial and error mechanism of the ciliary muscle around an equilibrium position (Gray *et al.*, 1993b). This is an intriguing hypothesis, which implies that the steady-state accommodative response is maintained by the inherent fluctuations. By examination of microfluctuations, therefore, one may be able to elicit information regarding the control system of the steady-state accommodative response. Table 1.2 illustrates various investigations looking at how external factors can influence the LFC and HFC of the accommodative microfluctuations.

RESEARCHERS	VARIABLE	EFFECT ON LFC	EFFECT ON HFC
Iwasaki and Kurimoto (1987)	- VDT work - Paper work	- Increase after VDT work - No significant increase	No significant change
Winn, Pugh, Gilmartin and Owens (1990a)	Crystalline lens zone	Consistent over lens surface	Consistent over lens surface
Winn, Pugh, Gilmartin and Owens (1990b)	Arterial pulse frequency	n/a	Positive correlation
Owens, Winn, Gilmartin and Pugh (1991)	Topical instillation of a β-antagonist (timolol)	No consistent variation	Reduction in power and frequency
Gray, Winn and Gilmartin (1993a)	Target luminance	Increase in power as retinal image quality degraded	No systematic change
Gray, Winn and Gilmartin (1993b)	Real artificial pupil size (0.5 to 5 mm)	- Pupils <2 mm increase in power as pupil decreases - Pupils >2 mm constant power	No systematic change
Owens, Bhat and Jacobs (1994)	Artificial pupil size (0.5 to 3 mm)	Magnitude inversely proportional to pupil size	No significant variation
Strang, Winn, Gilmartin and Brosnahan (1994)	Topical instillation of a non-selective β-antagonist (betaxolol)	No significant variation	No significant variation
Stark and Atchison (1997)	Artificial pupil size (1 to 6 mm)	Magnitude inversely proportional to pupil size	No significant variation
Toshida, Okuyama and Tokoro (1998)	Accommodative stimulus	Minimum at subject's far point, increased as target brought closer to the eye	Reached a maximum at the centre of the accommodative range
Niwa and Tokoro (1998)	Target blur	Increased as target sharpness was reduced	Little variation as blur increased
Gray, Gilmartin and Winn (2000)	Viewing a VDT	No significant variation in power with display or task duration	No significant variation in power with display or task duration
Simmers, Gray and Wilkins (2001)	Tinted lenses (coloured and neutral density)	Decreased magnitude with tinted lenses cf no lens	No overall effect
Day, Strang, Seidel, Gray, Mallen (2004)	Accommodative stimulus	Increase in magnitude	No overall effect

Table 1.2 A selection of factors that influence the LFC and HFC of microfluctuations of accommodation.

Gray and co-workers (1993a) investigated the effect of target luminance on accommodative microfluctuations. In this study, three emmetropes viewed a high contrast (90%) Maltese cross placed at a vergence equal to the subjects' tonic accommodation level. The luminance of the target was varied from 0.002 to 11.63 cdm^{-2}. They found that variation in the RMS value of the microfluctuations was attributed mainly to the increase in the RMS for the two lowest luminance levels (0.002 and 0.004 cdm^{-2}). There was also a concurrent increase in the power of the LFC of the power spectra. However, no systematic variation of the HFC was found with changes in luminance levels. Gray and co-workers proposed that the increase in the LFC power, as retinal-image quality was degraded, suggests that the LFC is utilised in the control of the blur-driven accommodative response.

A second investigation examined the effect of pupil size on microfluctuations (Gray *et al.*, 1993b). With pupils less than or equal to 2 mm in size, the LFC increased as pupil diameter decreased. For pupils greater than 2 mm, the LFC remained relatively constant. Once again, no systematic variation was detected in the HFC. This experiment supports the previous work by Campbell *et al.* in which there was an increase in the LFC when subjects viewed a target through a 1 mm pupil compared to a 7 mm pupil (Campbell *et al.*, 1959).

In conclusion, the studies presented to date show that:

- There are two primary temporal variations in the complex Fourier waveform (LFC and HFC)
- LFC are a consequence of neurological control.
- HFC appear to be a consequence of physiological rhythmic variations (e.g. pulse).

1.11 Accommodative adaptation

Schor *et al.* (1986) and Schor and McLin (1988) observed differences in the rate of decay of accommodative adaptation from a near task depending on the method used to open the accommodative loop (pinhole, empty field, and darkness). They concluded that adaptation was relatively sustained if the subject viewed an illuminated difference of Gaussian (DoG) target through a 0.5 mm pinhole when compared to the results found in darkroom conditions (the DoG target was not used as a method of opening the loop itself).

Wolfe and O'Connell (1987) also found a disparity between measures conducted in darkroom conditions compared to light empty field conditions. Of the 21 subjects, 5 showed a significantly greater accommodative adaptation under illuminated conditions compared to the dark condition. Conversely, Bullimore and Gilmartin (1989) did not find any significant difference between the mean values of tonic accommodation obtained using an objective, open-view, infrared autorefractor under both darkroom conditions and an illuminated Ganzfeld field ($n = 10$).

Prior knowledge of target proximity and the surrounding environment could be a factor causing the disparity between these investigations. Rosenfield and Ciuffreda (1991) examined the effect of surrounding propinquity on the open-loop accommodative response in two different sized rooms in darkness. They found that prior knowledge of the surroundings had an effect on the accommodative response. For example, when subjects ($n = 10$) were initially able to observe the room size, the accommodative response in darkness was significantly higher ($p < 0.01$) in the smaller laboratory. Chiu and Rosenfield (1994) examined tonic accommodation and tonic vergence and their interactions with adjacent surroundings. Here, using a pinhole to open the loop and a distant target, the mean level of tonic accommodation (mean: 0.28 D) was significantly lower ($p = 0.01$) than that observed in total darkness (mean: 0.60 D). Chiu and Rosenfield concluded that more accurate measurement of tonic accommodation might be obtained by having subjects view distant targets while placing the accommodation system under open-loop conditions.

1.12 Non-optical (spatiotopic) influences

As stated previously, the ciliary muscle of the human eye is innervated by the autonomic nervous system (Cogan, 1937; Gilmartin, 1986; 1998). Accommodation therefore, is not always affected by a direct accommodative stimulus. Non-optical factors also have an effect on accommodation for example mood changes (Miller, 1978b), age (Whitefoot and Charman, 1992; Mordi and Ciuffreda, 1998, 2004), excitation (Morgan, 1944), stress (Westheimer, 1957), menstrual cycle (Jordan and Jaschinski-Kruza, 1986), caffine (Zhai *et al.*, 1993) personality (Gawron, 1983), surround propinquity (Rosenfield and Ciuffreda, 1991; Chiu and Rosenfield, 1994), volitional control (Cornsweet and Crane, 1973), whiplash injury (Brown, 2003) and cognitive demand (Bullimore and Gilmartin, 1988; Wolffsohn *et al.*, 2003b).

As early as 1944, Morgan observed that if rabbits were refracted by skiascopy (retinoscopy) before and immediately after excitation, the degree of hypermetropia was greater when the rabbit was in the excited state compared to the unexcited state (Morgan, 1944).

Overestimation of the accommodative response can also occur when subjective methods are used to quantify accommodative effort (Bullimore *et al.*, 1986). Consequently, subsequent studies have adopted more modern open-view objective infrared optometers to negate this confounding variable (McBrien and Millodot, 1985; Mallen *et al.*, 2001; Wolffsohn *et al.*, 2002; Davies *et al.*, 2003). Given this, the findings of previous studies into the proposed correlation between the autonomic nervous system and cognitive demand, using optometers requiring subjective responses (such as the laser optometer) may be confounded.

1.12.1 Cognition

Living and working in the modern world often requires prolonged and intensive periods of cognition, such as the use of VDUs. Over the last thirty years much work has been undertaken to investigate the role of cognition and its interaction with ocular accommodation (see Table 1.3). Previous studies have concluded that cognitive effort can induce a relative 'outward' shift in accommodation (Rosenfield and Ciuffreda, 1990) while others show an 'inward' shift (Wolffsohn *et al.*, 1998). There is, therefore, a dispute as to the effect of mental effort or cognitive demand on accommodation and the precise mechanisms that induce these responses.

Kruger (1980) actively monitored the accommodation of subjects to determine whether an increase in cognitive demand would result in an increase in the level of their accommodation. When his subjects ($n = 20$) changed from reading a two-digit number at 40 cm to adding the numbers, with no alteration in the visual stimulus, the average level of accommodation increased in 75% of the subjects with the mean level of accommodation increasing by 0.28 D ($p < 0.01$). Further, Post and co-workers (1985) concluded that 'effort to see' might influence the resting focus of some subjects stating that an increase in cognitive demand can influence the accommodative state of certain subjects.

Malmstrom *et al.* (1980) documented, however, that a written backward-counting task could produce a decrease in accommodative response of 0.25-0.75 D for a 3.0 D target. Malmstrom and his co-workers have suggested that cognitive induced shifts in accommodation are propagated by changes in the autonomic balance of the subject as recounted by Bullimore and Gilmartin (1988).

The imposition of mental effort was found by Bullimore and Gilmartin (1988) to induce a significant increase in the mean accommodative response for a 1.0 D stimulus, a response equivalent to a passive condition at 3.0 D and a reduction in response at 5.0 D. Mental effort induced similar responses for 1.0 D and 3.0 D stimuli when sympathetic innervation to the ciliary muscle was blocked with the β-sympathetic antagonist timolol maleate. Responses for the 5.0 D stimulus, however, increased. It appeared that there was greater sympathetic inhibition with underlying parasympathetic tonus, therefore the distance of a task will affect the direction of the accommodative response. Consequently, when viewing a distant target, the presence of mental effort induces an increase in the accommodative response (parasympathetic mediation). Conversely, when viewing a near target the accommodative response decreases with mental effort (due to sympathetic input which increases due to a concurrent rise in the parasympathetic response).

The augmentation of the sympathetic system occurs on two counts: firstly, sympathetic inhibition will only become apparent when there is sufficient muscle tonus to inhibit, therefore there is a minimum level of parasympathetic activity. Secondly, parasympathetic activity above this level appears to augment a concurrent sympathetic response but not to a level greater than 2.0 D (Gilmartin and Bullimore, 1987a) even for very high parasympathetic levels (Winn *et al.*, 1991).

Variations in accommodative level during a cognitive task also vary with refractive error. The imposition of a task, requiring mental effort, was found by Bullimore and Gilmartin (1987) to induce a positive shift in the tonic level of accommodation for myopic subjects (n = 15). Furthermore, this shift was significantly greater than that for an emmetropic subject group (n = 15). Given this, an investigation to show the autonomic response would illustrate the genesis of the resultant accommodative levels found during a cognitive task.

RESEARCHERS	COGNITIVE TASK	NUMBER OF SUBJECTS (N)	BASELINE	OPTOMETER	TARGET DISTANCE	INFLUENCE ON ACCOMMODATION (D)
Kruger (1975)	Read five different levels of graded text Add Numbers	10	n/a	IR Retinoscope	2.00 D	No difference between texts levels Increase in luminance when adding numbers
Kruger (1977a)	Add two digit numbers	19	Passively read two digits	IR Retinoscope	2.50 D	Luminance increase
Kruger (1977b)	Add two digit numbers	3	Passively read two digits	IR Retinoscope	2.50 D	Luminance increase
Kruger (1980)	Add two digits	20	Passively read two digits	IR Retinoscope	2.50 D	+0.25 D
Malmstrom, Randle, Bendix and Weber (1980)	Write backwards in ones from two digit number	5	Black 'X'	Laser Optometer	Infinity 3.00 D Empty field	-0.05 D +0.30 D 0.00 D
Malmstrom and Randle (1984)	- Paced backwards counting in ones (mental/written) every two seconds	4	0-3 D sinusoidally changing 'X' (subtending 2.9)	Cornsweet and Crane IR Optometer	Infinity (0.00 D) to 3.00 D	-0.25 D to –0.50 D
Post, Johnson and Owens (1985)	- Passive viewing laser - Active judgement of laser pattern - Mental arithmetic (count back in 7's)	5 11	Dark Focus	Ophthalmetron IR Optometer	n/a	+0.05 D +0.34 D -0.02 D
Gawron, Paap and Malmstrom (1985)	- Complete vowel between two consonants - Count backwards in 7's	12 10	Dark focus	IR Optometer	2.90 D n/a	Visual +0.07 D Auditory +0.38 D -0.65 D
Bullimore and Gilmartin (1987a)	- Count backwards in 7's	15 emmetropes 15 LOMs	Dark Focus	Canon IR Optometer	n/a	- Emmetropic group +0.07 ± 0.27 D - Myopic group +0.35 ± 0.31 D
Bullimore and Gilmartin (1987b)	- Reverse counting task from three digits verbally presented	20 emmetropes	Dark Focus (listening to popular music)	Canon IR Optometer	n/a	- With Saline +0.15 D - With Timolol +0.21 D
Bullimore and Gilmartin (1988)	- Adding numbers in rows/columns of five	12 emmetropes	Passive reading of numbers	Canon IR Optometer	1.00 D 3.00 D 5.00 D	Saline: +0.09 D Timolol: +0.06 D -0.01 D +0.01 D -0.04 D +0.04 D

Jaschinski-Kruza and Toenies (1988)	- Identify correct equations	18	Dark Focus	Laser Handheld Polaroid	n/a	Low DF: +0.20 High DF: +0.55 +0.10 +0.25 -0.30 +0.30
Rosenfield and Ciuffreda (1990)	- Counting backwards in 7's	12	Relaxation to popular music	Canon IR Optometer	0.17 D 3.00 D	-0.22 D -0.34 D
Winn, Gilmartin, Mortimer and Edwards (1991)	- Respond when a letter 'e' appears in a letter array presentation - Count backwards (7s)	10 emmetropes	Passive reading	Canon IR Optometer	Closed-loop 3.50 D Open-loop 0.00 D	+0.17 D -0.05 D
Iwasaki (1993)	Checking addition computations (i.e. 1+2=3): - 4s presentation speed - 2s presentation speed	17	Fixate on the centre of a CRT screen at 50 cm	IR Optometer	2.00 D	Change in steady accommodation: +0.18 D +0.23 D
Gray, Winn, Gilmartin and Eadie (1993c)	- Count backwards in 7's	20	Open-loop (Maltese cross viewed with a pinhole)	Canon IR Optometer	Infinity	+0.16 D
Edgar, Reeves, Craig and Pope (1994)	- View hashes on HUD - Reading backward words	10	Real world view (outside)	Laser optometer	Infinity	+0.40 D +0.76 D
Rosenfield and Ciuffreda (1994)	- Add pairs of single digits - Add four two digit numbers	12	Read aloud single digit numbers	Canon IR Optometer	5.00 D	+0.23 D
Wolffsohn, McBrien, Edgar and Stout (1998)	- Respond to HUD indicator - Respond to 1 HUD digit - Respond to 2 HUD digits	24 (8, 19-24 yrs; 8, 35-44 yrs; 8, 49-74 yrs)	Respond to brake light in an outside world scene	Canon IR Optometer	0.20 D	+0.18 D +0.29 D +0.42 D
Wolffsohn, Edgar, Stone, Williams and McBrien (1999)	- FLIR imagery - HUD imagery	15 emmetropes	Outside world scene	Canon IR Optometer	0.20 D	+0.17 D
Wolffsohn, Gilmartin, Thomas, Mallen (2003b)	Passive or active engagement of arithmetic sum (measure of NITM)	6 EMM 6 EOM 6 LOM	n/a	Shin-Nippon SRW-5000 IR Optometer	0.00 D 4.50 D	- EOM>LOM>EMM - LOM less accurate than EOM or EMM

Table 1.3 Summary of previous cognitive investigations on the ocular accommodative response (continued from page 39).

The consensus regarding the effect of cognition on accommodative response is that there is a greater lag in accommodative response for the high accommodative demand stimulus and a greater lead for targets situated close to infinity, with no overall effect found when targets are situated near the tonic level of the subject. However, inspection of the data indicates this general trend is not apparent in all investigations, indeed many contradict this hypothesis. Table 1.4 summarises the key investigations showing where the maximum and minimum cognitive effects were seen on accommodative response, along with studies showing shifts in accommodative response opposite to what is expected during cognitive tasks.

EFFECT	RESEARCHERS	TARGET	ACCOMMODATIVE RESPONSE (D)
Study showing largest shift in accommodation	Edgar, Reeves, Craig and Pope (1994)	Infinity	+0.76 D
Study showing smallest shift in accommodation	Malmstrom, Randle, Bendix and Weber (1980)	Empty field	0.00 D
Studies showing shifts in accommodation opposite to those expected	Kruger (1977b)	2.50 D	+0.25 D
	Malmstrom, Randle, Bendix and Weber (1980)	Infinity 3.00 D	-0.05 D +0.30 D
	Gawron, Paap and Malmstrom (1985)	2.90 D	+0.38 D
	Rosenfield and Ciuffreda (1990)	0.17 D	-0.22 D
	Winn, Gilmartin, Mortimer and Edwards (1991)	3.50 D	+0.17 D
	Rosenfield and Ciuffreda (1994)	5.00 D	+0.23 D

Table 1.4 Summary of significant cognitive investigations.

1.13 Accommodation and refractive error

Numerous studies have implied that the accommodative response is associated with the development of myopia (e.g. Culhane and Winn, 1999), in particular late-onset myopia (LOM); this section reviews the role of refractive error and the accommodative response.

1.13.1 Tonic accommodation

Studies investigating the correlation between TA and ocular refraction have provided conflicting results. The majority of studies show that hyperopic subjects exhibit the highest tonic response followed by emmetropes then myopes (Smith, 1983; Heron *et al.*, 1984, McBrien and Millodott, 1987; Miwa, 1992; Jiang, 1995). McBrien and Millodot (1987) investigated the relationship between TA and refractive error (n = 62; age 19 to 25 years). They found that the hypermetropic group (n = 15) had the highest level of TA with the late-onset myopes (n = 15) having the lowest level. Moreover, Bullimore and Gilmartin (1987a) showed that under darkroom conditions involving minimal mental effort there is a trend for late-onset myopes to have lower TA than emmetropes. Other studies, however, argue that the converse is true (Gawron, 1981; Simonelli, 1983). A large study by Simonelli (1983) (n = 301) found a definitive relationship between TA and refractive error. A third group of investigations have concluded that there is no overall effect showing no significant difference in TA between refractive groups (Whitefoot and Charman, 1992; Strang *et al.*, 1994).

Given the variety of ways in which the tonic response can be measured and simulated, it is not surprising to find that such disparities exist. In addition, refractive criterion, cognition and subject population may also play an important role, accounting for some of the differences between studies (Ong and Ciuffreda, 1997). In an attempt to combat the disparity between investigations, subsequent studies have divided the myopic group into sub-groups (McBrien and Millodot, 1986b; Rosenfield and Gilmartin, 1989; Bullimore *et al.*, 1992): early-onset myopes (EOM) where myopia onset is before the age of 15 years and late-onset myopes (LOM) where myopia onset is at 15 years of age or later (Goss and Winkler, 1983).

1.13.2 Steady-state blur-driven accommodation

Fewer investigations have examined the changes in accommodation produced solely by the effects of blur-driven accommodation (Rosenfield and Gilmartin, 1998). In such studies, to ensure only blur drives the accommodative response, investigations are usually conducted under monocular conditions with the stimulus presented within a Badal optical system, thus maintaining a constant retinal image size and luminance (Bennett and Rabbetts, 1998).

Gwiazda and co-workers reported that myopic children exhibit reduced accommodative gain to blur-stimuli (Gwiazda *et al.*, 1993). Here, concave lenses were used to vary the accommodative stimulus. Mean slopes of the accommodative stimulus-response curve of 0.61 and 0.20 D/D were reported for the emmetropic and myopic cohorts, respectively. Rosenfield (1998), however, questions these findings suggesting that the results for both refractive groups reach pathological levels. As such, it was unlikely that the children ever saw the targets clearly.

Abbott *et al.* (1998) also investigated the accommodative stimulus-response function in 33 young adult emmetropes and myopes. Three methods of stimulating accommodation were adopted: a decreasing distance series (DDS); a negative lens series (NLS) and a positive lens series (PLS). In this study, a statistically significant reduction in accommodative response accompanied the progressing myopes (when accommodation was stimulated by the NLS). However, when either target distance or convex lenses (at a near target) were used to augment the accommodative stimulus, no statistically significant difference in accommodative response was observed. Jones (1990) also examined the gradient of the monocular stimulus-response function reporting attenuation of the slope in the myopic group.

The differences in blur-driven accommodation between refractive groups appear to reflect the ability of myopic subjects to detect retinal defocus. Indeed, an elegant study by Abraham-Cohen *et al.* (1997) illustrated that the ability of emmetropes to detect the presence of blur occurs significantly earlier than myopes.

1.13.3 Accommodative lags: A risk factor or a consequence of myopia?

Substantial amounts of work have tested the hypothesis that accommodation, or more importantly accommodative lags at near, are a precursor to, or a consequence of myopia onset. Several studies have observed reduced accommodative responses in myopic individuals, when compared to emmetropes. Ramsdale (1979), using a laser optometer, compared the accommodative responses of subjects to a range of stimuli (-2.0 to +7.0 D), reporting lower accommodative responses in the myopic group at all stimulus levels. A later publication by Ramsdale (1985), however, contradicted this earlier finding by showing no statistically significant difference between the accommodative responses of myopic and emmetropic subjects.

McBrien and Millodot (1986b), using the Canon R-1 infrared optometer, found that in support of Ramsdale's early work, myopes exhibited a reduction in accommodative response compared to emmetropes. Further studies by Rosenfield and Gilmartin (1988a), Bullimore *et al.* (1992) and Gwiazda *et al.* (1993) have all confirmed lower accommodative responses in myopes, with differences between refractive groups ranging from 0.08 D to ~ 0.90 D.

More recently, Portello and co-workers measured the lag of accommodation in a cohort of emmetropic subjects. A significantly greater lag of accommodation was shown in subjects who later became myopic compared to subjects that remain emmetropic (Portello *et al.*, 1997).

CARDIOVASCULAR FUNCTION AND AUTONOMIC INNERVATION

1.14 Introduction

It has long been recognised that the instantaneous heart rate, arterial blood pressure, and other haemodynamic parameters fluctuate on a beat-to-beat basis (Akselrod *et al.*, 1981; Martin *et al.*, 1987; Moak *et al.*, 2002; Manzella *et al.*, 2004). These beat-to-beat fluctuations reflect the dynamic response of the cardiovascular control systems to a host of naturally occurring physiological factors, which include those relating to the eye (Gherghel *et al.*, 2004). It is now established that there is a significant relationship between the autonomic nervous system, heart rate and heart rate variability (HRV) (e.g. Winchell and Hoyt, 1996; Bates *et al.*, 1997; Vongpatanasin *et al.*, 2004).

The apparently easy derivation of HRV has popularised its use in recent years (Chiu *et al.*, 2003; Pyetan *et al.*, 2003; Antelmi *et al.*, 2004). With the advent of many commercial devices, the researcher has access to an effective non-invasive tool for clinical studies. The data produced, however, are complex and there is potential for incorrect assertions and conclusions to be made (Cammann and Michel, 2002). Given this, the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology was issued with the remit to provide structure and form to the measurement of heart rate and HRV measurements, thus providing a framework on which to base methodologies (Task Force, 1996). All heart rate and HRV measurements within this thesis, therefore, are based on the Task Force's guidelines.

1.15 Autonomic influences of heart rate

Although cardiac tissue has an innate, myogenic beat, heart rate and rhythm are largely under the control of both branches of the ANS (Ursino and Magosso, 2003). The parasympathetic influence on heart rate is mediated via the release of acetylcholine by the vagus nerve and the ensuing interaction with muscarinic receptors; leading to a reduction in heart rate. The sympathetic influence on heart rate is mediated by the release of epinephrine (adrenaline) and norepinephrine (noradrenaline). Subsequent activation of β-adrenergic receptors leads to an increase in heart rate (Longmore, 1971; Noble, 1979). The effects of the ANS on heart rate are summarised in Table 1.5.

ANS BRANCH	NEUROTRANSMITTER	RECEPTOR	EFFECT
Parasympathetic	Acetylcholine	Muscarinic	Reduces heart rate
Sympathetic	Adrenaline Noradrenaline	β-adrenergic	Increases heart rate

Table 1.5 Autonomic components with respect to cardiovascular function.

1.15.1 History

Hon and Lee (1963a,b) first recognised the clinical relevance of HRV noting that foetal distress was preceded by alterations in inter-beat intervals before any appreciable change occurred in the heart rate itself. Later, Sayers (1973) focused attention on the existence of physiological rhythms embedded in the beat-to-beat heart rate signal. Sayers spectrally analysed the records of four 256 heart beat sequences. Figures 1.4 and 1.5 show the data collected and the resulting power spectra. He concluded that although there appeared to be variability between the recordings it did not constitute a wholly sporadic fluctuation. The association of higher risk of post-infarction mortality with reduced overall HRV was first shown by Wolf *et al.* (1978). Following this, Akselrod and co-workers introduced power spectral analysis of heart rate fluctuations to evaluate quantitatively beat-to-beat cardiovascular control (Akselrod *et al.*, 1981). It is this frequency-domain analysis that first contributed to the understanding of the autonomic aetiology of inter-beat interval fluctuations in the heart rate. During the 1980s, Ewing *et al.* (1985) devised a number of simple bedside tests of short-term inter-beat differences to detect autonomic neuropathy in diabetic patients.

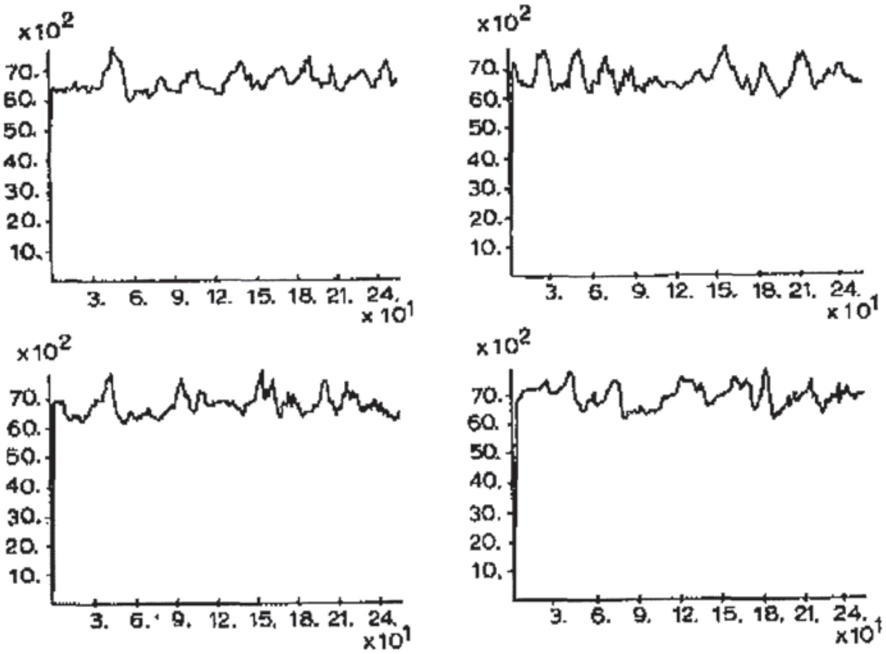

Figure 1.4 Four HRV tachograms, each of 256 inter-beat intervals (after Sayers, 1973). Units: *x*-axis (Heart beats [number]); *y*-axis (Inter-beat interval [ms]).

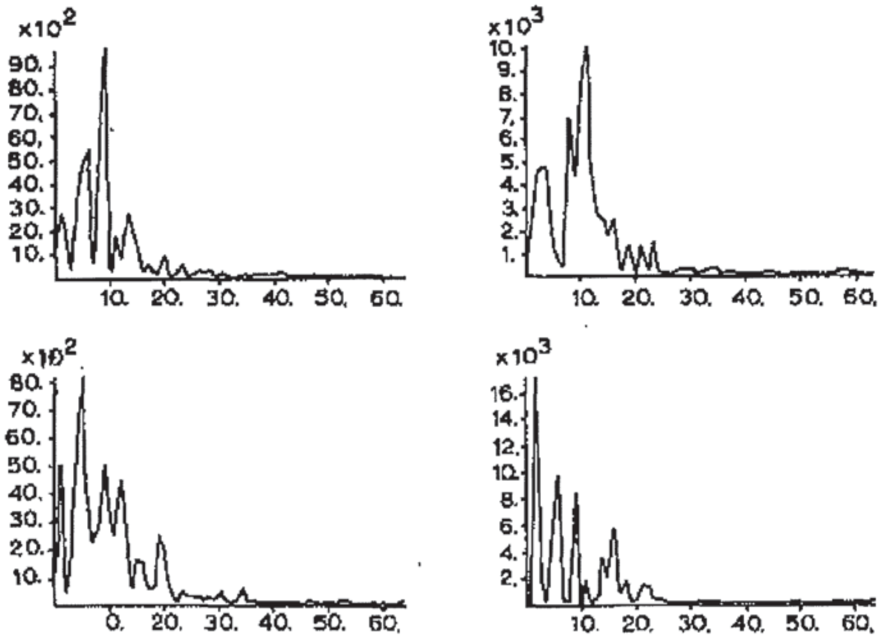

Figure 1.5 The corresponding interval FFT power spectra of the HRV data presented in Figure 1.4 (after Sayers, 1973). Units: *x*-axis (Frequency [Hz x 10^{-2}]); *y*-axis (Spectral power [ms^2Hz^{-1}]).

1.16 Evaluation of HRV

1.16.1 Time-domain methods

Variations in heart rate may be evaluated in a variety of ways; the simplest are measures in the time domain. With these methods either the heart rate at any point in time or the intervals between successive normal beats are determined. For example, in a continuous ECG recording, each heart beat is detected and the so-called normal-to-normal (NN or RR), or instantaneous heart rate is determined. Simple time-domain variables that can be determined include the mean RR interval, the mean heart rate and the difference between the longest and shortest RR interval.

The simplest variable to calculate is the standard deviation of the RR interval (SDNN). As variance is mathematically equal to total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. It should be noted that the total variance of HRV increases with the length of the analysed recording (Saul *et al.*, 1988). Consequently, on arbitrary selection of heart rate data, SDNN is not a well-defined statistical entity because of its temporal dependence. Thus, in practice, it is inappropriate to compare SDNN measures obtained from data of different temporal durations. In standardising this, the Task Force (1996) recommended that short- (5 minute) and long-term (24 hour) recordings were appropriate temporal durations.

1.16.2 Frequency-domain methods

Although measurements of changes in heart rate can indicate that a change has occurred in the autonomic equilibrium, such measures are not sufficient to decipher the relative contributions of sympathetic and parasympathetic forces. For example, an increase in heart rate maybe due to sympathetic activation, parasympathetic attenuation or a combination of the two. Consequently, techniques have evolved to investigate this problem (Sayers, 1973; Akselrod *et al.*, 1981).

In contrast to the time-domain measures of HRV, recent developments have enabled the calculation of frequency measures based on mathematical manipulations performed on the same ECG-derived data. Frequency measures involve the spectral analysis of HRV. Inter-beat interval data are represented on a tachogram, in which the y-axis plots the RR intervals, and the x-axis the total number of beats (Figure 1.4). Spectral analysis of a tachogram transforms the signal from time to frequency on the x-axis, by representing the signal as a combination of sine and cosine waves, with different amplitudes and frequencies (Figure 1.5). As such, for short-term (5 minute) recordings, a minimum of 256 consecutive heartbeat intervals are required (i.e. 2^8 data points).

Frequency-domain components

The sympathetic and parasympathetic nervous systems are generally considered to be the principle systems involved in short-term cardiovascular control on the time scale of seconds to minutes. There is also evidence to suggest that the rennin-angiotensin system plays a minor role in short-term cardiovascular control, however, the literature remains inconclusive (Akselrod *et al.*, 1981; Task Force, 1996; Gherghel *et al.*, 2004).

Chess and co-workers (1975) analysed the frequency content of heart rate fluctuations by measuring the power spectral decomposition (see Figure 1.6). They found three main peaks/fluctuations of the heart rate: 0.04 Hz; 0.12 Hz; and 0.4 Hz (the latter centred at the respiratory frequency). In any given spectrum, however, one or more of the three peaks may not be evident because of low amplitude or overlap (Cammann and Michel, 2002). Furthermore, the high-frequency peak will not be present if the respiratory rate exceeds the mean heart rate. Consequently, in any investigation, respiration rate should be monitored and controlled (normally with the aid of a metronome).

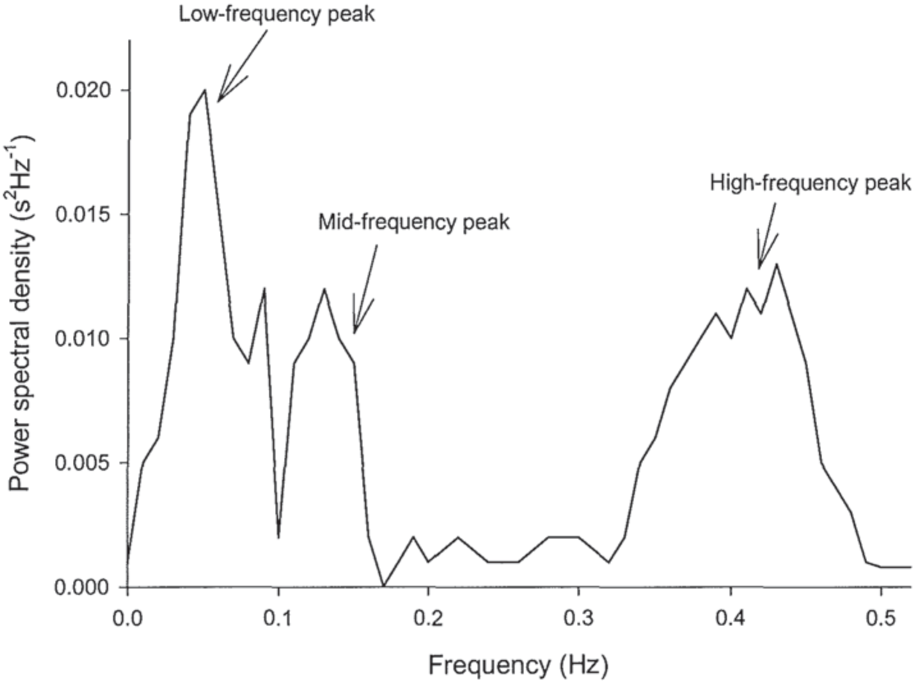

Figure 1.6 Spectral decomposition of heart rate variability (redrawn from Akselrod *et al.*, 1981).

Akselrod and co-workers (1981) illustrated that combined β-sympathetic and parasympathetic blockage abolishes all HRV in dog hearts, whereas sympathetic blockage alone tends to reduce the amplitude of the low-frequency peak (Figure 1.7). Further manipulation of the ANS, however, showed that increasing the activity of either the sympathetic or parasympathetic nervous system augments the area under the low-frequency peak. Therefore, the parasympathetic nervous system mediates heart rate fluctuations at frequencies corresponding to the mid- and high-frequency peaks of the power spectrum, whereas both the sympathetic or parasympathetic systems mediate the low frequency fluctuations (Pagani *et al.*, 1992).

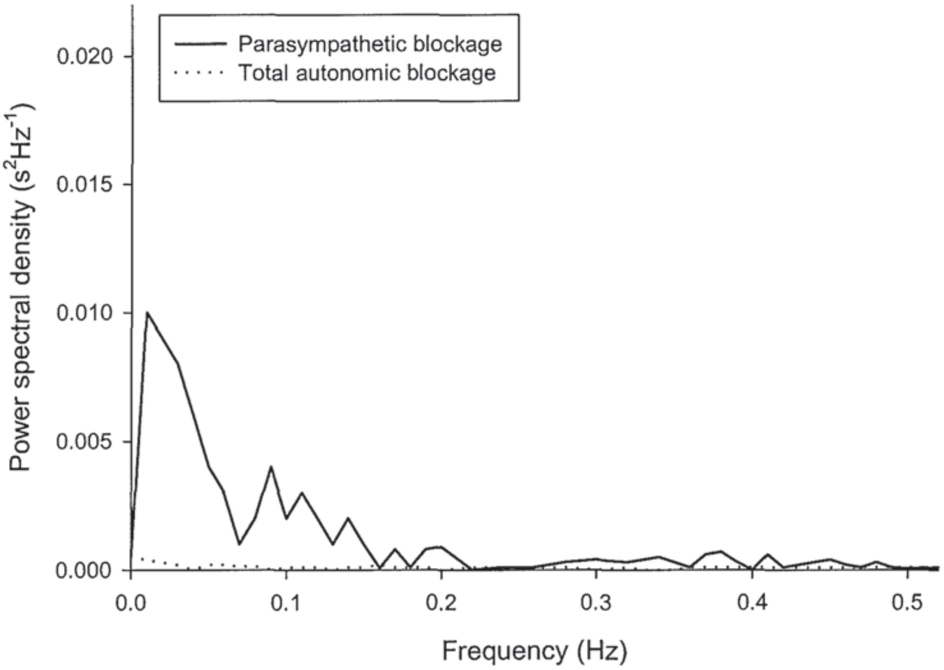

Figure 1.7 Spectral decomposition of heart rate variability following partial and total autonomic blockage (redrawn from Akselrod *et al.*, 1981).

Tyrrell and co-workers (2000) elaborated further by proposing that the spectral decomposition of variations in heart rate yields two primary sources of variability, a low frequency component (LFC) (~0.1 Hz) and a high frequency component (HFC) (centred around the respiratory frequency ~0.4 Hz). The power of the HFC is a useful index of parasympathetic activity while the LFC was suggested to be primarily due to sympathetic influences. This dual mechanism has been utilised in other investigations (Tyrrell *et al.*, 1992; Tyrrell *et al.*, 1994).

The comprehensive review of HRV factors by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996) concluded that for short-term recordings (5 minutes), three main spectral components are distinguished: a very low frequency (VLF); a low frequency (LF) and a high frequency (HF). The LF and HF are not fixed parameters but vary in association with manipulations of the ANS. The VLF component, however, is much less defined and the precise physiological process attributable to these heart rate changes is questionable. Thus, for short-term recordings, the VLF component is a dubious measure and should be avoided when interpreting the power spectrum (Task Force, 1996).

Further, measurement of the spectral components is usually made in absolute values of power (s^2Hz^{-1}), however, LF and HF components may also be quantified and measured in normalised units (n.u.) which represent the relative power of each component in proportion to the overall power spectra minus the VLF component, thus eliminating inter- and intra-subject variation caused by background noise.

1.17 Influences on HRV

Bernardi and colleagues (2000) assessed the effects of mental activity on spontaneous breathing and heart rate variability. In 12 healthy subjects they found that compared with spontaneous breathing, reading silently increased the speed of breathing ($p < 0.05$), decreased mean RR interval and RR variability. They concluded that simple mental activities markedly affect heart rate variability (HRV) through changes in the respiratory frequency. Thus, in the absence of simultaneous analysis of respiration, the changes in LF/HF ratio should not be taken as clear evidence of changes in autonomic tone. They also concluded that although there is a complex interplay between mental activities and respiration pattern, mental activity appears invariably associated with some degree of sympathetic activation, whose degree depends upon the amount of stress involved in performing the mental task (Bernardi *et al.*, 2000).

Non-neural factors can also influence HRV. Age (Pagani *et al.*, 1986; Tsuji *et al.*, 1996) and heart rate (Tsuji *et al.*, 1996) must also be taken into account when evaluating HRV. Tsuji and colleagues recorded the electrocardiogram of 2722 subjects (mean age: 55 ± 14 years) and analysed the resulting spectral decomposition. They concluded that the RR interval variability parameters were attenuated by a higher heart rate (in 22.6% of the sample) and older age (in 38.9% of the sample). From the study two frequencies in the HRV became apparent, a low frequency power (0.04 to 0.15 Hz) and a high frequency power (0.15 to 0.4 Hz).

Age, gender and body mass index were studied by Antelmi and co-workers (2004) on a cohort of subjects without heart disease. In their study, time- and frequency-domain indexes of HRV were studied in 653 subjects. There was an inverse correlation of HRV with heart rate ($p < 0.001$) whereas, HRV indexes decreased with increasing age. No correlation, however, was noted between HRV and body mass index.

1.18 Quantification of cardiovascular data

The conventional technique used to measure heart rate has been the electrocardiogram (Akselrod, 1981; Pagani *et al.*, 1986; Tyrrell *et al.*, 1994). In order to calculate the inter-beat-interval (IBI), various software packages have been utilised to compute the temporal duration between R-spikes for later analysis. R-spikes are produced during a conventional ECG recording. Figure 1.8 illustrates a normal tachogram trace, produced by a piezo-electric finger pulse transducer, with the prominent R-spike.

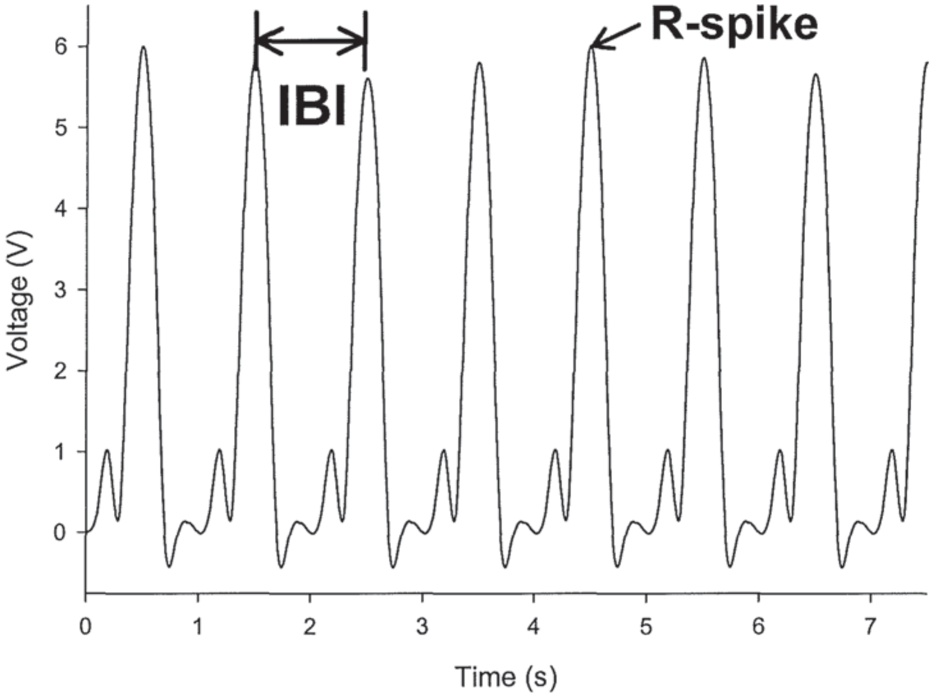

Figure 1.8 Normal healthy human heart trace (as recorded by a piezo-electric finger pulse transducer).

Following data acquisition, an autoregressive spectral decomposition of the temporal heart sequence is performed (usually off-line). This produces a frequency dependent spectral decomposition of the inter-beat-intervals, expressed in graphical form (s^2Hz^{-1}; Figure 1.6). From this, the fundamental derivatives can be extracted and used to quantify the relative autonomic contribution. In order to obtain indices that are independent of the total variation in the inter-beat-intervals, the LF and HF components are expressed as a percentage of the total power spectra. The ratio of LFC to HFC then provides an index of the relative strength of sympathetic and parasympathetic forces (larger values indicate relative sympathetic dominance).

By exploiting the link between the eye, the autonomic nervous system and heart rate variability, the aim is to provide a useful tool for the quantification of the autonomic response to visual stimuli based solely on analysis of the variability of the heart rate signal.

1.19 General summary

The influence of the autonomic nervous system on the oculomotor system has been researched extensively. However, most studies have centred on pharmacological manipulations of the ANS. It must be remembered that for both accommodative and cardiovascular behaviour, sympathetic and parasympathetic forces are known to interact in significant and convoluted ways (Gilmartin, 1986). Thus, when a pharmacological agent is used to block activity in one of the branches, the resulting behaviour may not reflect the true nature of the remaining branch. As Anisman (1975) proposed, excessive stimulation or inhibition of one system induces a compensatory antagonistic rebound in the complementary system thereby maintaining homeostasis. A non-invasive method, measuring both branches of the ANS simultaneously, removes this confounding variable. Furthermore, in removing completely an autonomic branch (e.g. sympathetic innervation of the ciliary muscle with the non-selective beta-antagonist, timolol maleate [0.5%]) previous studies have assumed that sympathetic inhibition of ocular accommodation is either present of absent in an individual; no measure of relative or graded sympathetic response response has been studied. Again, quantification of autonomic innervation via HRV may provide a more subtle index of ocular autonomic innervation.

The literature shows that further research is required into the autonomic mechanism governing the oculomotor response using online, real-time, recordings of heart rate and accommodation. In practical terms, with the understanding that behavioural and autonomic demands can influence dark focus (Tyrrell *et al.*, 1992; 1994; 2000), it is possible that these demands can influence visual performance in stressful conditions. For an aircraft pilot, the propensity to suffer stress is extremely high. Consequently, if ANS levels of pilots could be monitored, a system could be devised to inform the pilot that their stress/workload levels are too high which would otherwise lead to an attenuation of their visual performance.

Further research needs to be conducted into the impact cognition has on the ANS and accommodative response. Previous research has demonstrated that accommodative microfluctuations can be influenced by a variety of factors, for example: drug instillation (Owens *et al.*, 1991; Strang *et al.*, 1994) and target luminance (Gray *et al.*, 1993a,b). The effect of cognition, however, has not been explored fully.

1.20 Aims of the study

The main aim of this thesis is to investigate the eye-heart link. This will consist of examining various factors of both the oculomotor and cardiovascular systems using new measurement techniques and instrumentation for recording both the accommodative response and heart rate. Furthermore, the effect of spatiotopic (e.g. cognition) and retinotopic cues (e.g. retinal blur) on the two systems will also be investigated as measures of workload.

After reviewing the preceding literature, there is a variety of investigations that require further examination. The experiments are separated into main two areas:

1. Aspects of accommodation.
    - The effect of refractive error on the correlation of the accommodative stimulus-response function cross-over point with TA.
    - The influence of refractive error on the open-loop accommodation response.
    - The effect of refractive error on blur-driven accommodation.
    - Correlation of accommodative response, cardiovascular function and refractive error.
    - Correlation between accommodative microfluctuations and HRV.

2. Real-world applications.
    - Effect of cognition, workload and refractive error on accommodative microfluctuations and the autonomic nervous system.
    - Effect of varying the demand of a visually presented cognitive task on steady-state accommodative response.

CHAPTER 2

LABORATORY DESIGN

2.1 Introduction

The experimental chapters of the thesis involve the use of instrumentation to measure and automate the various experimental paradigms. As such, this chapter describes the methods employed and the instrumentation used to conduct these investigations. Details of additional bespoke hardware produced for the purpose of this thesis are also included.

2.2 Instrumentation for continuous accommodation measurement

An essential part of this thesis is the measurement of the ocular accommodative response; the recordings of which need to be objective, continuous, of high resolution, accurate and repeatable. Moreover, when quantifying accommodative microfluctuations, the apparatus employed needs to be sensitive to small oscillations in the accommodative response (Pugh and Winn, 1988). The instrumentation also has to facilitate measurement of visual stimuli in real-space to reduce proximal cues. Hitherto, the Canon R-1 infrared autorefractor was the instrument of choice (McBrien and Millodot, 1985; Abbott *et al.*, 1998; Baker and Gilmartin, 2002), however production of this system has ceased and new autorefractors have taken its place on the commercial market-place (Mallen *et al.*, 2001; Davies *et al.*, 2003).

An optometer is an instrument for measuring the refractive state of the eye (Millodot, 1997). Subjective optometers rely upon the subject's judgement and decisions of clarity or sharpness of the object of regard (e.g. the Hartinger optometer). Objective optometers contain an optical system that determines the vergence of light reflected off the subject's retina.

A study by the researchers Pugh and Winn (1988) suggested that for accurate accommodative recordings, an optometer should posses the following attributes:

- Be sensitive to modulations in the accommodative response levels to an order of magnitude less than the variability in the human response to a stationary distance target.

- Acquire accommodative measurements at an acquisition rate in excess of twice the Nyquist limit and have a uniform response up to ~10 Hz, as this range encompasses all frequencies of interest in dynamic accommodative studies (e.g. Owens *et al.*, 1991; Gray *et al.*, 1993a; Simmers *et al.*, 2001).
- Provide quick and efficient alignment while being operable under natural viewing conditions (i.e. open-view).
- Provide a method whereby variations in signal output due to misalignment are minimal (as described by Wolffsohn *et al.*, 2001b).

2.3 Evaluation of the Shin-Nippon NVision-K 5001

The importance of open-view autorefractors, both in general optometric practice and research, is well documented (McBrien and Millodot, 1985; Rubin and Harris, 1995; Mallen *et al.*, 2001). The Shin-Nippon NVision-K 5001 (also branded as the Grand Seiko WR-5100K) is a new infrared, open-view, objective autorefractor (Figure 2.1) with technical specifications similar to the Shin-Nippon SRW-5000 (Grand Seiko WV-500) fulfilling the criteria set by Pugh and Winn (1988). Previous studies have shown the SRW-5000 to be highly valid and repeatable in both adults (Mallen *et al.*, 2001) and children (Chat and Edwards, 2001) and the instrument has been converted to allow effective dynamic measurement of ocular accommodation (Wolffsohn *et al.*, 2001b). The lack of an internal fixation target or enclosed viewing reduces the risk of proximal accommodation and enables the observation of real world targets in a range of environments (Rosenfield and Ciuffreda, 1991; Hung *et al.*, 1996). Modification of the internal optics of the original SRW-5000 design provides the NVision-K with the additional facility of keratometry, but more attractively for this thesis the facility to measure through pupil sizes as small as 2.3 mm (compared to 2.9 mm with the SRW-5000). This study, therefore, extends that of Mallen *et al.* (2001) and evaluates validity and repeatability of both static refraction and central corneal radius of the instrument, to enable its use in this thesis.

2.3.1 The Shin-Nippon NVision-K 5001

The NVision-K comprises three measurement modes: both autorefraction and keratometry simultaneously; keratometry alone; and refraction alone. In the latter mode focus is achieved when the mires are thinnest. A focus detector enables precise focusing of the instrument in modes measuring corneal curvature. As with the SRW-5000 (Mallen *et al.*, 2001), refractive error is calculated in two stages. A ring target of infra-red light is imaged after reflection off the retina. Firstly, a lens is rapidly moved on a motorized track to place the ring approximately in focus. The image is then analysed digitally in multiple meridians to calculate the toroidal refractive prescription. For the latter stage the NVision-K substitutes the complete measurement ring used in the SRW-5000 with three arcs of infra-red light of a smaller radius of curvature, permitting refraction measurements to be taken with pupil sizes of 2.3 mm and greater. The distances between the ring segments are measured from the digital image to calculate the toroidal refractive prescription. The instrument can take up to 106 static prescription readings in 1 minute (less in modes measuring corneal curvature) in the range of ±22.00 D sphere, ±10.00 D cylinder in steps of 0.12 D for power and 1° for the cylindrical axis. Vertex distance allowance can be altered (to 0, 10, 12, 13.5 and 15 mm). The curvature of the cornea is calculated by image analysis of a ring of infrared light reflected off the cornea, with the diameter measured in three meridians separated by 60°. Keratometric parameters are expressed as a radius of curvature (range 5.0 to 10.0 mm) or corresponding refractive power (range: 33.75 to 67.50 D) in steps of 0.01 mm or 0.12/0.25 D for radius and 1° for the cylinder axis. Measurements can be made for inter-pupillary distances up to 85 mm.

A colour LCD monitor images the pupil to facilitate alignment of the instrument head with respect to the subject's visual axis, and displays refractive and keratometric data. A video port can provide output of the instrument display to a remote visual display unit. A built-in thermal printer provides hardcopy recording of clinical findings. An RS-232C port enables direct interfacing of the instrument to an IBM PC-AT compatible computer.

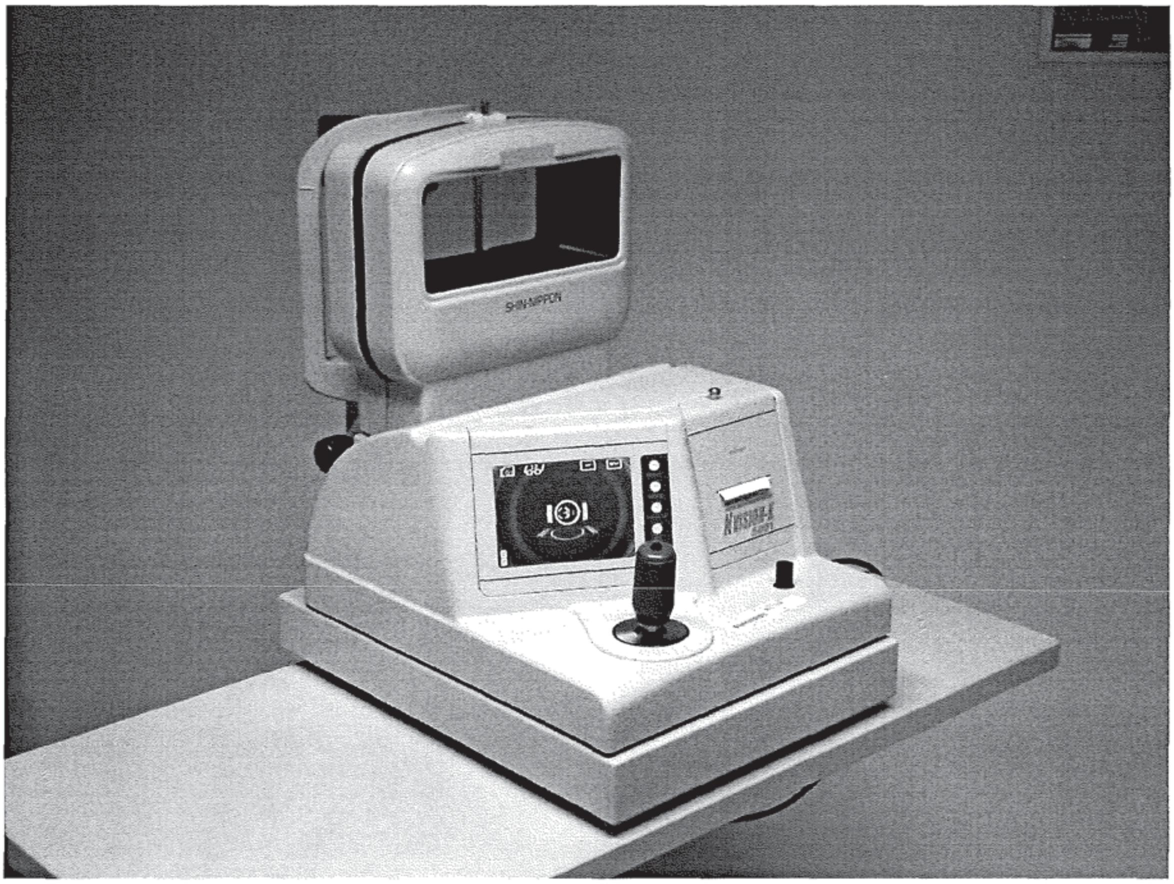

Figure 2.1 The Shin-Nippon NVision-K 5001.

2.3.1a Methods

Measurements of non-cycloplegic refractive error and corneal curvature were performed on 198 eyes of 99 staff and students of Aston University (36% of whom were male) after informed consent was given. As the difference between subjective refraction and autorefraction can alter with age (Joubert and Harris, 1995), subjects varied in age from 18 to 60 years (average 23.3 ± 7.4 years), although 82% of subjects were between 18 and 26 years.

All subjects had an orthodox, United Kingdom, routine distance (6 m) refraction performed on them by a qualified optometrist (EAHM) who was masked from the subjects' habitual prescription and the results of the autorefraction. Initially, distant interpupillary distance was measured. Retinoscopy was performed on all subjects followed by cross-cylinder to determine both the axis (in 2.5° increments) and power (in 0.25 D increments) of the cylinder component. Best sphere and binocular balancing were used to refine the spherical component of the prescription (in 0.25 D increments), adopting an endpoint criterion of maximum plus consistent with optimum visual acuity.

Keratometry was carried out on all subjects by a second United Kingdom qualified optometrist (LND), using a Javal-Schiotz keratometer, who was masked from the subjects' objective keratometry values. Readings of corneal radius (in 0.05 mm increments) and axis (in 2.5° increments) were taken for both horizontal and vertical meridians in each eye.

Autorefraction and keratometry was performed with the Shin-Nippon NVision-K 5001 autorefractor by the second optometrist (LND), who was masked from the subjects' habitual prescription. Subjects were positioned such that the eye under test viewed a distance letter target, so that the instrument was directly aligned with the visual axis of the eye. Subjects were asked to observe the smallest line of letters they could read binocularly without refractive correction or, if unaided visual acuity was below 6/60, to fixate a distant spotlight. Six consecutive autorefractor readings and six keratometry measurements were taken from each eye (the NVision-K internally computes the average keratometric reading and does not present the individual readings). The final autorefractor prescription was calculated from the average result (power in increments of 0.12 D, cylindrical component axis to 1°). Intra-session autorefraction repeatability was obtained by examining the differences between the six readings taken from each eye. Inter-session repeatability of autorefraction and keratometry measurements were calculated from the difference between the original results and the measures taken on all 198 eyes at a subsequent session, 7-14 days later. Measurement of the prescription and corneal curvature of both eyes took on average 2 minutes for each subject.

Statistical analysis

Prescriptions (in negative cylindrical form) and corneal curvatures were entered into a spreadsheet. The biases between measures (the mean difference, its standard deviation and 95% confidence intervals) were calculated as suggested by Bland and Altman (1986). Due to the inherent problems of analysing cylindrical components in their conventional form (Bullimore *et al.*, 1998), sphere, cylinder and axis were converted into a vector representation (Thibos *et al.*, 1997):

- a spherical lens of power MSE (equal to the mean spherical equivalent = sphere + [cylinder / 2])
- a Jackson cross-cylinder at axis 0° with power J_0 (= -[cylinder / 2] cos[2 x axis])
- a Jackson cross-cylinder at axis 45° with power J_{45} (= -[cylinder / 2] sin[2 x axis]).

Keratometry readings were compared along the horizontal and vertical meridians. Comparisons between measures were performed using a mixed-factor analysis of variance (ANOVA), treating the eyes of the same person as dependent variables.

2.3.1b Results

The refractive error of the sample, as represented by subjective refraction, ranged from -8.25 to +7.25 D mean spherical equivalent (mean = -1.85 ± 2.78 D). The maximum amount of astigmatism was -3.25 DC. The corneal curvature of the sample, as represented by Javal-Schiotz keratometry, ranged from 7.10 to 8.55 mm (mean = 7.70 ± 0.29 D). There was no significant difference in the mean refractive components (< 0.05 D) and corneal radii (< 0.02 mm) between the right and left eyes ($p > 0.05$).

Validity

Refractive error as measured by the NVision-K was found to be similar (MSE: difference, 0.14 ± 0.35 D; $F = 0.18$; $p = 0.67$; spherical component: difference, 0.18 ± 0.35 D; $F = 0.70$; $p = 0.60$) to that found by non-cycloplegic subjective refraction (Figure 2.2 and 2.3) over an extensive prescription range (–8.25 D to +7.25 D). No statistically significant difference was found between the eyes ($p > 0.05$). This was also the case with the cylindrical component (difference, -0.08 ± 0.34 D; $F = 1.07$; $p = 0.30$, Figure 2.4). Conversely, the mean autorefractor cylindrical vectors were slightly more negative (J_0 by -0.10 ± 0.16 D; $p < 0.05$; J_{45} by -0.04 ± 0.11 D; $p < 0.01$) than the subjective refraction (Figure 2.5), with a statistically significant difference between eyes ($p < 0.05$). Approximately 50% of autorefractor measures were within ±0.25 D and 85% within ±0.50 D of the spherical component of the prescription found by subjective refraction (Figure 2.3). Fifty-nine percent of autorefractor measures were within ±0.25 D and 89% within ±0.50 D of the cylindrical component of the prescription found by subjective refraction. The axis of the cylindrical component was less reliable than the spherical and cylindrical components, improving with cylinders ≥0.75 DC (see Table 2.1).

Keratometry as measured by the NVision-K was similar (horizontal: difference, 0.02 ± 0.09 mm; $F = 0.34$; $p = 0.56$; vertical: difference, 0.01 ± 0.14 mm; $F = 0.02$; $p = 0.88$) to that found by Javal-Schiotz keratometry. Figure 2.6 illustrates the difference in the horizontal and vertical corneal radius between Javal-Schiotz and NVision-K readings compared with the mean.

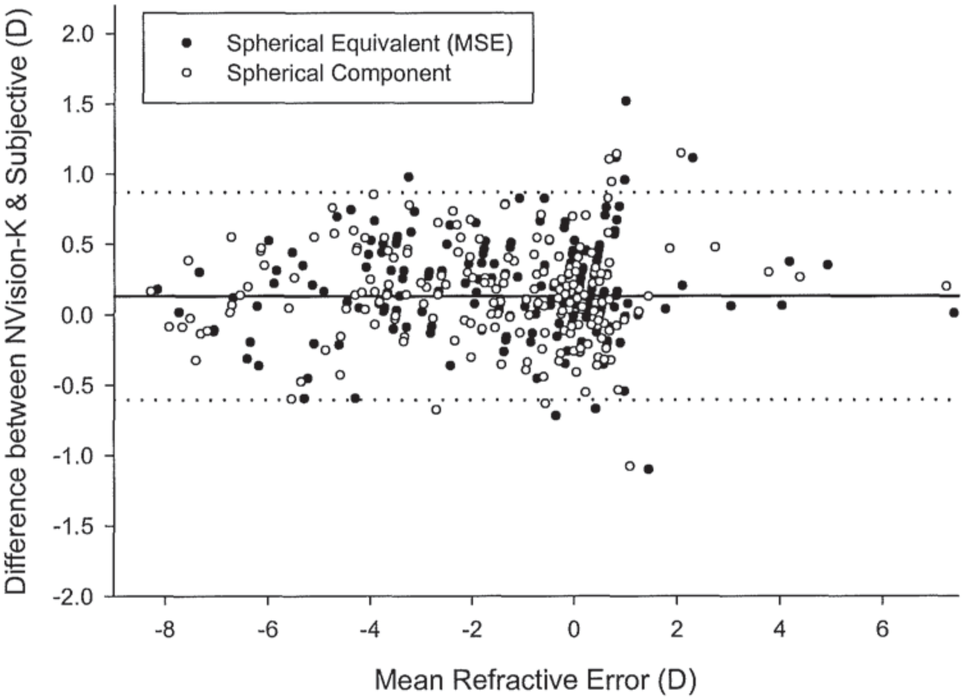

Figure 2.2 Difference between the results found by autorefraction and subjective refraction plotted against their mean for mean spherical equivalent and spherical component (N = 198 eyes). The solid line represents the mean bias, whereas the dotted lines represent the 95% confidence limits.

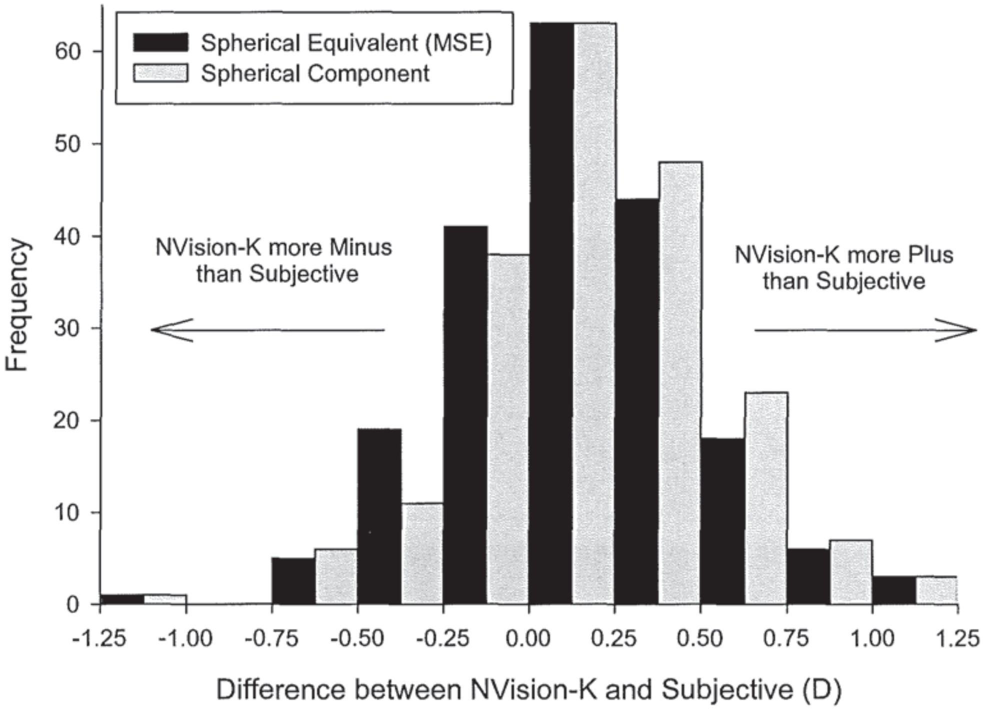

Figure 2.3 Comparison of the frequency of difference between the objective and subjective refraction techniques (N = 198 eyes).

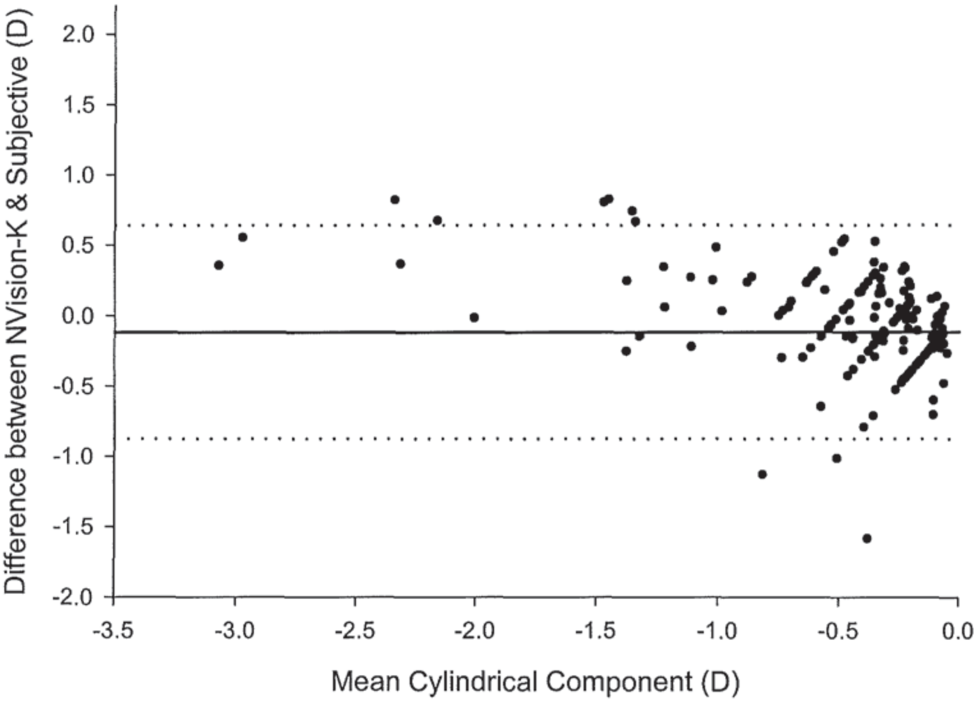

Figure 2.4 Difference in the cylindrical component between the NVision-K and subjective refraction compared with the mean (N = 198 eyes). The solid line represents the mean bias, whereas the dotted lines represent the 95% confidence limits.

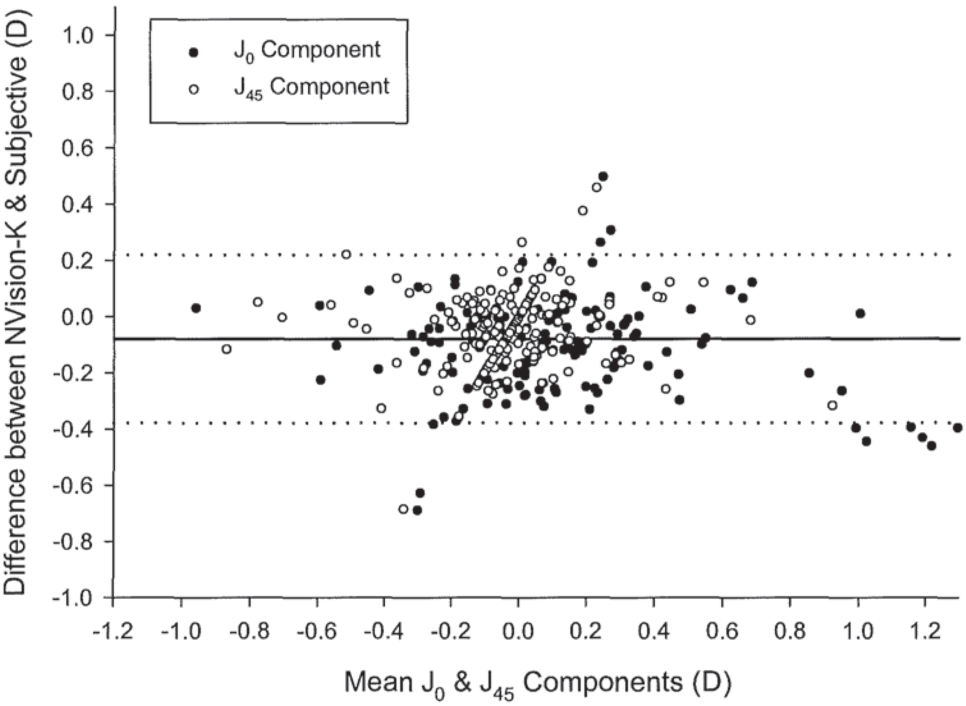

Figure 2.5 Difference in the vectors J_0 and J_{45} between the NVision-K and subjective refraction compared with the mean (N = 198). The solid line represents the mean bias of the J_0 component , whereas the dotted lines represent the 95% confidence limits. Bias and 95% limits of the J_{45} component were similar.

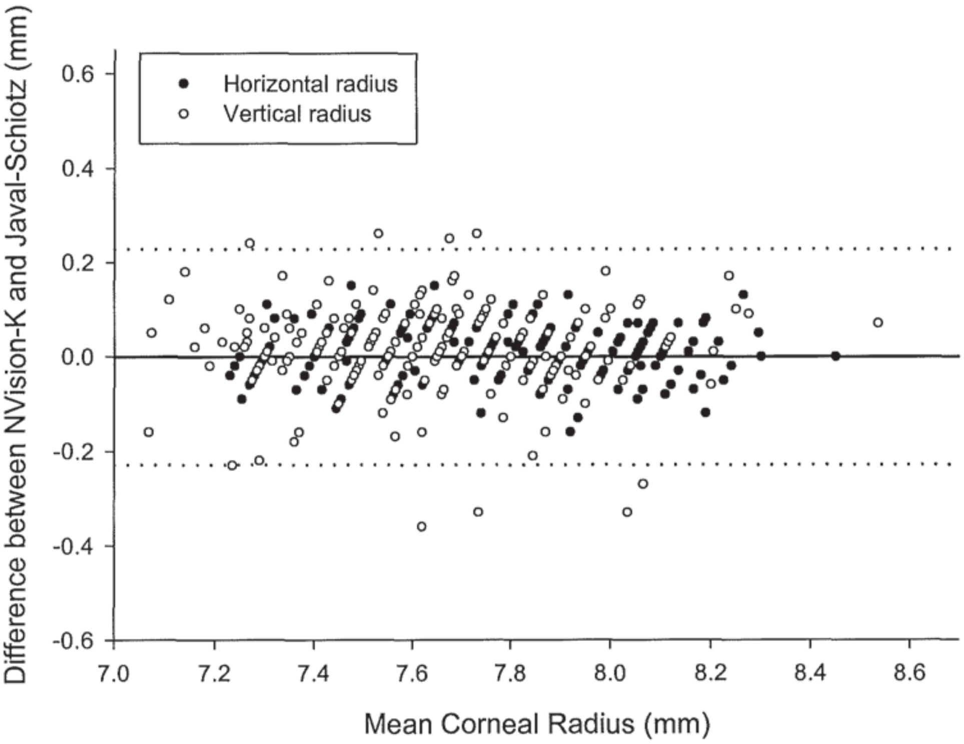

Figure 2.6 Difference in the corneal radius (horizontal and vertical) between the NVision-K and Javal-Schiotz keratometry compared with the mean (N = 198 eyes). The mean bias for the vertical meridian is indicated by the solid line, and the 95% confidence limits are shown by the dotted lines. Mean bias was similar in both meridians; however, 95% confidence limits were less in the horizontal meridian.

VARIATION IN CYLINDER AXIS	ALL PRESCRIPTIONS WITH A CYLINDRICAL COMPONENT N = 148	PRESCRIPTIONS WITH A CYLINDRICAL COMPONENT (SUBJECTIVE) ≥ 0.75 DC N = 52
± 5°	41 (28%)	22 (42%)
± 10°	72 (49%)	37 (71%)
± 15°	93 (63%)	49 (94%)
± 20°	105 (71%)	52 (100%)

Table 2.1 Comparison of the axis of the cylindrical component measured by the NVision-K autorefractor and by subjective refraction.

Repeatability

Repeatability of an autorefractor can be examined in two ways. Firstly, the variability between the six repeated readings taken on each subject in one session can be determined by observing the standard deviation of the results (Bullimore *et al.*, 1998). The average intra-session repeatability (average of six initial autorefractor readings) was 0.11 D for the spherical component, 0.13 D for the cylindrical component, 0.09 D for the mean spherical equivalent, 0.07 D for the J_0 vector and 0.06 D for the J_{45} component of the prescription.

Secondly, and perhaps more importantly, the difference in prescription found at different sessions can be examined. Table 2.2 presents the mean difference, standard deviation of the difference and the 95% confidence intervals between the prescription components. The inter-session repeatability was found to be small, with approximately 95% of second visit prescription findings within ± 0.50 D of the initial visit measurement. Inter-session repeatability for keratometric parameters was also found to be small with approximately 95% of second visit measures being within ± 0.10 mm for the horizontal (mean difference 0.00 ± 0.09 mm, p = 0.70) and ± 0.15 mm for the vertical (mean difference – 0.01 ± 0.15 mm, p = 0.37) meridian. Observation of graphical data revealed no bias in repeatability with the magnitude of the corneal curvature or refractive error.

	SPHERE	**CYLINDER**	**MSE**	**J_0**	**J_{45}**
MEAN DIFFERENCE	0.04	-0.02	0.03	-0.02	0.00
SD OF DIFFERENCE	0.24	0.32	0.32	0.27	0.11
95% LIMITS OF AGREEMENT	± 0.47	± 0.63	± 0.63	± 0.53	± 0.22
% WITHIN ± 0.25 D	78	80	78	-	-
% WITHIN ± 0.50 D	97	96	96	-	-
% WITHIN ± 1.00 D	100	99	97	-	-

Table 2.2 Difference in refractive components of the final NVision-K autorefractor prescription between different sessions (inter-session repeatability).

2.3.1c Conclusion

The Shin-Nippon NVision-K follows the increasing trend of optometric instrumentation in its use of reflected image analysis to measure the refractive state and corneal curvature of the eye (Wolffsohn *et al.*, 2002). The advent of the Shin-Nippon NVision-K 5001 expands the functionality of the SRW-5000 to enable both autorefraction and keratometry to be recorded by a single instrument. The modification of the internal optics to three, smaller radius, ring segments rather than a measurement ring has not reduced accuracy or repeatability and enables subjects with smaller pupils to be assessed. The results of the study show that the Shin-Nippon NVision-K 5001 is comparable to autorefractors currently available (Chat and Edwards, 2001; Mallen *et al.*, 2001), in that it is quick, accurate and repeatable.

The appropriateness of comparing autorefractors against subjective refraction has however been questioned (McCaghrey and Matthews, 1993). French and Jennings (1974) suggested that conventional refraction could be prone to errors. As non-cycloplegic subjective refraction is generally accepted by optometrists for adult prescribing, it provides the standard reference for autorefraction measurements and this methodology has been widely accepted by previous authors in autorefraction validation studies (Wood *et al.*, 1984; McBrien and Millodot, 1985; Reeves *et al.*, 1992; Rosenfield and Chiu, 1995; Elliott *et al.*, 1997; Bullimore *et al.*, 1998; Chat and Edwards, 2001; Mallen et al., 2001).

The results show that the mean refractive error was within 0.25 D of that found by subjective refraction in 51% of all eyes, the spherical component in 50% and the cylindrical component in 59% of eyes examined. These figures compare well will the recent validation of the Shin-Nippon SRW-5000 (Mallen *et al.*, 2001), the Hoya AR-570 (Bullimore *et al.*, 1998), the Nikon NRK-8000 and Nidek AR-1000 (Elliott *et al.*, 1997) and the Canon R-1 autorefractor (McBrien and Millodot, 1985).

Whereas variation in the keratometric parameters was small, they appeared to be greatest in the vertical meridian. Cronje and Harris (1997) found that diurnal variations in keratometric measurements differed between individuals and variation in corneal curvature tended to be greatest in or near the vertical meridian of the eye. This phenomenon was attributed to transient changes in the tear layer or the interaction of the lids on blinking.

Thus, the NVision-K was found to be both accurate and repeatable, enabling its use for research purposes (Davies *et al.*, 2003).

2.4 Attempted conversion to continuous recording of accommodation

As stated earlier, it was the author's intention to use the newly available Shin-Nippon NVision-K 5001 for the continuous measurement of ocular accommodation. On connection of the video output of the NVision-K in a similar manner to the conversion of the SRW-5000, however, it was noted that this was connected to the keratometer CCD (Charged Coupled Device) camera rather than the autorefractor CCD. Direct contact with Shin-Nippon in Japan gave directions to gain the output of the autorefractor CCD by removing the back of the instrument and redirecting the internal wiring (Figure 2.7), however this change removed the static measurement facility of the instrument. Shin-Nippon could not be convinced to make a modified fully functioning version of the instrument and therefore it was decided to rely on the previous converted dynamically recording Shin-Nippon SRW-5000 for the thesis (Chat and Edwards, 2001; Mallen *et al.*, 2001; Wolffsohn *et al.*, 2001b).

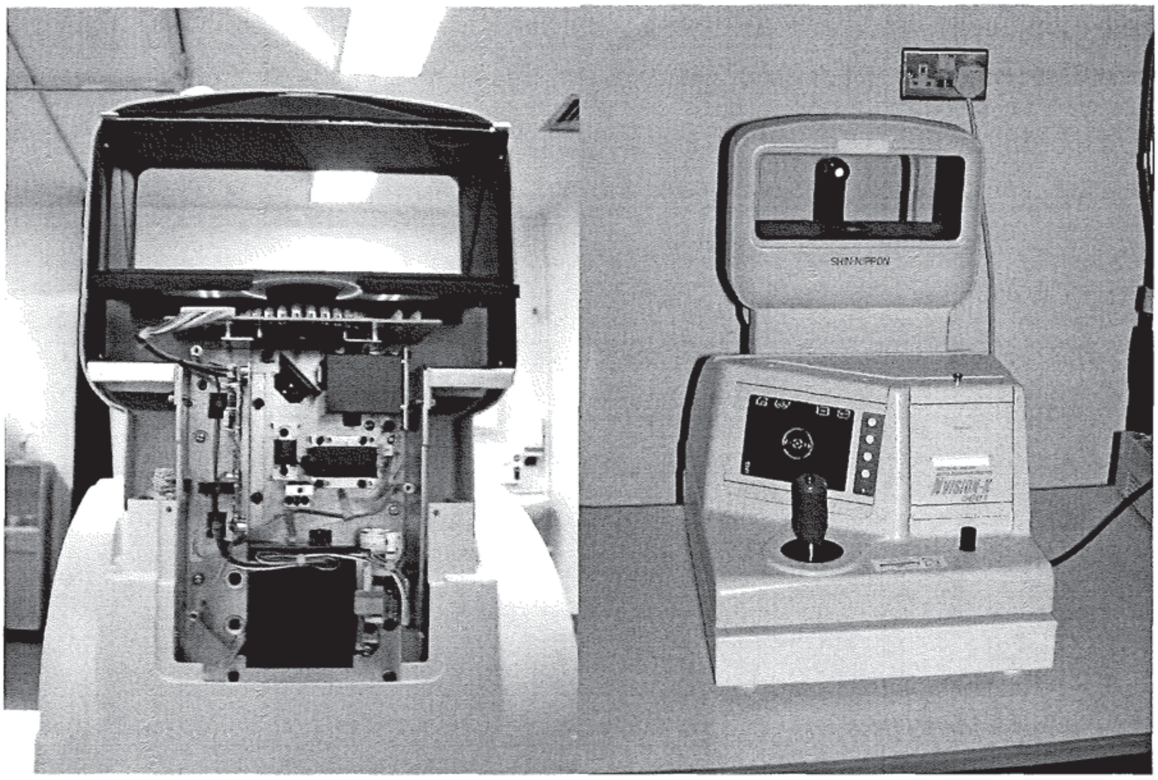

Figure 2.7 Internal circuitry of the Shin-Nippon NVision-K 5001.

2.5 Performance of the SRW-5000

In order to assess the performance and noise level of an optometer, an optically inert model eye is required. Model eyes have been used in previous investigations (Culhane, 1999; Wolffsohn *et al.*, 2001b) to evaluate both static and continuous measurements. A model eye is provided with the SRW-5000 to calibrate the instrument periodically. This was utilised to appraise the steady-state performance of the instrument in continuous mode using the data acquisition software.

A model eye was mounted on the head rest assembly of the SRW-5000 autorefractor to facilitate the measurement of the signal produced by the instrument. The continuous noise level of the optometer was assessed by recording the output of the optometer over 10 consecutive 17.07 second recordings at an acquisition rate of 60 Hz, thus providing 1024 data points per epoch for *post-hoc* fast Fourier analysis. Mean root mean square values were 0.009 D. Moreover, spectral decomposition of the model eye signal produced no significant frequency in the power spectrum (Figure 2.8). As such, the dynamic properties of the SRW-5000 were considered acceptable for measurement of accommodation microfluctuations.

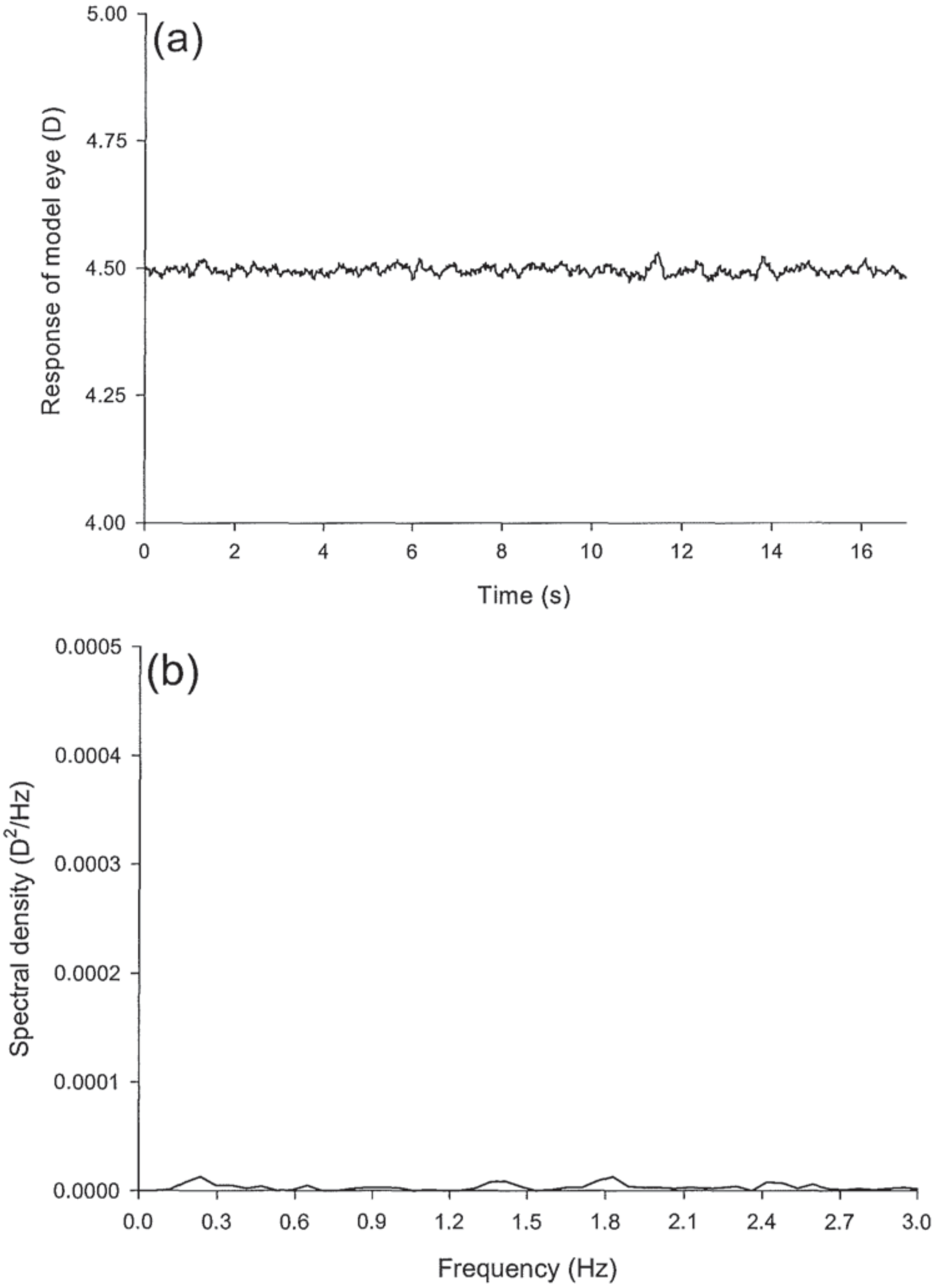

Figure 2.8 (a) Shin-Nippon SRW-5000 continuous recording output from model eye. (b) Spectral profile of noise signal.

2.6 Stimulus presentation

Throughout the thesis, reference is made towards a method of altering the subject's accommodative demand, the Badal stimulus optometer, the principle of which was first described by the French ophthalmologist Badal in 1876 (cited by Bennett and Rabbetts, 1998). The main advantages of this system are that its power scale is uniform, and the object of regard retains a constant image size and luminance irrespective of the dioptric power.

When a positive lens is placed before the eye so that the posterior focal point of the lens coincides with the entrance pupil of the eye, the image of an object on the anterior optical axis of the lens retains the same angular size, regardless of the distance of the object. Furthermore, small displacements of the object cause the image to move over a large distance (Bennett and Rabbetts, 1998). Figure 2.9 outlines the principle of the Badal optometer used in the subsequent studies of this thesis.

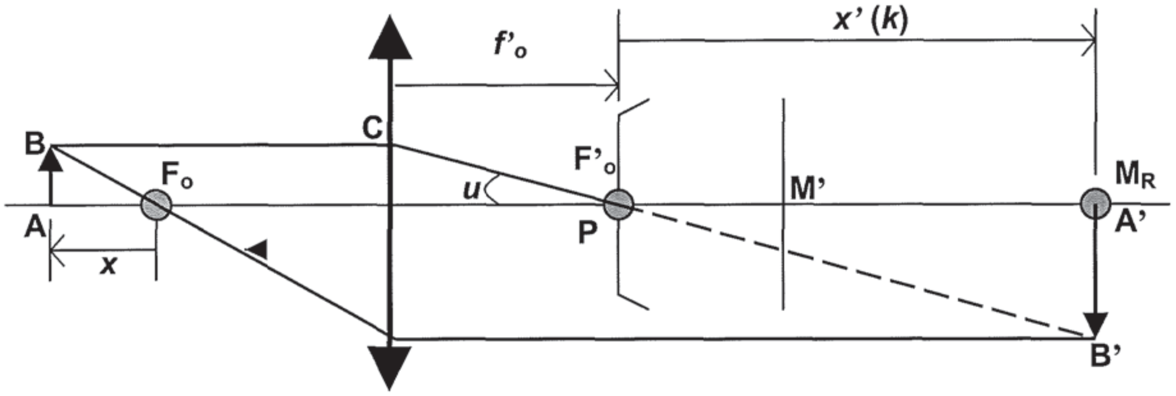

Figure 2.9 Principle of the Badal optometer (based on schematic diagram from Bennett and Rabbetts, 1998).

x is the distance of the object AB from the first principle focus (F_o) of the optometer lens, *x'* is the distance of the image A'B' from the second principle focus (F'_o) of the optometer lens and f'_o is the second principle focal length of the optometer lens. Thus, from Newton's equation:

$$xx' = -f_o'^2$$

so that

$$x = \frac{-f_o'^2}{x'}.$$

In order to be seen clearly without accommodation, the object AB must be positioned so that its image lies in the far-point plane of the subject's eye. Consequently,

$$x' = \mathrm{PM_R} = k$$

and

$$x = \frac{-f_o'^2}{k} = \frac{-1000\mathrm{K}}{F_o^2}\,\mathrm{mm}.$$

As the image of AB lies on the ray path CF'$_o$ (or CP), the image of the object of regard AB will subtend a constant angle (u) at the eye's principle point (Bennett and Rabbetts, 1998). Figure 2.10 illustrates the actual Badal optometer utilised in the thesis.

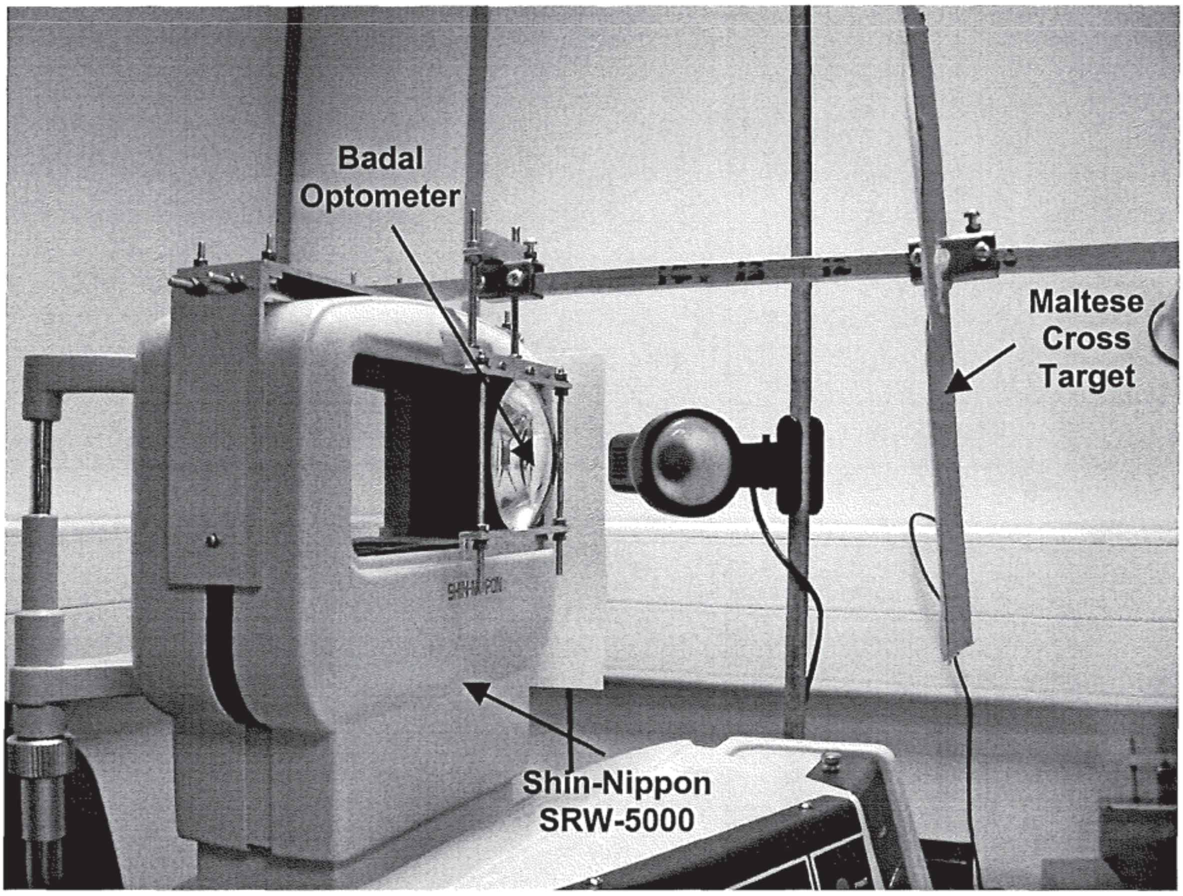

Figure 2.10 Badal optics and Maltese cross target attached to Shin-Nippon SRW-5000.

2.7 Open-loop accommodation measures: Difference of Gaussian (DoG) target

The difference of Gaussian target has been described previously in section 1.7.2 d. A DoG target with a special frequency of 0.1 cdeg^{-1} has been shown to be a non-accommodative stimulus (Kotulak and Schor, 1987). For the purpose of this study, a 0.1 cdeg^{-1} DoG target was produced on photographic paper. In order to ensure no textural imperfections in the photograph were visible to the subject, +0.50 D of myopic blur was induced within the Badal optical system.

To confirm that the DoG target was indeed opening the accommodation loop, the accommodative responses of 15 subjects aged 18 to 21 years (mean ± SD: 19.5 ± 0.8 years) were measured using the Shin-Nippon SRW-5000 in static mode (average of 5 individual measures [MSE]) by increasing the accommodative demand from 0.0 D to 4.0 D in 1.0 D steps. The results were compared to those with the subjects viewing a high contrast Maltese cross as an accommodative target under the same conditions. The data illustrated that the DoG target did open the accommodative loop (see Appendix 1). As such, and in accordance with previous studies (Kotulak and Schor, 1987; Tseuetaki and Schor, 1987; Rosner and Rosner, 1990; Baker, 2000; Mallen, 2002) the DoG target was selected for open-loop accommodation measures.

2.8 Pulse transducer

In order to quantify cardiovascular function (and thus autonomic response) to various visual environments, the heart rate of the subject is recorded. From this data, the inter-beat interval (IBI) provides a measure of the subjects' heart rate variability (HRV) and an approximation of the relative contributions of the sympathetic and parasympathetic nervous systems. Previous investigations have utilised the electrocardiogram (EKG) and extracted the IBI interval from this (Akselrod *et al.*, 1981; Bernardi *et al.*, 2000; Tyrrell *et al.*, 2000). However, this method is rather cumbersome and protracted when used for this purpose. A simpler, more versatile device capable of recording the pulse rate enabled greater flexibility in the experimental design.

To fulfil this remit, a piezo-electric finger pulse transducer was used. The device is a small circular pad, which is strapped to the index finger of the subject. Figure 2.11 illustrates the transducer set-up (note that the Shin-Nippon has been removed to show in more detail how the cardiovascular equipment was arranged). Once attached, the transducer produces a small voltage (~50 mV) on every heartbeat.

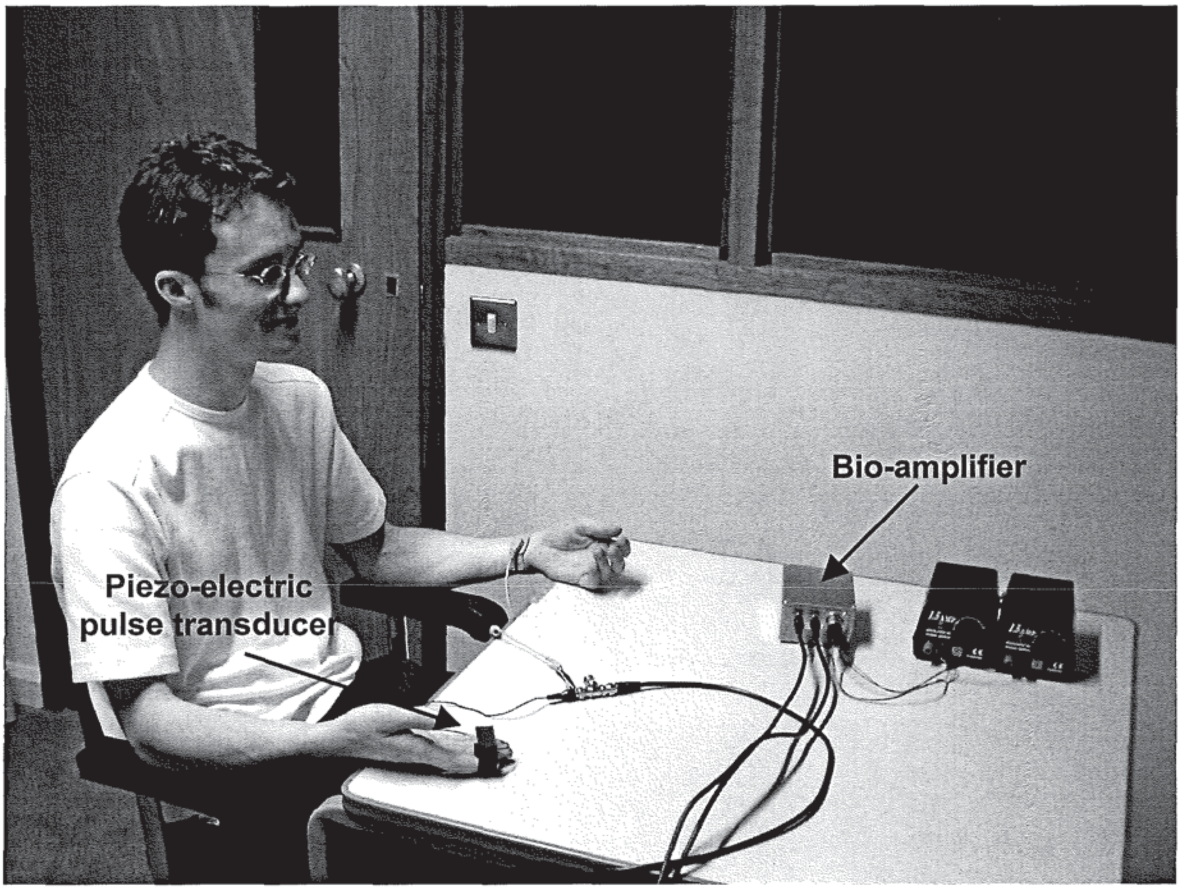

Figure 2.11 Piezo-electric finger pulse transducer with bio-amplifier.

2.9 Bio-amplifier

The voltage produced by the piezo-electric finger pulse transducer is small (~50 mV). The BNC 2090 I/O board is capable of reading signals between ± 0.5 V and ± 10 V. As such, a device was required to amplify the signal from the transducer (to approximately 6 V) prior to data acquisition with the *LabView* National Instruments hardware (National Instruments, Austin, Texas, USA). A bio-amplifier was designed and manufactured (see Figure 2.11). This apparatus acted as a link between the pulse transducer, the National Instruments PCI 6024E card and the BNC 2090 16 channel I/O device. The bio-amplifier was based on LM324 bipolar operational amplifiers, following the circuit diagram in Figure 2.12.

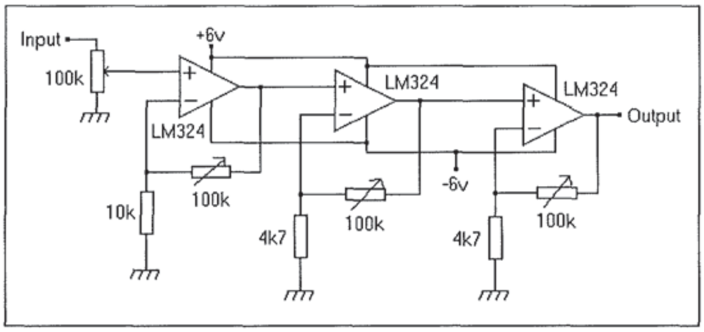

Figure 2.12 Circuit diagram for the pulse transducer bio-amplifier (after Mallen, 2002).

2.10 Schmitt trigger

The study described in Chapter 7 required the subjects to respond to a visually presented two-alternative forced choice cognitive task. Consequently, a response trigger was manufactured. This comprised a 4093 CMOS (Complementary Metal Oxide Semiconductor) logic gate, which acted as a Schmitt trigger. The benefit of the Schmitt trigger was that it removed any noise pre- and post-switch activation (thus preventing false positive results caused by switch noise). The device, held by the subjects, was connected to the PCI 6024E card via the BNC 2029 16 channel I/O board. Subjects responded to the task by pressing a small button on the device.

2.11 Data acquisition and analysis

In order to facilitate the acquisition and analysis of the oculomotor and cardiovascular response, various novel hard- and software devices were required, centred on the National Instruments *LabView* system (National Instruments, Austin, Texas, USA).

2.11.1 Hardware

LabView is a measurement and automation system devised for use in scientific and industrial laboratories. The system is capable of operating both within the Microsoft Windows and Macintosh environments. This study used an Intel Pentium III, 800 MHz processor personal computer (PC), with *Microsoft Windows XP* operating system. Additional National instruments boards inserted into the motherboard of the PC consisted of:

- A PCI 1408 video input board allowing capture and analysis of video signals. This device was used to capture the video output signal from the Shin-Nippon SRW-5000 for continuous recording of the accommodative response.
- A PCI 6024E card connected to a BNC 2029 16 channel Input/Output (I/O) device via a multi-way cable. The function of these appliances was to monitor the signal produced by the finger pulse transducer and the response produced by the Schmitt trigger in Chapter 7.

2.11.2 Software

The *LabView* system is programmed via an intuitive 'block-and-wire' diagram approach. This is assembled on the diagram window of the program with displays, tools and controls viewed on a separate control window. In order to capture oculomotor and cardiovascular data, a computer measurement and automation program was devised capable of recording the accommodative response (via threshold image analysis using the Shin-Nippon SRW-5000; Wolffsohn *et al.*, 2001b) and heart rate (using a piezo-electric finger pulse transducer) concurrently (see Chapter 5). The *LabView* program recorded both variables simultaneously and continuously.

Accommodation and pulse were sampled at a frequency of 60 Hz (giving 1024 data points in a 17.07 second accommodation recording), which is well above the Nyquist frequency. The Nyquist frequency is twice the highest frequency of interest in the signal. In the case of accommodation, this highest frequency should not normally exceed 2-2.5 Hz (Pugh *et al.*, 1987), while HRV frequencies reach ~0.4 Hz (Task Force, 1996). Once all data were collated, an additional *LabView* program computed an FFT power spectrum for both accommodative microfluctuations and HRV.

A Fast Fourier Transformation (FFT) was employed to analyse the cyclic changes in the acquired signal (accommodation, pulse and IBI interval). The resultant power spectrum gives the square of the amplitude of the cyclic changes versus their temporal frequency (s^2Hz^{-1} or D^2Hz^{-1}). A Hamming window was applied to the power spectrum analysis as suggested by Collins *et al.* (1995). The temporal resolution of the power spectrum is a function of the sampling time ($1/t$). Consequently, with a 10 second accommodation sample, the temporal resolution is 0.1 Hz (each frequency bin 0.1 Hz wide). A full explanation of power spectral analysis in the study of ocular mechanisms is given in Pugh *et al.* (1987).

2.11.3 Data coding

In an attempt to limit the confounding variable of bias in the interpretation of the accommodation and cardiovascular results, an alphabetical coding system was devised for each subject and each experimental condition. Following acquisition, data were exported to a *Microsoft Excel* file and saved under a specific code. This code was unique to each trial and, taken alone, meaningless. A key was created for the code and kept secret until data analysis had been completed. At this stage, the code was broken to reveal the accommodative/cognitive states pertinent to each trial and the refractive group of the subject.

Acknowledgements

Thanks must go to Dr. Edward Mallen for his collaboration and advice in the manufacture of many of the electrical components described in this Chapter, and Dr. Tim Meese for the production of the DoG target. Electronic components were supplied by CPC Ltd, Preston, Lancashire, UK.

Supporting publication

Davies, L. N., Mallen, E. A. H., Wolffsohn, J. S. and Gilmartin, B. (2003). Clinical evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR-5100K autorefractor. *Optometry and Vision Science* **80**, 320-324.

CHAPTER 3

ACCOMMODATIVE RESPONSES TO CHANGES IN RETINOTOPIC STIMULI

3.1 Introduction

The importance of environmental factors in the development of refractive error is unquestionable (Rosenfield and Gilmartin, 1998; Goldschmidt, 2003; Wolffsohn *et al.*, 2003a; Edwards and Lam, 2004). Now, more than ever, the role of near visual tasks (for example VDUs) in the development of myopia (particularly late-onset myopia [LOM]) is a topic for debate (Gray *et al.*, 2000; Ciuffreda and Lee, 2002; Vera-Diaz *et al.*, 2002; Wolffsohn *et al.*, 2003b; Ting *et al.*, 2004). For example, the link between academic achievement and myopia is established (Sperduto *et al.*, 1983). A classic example of this kind of environmental factor comes from the study of genetically homogeneous groups (i.e. Eskimo populations). Here, the prevalence of myopia increased significantly when formal education was introduced (Young *et al.*, 1969; Johnson *et al.*, 1979). This link between education/non-urban lifestyle and myopia has also been studied within other ethnic groups (Garner *et al.*, 1999; Jimenez *et al.*, 2004).

Image deprivation and thus reduced retinal image quality, has also been shown in a range of species (including man) to modify eye growth and produce myopic shifts (Wiesel and Raviola, 1977; Wallman *et al.*, 1978). As such, eye growth can be modulated by variations in retinal blur. Clearly, if increasing levels of nearwork are a factor in myopia development (Rosenfield, 1998), then the control of retinal blur by the ocular accommodation system is a fundamental factor in the aetiology of myopia together with refractive status and target viewing distance. Indeed, Flitcroft (1998) published a mathematical model of accommodation showing the effects of a variety of variables on the development of myopia. Reduced accommodative ability, with increasing amounts of nearwork, led to an increase in the amount of myopia. Moreover, Charman (1999) concluded that if the slope of the stimulus-response curve is low, as may be the case in emmetropes who are approaching myopia, the associated high levels of defocus blur at near may lead to a degraded retinal image and that a myopic shift is induced as a type of recalibration response.

The range of accommodation responses to naturally occurring closed-loop stimuli in young eyes is best represented by the well-documented accommodative stimulus-response curve (Figure 1.3; Charman, 1982; Gilmartin, 1998). The components of this curve consist of an initial non-linear region produced by a relative lead in the accommodative response for distant viewing, a pseudo-linear region, and a saturation region resulting in a relative lag of accommodation for high accommodative demand stimuli. The accommodation response has been investigated under a variety of experimental conditions between refractive groups (e.g. Jiang, 1994, 1995; Abbott *et al.*, 1998). Notwithstanding the variety of methodological approaches, the majority of studies have found a greater accommodative lag in myopic subject groups compared to emmetropes which, in turn, has been proposed as a possible risk factor that may contribute to nearwork-induced myopia (Jiang, 1995; Rosenfield and Gilmartin, 1998; Charman, 1999).

The accommodation stimulus-response function describes quantitatively the relationship between the stimulus to accommodation and the resultant steady-state response over a range of stimulus values (Rosenfield *et al.*, 1993; Charman, 1982). A point of debate has centred on the cross-over point of the function (the point at which the accommodative response intersects the unity ratio line). Here, the stimulus to accommodation and its response are equal in magnitude and may be modulated by retinotopic and autonomic factors (Charman, 1982). Some studies have proposed that this point is equal in magnitude to the level of tonic accommodation (TA; Johnson, 1976; Charman, 1982; Owens, 1984; Mordi *et al.*, 1986; Ramsdale and Charman, 1989). The principle being that at the point of intersection there is no stimulus to drive accommodation; therefore, the system assumes a resting state – tonic accommodation. There is, however, evidence to contradict this hypothesis (Owens, 1979; Ciuffreda *et al.*, 1984; Tan and O'Leary, 1988; Ong *et al.*, 1993; Rosenfield *et al.*, 1993). All studies, however, use relatively small subject groups (between 4 and 20 subjects), furthermore, little consideration is given to the effect refractive error may play in modulating the correlation between the two factors.

The aim of this study was, therefore, to examine the open- and closed-loop steady-state accommodative response to a variety of stimulus conditions in a large sample of hypermetropes (HYP), emmetropes (EMM), early- (EOM) and late-onset myopes (LOM). Furthermore, the relationship of the stimulus-response cross-over point with the level of TA was investigated between refractive groups.

3.2 Methods

3.2.1 Subjects

The cohort consisted of 60 subjects (29 male; 31 female) varying in age from 18 to 33 years (average: 20.3 ± 2.9 years). Fifteen subjects were hypermetropes (HYP; mean spherical equivalent [MSE]: +0.86 ± 0.34 D; range: +0.51 to +1.82 D), 15 subjects were emmetropes (EMM: MSE: 0.00 ± 0.24 D; range: -0.37 to +0.37 D), 15 subjects were early-onset myopes (EOM: MSE: -3.93 ± 2.28 D; range: -7.12 to -1.25 D), and 15 were late-onset myopes (LOM: MSE: -1.92 ± 1.52 D; range: -5.50 to -0.56 D). Subjects were considered LOMs when myopia onset was ≥ 15 years of age (Goss and Winkler, 1983; Edwards, 1998). The mean age of onset for the EOMs was 10.3 ± 2.8 years (range: 6 to 14 years) and 16.7 ± 0.7 years (range: 16 to 18 years) for the LOMs.

To ensure that the accommodative demand was virtually identical for each subject, all were corrected with soft contact lenses (2-hydroxyethyl methacrylate [HEMA] lenses, 58% water content; Acuvue Dailies, Vistakon, Johnson & Johnson Vision Care, Jacksonville, Florida, USA). All subjects achieved 0.00 logMAR visual acuity or better and uncorrected astigmatism was limited to ≤ 0.50 DC. None of the subjects reported any form of visual anomaly. All subjects had practice in remaining still and maintaining steady fixation in order to limit artefacts in the accommodative data. Subjects were provided with a full explanation of the experimental protocol and gave prior written consent before commencing the investigation. The research followed the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee (Appendix 2). Copies of the information sheets and consent forms given to subjects can be found in Appendix 3.

3.2.2 Procedure

Subjects viewed monocularly a stationary high contrast (90%) Maltese cross (angular subtense: 10°; luminance: 37.0 cdm^{-2}) through a +5.0 D Badal optometer. Five 20 second continuous objective recordings of the accommodative response (sampled at 60 Hz) measured with the open-view Shin-Nippon SRW-5000 infra-red autorefractor (Ryusyo Industrial Co. Ltd, Osaka, Japan) were obtained for accommodative levels of 0.0 D to 4.0 D in 1.0 D steps, presented in random order. In addition, a photographic 0.1 $cdeg^{-1}$ Difference-of-Gaussian (DoG) target was used in the place of the Maltese cross to open the accommodative loop for tonic accommodation to be measured. Subjects were required to observe the DoG target for 5 minutes prior to data collection, thus allowing the effects of any previous nearwork to dissipate (Krumholz *et al.*, 1986). Subjects were instructed to observe the target, rather than actively focus to avoid erroneous accommodation responses under the open-loop conditions (Stark and Atchison, 1994).

On commencement, the optical axis of the SRW-5000 was aligned with the subject's right eye, with the left eye occluded. The Shin-Nippon SRW-5000 infrared autorefractor was specially modified to record accommodative response continuously with a resolution of < 0.01 D and a temporal resolution of 60 Hz. Data acquisition and analysis were performed using the *LabView* software package (National Instruments, Austin, Texas, USA; Wolffsohn *et al.*, 2001b). Any blink within the continuous sampling time causes an abrupt change in signal amplitude (Collins *et al.*, 1995). Removal of these blink artefacts was performed by removing data greater than ± 2.0 D from the stimulus level (Wolffsohn *et al.*, 2003a).

The accommodative response was quantified by calculating both the gradient of the stimulus-response curve and the accommodative error index (*I*) as the validity of the regression slope has been questioned when quantifying the accuracy of the accommodative response (Chauhan and Charman, 1995). Fundamentally, *I* gives a measure of the area between the best fit curve and the unit ratio line. The unit response can be described by the equation $y = x$, and the best fit line of the stimulus-response function line by $y = mx + c$, where m is the slope and c is the intercept on the y-axis. The area (E) between the two lines is weighted for the interval of x (i.e. x_1 to x_2) therefore,

$$E = \left|(1-m)\left(\frac{x_2 + x_1}{2}\right) - c\right|$$

and

$$I = \frac{E}{r^2}$$

It must be noted, however, that using the single figure accommodation index leads to a loss in some of the information derived from the accommodative stimulus-response function. The index can only be applied to the region of the stimulus-response curve where the response can be considered linear in nature (Chauhan and Charman, 1995) as such, the area between 2.0 D (x_1) and 4.0 D (x_2) was used.

The equations presented above are true if the regression line does not intersect the unit ratio line. In this case, two triangular areas (E_A and E_B) are created either side of the unit ratio line. As such, the area of each triangle must be calculated using the following equations:

$$E_A = \left|(1-m)\left(\frac{x_1 + x_c}{2}\right) - c\right|$$

and

$$E_B = \left|(1-m)\left(\frac{x_2 + x_c}{2}\right) - c\right|$$

where x_c is the co-ordinate of the point where the two lines cross. A comprehensive description of the methodology behind the aforementioned formulae is given elsewhere (Chauhan and Charman, 1995).

3.2.3 Data and statistical analysis

Data analysis was performed with *Microsoft Excel*, SigmaPlot 2000 (version 6.0; Systat Software UK Ltd, London, UK) and SPSS for Windows (version 11.5; SPSS Inc., Chicago IL, USA). Data were treated with a two-way (vergence and refractive error) mixed ANOVA where vergence was taken as a within-subject variable and refractive error as the between-subject variable or a one-way between-subject ANOVA when the effect of refractive error on tonic accommodation was considered. A Scheffe's *post-hoc* comparison of means test was also used to compare differences between refractive groups as it provides a vigorous assessment of significance between a number of treatment conditions (Diekhoff, 1992) and provides protection against Type 1 errors (Armstrong *et al.*, 2000). Pearson's product moment correlation coefficients were used to compare the relationship between independent variables.

3.3 Results

3.3.1 Stimulus-response gradients and the accommodative error index

Figure 3.1 illustrates the accommodation stimulus-response curves for all subjects and the corresponding mean accommodation stimulus-response curves for each of the four refractive groups (n = 15 in each group). Individual stimulus-response curves and their standard deviations can be found in Appendix 4. Gradients (m) of the stimulus-response curves were calculated by fitting least squares regression lines to each curve as described elsewhere (Johnson, 1976; McBrien and Millodot, 1986b; Chauhan and Charman, 1995). In addition, an accommodative error index (I) was calculated for each subject (Chauhan and Charman, 1995). The individual accommodative slope and I data are presented in Appendix 5.

Table 3.1 illustrates the relationship between the four refractive groups (HYP, EMM, EOM and LOM); their mean accommodation response gradients and mean accommodative error indexes. Accommodation response slopes ranged from 0.23 to 1.12, while values of I ranged from 0.13 to 2.30. Both methods of analysis show that the LOM group exhibit less accurate accommodation responses. A one-way between-subject ANOVA illustrated that the effect of refractive grouping reached statistical significant for the stimulus-response gradient ($F_{(3,56)} = 4.3$, $p < 0.01$) and approached significance for the mean accommodative error index ($F_{(3,56)} = 2.3$, $p = 0.08$). Scheffe's *post-hoc* analysis illustrated a statistically significant difference in the mean stimulus-responses gradient between HYP and LOM (HYP vs. LOM: $p = 0.01$), all other refractive pairs, however, failed to show significant differences (HYP vs. EMM: $p = 0.22$; HYP vs. EOM: $p = 0.59$; EMM vs. EOM: $p = 0.91$; EMM vs. LOM: $p = 0.59$; EOM vs. LOM: $p = 0.22$). A non-significant difference in mean accommodative error index was also shown between the four refractive groups (HYP vs. EMM: $p = 0.86$; HYP vs. EOM: $p = 0.80$; HYP vs. LOM: $p = 0.53$; EMM vs. EOM: $p = 0.33$; EMM vs. LOM: $p = 0.94$; EOM vs. LOM: 0.12).

It is evident that, from Figure 3.1 and Table 3.1, LOMs show slightly higher lags of accommodation at higher accommodative demands. Indeed, the difference in response, between refractive groups, was only significant at the 4.0 D stimulus level (0.0 D: $F_{(3,56)} = 1.3$, $p = 0.27$; 1.0 D: $F_{(3,56)} = 2.2$, $p = 0.10$; 2.0 D: $F_{(3,56)} = 2.4$, $p = 0.08$; 3.0 D: $F_{(3,56)} = 1.4$; $p = 0.27$; 4.0 D: $F_{(3,56)} = 3.3$, $p = 0.03$).

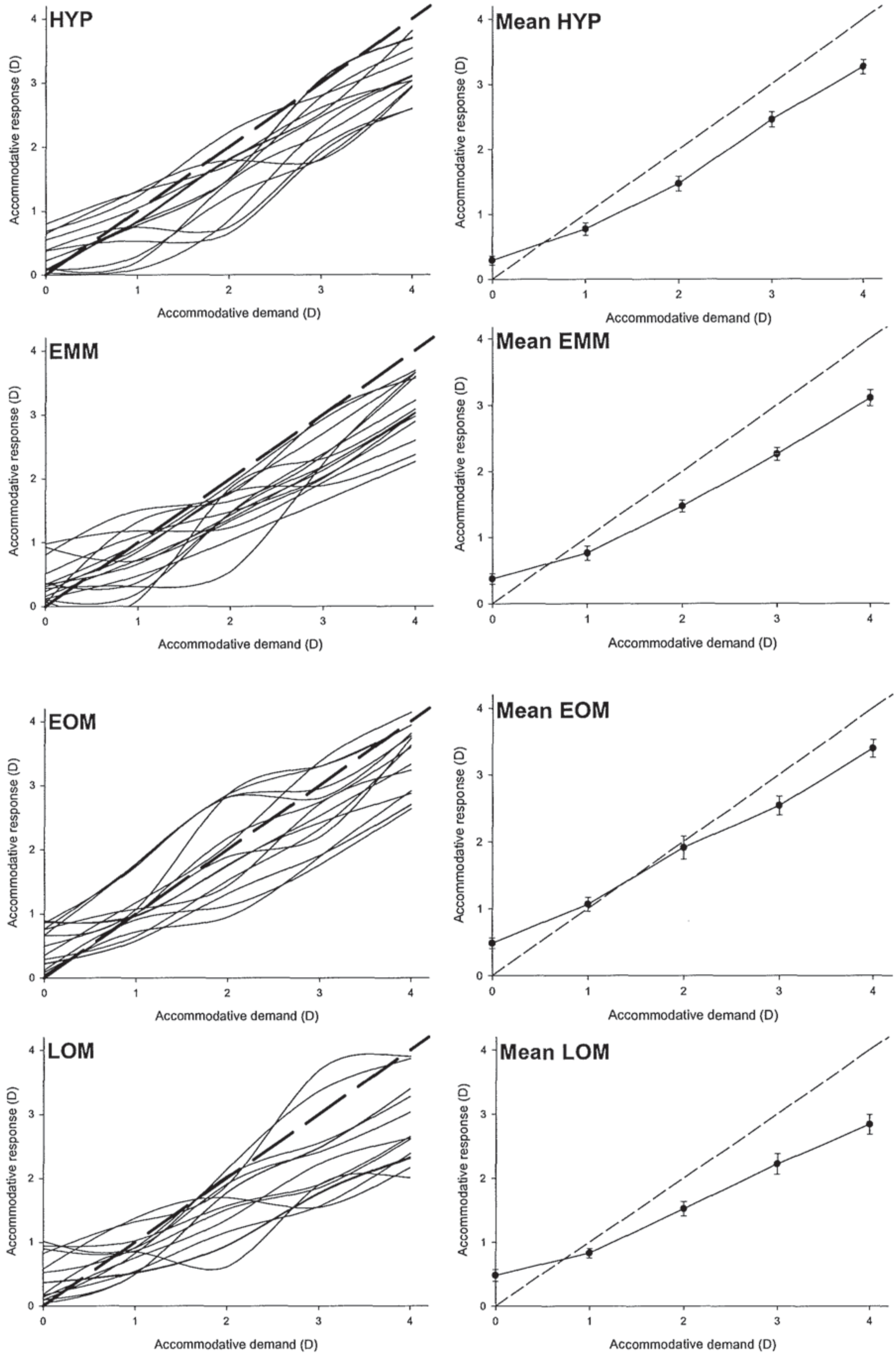

Figure 3.1 Left: Accommodation stimulus-response curves for all subjects. Right: Corresponding mean responses for each refractive group. Error bars represent ± 1 SEM. N = 15 in each refractive group.

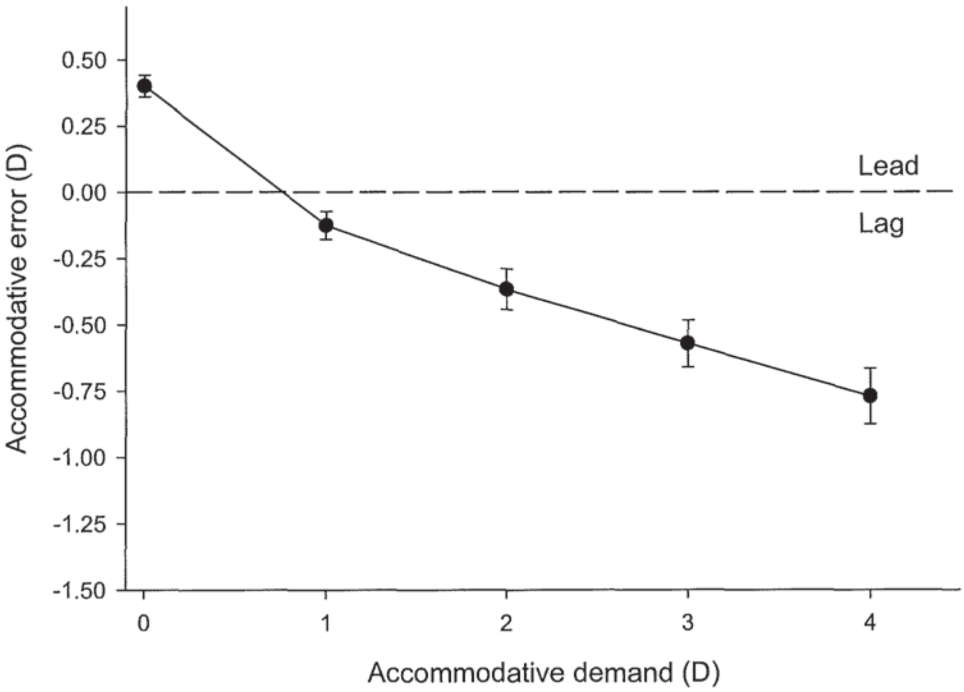

Figure 3.2 Accommodative errors associated with increasing accommodative demand for all subjects. Error bars represent ± 1 SEM.

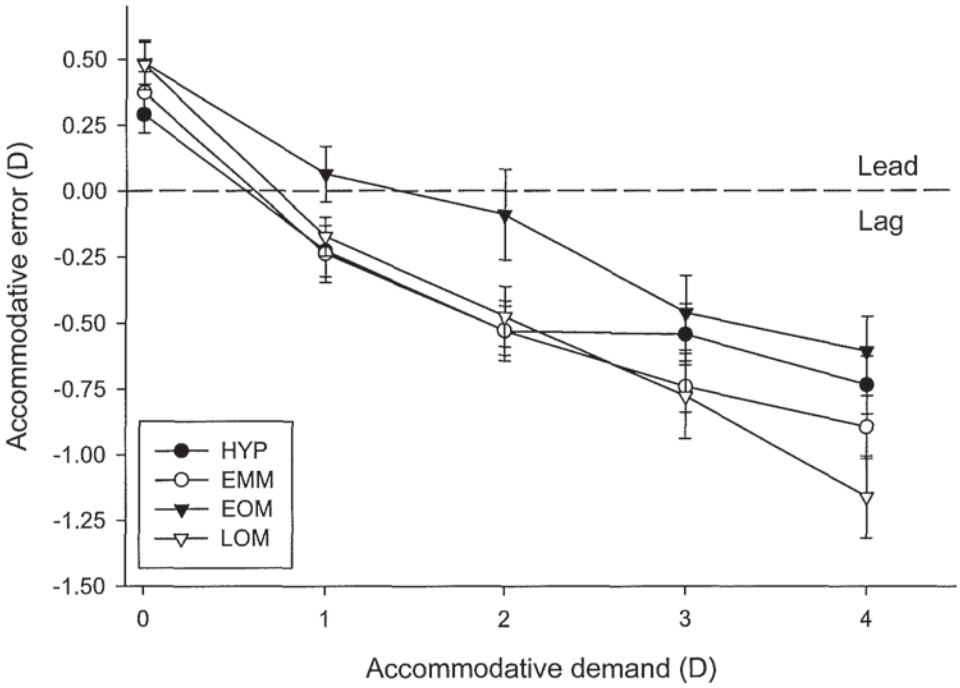

Figure 3.3 The effect of refractive error grouping on accommodation errors for varying accommodative demands. Error bars represent ± 1 SEM. N = 15 in each refractive group.

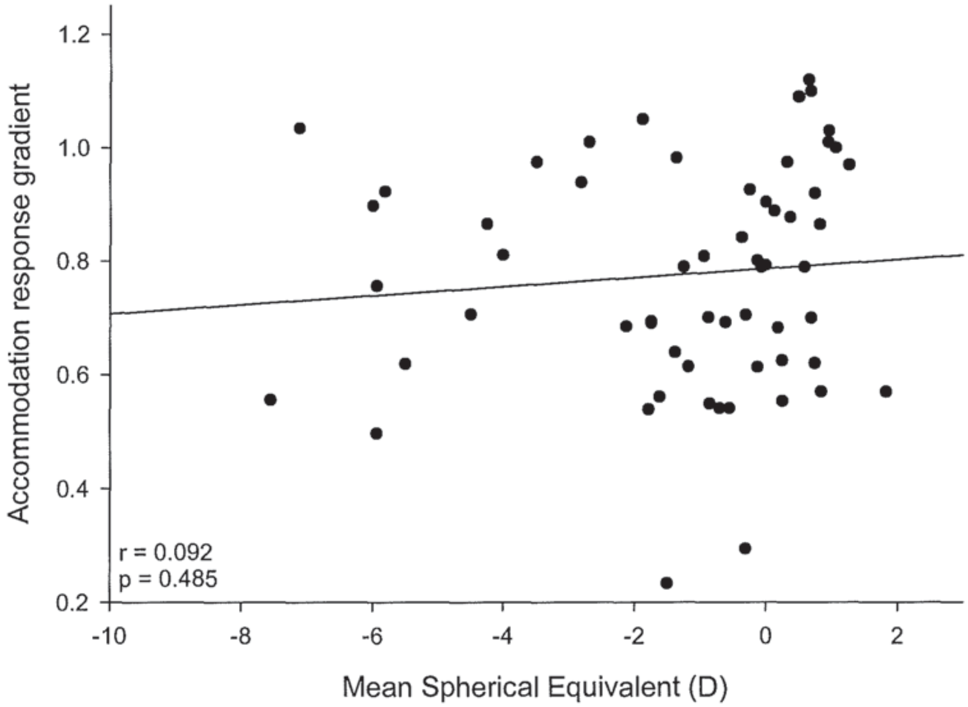

Figure 3.4 Individual accommodation response gradients as a function of refractive error.

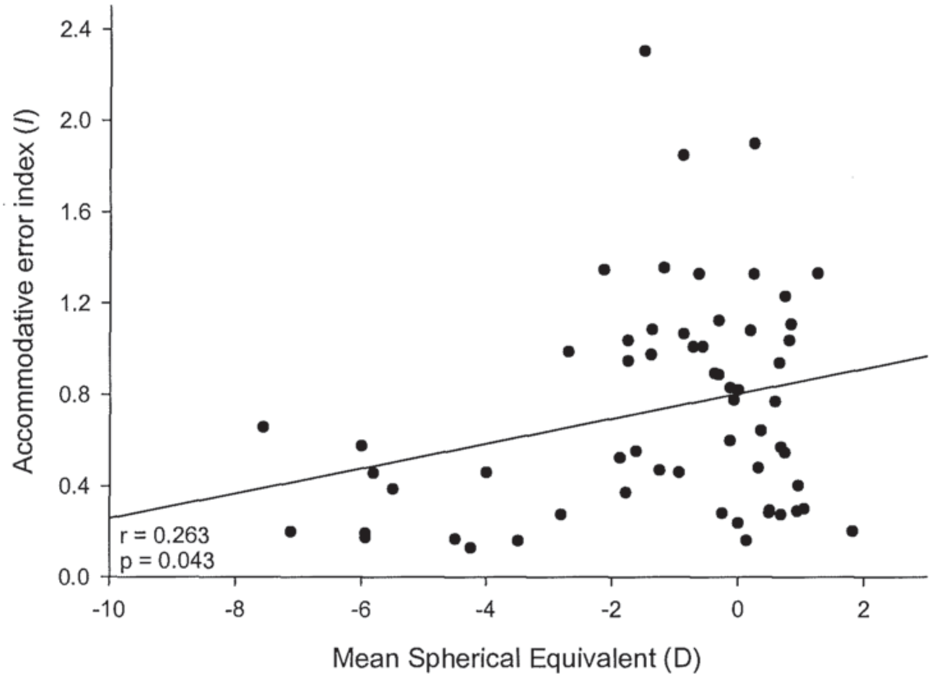

Figure 3.5 Individual accommodative error index (*I*) score as a function of refractive error.

REFRACTIVE GROUP	**SIZE (N)**	**MEAN ACCOMMODATION RESPONSE GRADIENT (*m*)**	**MEAN ACCOMMODATIVE ERROR INDEX (*I*)**
HYP	15	0.90 ± 0.20	0.64 ± 0.40
EMM	15	0.75 ± 0.18	0.80 ± 0.45
EOM	15	0.80 ± 0.19	0.54 ± 0.37
LOM	15	0.66 ± 0.18	0.96 ± 0.62

Table 3.1 Relationship of refractive group with mean accommodation response gradient (*m*) and the mean accommodative error index (*I*).

When considering the accommodative error as a function of accommodative stimulus demand (Figure 3.2 and 3.3) all subject groups show the well documented lead of accommodation for low demands and a lag in response for higher accommodative levels. The LOM subjects exhibit a slightly larger lag of accommodation at the higher accommodative demands compared to the other groups. When the stimulus to accommodation is zero, however, all subjects show the well documented lead of accommodation. Together with the EOMs, the LOM group demonstrates the largest lead in accommodation.

The relationship between mean refractive error and accommodative response was compared for the stimulus-response gradient (Figure 3.4) and accommodative error index (Figure 3.5). Clearly, the effect of refractive error has no influence on, or relationship to, the accommodative-response gradient ($r = 0.09$, $p = 0.49$). Interestingly, however, there is a significant positive correlation between the sign and magnitude of refractive error and the accommodative error index ($r = 0.26$, $p < 0.05$).

3.3.2 Tonic accommodation as a function of refractive error

Examination of the accommodation data to the DoG target showed that all subjects adopted an intermediate tonic focus when the stimulus to blur-driven accommodation was removed. The mean level of TA for the whole cohort (n = 60) was (mean ± SD) 1.19 ± 0.78 D. Figure 3.6 illustrates the mean TA for each refractive group discussed previously, with error bars representing ± 1 standard error of the mean (SEM). The effect of refractive error on the mean level of TA was significant ($F_{(3,56)} = 4.7$, $p < 0.01$). A Scheffe's *post-hoc* test demonstrated that the mean accommodative response to the DoG target was statistically lower in the LOM group, when compared to all other groups (HYP vs. EMM: p = 0.86; HYP vs. EOM: p = 0.88; HYP vs. LOM: p = 0.01; EMM vs. EOM: p = 0.98; EMM vs. LOM: $p < 0.05$; EOM vs. LOM: $p < 0.05$).

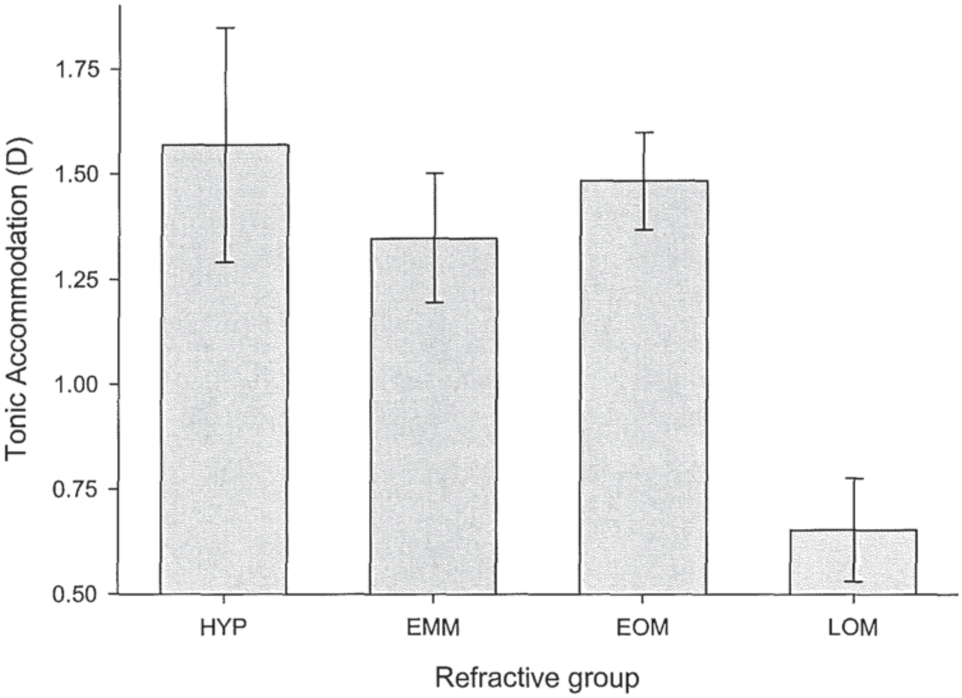

Figure 3.6 Mean level of tonic accommodation (to a DoG target) as a function of refractive group. Error bars represent ± 1 SEM. N = 15 in each refractive group.

3.3.3 Stimulus-response function cross-over versus tonic accommodation

Figure 3.7 shows the relationship between the stimulus-response cross-over points with the subjects' corresponding tonic level. In this part of the study, seven subjects (3 HYPs, 2 EOMs and 2 LOMs) of the main cohort were excluded from the analysis due to the lack of a cross-over point in the accommodative stimulus-response function with the unit ratio line or where the function crossed the unit line more than once. The correlation of the two factors was significant and appeared monotonic (r = 0.45, p = 0.001) with a few outliers. The dioptric value of the cross-over point, however, does not equal TA as the regression line departs from the unit ratio line. Instead, TA (mean ± SD: 1.27 ± 0.57 D) was approximately twice the dioptric value of the cross-over point (mean ± SD: 0.78 ± 0.40 D).

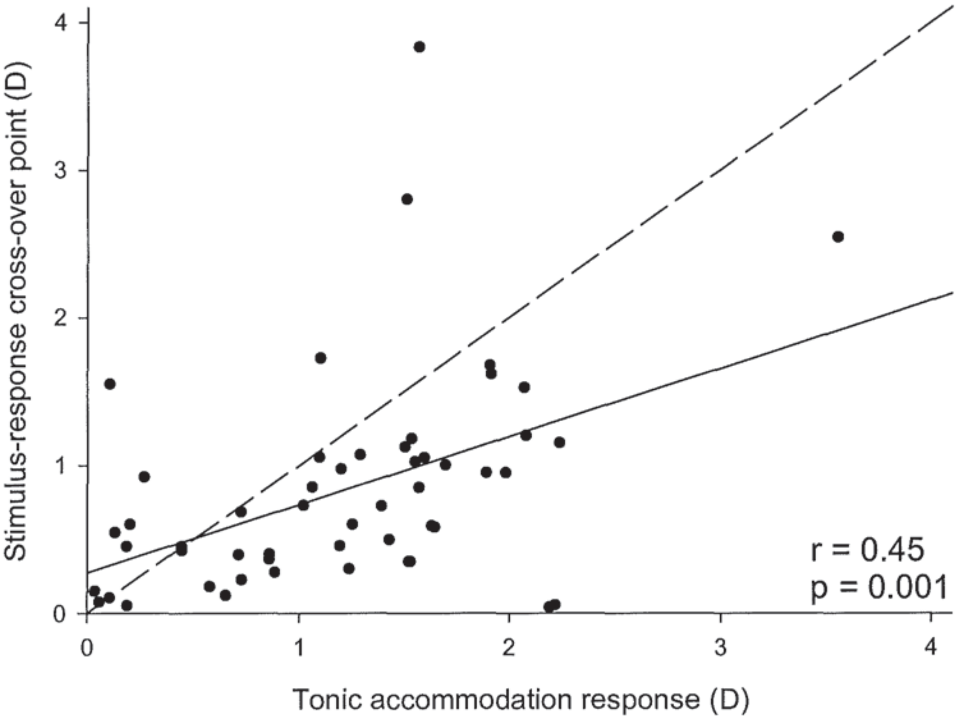

Figure 3.7 Relationship between tonic accommodation (TA) and the cross-over point of the accommodative stimulus-response function (n = 53). Dashed line indicates the unit ratio line.

Further inspection of the relationship between TA and the cross-over point of the accommodative stimulus-response function for each refractive group shows that there is no difference in slope of the HYP, EMM or LOM refractive groups. There is however a significant difference in the EOM group. This difference in the EOMs, however, appears to be due to the two outliers artificially increasing the slope of the regression line (Figure 3.8). Once these data points are removed, the EOM regression line conforms to the general trend.

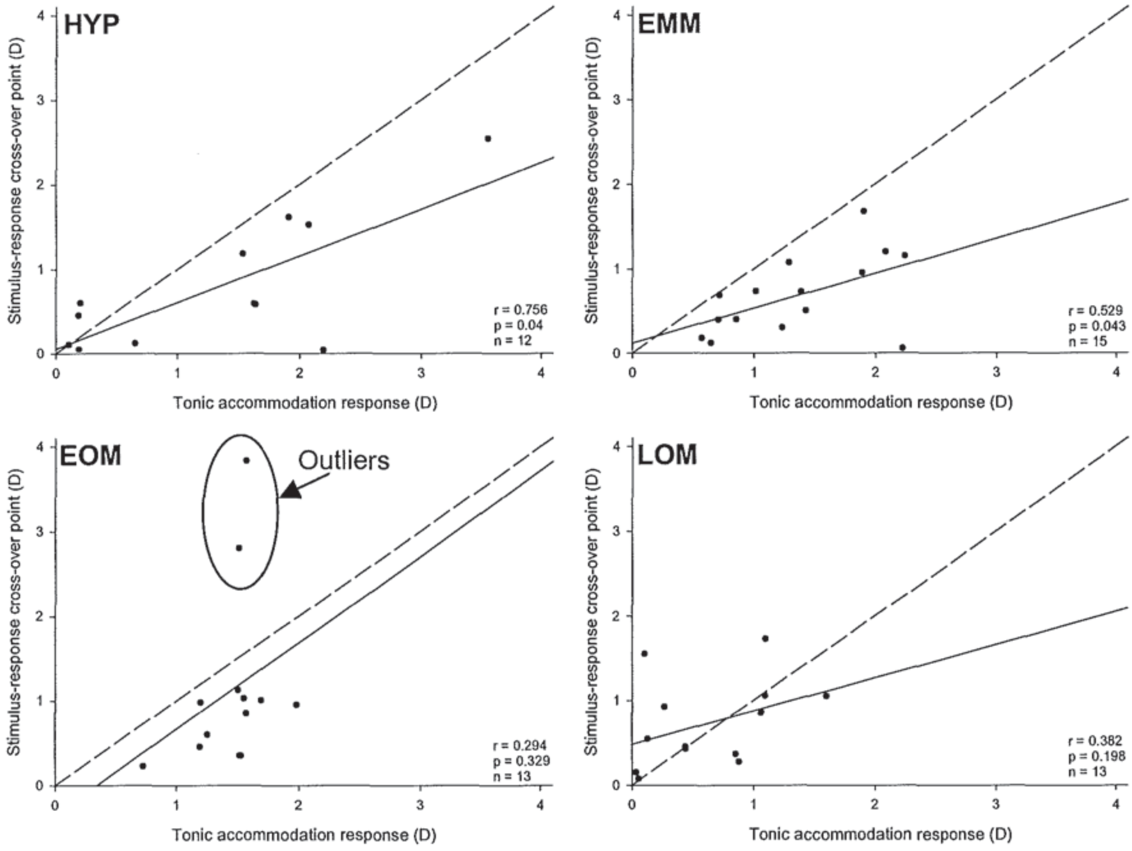

Figure 3.8 The relationship between tonic accommodation (TA) and the cross-over point of the accommodative stimulus-response function for each of the four refractive groups. Solid line represents the regression line. Dashed line indicates the unit ratio line. (HYP: n = 12; EMM: n = 15; EOM: n = 13; LOM: n = 13).

3.4 Discussion

The first part of the study investigated the accuracy of the steady-state accommodative response to a range of accommodative demands together with the influence refractive error has on the aggregate accommodative response. All subjects demonstrated the established accommodative stimulus-response function (Charman, 1982; Rosenfield *et al.*, 1993; Ciuffreda, 1998). Statistical analysis of the stimulus-response gradient for each refractive group showed that the effect of refractive error reached statistical significance. When using the mean accommodative error index (*I*) to quantify the responses, the effect of ametropia tended towards significance. *Post-hoc* analysis illustrated that the greatest difference in the stimulus-response gradient existed between the HYP and LOM groups. All other refractive group pairs showed no significant difference. Moreover, Figure 3.1 shows that at higher accommodative demands (i.e. 4.0 D) the LOM group showed higher lags of accommodation as demonstrated in previous studies (McBrien and Millodot, 1986b; Rosenfield and Gilmartin, 1988b; Bullimore *et al.*, 1992; Jiang, 1994).

McBrien and Millodot (1986b) found that the accommodative response for near targets (4.0 and 5.0 D) was lower in LOMs than in EMMs. Rosenfield and Gilmartin (1988b) found that the accommodative responses to a 3.0 D target for the LOM group were lower than those for the EMM group. Likewise, Bullimore and co-workers (1992) showed that LOMs have a lower response for near targets under a passive viewing condition (recognising numbers). Jiang (1994) measured the slope of the stimulus-response function produced by presenting targets at 1.0, 2.0, 3.0 and 4.0 D in a variety of conditions (i.e. monocular, binocular and monocular with a Badal optical system). In this study, the gradient of the stimulus-response function for the LOM group was lower than the mean gradient for the EMMs in both the monocular ($p < 0.05$) and monocular with Badal condition ($p < 0.05$), no statistical difference was detected in the binocular condition ($p = 0.65$). The disparity in the slopes between groups was attributed to the larger lags of accommodation seen in the LOMs at higher dioptric stimuli. The data presented in this Chapter confirms Jiang's hypothesis as significant differences between groups was only present at the 4.0 D stimulus level.

The mean levels of tonic accommodation for the cohort of 1.19 D falls within the expected range of TA as found by previous investigations (Bullimore *et al.*, 1986; Jiang, 1995; Jiang and Morse, 1999). Interestingly, the value appears to lie between the values found in some studies using laser optometers (Leibowitz and Owens, 1975a, b, 1978) and infrared optometers (Mallen, 2002). The study also confirms that corrected hypermetropes exhibit higher dioptric levels of TA than emmetropes or myopes as suggested previously (e.g. McBrien and Millodot, 1987). Further, the LOM subjects have a statistically lower level of TA; mean values of TA were lowest in the LOM (0.65 D) with the HYPs, EMMs and EOMs showing higher levels (~1.40 D). The data support the findings of previous investigations (McBrien and Millodott, 1987; Rosenfield and Gilmartin, 1987; Miwa, 1992; Jiang, 1995). In a similar study, containing all four refractive groups, McBrien and Millodot (1987) investigated the relationship between TA and refractive error (n = 62; age 19 to 25 years). They found that the hypermetropic group (n = 15) had the highest level of TA (1.33 D) with the late-onset myopes (n = 15) having the lowest level (0.49 D). Again, the results of this work would seem to support the findings of McBrien and Millodot (1987)

Finally, consideration was given to the proposed correlation between the stimulus-response curve cross-over point with the unit ratio line and the individual level of TA. The data show that the correlation of the two factors was significant. The dioptric value of the cross-over point, however, does not directly represent TA. The gradient of the linear regression line equalled ~0.5 D/D; suggesting that TA is approximately twice the dioptric value of the cross-over point. The results are supported by previous work (Owens, 1979; Ciuffreda *et al.*, 1984; Tan and O'Leary, 1988; Ong *et al.*, 1993; Rosenfield *et al.*, 1993). Tan and O'Leary (1988) found a weakly significant correlation between the two factors ($r = 0.43$, $p < 0.05$) with a regression slope of 0.8 D/D. There was, however, a large intra-subject variation between the two values. An earlier study by Owens (1979), using a laser optometer, found that the mean data for four subjects showed a cross-over point in the stimulus-response function of ~3.5 D and a mean TA of ~2.0 D; opposite to that found in this study. The cross-over value appears to be very high given the current understanding of the stimulus-response function (Charman, 1982; Rosenfield *et al.*, 1993; Ciuffreda, 1998). Owen's results may have been contaminated by proximal or calibration factors. In addition to previous studies, this Chapter illustrates that the TA/stimulus-response relationship is consistent across all refractive groups (see Figure 3.8).

The author would like to stress that, although the results are encouraging and support previous work, data were collected under controlled laboratory conditions with subjects in the monocular state. Clearly, real-world conditions expose individuals to a myriad of environments, both monocular and binocular, which may or may not contribute to the aggregate accommodative response (e.g. cognition, surround propinquity, variations in luminance, dynamic tasks and sound). As such, the everyday near visual task may place the subject in a very different environment to the laboratory situation. Obviously, quantification of the near visual response to real-world tasks should be undertaken and examined. This, however, raises a plethora of problems. Recently validated photorefraction systems (e.g. the *PowerRefractor*; Wolffsohn *et al.*, 2002) could be utilised to monitor oculomotor changes (i.e. vergence, accommodative response and pupil size) to natural visual tasks. Such a system would provide a more naturalistic profile of the oculomotor system when responding to real-world near visual tasks.

3.5 Conclusion

The study has examined the steady-state accommodative response in a large cohort of HYPs, EMMs, EOMs and LOMs; the results of which are in general agreement with previous investigations. Clearly, the steady-state accommodative response in both open- and closed-loop conditions is modified by both the sign and onset of refractive error.

The main findings of this study are:

- Refractive error appears to modulate the steady-state accommodative response, in that LOMs display a less accurate response when compared to other refractive groups.
- LOMs demonstrate a statistically significant lower level of TA than HYP, EMM or EOM.
- No statistically significant difference in TA exists between HYP, EMM or EOM.
- The dioptric value of the stimulus-response function cross-over point does not directly represent TA.
- TA is approximately twice the dioptric value of the cross-over point.

Chapter 4 continues the examination of the accommodative response by quantifying both the time- and frequency-domain components of the accommodative system to a range of accommodative demands in HYPs, EMMs, EOMs and LOMs.

CHAPTER 4

EFFECT OF RETINOTOPIC STIMULI AND AMETROPIA ON STEADY-STATE ACCOMMODATION MICROFLUCTUATIONS

4.1 Introduction

The work of Collins (1937) first led to the discovery of rapid fluctuations (microfluctuations) in the accommodative response around a mean level during steady-state viewing. An important development in the analysis of the microfluctuations followed when Campbell and co-workers utilised Fourier analysis to spectrally decompose the microfluctuations into spatial frequency bands (Campbell *et al.*, 1958; Campbell *et al.*, 1959). Since then, various investigations have explored the nature and characteristics of these accommodative microfluctuations (e.g. Charman and Heron, 1988; Winn and Gilmartin, 1992; Gray *et al.*, 1993a; Gray *et al.*, 1993b; van der Heijde *et al.*, 1996; Seidel *et al.*, 2003; Day *et al.*, 2004).

Ocular accommodative microfluctuations, in humans, occur in both the steady-state and dynamic response profile with a magnitude of approximately 0.20 D (Charman and Heron, 1988; Charman, 2000). The microfluctuations consist of two principal temporal frequencies in the power spectra: a low frequency component (LFC < 0.6 Hz) and a high frequency component (1.0 Hz < HFC < 2.1 Hz; Gray *et al.*, 2000). Most investigations quantify the total fluctuation in the accommodative response (in the time-domain) by using the standard deviation of the response (i.e. the root-mean-square [RMS]; Charman and Heron, 1988).

A variety of explanations exist as to the exact aetiology of accommodative microfluctuations. The oscillations are believed to be produced by a combination of noise (respiration and arterial pulse) and neurological control (Collins *et al.*, 1995). The latter is reported to be associated with the LFC (Winn and Gilmartin, 1992; Gray *et al.*, 1993b). It has been proposed that accommodative microfluctuations operate by a continuous trial and error mechanism of the ciliary muscle around an equilibrium position. This negative feed-back process may facilitate the acquisition of a clear retinal image at various dioptric distances from the eye (Gray *et al.*, 1993b). Consequently, by examination of the accommodative microfluctuations, information may be elicited regarding the control system of the steady-state accommodative response.

The dependency of the accommodative microfluctuations on various factors has been investigated: pupil diameter (Campbell *et al.*, 1959); central and peripheral zones of the crystalline lens (Winn *et al.*, 1990a); target form (Bour, 1981); target luminance (Denieul, 1980); age (Toshida *et al.*, 1998); pharmacological manipulation (Owens *et al.*, 1991; Strang *et al.*, 1994); arterial pulse (Winn *et al.*, 1990b; see Chapter 6) and ametropia (Seidel *et al.*, 2003). For a review see Chapter 1.

With smaller pupil sizes, the HFC fluctuations are less prominent than the LFC; the converse is found with larger pupil sizes (Campbell *et al.*, 1959), thus suggesting a role for the LFC in the active feedback mechanism. The diminished HFC fluctuations with reduced pupil size, however, has led to the suggestion that they may not contribute directly to steady-state accommodation control, but may be a form of plant noise (Charman and Heron, 1988). Furthermore, a later study by Gray *et al.* again showed that the LFC and not the HFC was affected by changes in artificial pupil size (Gray *et al.*, 1993b) or target luminance (Gray *et al.*, 1993a). For artificial pupil sizes > 2 mm, no relationship between the size of the pupil and the fluctuations are observed, conversely, for apertures < 2 mm the LFC has been shown to increases as a function of pupil reduction (Gray *et al.*, 1993b). These changes were attributed to depth-of-focus (DoF). As such, during this investigation pupil size was at least 3 mm in size for all stimulus conditions.

The effect of target vergence on the accommodative microfluctuations was first investigated by Arnulf and Dupuy (1960). They quantified the exact form of the fluctuations over a range of target vergences. Their data, however, cannot be analysed easily as they did not corrected their subjects' significant refractive errors. Subsequent authors have established that, when a high-contrast target is viewed monocularly through a Badal optical system at a series of fixed vergences, the fluctuations present in the accommodative response increase as the accommodative demand increases (Kotulak and Schor, 1986; Stark and Atchison, 1997; Toshida *et al.*, 1998). Moreover, a recent study by Seidel and co-workers (2003) using the Canon R-1 optometer assessed the effect of ametropia on the microfluctuations. Fourteen emmetropes (EMM), 10 early-onset myopes (EOM) and 8 late-onset myopes (LOM) viewed a high-contrast (80%) Maltese cross at 4.0

D. LOMs (0.56 ± 0.17 D) exhibit greater accommodative fluctuations than both EMMs (0.24 ± 0.05 D) and EOMs (0.28 ± 0.07 D). No statistically significant differences were found between the EMM and EOM groups. These findings suggest that LOMs demonstrate a reduction in retinotopic processing, which in turn leads to an increase in the steady-state accommodative response caused by an enlargement of their depth-of-focus (DoF).

There is evidence that DoF varies between refractive groups. Rosenfield and Abraham-Cohen (1999) measured the DoF in a group of emmetropes and myopes, demonstrating significantly larger values in myopes. They concluded that myopes are, on the whole, less sensitive to retinal defocus, thus providing a possible explanation to the large accommodative errors seen in previous investigations (Gwiazda *et al.*, 1993; Abbott *et al.* 1998).

The effects observed in the accommodative response, however, seem to vary greatly between investigations and between subjects in both the magnitude of the fluctuations and their changes with target distance. Numerous factors may be responsible for these differences, for example refractive error, sample size and method of measurement.

Using an open-field, infrared optometer (Mallen *et al.*, 2001; Wolffsohn *et al.*, 2001b), this study aims to quantify both the time- and frequency-domain components of the accommodative response over a range of accommodative demands in hypermetropes, emmetropes and myopes. In addition to previous investigations, microfluctuations of accommodation in the frequency-domain were further sub-divided into both relative and absolute values.

4.2 Methods

4.2.1 Subjects

Fifty-two subjects (25 male; 27 female) varying in age from 18 to 33 years (average: 21.2 ± 3.2 years) took part in the study. Thirteen subjects were hypermetropes (HYP; mean spherical equivalent [MSE]: +0.88 ± 0.35 D; range: +0.51 to +1.82 D), 13 subjects were emmetropes (EMM: MSE: +0.03 ± 0.24 D; range: -0.37 to +0.37 D), 13 subjects were early-onset myopes (EOM: MSE: -3.81 ± 2.15 D; range: -7.12 to -1.25 D), and 13 were late-onset myopes (LOM: MSE: -1.84 ± 1.50 D; range: -5.00 to -0.56 D). The mean age of onset for the EOMs was 10.2 ± 2.6 years (range: 6 to 13 years) and 16.7 ± 0.8 years (range: 16 to 18 years) for the LOMs.

Ametropic subjects were fitted with conventional ultrathin soft contact lenses (2-hydroxyethyl methacrylate [HEMA] lenses, 58% water content; Acuvue Dailies, Vistakon, Johnson & Johnson Vision Care, Jacksonville, Florida, USA) to fully correct their refractive error. Sufficient time was given for adaptation to the soft contact lenses; all subjects had previously worn soft contact lenses and no subject experienced difficulties. All subjects achieved 0.00 logMAR visual acuity or better in the eye tested, with an amplitude of accommodation $\geq$ 8.0 D. None of the subjects had any form of visual or pathological anomaly. All subjects were experienced with visual experiments and were trained to maintain steady fixation in order to limit artefacts in the data. Subjects were furnished with a full explanation of the procedures involved in the investigation and gave informed consent to their participation in the study under the terms of the Declaration of Helsinki (copy of consent form is provided in Appendix 3). Ethical approval was granted by the human ethics committee of Aston University (Appendix 2).

4.2.2 Stimulus and Instrumentation

Each subject viewed monocularly a stationary high contrast (90%), 37.0 cdm^{-2} Maltese cross (angular subtense 10°) through a +5.0 D Badal optical system, thus ensuring both contrast, luminance and image size remained constant, but inducing a blur-driven accommodative stimulus. Five closed-loop stimulus conditions were employed (0.0 D to 4.0 D accommodative demand in 1.0 D steps).

A specially modified Shin-Nippon SRW-5000 infrared autorefractor (Ryusyo Industrial Co. Ltd, Osaka, Japan) was used to record continuously the accommodative response (Mallen *et al.*, 2001; Wolffsohn *et al.*, 2001b) as described in Chapter 2. Data acquisition and analysis were performed using the *LabView* software package (National Instruments, Austin, Texas, USA; see Chapter 2).

4.2.3 Procedure

Initially, the refractive error of each subject was measured through the Badal optical system with the target placed at 0.0 D. Subjects' contact lens correction was modified if their residual mean refractive error was > ± 0.25 D or if the cylindrical component was ≥ 0.50 DC. The optical axis of the SRW-5000 was aligned with the subject's right eye, with the left eye occluded. Five 17.07 second continuous recordings of the accommodative response were obtained for each accommodative level (as in Winn and Gilmartin, 1992; Gray *et al.*, 1993a, 1993b, 2000) at a sampling rate of 60 Hz, giving 1024 data points for each recording. Respiration was regulated to 15 breaths per minute (0.25 Hz) with the aid of a digital quartz metronome (*SQ 50*, Seiko, Japan) as in previous investigations (Tyrrell *et al.*, 1994, 1995, 2000; Davies *et al.*, 2004) as this has been shown to influence components of the accommodative response (Collins *et al.*, 1995).

The accommodative signals were exported to a *Microsoft Excel* file and filtered with a high frequency cut at 10 Hz, as it is known that variations in accommodation do not contain frequencies higher than this level (Charman and Heron, 1988). A Fast Fourier Transform (FFT) power spectrum was calculated for each individual trace with a power frequency resolution of 0.06 Hz. The five individual power spectra from each accommodative level were then averaged. Pugh and colleagues have shown previously that the probability density function of any one frequency bin in a power spectrum obtained by a single FFT is that of a Chi-squared distribution of order 2 (Pugh *et al.*, 1987). For such a distribution the standard deviation is equal to the mean value. By averaging more power spectra the confidence in the distribution increases and the standard deviation correspondingly decreases and becomes equal to $\sqrt{(2/2m)}$ × mean value in each frequency bin (where m = number of spectra; Pugh *et al.*, 1987).

Mean RMS values, and dominant frequency bins in the mean power spectra were averaged for all four refractive groups. Dominant frequency bins in the range of 0.12 Hz to 0.60 Hz (LFC) and 1.02 Hz to 2.52 Hz (HFC) were chosen to reflect previous studies and the current data set. In contrast to previous investigations, however, spectral power was expressed in both absolute (D^2Hz^{-1}) and normalised units (n.u.). In the latter, each dominant frequency is expressed as a percentage of the total power in the power spectrum (see Figure 4.1). As with spectral analysis of heart rate variability (Task Force, 1996; see Chapter 1) errors in analysis can occur if the heart rate or accommodation signal is corrupted by background noise. As such, if two power spectra are compared for different conditions, one with elevated background noise, any real alteration in the frequency components will be masked and may lead to inappropriate conclusions.

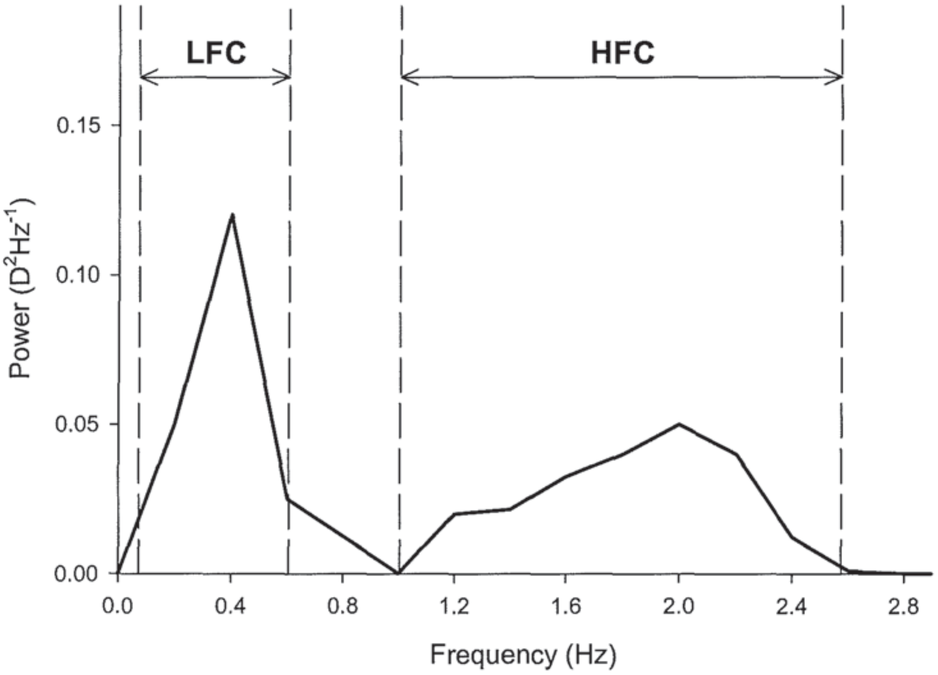

Figure 4.1 Example of an accommodation power spectrum for an EMM subject. Arrows indicate the limits of the typical dominant low- and high-frequency components analysed. Each frequency component was integrated and compared to the total area under the function, thus providing a relative measure.

4.2.4 Data and statistical analysis

Data analysis was performed with *Microsoft Excel*, SigmaPlot 2000 (version 6.0; Systat Software, UK) and SPSS for Windows (version 11.5). Data were treated with a two-way (vergence, refractive error) mixed ANOVA where vergence was taken as a within-subject variable and refractive error as the between-subject variable. A Scheffe's *post-hoc* comparison of means test was also used to compare differences between refractive groups.

4.3 Results

4.3.1 Time-domain analysis

Examples of accommodative recordings for one observer from each refractive group with different accommodative stimuli (0.0 D, 2.0 D and 4.0 D accommodative demand) are shown in Figure 4.2.

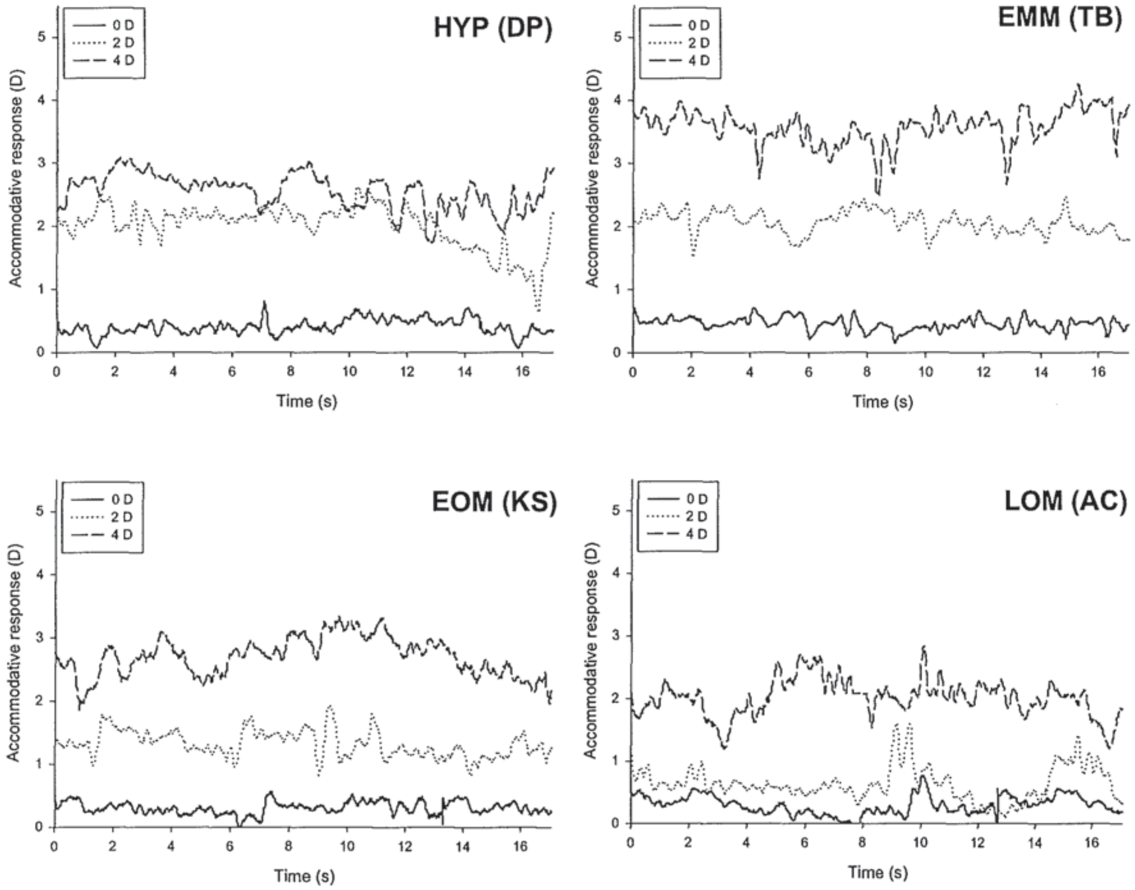

Figure 4.2 Sample traces of 17.07 seconds of accommodative microfluctuations of a HYP, EMM, EOM and LOM at 0.0 D, 2.0 D and 4.0 D accommodative demands. The traces have been treated with a 10 Hz filter.

Figure 4.3 illustrates the mean RMS values for all refractive groups over each accommodative demand level (see Appendix 6). On average RMS values increased by + 0.08 ± 0.10 D (HYP: + 0.07 ± 0.08 D; EMM: + 0.08 ± 0.08 D; EOM: + 0.09 ± 0.10 D; LOM: + 0.09 ± 0.12 D) from 0.0 D to 4.0 D accommodative demand. A two-way mixed factor ANOVA (where accommodative demand was taken as the within-subject factor and refractive group as the between-subject factor) showed a statistically significant increase in RMS value on increasing demand ($F_{(4,192)} = 18.95$; $p < 0.0005$). Further analysis showed that the trend was linear ($F_{(1,48)} = 43.88$; $p < 0.0005$).

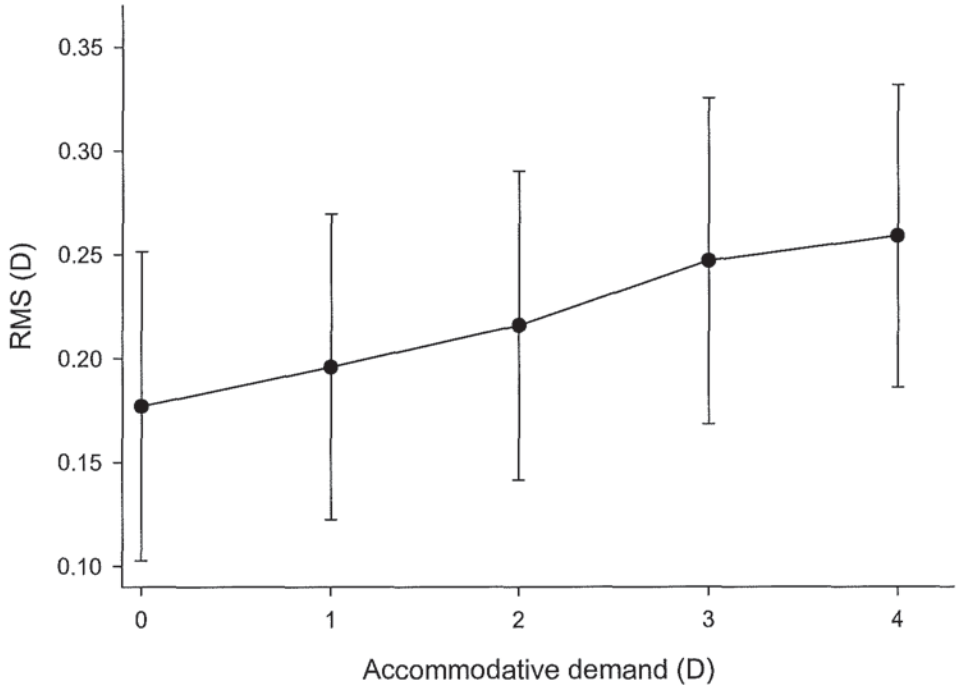

Figure 4.3 Effect of accommodative demand on RMS for all subjects (n = 52). Error bars represent ± 1 SD.

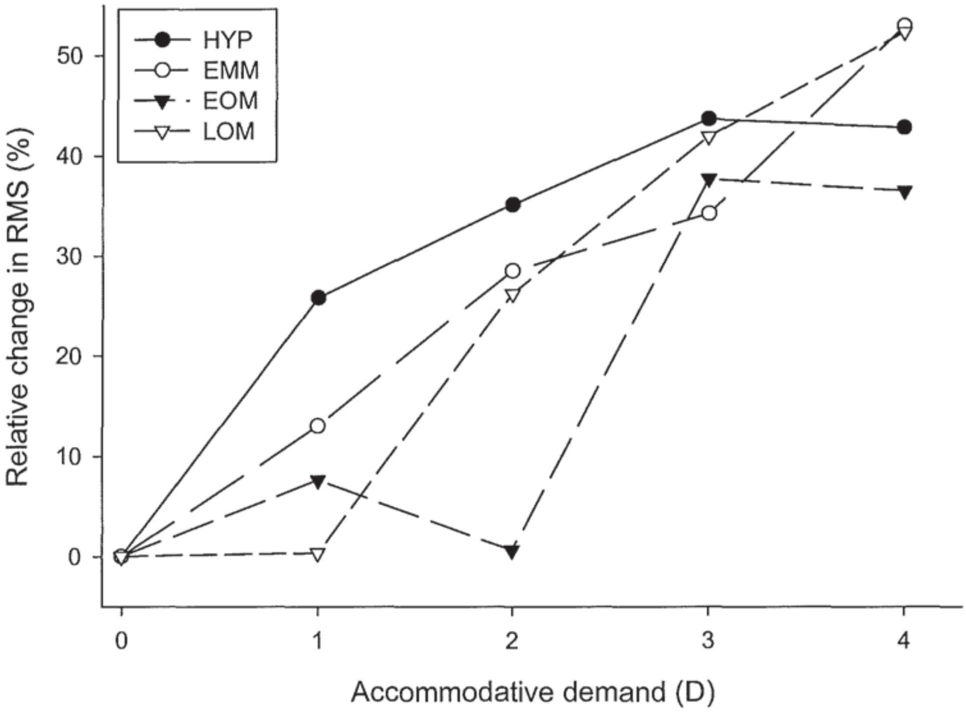

Figure 4.4 Percentage change in RMS with increasing accommodative demand for all four refractive groups. Here, the relative change in RMS value is shown by comparing each accommodative demand with the response found at optical infinity (0.0 D). Error bars are omitted for clarity.

Figure 4.4 shows the relative percentage change in RMS values for each refractive group. EMMs and LOMs exhibit the greatest relative increase (52.9% and 52.3%, respectively), followed by HYPs (42.8%) and EOMs (36.5%). Interestingly, both myopic groups display little increase in RMS with low levels of accommodative demand, followed by a steep increase with higher levels of accommodative demand , whereas HYPs and EMMs exhibit a more linear-type increase in RMS value with increasing accommodative demand.

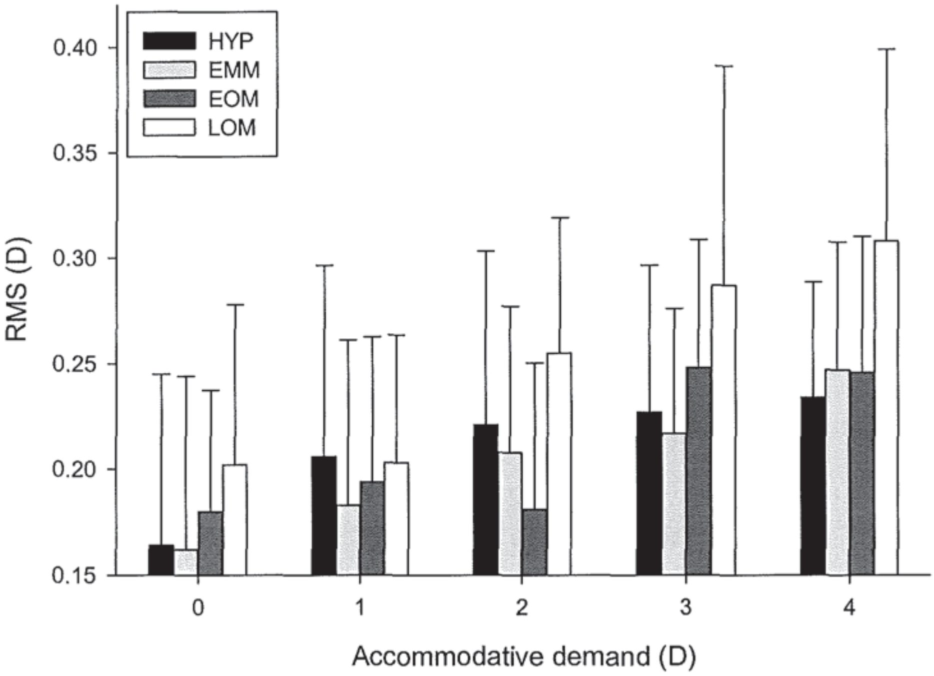

Figure 4.5 Effect of accommodative demand on accommodative RMS values for all four refractive groups. Overall, there is no statistically significant effect of refractive error on the RMS result (p = 0.108). When only higher demand levels are considered (3.0 D and 4.0 D), however, LOMs show a statistically significant increase compared to the other groups (p = 0.047). Error bars represent 1 SD.

If the actual RMS values are considered for each refractive group (see Figure 4.5), refractive error was shown to have no statistically significant influence on mean RMS value over all demand levels ($F_{(3,48)} = 2.13$; p = 0.11). A Scheffe's *post-hoc* test revealed no statistically significant difference between any refractive group combination (HYP vs. EMM: p = 0.99; HYP vs. EOM: p = 1.00; HYP vs. LOM: p = 0.30; EMM vs. EOM: p = 0.99; EMM vs. LOM: p = 0.18; EOM vs. LOM: 0.30). If, however, as shown in Figure 4.4 and Chapter 3, and as suggested in previous studies (Seidel *et al.*, 2003), only higher demand levels (3.0 D and 4.0 D) are considered, the overall effect of refractive error is significant ($F_{(3,48)} = 2.85$; p = 0.047). A Scheffe's *post-hoc* comparison between refractive groups shows that the difference between LOMs and HYPs ($p = 0.065$) and LOMs and EMMs ($p = 0.076$) approaches significance.

4.3.2 Frequency-domain analysis

Figure 4.6 illustrates the relationship between accommodative demand and the FFT power spectral decomposition of the accommodative response for subject TB (EMM) when viewing targets at 0.0 D, 2.0 D and 4.0 D. The spectra illustrate the characteristic low and high frequency components described earlier (see Figure 4.1). Within the four refractive groups, large disparities in low and high frequency components were observed between subjects (see Appendix 7) although there were no apparent differences between refractive groups. In an attempt to minimise these variations (as stated in Chapter 1), two methods of analysing the fast Fourier transformations were utilised: relative (n.u.) and absolute (D^2Hz^{-1}) values.

Relative values (normalised units [n.u.])

A two-way mixed factor ANOVA showed that the overall effect of increasing accommodative demand (0.0 D to 4.0 D) was not statistically significant for the relative spectral power of the LFC (by -0.01 ± 0.19 n.u., $F_{(4,192)} = 1.33$; $p = 0.26$), but approached significance for the HFC (by +0.01 ± 0.11 n.u., $F_{(4,192)} = 2.40$; $p = 0.052$).

The effect of refractive error was statistically significant for the LFC ($F_{(3,48)} = 4.182$; $p = 0.01$). A Scheffe's *post-hoc* comparison of means illustrated a statistically significant difference between HYPs and LOMs ($p = 0.01$; Figure 4.7a), with LOMs having a higher normalised power in their LFC. All other comparisons between refractive groups were not significant (HYP vs. EMM: $p = 0.69$; HYP vs. EOM: $p = 0.23$; EMM vs. EOM: $p = 0.85$; EMM vs. LOM: $p = 0.20$; EOM vs. LOM: $p = 0.64$). Refractive error had no significant effect on the HFC ($F_{(3,48)} = 2.15$; $p = 0.11$; Figure 4.7b).

Again, if only the high accommodative demand (3.0 D and 4.0 D) targets are considered, large statistically significant differences in relative power of both the LFC ($F_{(3,48)} = 8.13$; $p < 0.0005$) and HFC ($F_{(3,48)} = 3.22$; $p = 0.03$) are observed between refractive groups (Figure 4.8a and 4.8b). Scheffe's *post-hoc* comparisons showed that LOMs had significantly more LFC power than HYPs ($p < 0.001$) and EMMs ($p < 0.005$), but LOMs were not different from EOMs (p = 0.41). Therefore, the LFC appears to contribute to the significant increase in accommodative oscillations at the higher accommodative demand levels in LOMs.

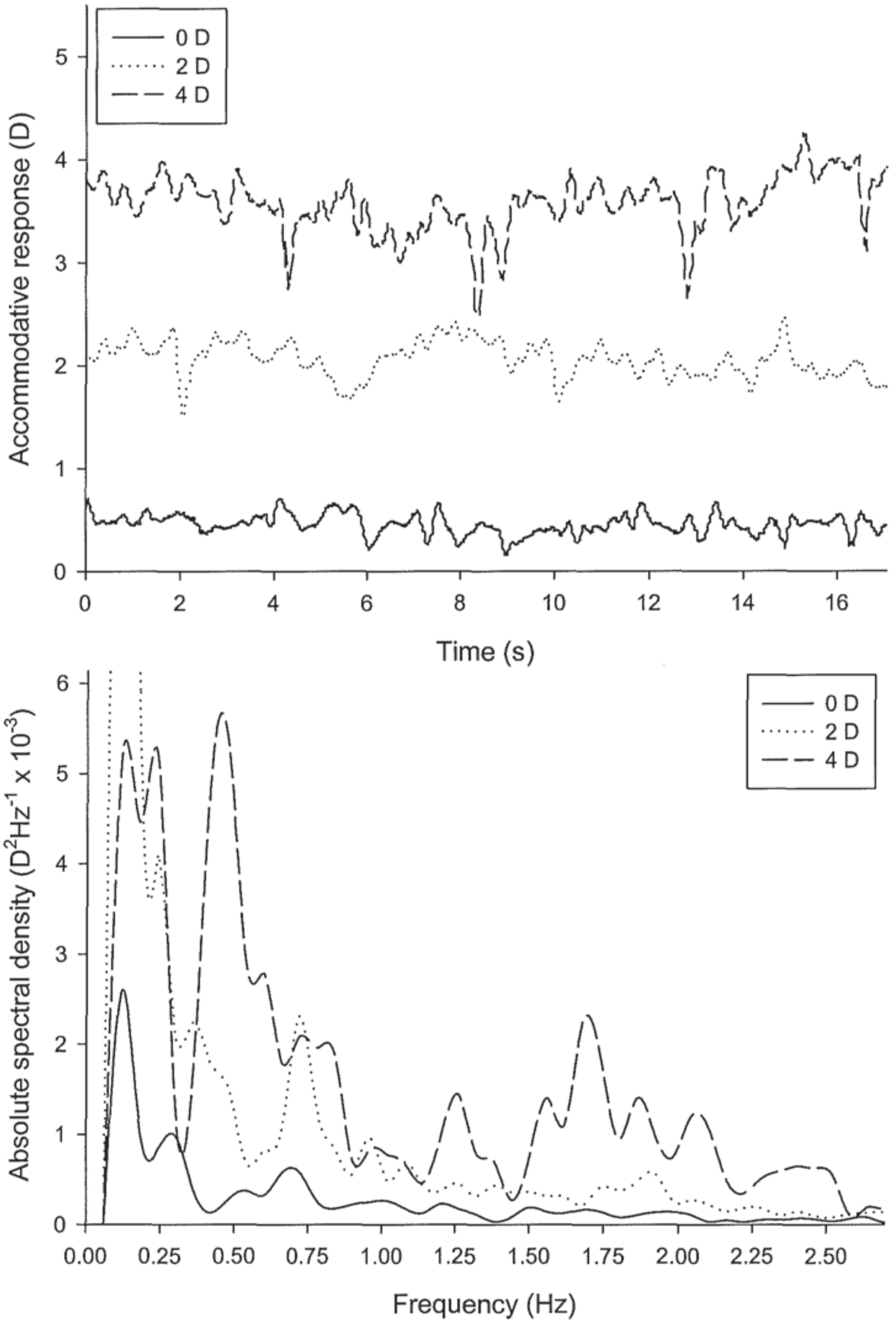

Figure 4.6 Top: Sample traces of 17.07 seconds of accommodative microfluctuations of an EMM (subject: TB) at 0.0 D, 2.0 D and 4.0 D accommodative demands. The traces have been smoothed with a 10 Hz filter. Bottom: The associated power spectra representing the mean absolute power of five 17.07 second traces for each accommodative demand.

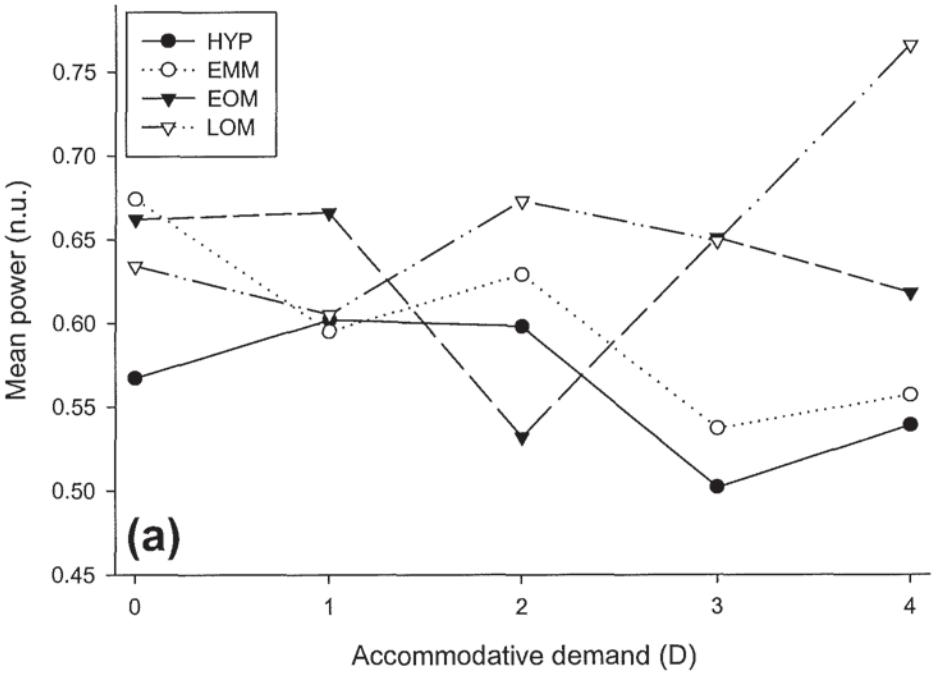

Figure 4.7a Mean power of the LFC in normalised units (n.u.) over all accommodative demands for the four refractive groups. Error bars have been omitted for clarity.

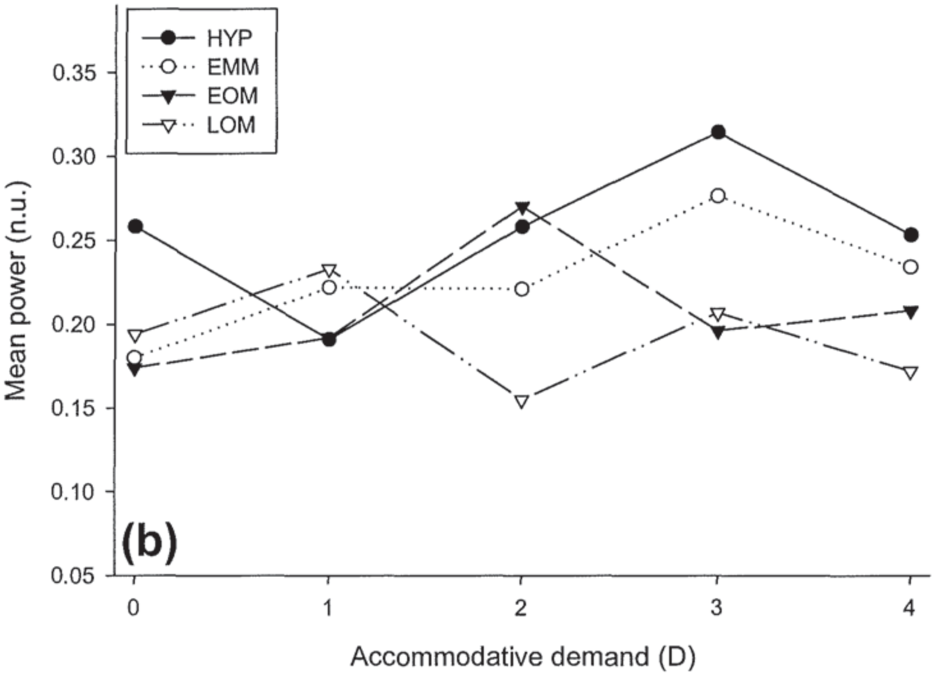

Figure 4.7b Mean power of the HFC in normalised units (n.u.) over all accommodative demands for the four refractive groups. Error bars have been omitted for clarity.

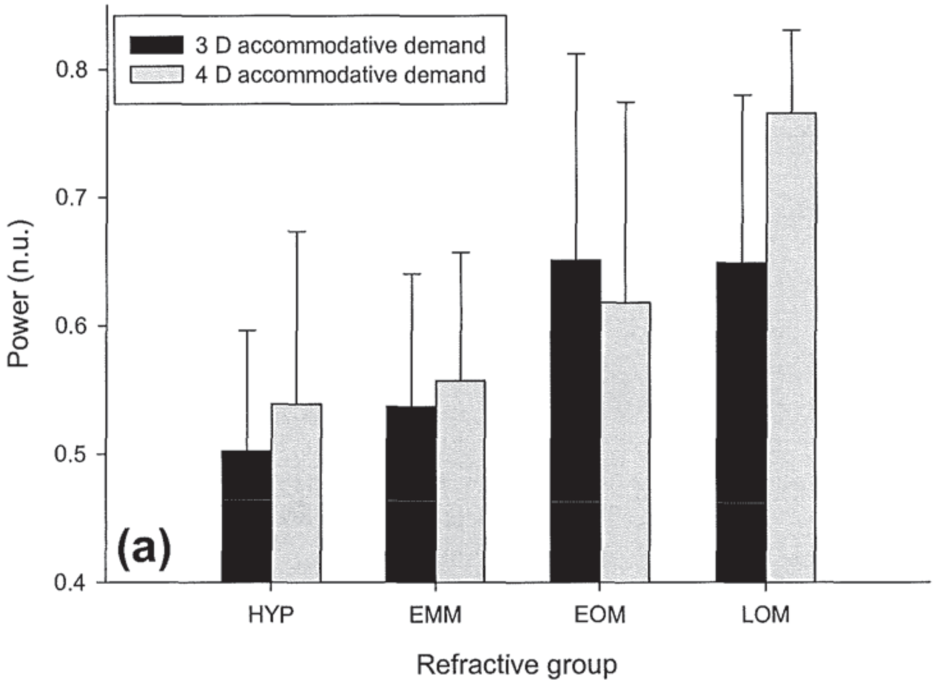

Figure 4.8a Mean power of the LFC in normalised units (n.u.) between all four refractive groups at 3.0 D and 4.0 D accommodative demands. Error bars represent 1 SD.

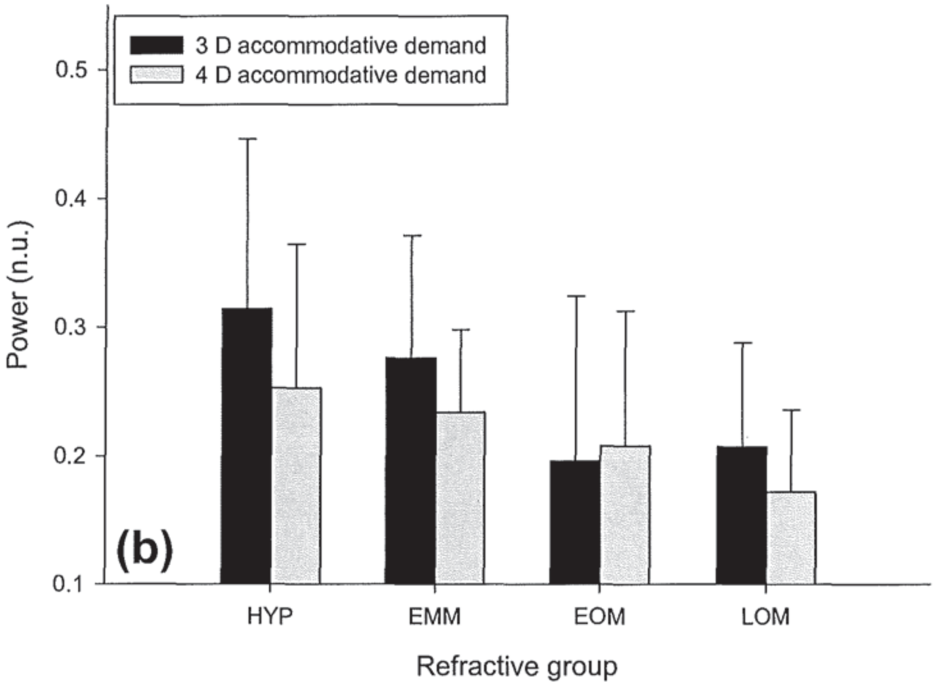

Figure 4.8b Mean power of the HFC in normalised units (n.u.) between all four refractive groups at 3.0 D and 4.0 D accommodative demands. Error bars represent 1 SD.

Absolute values (D^2Hz^{-1})

Figure 4.9 shows the relationship between accommodative demand and the resultant absolute powers of the LFC and HFC in the microfluctuations. Analysis of variance showed that the overall effect of increasing accommodative demand (0.0 D to 4.0 D) lead to a non-significant increase in the absolute spectral power of the LFC (by +0.014 ± 0.044 D, $F_{(4,192)} = 1.29$; $p = 0.28$). Conversely, demand produced a highly significance increase in the HFC (by +0.007 ± 0.009 D, $F_{(4,192)} = 6.14$; $p < 0.0005$).

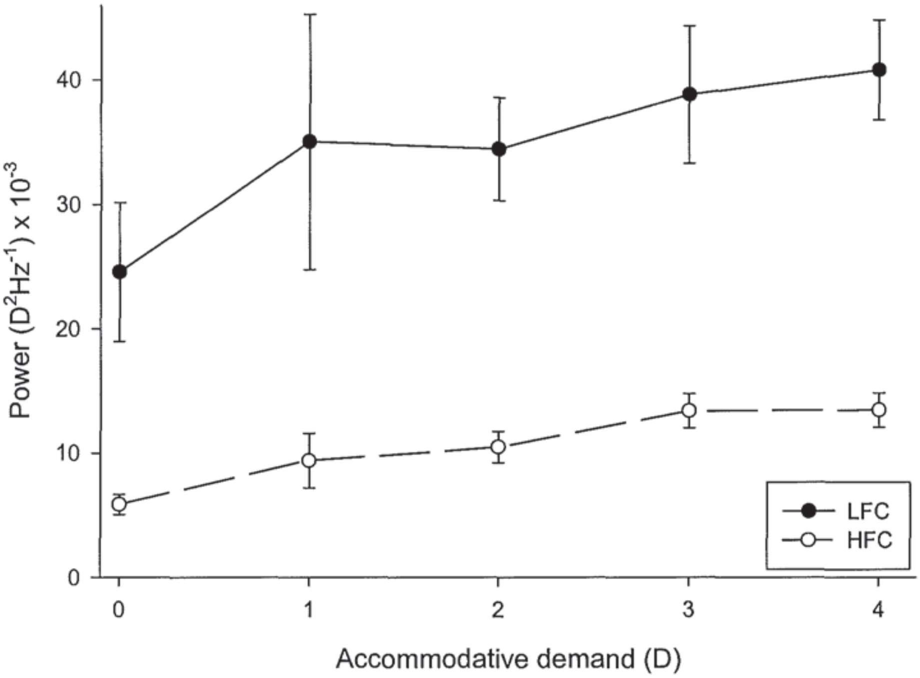

Figure 4.9 Effect of increasing accommodation on the absolute spectral power of the LFC and HFC. Error bars represent ± 1 SEM.

As with the relative values, refractive error augmented the LFC significantly ($F_{(3,48)} = 2.88$; $p = 0.045$). Interestingly, however, a Scheffe's *post-hoc* test illustrated that only the LOM group showed a tendency towards statistically significant differences between the other refractive groups (HYP vs. EMM: $p = 1.00$; HYP vs. EOM: $p = 1.00$; HYP vs. LOM: $p = 0.15$; EMM vs. EOM: $p = 1.00$; EMM vs. LOM: $p = 0.12$; EOM vs. LOM: $p = 0.14$). Once again, refractive error had no significant effect on the HFC ($F_{(3,48)} = 0.33$; $p = 0.80$).

4.4 Discussion

The principle aim of this study was to examine the time- and frequency-domain characteristics of the steady-state accommodative response in a large cohort (n = 52) encompassing the four refractive groups (HYP, EMM, EOM and LOM) to changes in blur-driven retinotopic stimuli (0.0 D to 4.0 D in 1.0 D steps). Previous studies have suggested that increasing the accommodative demand leads to an increase in the accommodative microfluctuations in the stimulus intensity range of 0.0 D to 5.0 D (Denieul, 1982; Kotulak and Schor, 1986; Miege and Denieul, 1988; Toshida *et al.*, 1998). These studies, however, have investigated a limited number of subjects and refractive groupings (see Table 4.1). As Appendix 6 and 7 illustrate, large inter-subject variations exist in accommodative response profiles, therefore, this study was performed on a relative large cohort.

RESEARCHERS	SIZE (N)	REFRACTIVE GROUPS	STIMULUS RANGE	EFFECT ON RMS	EFFECT ON FFT
Denieul (1982)	3	n/a	0 to -5 D	Increases	LFC increases HFC inversely related
Kotulak and Schor (1986)	3	n/a	0 to -5 D	Increases	HFC increases
Miege and Denieul (1988)	2	EMMs	+3 to -9 D	Largest between -1 to -4 D	LFC no systematic change HFC positively correlated
Toshida, Okuyama and Tokoro (1998)	18	EMMs and MYOs	+5 to -12 D	Increases	LFC increases HFC peaks in centre of range
Day, Strang, Seidel, Gray and Mallen (2004)	20	10 MYO 10 EMM	0 to -4 D (1 D steps)	Increase in both refractive groups	LFC increase No change in HFC

Table 4.1 A selection of studies that have examined the effect of increasing accommodative demand on the accommodative response in both the time- and frequency-domain.

In support of previous investigations (Denieul, 1982; Kotulak and Schor, 1986; Miege and Denieul, 1988; Toshida *et al.*, 1998), increasing the accommodative demand (from optical infinity to 4.0 D) led to an increase in the mean RMS response (on average by ~0.02 D/D). In general, myopes and more specifically LOMs found it more difficult to maintain steady accommodation on stimuli with higher accommodative demands. Myopes showed the largest increase in both absolute and relative RMS value. Power spectral analysis revealed that the LFC was the primary cause for augmentation of the oscillations in the LOM group compared to the HYP and EMM groups.

The complex accommodative response waveform is believed to be a consequence of the combination of neurological control and physiological noise: the former is attributable to the LFC; the latter to the HFC (Winn, 2000). Other workers, however, have suggested that the HFC fluctuations may also, in part, be associated with autonomic control (Toshida *et al.*, 1998). Indeed, Collins and co-workers suggested that the two principle regions in the accommodative FFT power spectra demonstrated an apparent association between rhythms in the cardiopulmonary system and rhythms in the steady-state accommodative response (Collins *et al.*, 1995). In their study, LFC regions corresponded to the respiration/sinus arrhythmia cycle, whereas HFC regions corresponded to the instantaneous vascular pulse cycle.

The data presented in this study also alludes to a role for the HFC, as suggested by Kotulak and Schor (1986). Figure 4.9 illustrates the linear increase in FFT spectral power of the HFC (absolute values) with increasing levels of accommodation ($p < 0.0005$). This increase in HFC power may be enhanced neurologically, thus suggesting a role for the HFC in the control of accommodation, or maybe a consequence of an increase in overall noise level in the system. As such, if the relative HFC values are considered where noise factors are negated, again, an increase in HFC power is apparent. However, this increase does not reach significance (Figure 4.7b). The HFC also seems to be modulated by the refractive error of the individual, with myopes showing little change in accommodative microfluctuations with low degrees of accommodative demand compared to EMM and HYP. In addition, LOMs have generally greater accommodative microfluctuations at all accommodative levels, principally due to an increase in the LFC. As the LFC has principally been attributed to the neurological control of accommodation (Winn, 2000), this finding fits well with the suggestion that myopes have a less critical tolerance to blur (Abraham-Cohen *et al.*, 1997). Furthermore, at higher accommodative demands (Figure 4.8b) significant differences in HFC power is exhibited between refractive groups.

In order to test further this apparent association between the spectral components of the accommodative response and the autonomic nervous system, plus the role of the HFC, Chapters 5 and 6 will compare and contrast autonomic correlates of oculomotor (accommodation) and autonomic (cardiovascular) function.

4.5 Conclusions

The main findings of this investigation are:

- Increasing the accommodative demand leads to a significant linear increase in the accommodative RMS values.
- Refractive error only has an influence on the RMS at higher accommodative demands (3.0 D and 4.0 D).
- Accommodative demand had no significant effect on the LFC of the accommodative Fourier transformation.
- Accommodative demand had a significant effect on the HFC of the accommodative Fourier transformation.
- LOMs had significantly higher accommodative variability, principally due to the LFC of the Fourier transformation.
- Refractive error had no significant influence on the HFC of the Fourier transformation.
- At higher accommodative demands (3.0 D and 4.0 D) significant differences in relative power of the low- and high-frequency components were observed between refractive groups.
- LOMs have more LFC power than HYPs or EMMs at higher demands.

The results of this study may have ramifications on the understanding of the development of myopia and the putative role accommodation plays.

CHAPTER 5

AUTONOMIC CORRELATES OF OCULOMOTOR AND CARDIOVASCULAR FUNCTION

5.1 Introduction

Previous investigations have shown that analysis of heart rate variability (HRV) can be utilised to quantify a number of physiological systems, such as autonomic function (Akselrod *et al.*, 1981; Bates *et al.*, 1997; Fauchier *et al.*, 1998; Murray *et al.*, 2001). The autonomic nervous system (ANS) exists in equilibrium between the sympathetic and parasympathetic branches and provides a signal to most bodily organs and systems including the eye (Cogan, 1937; Gilmartin, 1986).

The evolutionary purpose of the ANS is to enable an individual to adapt and react to their surrounding environment – 'fight or flight'; when presented with a confrontational situation, the human ANS prepares the body for evasive action. For example, an increase in sympathetic innervation leads to constriction of blood vessels, increased respiration, dilation of the pupil and accelerated heart rate. On recovery, the body returns to homeostasis: blood vessels dilate; respiration decreases; pupils constrict and heart rate decreases.

Qualification of the action of the ANS in ocular accommodation, for example in myopia studies (Gilmartin *et al.*, 2002), is currently a protracted procedure requiring the use of pharmacological drugs, which either negate one or both of the autonomic branches (Gilmartin, 1986; Bullimore and Gilmartin, 1987a, 1988; Rosenfield *et al.*, 1990; Gilmartin and Winfield, 1995; Mallen, 2002). These studies have elucidated that both the sympathetic and parasympathetic branches are responsible for the control of ocular accommodation. Moreover, a recent study by Gilmartin and co-workers suggested that inhibitory sympathetic innervation of the ciliary muscle exists in approximately 30% of the population (Gilmartin *et al.*, 2002), which supports previous investigations (Gilmartin and Bullimore, 1987a; Owens, 1991; Gilmartin and Winfield, 1995).

Studies have hypothesised that as myopes (in particular LOMs) exhibit differences in their accommodative response compared to other refractive groups, an imbalance in the underlying autonomic tonus may induce atypical accommodative responses during sustained nearwork, thus leading to an increased risk of myopia development. Few studies, however, have been able to quantify the precise contribution of each ANS branch during sustained nearwork. Both sympathetic and parasympathetic forces are known to interact in convoluted mechanisms (Gilmartin, 1986). Therefore, when a pharmacological agent is used to block one of the autonomic branches, the resultant behaviour may not reflect the true nature of the remaining branch; potentially leading to spurious results. Furthermore, it is not known how the proposed autonomic imbalance in myopes arises.

As described in Chapter 1, heart rate and rhythm are largely under the control of the autonomic nervous system; sympathetic activation increases heart rate while parasympathetic forces reduce heart rate. By spectrally analysing the inter-beat intervals that lead to HRV, one can non-invasively elicit information regarding the systemic nature of the sympathetic and parasympathetic nervous systems (Akselrod *et al.*, 1981; Tyrrell *et al.*, 2000). Two dominant frequencies are present in the fast Fourier power spectrum. A frequency band from approximately 0.15 Hz to 0.40 Hz is commonly designated as the high frequency component (HFC), with 0.05 Hz to 0.15 Hz being the low frequency component (LFC) (Akselrod *et al.*, 1981; Task Force, 1996; Cammann and Michel, 2002). It should be noted, however, that there is variation in these frequency bands between investigations (Task Force, 1996). A third very low frequency (VLF) band (< 0.05 Hz) is also present in the power spectra. The physiological nature of this component is not clearly understood and the existence of a specific physiological mechanism attributable to these heart period changes is questionable. Consequently, frequencies below 0.05 Hz are subtracted from the total spectral content in short- (5 minute) and long-period (24 hour) heart rate recordings when interpreting the power spectral density (Task Force, 1996).

As the eye and heart receives neural innervation from both branches of the autonomic nervous system, it could be hypothesised that a connection between the two organs may exist. Indeed, Tyrrell and co-workers first proposed this link by measuring tonic accommodation (TA) and tonic vergence (TV) in 19 young adults, whilst their electrocardiograms were recorded. They found that heart rate was positively correlated to TV and that the spectral decomposition of the HRV accounted for, in part, the individual disparities in TA and TV (Tyrrell *et al.*, 1992).

As stated in Chapters 1 and 3, the accommodative stimulus-response function describes the relationship between the response of and demand to the accommodative system. Figure 1.3 illustrates the typical accommodative stimulus-response function acquired under photopic conditions with a high-contrast target. Traditionally, any increase in accommodative response above the intersection/cross-over point with the unit ratio line ('resting state') is considered to be facilitated by parasympathetic initiation, whereas, below the cross-over point sympathetic factors prevail (Charman, 1982). Such a model implies that the two branches of the ANS are balanced at the cross-over point. No study to date, however, has directly tested this hypothesis using non-invasive techniques to measure autonomic innervation.

Previous investigations of the stimulus-response function have found a relationship with refractive error (McBrien and Millodot, 1986b; Schaeffel *et al.*, 1993), inaccurate accommodation in myopia (Abbott *et al.*, 1998) and the accommodative response to real-world visual tasks (Wolffsohn, 1997; Wolffsohn *et al.*, 1998; 1999). Furthermore, TA has been shown to relate to a number of factors including the subject's surroundings (Rosenfield and Ciuffreda, 1991), refractive error (McBrien and Millodot, 1987; Jiang, 1995); stability of refractive error (Jiang and Morse, 1999) and physical exercise (Ritter and Huhn-Beck, 1993) (See Chapter 1 for a review). Investigations into the innervation of the stimulus-response function and TA will, therefore, further aid in understanding the oculomotor response model and variations in refractive error development.

The present study, therefore, sought to determine whether measures of accommodation are related to measures of cardiovascular activity. New methods of measurement and analysis to examine the underlying within-task systemic autonomic profile to open- and closed-loop accommodation responses are used. The study examines the hypothesis that arousal of the autonomic nervous system can be shown through covariations in oculomotor and cardiovascular function.

5.2 Methods

5.2.1 Subjects

Sixty subjects (29 male; 31 female) varying in age from 18 to 33 years (average: 20.3 ± 2.9 years) took part in the study. Fifteen subjects were hypermetropes (HYP; mean spherical equivalent [MSE]: +0.86 ± 0.34 D; range: +0.51 to +1.82 D), 15 subjects were emmetropes (EMM: MSE: 0.00 ± 0.24 D; range: -0.37 to +0.37 D), 15 subjects were early-onset myopes (EOM: MSE: -3.93 ± 2.28 D; range: -7.12 to -1.25 D), and 15 were late-onset myopes (LOM: MSE: -1.92 ± 1.52 D; range: -5.50 to -0.56 D). The mean age of onset for the EOMs was 10.3 ± 2.8 years (range: 6 to 14 years) and 16.7 ± 0.7 years (range: 16 to 18 years) for the LOMs.

The research followed the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee (Appendix 2). Copies of the information sheets and consent forms given to subjects can be found in Appendix 3. Subjects were rendered functionally emmetropic with conventional daily disposable spherical soft contact lenses (2-hydroxyethyl methacrylate [HEMA] lenses, 58% water content; Acuvue Dailies, Vistakon, Johnson & Johnson Vision Care, Jacksonville, Florida, USA) to ensure that the accommodative demand was virtually identical for each subject. All subjects had 0.00 logMAR visual acuity or better, none had any form of visual or heart anomaly. None of the subjects were taking any topical or systemic medication that may alter autonomic, oculomotor or cardiovascular function. All subjects were trained to remain still and maintain steady fixation in order to limit artefacts in both the heart period and accommodative data by running the complete study prior to data collection.

5.2.2 Stimulus

Each subject was required to monocularly view a stationary high contrast (90%), 37.0 cdm^{-2} Maltese cross through a +5.0 D Badal optical system, thus ensuring both contrast and image size remained constant. Five stimulus conditions were employed in a random order within the Badal system (0.0 D to 4.0 D in 1.0 D steps). In accordance with previous investigations (Tyrrell *at al.*, 1994; Pearson *et al.*, 1996), a further angular subtense and luminance matched Maltese cross target was used at 6.0 D (in free-space) due to the eye to combiner distance of the SRW-5000 limiting the accommodative demand of a Badal system to < 5.0 D; only HRV was recorded at this stimulus level for use in FFT power spectrum analysis. At all levels, subjects were encouraged to concentrate on the Maltese cross as attentional factors have been shown to play an important role in accommodation measurement (Francis *et al.*, 2003). For open-loop measurements (TA), a photographic 0.1 $cdeg^{-1}$ Difference-of-Gaussian (DoG) target was used (Kotulak and Schor, 1987).

5.2.3 Instrumentation

Accommodative response was measured with a Shin-Nippon SRW-5000 infrared autorefractor (Ryusyo Industrial Co. Ltd, Osaka, Japan) specially modified to record accommodative response continuously with a spatial resolution of < 0.01 D and a temporal resolution of 60 Hz (Mallen *et al.*, 2001; Wolffsohn *et al.*, 2001b). The temporal resolution was well above the Nyquist frequency (in accommodation recordings the highest frequency does not exceed 2.5 Hz; Pugh *et al.*, 1987). The instrument provides an open-view arrangement and measures the accommodative response by image-analysis of an infrared ring reflected off the retina (see Mallen *et al.*, 2001 for a full account). Previous investigations have shown that the optometer is highly repeatable and accurate in both children (Chat and Edwards, 2001) and adults (Mallen *et al.*, 2001). Data acquisition and analysis were performed using purpose written *LabView* software programs (National Instruments, Austin, Texas, USA). Any blink within the continuous sampling time causes an abrupt change in signal amplitude (Collins *et al.*, 1995). Removal of these blink artefacts was performed by extracting data greater than ± 2.0 D from the stimulus level (Wolffsohn *et al.*, 2003).

The alignment system of the optometer provides a magnified image (× 6) of the subject's eye on the video display allowing pupil size to be monitored and measured with the aid of a measurement scale overlay during the experiment. The coefficient of repeatability (CoR) for a 3 mm fixed pupil using this technique was 0.02 mm, and 0.04 mm for a 6 mm pupil. As such, pupil size was recorded throughout the experiment by averaging three readings taken from the SRW-5000 video display at each stimulus level. Minimum pupil size was 3 mm for all accommodative conditions (mean: 4.42 ± 0.38 mm; range: 3.0 to 6.7 mm).

Heart rate variability was recorded with a piezo-electric pulse transducer (*MLT 1010*, UFI Instruments, Morro Bay, California, USA) attached to the index finger of the subject's left hand with a Velcro® strap. The piezo-electric transducer converts physical pulse activity into an electrical signal. The voltage signal produced from the transducer (approximately 50 mV) was amplified with a bio-amplifier to produce an output voltage of approximately 6 V. The signal was then sampled by the *LabView* software and the inter-beat interval calculated for each heart period by using a peak detector. The peak detector algorithm fits a quadratic polynomial to sequential groups of data points. The number of data points included in the fit is specified by a given width value. For each peak, the quadratic fit is tested against a specified threshold level. Peaks with heights lower than the threshold level are ignored. As heat rate is a dynamic entity, online manipulation of the threshold value was available to counteract any sudden attenuation in the R-wave. Consequently, any high frequency, low amplitude noise in the heart rate signal was not mistaken for a heart beat. The resultant data were also screened for erroneous ectopic heart beats by eye as suggested by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996).

In order to reduce variations in the frequency-domain components in both the accommodation (Collins *et al.*, 1995) and cardiovascular (Task Force, 1996) data, respiration was regulated by the subjects to 15 breaths per minute (0.25 Hz) with the aid of a digital quartz metronome (*SQ 50*, Seiko, Japan) as in previous investigations (Tyrrell *et al.*, 1994, 2000; Davies *et al.*, 2004) during all stimuli presentations.

5.2.4 Procedure

Initially, the residual refractive error of each subject with contact lens correction was measured through the Badal system with the target placed at 0.0 D. Subjects were excluded if their mean residual refractive error was > ± 0.25 D or if the cylindrical component was 0.50 DC.

On commencement, the optical axis of the SRW-5000 was aligned with the subject's right eye, with the left eye occluded. Both heart rate and accommodative response were recorded concurrently. Five 17.07 second continuous recordings of the accommodative response were obtained for each accommodative level at a sampling rate of 60 Hz, giving 1024 data points for each accommodative recording while the subject's heart rate was continuously recorded for 5 minutes (providing at least 256 data points) at each target vergence. Before recording the accommodative and heart rate response in open-loop conditions, subjects were required to observe the DoG target for 5 minutes, to allow the effects of any previous nearwork to dissipate (Krumholz *et al.*, 1986).

Using the heart rate signals, from the finger pulse transducer, inter-beat intervals were calculated, and exported to a *Microsoft Excel* file. To examine the periodic variations in the signals, Fourier transforms were calculated for each 5 minute recording (Task Force, 1996; Hansen *et al.*, 2003). The HRV spectra produced for each accommodative demand were analysed for LFC and HFC. Measurement of the spectral components were quantified in both absolute values of power (s^2Hz^{-1}) and in normalised units (n.u.) which represent the relative power of each component in proportion to the overall power spectra minus the VLF component, thus eliminating inter- and intra-subject variation caused by background noise.

The accommodative signals were also exported to a *Microsoft Excel* file, filtered for blinks and frequencies >10 Hz were filtered. A power spectrum was calculated for each individual trace. Five individual accommodative power spectra from each recording condition were averaged as in previous studies (Winn and Gilmartin, 1991; Gray *et al.*, 1993a, 1993b, 2000) to decrease the uncertainty in the mean power spectrum (Pugh *et al.*, 1987).

5.2.5 Data and statistical analysis

Data analysis was performed with *Microsoft Excel*, SigmaPlot 2000 (version 6.0; Systat Software UK Ltd, London, UK) and SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). Data were treated with a two-way (vergence, refractive error) mixed ANOVA where vergence was taken as a within-subject variable and refractive error as the between-subject variable. A Scheffe's *post-hoc* comparison of means test was also used to compare differences between refractive groups. Pearson's product moment correlation coefficients were used to compare the relationship between independent variables.

5.3 Results

5.3.1 Relationship between TA and heart period

For each subject, the mean heart period was measured while the subject was in the open-loop state (i.e. while viewing a DoG target). The relationship between mean heart period and TA indicates that those subjects with a faster heart rate (lower heart period) tend to have a higher TA value (r = -0.27, p = 0.04; Figure 5.1). The results imply that higher levels of TA are associated with relatively higher levels of systemic sympathetic tonus.

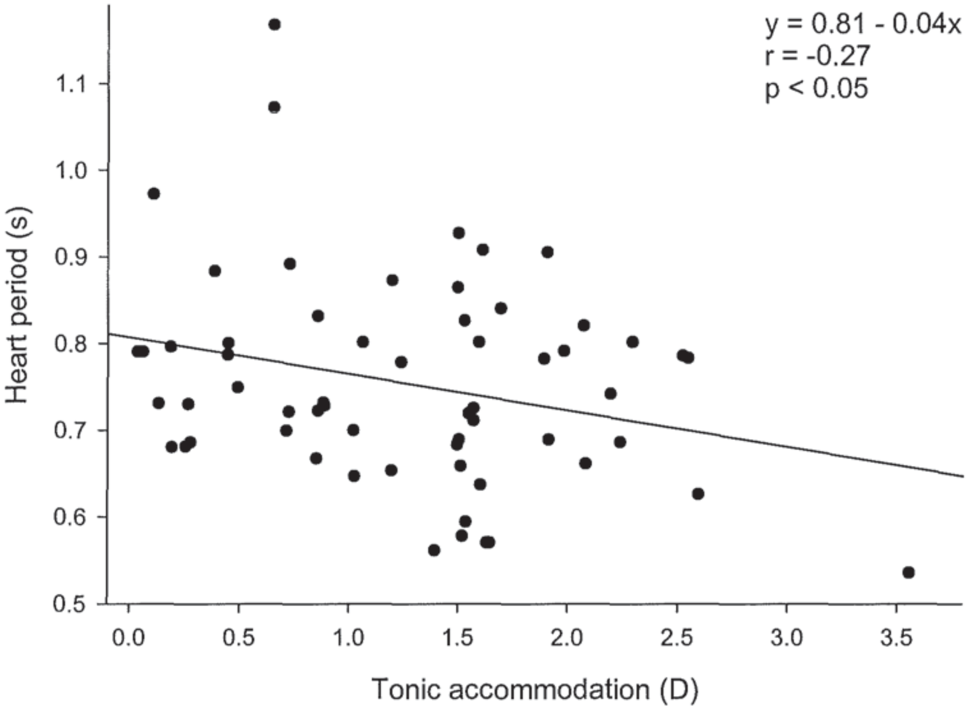

Figure 5.1 The relationship between mean heart period and tonic accommodation for the whole cohort (n = 60).

5.3.1 Effect of accommodative demand on heart period

Figure 5.2 indicates that with increased accommodative demand there is a concurrent decrease in heart period (increase in heart rate), of approximately 2 beats/min for a 4.0 D increase in accommodative demand. The mean change in heart period was significant (by -0.014 ± 0.050 s, $F_{(4,224)} = 2.6$; $p < 0.05$). However, refractive grouping had no significant influence ($F_{(3,\ 56)} = 1.1$; p = 0.36). A Scheffe's *post-hoc* comparison of means test showed no significant difference between all refractive group combinations (HYP vs. EMM: p = 0.38; HYP vs. EOM: p = 0.77; HYP vs. LOM: p = 0.69; EMM vs. EOM: p = 0.92; EMM vs. EOM: p = 0.96; EOM vs. LOM: p = 0.99).

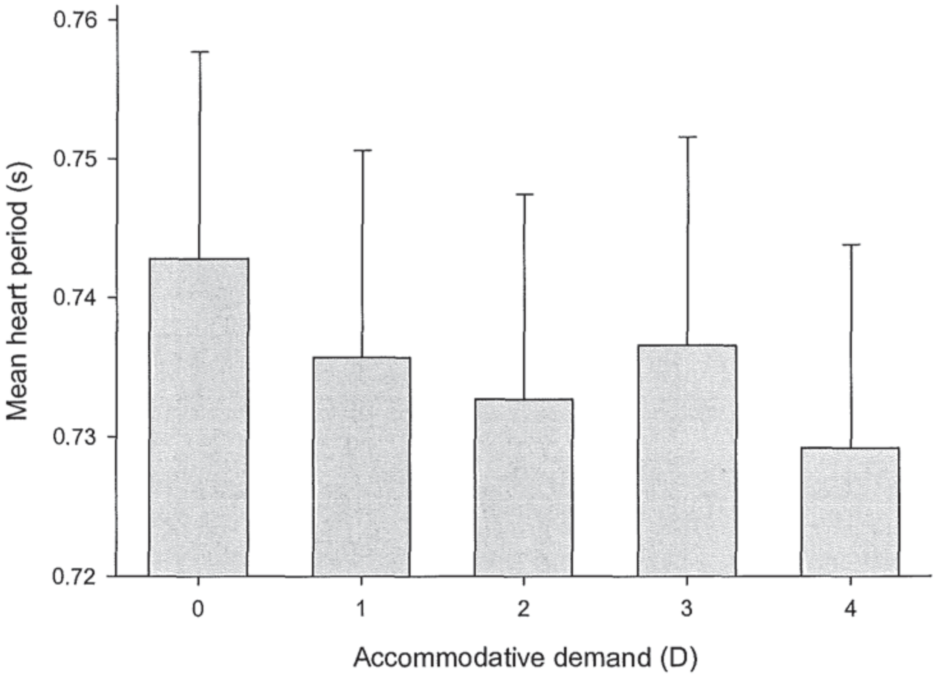

Figure 5.2 Effect of accommodative demand on mean heart period (n = 60). Error bars represent 1 SEM.

The grouped data seems to provide compelling evidence to suggest that there is an increase in sympathetic dominance of heart activity with increased accommodative demand with no contribution from refractive error. When the individual heart period plots are considered, however, not all show this trend in heart period. Indeed, 71% of the HYP, EOM and LOM subjects show the reduction in heart period whereas only 33% of EMMs follow the trend. Figures 5.3, 5.4, 5.5 and 5.6 show a selection of individual heart period plots, one subject from each refractive group. Figures 5.3 and 5.4 show a strong positive correlation (relative parasympathetic augmentation), while figures 5.5 and 5.6 illustrate a negative correlation (relative sympathetic augmentation). If the accommodative responses of all subjects are compared to the mean shift in heart period, again no single significant trend is apparent (r = -0.09, p = 0.15). There are in fact a number of subjects who exhibit increases in heart period (see Figure 5.7). Appendix 8 shows the heart period values for all subjects.

The results appear to suggest tentatively that the systemic response of ametropic subjects (HYP, EOM and LOM) is sympathetically mediated whereas EMM subjects, on the whole, respond parasympathetically. These results, however, are not conclusive. Consequently, due to this inconsistency between individuals, further analysis was undertaken. In order to decipher the precise aetiology of the eye-heart correlation, the relative powers of the HRV LFC and HFC spectral components were analysed for each subject.

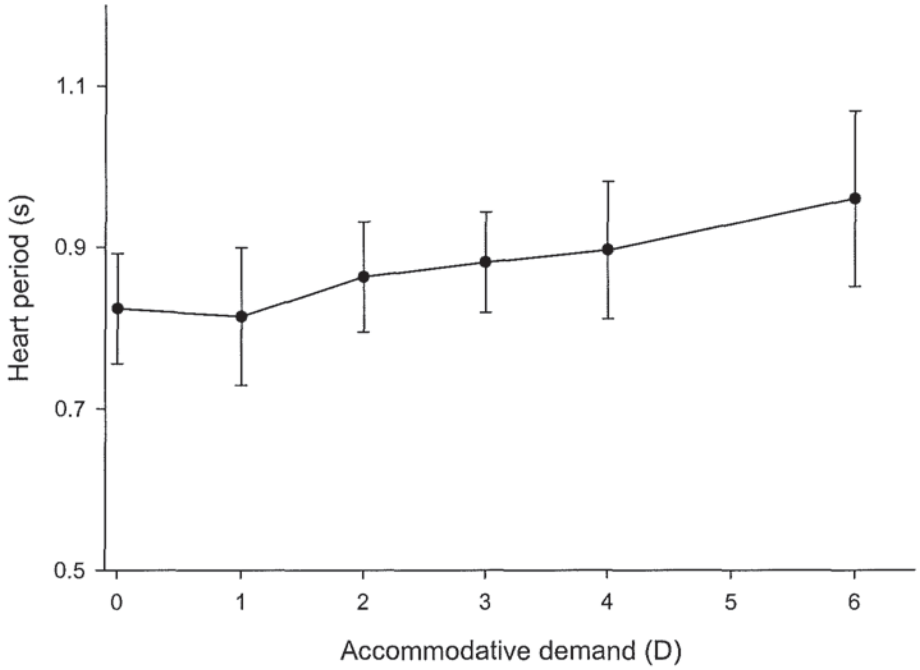

Figure 5.3 Effect of accommodative demand on mean heart period for subject CH (HYP). Error bars represent ± 1 SD.

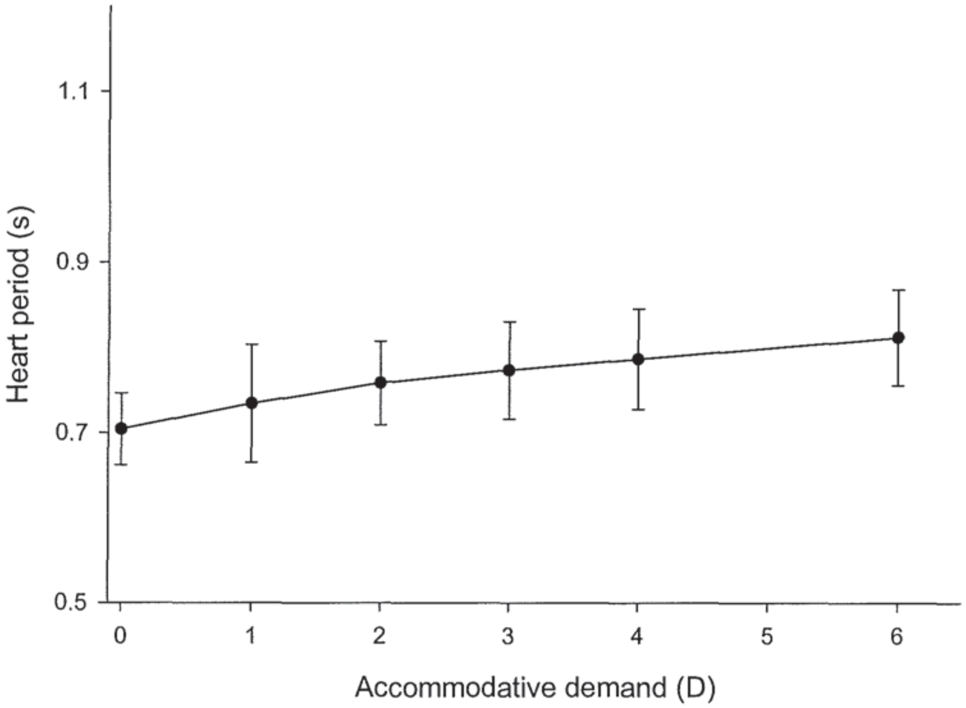

Figure 5.4 Effect of accommodative demand on mean heart period for subject SL (LOM). Error bars represent ± 1 SD.

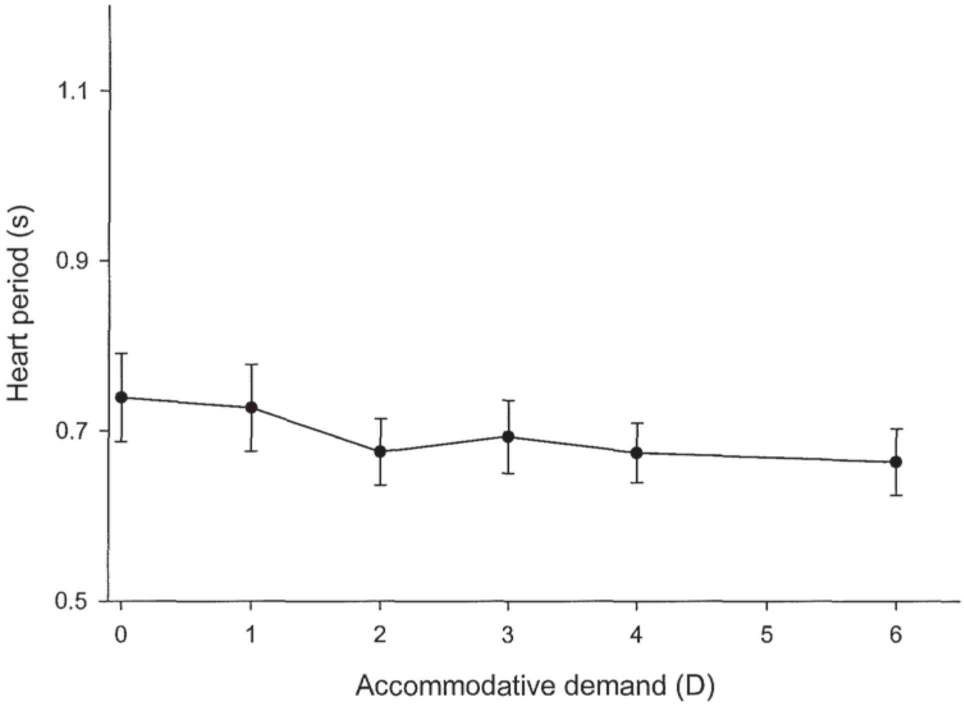

Figure 5.5 Effect of accommodative demand on mean heart period for subject EM (EOM). Error bars represent ± 1 SD.

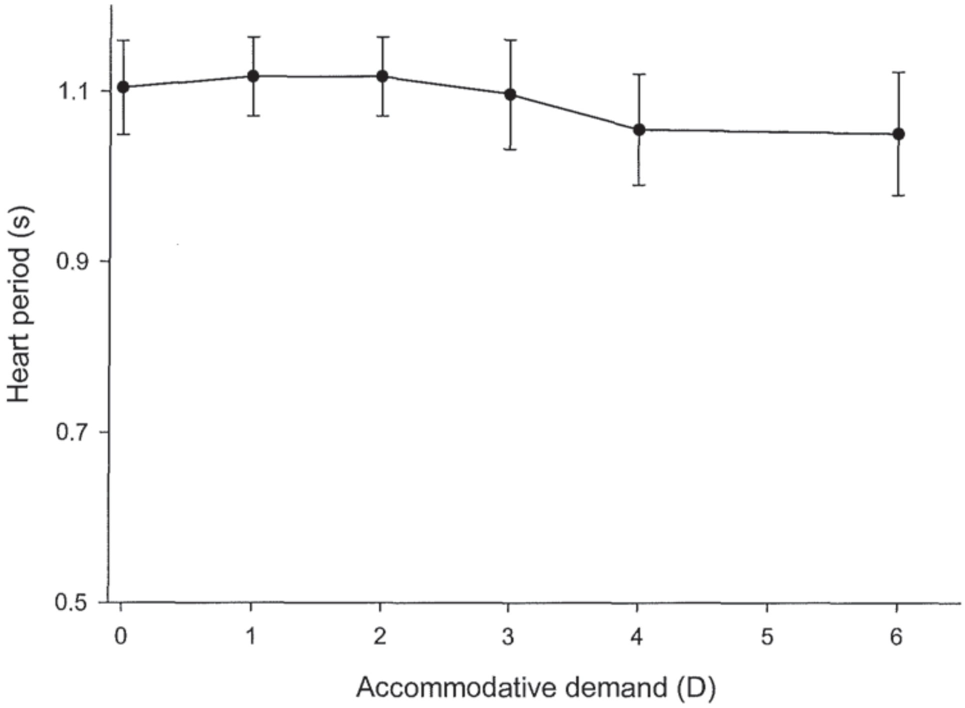

Figure 5.6 Effect of accommodative demand on mean heart period for subject GG (EMM). Error bars represent ± 1 SD.

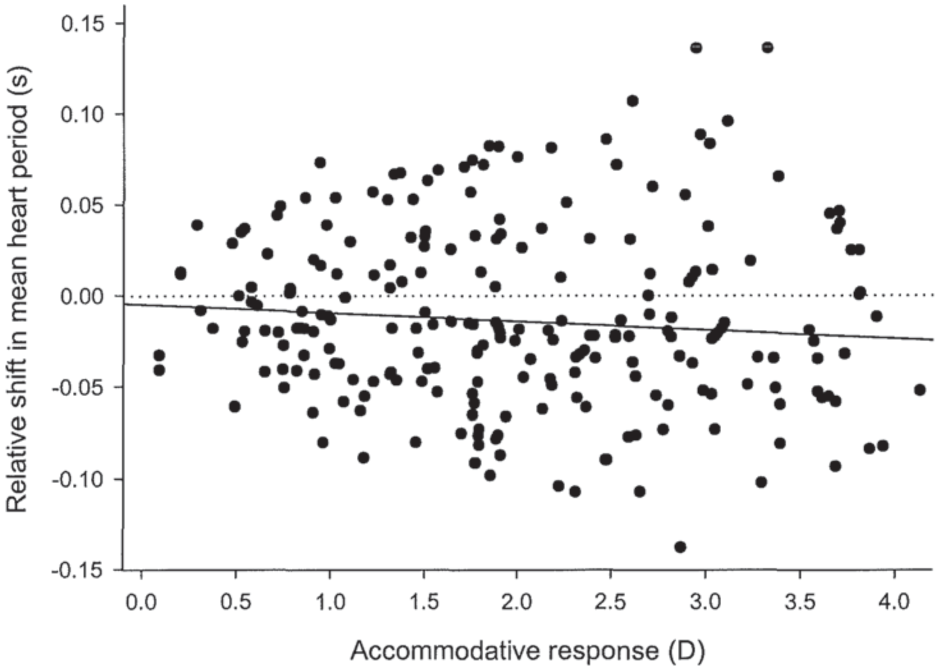

Figure 5.7 The relationship between the relative shift in mean heart period and the corresponding accommodative response (n = 60). Solid line represents regression line. Dotted line represents no relative shift in mean heart period.

5.3.3 Effect of accommodative demand on power of HRV LFC and HFC quantified by FFT power spectral analysis (absolute and relative power of LFC and HFC)

Figure 5.8 gives an example of a HRV FFT power spectrum. It demonstrates clearly the well documented LF and HF components (Akselrod *et al.*, 1981; Task Force, 1996), with the LF component centred at 0.1 Hz and with the HF component at approximately 0.25 Hz (Task Force, 1996; Bates *et al.*, 1997).

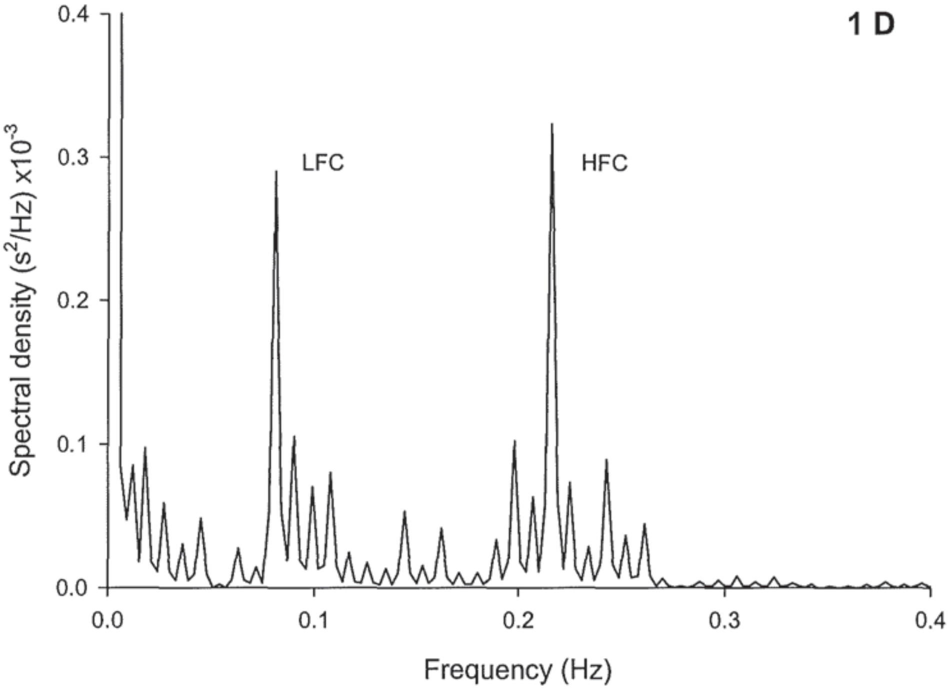

Figure 5.8 Fast Fourier transformation of a HRV tachogram for subject GS viewing a target at 1.0 D accommodative demand illustrating the classic LFC (~0.1 Hz) and HFC (~0.25 Hz) in the power spectrum.

Typical HRV tachograms for one EMM subject (RZ) taken with different accommodative stimuli along with their corresponding power spectra are shown in Figure 5.9 for the 0.0 D, 2.0 D, 4.0 D and 6.0 D accommodative demand levels. In order to express the absolute and relative contributions of the sympathetic and parasympathetic nervous system during various accommodative stimuli, LF and HF components were expressed in both absolute (s^2Hz^{-1}) and normalised units (n.u.).

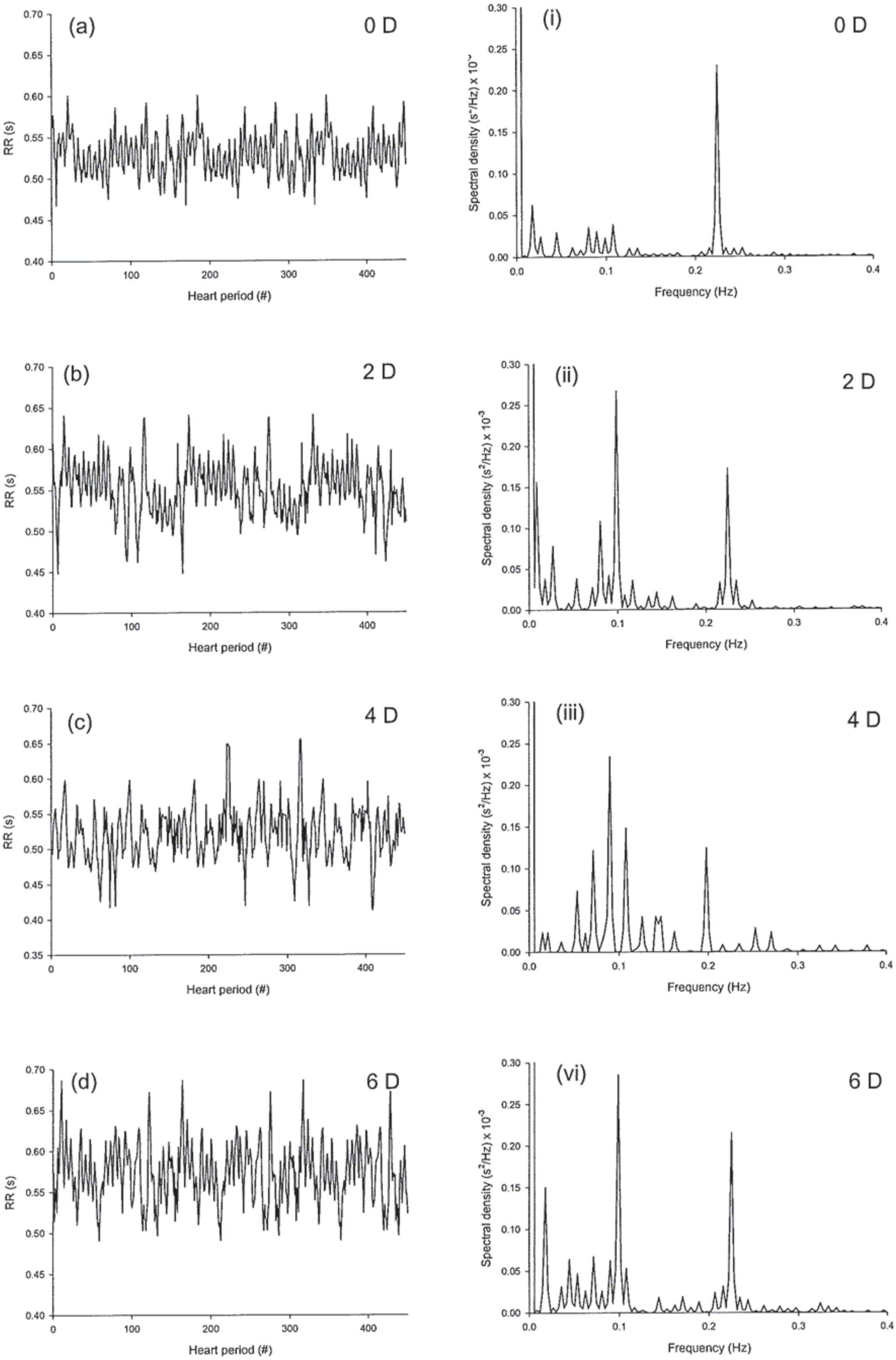

Figure 5.9 Typical tachograms (a to d) and corresponding power spectra (i to iv) for subject RZ (at 0.0 D to 6.0 D accommodative demand in 2.0 D steps).

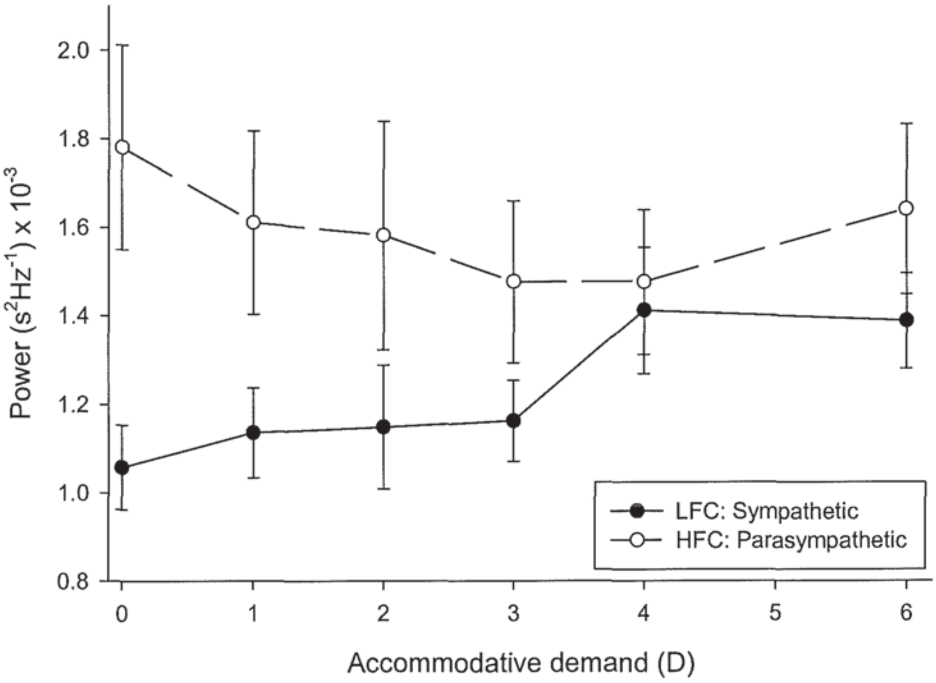

Figure 5.10 Effect of accommodative demand on the systemic sympathetic and parasympathetic profile in all subjects. Power expressed in absolute units (s^2Hz^{-1}). Error bars represent ± 1 SEM.

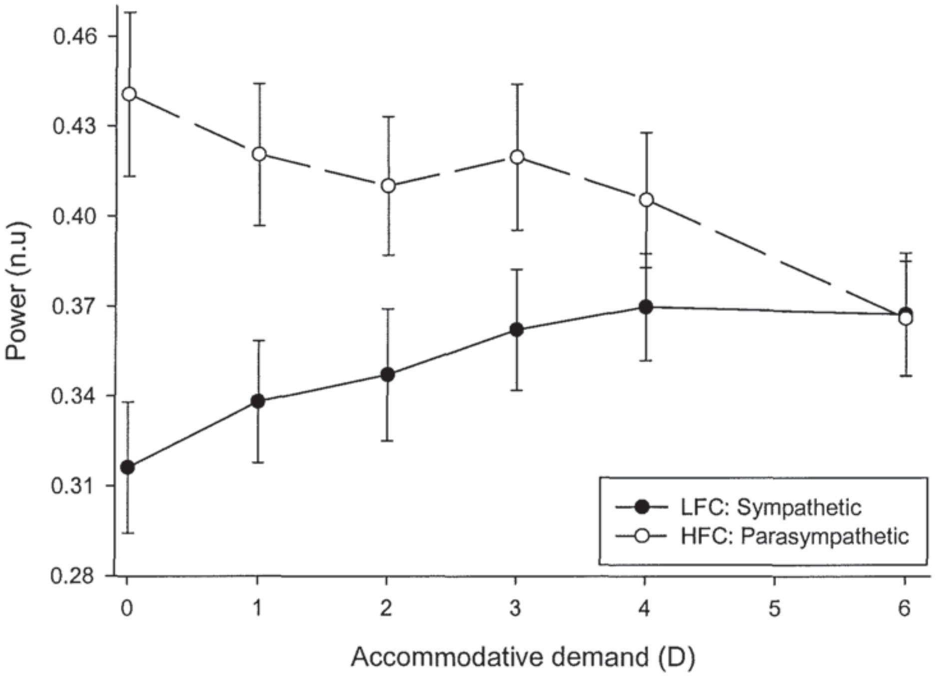

Figure 5.11 Effect of accommodative demand on the systemic sympathetic and parasympathetic profile in all subjects. Power expressed in normalised units (n.u.). Error bars represent ± 1 SEM.

Visual inspection of the data shows that both the absolute and relative HRV LFC increases and the HFC decreases with rising levels of accommodative demand. Figures 5.10 and 5.11 illustrate the frequency-domain response in absolute (s^2Hz^{-1}) and relative values (n.u.) respectively. The data were treated with a two-way mixed factor ANOVA (where accommodative demand was taken as the within-subject factor and refractive error as the between-subject factor), the results of which are shown in Tables 5.1 and 5.2.

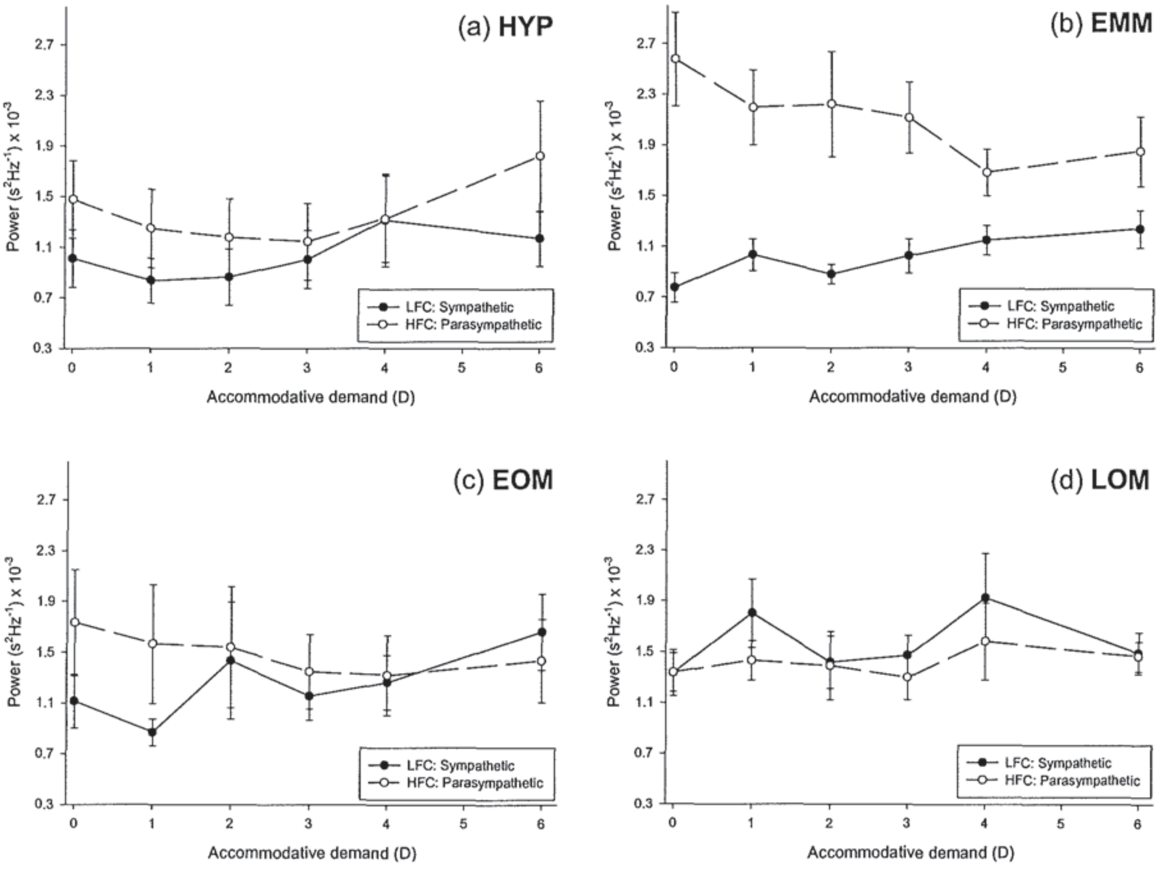

Figure 5.12 Effect of accommodative demand on the systemic sympathetic and parasympathetic profile in HYP, EMM, EOM and LOM subjects. Power expressed in absolute units (s^2Hz^{-1}). Error bars represent ± 1 SEM.

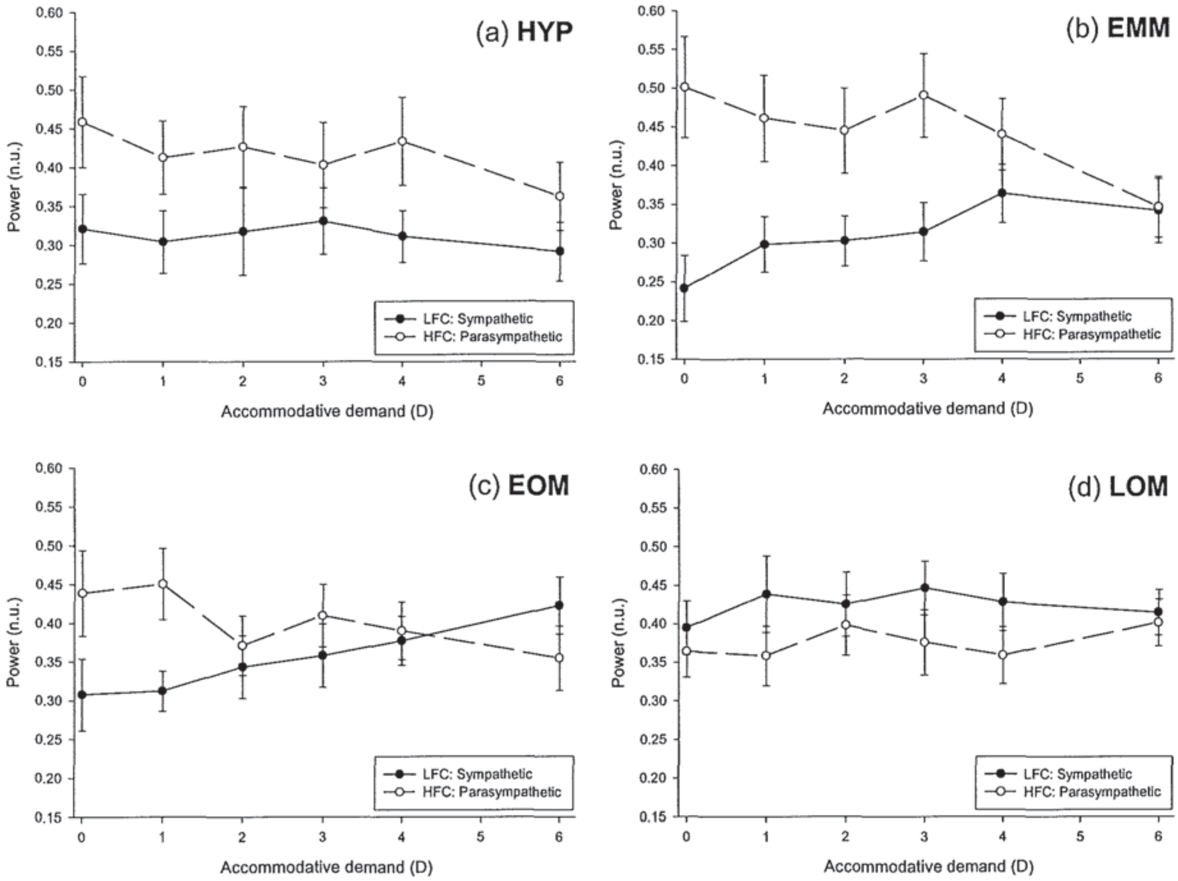

Figure 5.13 Effect of accommodative demand on the systemic sympathetic and parasympathetic profile in HYP, EMM, EOM and LOM subjects. Power expressed in normalised units (n.u.). Error bars represent ± 1 SEM.

HRV COMPONENT	ANOVA F VALUE	STATISTICAL SIGNIFICANCE
ABSOLUTE LFC	$F_{(5,280)} = 2.8$	p = 0.06
ABSOLUTE HFC	$F_{(5,280)} = 2.0$	p = 0.07
RELATIVE LFC	$F_{(5,280)} = 2.1$	p = 0.07
RELATIVE HFC	$F_{(5,280)} = 4.1$	p = 0.001*

Table 5.1 ANOVA results showing the statistical significance of accommodative demand on the absolute and relative values of the cardiovascular components of HRV. * denotes a significant effect at the 95% confidence level.

HRV COMPONENT	ANOVA F VALUE	STATISTICAL SIGNIFICANCE
ABSOLUTE LFC	$F_{(3,56)} = 0.5$	$p = 0.70$
ABSOLUTE HFC	$F_{(3,56)} = 3.3$	$p < 0.05$*
RELATIVE LFC	$F_{(3,56)} = 1.3$	$p = 0.29$
RELATIVE HFC	$F_{(3,56)} = 0.5$	$p = 0.67$

Table 5.2 ANOVA results showing the statistical significance of refractive error on the absolute and relative values of the cardiovascular components of HRV. * denotes a significant effect at the 95% confidence level.

Tables 5.1 and 5.2 demonstrate clearly that accommodative demand had a significant effect on the relative HFC, whereas refractive error modulated significantly the absolute HFC. A Scheffe's *post-hoc* test illustrated that the absolute HFC in the EMM and LOM group differed significantly ($p < 0.05$). All other components were unaffected by refractive error (Figures 5.12 and 5.13). Raw HRV data, in both relative and absolute terms are presented in Appendix 9.

5.3.4 Correlates of autonomic and oculomotor function

To express the subjects' autonomic profile to an open- and closed-loop accommodative stimulus, the intersection of the cardiovascular LFC and HFC was taken as the point of equilibrium (i.e. where the two autonomic branches were balanced in the relative data plots, Figure 5.14b). Figure 5.14a illustrates the stimulus-response function for the EMM subject RZ and the corresponding autonomic profile (Figure 5.14b). Figures 5.15 and 5.16 show the correlation of the position of the autonomic equilibrium point with the accommodative stimulus-response cross-over point and TA respectively in all subjects. As in Chapter 3, 26 subjects (11 HYPs, 5 EMMs, 4 EOMs and 6 LOMs) of the main cohort were excluded from the TA analysis and 29 (12 HYPs, 5 EMMs, 5 EOMs and 7 LOMs) from the stimulus-response analysis due to the lack of a cross-over point in the accommodative stimulus-response function with the unit ratio line or where the function crossed the unit line more than once or where no equilibrium point was found in the cardiovascular data. There does not appear to be a relationship between the autonomic resting state and the stimulus-response cross-over ($r = 0.27$, $p = 0.16$; Figure 5.15) or TA ($r = 0.02$, $p = 0.92$; Figure 5.16).

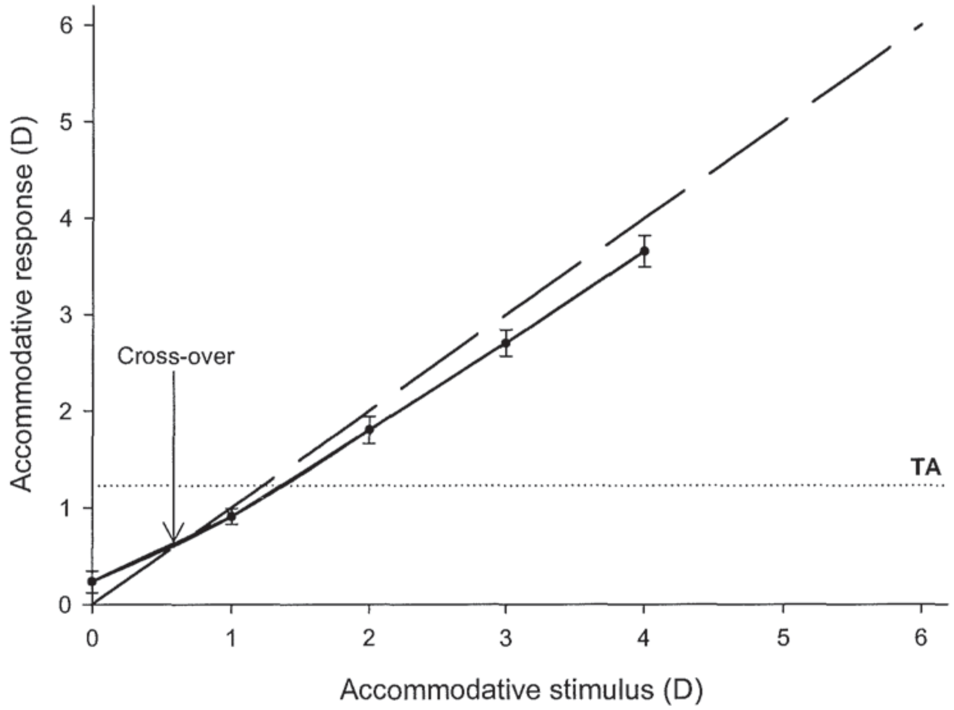

Figure 5.14a Accommodative stimulus-response function (subject RZ). Dashed line represents the unit ratio line. Dotted line represents tonic response level. Error bars represent ± 1 SEM.

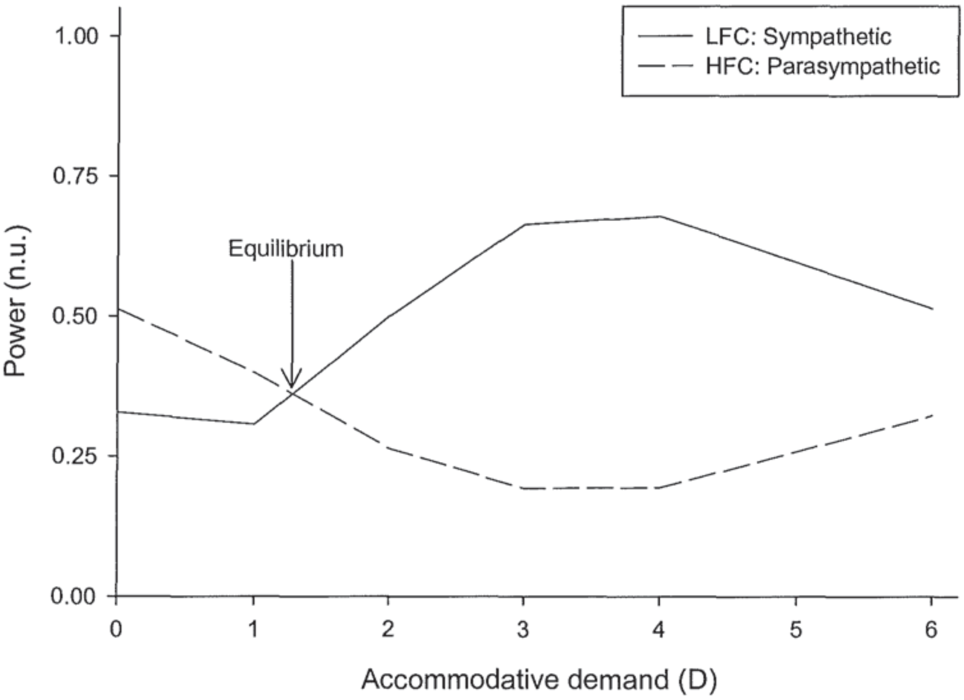

Figure 5.14b Autonomic profile illustrating the relative powers of the HRV LFC and HFC with increasing accommodative demand (subject RZ).

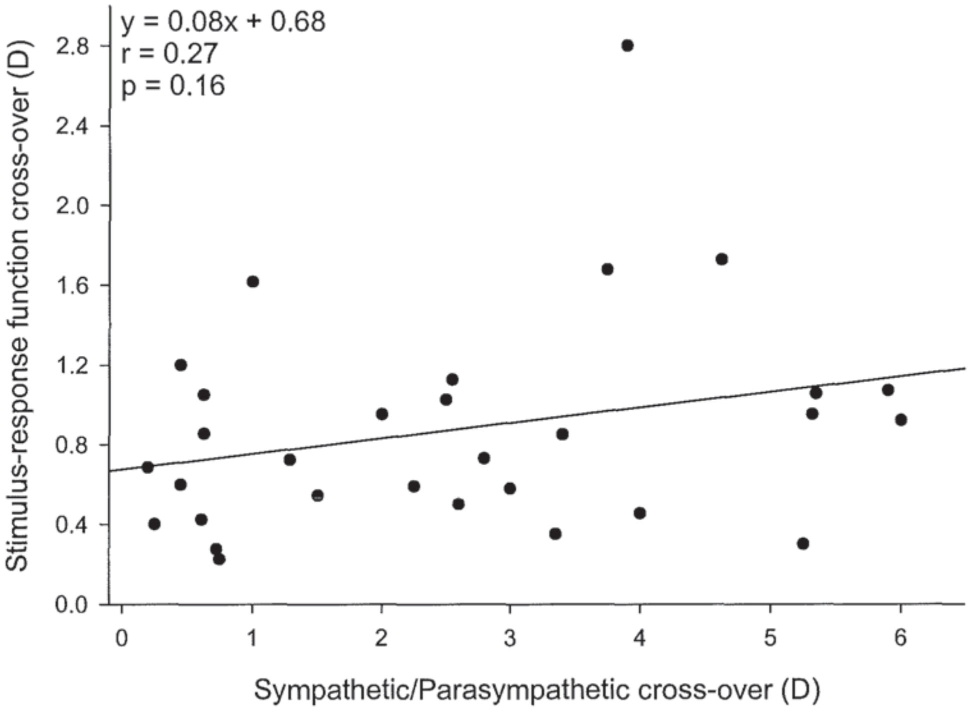

Figure 5.15 Relationship between autonomic equilibrium point and accommodative stimulus-response cross-over point. N = 60.

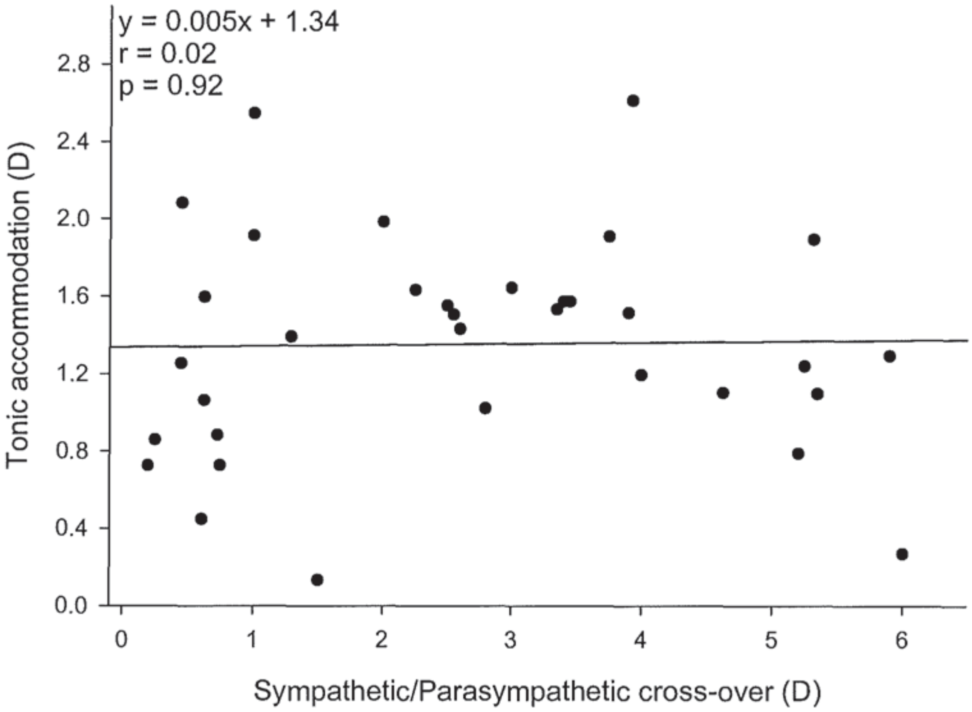

Figure 5.16 Relationship between autonomic equilibrium point and tonic accommodation. N = 60.

5.4 Discussion

The data presented in this Chapter sought to determine whether measures of accommodation are related to measures of cardiovascular function. The study examined the hypothesis that arousal of the autonomic nervous system can be shown through covariations in oculomotor and cardiovascular function. The data does demonstrate, in part, covariation between the oculomotor and cardiovascular systems.

Examination of the relationship between TA and mean heart period showed that those subjects with a faster heart rate (lower heart period) tend to have a higher TA value. The results suggest that higher levels of TA are associated with relatively higher levels of systemic sympathetic tonus. This is a similar trend to that found by Tyrrell and co-workers who found that of their 19 subjects, those with a faster heart rate had a propensity to have a higher tonic vergence value ($r = 0.41$, $p < 0.05$; Tyrrell *et al.*, 1995). Furthermore, Ritter and Huhn-Beck (1993) examined the relationship between physical exercise and dark focus of accommodation. In their study, twelve healthy subjects participated with measurements of TA and pulse rate taken before and immediately after running 400 metres. The data show a statistically significant difference ($p < 0.05$) in accommodation responses from pre-test (mean ± SD: 1.06 ± 0.78 D) to post-test (1.74 ± 1.03 D), confirming that systemic sympathetic augmentation leads to an increase in the accommodative response.

It appears from the trends in this study that an increase in accommodative demand accompanies a decrease in heart period (increase in heart rate; see Figure 5.2), thus suggesting that there is an increase in sympathetic dominance of heart activity with increased accommodative demand. Similar conclusions have been drawn from work conducted by Tyrrell and colleagues (1994). As in this Chapter, Tyrrell *et al.* tested the hypothesis that a visual task can influence cardiovascular behaviour. In their study, seventeen young adults (mean age: 25 years) spent 20 minutes reading text at a distance of 15 cm (6.67 D accommodative demand). Before and after this reading period TA was measured using the Canon R-1 infrared autorefractor. During the reading period, the subject's cardiovascular response was monitored. Forty-two percent of all subjects illustrated an inward shift in TA following the reading period, additionally, all of these subjects also displayed significant reductions heart period ($p < 0.01$). Those subjects who did not experience oculomotor shifts exhibited fewer, smaller non-significant cardiovascular changes. As in Tyrrell's investigation, not all subjects in the present study showed the reduction in heart period. Across all subjects, 62% showed significant decreases in heart period, the remaining 32% either exhibited no significant change or an increase in heart period.

In an attempt to decipher the aetiology of the cardiovascular response to changes in accommodative demand, data were quantified by FFT spectral analysis. All subjects demonstrated the classic power spectrum (Figure 5.8) seen in previous studies (Akselrod *et al.*, 1981; Bates *et al.*, 1997). Furthermore, the LFC and HFC were expressed in both absolute (s^2Hz^{-1}) and normalised units (n.u.) as suggested by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996). Interestingly, however, it is the relative cardiovascular HFC that is affected (reduced) significantly by accommodative demand. Conversely, the LFC shows a non-significant increase in power. The data seem to suggest that changes in heart period are controlled by an attenuation of the relative systemic parasympathetic nervous system. Tyrrell's studies again support these findings (Tyrrell *et al.*, 1994, 2000). Thus, an acute reduction in the parasympathetic innervation to the heart accompanies the oculomotor shifts that can be induced by near visual work. The effect of refractive error on the cardiovascular response to changes in accommodative demand again appears to be tenuous, with only EMMs differing significantly from LOMs in the absolute HFC. This would suggest that EMMs show a greater reduction in the absolute cardiovascular HFC than LOMs.

Finally, the correlation of the autonomic 'resting point' (the intersection of the relative LFC and HFC) with TA and the accommodative stimulus-response function was unfruitful; neither TA nor the stimulus-response function cross-over point reached significance. However, this is assuming that the autonomic resting point, quantified in this manner, is truly a measure of homeostasis. One must remember that the ANS is a dynamic entity that may be 'balanced' when the two divisions are at different levels. As such, this method of analysis may be too simplistic in nature and not representative.

5.5 Conclusion

This investigation demonstrates some covariation between the oculomotor and cardiovascular system consistent with previous investigations (Ritter and Huhn-Beck, 1993; Tyrrell *et al.*, 1995; Pearson *et al.*, 1996) in that a near visual task can influence cardiovascular behaviour. Tyrrell and co-worker's manipulation of the oculomotor system, however, was limited in that, at the most, only two visual stimulus conditions were used to evoke an autonomic response (mainly a target distance of 15 cm (6.67 D) and measures of TA). Unlike previous investigations, this study monitored the autonomic system over a range of increasing accommodative demands (0.0 to 6.0 D) to create an autonomic profile. This profile was then utilised and correlated with oculomotor components (TA and stimulus-response function) to elicit information on the control of ocular accommodation.

The main findings of this study are:

- Subjects with a faster heart rate (lower heart period) tend to have a higher TA value.
- Mean responses indicate sympathetic dominance of heart activity with increased accommodative demand.
- Only 62% of all subjects showed the reduction in heart period.
- Systemic ANS changes linked to reduction in HFC power, therefore, parasympathetic withdrawal.
- Effect of refractive error is equivocal.

Clearly then there is covariation between the eye and the heart. Are these responses caused by changes in ocular physiology or is there an additional factor that confounds the response? To investigate further the eye-heart link, Chapter 6 examines the correlation between accommodative microfluctuations and the ANS while Chapter 7 examines the ocular and cardiovascular responses to changes in cognition.

Supporting publications

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). Autonomic correlates of ocular accommodation and cardiovascular function. *American Academy of Optometry's Global-Pacific Rim Meeting, Hawaii, USA.*

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). Autonomic correlates of ocular accommodation and cardiovascular function in myopic subjects. *10th International Myopia Conference, Cambridge, UK.*

CHAPTER 6

MICROFLUCTUATIONS OF ACCOMMODATION: AN INDICATOR OF AUTONOMIC BEHAVIOUR OR PHYSIOLOGICAL MODULATIONS?

6.1 Introduction

The source and characteristics of the microfluctuations of accommodation have been investigated by several studies (e.g. Campbell and Westheimer, 1959, 1960; Charman and Heron, 1988; Winn *et al.*, 1990a, b; Collins *et al.*, 1995; Winn, 2000; Day *et al.*, 2004). The diminished fluctuations in the HFC seen with small pupils (Campbell and Westheimer, 1959) has led to the suggestion that the oscilations are a display of noise within the accommodation system, having little or no effect on the accommodation control process. Charman and Heron (1988) proposed that this noise originates from the mechanical and elastic characteristics of elements of the peripheral crystalline lens and its supporting structures. This hypothesis was based on observations of Foucalt knife-edge shadow patterns from which it was deduced that greater wavefront aberrations occur where the zonular fibres attach to the peripheral lens (Berny and Slansky, 1970).

A later study by Winn and co-workers, however, tested this hypothesis by measuring the magnitude of the microfluctuations in central and peripheral zones of the crystalline lens in 5 young EMM subjects while they viewed a near target (4.0 D accommodative demand) (Winn *et al.*, 1990a). To enable peripheral lens zones to be measured, the mydriatic 10% phenylepherine hydrochloride was used to dilate the pupil. The study reported data suggesting that the magnitude of the power spectral density of the HFC is a constant characteristic of accommodative microfluctuations present across the whole crystalline lens surface and is not solely restricted to peripheral zones. Moreover, Chapter 4 of this thesis alludes to a tenuous role for the HFC, which appears to be modulated by the refractive error of the individual, with myopes (EOM and LOM) showing little change in accommodative microfluctuations with low degrees of accommodative demand compared to EMM and HYP.

Consequently, the source of the HFC has generated interest in previous studies. Denieul and Corno (1986) detected significant inter-subject variations in the location of the HFC. As such, Winn *et al.* (1990b) considered the relationship between HFCs and other physiological systems which provide intraocular rhythmic variations. In their study, simultaneous measurements of ocular accommodation and systemic arterial pulse, made on 20 normal, healthy subjects showed that the locality of the HFC is significantly correlated with arterial pulse frequency ($r = 0.99$, $p < 0.001$). Indeed, exercise-induced changes in pulse rate were investigated in a subset of 3 subjects, demonstrating that the correlation between the HFC and arterial pulse frequency is retained. A later study ($n = 10$), confirmed that, at two vergences (0.0 D and 4.0 D), there is a positive correlation between the accommodative HFC and arterial pulse frequency (Culhane, 1999).

Since vascular pulse appears to augment microfluctuations of accommodation, the association between the temporal frequency of arterial pulse and the HFC frequency of the accommodative response was investigated at five vergence levels. Furthermore, as arterial pulse rate varies under the influence of the autonomic nervous system (Task Force, 1996), the relationship between the FFT spectral components of HRV and oscillations in the accommodative response were compared and contrasted. The aim of this study was, therefore, to determine if the reported correlation between the HFC of accommodative microfluctuations and arterial pulse could be detected using the continuously recording, Shin-Nippon SRW-5000 open-view infrared optometer over a range of accommodative demand levels (0.0 D to 4.0 D in 1.0 D steps), whether this varied between the main four refractive groupings, and to investigate other cardiovascular/oculomotor correlates using measures of HRV.

6.2 Methods

6.2.1 Subjects

Fifty-two subjects (25 male; 27 female) varying in age from 18 to 33 years (average: 21.2 ± 3.2 years) participated in the study. Thirteen subjects were hypermetropes (HYP; mean spherical equivalent [MSE]: +0.88 ± 0.35 D; range: +0.51 to +1.82 D), 13 subjects were emmetropes (EMM: MSE: +0.03 ± 0.24 D; range: -0.37 to +0.37 D), 13 subjects were early-onset myopes (EOM: MSE: -3.81 ± 2.15 D; range: -7.12 to -1.25 D), and 13 were late-onset myopes (LOM: MSE: -1.84 ± 1.50 D; range: -5.00 to -0.56 D). The mean age of onset for the EOMs was 10.2 ± 2.6 years (range: 6 to 13 years) and 16.7 ± 0.8 years (range: 16 to 18 years) for the LOMs.

To standardise the accommodative demand between subjects, ametropic subjects were fitted with conventional ultrathin soft contact lenses (2-hydroxyethyl methacrylate [HEMA] lenses, 58% water content; Acuvue Dailies, Vistakon, Johnson & Johnson Vision Care, Jacksonville, Florida, USA) to fully correct their refractive error. Sufficient time was given for adaptation to the soft contact lenses and no subject experienced any difficulties with their wear. All subjects achieved 0.00 logMAR visual acuity or better in the eye tested, with an amplitude of accommodation ≥ 8.0 D. None of the subjects had any form of visual or pathological anomaly. All subjects were experienced with visual experiments and were trained to maintain steady fixation in order to limit artefacts in the data. Subjects were furnished with a full explanation of the procedures involved in the investigation and gave informed consent to their participation in the study under the terms of the Declaration of Helsinki. Ethical approval was granted by the human ethics committee of Aston University (Appendix 2). Copies of the information sheets and consent forms given to subjects can be found in Appendix 3.

6.2.2 Stimulus and Instrumentation

Each subject viewed monocularly a stationary high contrast (90% Michelson contrast), 37.0 cdm^{-2} Maltese cross (angular subtense: 10°) through a +5.0 D Badal optical system, thus ensuring both contrast, luminance and image size remained constant, but inducing a blur-driven accommodative stimulus. Five closed-loop stimulus conditions were employed (0.0 D to 4.0 D accommodative demand in 1.0 D steps).

A specially modified Shin-Nippon SRW-5000 infrared autorefractor (Ryusyo Industrial Co. Ltd, Osaka, Japan) was used to record continuously the accommodative response (Mallen *et al.*, 2001; Wolffsohn *et al.*, 2001b) as described in Chapter 2. Data acquisition and analysis were performed using the *LabView* software package (National Instruments, Austin, Texas, USA; see Chapter 2).

Cardiovascular parameters (time- and frequency-domain) were recorded with a piezo-electric pulse transducer (*MLT 1010*, UFI Instruments, USA) attached to the index finger of the subject's left hand with a Velcro® strap (see Chapter 2). The signal was sampled at 60 Hz by the *LabView* software and the inter-beat interval calculated for each heart period.

During all stimuli presentations, respiration was regulated by each subject to 15 breaths per minute (0.25 Hz) with the aid of a digital quartz metronome (*SQ 50*, Seiko, Japan) as in previous investigations (Tyrrell *et al.*, 1994; 2000; Davies *et al.*, 2004).

6.2.3 Procedure

Firstly, the refractive error of each subject was measured with the Shin-Nippon SRW-5000 optometer through the Badal optical system with the target placed at 0.0 D. Subjects were excluded if their residual mean refractive error was > ± 0.25 D or if the cylindrical component was ≥ 0.50 DC.

The optical axis of the SRW-5000 was aligned with the subject's right eye, with the left eye occluded. Five 17.07 second continuous recordings of the accommodative response were acquired for each accommodative level at a sampling rate of 60 Hz, giving 1024 data points for each recording. The accommodative signals were exported to a Microsoft Excel file and filtered with a high frequency cut at 10 Hz, as it is known that variations in accommodation do not contain frequencies higher than this level (Charman and Heron, 1988). A fast Fourier transform (FFT) power spectrum was calculated for each individual trace with a power frequency resolution of 0.06 Hz. The five individual power spectra from each accommodative level were then averaged (Pugh *et al.*, 1987). Mean RMS values, representing the overall variation in the accommodative response, and dominant frequency bins in the mean power spectra were averaged for all four refractive groups. Dominant frequency bins in the range of 0.12 Hz to 0.60 Hz (LFC) and 1.02 Hz to 2.52 Hz (HFC) were chosen, with spectral power expressed in both absolute (D^2Hz^{-1}) and relative/normalised units (n.u.).

Using the heart rate signals, from the piezo-electric finger pulse transducer, inter-beat intervals were calculated, filtered for erroneous beats and exported to a *Microsoft Excel* file for analysis. Fast Fourier transformation, using the *LabView* software, of the inter-heartbeat interval provided an index of the relative and absolute parasympathetic and sympathetic components of the systemic autonomic response.

6.2.4 Data and statistical analysis

Data analysis was performed with *Microsoft Excel*, SigmaPlot 2000 (version 6.0; Systat Software UK Ltd, London, UK) and SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). Pearson's product moment correlation coefficients were used to compare the relationship between independent variables.

6.3 Results

6.3.1 Relationship between accommodation HFC and arterial pulse

The well documented characteristic LFC and HFC microfluctuations of accommodation were present in all subjects. An example of an accommodative FFT power spectrum is shown in Figure 6.1. The dominant frequency components were evident at ~0.25 Hz and ~1.80 Hz (LFC range: 0.12 Hz to 0.60 Hz; HFC range: 1.02 Hz to 2.52 Hz). The locations of the dominant frequency bins were taken as being that frequency which contained the maximum spectral power. Arterial pulse frequency varied from 0.91 Hz to 1.79 Hz (i.e. 55 beatsmin^{-1} to 107 beatsmin^{-1}) for the whole cohort. This range of values is within the normal expected range of arterial pulse rates (Noble, 1979).

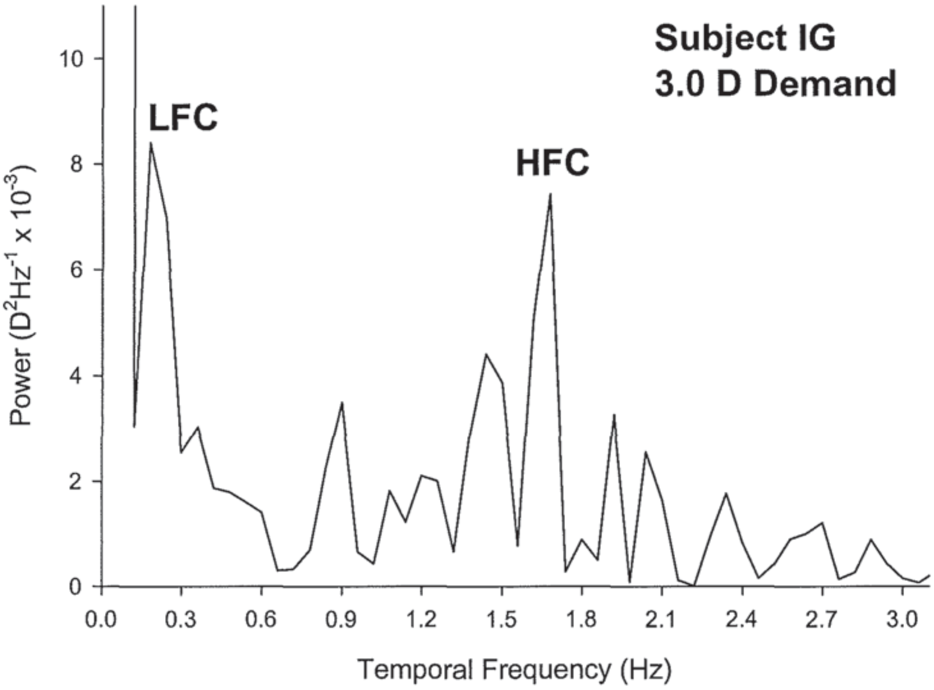

Figure 6.1 FFT power spectrum of an accommodative response trace for subject IG (EOM) illustrating the characteristic LFC and HFC at 3.0 D accommodative demand.

By averaging the power spectra, the statistical confidence in the distribution increases and the standard deviation correspondingly decreases (Pugh *et al.*, 1987). The five consecutive 17.07 second accommodation traces recorded for each individual under identical conditions were therefore averaged. A mean accommodative power spectrum was determined for each subject at each accommodative demand level with a discrete frequency resolution of 0.06 Hz. Pulse frequency was calculated from the average heart period over the 5 minute period and converted into cycles per second (Hz) thus providing a continuous range of values. Simultaneous measurements of ocular accommodation and systemic arterial pulse on the 52 subjects while viewing the 0.0 D, 1.0 D, 2.0 D, 3.0 D and 4.0 D stimuli demonstrated that the temporal frequency location of the HFC correlated significantly with the arterial pulse frequency (Figure 6.2 to 6.6). This significant trend was also apparent in each refractive group (Table 6.1 to 6.5). Analysis of variance showed no difference between groups for either the slope (F = 3.0, p = 0.07) or *y*-intercept (F = 1.6, p = 0.22) of the regression line.

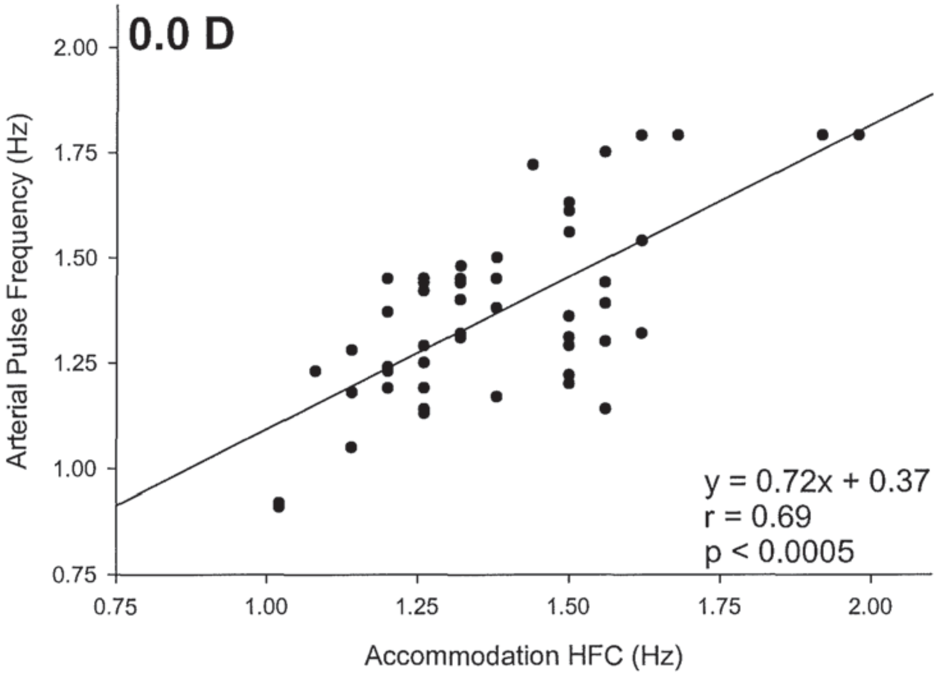

Figure 6.2 Correlation between arterial pulse frequency and the HFC of accommodation for the group data at 0.0 D accommodative demand (n = 52).

REFRACTIVE ERROR	$F_{(x)}$	PEARSON'S CORRELATION COEFFICIENT (r)	SIGNIFICANCE OF CORRELATION (p)
HYP	$y = 0.86x + 0.13$	0.82	< 0.001
EMM	$y = 0.86x + 0.22$	0.82	< 0.001
EOM	$y = 1.05x + 0.00$	0.66	< 0.05
LOM	$y = 0.28x + 0.93$	0.57	< 0.05

Table 6.1 Correlation between arterial pulse frequency and the HFC of accommodation for all refractive groups at 0.0 D accommodative demand (n = 13 in each group).

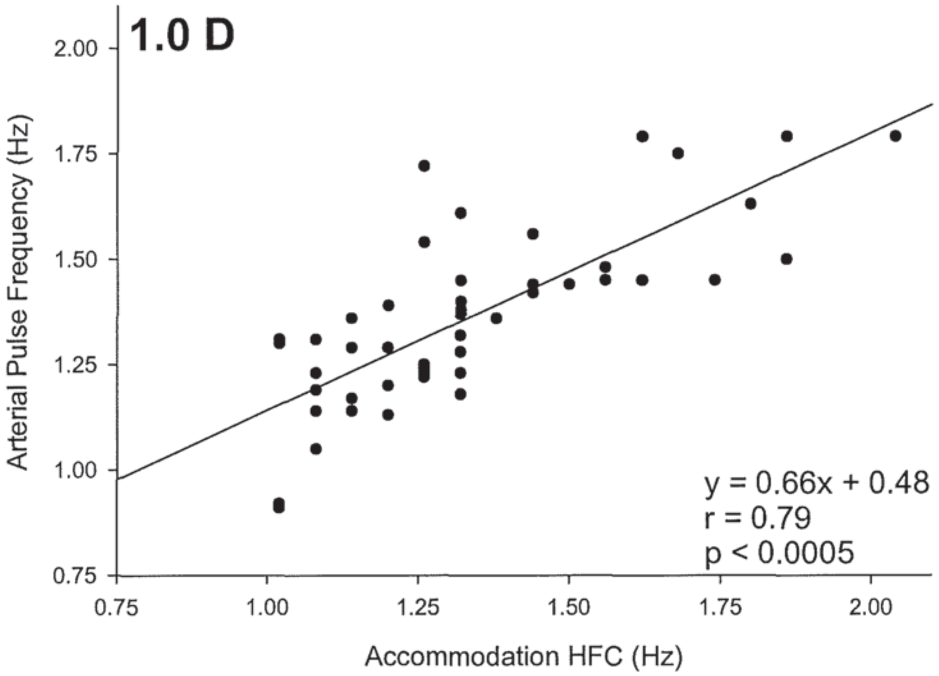

Figure 6.3 Correlation between arterial pulse frequency and the HFC of accommodation for the group data at 1.0 D accommodative demand (n = 52).

REFRACTIVE ERROR	$F_{(x)}$	PEARSON'S CORRELATION COEFFICIENT (r)	SIGNIFICANCE OF CORRELATION (p)
HYP	$y = 0.69x + 0.42$	0.91	< 0.0005
EMM	$y = 0.73x + 0.35$	0.81	< 0.001
EOM	$y = 0.53x + 0.69$	0.57	< 0.05
LOM	$y = 0.51x + 0.67$	0.61	< 0.05

Table 6.2 Correlation between arterial pulse frequency and the HFC of accommodation for all refractive groups at 1.0 D accommodative demand (n = 13 in each group).

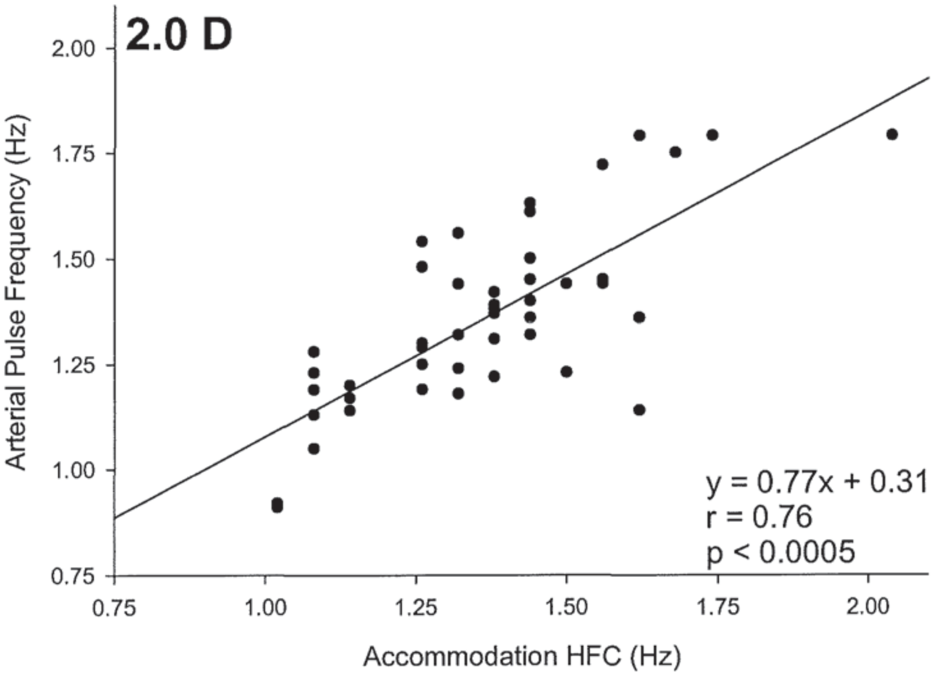

Figure 6.4 Correlation between arterial pulse frequency and the HFC of accommodation for the group data at 2.0 D accommodative demand (n = 52).

REFRACTIVE ERROR	$F_{(x)}$	PEARSON'S CORRELATION COEFFICIENT (r)	SIGNIFICANCE OF CORRELATION (p)
HYP	$y = 0.78x + 0.26$	0.78	< 0.01
EMM	$y = 0.86x + 0.14$	0.77	< 0.01
EOM	$y = 0.88x + 0.23$	0.82	< 0.001
LOM	$y = 0.72x + 0.38$	0.73	< 0.01

Table 6.3 Correlation between arterial pulse frequency and the HFC of accommodation for all refractive groups at 2.0 D accommodative demand (n = 13 in each group).

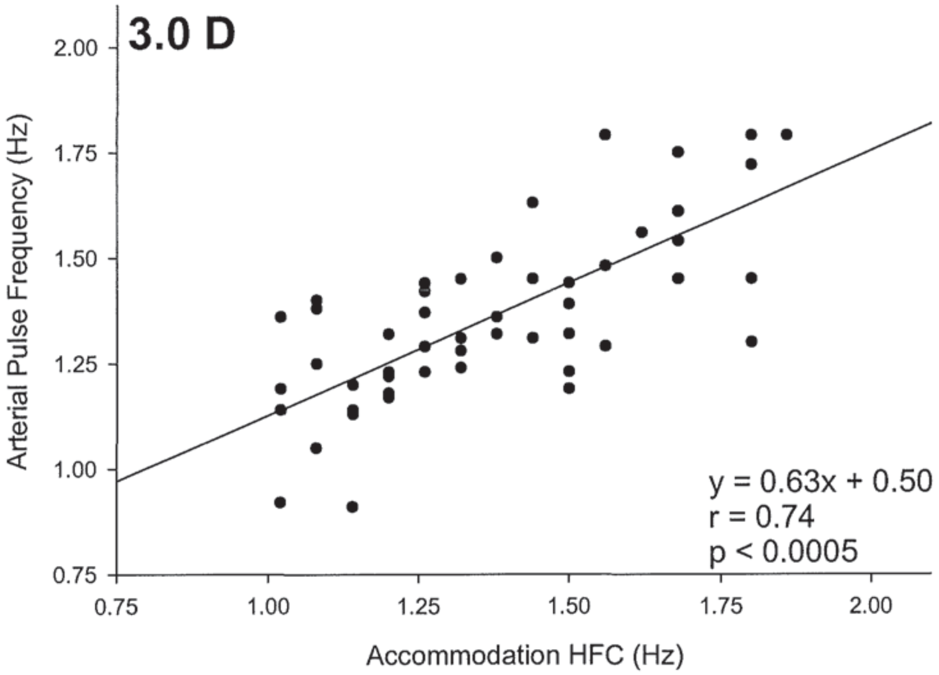

Figure 6.5 Correlation between arterial pulse frequency and the HFC of accommodation for the group data at 3.0 D accommodative demand (n = 52).

REFRACTIVE ERROR	$F_{(x)}$	PEARSON'S CORRELATION COEFFICIENT (r)	SIGNIFICANCE OF CORRELATION (p)
HYP	$y = 0.98x + 0.08$	0.88	< 0.0005
EMM	$y = 0.47x + 0.68$	0.62	< 0.05
EOM	$y = 0.77x + 0.35$	0.92	< 0.0005
LOM	$y = 0.32x + 0.88$	0.56	< 0.05

Table 6.4 Correlation between arterial pulse frequency and the HFC of accommodation for all refractive groups at 3.0 D accommodative demand (n = 13 in each group).

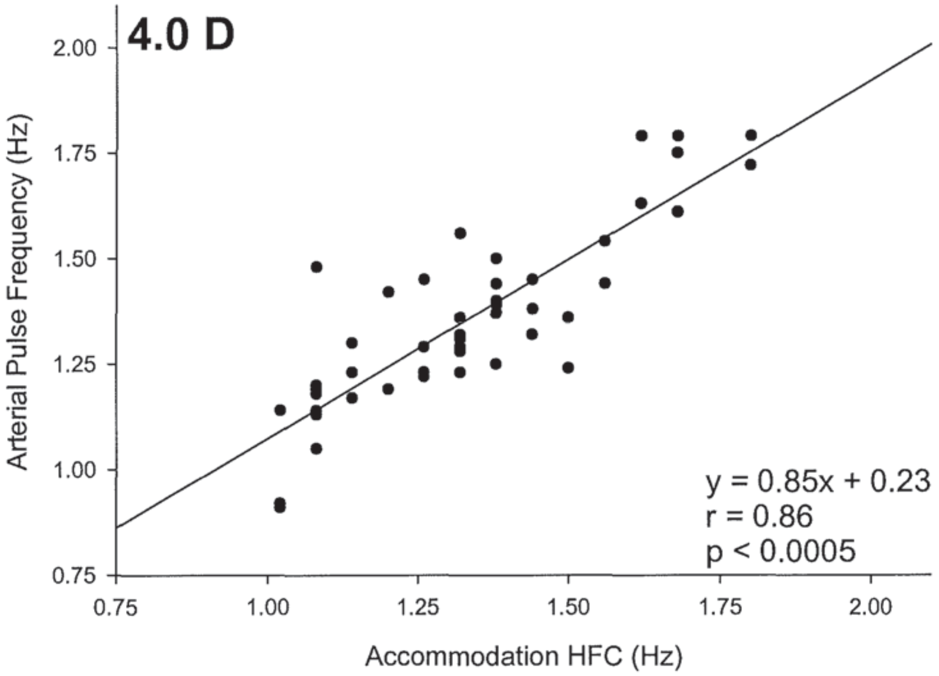

Figure 6.6 Correlation between arterial pulse frequency and the HFC of accommodation for the group data at 4.0 D accommodative demand (n = 52).

REFRACTIVE ERROR	$F_{(x)}$	PEARSON'S CORRELATION COEFFICIENT (r)	SIGNIFICANCE OF CORRELATION (p)
HYP	y = 0.91x + 0.18	0.89	< 0.0005
EMM	y = 1.00x + 0.00	0.92	< 0.0005
EOM	y = 0.82x + 0.27	0.89	< 0.0005
LOM	y = 0.51x + 0.65	0.66	< 0.05

Table 6.5 Correlation between arterial pulse frequency and the HFC of accommodation for all refractive groups at 4.0 D accommodative demand (n = 13 in each group).

6.3.2 Cardiovascular and oculomotor correlates

In order to elaborate further on the potential relationship between microfluctuations of accommodation and haemodynamic parameters, correlations were assessed between each cardiovascular and accommodation factor. Here, the spectral powers (magnitude) of the Fourier transformations (not frequency) in absolute and relative terms were compared for each spectral factor. Table 6.6 illustrates the correlates. Only 2 of the 25 combinations demonstrate any significant correlation; heart period showed a significant correlation with the power of the relative and absolute accommodative HFC.

CARDIOVASCULAR FACTOR	ACCOMMODATION FACTOR	PEARSON'S CORRELATION COEFFICIENT (r)	SIGNIFICANCE OF CORRELATION (p)
Heart Period	**RMS**	-0.03	0.60
Heart Period	**Absolute LFC**	-0.03	0.60
Heart Period	**Absolute HFC**	-0.14	0.03*
Heart Period	**Relative LFC**	+0.05	0.40
Heart Period	**Relative HFC**	-0.13	0.04*
Absolute LFC	**RMS**	+0.06	0.31
Absolute LFC	**Absolute LFC**	+0.05	0.43
Absolute LFC	**Absolute HFC**	-0.02	0.80
Absolute LFC	**Relative LFC**	+0.10	0.12
Absolute LFC	**Relative HFC**	-0.12	0.05#
Absolute HFC	**RMS**	-0.05	0.39
Absolute HFC	**Absolute LFC**	-0.05	0.44
Absolute HFC	**Absolute HFC**	-0.12	0.07#
Absolute HFC	**Relative LFC**	+0.03	0.59
Absolute HFC	**Relative HFC**	-0.05	0.39
Relative LFC	**RMS**	+0.11	0.05#
Relative LFC	**Absolute LFC**	+0.11	0.05#
Relative LFC	**Absolute HFC**	+0.05	0.40
Relative LFC	**Relative LFC**	+0.11	0.05#
Relative LFC	**Relative HFC**	-0.11	0.05#
Relative HFC	**RMS**	-0.05	0.44
Relative HFC	**Absolute LFC**	-0.11	0.07#
Relative HFC	**Absolute HFC**	-0.06	0.32
Relative HFC	**Relative LFC**	-0.06	0.31
Relative HFC	**Relative HFC**	+0.07	0.28

Table 6.6 Relationship between accommodation and cardiovascular function for responses to targets at 0.0 D to 4.0 D in 1.0 D steps (* denotes significant correlations, # denotes near significant correlations).

6.4 Discussion

6.4.1 HFC and arterial pulse

The first part of this study examined the HFC of the accommodative microfluctuations in the FFT power spectrum, demonstrating a positive correlation with arterial pulse frequency at a range of accommodative demands (0.0 D to 4.0 D in 1.0 D steps), therefore, showing no dose effect (ANOVA: F = 1.3, p = 0.31). The finding is in agreement with previous studies (Winn *et al.*, 1990b; Owens *et al.*, 1991; Collins *et al.*, 1995; Culhane, 1999). Together with the range of demand levels and the large sample size, this study, however, extends previous investigations by examining the effect of refractive error on the relationship, showing that the trend holds true in all refractive groups (see Table 6.1 to 6.5). The data illustrates the well documented characteristic LFC and HFC microfluctuations of accommodation (Figure 6.1), which were present in all subject groups. The findings of this study suggest that the HFC in the accommodative microfluctuations is augmented by physiological factors (i.e. arterial pulse oscillations) and is not influenced directly by the accommodative control mechanism.

As outlined in Chapter 1, the mechanism by which the arterial pulse augments the HFC is thought to take place via two systems. Firstly, that choroidal blood flow leads to a pulsatile change in blood volume in the choroid and ciliary muscle, thus producing accommodative HFC microfluctuations on each heart beat (Strang *et al.*, 1994; Winn, 2000). However, this theory does not differentiate between the dynamic fluctuation caused by the choroid or the ciliary muscle. An investigation using ultrasonography to observe the steady-state accommodative response illustrated (using spectral analysis) that the axial length of a human eye has its own HFC around 1.35 Hz whereas no HFC fluctuations were present in the crystalline lens or the anterior chamber depth (van der Heijde *et al.*, 1996), a hypothesis which was also suggested by Collins and co-workers (Collins *et al.*, 1995). This would suggest that the choroid alone is responsible for the HFC. An earlier study by Fercher *et al.* (1982), however, demonstrated that pulse related changes that occur in axial length are too small to account for the accommodative microfluctuations.

Secondly, fluctuations in intra-ocular pressure (IOP) could produce small lens movements that could contribute to the microfluctuations in the overall power of the eye. Again taking the data from van der Heijde and co-workers, no HFC was detected in either lens thickness or anterior chamber depth (van der Heijde *et al.*, 1996). In contrast, Winn and colleagues showed that when the steady-state microfluctuations of accommodation were measured from an aphakic eye and a phakic eye of the same subject, the HFC was absent in the aphakic eye but present in the phakic eye, thus suggesting that the origin of the HFC is lenticular in nature (Winn *et al*., 1990b). However, a 0.25 D fluctuation in accommodation (through lens movement alone), would require the crystalline lens to move forward by ~200 μm with each intraocular pulse beat (Collins *et al*., 1995). A further intriguing statement was presented by Judge and Flitcroft who argued that if the HFC in accommodation is caused by or linked to arterial pulse, it is puzzling to find that macaque monkeys, which have considerable higher pulse rates than humans, have HFC fluctuations of a similar frequency to humans (again centred around ~2 Hz) (Judge and Flitcroft, 1999). As such, the precise mechanism which relates arterial pulse rate with the HFC in the accommodative microfluctuations is equivocal.

6.4.2 Cardiovascular and oculomotor correlates

The second part of the study extended the concept that microfluctuations of accommodation are modified by both physiological and neurological factors. Again, as with comparisons of frequency, heart period showed a significant correlation with the absolute and relative power of the accommodative HFC. These findings again seem to suggest that the HFC in the accommodative microfluctuations is modulated by arterial pulse oscillations and not variations in the accommodation mechanism.

6.5 Conclusions

When considering data from previous investigations (Collins *et al.*, 1995; Winn *et al.*, 1990a, b; Culhane, 1999), from this study and Chapter 4 of this thesis, questions are raised as to the role microfluctuations of accommodation play in facilitating the accommodative mechanism. Notwithstanding the fact that the accommodative LFC is augmented by changes in target parameters, the LFC oscillates at a frequency that is too slow to provide an adequate odd-error signal to achieve the temporal accommodative response times that have been established previously. The possibility of a functional role in providing an odd-error signal for the microfluctuations of accommodation, however, has not yet been abolished. A possible role for the microfluctuations of accommodation as a feedback error-detector in the maintenance of a steady-state target and not in the control of accommodation to moving targets (e.g. responses to step changes) is more appealing.

Despite the cardiovascular system influencing the HFC (and the LFC to a lesser extent [Collins *et al.*, 1995]), the HFC of the accommodative response may still be utilised by the accommodation system in optimising the steady-state accommodative response even though they are not under the active control of the visual system. Perhaps an integrated response, containing both LFC and HFC oscillation enables the accommodation system to maintain adequate focus.

The main findings of this investigation are:

- The temporal frequency location of the accommodative HFC correlated significantly with the arterial pulse frequency.
- The accommodative HFC frequency and arterial pulse frequency correlation existed at 0.0 D, 1.0 D, 2.0 D, 3.0 D and 4.0 D stimuli.
- This significant trend was also apparent in each refractive group.
- Of the cardiovascular and accommodative parameters, only heart period showed a statistically significant correlation with the absolute and relative power of the accommodative HFC.

The results of this study provide further information as to the complex nature of the microfluctuations of accommodation. Further research is required to assess the role the oscillations may or may not contribute to the accommodative control mechanism.

CHAPTER 7

THE INFLUENCE OF COGNITION AND REFRACTIVE ERROR ON OCULOMOTOR AND CARDIOVASCULAR FUNCTION

7.1 Introduction

Over the last thirty years much work has been undertaken to investigate the role of cognition and its interaction with ocular accommodation (Table 1.3). The effect of cognition on the direction of the accommodative response, however, is equivocal. On exposure to cognitive tasks, some studies have shown a greater lag in accommodative response for high accommodative demand stimuli (e.g. Bullimore and Gilmartin, 1988; Rosenfield and Ciuffreda, 1990), while other studies contradict this finding showing a greater lead in the accommodative response for near targets (≥ 3.0 D accommodative demand; e.g. Malmstrom *et al.*, 1980; Winn *et al.*, 1991). There is, therefore, a dispute as to the effect mental effort or cognitive demand has on the accommodative response. The highly complex nature of the influence cognitive factors have on the accommodative response is emphasised by research that has indicated that other factors such as the method of presentation of the task (Iwasaki, 1993), the nature of the processing task (Post *et al.*, 1985), and the distance at which it is presented (Bullimore and Gilmartin, 1988) may also have an influence on the resultant accommodative response. To investigate these factors, studies have utilised a variety of paradigms to augment the cognitive demand such as counting backwards in 7s (Post *et al.*, 1985; Gawron *et al.*, 1985; Bullimore and Gilmartin, 1987a; Rosenfield and Ciuffreda, 1990; Gray *et al.*, 1993c), adding pairs of digits (Kruger, 1980; Rosenfield and Ciuffreda, 1994), and checking computations (Iwasaki, 1993; Wolffsohn *et al.*, 2003). However, the cognitive demand necessary to perform such tasks is unlikely to be equivalent between individuals, varying with factors such as their mathematical ability and concentration. As such, comparison between investigations and more importantly between subjects is both difficult and potentially misleading.

A number of visual functions and phenomena are influenced by refractive error, for example, amplitude of accommodation (McBrien and Millodot, 1986a), tonic accommodation (TA; Rosenfield and Gilmartin, 1987) and the stimulus-response function (McBrien and Millodot, 1986b). Variations in accommodative level during a cognitive task also vary with refractive error. Bullimore and Gilmartin (1987) found that the imposition of a mental task induced a significantly greater positive shift in the TA of myopic compared to emmetropic subjects. Moreover, in a later study, the authors suggested that negative shifts (mean: -0.04 ± 0.03 D) seen in the accommodative response to a near (5.0 D) target during workload, were augmented by the sympathetic nervous system. Their hypothesis was supported when, using the β-antagonist timolol maleate, positive shifts (mean: +0.04 ± 0.01 D) in the accommodative response were observed for the same visual stimulus (Bullimore and Gilmartin, 1988).

The precise role of the autonomic nervous system (ANS) during cognitive tasks is also ambiguous. Cognitive demand or mental effort manifests itself in a variety of different forms, such as increased heart rate, vasodilation and increased sweating. These changes are indicative of increased activity in the sympathetic branch of the ANS (Malmstrom *et al*., 1980). Sympathetic activation serves to mobilise and prepare the body for action in response to stressor agents, objects of attention, and information being processed (Birnbaum, 1984). These evolutionary reflexes are biologically effective in 'fight or flight' situations, but may be detrimental when activated in response to a near task. Real-world environments impose demands on the visual system inconsistent with its evolutionary purpose; visual tasks (e.g. VDU work stations) require accurate accommodation, yet enforce concurrent demands for mental processing which appear to activate the sympathetic nervous system leading to a reduction in the accommodative response (Malmstrom *et al*., 1980; Bullimore and Gilmartin, 1988). In practical terms, this mismatch between the innervation to accommodation and the required level forms a stress which may lead to diplopia, blur and asthenopic symptoms. In turn, image blur may disrupt the emmetropization process, leading to the progression of myopia (Gilmartin, 1998).

The use of cardiovascular function to quantify the components of the autonomic nervous system (ANS) is an establised proceedure (Akselrod *et al*., 1981; Task Force, 1996). In general, time-domain measures of heart rate variability (HRV) show that an increase in heart rate is initiated by an increase in the sympathetic nervous system (Task Force, 1996). Although measurements of changes in heart rate can indicate that a change has occurred in the autonomic equilibrium, such measures are not sufficient to decipher the relative contributions of sympathetic and parasympathetic forces. For example, an increase in heart rate maybe due to sympathetic activation, parasympathetic attenuation or a combination of the two. In contrast to the time-domain measures of HRV, frequency measures involve the spectral analysis of HRV. The comprehensive review of HRV factors by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996) concluded that for short-term recordings (5 minute), three main spectral components are distinguished: a very low frequency < 0.05 Hz (VLF); a low frequency from 0.05 Hz to 0.15 Hz (LF, sympathetic component) and a high frequency from 0.15 Hz to 0.40 Hz (HF, parasympathetic component). The LF and HF are not fixed parameters but vary in association with manipulations of the ANS. The VLF component, however, is much less defined and the precise physiological process attributable to these heart rate changes is questionable. The results of the Fast Fourier transformation are expressed in absolute values of power (s^2Hz^{-1}), however, LF and HF components may also be quantified and measured in normalised units (n.u.) which represent the relative power of each component in proportion to the overall power spectra minus the VLF component, thus eliminating inter- and intra-subject variation caused by background noise (Task Force, 1996).

Measures of ocular accommodation appear to reflect directly neurological brain activity and may be a reliable objective index of information processing load (Rosenfield and Ciuffreda, 1990). However, the few studies that have directly tested the proposition that autonomic factors are involved in augmenting the accommodative response during cognitive tasks have all utilised pharmacological agents (Bullimore and Gilmartin, 1987a; 1987b; 1998), which in effecting the balance between the autonomic components, may not isolate the output of a single component in the normal environment.

Bullimore and Gilmartin (1988) suggested that stimulus distance is an important factor in determining the direction of the change in the accommodative response. As reported previously, the ciliary muscle is innervated by the dual actions of the sympathetic and parasympathetic branches of the ANS (Cogan, 1937; Gilmartin, 1986). Furthermore, greater parasympathetic activity leads to a concurrent increase in the activity of the sympathetic branch (Gilmartin and Bullimore, 1987). Thus, for distant stimuli, alterations in the accommodative response are likely to be mediated by the parasympathetic branch, whereas, for closer stimuli the influence of the sympathetic branch increases. Given this, one may hypothesise that, for distant targets, mental effort is likely to have little effect (as sympathetic influences are minimal), whereas, for near targets, cognitive demand is likely to lead to a decrease in the accommodative response.

A practical understanding of the innervation and response of the ocular accommodative system during workload conditions is important for industries and laboratories that are involved with the man-machine interface, such as the aerospace industry. Loss or reduced visual acuity produced by such shifts in closed-loop accommodation during cognitive processing, have serious ramifications on a number of visual tasks including VDU work (Ostberg, 1980; Gray *et al.*, 2000), and car/aircraft head-up displays (Wolffsohn *et al.*, 1998; 1999). The visual and cardiovascular systems are capable of providing a vehicle to measure objectively visual workload; an invaluable tool in human factors research. Moreover, the wide use of VDUs, and more importantly the inter-user variations in symptoms experienced (Ostberg, 1980), requires further attention: the propensity to suffer symptoms may be manifest in individuals with inappropriate autonomic profile. Finally, as near vision in modern visual environments often requires intensive periods of sustained processing of information, cognition is believed to be an important factor in the association between near vision and myopia (particularly late-onset myopia (LOM), van Alphen, 1990; Birnbaum, 1993; Gilmartin, 1998).

The aim of this study was, therefore, to determine the effect of increasing levels of cognition on oculomotor and cardiovascular function in myopes and emmetropes at two stimulus vergences.

7.2 Methods

7.2.1 Subjects

The cohort consisted of 16 subjects (10 male, 6 female) aged between 18 to 34 years (mean ± SD: 22.6 ± 4.4 years). Eight were emmetropic (EMMs; ± 0.25 D; mean spherical equivalent refractive error [MSE], mean ± SD: 0.05 ± 0.24 D) and 8 late-onset myopes (LOMs; < -0.50 D; MSE, mean ± SD: -3.66 ± 2.31 D). Subjects were considered LOMs when myopia onset was ≥ 15 years of age (Edwards, 1998).

To ensure that the accommodative demand was virtually identical for each subject, all were corrected with accurately prescribed soft contact lenses (2-hydroxyethyl methacrylate [HEMA] lenses, 58% water content; Acuvue Dailies, Vistakon, Johnson & Johnson Vision Care, Jacksonville, Florida, USA). All subjects had 0.00 logMAR visual acuity or better and uncorrected astigmatism was limited to ≤ 0.50 DC. None of the subjects reported any form of visual or heart anomaly. All subjects had practice in remaining still and maintaining steady fixation in order to limit artefacts in both the heart period and accommodative data. Subjects were provided with a full explanation of the experimental protocol and gave prior written consent before commencing the investigation. The research followed the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee (Appendix 2). Copies of the information sheets and consent forms given to subjects can be found in Appendix 3.

7.2.2 Procedure

Subjects monocularly viewed stationary numerical digits (at both 0.0 D and 3.0 D accommodative demand, through a Badal optical system; angular subtense: 3°), randomly presented between 1 and 100 (displayed on a 5×4 cm liquid crystal display [LCD] screen). The screen was mounted on a purpose built gantry to aid alignment of the LCD screen with the Badal optics (Figure 7.1). The cognitive task consisted of a two-alternative forced choice paradigm, where subjects responded when the number presented was between 25 and 74 inclusive. Cognitive demand was varied by altering the speed of presentation (between 100 and 2000 ms) and calculating the correct response rate. Applying a Weibull curve-fitting function (Weibull, 1951) to the results, five individually determined, equivalent, cognitive levels of increasing difficulty (corresponding to 0.1 s slower than 0% incorrect, 12.5%, 25%, 37.5% and 0.1 s faster than 50% incorrect) were determined and

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The subjective workload of each of the cognitive levels was determined using the National Aeronautics and Space Administration (NASA) Task Load Index questionnaire (TLX) completed at the end of each trial (Hancock, 1996). This questionnaire involves the rating of mental demand, physical demand, temporal demand, effort, performance and frustration on a linear line scale. Subjects also weight the measures according to their relative importance and this is used to arrive at a total score.

7.2.3 Data and statistical analysis

Data analysis was performed with *Microsoft Excel*, SigmaPlot 2000 (version 6.0; Systat Software UK Ltd, London, UK) and SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). Data were treated with a three-way (vergence, cognitive level, refractive error) mixed ANOVA where vergence and cognitive level were taken as within-subject variables and refractive error as the between-subject variable. Pearson's product moment correlation was used to compare the mean accommodative and cardiovascular responses.

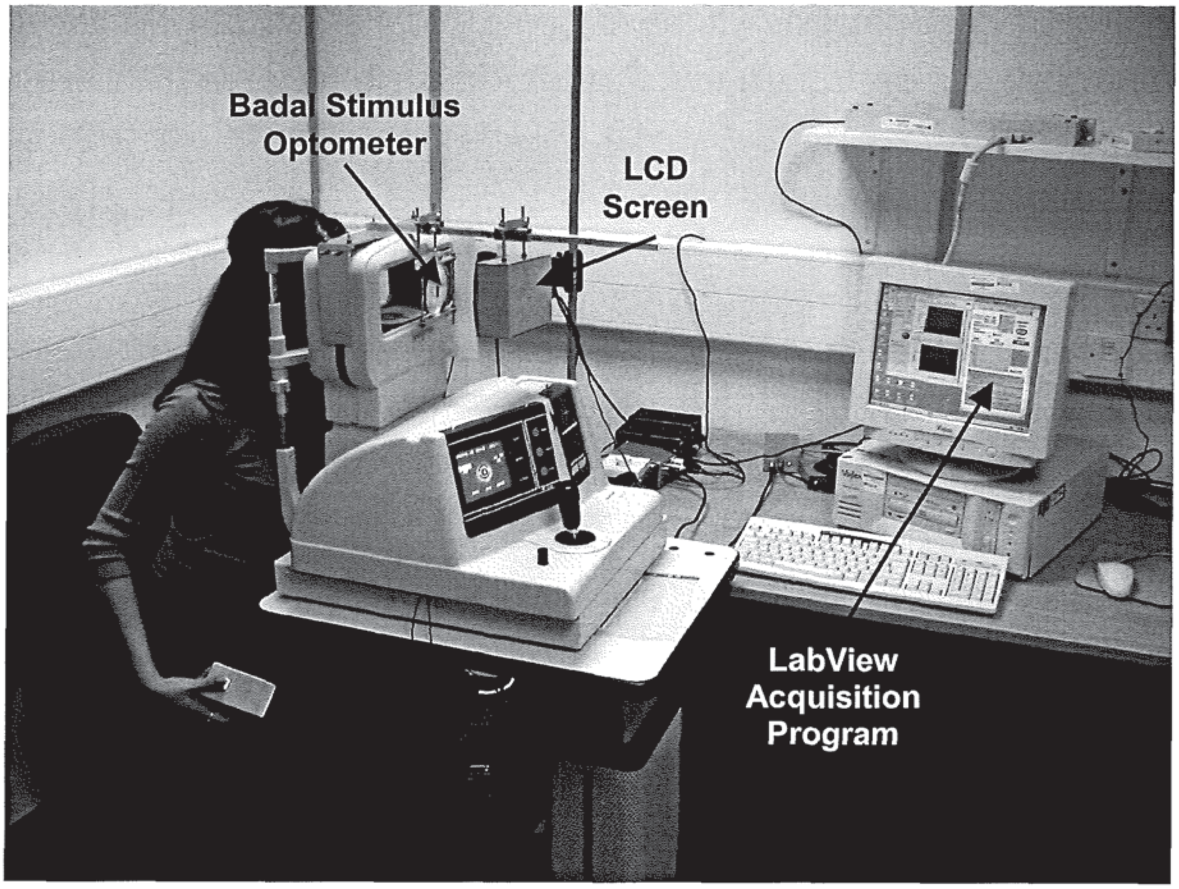


Figure 7.1 Laboratory setup showing the Shin-Nippon SRW-5000 autorefractor, Badal stimulus optometer and LCD display.

7.3 Results

7.3.1 Accommodative response

Across all subjects (n = 16), there was a reduction in the mean accommodative response with increased cognitive demand from the 0 to 50% incorrect level (by -0.35 ± 0.33 D for the 0.0 D stimulus and by -0.31 ± 0.40 D for the 3.0 D stimulus, Figure 7.2). The EMM group showed a significant reduction in the mean accommodative response with increased cognitive demand (by -0.16 ± 0.30 D, for the 0.0 D stimulus and by -0.24 ± 0.33 D, for the 3.0 D stimulus). The LOMs also showed a significant decrease (by -0.54 ± 0.25 D, for the 0.0 D stimulus and by -0.38 ± 0.46 D, for the 3.0 D stimulus). Analysis indicated that the effect of cognitive demand ($F_{(4,56)} = 13.0$; $p < 0.0005$) was statistically significant. The difference between refractive groups approached significance ($F_{(1,14)} = 3.7$, $p = 0.07$), whereas accommodation demand had no significant effect ($F_{(1,14)} = 0.09$; $p = 0.77$).

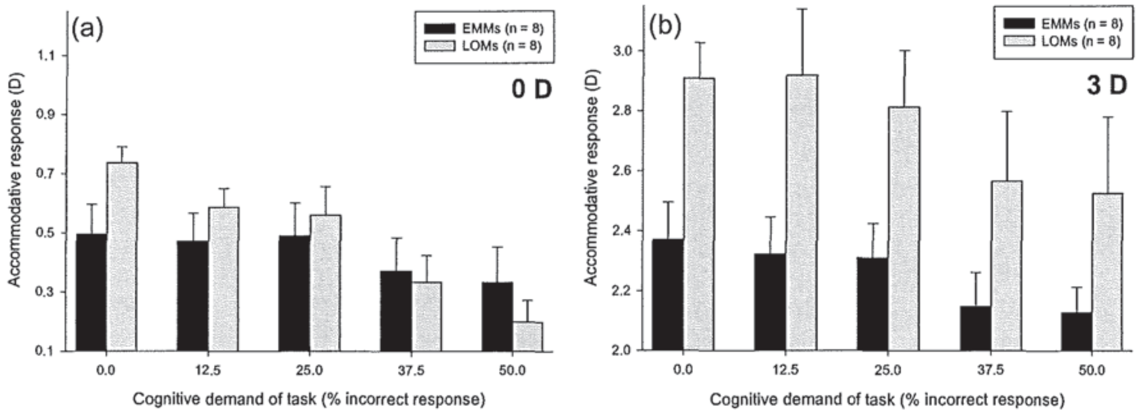


Figure 7.2 Effect of cognitive demand on the accommodative response for EMMs and LOMs at (a) optical infinity and (b) 3.0 D of accommodative demand. Error bars represent ±1 SEM. N=8 in each refractive group.

Figure 7.3 illustrates a typical on-line dynamic accommodative response to a 3.0 D target for an EMM subject (RZ) under three cognitive levels: low (0% incorrect response); medium (25% incorrect response) and high (50% incorrect response) with each cognitive level evoking a distinct level of accommodative response.

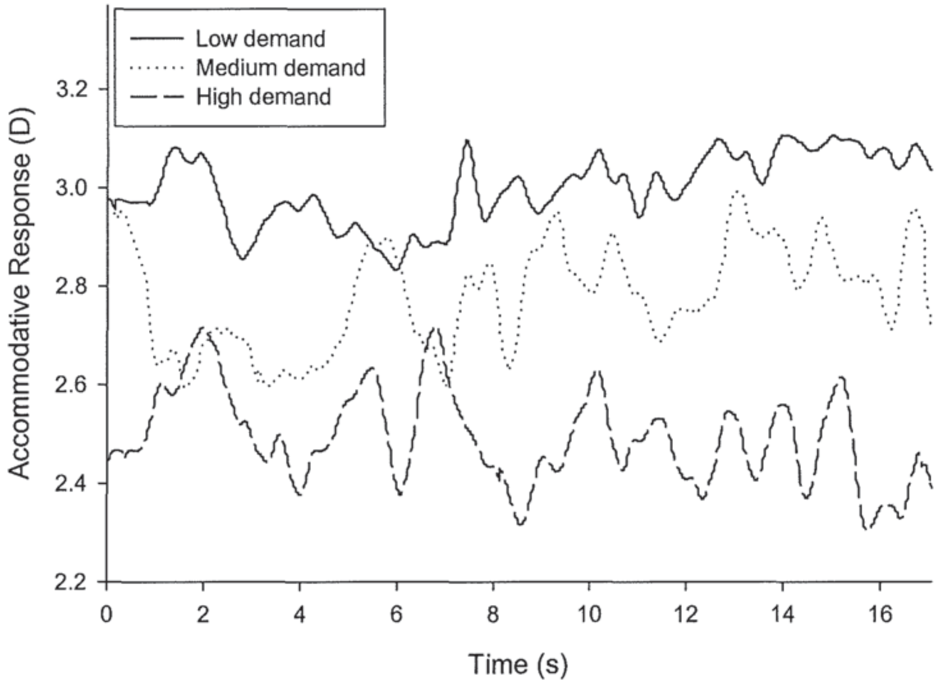


Figure 7.3 Dynamic (60 Hz) accommodative response (3.0 D accommodative stimulus) of an EMM subject (RZ) under three cognitive levels: low (0% incorrect response); medium (25% incorrect response) and high (50% incorrect response).

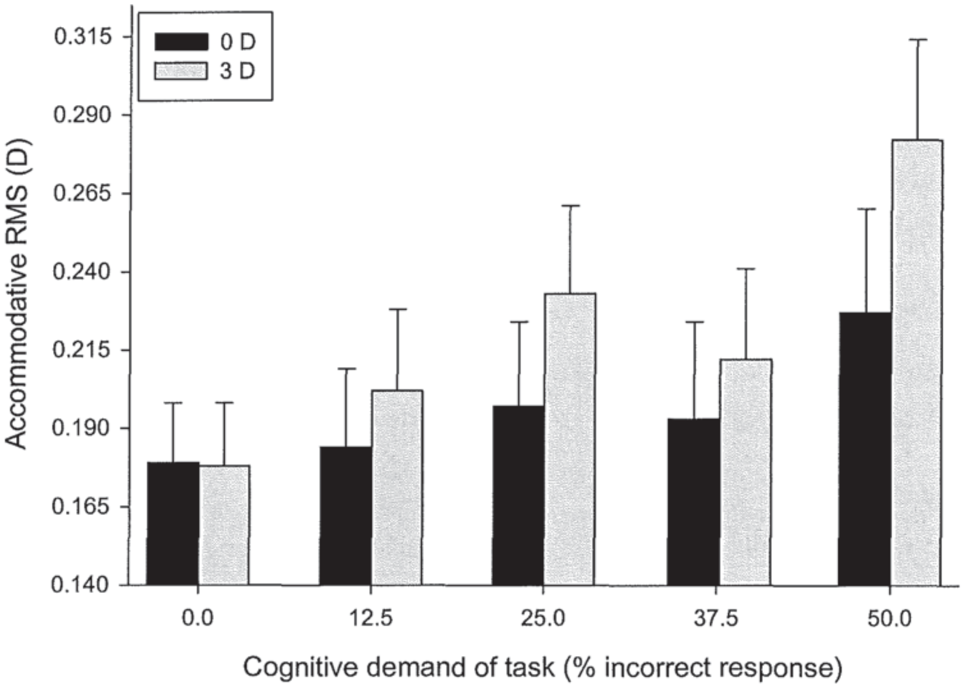
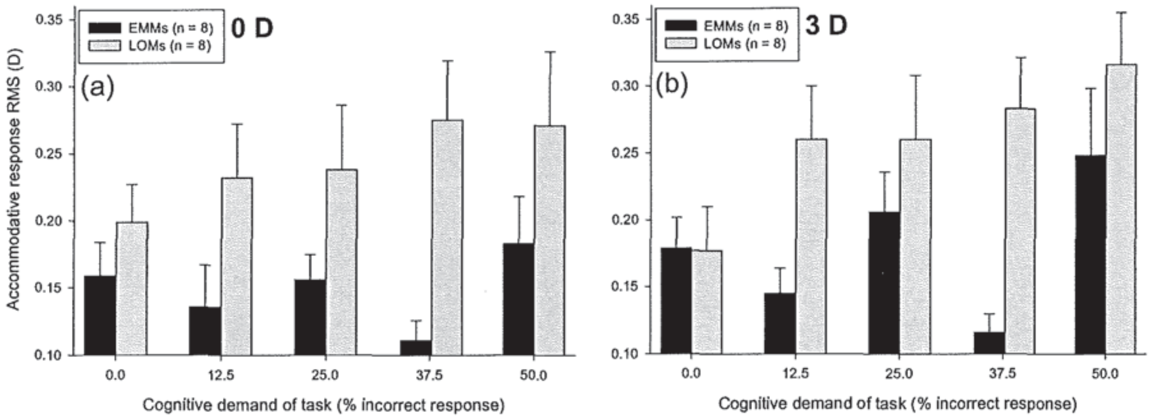


Figure 7.4 Effect of cognitive demand on the monocular RMS of accommodation microfluctuations for all subjects (n = 16) at two vergence levels (0.0 and 3.0 D). Error bars represent 1 SEM.

7.3.2 Microfluctuations of Accommodation

Figure 7.4 illustrates the effect of increasing cognitive load on the accommodative root-mean-square (RMS) response. On average, RMS values of accommodative microfluctuations were amplified with increased workload (by 0.05 ± 0.11 D, and 0.10 ± 0.11 D for the 0.0 D and 3.0 D stimulus levels respectively for all subjects). Both EMMs (by 0.02 ± 0.07 D, for the 0.0 D stimulus and by 0.07 ± 0.12 D, for the 3.0 D stimulus) and LOMs (by 0.07 ± 0.14 D, for the 0.0 D stimulus and by 0.14 ± 0.11 D, for the 3.0 D stimulus) showed a significant increase in the RMS at both vergences with increasing cognitive load (Figure 7.5). Statistical analysis showed that cognitive demand ($F_{(4,56)} = 4.3$; $p = 0.004$) and refractive error ($F_{(1,14)} = 9.1$; $p = 0.009$) were statistically significant. The effect of accommodative demand ($F_{(1,14)} = 2.8$; $p = 0.11$) was not significant (Figure 7.5).



Figures 7.5 Effect of cognitive demand on the mean accommodative RMS for the EMM and LOM sub-groups at (a) optical infinity and (b) 3.0 D of accommodative demand. Error bars represent 1 SEM.

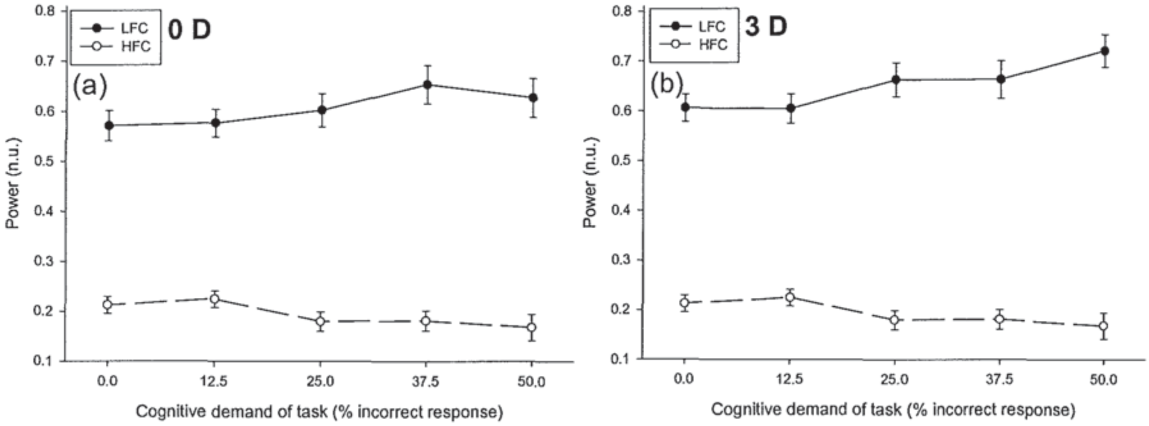


Figure 7.6 The relative power of the low and high frequency components of the accommodative microfluctuations for all subjects (n = 16) at (a) optical infinity and (b) 3.0D accommodative demand. Error bars represent ± 1 SEM.

Fast Fourier transformation shows that two dominant frequencies prevail in the accommodative power spectrum ($0.12 \leq$ LFC ≤ 0.60 Hz and $1.0 \leq$ HFC ≤ 2.5 Hz), as reported previously (Owens *et al.*, 1991; Gray *et al.*, 2000; Simmers *et al.*, 2001). In this study, however, LFC and HFC were quantified and measured in normalised units (n.u.); representing the relative power of each component in proportion to the overall power spectra minus the VLF component as seen in previous accommodative studies (Seidel *et al.*, 2003), thus reducing inter- and intra-subject variation caused by background noise.

There was a systematic relative decrease in the HFC and a corresponding relative increase in the LFC of accommodative microfluctuations with increased cognitive demand of the task for the whole cohort ($F_{(4,56)} = 2.9$; $p = 0.03$, Figure 7.6). However, the main accommodative microfluctuation frequency attributable to the increase in overall RMS appears to be the increase in relative power of the LFC (which was more pronounced in the LOM group, Figure 7.7). The change in accommodative microfluctions with vergence was significant ($F_{(1,14)} = 8.3$; $p < 0.01$), but was not different between the refractive groups ($F_{(4,56)} = 2.4$; $p = 0.15$).

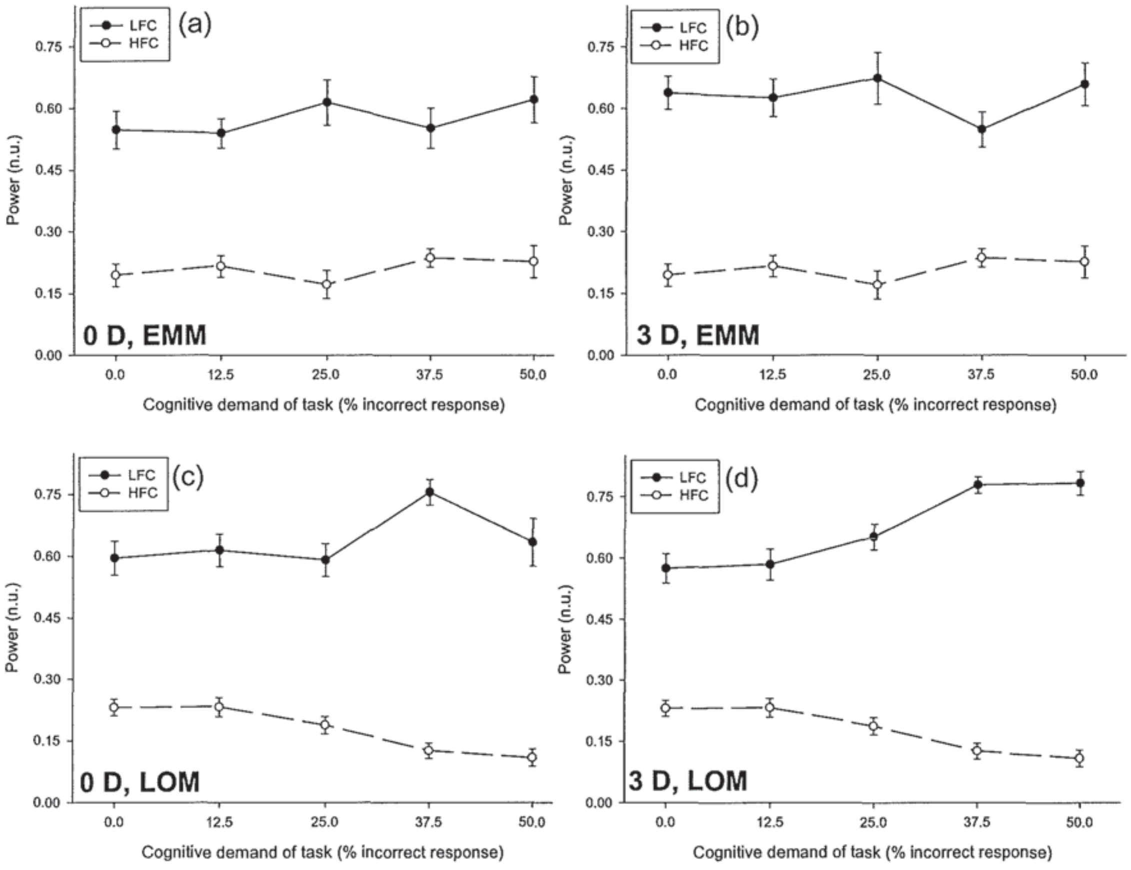


Figure 7.7 Effect of cognitive demand on the mean LFC and HFC of accommodative microfluctuations in EMMs and LOMs at 0.0 D and 3.0 D accommodative demand. Error bars represent ± 1 SEM. N = 8 in each refractive group.

7.3.3 Cardiovascular function

Mean heart period showed a significant reduction ($F_{(4,56)} = 21.6$; $p < 0.0005$) with increasing levels of workload in all subjects (by -0.05 ± 0.02 s for the 0.0 D stimulus and by -0.05 ± 0.02 s for the 3.0 D stimulus, Figure 7.8) signifying an increase in systemic sympathetic innervation. Indeed, both refractive groups showed a significant reduction with increasing levels of workload for (EMMs: by -0.04 ± 0.04 s, for the 0.0 D stimulus and by -0.04 ± 0.04 s, for the 3.0 D stimulus; LOMs: by -0.06 ± 0.03 s, for the 0.0 D stimulus and by -0.05 ± 0.03 s, for the 3.0 D stimulus). There was no significant difference with vergence ($F_{(1,14)} = 1.7$; $p = 0.21$) or refractive error ($F_{(1,14)} = 1.3$; $p = 0.27$).

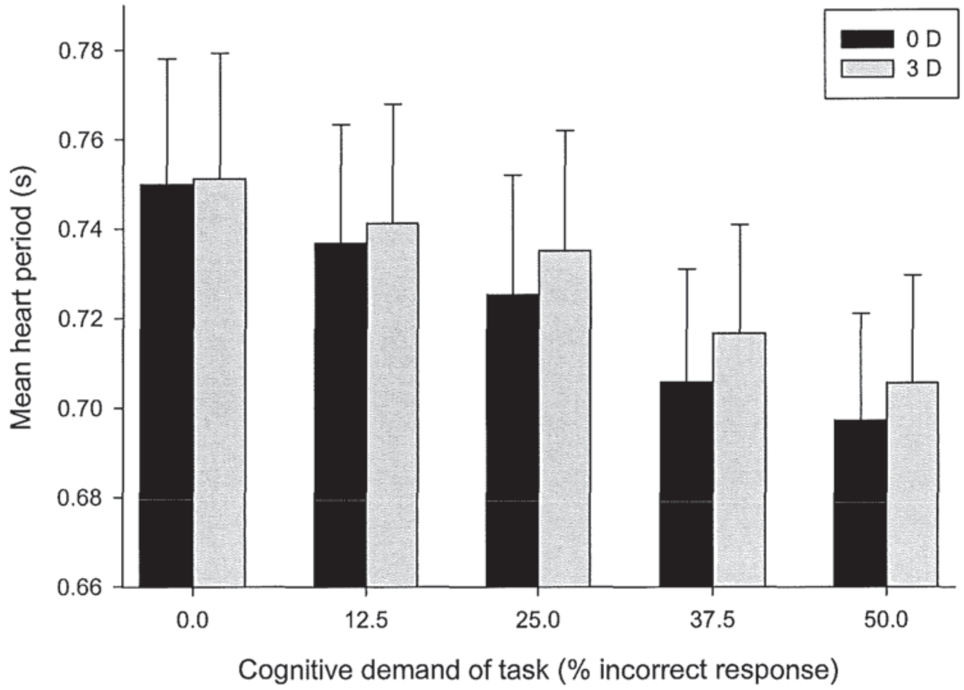


Figure 7.8 Effect of cognitive demand on mean heart period for all subjects (n = 16). Error bars represent 1 SEM.

Fast Fourier transformation of the inter-heartbeat-intervals revealed two dominant frequency bands as described previously (Akselrod *et al.*, 1981; Task Force, 1996). With increasing cognition, the LFC (sympathetic nervous system component) increased in power (by 0.12 ± 0.18 n.u., for the 0.0 D stimulus and by 0.12 ± 0.16 n.u., for the 3.0 D stimulus $F_{(4,56)} = 3.8$, $p < 0.01$) while the HFC (parasympathetic nervous system component) decreased in power (by -0.09 ± 0.10 n.u., for the 0.0 D stimulus and by -0.10 ± 0.11 n.u., for the 3.0 D stimulus, $F_{(4,56)} = 3.1$, $p < 0.05$; Figure 7.9) in all subjects. The effect of target accommodative demand on the spectral components, however, was not statistically significant (LFC: $F_{(1,14)} = 0.0$, $p = 0.96$; HFC: $F_{(1,14)} = 1.8$, $p = 0.20$). Examination of figure 7.10 (c) and (d) shows that LOMs exhibit a relative elevation of the LFC (sympathetic) over all cognitive levels compared to the EMM group ($F_{(1,14)} = 6.0$, $p < 0.05$) whereas, no significant difference occurs in the HFC (parasympathetic) between the refractive groups ($F_{(1,14)} = 0.1$, $p = 0.83$).

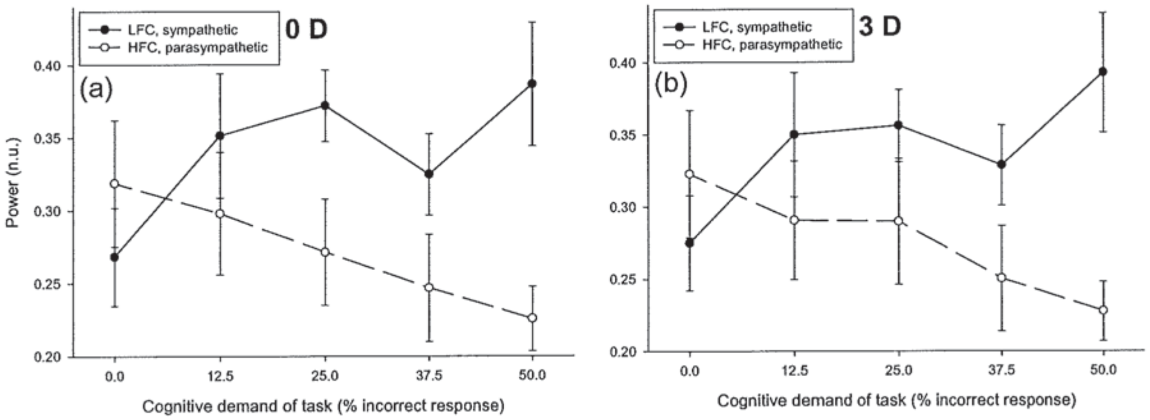


Figure 7.9 The effect of cognitive demand on the systemic sympathetic and parasympathetic autonomic profile in all subjects (n = 16) at (a) optical infinity and (b) 3.0 D accommodative demand. Error bars represent ± 1 SEM.

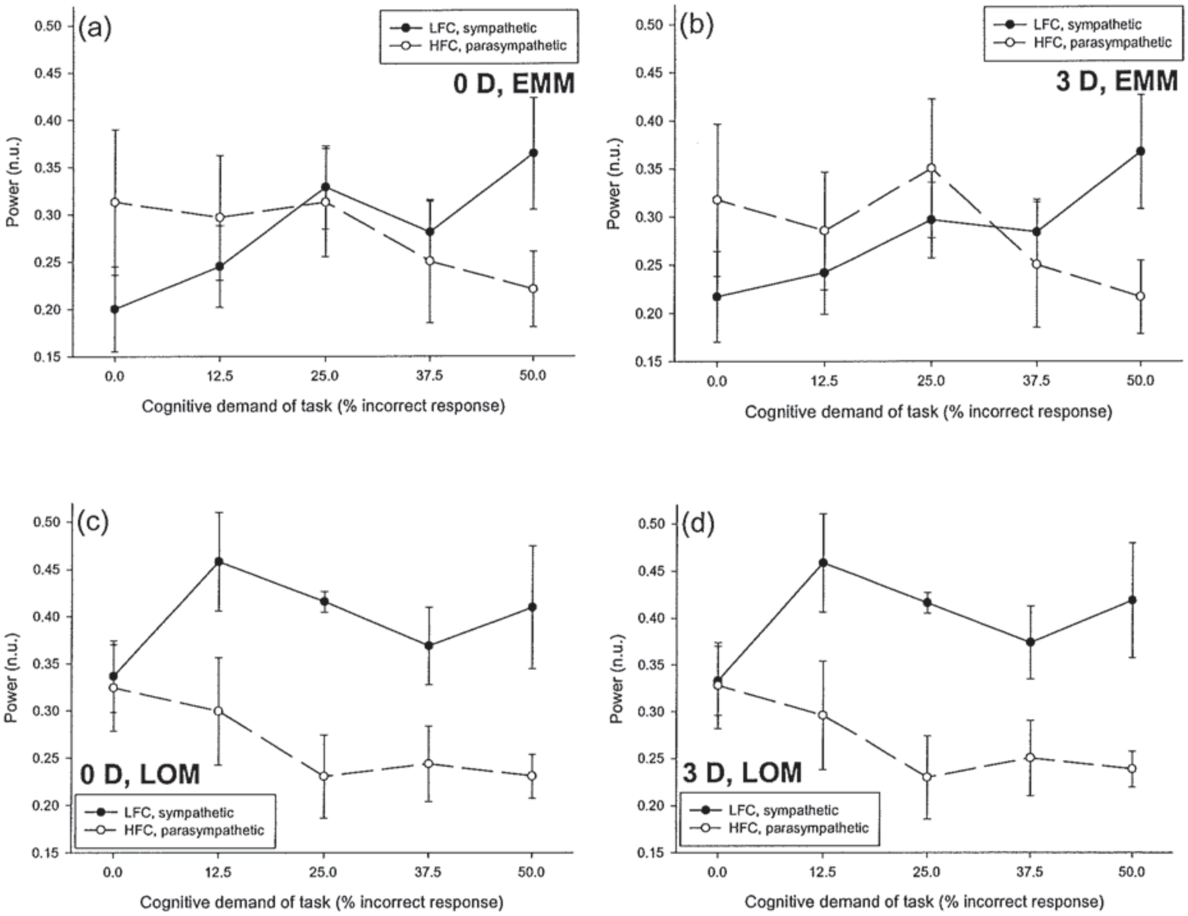


Figure 7.10 Effect of cognitive demand on the systemic sympathetic and parasympathetic autonomic profile in EMMs and LOMs at 0.0 and 3.0 D accommodative demand. Error bars represent ± 1 SEM. N = 8 in each refractive group.

7.3.4 Oculomotor and cardiovascular correlates

Comparison of shifts in accommodation with concurrent variations in cardiovascular function revealed a strong positive Pearson's product moment correlation between accommodative response and mean heart period. (0.0 D stimulus: $r = 0.97$, $p < 0.005$; 3.0 D stimulus: $r = 0.98$, $p < 0.005$, Figure 7.11). A strong positive correlation between accommodative response and mean heart period in both EMMs ($y = 0.25x + 0.62$, $r = 0.95$, $p < 0.02$, for the 0.0 D stimulus; $y = 0.14x + 0.40$, $r = 0.95$, $p < 0.02$, for the 3.0 D stimulus) and LOMs ($y = 0.11x + 0.67$, $r = 0.90$, $p < 0.05$, for the 0.0 D stimulus; $y = 0.11x + 0.42$, $r = 0.93$, $p < 0.05$, for the 3.0 D stimulus) also existed (Figure 7.12).

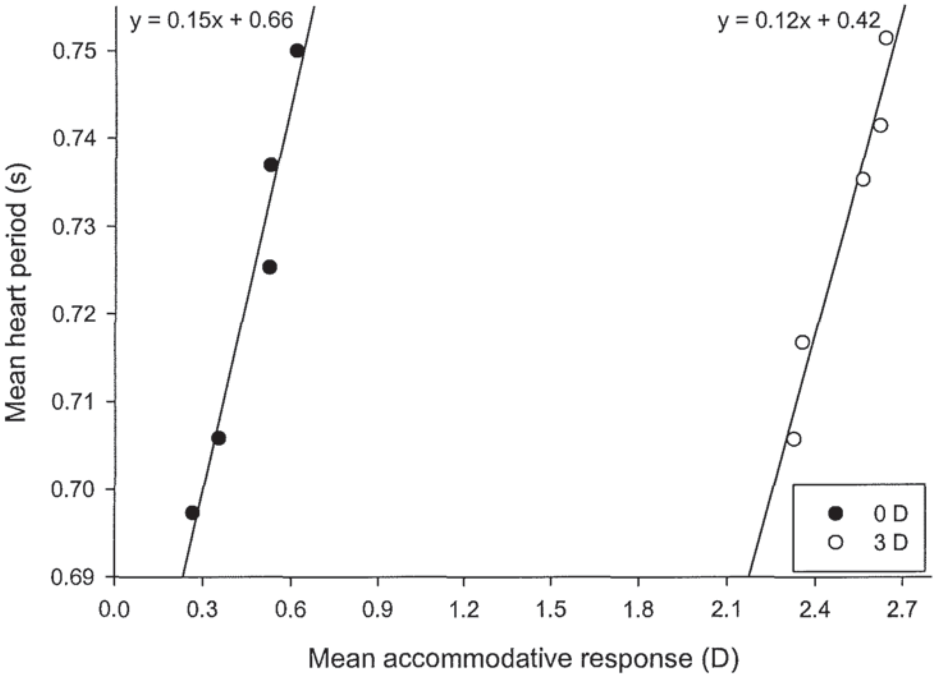


Figure 7.11 Correlation of mean accommodative response and mean heart period when viewing at both 0.0 and 3.0 D accommodative demand. Error bars are omitted for clarity.

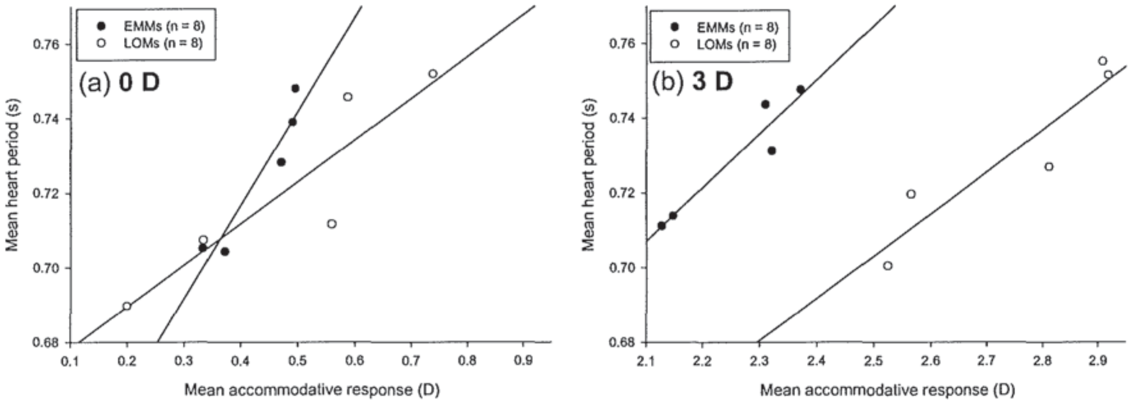
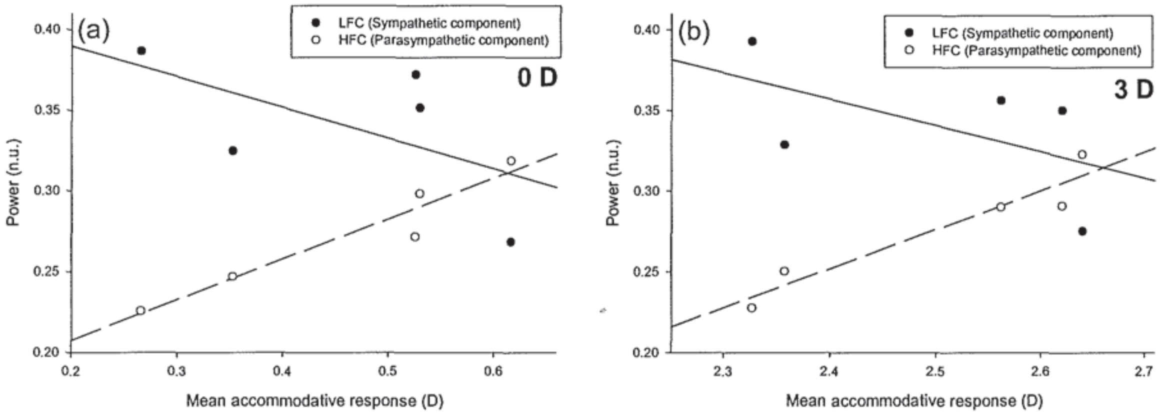


Figure 7.12 Correlation of mean accommodative response and mean heart period for EMMs and LOMs at 0.0 and 3.0 D accommodative demand. Error bars are omitted for clarity.

Across all subjects, the accommodative shift was correlated with the parasympathetic autonomic innervation (HFC: $y = 0.25x + 0.16$, $r = 0.96$, $p < 0.01$ for the 0.0 D stimulus; $y = 0.24x - 0.33$, $r = 0.95$, $p < 0.01$, for the 3.0 D stimulus), but not the sympathetic innervation (LFC: $y = 0.43 - 0.19x$, $r = 0.58$, $p = 0.30$ for the 0.0 D stimulus; $y = 0.75 - 0.16x$, $r = 0.56$, $p = 0.33$, for the 3.0 D stimulus) at both levels of accommodative demand examined (Figure 7.13).

The correlation between the accommodative shift and autonomic innervation was significant for the parasympathetic (HFC) component at optical infinity viewing, but not the sympathetic (LFC) component in EMM (LFC, $r = -0.62$, $p = 0.27$; HFC, $r = 0.99$, $p < 0.0005$ for the 0.0 D stimulus. LFC, $r = -0.81$, $p = 0.10$; HFC, $r = 0.85$, $p = 0.07$ for the 3.0 D stimulus), but neither component of the autonomic nervous system was correlated to the accommodative shift with cognitive demand in the LOMs at both levels of accommodative demand at the 5% level of significance (LFC, $r = -0.17$, $p = 0.78$; HFC, $r = 0.78$, $p = 0.12$ for the 0.0 D stimulus. LFC, $r = 0.24$, $p = 0.97$; HFC, $r = 0.69$, $p = 0.20$ for the 3.0 D stimulus; Figure 7.14).



Figures 7.13 Correlation of the LFC (sympathetic) and HFC (parasympathetic) from the cardiovascular Fourier transformation with the accommodative response for each of the five cognitive levels at (a) optical infinity and (b) 3.0 D of accommodative demand. Error bars are omitted for clarity.

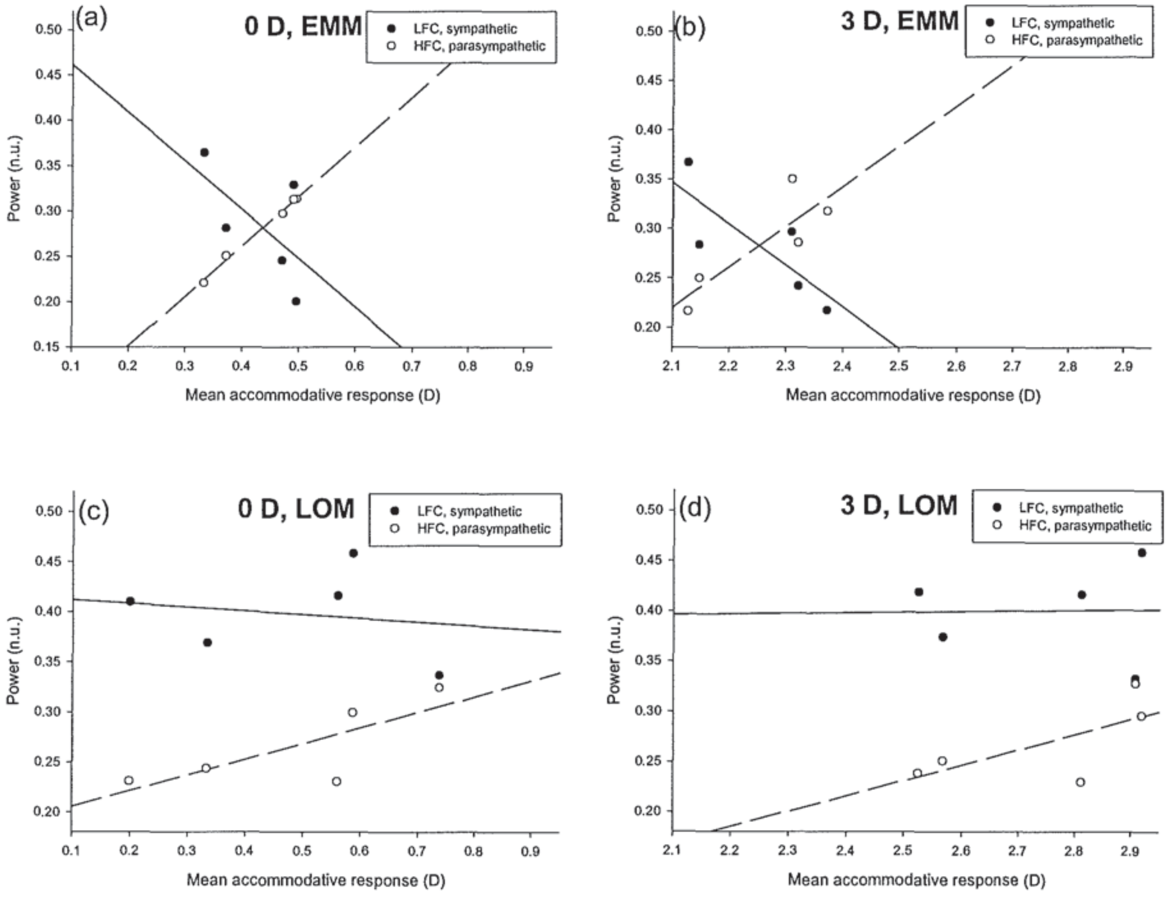


Figure 7.14 Correlation of the LFC (sympathetic) and HFC (parasympathetic) from the cardiovascular Fourier transformation with the accommodative response for each of the five cognitive levels at optical infinity and 3.0 D for EMMs and LOMs. Error bars are omitted for clarity.

7.3.5 Subjective response

The post-task subjective questionnaire indicated that subjects perceived five distinct levels of increasing difficulty between the five cognitive tasks ($F_{(4,56)} = 1048.8$, $p < 0.005$, Table 7.1). No statistically significant difference in mean TLX score ($p > 0.05$) existed between refractive groups.

Response (% correct)	Mental Demand	Physical Demand	Temporal Demand	Effort	Performance	Frustration	Overall Work-load
100	5.6 ± 0.9	1.5 ± 0.7	6.2 ± 1.5	3.5 ± 0.7	4.2 ± 1.4	2.5 ± 0.9	3.9 ± 1.0
87.5	9.7 ± 1.5	2.4 ± 1.3	9.4 ± 2.2	7.5 ± 2.3	6.9 ± 2.3	5.7 ± 2.6	6.9 ± 2.0
75	13.2 ± 2.2	3.2 ± 1.8	12.8 ± 2.2	10.5 ± 2.7	9.3 ± 2.1	8.4 ± 3.3	9.6 ± 2.4
62.5	17.8 ± 2.7	4.0 ± 2.0	17.1 ± 2.6	13.8 ± 2.6	12.6 ± 3.0	10.2 ± 3.5	12.6 ± 2.7
50	21.8 ± 3.1	5.2 ± 2.2	20.5 ± 3.2	16.2 ± 2.8	14.5 ± 2.8	11.9 ± 4.0	15.0 ± 3.0

Table 7.1 NASA TLX questionnaire weighted scores for workload for the visual cognitive tasks for all 16 subjects (± 1 S.D.).

7.4 Discussion

The study extends previous investigations (see Table 1.3) by quantifying the ocular accommodation and cardiovascular responses to intersubject-matched changes in cognitive demand at two stimulus vergences.

The significant decrease in the subjects' accommodative response from the under- to the over-workload condition in all subjects (0% to 50% incorrect response rate, Figure 7.2) of on average approximately one third of a dioptre occurred despite constant retinotopic stimuli in a closed-loop accommodative environment. It is well established that the accommodative response is determined by a complex interaction of retinotopic (Seidel *et al.*, 2003) and spatiotopic (Wolffsohn *et al.*, 2003b) factors. It has also been proposed that increased cognitive demand invokes a shift in the sympathetic input to the ciliary body (Bullimore and Gilmartin, 1988; Bullimore *et al.*, 1992). Bullimore and Gilmartin (1988) measured the closed-loop accommodative response in 12 EMMs at three accommodative stimulus levels (1.0, 3.0 and 5.0 D). Mental effort was shown to induce a significant increase in mean response for the 1.0 D task, a response equivalent to the passive condition for the 3.0 D task and a significant reduction in response for the 5.0 D task. Sympathetic blocking with timolol maleate only affected the accomodative response for the 5.0 D task in that it was significantly increased.

In this study, however, the strongest correlation between the systemic autonomic nervous system and the accommodative response, within each refractive group, occurred in the parasympathetic system (accounting for between 47% and 99% of the variance). The systemic sympathetic system showed a generally weaker non-significant correlation where only 0% to 65% of the variance in the autonomic branch was accounted for by the change in accommodative response within each refractive group. This suggests that the dominant factor in the retardation of the accommodative response is facilitated by the attenuation in the systemic parasympathetic innervation, including that of the ciliary muscle. The adaptive function of the ANS appears to reside principally in its sympathetic branch as its structural organisation is such to provide integration and dissemination of responses according to need; in contrast, the parasympathetic branch has a more focal response profile (Hamill, 1996). The results of the study appear to support this hypothesis.

Further evidence of the role of parasympathetic innervation in the cognitive response, lies with the 'two component model of attention' as suggested by Porges (1976). Here, physiological responses to attention may be divided into reactive and sustained components. Importantly, these two components may be mediated via parasympathetic and sympathetic innervation respectively. As such, responses to increased cognitive demand are augmented not only by sympathetic activity, but also by parasympathetic activity; a hypothesis which is again supported by this study.

In contrast, when considering the effect of refractive error on oculomotor and cardiovascular function, it is the sympathetic nervous system that appears be the controlling factor. On average, LOMs show over twice the reduction in accommodative response compared to EMMs (mean shift: -0.46 D *vs.* -0.20 D). Furthermore, LOMs also show a greater increase in the accommodative RMS value when compared to EMMs (mean shift: 0.11 D *vs.* 0.05 D). Although the difference between refractive groups did not reach significance, the results are intriguing when considered concurrently with the effect on the cardiovascular system. Here, the LOM group showed a statistically significant increase in the systemic sympathetic innervation over all cognitive levels, whereas, no change occurred in the parasympathetic system between refractive groups. The evidence suggests then that discrepancies in the accommodative response between refractive groups, are attributable to the increase in systemic sympathetic innervation in LOMs.

7.5 Conclusions

In conclusion, the data demonstrate a significant reduction in accommodative response and an increase in the accommodative microfluctuations with increasing cognitive demand that is predominantly attributable to a concurrent reduction in the relative power of the systemic parasympathetic nervous system. The disparity and accuracy of the accommodative response between refractive groups, however, appears to be augmented by changes in the sympathetic nervous system.

The main findings of the study are:

- Cognitive demand leads to a significant decrease in the accommodative response from the under- to the over-workload condition; greater in LOMs.
- Shift in accommodation is related to a concurrent attenuation in systemic parasympathetic innervation.
- Disparity in accommodative response appears to be related to changes in systemic sympathetic innervation.
- Microfluctuations of accommodation are amplified by increasing levels of cognition.

The findings suggest that concomitant measures of cardiovascular function can provide systematic monitoring of the effect of cognition on accommodative response.

Supporting publications

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (In review). Effect of cognition and ametropia and oculomotor and cardiovascular function. *Investigative Ophthalmology and Visual Science.*

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). The influence of cognition on oculomotor and cardiovascular function. *Ophthalmic and Physiological Optics* **24**, 155.

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). The effect of cognition and refractive error on oculomotor and cardiovascular function. *10th International Myopia Conference.*

CHAPTER 8

CONCLUSIONS AND FUTURE INVESTIGATIONS

8.1 General conclusions

The principal theme of this thesis has been the effect of workload, induced by both retinotopic and spatiotopic stimuli, on both the oculomotor and cardiovascular systems together with investigating the covariation between the two systems – the 'eye-heart' link. Furthermore, the influence of refractive error on oculomotor and cardiovascular function was assessed. These studies have involved the investigation of not only gross changes in both ocular accommodation and cardiovascular function, but also more subtle changes (e.g. accommodative microfluctuations and heart rate variability) which required more detailed examination. In order to examine these parameters, a series of novel software programs and hardware components were designed and manufactured (as described in Chapter 2).

A large sample, cross-sectional study showed that refractive error modulates the steady-state accommodative response, such that, at high accommodative demand levels (3.0 to 4.0 D), late-onset myopes (LOMs) display less accurate responses when compared to other refractive groups. Furthermore, LOM subjects demonstrate statistically significant lower levels of tonic accommodation (TA). In Chapters 4 and Chapter 7, root-mean square (RMS) values of the accommodative response amplified with increased levels of accommodative demand, suggesting that accommodative control becomes more demanding for closer targets. Again, changes in refractive error only became significant between groups at higher demand levels (3.0 and 4.0 D) with the LOMs showing the largest magnification in oscillations. The primary cause of the changes in RMS value was attributed to changes in the LFC of the microfluctuations. As suggested in previous studies (McBrien and Millodot, 1986b, 1987; Jiang, 1995; Rosenfield and Gilmartin, 1998) these factors could predispose individuals to the development of myopia particularly for near-work performed between 25 cm and 33 cm from the subject.

Examination of the stimulus-response cross-over point with the unit ratio line and TA has generated much interest (Johnson, 1976; Owens, 1979; Charman, 1982; Ciuffreda *et al.*, 1984; Owens, 1984; Mordi *et al.*, 1986; Ramsdale and Charman, 1989; Tan and O'Leary, 1988; Ong *et al.*, 1993; Rosenfield *et al.*, 1993). As such, this thesis considered the relationship between these factors. The data show that there is indeed a connection between the two parameters, however, they are not directly equal. Tonic accommodation is approximately twice the dioptric value of the stimulus-response cross-over point.

The role of the microfluctuations of accommodation was investigated in Chapter 6. Here, the temporal frequency location of the accommodative high frequency component (HFC) correlated significantly with the arterial pulse frequency, as shown previously in smaller studies (Winn *et al.*, 1990b). In addition to the findings of previous studies, this correlation was present at a range of accommodative demands from 0.0 D to 4.0 D (in 1.0 D steps) and in all refractive groups. The findings of this study suggest that the HFC is augmented by physiological factors that are independent of accommodative status and is not influenced directly by the accommodative control mechanism. However, the HFC of the accommodative response may still be utilised by the accommodation system in optimising the steady-state accommodative response (also see Chapter 4) even though they are not under the active control of the visual system. Perhaps an integrated response, utilising both low frequency (LFC) and HFC oscillation enables the accommodation system to maintain adequate focus.

An important facet of this work has been the ability to monitor the systemic autonomic nervous system non-invasively via cardiovascular system responses, while examining simultaneously the ocular accommodation response to changes in retinotopic and spatiotopic stimuli. The study sought to determine whether measures of accommodation are related to measures of cardiovascular function. The investigation examined the hypothesis that arousal of the autonomic nervous system is manifest through covariations in oculomotor and cardiovascular function. The data does demonstrate, in part, covariation between the oculomotor and cardiovascular systems. From the work carried out, the relationship between TA and mean heart period showed that those subjects with a faster heart rate (i.e. lower heart period) tend to have a higher TA value. Further, an increase in accommodative demand accompanies a decay in the heart period. *Post-hoc* spectral analysis suggests that the changes in heart period are controlled by a relative attenuation of the systemic parasympathetic (HFC) nervous system. The influence of refractive error on the cardiovascular response to changes in accommodative demand, was however equivocal. Only emmetropes (EMMs) differed significantly from LOMs in the absolute power of the HFC; suggesting that EMMs show a greater reduction in the absolute cardiovascular HFC than LOMs.

Finally, examination of the effect cognition has on the oculomotor and cardiovascular system, confirms that increasing levels of cognition do affect the accommodative response. Importantly, in contrast to all previous studies that have examined the effect of cognition on the oculomotor response, this study normalised the cognitive demand between-subjects, such that each subject experienced the same mental demands. Also, in contrast to previous studies, the accommodative response does not tend towards the tonic level (Bullimore and Gilmartin, 1988), but in fact recedes at both near and far. Moreover, this recession in response accompanies the decay in the systemic parasympathetic innervation to the heart. Differences between refractive groups also exist in that LOMs show more inaccurate responses than EMMs. This disparity, however, appears to be augmented by the sympathetic nervous system.

8.2 Analysis of experimental work: suggestions for improvement

The main instrument used in the thesis was the Shin-Nippon SRW-5000. It was the intention of the author to utilise a newly available autorefractor/autokeratometer in the thesis (the Shin-Nippon NVision-K 5001). Due to technical difficulties in the adaptation of the instrument to continuous recording, however, this was not possible (see Chapter 2). A clinical evaluation of the instrument was conducted and published (see supporting publications). The main advantage of the new instrument is that it can record refractive error/accommodative response through pupils ≥ 2.3 mm (0.6 mm smaller than the SRW-5000), the greater range offsetting the miosis induced by higher levels of accommodative demand.

The accommodative range could be extended when assessing the autonomic profile in certain subjects. In Chapter 5, approximately 40% of subjects showed no equilibrium point within the range of 0.0 D to 6.0 D. This range of demands was chosen as targets (excluding the 6.0 D stimulus) were presented within a Badal optical system, therefore, limiting the range of accommodation demands available. Extending the range to higher accommodation demands (therefore real-world targets) may enable more subjects to be included in the data analysis.

Studies were conducted in the monocular state. The main reason for this was to control confounding variables (i.e. luminance, target size, target contrast, vergence). Responses (both oculomotor and cardiovascular) therefore, were as a consequence of blur-driven stimuli. As suggested in Chapter 3, however, real-world conditions expose individuals to a myriad of environments, both monocular and binocular, which may or may not contribute to the aggregate accommodative response (e.g. cognition, surround propinquity, variations in luminance, dynamic tasks and sound). As such, the everyday near visual task may place the subject in a very different environment to the laboratory situation. Obviously, quantification of the near visual response to real-world tasks should be undertaken and examined. This, however, raises a plethora of problems. Recently validated photorefraction systems (e.g. the *PowerRefractor*; Wolffsohn *et al.*, 2002) could be utilised to monitor oculomotor changes (i.e. vergence, accommodative response and pupil size) to natural visual tasks. Such a system would provide a more naturalistic profile of the oculomotor system when responding to real-world near visual tasks. It must be noted, however, that such systems do have complications (e.g. calibration problems).

Finally, how does the data acquired in this manner (i.e. cardiovascular function) compare to more traditional pharmalogical methods of assessing ANS function in oculomotor investigations (e.g. Gilmartin *et al.*, 2002; Mallen, 2002). It was the intention of the author to cross-correlate the oculomotor and cardiovascular responses in a cohort that had undergone autonomic profiling via pharmacological manipulation in a previous study (Mallen, 2002). Unfortunately, as the subjects were undergraduate optometry students when the initial study was conducted (1999 to 2002), they were no longer available for this study. However, the techniques described in this thesis could be used to differentiate subjects who have been described as 'responders' or 'non-responders' with respect to sympathetic facility of the ciliary muscle.

8.3 Concluding statement

Collectively, the investigations discussed in this thesis explore the role of oculomotor and cardiovascular function in workload environments, providing evidence for a behavioural link between the cardiovascular and oculomotor systems. The findings of this work support and develop the findings of previous studies (Tyrrell *et al.*, 1992; 1994; 1995; 2000; Ritter and Huhn-Beck, 1993; Pearson *et al.*, 1996). These findings are important for industries that are involved with the man-machine interface, such as the aerospace industry, to more fully understand the effects of workload on the visual system. The thesis provides further evidence that the visual system can provide objective measures of task workload which would be invaluable in human factors research. Given that behavioural demands can influence autonomic activity (Tyrrell *et al.*, 2000) which, in turn, can influence oculomotor behaviour (Davies *et al.*, 2004), the question arises as to the impact such demands may have on visual performance in stressful real-world environments.

The ANS provides control processes which normally ensure the efficacy of sustained near vision in the pre-presbyopic eye. The proposition that near vision may be a precursor to the development of myopia (Rosenfield and Gilmartin, 1998) implies that some anomaly of the ANS is a factor in inducing the principal structural correlate of myopia (i.e. elongation of the vitreous chamber). Hitherto, the majority of *in vivo* human investigations have been constrained to pharmacological manipulations of the ANS. The methodologies and techniques described in this thesis, however, provide a new, non-invasive tool for the exploration of the ANS in studies of oculomotor function.

This thesis and the preceding literature in this area, has merely begun to explore this intricate and perplexing area of research; much work in this field remains to be done. The statement provided by Bernard (1878) eloquently summarises the elusive nature of ANS function: 'Nature thought it prudent to remove the important phenomena which it controls from the caprice of an ignorant will.'

REFERENCES

Abbott, M. L., Schmid, K. L. and Strang, N. C. (1998). Differences in the accommodation stimulus response curves of adult myopes and emmetropes. *Ophthalmic and Physiological Optics*. **18**, 13-20.

Abraham-Cohen, J. A., Rosenfield, M. and Jiang, C. (1997). Blur sensitivity in myopes. *Optometry and Vision Science*. (suppl.) **74**, 177.

Adams, D. W. and McBrien, N. A. (1993). A longitudinal study of the relationship between tonic accommodation (dark focus) and refractive error in adulthood. *Investigative Ophthalmology and Visual Science*. (suppl.) **34**, 1308.

Akselrod, S., Gordon, D., Ubel, F. A., Shannon, D. C., Barger, A. C. and Cohen, R. J. (1981). Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science*. **213**, 220-222.

Anisman, H. (1975). Time-dependent variations in aversively motivated behaviours: non-associative effects of cholinergic and catecholaminergic activity. *Psychology Review*. **82**, 359-385.

Antelmi, I., DePaula, R. S., Shinzato, A. R., Peres, C. A., Mansur, A. J. and Grupi, C. J. (2004). Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *American Journal of Cardiology*. **93**, 381-385.

Armaly, M. F. and Burian, M. L. (1958). Changes in the tonogram during accommodation. *Archives of Ophthalmology*. **60**, 60-69.

Armalay, M. F. and Rubin, M. L. (1961). Accommodation and applanation tonometry. *Archives of Ophthalmology*. **65**, 415-423.

Armstrong, R. A., Slade, S. V. and Eperjesi, F. (2000). An introduction to analysis of variance (ANOVA) with special reference to data from clinical experiments in optometry. *Ophthalmic and Physiological Optics*. **20**, 235-241.

Arnulf, A. and Dupy, O. (1960). Contribution a l'étude des microfluctuations d'accommodation de l'œil. Rev Opt (Paris) **39**, 195-208.

Badal, J. (1876). Optomètre métrique international : pour la mesure simultané de la réfraction et de l'acuité visuelle même chez les illettrés. *Ann. Ocul.* **75**, 101-107.

Baker, F. J. (2000). Oculomotor function in incipient presbyopia. PhD Thesis, Aston University, UK.

Baker, F. J. and Gilmartin, B. (2002). The effect of incipient presbyopia on the correspondence between accommodation and vergence. *Graefes Archive for Clinical and Experimental Ophthalmology*. **240**, 488-494.

Bates, R. A., Hilton, M. F., Godtrey, K. R. and Chappell, M. J. (1997). Autonomic function assessment using analysis of heart rate variability. *Control Engineering Practice*. **5**, 1731-1737.

Bennett, A. G. and Rabbetts, R. B. (1998). *Clinical Visual Optics*. 2nd edn, Butterworth-Heinemann, Oxford, UK.

Bernard, C. (1878). *La Science Experimentale*. Balliere, p. 150.

Bernardi, L., Wdowczyk-Szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G. and Sleight, P. (2000). Effects of controlled breathing, mental activity and mental stress with or without verbalisation on heart rate variability. *Journal of the American College of Cardiology*. **35**, 1462-1469.

Berny, F. and Slansky, S. (1970). Wavefront determination resulting from Foucault test as applied to the human eye and visual instruments. In: *Optical Instruments and Techniques*. (J. Home, ed). Oriel, Newcastle-upon-Tyne, UK.

Birnbaum, M. H. (1983). *Optometric Management of Nearpoint Vision Disorders*. Butterworth-Heinemann.

Birnbaum, M. H. (1984). Nearpoint visual stress: A physiological model. *Journal of the American Optometric Association*. **55**, 825-835.

Bland, J. M. and Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. **1**, 307-310.

Bour, L. J. (1981). The influence of the special distribution of a target on the dynamic response and fluctuations of the accommodation of the human eye. *Vision Research*. **21**, 1287-1296.

Brown, N. (1973). The change in shape and internal form of the lens of the eye on accommodation. *Experimental Eye Research*. **15**, 441-459.

Brown, S. (2003). Effect of whiplash injury on accommodation. *Clinical and Experimental Ophthalmology*. **31**, 424-429.

Bullimore, M. A., Fusaro, R. E. and Adams C. W. (1998). The repeatability of automated and clinical refraction. *Optometry and Vision Science*. **75**, 617-622.

Bullimore, M. A. and Gilmartin, B. (1987a). Tonic accommodation, cognitive demand, and ciliary muscle innervation. *American Journal of Optometry and Physiological Optics*. **64**, 45-50.

Bullimore, M. A. and Gilmartin, B. (1987b). Aspects of tonic accommodation in emmetropia and late-onset myopia. *American Journal of Optometry and Physiological Optics*. **64**, 499-503.

Bullimore, M. A. and Gilmartin, B. (1988). The accommodative response, refractive error and mental effort: 1. The sympathetic nervous system. *Documenta Ophthalmologica*. **69**, 385-397.

Bullimore, M. A. and Gilmartin, B. (1989). The measurement of adaptation of tonic accommodation under two open-loop conditions. *Ophthalmic and Physiological Optics*. **9**, 72-75.

Bullimore, M. A., Gilmartin, B. and Hogan, R. E. (1986). Objective and subjective measurement of tonic accommodation. *Ophthalmic and Physiological Optics*. **6**, 57-62.

Bullimore, M. A., Gilmartin, B. and Royston, J. M. (1992). Steady-state accommodation and ocular biometry in late-onset myopia. *Documenta Ophthalmologica*. **80**, 143-155.

Burrow, C. A. (1841). *Beitrage zur Physiologie und Physik des menschlichen Auges*. Haatlem, Berlin. 212.

Cammann, H. and Michel, J. (2002). How to avoid misinterpretation of heart rate variability power spectra? *Computer Methods and Programs in Biomedicine*. **68**, 15-23.

Campbell, F. W. (1954). The minimum quantity of light required to elicit the accommodation reflex in man. *Journal of Physiology*. **123**, 357-366.

Campbell, F. W. and Robson, J. G. (1959). A high-speed infra-red optometer. *Journal of the Optical Society of America*. **49**, 268-272.

Campbell, F. W., Robson, J. G. and Westheimer, G. (1959). Fluctuations of accommodation under steady state viewing conditions. *Journal of Physiology*. **145**, 579-594.

Campbell, F. W. and Westheimer, G. (1959). Factors influencing the accommodation responses of the human eye. *Journal of the Optical Society of America*. **49**, 568-571.

Campbell, F. W. and Westheimer, G. (1960). Dynamics of accommodation responses of the human eye. *Journal of Physiology*. **181**, 285-295.

Campbell, F. W., Westheimer, G. and Robson, J. G. (1958). Significance of fluctuations of accommodation. *Journal of the Optical Society of America*. **48**, 669.

Charman, W. N. (1982). The accommodative resting point and refractive error. *Ophthalmic Optician*. **21**, 469-473.

Charman, W. N. (1999). Near vision, lags of accommodation and myopia. *Ophthalmic and Physiological Optics*. **19**, 126-133.

Charman, W. N. (2000). Accommodation and the through-focus changes of the retinal image. In: *Accommodation and Vergence Mechanisms in the Visual System*. (O. Franzén, H. Richter and L. Stark, eds). Berkhauser Verlag, Switzerland. 115-127.

Charman, W. N. and Heron, G. (1988). Fluctuations in accommodation: a review. *Ophthalmic and Physiological Optics*. **8**, 153-164.

Chat, S. W. S. and Edwards, M. H. (2001). Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in children. *Ophthalmic and Physiological Optics*. **21**, 87-100.

Chauhan, K. and Charman, W. N. (1995). Single figure indices for the steady-state accommodative response. *Ophthalmic and Physiological Optics*. **15**, 217-221.

Chen, J. C., Schmid, K. L and Brown, B. (2003). The autonomic control of accommodation and implications for human myopia development: a review. *Ophthalmic and Physiological Optics*. **23**, 401- 422.

Chess, G. F., Tam, R. M. K. and Carlaresu, F. R. (1975). Influence of cardiac neural inputs on rhythmic variations of heart period in the cat. *American Journal of Physiology*. **228**, 775.

Chiu, N. N. and Rosenfield, M. (1994). Tonic accommodation, tonic vergence and surround propinquity. *Ophthalmic and Physiological Optics*. **14**, 290-292

Chiu, H. W., Wang, T. H., Huang, L. C., Tso, H. W. and Kao, T. (2003). The influence of mean heart rate on measures of heart rate variability as markers of autonomic function: a model study. *Medical Engineering and Physics*. **25**, 475-481.

Ciuffreda, K. J. (1998). Accommodation, the pupil, and presbyopia. In: *Borish's Clinical Refraction*. (W. J. Benjanin, ed). W. B. Saunders Company, Philadelphia. 77-120.

Ciuffreda, K. J., Hokoda, S. C., Hung, G. K. and Semmlow, J. L. (1984). Accommodative stimulus-response function in human amblyopia. *Documenta Ophthalmologica*. **56**, 303-326.

Ciuffreda, K. J. and Lee, M. (2002). Differential refractive susceptibility to sustained nearwork. *Ophthalmic and Physiological Optics*. **22**, 372-379.

Ciuffreda, K. J., Rosenfield, M. and Gillard, M. A. (1999). Near-vision lens effects on nearwork-induced transient myopia. *Clinical Eye and Vision Care*. **10**, 205-207.

Cogan, D. G. (1937). Accommodation and the autonomic nervous system. *Archives of Ophthalmology*. **18**, 739-766.

Collins, G. (1937). The electronic refractometer. *British Journal of Physiological Optics*. **1**, 30-40.

Collins, M., Davis, B. and Wood, J. (1995). Microfluctuations of steady-state accommodation and the cardiopulmonary system. *Vision Research*. **35**, 2491-2502.

Cook, C. A., Koretz, J. F., Pfahnl, A., Hyun, J. and Kaufman, P. L. (1994). Aging of the human crystalline lens and anterior segment. *Vision Research*. **34**, 2945-2954.

Cornsweet, T. N. and Crane, H. D. (1973). Training the visual accommodation system. *Vision Research*. **13**, 713-715.

Cramer, A. (1851). Tijdschrift der maatschappij vor geneeskunde. *Netherlands Lancet* (Ser.2). **1**, 529.

Cronje, S., Harris, W. F. (1997). Short-term keratometric variation in the human eye. *Optometry and Vision Science*. 74, 420-424.

Culhane, H. M. (1999). Physiological and perceptual correlates of the temporal accommodative response. PhD Thesis, University of Bradford, UK.

Culhane, H. M. and Winn, B. (1999). Dynamic accommodation and myopia. *Investigative Ophthalmology and Visual Science*. **40**, 1968-1974.

Davies, L. N., Mallen, E. A. H., Wolffsohn, J. S. and Gilmartin, B. (2003). Clinical evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR-5100K autorefractor. *Optometry and Vision Science* **80**, 320-324.

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). The influence of cognition on oculomotor and cardiovascular function. *Ophthalmic and Physiological Optics*. **24**, 155.

Day, M., Strang, N. C., Seidel, D., Gray L. S. and Mallen, E. (2004). Target vergence related increases in accommodation microfluctuations in myopia and emmetropia. In: *Proceedings of the 10th International Myopia Conference*. Cambridge.

Denieul, P. (1980). Etude des fluctuations d'accommodation de l'œil par Optométrie Infra Rouge. Thèse, L'Université de Paris-Sud.

Denieul, P. (1982). Effects of stimulus vergence on mean accommodation response, microfluctuations of accommodation and optical quality of the human eye. *Vision Research*. **22**, 561-569.

Denieul, P. and Corno, F. (1986). Accommodation et contraste. *L'Optométrie*. **32**, 4-8.

Descartes, E. (1677). *Traité de l'Homme*.

Diekhoff, G. (1992). Statistics for the social and behavioural sciences: univariate, bivariate, multivariate. Wm. C. Brown Publishers, Dubuque.

Dubbelman, M. and van der Heijde, G. L. (2001). The shape of the aging human lens: curvature, equivalent refractive index and the lens paradox. *Vision Research*. **41**, 1867-1877.

Dubbelman, M., van der Heijde, G. L., Weeber, H. A. and Vrensen, G. F. J. M. (2003). Changes in the internal structure of the human crystalline lens with age and accommodation. *Vision Research*. **43**, 2363-2375.

Duke-Elder, S. (1970). *System of Ophthalmology*. **Vol. 5**. Henry Kimpton, London. 153-204

Edgar, G. K., Reeves, C. A., Craig, I. and Pope, J. C. D. (1994). The effect of mental processing on the closed-loop accommodation response. *Investigative Ophthalmology and Visual Science*. (suppl.) **35**, 1280.

Edwards, M. H. (1998). Myopia: definitions, classifications and economic implications. In: *Myopia and Nearwork*. (M. Rosenfield and B. Gilmartin, eds). Butterworth-Heinemann, Oxford, UK. 1-12.

Edwards, M. H. and Lam, C. S. Y. (2004). The epidemiology of myopia in Hong Kong. *Annals Academy of Medicine Singapore*. **33**, 34-38.

Elliott, M., Simpson, T., Richter, D. and Fonn, D. (1997). Repeatability and accuracy of automated refraction: a comparison of the Nikon NRK-8000, the Nidek AR-1000, and subjective refraction. *Optometry and Vision Science*. **74**, 434-438.

Ewing, D. J., Martin, C. N., Young, R. J. and Clarke, B. F. (1985). The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetic Care*. **8**, 491-498.

Fauchier, L., Babuty, D., Autret, M. L., Poret, P., Cosnay, P. and Fauchier, J. P. (1998). Influence of duration and hour of recording on spectral measurements of heart rate variability. *Journal of the Autonomic Nervous System*. **73**, 1-6.

Fercher, A. F., Hu, H. Z., Steeger, P. F. and Briers, J. D. (1982). Eye deformation measurement by laser interferometry. *Optica Acta*. **29**, 1402-1406.

Fincham, E. F. (1925). The changes in the form of the crystalline lens in accommodation. *Transactions of the Optical Society of UK*. **26**, 239-269.

Fincham, E. F. (1937). The mechanism of accommodation. *British Journal of Ophthalmology*. Monograph Supplement VIII. 7-80.

Fincham, E. F. (1951). The accommodation reflex and its stimulus. *British Journal of Ophthalmology*. **35**, 381-393.

Fincham, E. F. and Walton (1957). The reciprocal actions of accommodation and vergence. *Journal of Physiology*. **137**, 488.

Flitcroft, D. I. (1998). A model of the contribution of oculomotor and optical factors to emmetropization and myopia. *Vision Research*. **38**, 2869-2879.

Flitcroft, D. I. (1999). The lens paradigm in experimental myopia: oculomotor, optical and neurophysiological considerations. *Ophthalmic and Physiological Optics*. **19**, 103-111.

Francis, E. L., Jiang, B., Owens, D. A. and Tyrrell, R. A. (2003). Accommodation and vergence require effort-to-see. *Optometry and Vision Science*. **80**, 467-473.

French, C. N. and Jennings, J. A. M. (1974). Errors in subjective refraction – an exploratory study. *Ophthalmic and Physiological Optics*. **14**, 797-806.

Garner, L. F., Owens, H., Kinnear, R. F. and Frith, M. J. (1999). Prevalence of myopia in Sherpa and Tibetan children in Nepal. *Optometry and Vision Science*. **76**, 282-285.

Gawron, V. J. (1981). Differences among myopes, emmetropes, and hypermetropes. *American Journal of Optometry and Physiological Optics*. **58**, 753-760.

Gawron, V. J. (1983). Ocular accommodation, personality, and autonomic balance. *American Journal of Optometry and Physiological Optics*. **60**, 630-639.

Gawron, V. J., Paap, K. R. and Malmstrom, F. V. (1985). The effects of task performance on ocular accommodation and perceived size. *Aviation, Space and Environmental Medicine*. **56**, 225-232.

Gherghel, D., Hosking, S. L. and Orgül, S. (2004). Autonomic nervous system, circadian rhythms and primary open-angle glaucoma. *Survey of Ophthalmology*. **49**, 491-508.

Gilmartin, B. (1986). A review of the role of sympathetic innervation of the ciliary muscle in ocular accommodation. *Ophthalmic and Physiological Optics*. **6**, 23-37.

Gilmartin, B. (1998). Autonomic correlates of near-vision in emmetropia and myopia. In: *Myopia and Nearwork*. (M. Rosenfield and B. Gilmartin, eds). Butterworth-Heinemann, Oxford, UK. 117-146.

Gilmartin, B. and Bullimore, M. A. (1987). Sustained near-vision augments sympathetic innervation of the ciliary muscle. *Clinical Visual Science*. **1**, 197-208.

Gilmartin, B., Bullimore, M. A., Rosenfield, M., Winn, B. and Owens, H. (1992). Pharmacological effects on accommodative adaptation. *Optometry and Vision Science*. **69**, 276-282.

Gilmartin, B. and Hogan, R. E. (1985). The relationship between tonic accommodation and ciliary muscle innervation. *Investigative Ophthalmology and Visual Science*. **26**, 1024-1028.

Gilmartin, B., Mallen, E. A. H. and Wolffsohn, J. S. (2002). Sympathetic control of accommodation: evidence for inter-subject variation. *Ophthalmic and Physiological Optics*. **22**, 366-371.

Gilmartin, B. and Winfield, N. R. (1995). The effect of topical β-adrenoceptor antagonists on accommodation in emmetropia and myopia. *Vision Research*. **35**, 1305-1312.

Goldschmidt, E. (2003). The mystery of myopia. *Acta Ophthalmologica Scandinavica*. **81**, 431-436.

Goss and Winkler (1983). Progression of myopia in youth: age of cessation. *American Journal of Optometry and Physiological Optics*. **60**, 651-658.

Gray, L. S., Gilmartin, B. and Winn, B. (2000). Accommodation microfluctuations and pupil size during sustained viewing of visual display terminals. *Ophthalmic and Physiological Optics*. **20**, 5-10.

Gray, L. S., Winn, B. and Gilmartin, B. (1993a). Effect of target luminance on microfluctuations of accommodation. *Ophthalmic and Physiological Optics*. **13**, 258-265.

Gray, L. S., Winn, B. and Gilmartin, B. (1993b). Accommodative microfluctuations and pupil diameter. *Vision Research*. **33**, 2083-2090.

Gray, L. S., Winn, B., Gilmartin, B. and Eadie, A. S. (1993c). Objective concurrent measures of open-loop accommodation and vergence under photopic conditions. *Investigative Ophthalmology and Visual Science*. **34**, 2996-3003.

Gullstrand, A. (1909). Appendices to Part 1 of J. P. C. Southall (ed.) *Handbuch der Physiologischen Optik*, (3rd edn) (translated by J. P. C. Southall). Dover Publications, New York. **1**, 439.

Gwiazda, J., Thorn, F., Bauer, J. and Held, R. (1993). Myopic children show insufficient accommodative response to blur. *Investigative Ophthalmology and Visual Science*. **34**, 690-694.

Hamill, R. W (1996). In: *Primer on the Autonomic Nervous System* (D. Robertson, P. A. Low and R. J. Polinsky, eds). Academic Press. 12-25.

Hancock, P. A. (1996). Effects of control order, augmented feedback, input device and practice on tracking performance and perceived workload. *Ergonomics*. **39**, 1146-1162.

Hansen, A. L., Johnsen, B. H. and Thayer, J. F. (2003). Vagal influence on working memory and attention. *International Journal of Psychophysiology*. **48**, 263-274.

Heath, G. G. (1956). Components of accommodation. *American Journal of Optometry and Archives of American Academy of Optometry*. **33**, 569-579.

Helmholtz, H. (1855). Ubar die Akkommodation des Auges. *Albrecht v. Graefes Archives of Ophthalmology*. **1**, 1-74.

Hennessy, R. T. and Leibowitz, H. W. (1971). The effect of a peripheral stimulus on accommodation. *Perception and Psychophysics*. **10**, 129-132.

Hensen, V. and Völkers, C. (1898). Über den Ursprung der Accommodationsnerven. *Albrecht v. Graefes Archives of Ophthalmology*. **24**, 1-26.

Heron, G., Bahri, P. K., Burnside, J. A., Kacouli, K. and Mackintosh, S. R. (1984). The relationship between dark focus of accommodation and refractive error. *Ophthalmic and Physiological Optics*. **4**, 187.

Heron, G., Smith, A. C. and Winn, B. (1981). The influence of method on the stability of dark focus position of accommodation. *Ophthalmic and Physiological Optics*. **1**, 79-90.

Hon, E. H. and Lee, S. T. (1963a). The fetal electrocardiogram 1. The electrocardiogram of the dying foetus. *American Journal of Obstetrics and Gynecology*. **87**, 804-813.

Hon, E. H. and Lee, S. T. (1963b). Electronic evaluation of the fetal heart rate. *American Journal of Obstetrics and Gynecology*. **87**, 814-826.

Hung, G. K., Ciuffreda, K. J. and Rosenfield, M. (1996). Proximal contribution to a linear static model of accommodation and vergence. *Ophthalmic and Physiological Optics*. **16**, 31-41.

Iwasaki, T. (1993). Effects of a visual task with cognitive demand on dynamic and steady-state accommodation. *Ophthalmic and Physiological Optics*. **13**, 285-290.

Iwasaki, T. and Kurimoto, S. (1987). Objective evaluation of eye strain using measurements of accommodative oscillation. *Ergonomics*. **30**, 581-587.

Jaschinski-Kruza, W. and Toenies, U. (1988). Effect of a mental arithmetic task on dark focus of accommodation. *Ophthalmic and Physiological Optics*. **8**, 432-437.

Jiang, B. C. (1994). Comparison of accommodative response in emmetropia and late-onset myopia. *Optometry and Vision Science*. **71**, 64.

Jiang, B. C. (1995). Parameters of accommodative and vergence systems and the development of late-onset myopia. *Investigative Ophthalmology and Visual Science*. **36,** 1737-1742.

Jiang, B. C. and Morse, S. E. (1999). Oculomotor functions and late-onset myopia. *Ophthalmic and Physiological Optics*. **19**, 165-172.

Jimenez, J. R., Bermudez, J., Rubino, M., Gomez, L. and Anera, R. G. (2004). Prevalence of myopia in an adult population of two different ethnic groups in the Ecuadorian Amazon. *Japanese Journal of Ophthalmology*. **48**, 163-165.

Johnson, C. A. (1976). Effects of luminance and stimulus on accommodation and visual resolution. *Journal of the Optical Society of America*. **66**, 138-142.

Johnson, G, J., Matthews, A. and Perkins, E. S. (1979). Survey of ophthalmic conditions in a Labrador community. I. refractive errors. *British Journal of Ophthalmology*. **63**, 440-448.

Jones, R. (1990). Accommodative and convergence control system parameters are abnormal in myopia. *Investigative Ophthalmology and Visual Science* (Suppl.) **31**, 81.

Jordan, G. and Jaschinski-Kruza, W. (1986). Dark focus and visual acuity in relation to the menstrual cycle. *Perception*. **15**, A20.

Joubert, L and Harris, W. F. (1995). Excess of autorefraction over subjective refraction: dependence on age. *Optometry and Vision Science*. **72**, 403-410.

Judge, S. J. and Cummings, R. G. (1986). *Journal of Neurophysiology*. **55**, 915-930.

Judge, S. J. and Flitcroft, D. I. (1999). Control of accommodation. In: *Nervous Control of the Eye*. (G. Burnstock and A. M. Sillito, eds). Harwood Academic, Amsterdam. 93-115.

Jumblatt, J. E. (1999). Innervation and pharmacology of the iris and ciliary body. In: *Nervous Control of the Eye*. (G. Burnstock and A. M. Sillito, eds). Harwood Academic, Amsterdam. 1-40.

Kaufman, P. L. (1992). Accommodation and presbyopia: Neuromuscular and biophysical aspects. In: *Adler's Physiology of the Eye*. Mosby Year Book, Missouri, USA.

Koretz, J. F., Cook, C. A. and Kaufman, P. L. (1997). Accommodation and presbyopia in the human eye. Changes in the anterior segment and crystalline lens with focus. *Investigative Ophthalmology and Visual Science*. **38**, 569-578.

Koretz, J. F., Cook, C. A. and Kuszak, J. R. (1994). The zones of discontinuity in the human lens: development and distribution with age. *Vision Research*. **34**, 2955-2962.

Kotulak, J. C. and Schor, C. M. (1986). Temporal variations in accommodation during steady-state conditions. *Journal of the Optical Society of America A*. **3**, 223-227.

Kotulak, J. C. and Schor, C. M. (1987). The effects of optical vergence, contrast, and luminance on the accommodative response to spatially band pass filtered targets. *Vision Research*. **27**, 1797-1806.

Kruger, P. B. (1975). Luminance changes of the fundus reflex. *American Journal of Optometry and Physiological Optics*. **52**, 847-861.

Kruger, P. B. (1977a). Changes in fundus reflex luminance with increased cognitive processing. *American Journal of Optometry and Physiological Optics*. **54**, 445-451.

Kruger, P. B. (1977b). The role of accommodation in increasing the luminance of the fundus reflex during cognitive processing. *Journal of the American Optometric Association*. **48**, 1493-1496.

Kruger, P. B. (1980). The effect of cognitive demand on accommodation. *American Journal of Optometry and Physiological Optics*. **57**, 440-445.

Krumholz, D. M., Fox, R. S. and Ciuffreda, K. J. (1986). Short-term changes in tonic accommodation. *Investigative Ophthalmology and Visual Science*. **27**, 552-557.

Langenbeck, M. (1849). *Klinische Beitrage aus dem Gebiete der Chirugie und Ophthalmologie*. Schwartz, Gottingen.

Lee, J. H., Stark, L. R., Cohen, S. and Kruger, P. B. (1999). Accommodation to static chromatic simulations of blurred retinal images. *Ophthalmic and Physiological Optics*. **19**, 223-235.

Leibowitz, H. W. and Owens, D. A. (1975a). Anomalous myopias and the intermediate dark focus of accommodation. *Science*. **189**, 646-648.

Leibowitz, H. W. and Owens, D. A. (1975b). Night myopia and the intermediate dark focus of accommodation. *Journal of the Optical Society of America*. **65**, 1121-1128.

Leibowitz, H. W. and Owens, D. A. (1978). New evidence for the intermediate position of relaxed accommodation. *Documenta Ophthalmologica*. **46**,133-147.

Longmore, D. (1971). *The heart*. World University Library, London, UK.

Magendie, F. (1816). *Précis élémentaire d physiologie*. **1**, 73. Paris.

Mallen, E. A. H. (2002). Autonomic, biometric and oculomotor correlates of myopia in young adults. PhD Thesis, Aston University, UK.

Mallen, E. A. H., Wolffsohn, J. S., Gilmartin, B. and Tsujimura, S. (2001). Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic and Physiological Optics*. **21**, 101-107.

Malmstrom, F. V., Randle, R. J., Bendix, J. S. and Weber, R. J. (1980). The visual accommodation response during concurrent mental activity. *Perceptual Psychophysics*. **28**, 440-448.

Malmstrom, F. V. and Randle, R. J. (1984). Effect of a concurrent counting task on dynamic visual accommodation. *American Journal of Optometry and Physiological Optics*. **61**, 590-594.

Mandelbaum, J. (1960). An accommodation phenomenon. *Archives of Ophthalmology*. 63, 49-52.

Manzella, D., Grella, R., Esposito, K., Giugliano, D., Barbagallo, M. and Paolisso, G. (2004). Blood pressure and cardiac autonomic nervous system in obese type 2 diabetic patients: effect of metformin administration. *American Journal of Hypertension*. **17**, 223-227.

Martin, G. J., Magid, N. M., Myers, G., Barnett, P. S., Schaad, J. W., Weiss, J. S., Lesch, M. and Singer, D. H. (1987). Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. *American Journal of Cardiology*. **60**, 86-89.

Maskelyne, N. (1789). An attempt to explain a difficulty in the theory of vision, depending on the different refrangibility of light. *Phil Trans Royal Society Ser B*. **79**, 256-264.

Mauger, R. R., Likens, C. P. and Applebaum, M. (1984). Effects of accommodation and repeated applanation tonometry on intraocular pressure. *American Journal of Optometry and Physiological Optics*. **61**, 28-30.

McBrien, N. A. and Millodot, M. (1985). Clinical evaluation of the Canon Autoref R-1. *American Journal of Optometry and Physiological Optics*. **62**, 786-792.

McBrien, N. A. and Millodot, M. (1986a). Amplitude of accommodation and refractive error. *Investigative Ophthalmology and Visual Science*. **27**, 1187-1190.

McBrien, N. A. and Millodot, M. (1986b). The effect of refractive error on accommodative response gradient. *Ophthalmic and Physiological Optics*. **6**, 145-149.

McBrien, N. A. and Millodot, M. (1987). The relationship between tonic accommodation and refractive error. *Investigative Ophthalmology and Visual Science*. **28**, 997-1004.

McCaghrey, G. E. and Matthews, F. E. (1993). Clinical evaluation of autorefractors. *Ophthalmic and Physiological Optics*.**13**, 129-137.

Mershon, D. H. and Amerson, T. L. (1980). Stability of measures of the dark focus of accommodation. *Investigative Ophthalmology and Visual Science*. **19**, 217-221.

Miege, C. and Denieul, P. (1988). Mean response and oscillations of accommodation for various stimulus vergences and feedback control of the accommodation system. *Ophthalmic and Physiological Optics*. **8**, 165-171.

Miller, R. J. (1978a). Temporal stability of the dark focus of accommodation. *American Journal of Optometry and Physiological Optics*. **55**, 447-450.

Miller, R. J. (1978b). Mood changes and the dark focus of accommodation. *Perception and Psychophysics*. **24**, 437-443.

Millodot, M. (1997). *Dictionary of optometry and visual science*, 4th edn, Butterworth-Heinemann, Oxford, UK.

Miwa, T. (1992). Instrument myopia and the resting state of accommodation. Optometry *and Vision Science*. **69**, 55-59.

Moak, J. P., Bailey, J. J. and Makhlouf, F. T. (2002). Simultaneous heart rate and blood pressure variability analysis: insight into mechanisms underlying neurally mediated cardiac syncope in children. *Journal of the American College of Cardiology*. **40**, 1466-1474.

Mordi, J. A. and Ciuffreda, K. J. (1998). Static aspects of accommodation: age and presbyopia. *Vision Research*. **38**, 1643-1653.

Mordi, J. A. and Ciuffreda, K. J. (2004). Dynamic aspects of accommodation: age and presbyopia. *Vision Research*. **44**, 591-601.

Mordi, J., Tucker, J. and Charman, W. N. (1986). Effects of 0.1% cyclopentolate or 10% phenylephrine on pupil diameter and accommodation. *Ophthalmic and Physiological Optics*. **6**, 221-227.

Morgan, M. W. (1944). The nervous control of accommodation. *American Journal of Optometry and Archives of American Academy of Optometry*. **21**, 87-93.

Murray, P. G., Hamilton, R. M. and Macfarlane, P. W. (2001). Reproducibility of a non-invasive real-time measure of cardiac parasympathetic activity. *Physiological Measurements*. **22**, 109-115.

Niwa and Tokoro (1998). Influence of spatial distribution with blur on fluctuations in accommodation. *Optometry and Vision Science*. **75**, 227-232.

Noble, D. (1979). *The initiation of the heartbeat*. Clarendon Press, Oxford, UK.

Ohtsuka, K., Maekawa, H., Takeda, M., Uede, N. and Chiba, S. (1988). Accommodation and convergence insufficiency with left middle cerebral-artery occlusion. *American Journal of Ophthalmology*. **106**, 60-64.

Ong, E. and Ciuffreda, K. J. (1997). *Accommodation, nearwork and myopia*. Optometric Extention Program Foundation, Santa Ana, USA.

Ong, E., Ciuffreda, K. J. and Tannen, B. (1993). Static accommodation in congenital nystagmus. *Investigative Ophthalmology and Visual Science*. **34**, 194-204.

Ostberg, O. (1980). Accommodation and visual fatigue in display work. *Displays*. **2**, 81-85

Owens, D. A. (1979). The Mandelbaum effect: evidence for an accommodative bias toward intermediate viewing distances. *Journal of the Optical Society of America*. **69**, 646-652.

Owens, D. A. (1984). The resting state of the eyes. *American Scientist*. **72**, 378-387.

Owens, H. (1991). The effect of beta-adrenergic receptor antagonists on the temporal accommodative response. PhD Thesis, Aston University, Birmingham. UK.

Owens, H., Bhat, K. and Jacobs, R. J. (1994). Maxwellian and real pupils – effects on accommodative microfluctuations. *Investigative Ophthalmology and Visual Science*. **35**, 1280.

Owens, H., Winn, B., Gilmartin, B. and Pugh, J. R. (1991). The effect of topical beta-adrenergic antagonists on the dynamics of steady-state accommodation. *Ophthalmic and Physiological Optics*. **11**, 99-104.

Owens, R. L. and Higgins, K. E. (1983). Long-term stability of the dark focus of accommodation. *American Journal of Optometry and Physiological Optics*. **60**, 32-38.

Pagani, M., Lombardi, F., Guzetti, S. *et al.* (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympato-vagal interaction in Man and conscious Dog. *Circulation Research*. **59**, 178-193.

Pagani, M., Rimolda, O. and Malliani, A. (1992). Low-frequency components of cardiovascular variabilities of sympathetic modulation. *Trends in Pharmacological Science*. **13**, 50-54.

Patnaik, B. (1967). A photographic study of accommodative mechanisms: Changes in the lens nucleus during accommodation. *Investigative Ophthalmology*. **6**, 601-611.

Pearson, M. A., Tyrrell, R. A., Thayer, J. F. and Jiang, B. C. (1996). Adaptation of oculomotor resting states depends on both task and refractive status. *Investigative Ophthalmology and Visual Science*. **37**, S166.

Pierscionek, B. K. and Chan, D. Y. (1989). Refractive index gradient of the human lens. *Optometry and Vision Science*. **66**, 822-829.

Popiolek-Masajada, A. and Kasprzak, H. (2002). Model of the optical system of the human eye during accommodation. *Ophthalmic and Physiological Optics*. **22**, 201-208.

Porges, S. W. (1976). Peripheral and neurochemical parallels of psychopathy: A psychophysiological model relating autonomic imbalance to hyperactivity, psychopathy, and autism. In: *Advances in child development and behaviour* (H. W. Reese, ed). New York: Academic Press. **11**, 36-65.

Portello, J. K., Rosenfield, M. and O'Dwyer, M. (1997). Clinical characteristics of pre-myopic individuals. *Optometry and Vision Science*. (suppl.) **74**, 176.

Post, R. B., Johnson, C. A. and Owens, D. A. (1985). Does performance of tasks affect the resting focus of accommodation? *American Journal of Optometry and Physiological Optics*. **62**, 533-537.

Pugh, J. R., Eadie, A. S., Winn, B. and Heron, G. (1987). Power spectrum analysis in the study of ocular mechanisms. *Ophthalmic and Physiological Optics*. **7**, 321-324.

Pugh, J. R. and Winn, B. (1988). Modification of the Canon Auto Ref R1 for use as a continuously recording optometer. *Ophthalmic and Physiological Optics*. **8**, 460-464.

Purkinje, J. E. (1823). De examine physiologico organi visus et sytematis cutanei. *Wratislaviae*.

Pyetan, E., Toledo, E., Zoran, O. and Akselrod, S. (2003). Parametric description of cardiac vagal control. *Autonomic Neuroscience: Basic and Clinical*. **109**, 42-52.

Ramsdale, C. (1979). Monocular and binocular accommodation. *Ophthalmic Optician*. **19**, 606-622.

Ramsdale, C. (1985). The effect of ametropia on the accommodative response. *Acta Ophthalmologica*. **63**, 167-174.

Ramsdale, C. and Charman, W. N. (1989). A longitudinal study of the changes in the static accommodative response. *Ophthalmic and Physiological Optics*. **9**, 255-263.

Reeves, B. C., Hill, A. R., Carter, S. C. and Sparrow, J. (1992). Evaluation of two infrared autorefractors in pseudophakia. *Ophthalmic and Physiological Optics*. **12**, 405-410.

Ritter, A. D. and Huhn-Beck, H. (1993). Dark focus of accommodation and nervous system activity. *Optometry and Vision Science*. **70**, 532-534.

Rosenfield, M. (1989). Evaluation of clinical techniques to measure tonic accommodation. *Optometry and Vision Science*. **66**, 809-814.

Rosenfield, M. (1998). Accommodation and myopia. In: *Myopia and Nearwork*. (M. Rosenfield and B. Gilmartin, eds). Butterworth-Heinemann, Oxford, UK. 91-116.

Rosenfield, M. and Abraham-Cohen, J. A. (1999). Blur sensitivity in myopes. *Optometry and Vision Science*. **76**, 303-306.

Rosenfield, M. and Chiu, N. N. (1995). Repeatability of subjective and objective refraction. *Optometry and Vision Science*. **72**, 577-579.

Rosenfield, M. and Ciuffreda, K. J. (1990). Proximal and cognitively-induced accommodation. *Ophthalmic and Physiological Optics*. **10**, 252-256.

Rosenfield, M. and Ciuffreda, K. J. (1991). Effect of surround propinquity on the open-loop accommodative response. *Investigative Ophthalmology and Visual Science*. **32**, 142-147

Rosenfield, M. and Ciuffreda, K. J. (1994). Cognitive demand and transient nearwork-induced myopia. *Optometry and Vision Science*. **71**, 381-385.

Rosenfield, M., Ciuffreda, K. J., Hung, G. K. and Gilmartin, B. (1993). Tonic accommodation: a review I. Basic aspects. *Ophthalmic and Physiological Optics*. **13**, 266-284.

Rosenfield, M., Ciuffreda, K. J., Hung, G. K. and Gilmartin, B. (1994). Tonic accommodation: a review II. Accommodative adaptation and clinical aspects. *Ophthalmic and Physiological Optics*. **14**, 265-284.

Rosenfield, M. and Gilmartin, B. (1987). Effect of a near-vision task on the response AC/A of a myopic population. *Ophthalmic and Physiological Optics*. **7**, 225-233.

Rosenfield, M. and Gilmartin, B. (1988a). Disparity-induced accommodation in late-onset myopia. *Ophthalmic and Physiological Optics*. **8**, 353-355.

Rosenfield, M. and Gilmartin, B. (1988b). Accommodative adaptation induced by sustained disparity-vergence. *American Journal of Optometry and Physiological Optics*. **65**, 118-126.

Rosenfield, M. and Gilmartin, B. (1989). Temporal aspects of accommodative adaptation. *Optometry and Vision Science*. **66**, 229-234.

Rosenfield, M. and Gilmartin, B. (1990). Effect of target proximity on the open-loop accommodative response. *Optometry and Vision Science*. **67**, 74-79.

Rosenfield, M. and Gilmartin, B. (eds) (1998). *Myopia and Nearwork*. Butterworth-Heinemann, Oxford, UK.

Rosenfield, M., Gilmartin, B., Cunningham, E. and Dattani, N. (1990). The influence of alpha-adrenergic agents on tonic accommodation. *Current Eye Research*. **9**, 267-272.

Rosner, J. and Rosner, J. (1989). relation between clinically measured tonic accommodation and refractive status in 6- to 14-year-old children. *Optometry and Vision Science*. **66**, 436-439.

Rosner, J. and Rosner, J. (1990). Comparison of two clinical methods for measuring tonic accommodation in children. *Optometry and Vision Science*. **67**, 692-694.

Rubin, A. and Harris, W. F. (1995). Refractive variation during autorefraction: multivariate distribution of refractive error. *Optometry and Vision Science*. **72**, 403-410.

Santodomingo-Rubido, J., Mallen, E. A. H., Gilmartin, B. and Wolffsohn, J. S. (2002). A new non-contact optical device for ocular biometry. *British Journal of Ophthalmology*. **86**, 458-462.

Saul, J. P., Albrecht, P., Berger, R. D. and Cohen, R. J. (1988). Analysis of long term heart rate variability: methods, 1/f scaling and implications. *Computers in Cardiology*. IEEE Computer Society press, Washington. 419-422.

Sayers, B. McA. (1973). Analysis of heart rate variability. *Ergonomics*. **16**, 17-32.

Schachar, R. A. (1992). Cause and treatment of presbyopia with a method for increasing the amplitude of accommodation. *Annals of Ophthalmology*. **24**, 442-452.

Schachar, R. A. and Anderson, D. A. (1995). The mechanism of ciliary muscle function. *Annals of Ophthalmology*. **27**, 126-132.

Schachar, R. A., Cudmaore, D. P. and Black, T. D. (1993a). Experimental support for Schachar's hypothesis of accommodation. *Annals of Ophthalmology*. **25**, 404-409.

Schachar, R. A., Cudmaore, D. P., Torti, R., Black, T. D. and Huang, T. (1994). A physical model demonstrating Schachar's hypothesis of accommodation. *Annals of Ophthalmology*. **26**, 4-9.

Schachar, R. A., Huang, T. and Huang, X. (1993b). Mathematic proof of Schachar's hypothesis of accommodation. *Annals of Ophthalmology*. **25**, 5-9.

Schaeffel, F., Wilhelm, H. and Zrenner, E. (1993). Inter-individual variability in the dynamics of natural accommodation in humans: relation to age and refractive errors. *Journal of Physiology*. **461**, 301-320.

Schor, C. M., Kotulak, J. C. and Tsuetaki, T. (1986). Adaptation of tonic accommodation reduces accommodative lag and is masked in darkness. *Investigative Ophthalmology and Visual Science*. **27**, 820-827.

Schor, C. M., McLin, L. N. (1988). The effect of luminance on accommodative and convergence aftereffects. *Clinical Vision Science*. **3**, 143-154.

Seidel, D., Gray, L. S. and Heron, G. (2003). Retinotopic accommodation responses in myopia. *Investigative Ophthalmology and Visual Science*. **44**, 1035-1041.

Simonelli, N. M. (1983). The dark focus of the human eye and its relationship to age and visual defect. *Human Factors*. **25**, 85-92.

Simmers, A. J., Gray, L. S. and Wilkins, A. J. (2001). The influence of tinted lenses upon ocular accommodation. *Vision Research*. **41**, 1229-1238.

Smith, G. (1983). The accommodative resting states, instrument accommodation and their measurement. *Optica Acta*. **30**, 347-359.

Smith, G., Atchison, D. A. and Pierscionek, B. K. (1992). Modelling the power of the aging human eye. *Journal of the Optical Society of America A-Optics and Image Science*. **9**, 2111-2117.

Snell, R. S. and Lemp, M. A. (1998). *Clinical anatomy of the eye*. 2nd edn, Blackwell Science, Oxford, UK.

Sperduto, R. D., Seigel, D., Roberts, J. and Rowland, M. (1983). Prevalence of myopia in the United States. *Archives of Ophthalmology*. **101**, 405-407.

Stark, L. R. and Atchison, D. A. (1994). Subject instructions and methods of target presentation in accommodation research. *Investigative Ophthalmology and Visual Science*. **35**, 528-537.

Stark, L. R. and Atchison, D. A. (1997). Pupil size, mean accommodative response and the fluctuations of accommodation. *Ophthalmic and Physiological Optics*. **17**, 316-323.

Strang, N. C., Gilmartin, B., Gray, L. S., Winfield, N. R. and Winn, B. (2000). Open-loop accommodation in emmetropia and myopia. *Current Eye Research*. **20**, 190-194.

Strang, N. C., Winn, B. and Gilmartin, B. (1994). Repeatability of post-task regression of accommodation in emmetropia and late-onset myopia. *Ophthalmic and Physiological Optics*. **14**, 88-91.

Sturm, J. C. F. (1845). *Academy of Science*. **20**, 554, 761, 1238. Paris

Tan, R. K. T. and O'Leary, D. J. (1988). Accommodation characteristics before and after near work. *Clinical and Experimental Optometry*. **71**, 165-169.

Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996). Heart rate variability – standards of measurement physiological interpretation and clinical use. *European Heart Journal*. **17**, 354-381.

Tehrani, M., Krummenauer, F., Kumar, R. and Dick, H. B. (2003). Comparison of biometric measurements using partial coherence interferometry and applanation ultrasound. *Journal of Cataract and Refractive Surgery*. **29**, 747-751.

Thibos, L. N., Wheeler, W. and Horner, D. (1997). Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optometry and Vision Science*. **74**, 367-375.

Ting, P. W. K., Lam, C. S. Y., Edwards, M. H. and Schmid, K. L. (2004). Prevalence of myopia in a group of Hong Kong microscopists. *Optometry and Vision Science*. **81**, 88-93.

Toates, F. M. (1972). Accommodation function of the human eye. *Physiology Review*. **52**, 828-863.

Törnqvist, G. (1966). Effect of cervical sympathetic stimulation on accommodation in monkeys. *Acta Physiology of Scandinavia*. **67**, 363-372.

Törnqvist, G. (1967). The relative importance of the parasympathetic and sympathetic nervous systems for accommodation in monkeys. *Investigative Ophthalmology*. **6**, 612-617.

Toshida, K., Okuyama, F. and Tokoro, T. (1998). Influences of the accommodative stimulus and aging on the accommodative microfluctuations. *Optometry and Vision Science*. **75**, 221-226.

Tscherning, M. (1909). *Herman von Helmholtz et la Théorie de l'Accommodation*. Bardinot et Pigne, Paris.

Tsuetaki, T. K. and Schor, C. M. (1987). Clinical method for measuring adaptation of tonic accommodation and vergence accommodation. *American Journal of Optometry and Physiological Optics*. **64**, 437-449.

Tsuji, H., Venditti, F. J., Manders, E. S., Evans, J. C., Larson, M. G., Feldman, C. L. and Levy, D. (1996). Determinants of heart rate variability. *Journal of the American College of Cardiology*. **28**, 1539-1546.

Tucker, J. and Charman, W. N. (1987). Effect of target content at higher spatial frequencies on the accuracy of the accommodative response. Ophthalmic and Physiological Optics. 7, 137-142.

Tyrrell, R. A., Pearson, M. A. and Thayer, J. F. (2000). Behavioural links between the oculomotor and cardiovascular systems. In: *Accommodation and Vergence Mechanisms in the Visual System*. (O. Franz n, H. Richter and L. Stark, eds). Berkhauser Verlag, Switzerland.

Tyrrell, R. A., Thayer, J. F., Friedman, B. H., Leibowitz H. W. and Francis, E. L. (1992). A link between autonomic innervations to the oculomotor and cardiovascular systems. *Investigative Ophthalmology and Visual Science*. (suppl.), **33**, S1149.

Tyrrell, R. A., Thayer, J. F., Friedman, B. H., Leibowitz H. W. and Francis, E. L. (1995). A behavioural link between the oculomotor and cardiovascular systems. *Integrative Physiological and Behavioural Science*. **30**, 46-67.

Tyrrell, R. A., Thayer, J. F. and Leibowitz H. W. (1994). Cardiovascular changes covary with oculomotor adaptation induced by near work. *Investigative Ophthalmology and Visual Science*. (suppl.) **35**, S1282.

Ursino, M. and Magosso, E. (2003). Role of short-term cardiovascular regulation in heart period variability: a modelling study. *American Journal of Physiology-Heart and Circulatory Physiology*. **284**, H1479-H1493.

van Alphen, G. W. H. M. (1990). Emmetropization in the primate eye. In: *Myopia and the Control of Eye Growth*. Ciba Foundation Symposium No. 155 (G. R. Buck and K. Widdows, eds). Wiley, pp. 115-125.

van der Heijde, G. L., Beers, A. P. and Dubbelman, M. (1996). Microfluctuations of steady-state accommodation measured with ultrasonography. *Ophthalmic and Physiological Optics*. **16**, 216-221.

Vera-Diaz, F. A., Strang, N. C. and Winn, B. (2002). Nearwork induced transient myopia during myopia progression. *Current Eye Research*. **24**, 289-295.

Vongpatanasin, W., Taylor, A. and Victor, R. G. (2004). Effects of cocaine on heart rate variability in healthy subjects. *American Journal of Cardiology*. **93**, 385-388.

Wallman, J., Turkel, J. and Trachtman, J. (1978). Extreme myopia produced by modest change in early visual experience. *Science*. **201**, 1249-1251.

Ward, P. A. and Charman, W. N. (1985). Effect of pupil size on steady-state accommodation. *Vision Research*. **25**, 1317-1326.

Ward, P. A. and Charman, W. N. (1987). On the use of small artificial pupils to open-loop the accommodation system. *Ophthalmic and Physiological Optics*. **7**, 191-193.

Weibull, W. (1951). A statistical distribution function of wide applicability. *Journal of Applied Mechanics*. 292-297.

Westheimer, G. (1957). Accommodation measurements in empty visual fields. *Journal of the Optical Society of America*. **47**, 714-718.

Whiteacre, M. M. and Stein, R. (1993). Sources of error with use of Goldmann-type tonometers. *Survey of Ophthalmology*. **38**, 1-30.

Whitefoot, H. and Charman, W. N. (1992). Dynamic retinoscopy and accommodation. *Ophthalmic and Physiological Optics*. **12**, 8-17.

Wiesel, T. N. and Raviola, E. (1977). Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature*. **266**, 66-68.

Winchell, R. J. and Hoyt, D. B. (1996). Spectral analysis of heart rate variability in the ICU: A measure of autonomic function. *Journal of Surgical Research*. **63**, 11-16.

Winn, B. (2000). Accommodation microfluctuations: a mechanism for steady-state control of accommodation. In: *Accommodation and Vergence Mechanisms in the Visual System.* (O. Franz n, H. Richter and L. Stark, eds). Berkhauser Verlag, Switzerland. 129-140.

Winn, B. and Gilmartin, B. (1992). Current perspective on microfluctuations of accommodation. *Ophthalmic and Physiological Optics.* **12**, 252-256.

Winn, B., Gilmartin, B., Mortimer, L. C. and Edwards, N. R. (1991). The effect of mental effort on open- and closed-loop accommodation. *Ophthalmic and Physiological Optics.* **11**, 335-339.

Winn, B., Gilmartin, B. and Strang, N. C. (1993). Temporal closed-loop measures of accommodation show that sustained accommodation augments sympathetic innervation of the ciliary muscle. Investigative Ophthalmology and Visual Science. (suppl.) **34**, 1310.

Winn, B., Pugh, J. R., Gilmartin, B. and Owens, H. (1990a). The frequency characteristics of accommodative microfluctuations for central and peripheral zones of the human crystalline lens. *Vision Research.* **30**, 1093-1099.

Winn, B., Pugh, J. R., Gilmartin, B. and Owens, H. (1990b). Arterial pulse modulates steady-state ocular accommodation. *Current Eye Research.* **9**, 971-975.

Woessner, W. M. and Jiang, B. C. (1993). Predicting dark vergence from dark focus. *Investigative Ophthalmology and Visual Science.* (suppl.) **34**, S1308.

Wolf, M. M., Varigos, G. A., Hunt, D. and Sloman, J. G. (1978). Sinus arrhythmia in acute myocardial infarction. *Medical Journal of Australia.* **2**, 52-53.

Wolfe, J. M. and O'Connell, K. M. (1987). Adaptation of the resting states of accommodation. Dark and light field measures. *Investigative Ophthalmology and Visual Science.* **28**, 992-996.

Wolffsohn, J. S. (1997). Ocular accommodative responses and task performance with head-up display virtual imagery. PhD thesis. Cardiff University, UK.

Wolffsohn, J. S., Edgar, G. K. and McBrien, N. A. (2001a). Using diplopia as a warning of an inappropriate visual (ocular) accommodative response (WIVAR). *Aviation, Space, and Environmental Medicine*. **72**, 652-658.

Wolffsohn, J. S., Edgar, G. K., Stone, H. E., Williams, M. and McBrien, N. A. (1999). Does over-accommodation occur when using aircraft head-up displays? *Aviation, Space, and Environmental Medicine*. **70**, 666-673.

Wolffsohn, J. S., Gilmartin, B., Li, R. W., Edwards, M. H., Chat, S. W., Lew, J. K. and Yu, B. S. (2003a). Nearwork-induced transient myopia in preadolescent Hong Kong Chinese. *Investigative Ophthalmology and Visual Science*. **44**, 2284-2289.

Wolffsohn, J. S., Gilmartin, B., Mallen, E. A. H. and Tsujimura, S. (2001b). Continuous recording of accommodation and pupil size using the Shin-Nippon SRW-5000 autorefractor. *Ophthalmic and Physiological Optics*. **21**, 108-113.

Wolffsohn, J. S., Gilmartin, B., Thomas, R. and Mallen, E. A. H. (2003b). Refractive error, cognitive demand and nearwork-induced transient myopia. *Current Eye Research*. **27**, 363-370.

Wolffsohn, J. S., Hunt, O. A. and Gilmartin, B. (2002). Continuous measurement of accommodation in human factor applications. *Ophthalmic and Physiological Optics*. **22**, 380-384.

Wolffsohn, J. S., McBrien, N. A., Edgar, G. K. and Stout, T. (1998). The influence of cognition and age on accommodation, detection rate and response times when using a car head-up display (HUD). *Ophthalmic and Physiological Optics*. **18**, 243-253.

Wood, I. C. J., Papas, E., Burghardt, D. and Hardwick, G. (1984). A clinical evaluation of the Nidek autorefractor. *Ophthalmic and Physiological Optics*. **4**, 169-178.

Young, F. A., Leary, G. A. and Baldwin, W. R. (1969). The transmission of refractive errors within Eskimo families. *American Journal of Optometry and Physiological Optics*. **46**, 676-685.

Young, T. (1801). On the mechanism of the eye. *Phil Trans of the Royal Society Series B*. **91**, 23-88.

Zhai, H., Goss, D. A. and Hammond, R. W. (1993). The effect of caffeine on the accommodative response/accommodative stimulus function and on the response AC/A ratio. *Current Eye Research*. **12**, 489-499.

APPENDIX 1

THE VALIDITY OF USING A DIFFERENCE OF GAUSSIAN (DoG) TARGET FOR OPEN-LOOP ACCOMMODATION MEASURES

A1.1 Purpose

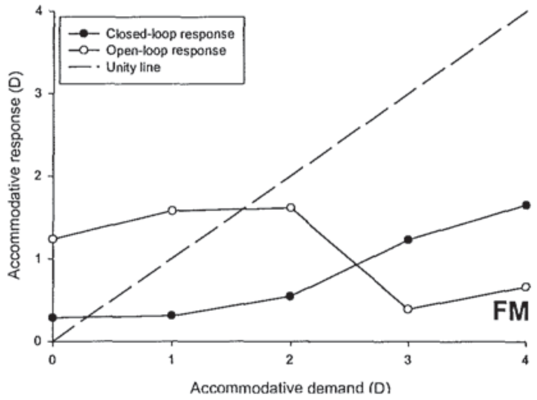
A study was conducted to test the hypothesis that the 0.1 cdeg^{-1} Difference of Gaussian (DoG) target, used to open the accommodation loop, did not provide a stimulus to accommodation.

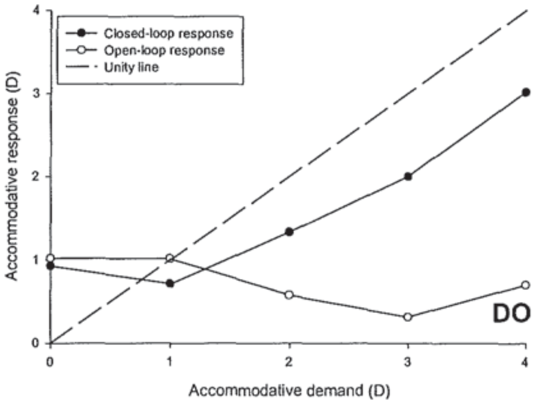
A1.2 Methods

Fifteen pre-presbyopic, emmetropic subjects aged 18 to 21 years (mean ± SD: 19.5 ± 0.8 years) monocularly viewed a 0.1 cdeg^{-1} DoG target placed within a Badal optical system. Using the Shin-Nippon SRW-5000 in static mode 5 individual measures of accommodative response (MSE) were recorded with the DoG target placed at increasing levels of accommodative demand (0.0 D to 4.0 D in 1.0. D steps). The results were compared graphically to those with the subjects viewing a high contrast (90%) Maltese cross as an accommodative target under the same conditions (see Figure A1.1). The data for all 15 subjects are illustrated. Data were treated statistically with a one-way within subject ANOVA.

A1.3 Results and Conclusion

Quite clearly, even with the DoG target placed at different accommodative demand levels, the DoG target did not act as a stimulus to blur-driven accommodation. (ANOVA: $F_{(4,56)} = 1.2$, $p = 0.33$). The results are in agreement with previous data (Kotulak and Schor, 1987; Tsuetaki and Schor, 1989; Rosenfield, 1989; Baker, 2000). As such, all open-loop accommodation measures were conducted with a 0.1 cdeg^{-1} DoG target.


Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
0
1
2
3
4
FM


Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
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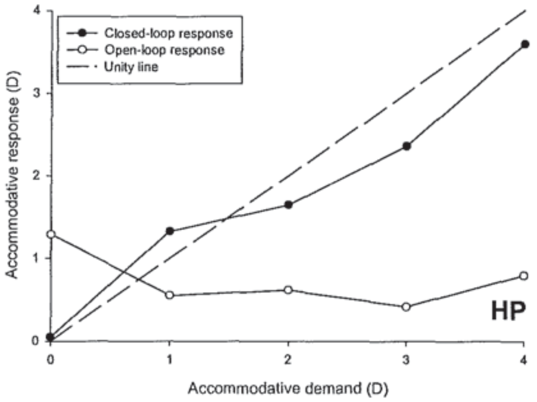
Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
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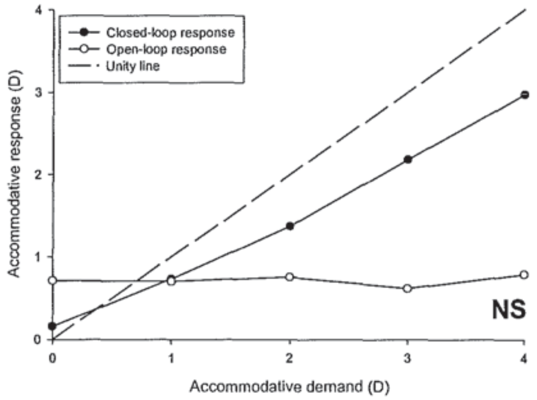
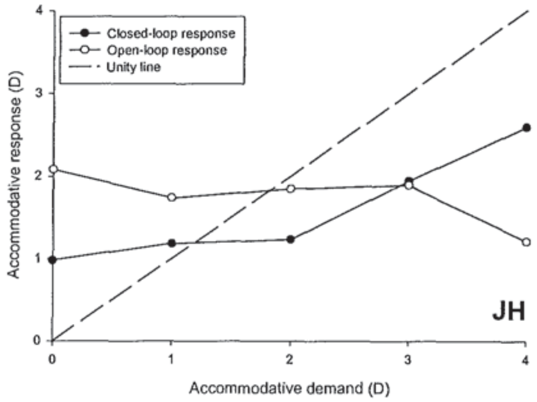
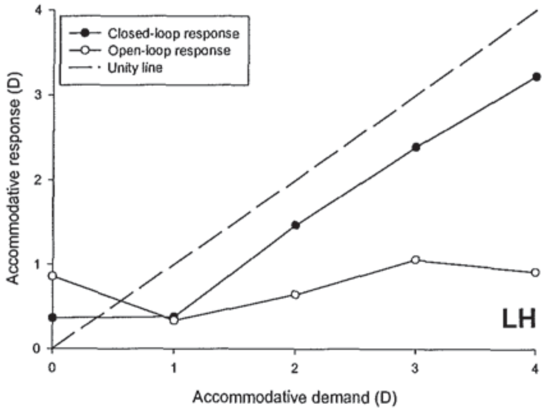
HP


Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
0
1
2
3
4
NS


Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
0
1
2
3
4
JH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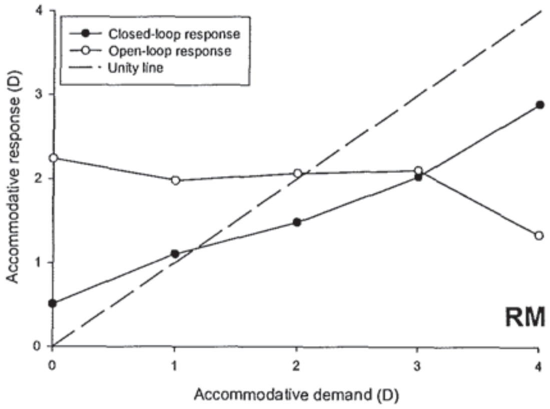
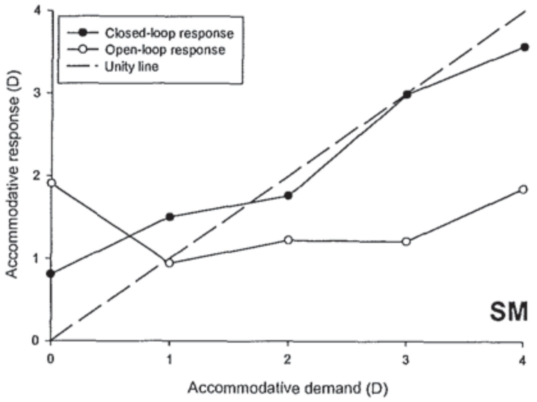
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
0
1
2
3
4
LH


Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
0
1
2
3
4
RM


Closed-loop response
Open-loop response
Unity line
Accommodative response (D)
Accommodative demand (D)
0
1
2
3
4
SM

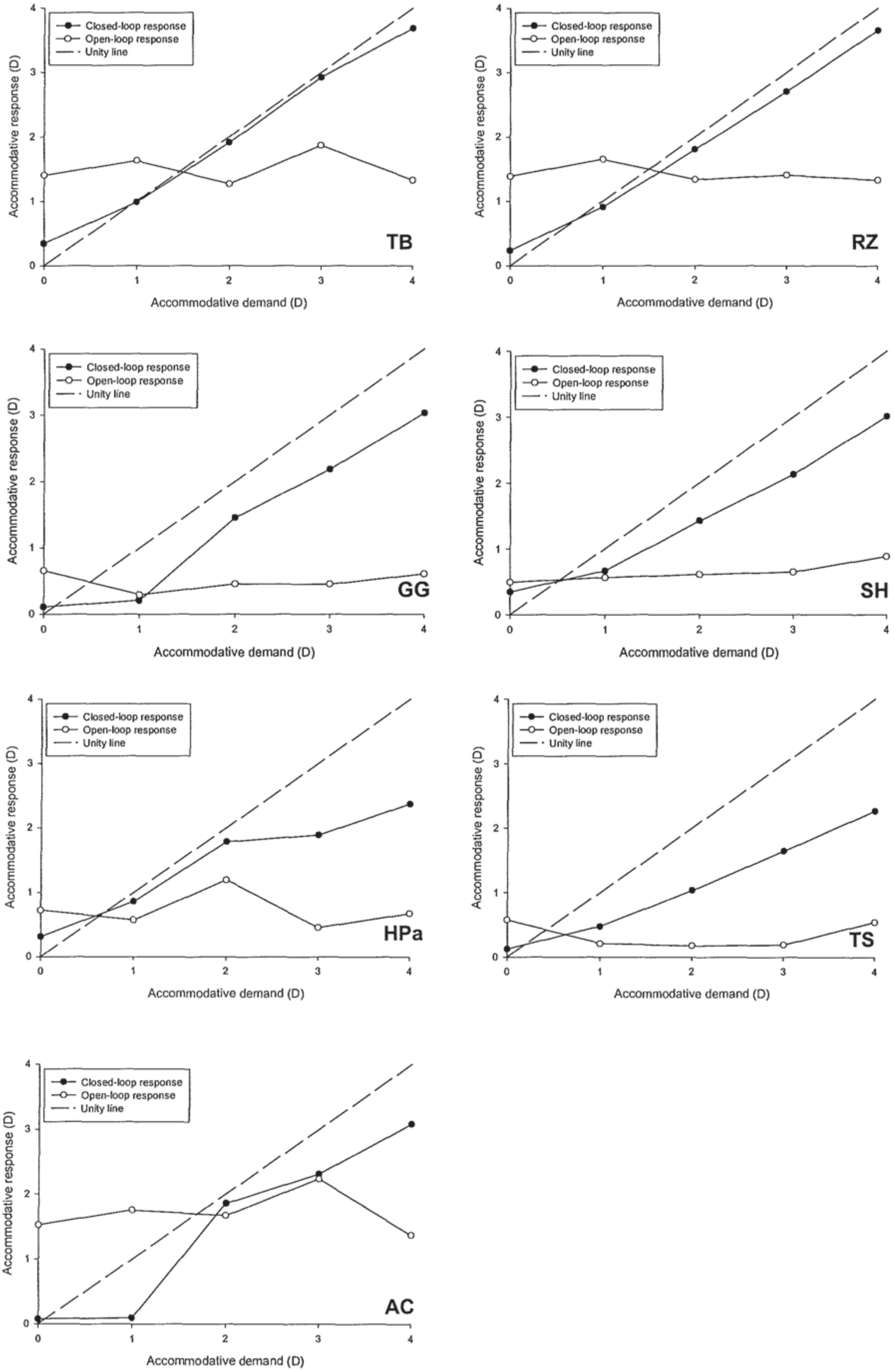


Figure A1.1 Open- and closed-loop accommodation responses to changes in accommodative demand.

APPENDIX 2

HUMAN SCIENCES ETHICAL COMMITTEE SUBMISSION

The following document details the application to the Human Sciences Ethical Committee, School of Life and Health Sciences, Aston University, for the approval of the use of oculomotor and cardiovascular measurement devices on human subjects.

ASTON UNIVERSITY **PROJECT NO..............**

THE SENATE **REG/00/174**

HUMAN SCIENCE ETHICAL COMMITTEE

Application for approval of a research project involving human volunteers

Please read the enclosed guidelines before completing this form - in typescript or black ink - and return the form to: The Secretary of the Human Science Ethical Committee, Registry. If you intend to administer any substance or expose the volunteers to a physical procedure other than simple venepuncture **you must also submit an experimental protocol.**

Project title:

Ocular Motor and Autonomic Function in Human Factor Applications

---

Investigator(s):	**Department/Address:**	**Telephone:**
Dr James Wolffsohn	Optometry, NRI	0121 359 3611 ext 5160
Professor Bernard Gilmartin	Optometry, NRI	0121 359 3611 ext 5159
Mr Leon Davies	Optometry, NRI	0121 359 3611 ext 5100
....	....	....
....	....	....

A
Details of sponsoring/collaborating organisation (if any)

1	Name:	British Aerospace, Filton, Bristol and EPSRC
2	Does the sponsoring/collaborating organisation provide insurance?	NO
3	If drugs are used, do any require a clinical trials certificate or clinical trials exemption certificate?	N/A

*If yes, please provide a copy of the certificate

B
Summary of Project

1	Starting date	1st November 2002
2	Duration:	3 years
3	Location:	Aston University, Birmingham (majority) and BAe, Bristol

4 Physical procedures:

Measurement of different ocular parameters using commercially available devices:

I. Oculomotor function using standard auto-refractors (*Shin Nippon*)*PowerRefractor*)

II. Ocular biometry using a non contact partial coherence interferometer (*IOL Master,* Zeiss)
III. Autonomic function using a finger pulse transducer

Subjective Refraction and bionocular vision assessment

Viewing or responding to images on static or moving visual displays

Contact lens fitting of daily disposable lenses (worn for up to 2 hours)

5 Substances to be administered (a substance is anything other than normal food - chemical constituents of food stuffs, ethanol and variation of the diet should be included here) and method of delivery should be specified:

None

6 Psychological assessment:

None

7 Questionnaires: (only to be completed when project contains questionnaire(s) which fall within the types of questionnaire requiring HSEC approval [Guidelines D (3)])

None requiring HSEC approval

C

Subjects

1 Number of volunteers to be used: approximately 500

2 Over what time span? 3 years

3 Age of volunteers: 18-45 years

4 Sex of volunteers: Male and Female

5 Source: Aston University and BAe staff and undergraduate students,

6 Will payments be made to the volunteers and if so, how much will each be paid?

No

7 Are the volunteers' patients or healthy volunteers? (If patients give diagnosis, clinic/responsible practitioner).

The patients are all healthy volunteers.

8 Will any volunteers be excluded and if so, on what grounds?

Volunteers with high astigmatism (>1.50D) will be excluded from the study as this makes it difficult to render then functionally emmetropic with soft contact lenses

9 Is the activity of the volunteer to be restricted in any way either before or after the procedure? (eg diet, driving)

No

10 Consent: Please attach a copy of the consent form you intend to use, detailing how procedures and hazards will be explained.
Attached

D
Risk Assessment: *a thorough Risk Assessment of the project must be undertaken (including for example welfare issues arising from the procedure, and the possible risk of residual effects in volunteers and the consequences thereof).*

1 Please give full details of any hazards, which could affect the health, safety or welfare of any volunteer, or any other person who might be harmed as a result of the experiment.

Contact lens may be inserted into the volunteers' eyes to make them functionally emmetropic. When using contact lenses there is very slight risk of infection, but no know risk exists with short-term use (<1 day). The lenses used will be commercially available daily disposable contact lenses worn for a maximum of 2 hours.

The instruments used are all non-invasive commercially available instruments.
The finger pulse transducer is commonly used in hospital clinics.
There are no known risks associated with its use.

2 What levels of risk are associated with these hazards?

Virtually none - see above

3 How do you propose to control the risks associated with these hazards?

Use single use disposable soft contact lenses to eliminate the risk of cross-infection.

4 What criteria have you used to determine whether the risks are acceptable?

Common usage in optometric and medical practice with no reports of adverse effects

5 Is there any precedent for these experiments? If so, please give details with references if possible.

Screening of refractive error and axial length. Ref 01/D

Akselrod, S., Gordon, D., Ubel, F. A., *et al.* Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981; 213:220-222.

Choi, M; Weiss, S; Schaeffel, F; Seidemann, A; Howland, H.C; Wilhelm, B. and Wilhelm, H. Laboratory, Clinical, and Kindergarten Test of a new Eccentric Infrared Photorefractor. Optometry and Vision Science 2000; 77:537-548.

Collins, M., Davis, B. and Wood, J. Microfluctuations of steady-state accommodation and the cardiopulmonary system. Vision Research. 1995; 35:2491-2502.

Mallen, E.A.H; Wolffsohn, J.S; Gilmartin, B. and Tsujimura, S. Clinical Evaluation of the Shin-Nippon SRW-5000 autorefraction in Adults. Ophthalmic and Physiological Optics 2001; 21:101-107.

Schaeffel, F; Weiss, S. and Seidel, J. How good is the match between the plane of the text and the focus during reading? Ophthalmic and Physiological Optics 1999; 19:180-92

Schaeffel, F; Wilhelm, H. and Zrenner, E. Inter-individual Variability in the Dynamic of Natural Accommodation in Humans: Relation to Age and Refractive errors. Journal of Physiology 1993; 461:301-320.

6 Has this project been considered/is it being considered by any other Ethical Committee? If so, please give details and decision made.

No

E

STATEMENT BY NAMED INVESTIGATORS, HEAD OF SCHOOL AND (if necessary) RESEARCH SUPERVISOR

I consider that the details given constitute a true summary of the project and that the hazards and potential risks to any volunteer are accurately described. The Principal Investigator is the main point of contact for the Human Sciences Ethical Committee, and accordingly should be a member of academic staff of the University (this implies that supervisors of research students will be the main point of contact)

Principal Investigator or...
date..
Supervisor of Student

Investigator..
date..

Investigator..
date..

Investigator..
date..

Head of School...
date..
(or nominee)

The following should be attached:

- * volunteer consent form
- * insurance certificate (if available)
- * clinical trials certificate or clinical trials exemption certificate (if appropriate)
- * experimental protocol

APPENDIX 3

INFORMATION AND CONSENT FORMS FOR EXPERIMENTAL PARTICIPANTS

The following documents are copies of the information and consent forms given to subjects participation in the studies detailed in this thesis.

ASTON UNIVERSITY

REG/00/175

HUMAN SCIENCE ETHICAL COMMITTEE

CONSENT FORM FOR VOLUNTEERS

PROJECT TITLE

Ocular Motor and Autonomic Function in Human Factor Applications

RESEARCH WORKERS, SCHOOL AND SUBJECT AREA RESPONSIBLE

Dr James Wolffsohn, Life and Health Science, Vision Sciences
Professor Bernard Gilmartin, Life and Health Science, Vision Sciences
Miss Olivia Hunt, Life and Health Science, Vision Sciences
Mr Leon Davies, Life and Health Science, Vision Sciences

EXPLANATION OF ANY POSSIBLE HAZARDS AND THE PROCEDURES TO BE USED

1. As part of our ongoing research programme we would be grateful if you would participate in our study into the changes in eye and autonomic system that occur with human factor applications, such as a cognitive task or flying a plane. The tests allow us to measure these effects

2. The procedure uses standard consulting room equipment used widely by optometrists and medical professionals in every day practice, taking only a few minutes. This is not a full eye examination. There are no known hazards involved.

3. If you have a refractive error, you will be fitted with daily-disposable soft contact lenses for up to 2 hours. There are no known adverse effects of such short-term wear.

4. Participation in this study is not a requirement of your university course and you are free to withdraw at any time.

CONFIDENTIALITY OF INFORMATION

The confidentiality of personal information and the anonymity of all volunteers involved in this investigation will be preserved by storage of the data in a locked filing cabinet, and will be accessible only to the investigators

VOLUNTEER'S STATEMENT

I have read and understand the above explanation. I have had the opportunity to discuss it with the investigators and to ask any questions. I agree to take part in the above project and I have been informed that I am free to withdraw at any time.

Signed: ....

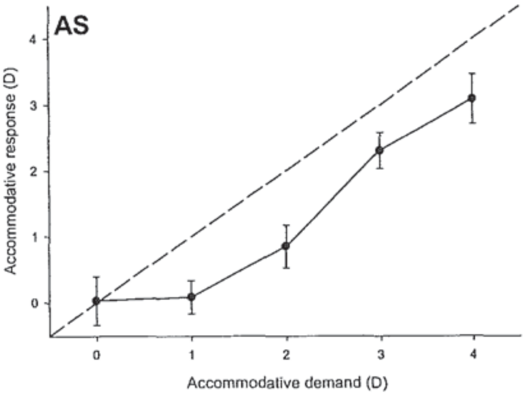
Dated: ....

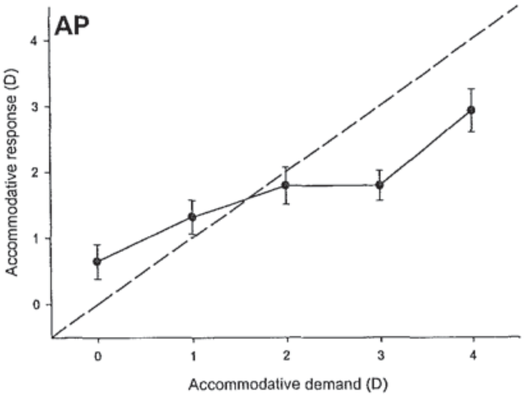
APPENDIX 4

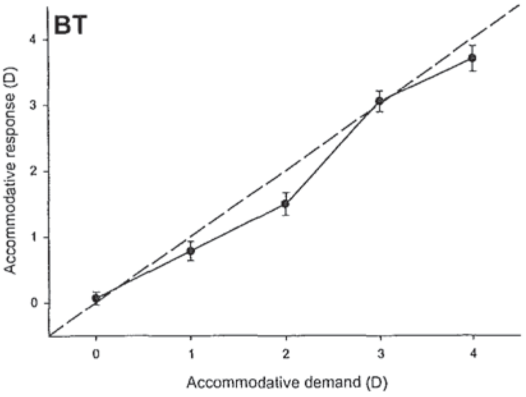
STIMULUS-RESPONSE CURVES

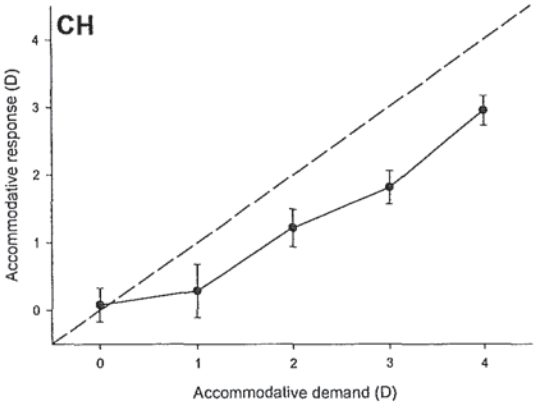
Stimulus-response curves of all 60 subjects in Chapter 3. Plots are divided into refractive groups: Hypermetropes; Emmetropes; Early-onset myopes and Late-onset myopes. Error bars represent ± 1 SD.

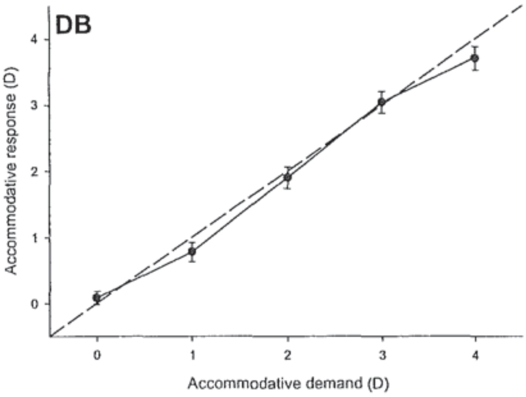
A4.1 HYPERMETROPES

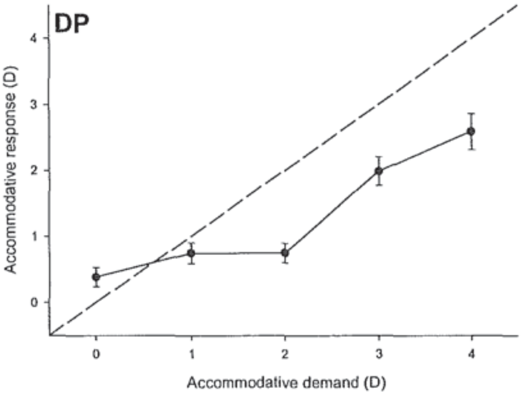


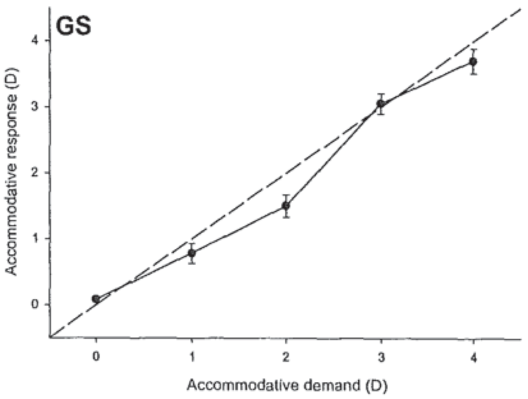








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3
4
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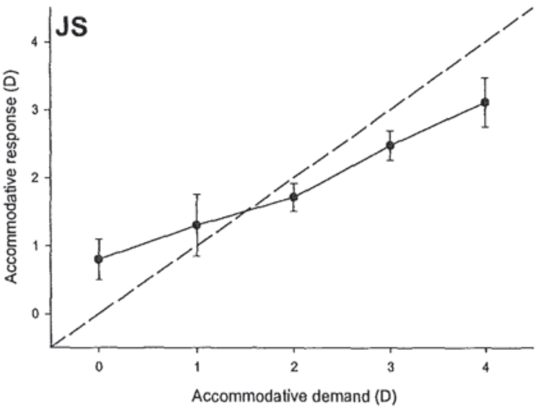
2
3
4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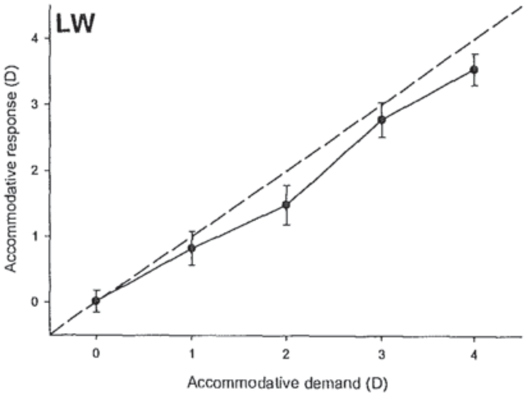
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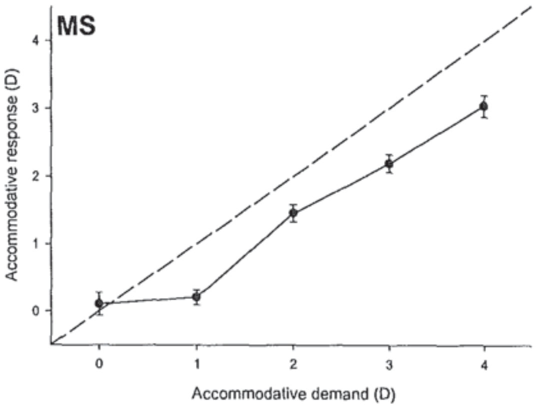
4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3
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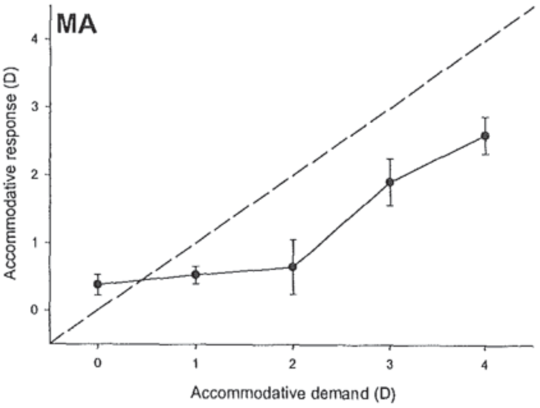
4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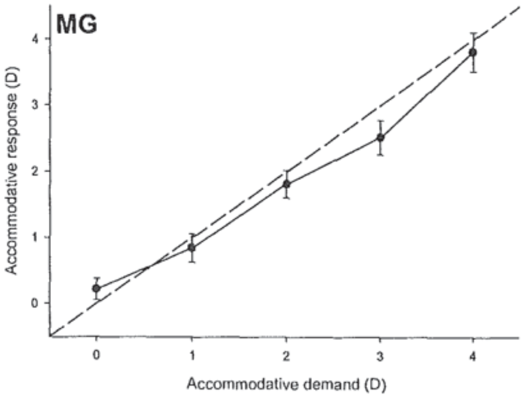
4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2
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4

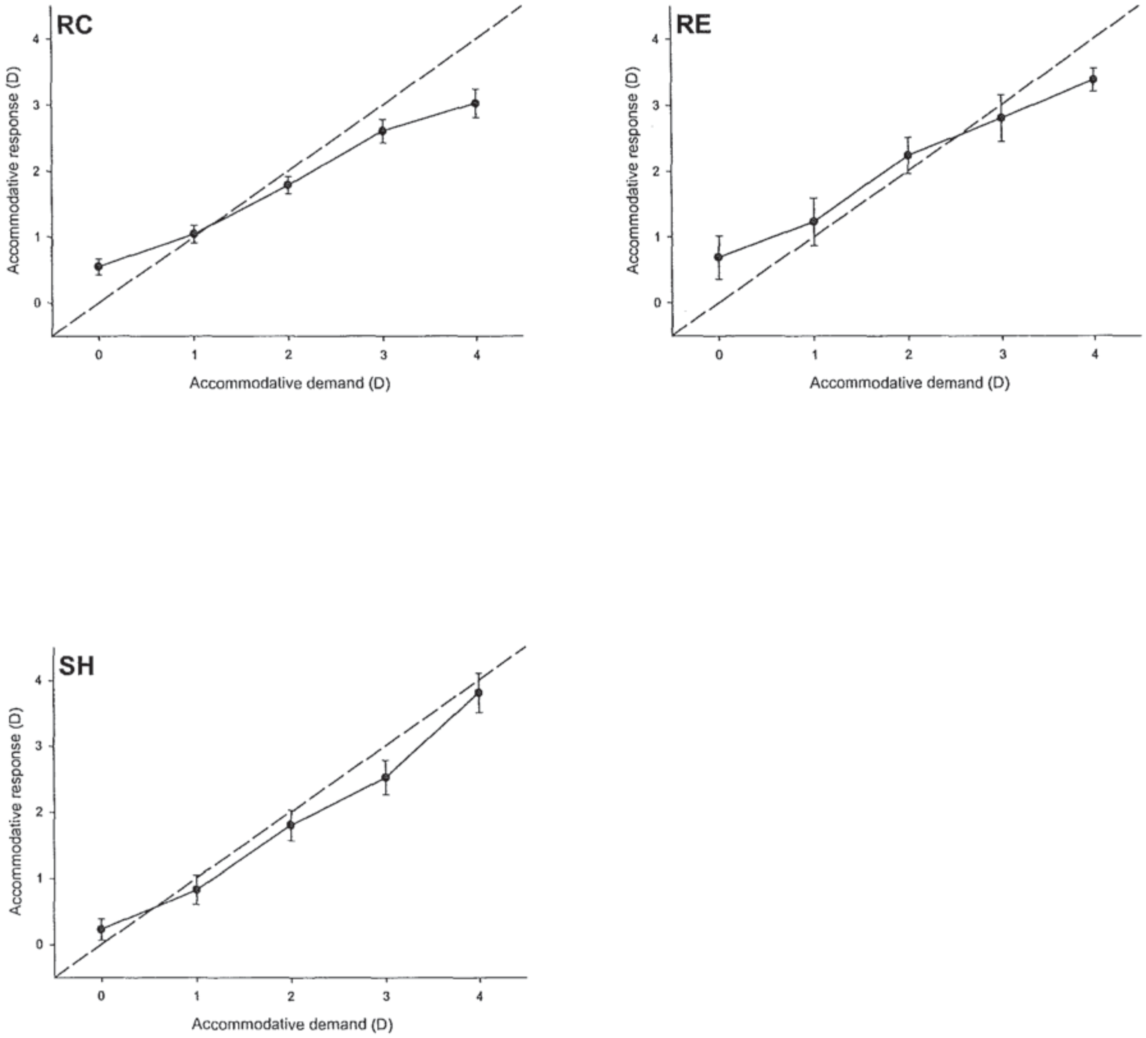
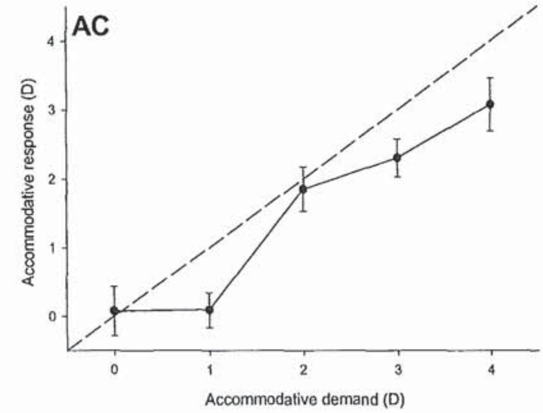
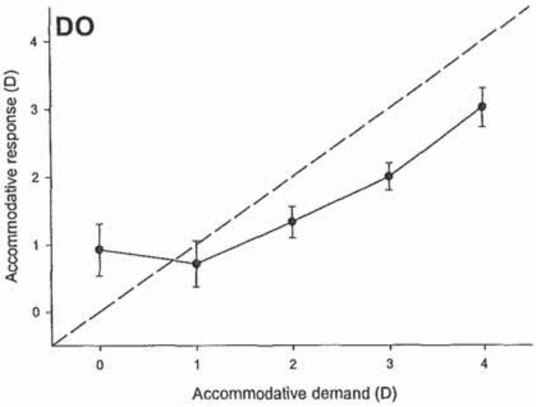
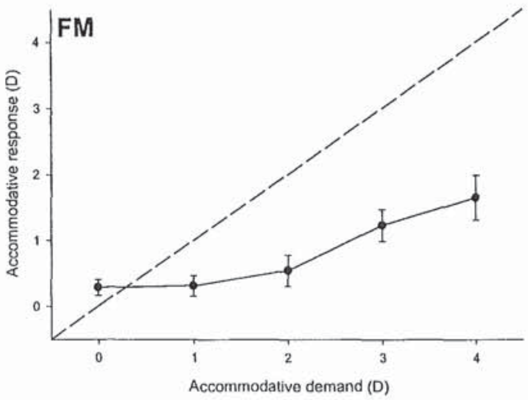


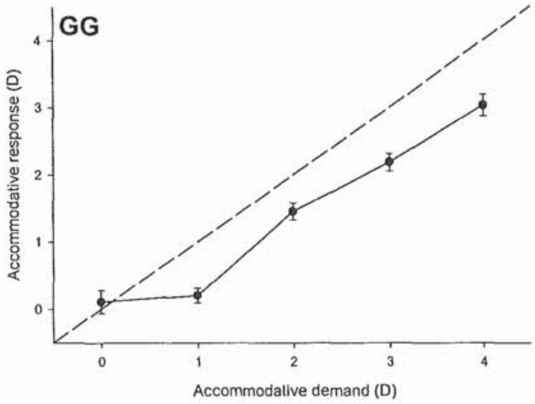
Figure A4.1 Hypermetropes stimulus-response curves.

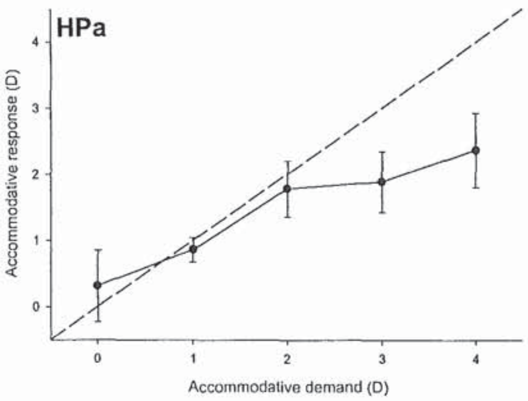
A4.2 EMMETROPES

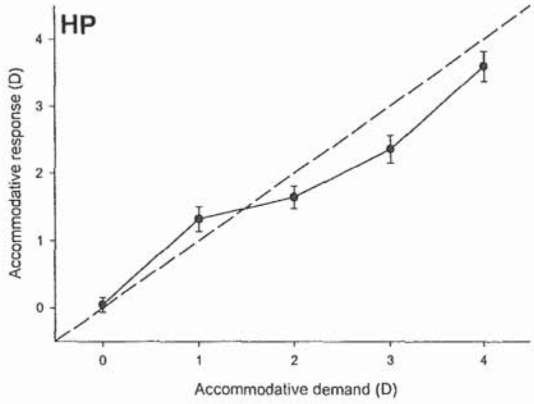


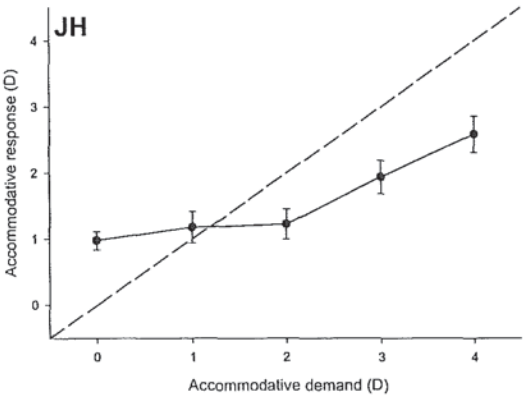








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1
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3
4
Accommodative demand (D)
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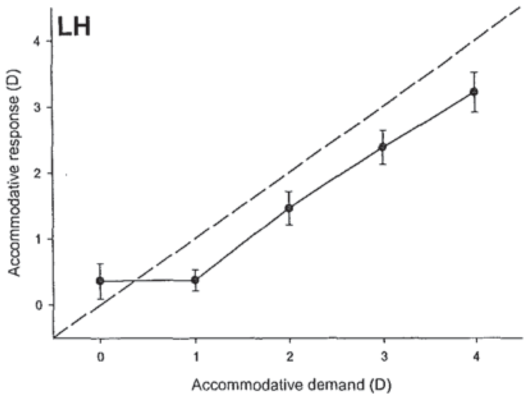
1
2
3
4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Accommodative demand (D)
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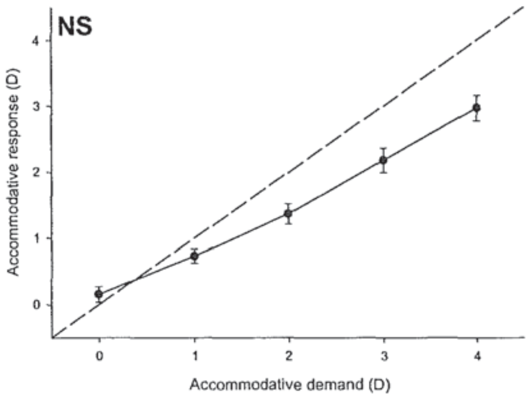
2
3
4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Accommodative demand (D)
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2
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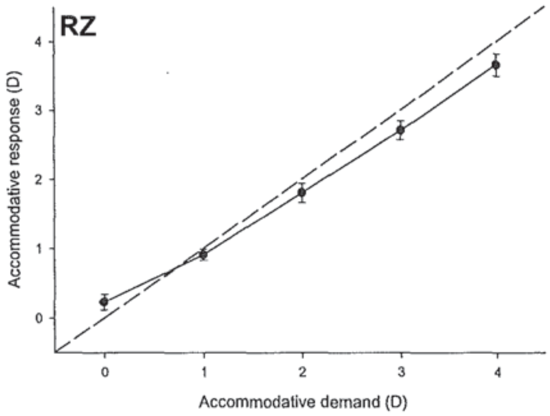
4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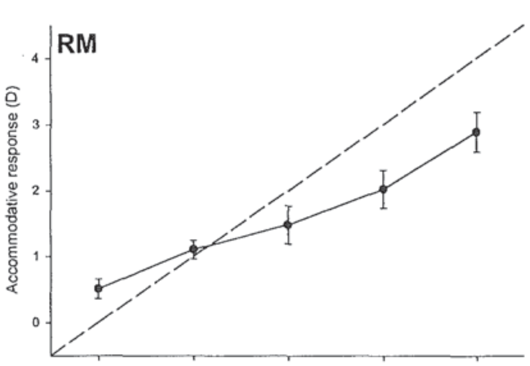
4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Accommodative demand (D)
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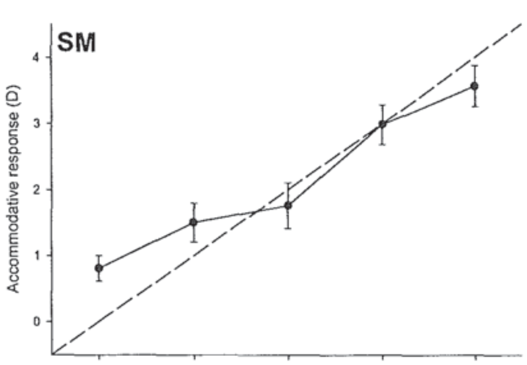
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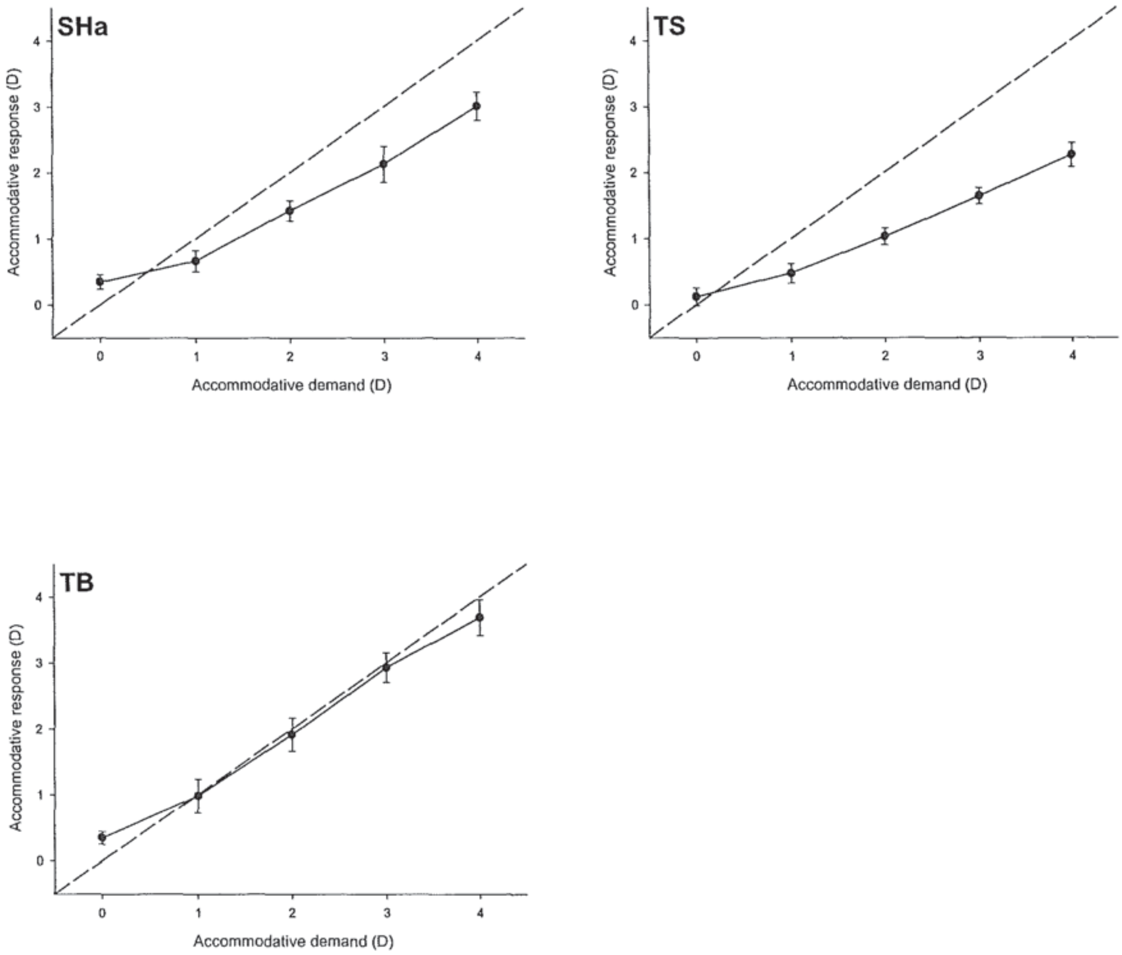
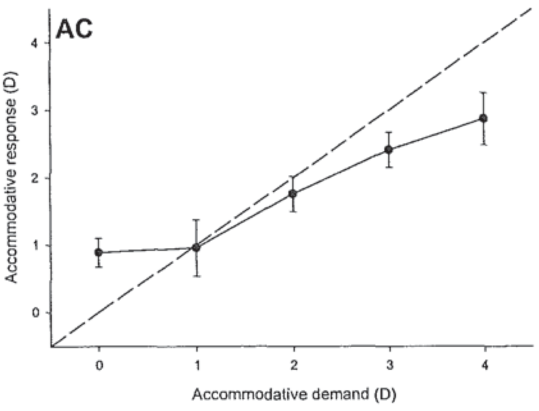
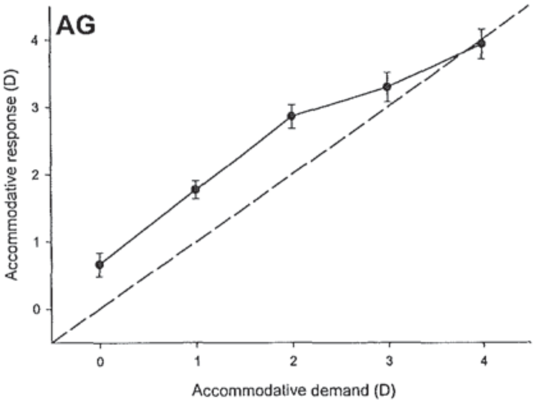
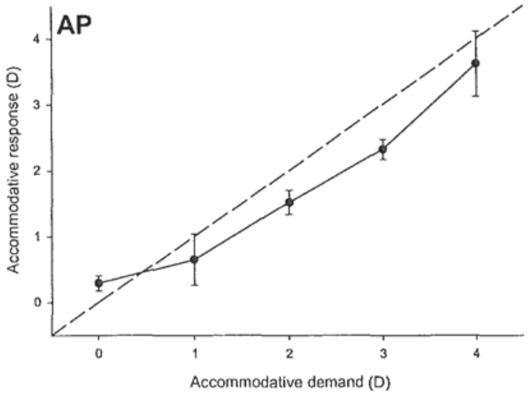


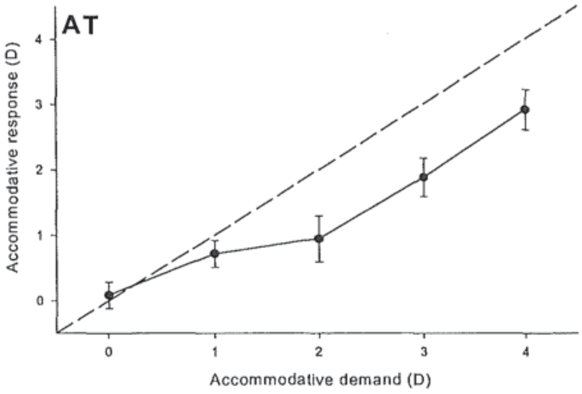
Figure A4.2 Emmetropes stimulus-response curves.

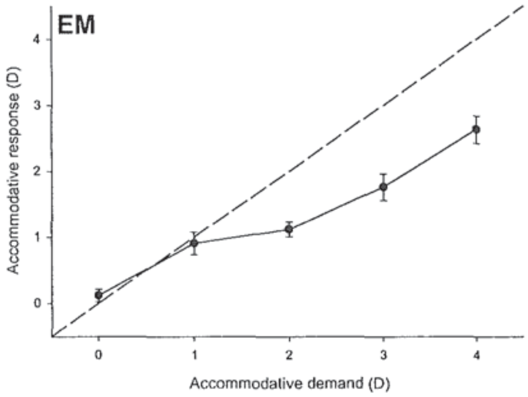
A4.3 EARLY-ONSET MYOPES

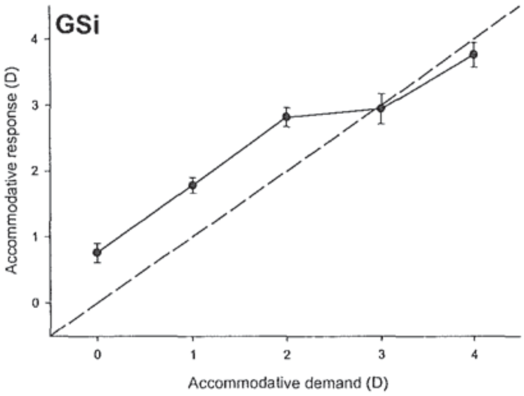


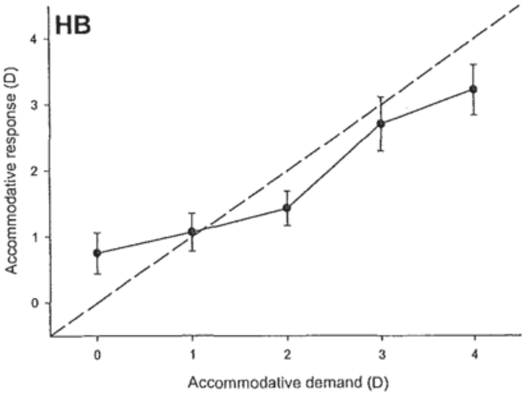








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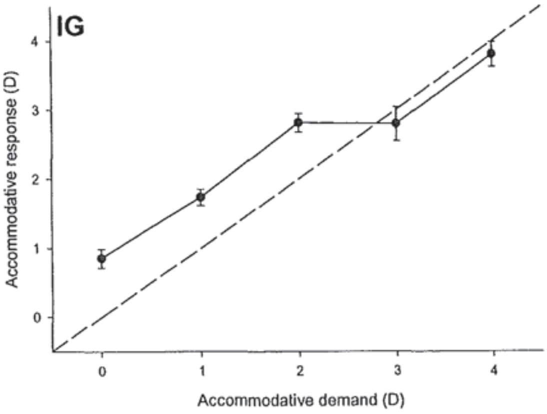
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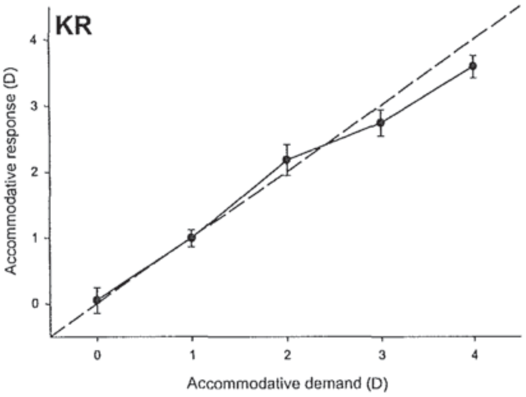
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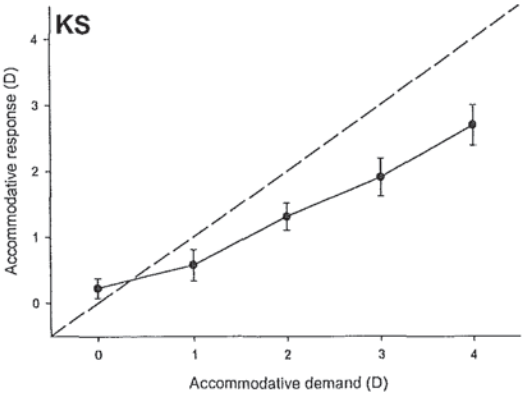
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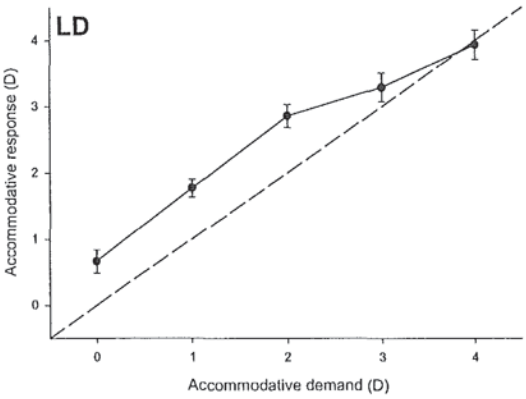
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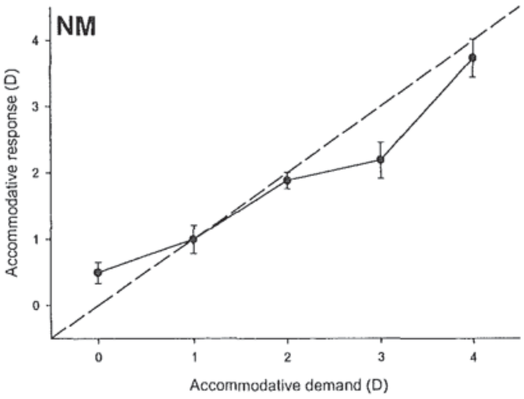

NM
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4

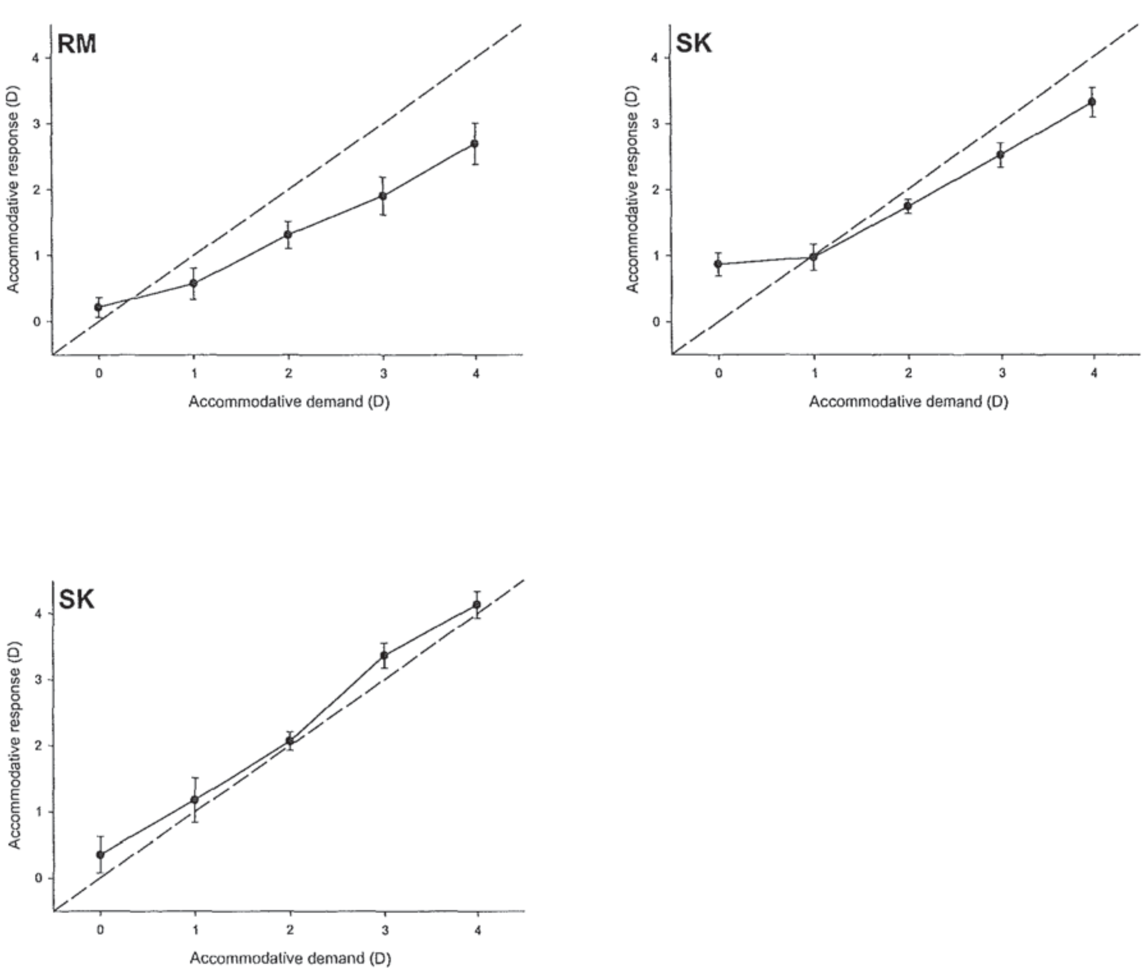
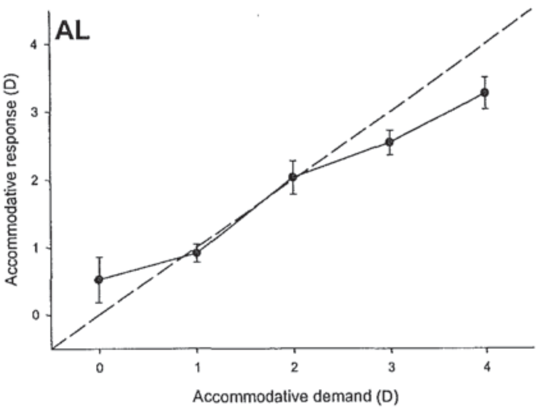
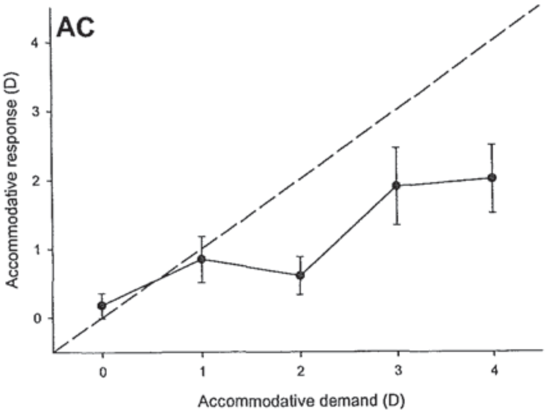
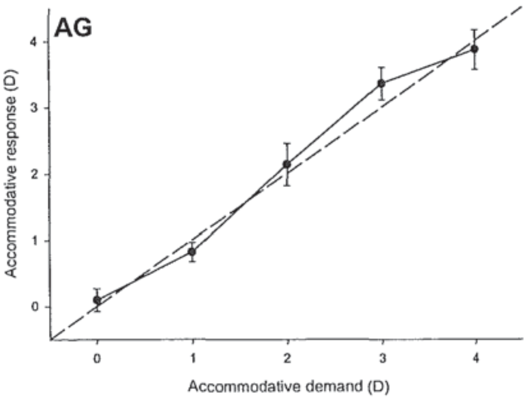


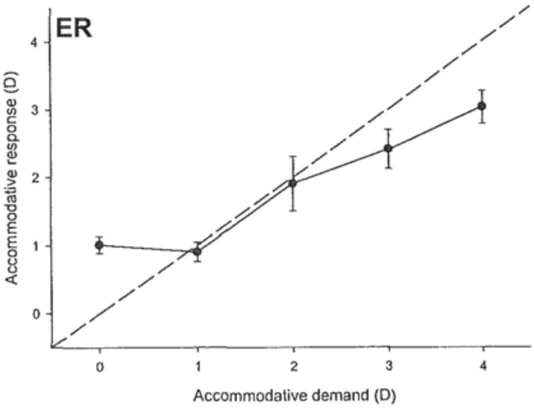
Figure A4.3 Early-onset myopes stimulus-response curves.

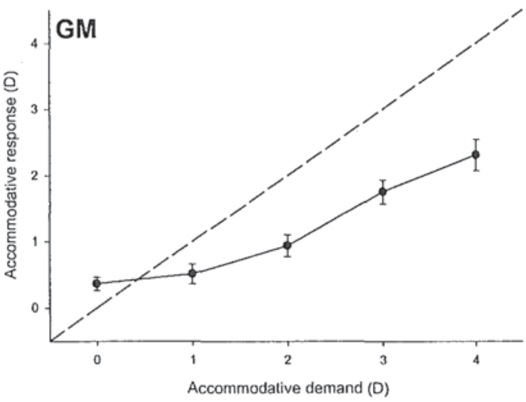
A4.4 LATE-ONSET MYOPES

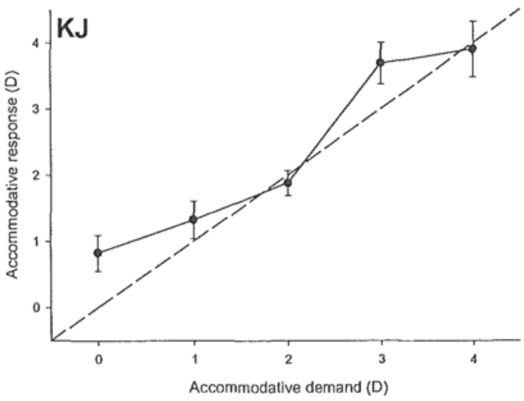


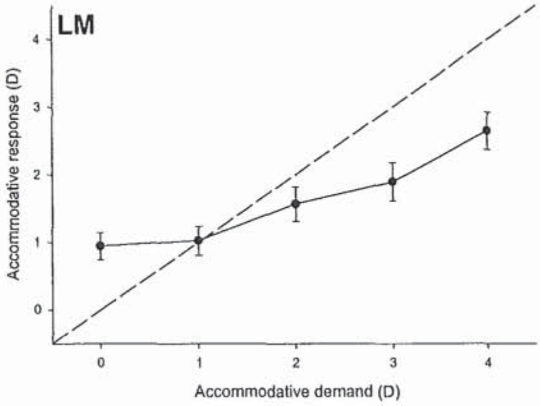


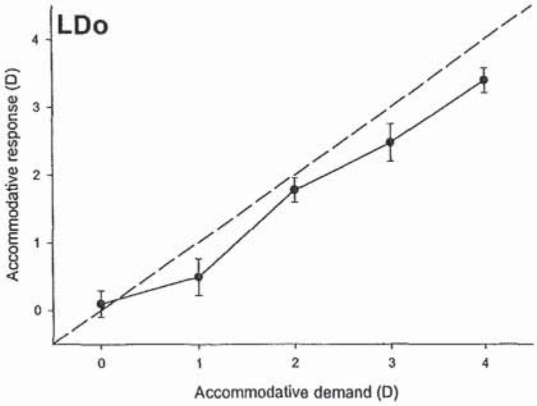


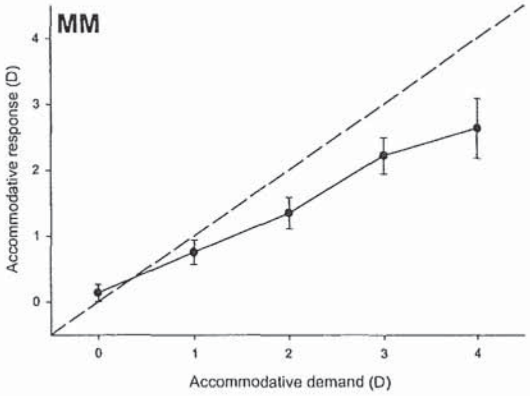


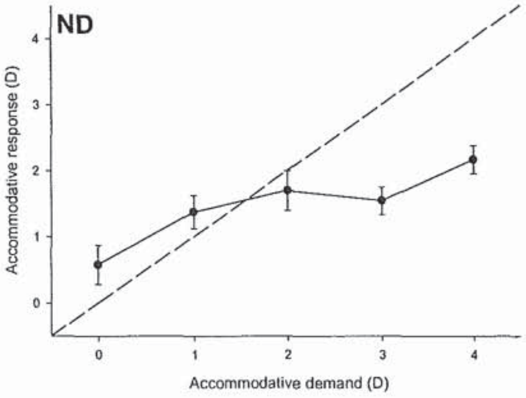


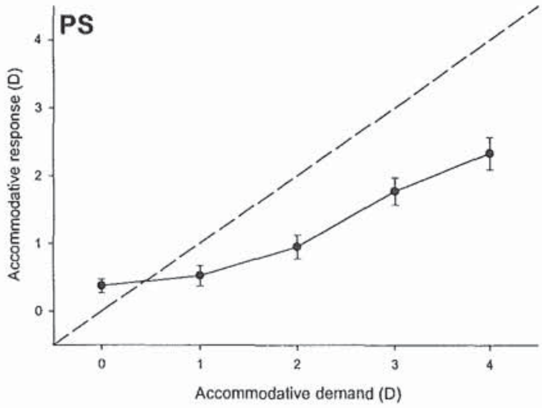


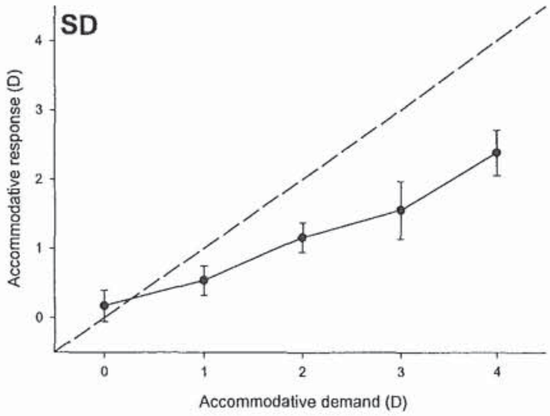

LM
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4


LDo
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4


MM
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4


ND
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4


PS
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4


SD
Accommodative response (D)
0
1
2
3
4
Accommodative demand (D)
0
1
2
3
4

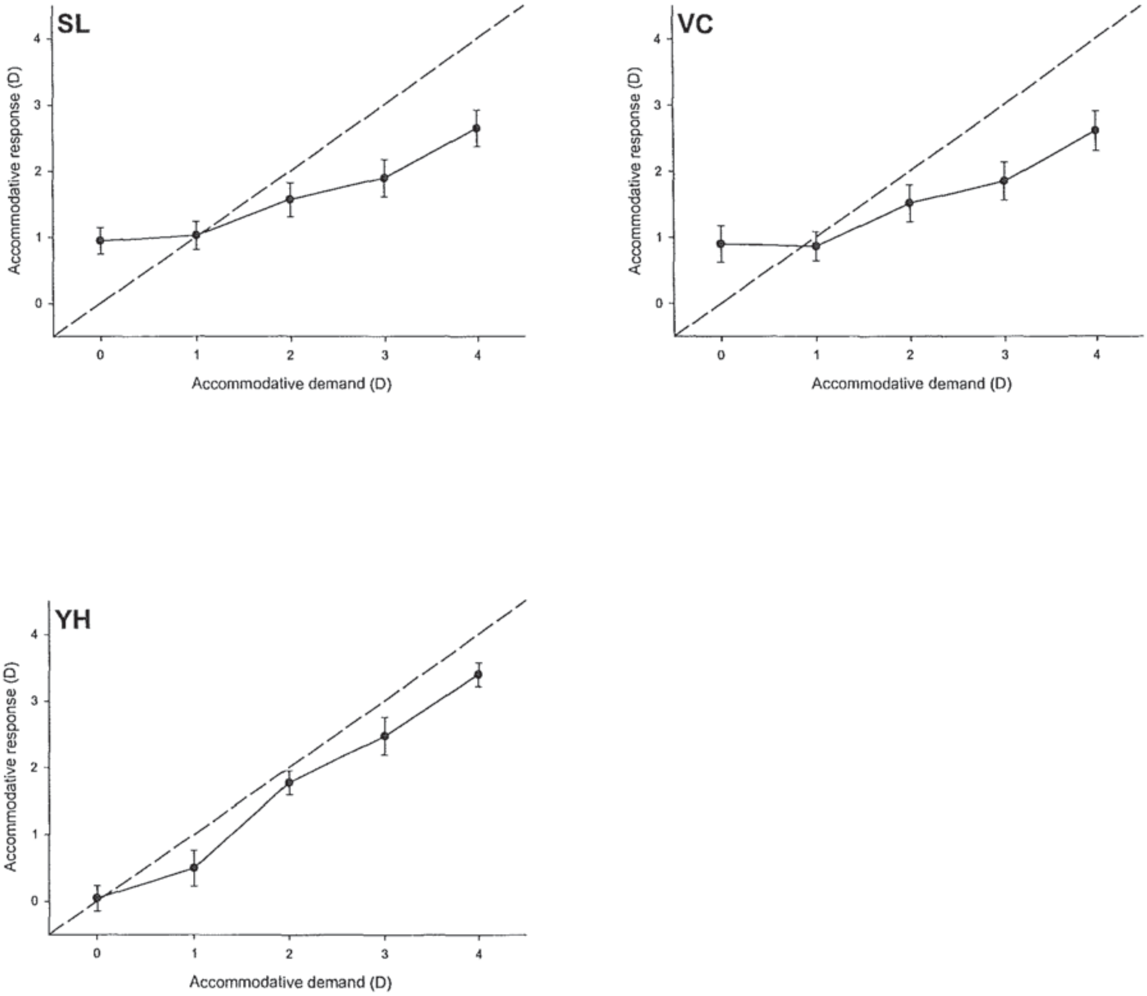


Figure A4.4 Late-onset myopes stimulus-response curves.

APPENDIX 5

STIMULUS-RESPONSE FUNCTION SLOPES AND ACCOMMODATIVE ERROR INDEX DATA

A5.1 Accommodative stimulus-response function slope and accommodative error index values relating to Chapter 3

Subject	Refractive Group	Slope (*m*)	AEI (*I*)
CH	HYP	0.865	1.036
DP	HYP	0.920	1.229
GS	HYP	1.090	0.284
BT	HYP	1.090	0.295
MG	HYP	1.000	0.299
AS	HYP	1.120	0.938
DB	HYP	1.100	0.274
MA	HYP	0.970	1.330
RE	HYP	0.570	0.200
SH	HYP	1.010	0.289
AP	HYP	0.570	1.107
RC	HYP	0.620	0.546
LW	HYP	1.030	0.402
JS	HYP	0.700	0.570
MS	HYP	0.790	0.770
TB	EMM	0.888	0.159
RZ	EMM	0.926	0.280
GG	EMM	0.789	0.776
SHa	EMM	0.793	0.819
FM	EMM	0.554	1.897
DO	EMM	0.842	0.892
HP	EMM	0.975	0.479
NS	EMM	0.801	0.829
JH	EMM	0.682	1.079
LH	EMM	0.878	0.642
RM	EMM	0.705	0.887
SM	EMM	0.904	0.236
HPa	EMM	0.294	1.123
TS	EMM	0.625	1.326
ACe	EMM	0.613	0.598

LD	EOM	0.939	0.274
EM	EOM	0.756	1.174
HB	EOM	0.898	0.574
GSi	EOM	0.975	0.158
SK	EOM	0.790	0.469
AG	EOM	0.539	0.171
SK	EOM	1.034	0.198
KS	EOM	0.691	0.946
AT	EOM	0.982	1.084
AP	EOM	1.050	0.523
ACh	EOM	0.555	0.657
KR	EOM	0.706	0.166
NM	EOM	0.923	0.456
RM	EOM	0.694	1.036
IG	EOM	0.497	0.193
SL	LOM	0.541	1.009
LM	LOM	0.541	1.009
PS	LOM	0.692	1.328
AC	LOM	0.701	1.846
LDo	LOM	0.809	0.459
AL	LOM	0.619	0.386
AG	LOM	0.866	0.127
MM	LOM	0.639	0.974
KJ	LOM	1.010	0.187
YH	LOM	0.811	0.459
VC	LOM	0.549	1.064
SD	LOM	0.614	1.354
GM	LOM	0.685	1.344
ER	LOM	0.561	0.552
ND	LOM	0.233	2.302

Table A5.1 Accommodative stimulus-response function slope and accommodative error index values.

APPENDIX 6

ACCOMMODATION MEAN ROOT-MEAN-SQUARE (RMS) DATA

A6.1 Accommodative response RMS data relating to Chapter 4

Subject	Refractive Group	Accommodative Demand (D)				
		0	1	2	3	4
CH	HYP	0.252	0.394	0.275	0.244	0.222
DP	HYP	0.146	0.159	0.146	0.218	0.273
GS	HYP	0.010	0.153	0.170	0.156	0.188
BT	HYP	0.098	0.144	0.172	0.160	0.194
MG	HYP	0.161	0.212	0.206	0.260	0.295
DB	HYP	0.099	0.145	0.162	0.163	0.179
MA	HYP	0.152	0.129	0.404	0.343	0.273
RE	HYP	0.328	0.362	0.276	0.353	0.174
SH	HYP	0.160	0.222	0.230	0.258	0.297
AP	HYP	0.262	0.258	0.280	0.227	0.328
RC	HYP	0.123	0.132	0.126	0.180	0.215
LW	HYP	0.166	0.256	0.300	0.262	0.238
MS	HYP	0.171	0.111	0.128	0.132	0.162
TB	EMM	0.098	0.255	0.248	0.224	0.271
RZ	EMM	0.112	0.082	0.139	0.137	0.162
GG	EMM	0.171	0.111	0.128	0.132	0.162
SHa	EMM	0.108	0.158	0.151	0.271	0.217
FM	EMM	0.117	0.157	0.238	0.241	0.340
DO	EMM	0.387	0.346	0.232	0.201	0.285
HP	EMM	0.110	0.183	0.166	0.208	0.224
NS	EMM	0.117	0.107	0.152	0.187	0.195
JH	EMM	0.138	0.239	0.230	0.255	0.271
LH	EMM	0.269	0.160	0.254	0.258	0.303
RM	EMM	0.149	0.139	0.290	0.288	0.299
SM	EMM	0.194	0.294	0.347	0.298	0.308
TS	EMM	0.134	0.147	0.128	0.124	0.180
LD	EOM	0.175	0.136	0.174	0.218	0.222
EM	EOM	0.096	0.172	0.115	0.200	0.209
HB	EOM	0.313	0.289	0.258	0.406	0.379
GSi	EOM	0.143	0.119	0.142	0.229	0.185
SK	EOM	0.174	0.197	0.104	0.186	0.222
AG	EOM	0.175	0.136	0.174	0.218	0.222

SK	EOM	0.273	0.338	0.139	0.191	0.202
KS	EOM	0.150	0.237	0.206	0.285	0.304
AT	EOM	0.204	0.205	0.350	0.293	0.307
KR	EOM	0.193	0.129	0.233	0.200	0.169
NM	EOM	0.161	0.211	0.122	0.270	0.287
RM	EOM	0.151	0.237	0.206	0.285	0.310
IG	EOM	0.136	0.117	0.134	0.246	0.181
SL	LOM	0.202	0.213	0.255	0.284	0.274
LM	LOM	0.202	0.213	0.255	0.284	0.274
PS	LOM	0.103	0.152	0.174	0.202	0.239
AC	LOM	0.185	0.336	0.275	0.559	0.493
AL	LOM	0.337	0.136	0.247	0.183	0.237
AG	LOM	0.172	0.146	0.321	0.245	0.301
MM	LOM	0.131	0.184	0.237	0.276	0.453
KJ	LOM	0.269	0.282	0.188	0.314	0.419
VC	LOM	0.277	0.221	0.282	0.287	0.299
SD	LOM	0.226	0.211	0.215	0.420	0.326
GM	LOM	0.102	0.149	0.168	0.182	0.234
ER	LOM	0.127	0.143	0.401	0.286	0.244
ND	LOM	0.295	0.251	0.299	0.207	0.209

Table A6.1 Accommodative response RMS data.

APPENDIX 7

MICROFLUCTUATIONS OF ACCOMMODATION: FFT RESULTS

A7.1 Absolute (D^2Hz^{-1}) accommodative LFC relating to Chapter 4

Subject	Refractive Group	Accommodative Demand (D)				
		0	1	2	3	4
CH	HYP	29.077	121.134	60.847	45.649	35.227
DP	HYP	7.946	24.061	24.061	29.360	38.680
GS	HYP	5.763	15.883	20.230	7.250	29.273
BT	HYP	7.152	8.889	14.856	9.942	13.766
MG	HYP	8.288	20.829	23.169	22.815	62.493
DB	HYP	7.076	9.316	15.911	10.855	12.358
MA	HYP	6.488	10.595	49.293	33.239	34.713
RE	HYP	118.446	69.866	64.626	45.539	12.610
SH	HYP	9.485	18.761	23.997	23.292	64.141
AP	HYP	23.977	24.780	25.943	54.426	33.307
RC	HYP	14.093	6.436	5.370	12.783	9.882
LW	HYP	13.237	53.902	96.598	41.917	41.916
MS	HYP	11.475	8.071	9.787	5.969	38.207
TB	EMM	6.940	24.280	34.934	34.624	33.792
RZ	EMM	4.744	2.051	17.671	7.049	14.702
GG	EMM	22.360	8.398	12.022	12.080	23.296
SHa	EMM	6.417	18.243	14.718	35.373	28.359
FM	EMM	9.987	25.125	38.700	30.085	60.732
DO	EMM	50.252	107.992	23.784	29.870	48.254
HP	EMM	7.039	23.292	8.214	22.304	29.564
NS	EMM	12.935	6.110	17.171	15.073	21.274
JH	EMM	11.642	47.028	52.374	29.322	37.593
LH	EMM	40.729	8.378	19.744	20.093	28.041
RM	EMM	12.763	6.679	83.407	25.055	87.141
SM	EMM	33.975	33.337	93.529	59.845	60.444
TS	EMM	6.818	6.425	12.505	5.338	14.653
LD	EOM	12.519	7.983	24.525	36.805	18.142
EM	EOM	5.866	13.223	6.908	25.222	27.930
HB	EOM	27.596	58.005	31.935	103.771	125.560
GSi	EOM	13.586	10.449	12.580	43.648	11.263
SK	EOM	18.572	50.921	4.490	16.523	10.671
AG	EOM	13.641	9.450	35.300	62.472	20.953
SK	EOM	33.872	43.552	14.233	45.790	33.209

KS	EOM	12.309	32.687	15.792	83.706	46.405
AT	EOM	8.977	21.244	30.537	9.290	25.751
KR	EOM	35.301	7.605	29.957	30.394	20.967
NM	EOM	10.896	12.120	6.770	89.395	30.928
RM	EOM	12.870	32.687	15.792	83.706	46.405
IG	EOM	16.143	8.707	6.709	29.656	2.298
SL	LOM	9.501	21.097	59.549	28.218	44.235
LM	LOM	15.284	28.456	60.103	23.711	48.819
PS	LOM	7.260	19.631	15.633	34.895	51.472
AC	LOM	28.134	528.954	110.186	270.145	50.619
AL	LOM	119.964	10.452	6.591	14.457	60.009
AG	LOM	22.601	15.914	75.564	24.668	70.887
MM	LOM	6.946	8.227	49.057	89.215	144.618
KJ	LOM	27.566	63.681	22.248	37.814	126.098
VC	LOM	260.194	50.789	99.937	39.749	57.152
SD	LOM	14.015	11.213	14.760	30.773	35.408
GM	LOM	4.778	12.672	13.985	28.690	46.892
ER	LOM	17.077	9.361	120.300	43.312	30.482
ND	LOM	32.850	21.773	42.247	22.075	18.332

Table A7.1 Absolute (D^2Hz^{-1}) accommodative LFC data.

A7.2 Absolute (D^2Hz^{-1}) accommodative HFC relating to Chapter 4

Subject	Refractive Group	Accommodative Demand (D)				
		0	1	2	3	4
CH	HYP	7.259	28.759	28.703	9.729	16.873
DP	HYP	5.509	5.912	5.912	10.806	6.128
GS	HYP	3.362	4.423	9.864	11.619	11.273
BT	HYP	4.417	6.625	11.999	11.942	14.893
MG	HYP	9.065	4.522	25.006	16.161	54.254
DB	HYP	4.564	5.930	9.241	13.055	12.198
MA	HYP	3.789	2.331	11.058	12.223	3.350
RE	HYP	15.491	15.372	18.677	16.432	9.809
SH	HYP	7.587	7.118	22.345	15.542	47.215
AP	HYP	12.195	8.957	4.710	21.790	12.728
RC	HYP	2.214	1.712	1.628	8.700	9.134
LW	HYP	3.323	10.910	12.540	12.170	10.161
MS	HYP	3.136	3.083	4.544	5.704	9.460
TB	EMM	2.886	6.000	8.244	19.505	23.534
RZ	EMM	0.932	1.505	3.232	4.887	5.094
GG	EMM	4.472	3.263	3.818	4.204	10.758
SHa	EMM	4.997	7.353	9.856	26.241	15.176
FM	EMM	2.050	5.563	18.497	10.303	16.423
DO	EMM	5.865	13.576	5.664	6.684	11.205
HP	EMM	2.508	4.266	7.086	7.915	15.154
NS	EMM	2.101	2.387	5.120	8.642	8.768
JH	EMM	3.206	7.334	7.896	11.892	13.489
LH	EMM	7.062	10.272	27.140	40.416	29.338
RM	EMM	3.946	2.859	5.115	10.869	17.173
SM	EMM	9.850	17.302	36.214	20.392	22.400
TS	EMM	1.989	3.137	3.393	4.157	6.770
LD	EOM	2.801	2.874	5.994	10.728	6.762
EM	EOM	2.333	4.717	2.554	10.036	9.949
HB	EOM	13.299	53.903	5.770	17.883	25.229
GSi	EOM	2.450	2.300	5.720	16.792	6.547
SK	EOM	1.822	5.047	2.936	3.199	3.307
AG	EOM	3.046	3.572	5.728	14.649	7.232
SK	EOM	12.804	6.880	2.559	2.354	7.183
KS	EOM	4.308	2.129	28.275	12.622	7.061
AT	EOM	7.533	6.930	32.592	10.896	8.466
KR	EOM	2.859	3.757	8.743	5.026	6.076
NM	EOM	1.635	5.143	6.062	20.274	6.415

RM	EOM	4.333	2.129	28.275	12.622	7.061
IG	EOM	3.379	2.720	6.096	46.011	7.469
SL	LOM	2.805	6.425	5.786	8.045	17.427
LM	LOM	6.419	13.497	5.944	6.410	7.278
PS	LOM	1.897	4.552	2.764	8.781	9.899
AC	LOM	6.218	105.180	18.671	50.928	15.699
AL	LOM	19.004	5.891	6.746	10.207	8.463
AG	LOM	4.122	9.966	9.087	7.743	21.714
MM	LOM	1.888	4.529	2.376	3.098	10.674
KJ	LOM	13.531	19.455	4.897	27.035	18.506
VC	LOM	34.750	7.152	6.969	10.954	23.281
SD	LOM	3.377	6.195	20.676	14.526	25.822
GM	LOM	2.057	3.377	2.332	7.966	11.265
ER	LOM	0.324	1.399	1.850	3.028	2.745
ND	LOM	12.768	7.794	5.415	11.138	3.872

Table A7.2 Absolute (D^2Hz^{-1}) accommodative HFC data.

A7.3 Relative (normalised units) accommodative LFC relating to Chapter 4

Subject	Refractive Group	Accommodative Demand (D)				
		0	1	2	3	4
CH	HYP	0.680	0.693	0.619	0.635	0.536
DP	HYP	0.384	0.737	0.737	0.572	0.653
GS	HYP	0.526	0.625	0.574	0.339	0.600
BT	HYP	0.534	0.424	0.455	0.404	0.340
MG	HYP	0.391	0.674	0.418	0.507	0.491
DB	HYP	0.512	0.452	0.539	0.404	0.348
MA	HYP	0.451	0.680	0.704	0.557	0.783
RE	HYP	0.767	0.527	0.677	0.534	0.382
SH	HYP	0.486	0.559	0.451	0.534	0.626
AP	HYP	0.611	0.512	0.676	0.561	0.562
RC	HYP	0.729	0.669	0.585	0.514	0.423
LW	HYP	0.720	0.762	0.852	0.603	0.637
MS	HYP	0.586	0.509	0.493	0.362	0.620
TB	EMM	0.552	0.621	0.673	0.502	0.472
RZ	EMM	0.736	0.464	0.696	0.511	0.567
GG	EMM	0.704	0.511	0.587	0.615	0.516
SHa	EMM	0.443	0.568	0.455	0.435	0.561
FM	EMM	0.727	0.649	0.582	0.642	0.632
DO	EMM	0.830	0.821	0.672	0.649	0.711
HP	EMM	0.585	0.762	0.438	0.551	0.478
NS	EMM	0.768	0.602	0.701	0.552	0.561
JH	EMM	0.701	0.761	0.824	0.590	0.574
LH	EMM	0.780	0.371	0.347	0.256	0.340
RM	EMM	0.579	0.559	0.899	0.593	0.724
SM	EMM	0.648	0.544	0.651	0.569	0.554
TS	EMM	0.708	0.503	0.657	0.520	0.552
LD	EOM	0.650	0.618	0.640	0.661	0.594
EM	EOM	0.480	0.628	0.645	0.606	0.615
HB	EOM	0.526	0.435	0.707	0.606	0.641
GSi	EOM	0.768	0.717	0.549	0.613	0.495
SK	EOM	0.863	0.859	0.481	0.650	0.626
AG	EOM	0.655	0.562	0.682	0.757	0.633
SK	EOM	0.612	0.760	0.782	0.894	0.727
KS	EOM	0.652	0.813	0.253	0.745	0.752
AT	EOM	0.408	0.678	0.492	0.362	0.627
KR	EOM	0.842	0.556	0.689	0.752	0.675
NM	EOM	0.719	0.562	0.374	0.758	0.741

RM	EOM	0.658	0.813	0.253	0.745	0.752
IG	EOM	0.769	0.654	0.370	0.314	0.157
SL	LOM	0.695	0.619	0.650	0.655	0.703
LM	LOM	0.531	0.515	0.747	0.778	0.820
PS	LOM	0.665	0.629	0.761	0.765	0.742
AC	LOM	0.705	0.765	0.708	0.730	0.760
AL	LOM	0.749	0.537	0.381	0.495	0.802
AG	LOM	0.602	0.450	0.754	0.582	0.798
MM	LOM	0.629	0.655	0.692	0.932	0.905
KJ	LOM	0.570	0.702	0.646	0.487	0.814
VC	LOM	0.844	0.742	0.674	0.670	0.710
SD	LOM	0.406	0.520	0.355	0.597	0.649
GM	LOM	0.532	0.596	0.762	0.611	0.769
ER	LOM	0.800	0.482	0.798	0.475	0.761
ND	LOM	0.510	0.653	0.820	0.660	0.722

Table A7.3 Relative (normalised units) accommodative LFC data.

A7.4 Relative (normalised units) accommodative HFC relating to Chapter 4

Subject	Refractive Group	Accommodative Demand (D)				
		0	1	2	3	4
CH	HYP	0.170	0.165	0.292	0.135	0.257
DP	HYP	0.266	0.181	0.181	0.211	0.103
GS	HYP	0.307	0.174	0.280	0.543	0.231
BT	HYP	0.330	0.316	0.367	0.485	0.368
MG	HYP	0.427	0.146	0.451	0.359	0.426
DB	HYP	0.330	0.316	0.367	0.485	0.343
MA	HYP	0.264	0.150	0.158	0.205	0.076
RE	HYP	0.100	0.116	0.193	0.193	0.297
SH	HYP	0.389	0.212	0.420	0.356	0.280
AP	HYP	0.311	0.185	0.123	0.224	0.215
RC	HYP	0.115	0.178	0.177	0.350	0.391
LW	HYP	0.181	0.154	0.111	0.189	0.154
MS	HYP	0.160	0.194	0.229	0.346	0.154
TB	EMM	0.229	0.154	0.159	0.283	0.329
RZ	EMM	0.144	0.340	0.127	0.354	0.197
GG	EMM	0.141	0.199	0.186	0.214	0.238
SHa	EMM	0.345	0.229	0.305	0.323	0.300
FM	EMM	0.149	0.144	0.278	0.220	0.171
DO	EMM	0.097	0.103	0.160	0.145	0.165
HP	EMM	0.209	0.140	0.373	0.196	0.245
NS	EMM	0.125	0.235	0.197	0.316	0.231
JH	EMM	0.193	0.119	0.124	0.239	0.206
LH	EMM	0.135	0.454	0.477	0.516	0.356
RM	EMM	0.178	0.239	0.055	0.257	0.143
SM	EMM	0.188	0.282	0.252	0.194	0.205
TS	EMM	0.207	0.246	0.178	0.327	0.255
LD	EOM	0.146	0.222	0.156	0.193	0.221
EM	EOM	0.191	0.224	0.238	0.241	0.219
HB	EOM	0.253	0.404	0.128	0.104	0.129
GSi	EOM	0.138	0.158	0.249	0.236	0.288
SK	EOM	0.085	0.085	0.314	0.126	0.194
AG	EOM	0.146	0.238	0.090	0.173	0.219
SK	EOM	0.231	0.120	0.141	0.046	0.136
KS	EOM	0.228	0.053	0.454	0.112	0.114
AT	EOM	0.342	0.221	0.419	0.425	0.206
KR	EOM	0.017	0.275	0.201	0.124	0.196

NM	EOM	0.108	0.238	0.335	0.172	0.154
RM	EOM	0.222	0.053	0.454	0.112	0.114
IG	EOM	0.161	0.204	0.336	0.488	0.512
SL	LOM	0.205	0.188	0.083	0.187	0.238
LM	LOM	0.265	0.244	0.084	0.183	0.107
PS	LOM	0.174	0.146	0.135	0.167	0.143
AC	LOM	0.156	0.152	0.137	0.138	0.187
AL	LOM	0.119	0.302	0.390	0.349	0.113
AG	LOM	0.110	0.282	0.091	0.183	0.183
MM	LOM	0.198	0.300	0.045	0.032	0.067
KJ	LOM	0.280	0.215	0.142	0.277	0.120
VC	LOM	0.113	0.105	0.061	0.185	0.249
SD	LOM	0.370	0.287	0.498	0.282	0.282
GM	LOM	0.229	0.159	0.127	0.170	0.167
ER	LOM	0.110	0.416	0.116	0.253	0.231
ND	LOM	0.198	0.234	0.105	0.282	0.153

Table A7.4 Relative (normalised units) accommodative HFC data.

APPENDIX 8

CARDIOVASCULAR FUNCTION: HEART PERIOD

A8.1 Mean heart period data (s) to changes in accommodative demand relating to Chapter 5

	Refractive	Accommodative Demand (D)					
Subject	**Group**	0	1	2	3	4	6
CH	HYP	0.824	0.814	0.863	0.881	0.896	0.960
DP	HYP	0.627	0.634	0.600	0.587	0.603	0.605
GS	HYP	0.730	0.722	0.734	0.765	0.709	0.777
BT	HYP	0.585	0.577	0.587	0.612	0.578	0.622
MG	HYP	0.556	0.526	0.538	0.529	0.533	0.557
AS	HYP	0.741	0.730	0.709	0.709	0.708	0.740
DB	HYP	0.733	0.722	0.734	0.765	0.710	0.773
MA	HYP	0.775	0.792	0.750	0.734	0.767	0.806
RE	HYP	0.516	0.514	0.527	0.515	0.515	0.581
SH	HYP	0.556	0.526	0.538	0.529	0.534	0.558
AP	HYP	0.679	0.649	0.636	0.603	0.598	0.642
RC	HYP	0.579	0.570	0.542	0.532	0.543	0.593
LW	HYP	0.722	0.682	0.681	0.675	0.649	0.703
JS	HYP	0.810	0.814	0.863	0.881	0.896	0.906
MS	HYP	1.104	1.117	1.116	1.086	1.055	1.050
TB	EMM	0.781	0.791	0.770	0.815	0.782	0.723
RZ	EMM	0.528	0.541	0.548	0.541	0.540	0.573
GG	EMM	1.104	1.117	1.117	1.096	1.055	1.050
SHa	EMM	0.681	0.714	0.704	0.713	0.718	0.719
FM	EMM	0.778	0.789	0.770	0.815	0.778	0.723
DO	EMM	0.667	0.686	0.711	0.733	0.743	0.750
HP	EMM	0.854	0.854	0.836	0.840	0.824	0.801
NS	EMM	0.662	0.686	0.711	0.729	0.743	0.750
JH	EMM	0.740	0.727	0.685	0.693	0.674	0.663
LH	EMM	0.756	0.779	0.738	0.724	0.787	0.707
RM	EMM	0.678	0.683	0.708	0.691	0.704	0.733
SM	EMM	0.830	0.831	0.821	0.814	0.778	0.805
HPa	EMM	0.756	0.779	0.738	0.724	0.787	0.695
TS	EMM	0.679	0.683	0.707	0.691	0.704	0.730
ACe	EMM	0.927	0.913	0.886	0.917	0.884	0.925
LD	EOM	0.792	0.734	0.734	0.759	0.690	0.710

EM	EOM	0.739	0.727	0.675	0.693	0.674	0.663
HB	EOM	0.685	0.685	0.684	0.738	0.745	0.704
GSi	EOM	0.700	0.676	0.670	0.688	0.713	0.725
SK	EOM	0.724	0.714	0.763	0.781	0.796	0.860
AG	EOM	0.792	0.734	0.734	0.759	0.690	0.710
SK	EOM	0.877	0.845	0.788	0.842	0.826	0.824
KS	EOM	0.802	0.789	0.798	0.819	0.782	0.802
AT	EOM	0.865	0.880	0.845	0.882	0.851	0.873
AP	EOM	0.694	0.694	0.675	0.654	0.638	0.700
ACh	EOM	0.873	0.854	0.793	0.820	0.839	0.736
KR	EOM	0.712	0.670	0.683	0.667	0.658	0.678
NM	EOM	0.851	0.829	0.838	0.843	0.827	0.883
RM	EOM	0.566	0.578	0.571	0.571	0.570	0.577
IG	EOM	0.643	0.647	0.628	0.620	0.623	0.643
SL	LOM	0.704	0.734	0.758	0.773	0.786	0.811
LM	LOM	0.811	0.786	0.774	0.758	0.734	0.704
PS	LOM	0.844	0.829	0.879	0.833	0.877	0.811
AC	LOM	0.693	0.685	0.685	0.688	0.676	0.675
LDo	LOM	0.830	0.766	0.769	0.739	0.740	0.749
AL	LOM	0.845	0.806	0.840	0.800	0.831	0.811
AG	LOM	0.685	0.687	0.667	0.678	0.650	0.601
MM	LOM	0.852	0.855	0.801	0.805	0.748	0.807
KJ	LOM	0.646	0.643	0.642	0.651	0.616	0.635
YH	LOM	0.830	0.766	0.769	0.739	0.740	0.770
VC	LOM	0.704	0.734	0.758	0.767	0.787	0.811
SD	LOM	0.710	0.701	0.691	0.704	0.670	0.688
GM	LOM	0.704	0.733	0.756	0.777	0.779	0.811
ER	LOM	0.740	0.732	0.720	0.717	0.718	0.716
ND	LOM	0.701	0.670	0.709	0.694	0.685	0.682

Table A8.1 Heart period data (s) to changes in accommodative demand.

APPENDIX 9

HEART RATE VARIABILITY: FFT RESULTS

A9.1 Absolute (s^2Hz^{-1} x 10^{-3}) cardiovascular LFC relating to Chapter 5

Subject	Refractive Group	Accommodative Demand (D)					
		0	1	2	3	4	6
CH	HYP	1.872	1.795	1.775	1.466	2.824	2.873
DP	HYP	2.163	1.106	1.869	2.003	3.168	0.452
GS	HYP	0.537	1.500	0.263	0.826	0.392	1.201
BT	HYP	0.373	0.960	0.181	0.528	2.109	0.756
MG	HYP	0.249	0.243	0.223	0.140	0.190	0.169
AS	HYP	0.182	0.245	0.161	0.161	0.195	0.389
DB	HYP	0.658	1.500	0.263	0.826	0.425	1.350
MA	HYP	3.098	1.797	2.993	2.989	4.471	0.713
RE	HYP	0.890	0.115	1.002	0.215	0.362	1.802
SH	HYP	0.093	0.095	0.070	0.087	0.093	0.072
AP	HYP	0.534	0.127	0.533	1.819	0.475	1.109
RC	HYP	0.570	0.232	0.404	0.273	0.370	1.182
LW	HYP	1.526	0.456	0.813	0.351	0.245	1.103
JS	HYP	1.872	1.795	1.775	1.466	2.824	2.873
MS	HYP	0.540	0.566	0.610	1.880	1.519	1.454
TB	EMM	1.487	1.495	1.075	1.272	1.370	1.493
RZ	EMM	0.269	0.445	0.802	2.040	1.161	0.904
GG	EMM	0.540	0.523	0.518	1.946	1.587	1.271
SHa	EMM	1.132	0.784	0.643	0.725	0.726	0.726
FM	EMM	1.487	1.495	1.075	1.272	1.370	1.493
DO	EMM	0.606	0.756	0.851	0.589	0.945	1.522
HP	EMM	0.331	0.661	0.784	0.404	0.364	1.039
NS	EMM	0.606	0.756	0.851	0.589	0.945	1.522
JH	EMM	0.350	1.204	0.610	1.434	0.936	0.938
LH	EMM	1.329	1.883	1.169	0.702	1.755	0.567
RM	EMM	0.627	1.052	1.307	1.145	1.439	1.625
SM	EMM	0.588	1.103	0.772	1.078	1.118	2.692
HPa	EMM	1.329	1.883	1.169	0.702	1.755	0.567
TS	EMM	0.627	1.052	1.307	1.145	1.439	1.625
ACe	EMM	0.289	0.415	0.275	0.300	0.308	0.532
LD	EOM	0.962	0.764	0.766	0.409	2.579	1.863
EM	EOM	0.340	1.204	0.610	1.423	0.927	0.938
HB	EOM	0.563	0.759	0.845	0.960	0.837	0.903

GSi	EOM	2.972	1.177	0.798	1.023	0.924	1.527
SK	EOM	1.872	1.795	1.775	1.466	2.824	2.873
AG	EOM	0.997	0.740	0.740	0.401	2.059	1.769
SK	EOM	0.470	0.777	0.828	0.642	0.854	1.348
KS	EOM	1.287	0.665	0.549	1.182	0.806	1.656
AT	EOM	2.256	1.420	4.316	2.156	2.342	4.697
AP	EOM	0.348	0.348	0.208	0.238	0.530	0.204
ACh	EOM	0.602	0.481	6.797	1.006	1.794	3.031
KR	EOM	1.973	0.510	1.249	1.451	0.509	1.391
NM	EOM	1.134	1.080	0.333	1.975	0.598	1.523
RM	EOM	0.131	0.296	0.658	0.280	0.387	0.387
IG	EOM	0.803	1.047	1.025	2.707	0.963	0.778
SL	LOM	0.795	2.891	1.702	2.209	2.235	1.892
LM	LOM	2.232	2.237	2.239	1.734	3.150	0.793
PS	LOM	2.507	1.392	2.488	1.676	0.874	1.091
AC	LOM	2.088	0.769	0.769	1.787	1.711	1.266
LDo	LOM	0.951	2.761	2.367	1.179	3.774	1.484
AL	LOM	1.770	1.770	1.709	1.069	4.334	2.719
AG	LOM	2.010	2.755	1.278	1.970	1.113	0.686
MM	LOM	0.795	2.891	1.502	2.021	1.924	1.892
KJ	LOM	0.475	0.303	0.235	1.020	0.234	0.295
YH	LOM	0.952	2.761	2.367	1.179	3.774	1.484
VC	LOM	0.795	2.091	1.702	2.209	2.235	1.892
SD	LOM	1.996	0.338	0.485	0.644	0.538	2.017
GM	LOM	0.795	2.891	1.702	2.209	2.235	1.892
ER	LOM	0.443	0.558	0.328	0.582	0.282	1.071
ND	LOM	1.395	0.617	0.390	0.565	0.423	1.877

Table A9.1 Absolute (s^2Hz^{-1} x 10^{-3}) cardiovascular LFC data.

A9.2 Absolute ($s^2Hz^{-1} \times 10^{-3}$) cardiovascular HFC relating to Chapter 5

Subject	Refractive Group	Accommodative Demand (D)					
		0	1	2	3	4	6
CH	HYP	3.800	3.776	3.800	3.429	2.666	4.679
DP	HYP	1.199	0.332	0.436	0.232	0.741	0.312
GS	HYP	1.904	1.783	1.491	1.348	1.267	3.332
BT	HYP	1.195	1.136	0.975	0.868	4.772	2.098
MG	HYP	0.206	0.195	0.197	0.239	0.138	0.197
AS	HYP	1.555	1.293	0.777	0.777	0.762	1.140
DB	HYP	1.865	1.783	1.491	1.348	1.328	3.368
MA	HYP	0.811	0.520	0.499	0.369	1.262	0.508
RE	HYP	0.103	0.058	0.178	0.092	0.121	0.229
SH	HYP	0.226	0.230	0.226	0.133	0.162	0.165
AP	HYP	0.183	0.182	0.305	0.478	0.206	0.420
RC	HYP	1.351	1.145	0.864	0.814	0.640	1.382
LW	HYP	1.379	0.713	0.790	0.601	0.459	0.986
JS	HYP	3.800	3.776	3.800	3.429	2.666	4.679
MS	HYP	2.572	1.791	1.809	2.980	2.632	3.763
TB	EMM	2.082	2.479	1.712	2.513	1.997	1.226
RZ	EMM	0.420	0.579	0.423	0.591	0.331	0.566
GG	EMM	2.381	1.805	1.854	2.979	2.692	3.819
SHa	EMM	0.465	0.557	0.589	0.782	0.787	0.787
FM	EMM	2.082	2.479	1.712	2.513	1.997	1.226
DO	EMM	0.317	0.368	0.554	0.673	1.073	1.113
HP	EMM	2.619	2.089	1.264	1.182	0.918	0.979
NS	EMM	0.317	0.368	0.554	0.673	1.073	1.113
JH	EMM	0.703	0.782	0.194	0.504	0.225	0.240
LH	EMM	1.616	1.064	0.805	0.671	1.151	0.577
RM	EMM	9.298	7.536	10.026	7.054	4.835	6.655
SM	EMM	3.059	2.192	1.550	1.692	0.926	0.402
HPa	EMM	1.616	1.064	0.805	0.671	1.151	0.577
TS	EMM	9.210	7.536	10.026	7.092	4.835	6.606
ACe	EMM	2.454	2.026	1.240	2.158	1.221	1.795
LD	EOM	2.024	1.202	1.202	0.671	1.279	1.018
EM	EOM	0.703	0.782	0.194	0.504	0.225	0.240
HB	EOM	0.447	0.525	0.504	1.679	0.919	0.593
GSi	EOM	0.767	0.840	0.650	1.252	0.962	0.744
SK	EOM	3.800	3.776	3.800	3.429	2.666	4.679
AG	EOM	1.997	1.174	1.174	0.648	1.180	1.031
SK	EOM	2.079	1.127	1.061	0.972	0.826	1.010

KS	EOM	1.387	1.060	1.334	1.272	0.665	1.346
AT	EOM	2.593	1.370	2.221	1.293	2.266	2.387
AP	EOM	1.213	1.213	0.941	0.706	0.456	1.384
ACh	EOM	6.447	7.488	7.383	4.464	5.061	3.877
KR	EOM	0.510	0.594	0.379	0.475	0.741	0.516
NM	EOM	0.989	0.872	0.733	1.260	0.705	1.268
RM	EOM	0.535	0.535	0.499	0.536	0.758	0.758
IG	EOM	0.494	0.931	0.981	1.035	1.065	0.659
SL	LOM	1.159	2.245	0.826	1.301	1.843	1.491
LM	LOM	1.832	1.860	1.295	0.760	1.926	1.004
PS	LOM	2.393	1.747	2.266	1.339	1.442	1.088
AC	LOM	1.246	0.761	0.761	1.268	0.968	0.656
LDo	LOM	1.691	1.689	2.610	2.614	1.903	2.080
AL	LOM	2.127	2.127	4.143	2.190	5.193	1.938
AG	LOM	1.123	1.415	0.911	0.524	0.354	1.354
MM	LOM	1.159	1.245	0.826	1.301	1.843	1.491
KJ	LOM	0.488	1.420	0.986	0.611	0.870	0.875
YH	LOM	1.691	1.689	2.610	2.614	1.903	2.080
VC	LOM	1.959	1.245	0.826	1.301	1.843	1.991
SD	LOM	0.602	0.733	0.784	0.819	0.885	1.802
GM	LOM	1.159	2.245	0.826	1.301	1.843	1.491
ER	LOM	0.668	0.637	0.634	0.830	0.492	1.060
ND	LOM	0.756	0.407	0.552	0.694	0.402	1.539

Table A9.2 Absolute (s^2Hz^{-1} x 10^{-3}) cardiovascular HFC data.

A9.3 Relative (normalised units) cardiovascular LFC relating to Chapter 5

Subject	Refractive Group	Accommodative Demand (D)					
		0	1	2	3	4	6
CH	HYP	0.298	0.290	0.287	0.280	0.286	0.177
DP	HYP	0.475	0.605	0.703	0.660	0.531	0.209
GS	HYP	0.170	0.333	0.084	0.257	0.180	0.194
BT	HYP	0.190	0.333	0.092	0.251	0.245	0.193
MG	HYP	0.268	0.244	0.364	0.205	0.202	0.264
AS	HYP	0.095	0.128	0.142	0.142	0.188	0.226
DB	HYP	0.213	0.333	0.084	0.257	0.193	0.214
MA	HYP	0.618	0.610	0.718	0.621	0.471	0.208
RE	HYP	0.634	0.489	0.660	0.381	0.553	0.817
SH	HYP	0.259	0.234	0.184	0.240	0.321	0.190
AP	HYP	0.561	0.149	0.294	0.617	0.459	0.622
RC	HYP	0.270	0.119	0.269	0.229	0.289	0.355
LW	HYP	0.349	0.217	0.391	0.222	0.213	0.327
JS	HYP	0.298	0.286	0.287	0.258	0.286	0.177
MS	HYP	0.115	0.190	0.201	0.339	0.252	0.195
TB	EMM	0.359	0.326	0.316	0.289	0.344	0.478
RZ	EMM	0.328	0.306	0.499	0.663	0.677	0.513
GG	EMM	0.134	0.183	0.179	0.357	0.276	0.174
SHa	EMM	0.435	0.268	0.355	0.267	0.274	0.274
FM	EMM	0.346	0.313	0.316	0.299	0.354	0.478
DO	EMM	0.512	0.517	0.410	0.321	0.407	0.513
HP	EMM	0.099	0.181	0.275	0.196	0.198	0.328
NS	EMM	0.522	0.517	0.400	0.315	0.407	0.513
JH	EMM	0.095	0.347	0.305	0.512	0.568	0.455
LH	EMM	0.235	0.446	0.430	0.398	0.479	0.223
RM	EMM	0.061	0.114	0.106	0.132	0.204	0.104
SM	EMM	0.102	0.244	0.276	0.338	0.388	0.522
HPa	EMM	0.235	0.455	0.430	0.384	0.479	0.234
TS	EMM	0.061	0.114	0.106	0.132	0.204	0.104
ACe	EMM	0.096	0.140	0.135	0.111	0.189	0.204
LD	EOM	0.251	0.250	0.250	0.231	0.551	0.576
EM	EOM	0.093	0.347	0.295	0.511	0.570	0.455
HB	EOM	0.416	0.372	0.403	0.197	0.225	0.307
GSi	EOM	0.643	0.409	0.281	0.319	0.407	0.506
SK	EOM	0.298	0.290	0.287	0.280	0.286	0.177
AG	EOM	0.261	0.252	0.252	0.224	0.505	0.555

SK	EOM	0.136	0.331	0.207	0.289	0.440	0.493
KS	EOM	0.405	0.295	0.209	0.437	0.371	0.514
AT	EOM	0.255	0.441	0.589	0.595	0.465	0.534
AP	EOM	0.201	0.201	0.135	0.207	0.452	0.114
ACh	EOM	0.078	0.056	0.427	0.152	0.233	0.407
KR	EOM	0.627	0.291	0.686	0.586	0.195	0.486
NM	EOM	0.273	0.387	0.202	0.438	0.319	0.479
RM	EOM	0.160	0.327	0.497	0.286	0.247	0.247
IG	EOM	0.516	0.435	0.429	0.612	0.389	0.484
SL	LOM	0.351	0.457	0.504	0.514	0.437	0.446
LM	LOM	0.201	0.433	0.524	0.514	0.516	0.363
PS	LOM	0.432	0.292	0.449	0.454	0.263	0.466
AC	LOM	0.462	0.394	0.394	0.470	0.576	0.490
LDo	LOM	0.258	0.607	0.515	0.299	0.576	0.366
AL	LOM	0.332	0.332	0.227	0.298	0.341	0.509
AG	LOM	0.613	0.562	0.516	0.598	0.582	0.281
MM	LOM	0.694	0.907	0.772	0.766	0.625	0.673
KJ	LOM	0.396	0.169	0.158	0.489	0.202	0.206
YH	LOM	0.258	0.607	0.515	0.299	0.576	0.366
VC	LOM	0.351	0.457	0.504	0.514	0.437	0.446
SD	LOM	0.461	0.103	0.299	0.311	0.241	0.429
GM	LOM	0.350	0.456	0.501	0.511	0.437	0.446
ER	LOM	0.281	0.352	0.221	0.339	0.277	0.256
ND	LOM	0.486	0.446	0.278	0.316	0.326	0.466

Table A9.3 Relative (normalised units) cardiovascular LFC data.

A9.4 Relative (normalised units) cardiovascular HFC relating to Chapter 5

Subject	Refractive Group	Accommodative Demand (D)					
		0	1	2	3	4	6
CH	HYP	0.604	0.610	0.614	0.655	0.674	0.289
DP	HYP	0.263	0.182	0.164	0.076	0.124	0.144
GS	HYP	0.604	0.395	0.477	0.420	0.581	0.538
BT	HYP	0.609	0.394	0.494	0.412	0.555	0.535
MG	HYP	0.222	0.196	0.322	0.349	0.146	0.308
AS	HYP	0.809	0.678	0.686	0.688	0.735	0.662
DB	HYP	0.605	0.395	0.477	0.420	0.602	0.534
MA	HYP	0.162	0.177	0.120	0.077	0.133	0.148
RE	HYP	0.073	0.247	0.117	0.163	0.185	0.104
SH	HYP	0.630	0.567	0.593	0.366	0.559	0.437
AP	HYP	0.192	0.213	0.168	0.162	0.199	0.236
RC	HYP	0.641	0.588	0.575	0.683	0.500	0.415
LW	HYP	0.315	0.339	0.380	0.380	0.399	0.292
JS	HYP	0.604	0.610	0.614	0.655	0.674	0.289
MS	HYP	0.549	0.600	0.597	0.537	0.436	0.506
TB	EMM	0.503	0.541	0.504	0.570	0.501	0.392
RZ	EMM	0.512	0.398	0.263	0.192	0.193	0.321
GG	EMM	0.590	0.632	0.640	0.546	0.468	0.523
SHa	EMM	0.179	0.191	0.325	0.288	0.297	0.297
FM	EMM	0.503	0.541	0.504	0.570	0.501	0.392
DO	EMM	0.273	0.252	0.261	0.360	0.462	0.375
HP	EMM	0.780	0.571	0.443	0.573	0.500	0.309
NS	EMM	0.273	0.252	0.261	0.360	0.462	0.375
JH	EMM	0.193	0.226	0.094	0.203	0.139	0.114
LH	EMM	0.286	0.257	0.296	0.367	0.314	0.239
RM	EMM	0.898	0.815	0.812	0.818	0.685	0.422
SM	EMM	0.529	0.484	0.554	0.530	0.322	0.078
HPa	EMM	0.286	0.257	0.296	0.367	0.314	0.239
TS	EMM	0.898	0.815	0.812	0.818	0.685	0.422
ACe	EMM	0.817	0.685	0.609	0.796	0.751	0.688
LD	EOM	0.527	0.394	0.394	0.380	0.273	0.315
EM	EOM	0.193	0.225	0.094	0.202	0.138	0.114
HB	EOM	0.331	0.257	0.240	0.345	0.247	0.202
GSi	EOM	0.166	0.292	0.229	0.390	0.423	0.247
SK	EOM	0.604	0.610	0.614	0.655	0.674	0.289
AG	EOM	0.524	0.400	0.400	0.361	0.289	0.323

SK	EOM	0.600	0.481	0.266	0.437	0.426	0.370
KS	EOM	0.437	0.469	0.507	0.471	0.306	0.418
AT	EOM	0.293	0.426	0.303	0.357	0.450	0.271
AP	EOM	0.701	0.701	0.610	0.613	0.389	0.772
ACh	EOM	0.833	0.872	0.464	0.676	0.657	0.520
KR	EOM	0.162	0.339	0.208	0.192	0.284	0.180
NM	EOM	0.238	0.312	0.445	0.280	0.377	0.399
RM	EOM	0.655	0.591	0.377	0.547	0.485	0.485
IG	EOM	0.318	0.387	0.411	0.234	0.430	0.410
SL	LOM	0.512	0.355	0.245	0.303	0.361	0.351
LM	LOM	0.165	0.360	0.303	0.225	0.316	0.459
PS	LOM	0.412	0.366	0.409	0.363	0.435	0.465
AC	LOM	0.276	0.390	0.390	0.334	0.326	0.254
LDo	LOM	0.458	0.372	0.568	0.663	0.291	0.513
AL	LOM	0.399	0.399	0.550	0.611	0.408	0.363
AG	LOM	0.342	0.289	0.368	0.159	0.185	0.555
MM	LOM	0.185	0.049	0.114	0.150	0.105	0.204
KJ	LOM	0.407	0.792	0.662	0.293	0.751	0.612
YH	LOM	0.458	0.372	0.568	0.663	0.291	0.513
VC	LOM	0.512	0.355	0.245	0.303	0.361	0.351
SD	LOM	0.139	0.224	0.483	0.396	0.397	0.383
GM	LOM	0.512	0.354	0.245	0.303	0.361	0.351
ER	LOM	0.423	0.402	0.427	0.483	0.483	0.254
ND	LOM	0.263	0.295	0.394	0.388	0.310	0.382

Table A7.4 Relative (normalised units) cardiovascular HFC data.

APPENDIX 10

COGNITION: WEIBULL RESPONSES

A10.1 Cognitive task presentation speeds (ms) as calculated by a Weibull function for a range of predetermined response rates (% incorrect) relating to Chapter 7

Subject	Refractive Group	Incorrect Response Rate (%)				
		0	12.5	25	37.5	50
RZ	EMM	1717	1171	835	541	163
TB	EMM	2200	780	620	420	260
SL	EMM	1969	1192	814	499	247
GG	EMM	2053	1108	625	352	110
EF	EMM	2137	982	709	520	268
ACe	EMM	2001	1294	915	503	250
TS	EMM	2109	1456	734	405	256
LH	EMM	2157	1197	804	568	321
CP	LOM	2137	1423	709	392	142
EM	LOM	1876	1084	650	354	186
LD	LOM	2116	1444	877	604	310
SH	LOM	2100	1100	770	525	262
MA	LOM	2200	1108	772	520	268
YH	LOM	2140	980	700	520	270
AC	LOM	1860	1095	805	508	237
AL	LOM	1985	843	603	582	295

Table A10.1 Cognitive task presentation speeds (ms) as calculated by a Weibull function for a range of predetermined response rates (% incorrect).

SUPPORTING PUBLICATIONS

Refereed Publications

Davies, L. N., Mallen, E. A. H., Wolffsohn, J. S. and Gilmartin, B. (2003). Clinical evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR-5100K autorefractor. *Optometry and Vision Science* **80**, 320-324.

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (In review). Effect of cognition and ametropia and oculomotor and cardiovascular function. *Investigative Ophthalmology and Visual Science*.

Refereed Abstracts

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). The influence of cognition on oculomotor and cardiovascular function. *Ophthalmic and Physiological Optics* **24**, 155.[*]

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). Autonomic correlates of ocular accommodation and cardiovascular function. *American Academy of Optometry's Global-Pacific Rim Meeting, Honalulu, USA*.

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). The effect of cognition and refractive error on oculomotor and cardiovascular function. *10th International Myopia Conference, Cambridge, UK.*

Davies, L. N., Wolffsohn, J. S. and Gilmartin, B. (2004). Autonomic correlates of ocular accommodation and cardiovascular function in myopic subjects. *10th International Myopia Conference, Cambridge, UK.*

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[*] Winner of the *Cambridge Research Systems Poster Prize*, December 2003.