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Myopia and defocus: the current understanding

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Abstract

The current theories relating to the development and progression of myopia are related to exposure of the eye to hyperopic defocus. This paper discusses these theories and the large body of recent research investigating the evidence behind them. As both human and animal studies demonstrate, when considering the potential influence of defocus on eye growth, the duration of exposure as well as the type and magnitude of the blur are important. In addition, we must understand the defocus threshold over which an eye growth signal can be made. Investigations with respect to central defocus alone have been unable to find a unified theory due to (1) insufficient evidence showing refractive group differences in the amount of central defocus actually present and (2) unsuccessful attempts to wholely reduce myopia progression using corrective lenses. Recent research measuring peripheral blur is summarised in this paper and modelled together with previous measurements of peripheral defocus thresholds, providing an up-to-date perspective on myopia.

Keywords: Myope, emmetrope, defocus, accommodation, periphery
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Introduction

Research investigating the cause(s) of the development and/or progression of myopia has made significant and exciting developments in recent years. It is accepted that myopia has an inherited component (Goss, Hampton, & Wickham, 1988; Teikari, Kaprio, Koskenvuo, & Vannas, 1988; Teikari, O'Donnell, Kaprio, & Koskenvuo, 1991; Teikari, Kaprio, Koskenvuo, & O'Donnell, 1992; Mutti & Zadnik, 1995; Pacella et al., 1999; Hammond, Snieder, Gilbert, & Spector, 2001), but the understanding of the extent of the impact of this and the other environmental, anatomical and neural factors as well as their relative contributions is far from certain. Possible environmental factors are highlighted by epidemiological studies that show evidence for associations with, and risk factors for, myopia. Animal studies are used to provide an insight into the potential mechanisms of eye growth although it is the measurements and the implementation of any possible treatments in human studies that ultimately prove theories of the cause of myopia.

Many epidemiological studies have found that myopia is moderated by environment and lifestyle. In particular it is associated with higher levels of education (Angle & Wissmann, 1978; Paritsis, Sarafidou, Koliopoulos, & Trichopoulos, 1983; Sperduto, Seigel, Roberts, & Rowland, 1983; Rosner & Belkin, 1987), intensive schooling and near work (Angle & Wissmann, 1980; Richler & Bear, 1980; Saw et al., 2002a; Saw et al., 2002c; Quek et al., 2004). This, compounded with the evidence that hyperopic defocus produces myopia in animals (Irving, Callender, & Sivak, 1991; Wildsoet, 1997; Smith & Hung, 1999; Zhu, Park, Winawer, & Wallman, 2005), has lead to the hypothesis that the accommodation system is involved in the development of myopia, given that hyperopic defocus possibly results from inaccurate accommodation during reading. Unfortunately the results of a whole host of studies investigating various aspects of the accommodation response in the different refractive groups have not provided a unified theory to date. With the utilisation of modern instrumentation the anatomy of the myopic eye is becoming increasingly understood, including the ocular shape (Logan, Gilmartin, Wildsoet, & Dunne, 2004; Atchison et al., 2005b; Atchison, Pritchard, & Schmid, 2006a; Singh, Logan, & Gilmartin, 2006), and this has led to a new area of research investigating the effect of the periphery on myopic development. Animal studies have confounded our understanding of the role of the retinal periphery in eye growth (Smith, Kee, Ramamirtham, Qiao-Grider, & Hung, 2005; Smith et al., 2007; Smith, Hung, & Huang, 2009b; Smith et al., 2010) and theoretical models of peripheral blur are now being experimented with. This paper reviews the recent literature in the investigation of the effect of both central and peripheral defocus and discusses the current hypotheses relating to the development and progression of myopia.

Central defocus

Over the last 20 years, myopia researchers have been exploring the hypothesis that the hyperopic defocus produced by the lag of accommodation during sustained reading tasks triggers eye growth. There are a number of possible hypotheses as to how this could occur in those who become myopic and not in those who remain emmetropic and hyperopic. The progression and/or development of myopia could be related to the type of defocus, the duration of exposure and the magnitude of the defocus, and the sensitivity of the visual system to this blur.

Duration and type of defocus

The association between the amount of near work and the incidence of myopia (Angle & Wissmann, 1980; Richler & Bear, 1980; Mutti, Mitchell, Moeschberger, Jones, & Zadnik, 2002; Saw et al., 2002a; Saw et al., 2002c; Quek et al., 2004) lends evidence towards the hypothesis that the length of time exposed to blur could be an important factor in myopia development. Only a short period of time is needed before the eyes respond to hyperopic defocus e.g. the choroidal thickness alters after 1 hour of negative lens wear in chicks (Zhu et al., 2005); only a few minutes is sufficient to produce a similar effect to wearing the lens full time (Zhu & Wallman, 2009).

The epidemiological studies that investigate the relationship between near work and myopia in more detail have however found little evidence that the actual current number of hours spent reading is related to the progression of myopia (Tan et al., 2000; Saw et al., 2001). Tan et al. (2000) proposed that exposure to blur may have a delayed effect, and Saw et al. (2002) explain that the statistical methods of controlling for factors such as parental myopia and education may not completely eliminate the interactions between these factors and the amount of near work undertaken.

The lack of a strong relationship between the exact number of hours of exposure to defocus and myopia progression could also be due to the effect of the complex interactions between the duration and type of defocus that occur in daily life. Even over a short space of time, the eyes receive information from objects at various distances which produce a combination of hyperopic and myopic defocus over time. The mechanisms underlying the integration of these signals, as well as the effects of the alternating hyperopic and myopic defocus, are currently of interest. Theoretical modelling and results from animal studies suggest that the effects of hyperopic and myopic blur are integrated non-linearly over time (Flitcroft, 1998, 1999; Winawer & Wallman, 2002; Zhu & Wallman, 2009). Additionally, the temporal effects of myopic and hyperopic blur differ from each other (Winawer & Wallman, 2002; Zhu et al., 2005; Zhu & Wallman, 2009); the effects of myopic blur occur after a shorter period of time than the hyperopic defocus (Zhu et al., 2005) and they last much longer than those of hyperopic blur (Zhu et al., 2005; Zhu & Wallman, 2009).

Despite these complexities it seems that if there is a combination of blur types. As occurs in real life viewing, the eye responds preferentially to no blur (Norton, Siegwart, & Amedo, 2006; Kee et al., 2007) and to myopic blur (Winawer & Wallman, 2002; Winawer, Zhu, Choi, & Wallman, 2005) over hyperopic blur. This stands even if hyperopic blur occurs for a much longer period of time (Winawer & Wallman, 2002; Norton et al., 2006; Kee et al., 2007).

Too short a duration of any one type of blur, however, yields no effect. For example 2 seconds every 2 minutes in chicks (Napper et al., 1997), or durations of less than 2 minutes at any given time (Winawer & Wallman, 2002) produce no effect. Further, if myopic and hyperopic blur are alternated at high temporal frequencies, the protective effect of myopic blur disappears (Winawer et al., 2005). This rapid change in blur is commonly combined with a change between myopic and hyperopic defocus in human eyes as a result of the accommodation microfluctuations (see page 4).

It seems from all of these results that the visual system, at least in these chicks and monkeys, may in fact work hard to refrain from becoming myopic. The work suggests that short periods of time with myopic defocus, such as looking in the distance where there is usually a lead of accommodation, or some near work induced transient myopia, may be protective but only if they are not too brief in duration.

Magnitude of defocus

One of the initial theories regarding defocus and myopia development suggests that if myopes (MYOs) have less accurate accommodation responses than emmetropes (EMMs) then the larger accommodation lag may provide a greater blur error signal encouraging the eye to grow axially towards the more distant focal point, in turn producing myopia. Unfortunately there is a lack of consensus in the results of previous studies measuring the accommodation response in myopia, some showing less accurate responses in MYOs compared with EMMs (McBrien & Millodot, 1986; Gwiazda, Thorn, Bauer, & Held, 1993; Abbott, Schmid, & Strang, 1998), while others identifying no difference between the two groups (Ramsdale, 1985; Abbott et al., 1998; Nakatsuka, Hasebe, Nonaka, & Ohtsuki, 2003; Seidel, Gray, & Heron, 2003; Day, Strang, Seidel, Gray, & Mallen, 2006).

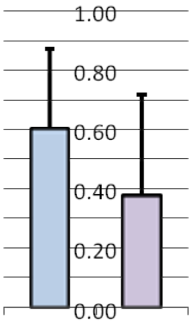
One possible reason for the differences in results between studies is that all of the experiments are conducted under slightly different artificial viewing conditions. Differences in the accuracy of the accommodation response have been found when examining progressing myopic subjects (Abbott et al., 1998) and when asking MYOs to accommodate to negative lenses, but these differences are not found when stable MYOs or real targets are used (Gwiazda et al., 1993; Abbott et al., 1998). The majority of these experiments have been conducted while viewing and recording monocularly and many are conducted with the target placed in a Badal lens system allowing only blur information to be presented to the eye. Such experimental conditions, where subjects have access to only a proportion of the usual cues available to the accommodation system during everyday viewing, may disadvantage those subjects who utilise other cues more effectively than blur.

The most comprehensive way to tackle the problems of artificial experimental conditions is to measure the accommodation response under normal binocular viewing conditions. In order for a true understanding of the accommodation response to be gained, a light and portable measuring device needs to be used in a natural environment during every day activities. It may be only at that point that the effect of accommodation in myopia can be fully realised.

In addition to the uncertainty as to whether MYOs actually experience larger lags of accommodation during near viewing is the equally pertinent question of whether such a small magnitude of blur can induce a change in axial length. Whilst the majority of studies use large amounts of defocus, small amounts have also been experimented with. No change in axial length was observed when +2.00 D was placed in front of one chick eye and -2.00 D in front of the other, however this was only conducted in one animal (Schaeffel, Glasser, & Howland, 1988). Schmid and Wildsoet (1997) used +1.00 D and -1.00 D in front of the eyes of 9 chicks and did report a compensatory change in axial length in comparison to controls. A similar effect has been demonstrated in monkeys where low levels of hyperopic anisometropia (+1.50 ± 0.40D) produced using photorefractive keratectomy (PRK) was overcome in 6 of 7 monkeys and this was mainly due to an increase in vitreous chamber depth of the more hyperopic eye (Zhong, Ge, Nie, & Smith, 2004). This evidence is supplemented by a recent paper presentation at the 13th International Myopia Conference where human adults showed a small but significant alteration in axial length in response to myopic and hyperopic defocus after 60 minutes (Read, Collins, & Sander, 2010). These studies suggest that small amounts of defocus such as those experienced by humans during reading could be sufficient to produce a change in axial length towards myopia.

Sensitivity to defocus

It was hypothesised by Schmid and Wildsoet (1997) that the dioptric threshold for stimulating eye growth in response to defocus could be the ocular depth of focus (DoF). The depth of field of the eye is the range within which a target can be moved without a conscious detection of defocus by the observer and the DoF is the corresponding amount of movement of the image plane that can be made before this occurs. DoF can be measured with both subjective and objective measurement types where subjective DoF is the amount of movement of the image plane that occurs before a subject consciously notices a change in image clarity and objective DoF is the smallest amount of blur that the visual system is able to detect. Subjective DoF measurements involve the subject indicating when the stimulus is blurred (Mordi & Ciuffreda, 1998; Rosenfield & Abraham-Cohen, 1999; Wang & Ciuffreda, 2004; Atchison, Fisher, Pedersen, & Ridall, 2005a). The objective DoF is dependent upon the optical aberrations degrading the retinal image and the internal neural noise of the visual pathway, which includes the retinal sampling limits as well as that of all post-retinal neurons involved in the interpretation of the visual signals. Therefore, objective DoF can be estimated by calculations based upon axial length and pupil diameter (Green, Powers, & Banks, 1980), visual acuity (Green

Subjective measures			Objective measures	
Study		DoF (D)		Study
Atchison et al., 1997	0.59		0.48	Collins et al., 2006
Atchison et al., 2005	0.61		0.20	Green et al., 1980[1]
Atchison et al., 2009	0.51		0.10	Green et al., 1980[2]
Atchison et al., 2010	0.37		0.24	Kotulak and Schor, 1986
Campbell, 1957	0.43		0.20	Ludlam et al., 1968
Kotulak & Schor, 1986	0.35		0.54	Mordi and Ciuffreda, 1998
Marcos et al., 1999	0.40		1.20	Vasudevan et al., 2006
Mordi and Ciuffreda, 1998	1.20		0.28	Winn et al., 1989
Ogle & Schwartz, 1958	0.70		0.18	Yao et al., 2010
Wang and Ciuffreda, 2004	0.89			
	0.61 ± 0.27	Average ± SD	0.38 ± 0.34	

[1] calculated DoF values based upon axial length and pupil diameter
[2] calculated DoF values based upon visual acuity

Figure 1. Previously measured objective and subjective values for central depth of focus (DoF, D). All subjective measurements involved movement of all or part of a high contrast target and subjects reported an alteration in image clarity. Subjective results are shown on the left of the table and graph. Objective measures are shown on the right.

et al., 1980) and aberration measurements (Collins, Buehren, & Iskander, 2006). Objective DoF is also estimated by measuring the smallest amount of dioptric change that elicits an accommodation response (Kotulak & Schor, 1986a; Mordi & Ciuffreda, 1998; Vasudevan, Ciuffreda, & Wang, 2006b, 2006a; Duffy, Day, Seidel, Gray, & Strang, 2010). This latter method of measurement could be thought of as an accommodation threshold, although it follows that if the accommodation system is able to respond to this level of defocus then it has been detected by the visual system. Some studies have used a combination of measurement and calculation to determine a threshold value (Jiang, 1997; Jiang & Morse, 1999). Figure 1 shows the findings of subjective and objective DoF in groups of subjects with an unspecified refractive error.

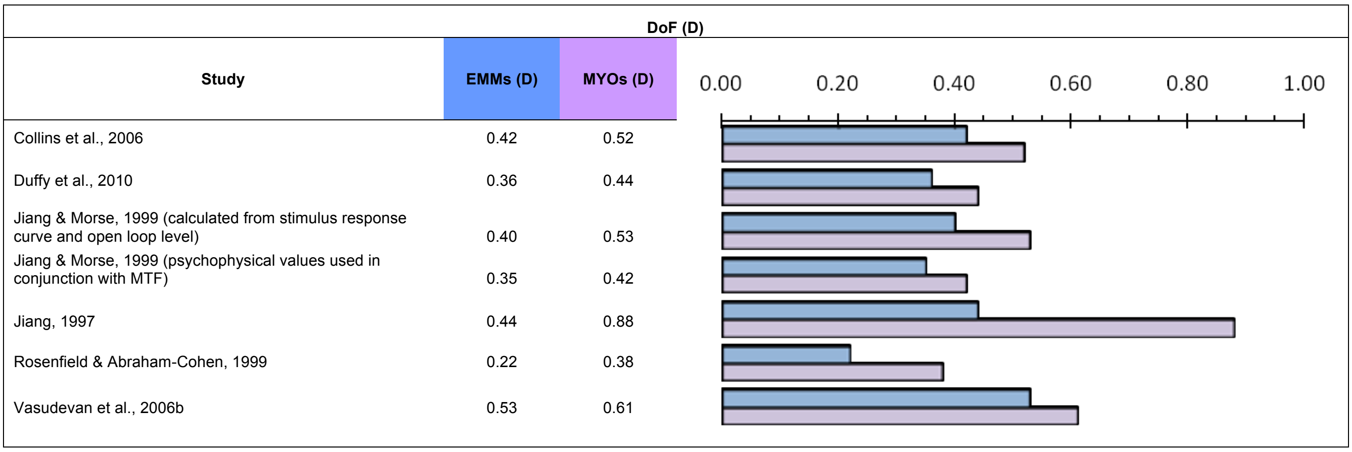
It is the objective rather than subjective DoF that is likely to be the relevant measure with respect to the threshold for eye growth and therefore any difference in this between refractive groups is potentially vitally important in understanding why an eye becomes myopic. It is currently difficult to know which of the methods, if any, measure the true intrinsic DoF, but nevertheless the results from these studies provide valuable information when comparing refractive groups. Both subjective (Rosenfield & Abraham-Cohen, 1999) and objective (Jiang, 1997; Jiang & Morse, 1999; Collins et al., 2006; Vasudevan, Ciuffreda, & Wang, 2006a; Duffy et al., 2010) studies have investigated refractive group differences in DoF, and all with the exception of two (Jiang & Morse, 1999; Duffy et al., 2010) have shown a significantly larger DoF in myopic (MYO) compared to emmetropic (EMM) subjects. Figure 2 shows a summary of the results of studies investigating the DoF in EMMs and MYOs.

A larger objective DoF would possibly be expected since the axial length elongation in myopia (Strang, Schmid, & Carney, 1998; Atchison et al., 2004) causes retinal stretching resulting in reduced visual performance (Atchison, Schmid, & Pritchard, 2006b). The DoF is also influenced by ocular aberrations, but there is currently limited evidence that the monochromatic aberrations are different in myopic subjects: they have been reported to be larger (He et al., 2002; Buehren, Collins, & Carney, 2005; Plainis & Pallikaris, 2008), smaller (Collins, Wildsoet, & Atchison, 1995; Carkeet, Luo, Tong, Saw, & Tan, 2002; Llorente, Barbero, Cano, Dorronsoro, & Marcos, 2004) and similar (Cheng, Bradley, Hong, & Thibos, 2003) to those of EMMs.

As mentioned, there are two studies that showed no difference in DoF between refractive groups. Rather than a high contrast target containing many different spatial frequencies (SF) as used in all the other studies, both of these used mid SF targets, and this could account for the differences in results. It has been reported that MYOs are less sensitive than EMMs to SF ≥ 8 cpd (Radhakrishnan, Pardhan, Calver, & O'Leary, 2004; Day, Gray, Seidel, & Strang, 2009a) and this could result in the relatively larger DoF in MYOs when viewing targets of mixed SF but not when viewing a target containing only mid SF information.

If MYOs do have a larger DoF and it is the DoF that is the threshold for stimulating eye growth then MYOs would require a larger magnitude of blur than EMMs before their axial lengths increased. In other words, if a MYO and an EMM experienced the same dioptric magnitude of blur which was larger than the DoF for the EMM but smaller than that for a MYO, then it would be the EMM whose axial length would increase. Studies showing that MYOs are less sensitive to defocus (Jiang, 1997; Jiang & Morse, 1999; Rosenfield & Abraham-Cohen, 1999; Collins et al., 2006; Vasudevan et al., 2006a), and this larger DoF, could lead to less accurate responses in MYOs and thus be the cause of the development and/or progression of myopia. As discussed earlier, however, larger accommodation lags in MYOs have not been universally reported and advances in equipment are needed to investigate this further.

An additional reason why the measurements and hypotheses described above are currently unable to explain why myopia develops, is that the visual experience is more complex than an amount of central defocus that exceeds the DoF being present for a certain duration of time. The DoF is constantly changing



Study	EMMs (D)	MYOs (D)
Collins et al., 2006	0.42	0.52
Duffy et al., 2010	0.36	0.44
Jiang & Morse, 1999 (calculated from stimulus response curve and open loop level)	0.40	0.53
Jiang & Morse, 1999 (psychophysical values used in conjunction with MTF)	0.35	0.42
Jiang, 1997	0.44	0.88
Rosenfield & Abraham-Cohen, 1999	0.22	0.38
Vasudevan et al., 2006b	0.53	0.61

Figure 2. Previously measured objective values for central depth of focus (DoF, D) in emmetropes (EMMs) and myopes (MYOs).

in magnitude, depending upon the SF content that is available within the cortical image, which in turn depends on numerous factors such as target luminance and pupil diameter (Day, Seidel, Gray, & Strang, 2009b). There are other sources of blur such as from the accommodation mircofluctuations, during fixational eye movements and accommodation steps, and importantly from the retinal periphery. These are discussed below.

Accommodation microfluctuations

The accommodation microfluctuations are relatively small oscillations in the power of the crystalline lens (Collins, 1937; Campbell, Robson, & Westheimer, 1959; Denieul, 1982; Kotulak & Schor, 1986c; Charman & Heron, 1988; Winn, Pugh, Gilmartin, & Owens, 1990a, 1990b; Collins, Davis, & Wood, 1995; Seidel et al., 2003). They are thought to monitor the contrast gradient of the edge profile of the cortical image (Day et al., 2009a; Day et al., 2009b), providing feedback to the accommodation control system so that it knows in which direction to respond. Theoretically, the microfluctuations need to be larger than the objective DoF in order for them to result in the necessary blur information, but they should not be noticeable by the observer and must therefore be smaller than the subjective DoF. Accordingly, experiments show that they alter systematically with the objective DoF (Day et al., 2009b), for example they increase when viewing low luminance targets (Gray, Winn, & Gilmartin, 1993b; Day et al., 2009b), through small pupils (Campbell et al., 1959; Gray, Winn, & Gilmartin, 1993a; Stark & Atchison, 1997; Day et al., 2009b) and low and high SF targets (Day et al., 2009a). Further, when they are measured in different refractive groups the accommodation microfluctuations are consistently larger in MYOs than in EMMs (Day et al., 2006; Langaas et al., 2008; Day et al., 2009a; Day et al., 2009b). This corresponds to the larger central DoF reported in MYOs (Jiang, 1997; Jiang & Morse, 1999; Rosenfield & Abraham-Cohen, 1999; Collins et al., 2006; Vasudevan et al., 2006a).

Since the visual system detects the blur produced by the microfluctuations during feedback, this blur could theoretically provide information that the eye responds to during axial length elongation in myopia. As discussed above, however, this is subject to the dependence of the response of human eye growth to the frequency and duration of a given blur signal. An animal study shows that changing blur at a fast temporal resolution (1 Hz) eliminates the effects of that defocus on eye growth in chicks (Winawer et al., 2005). The accommodation microfluctuations occur at frequencies up to 6 Hz (Denieul, 1982; Miege & Denieul, 1988) although the low frequency component, which is thought to contain the relevant feedback information, occurs at frequencies of up to 0.6 Hz (Denieul, 1982; Kotulak & Schor, 1986c, 1986b; Charman & Heron, 1988; Winn et al., 1990a, 1990b; Gray et al., 1993b, 1993a; Heron & Schor, 1995; van der Heijde, Beers, & Dubbelman, 1996; Gray, Gilmartin, & Winn, 2000). It is currently unknown whether the information extracted from the microfluctuations could be utilised by the visual system during eye growth and to date their potential influence on peripheral blur has not been explored.

Near work induced transient myopia (NITM)

During a period of prolonged near work, the accommodation system will adapt to the near level of accommodation response such that when the subject attempts to refocus to a distant target, a degree of myopia, or NITM, is temporarily induced. This induced myopia can last up to several minutes and its magnitude is on average 0.40 D, ranging between 0.12 D and 1.30 D (Ong & Ciuffreda, 1995; Ciuffreda & Wallis, 1998). Some individuals have been more susceptible to this effect than others and NITM has been found to vary between refractive groups (Ciuffreda & Wallis, 1998; Culhane & Winn, 1999; Ciuffreda & Lee, 2002; Vera-Diaz, Strang, & Winn, 2002; Wolffsohn et al., 2003a; Wolffsohn, Gilmartin, Thomas, & Mallen, 2003b; Ciuffreda & Vasudevan, 2008; Vasudevan & Ciuffreda, 2008). To summarise, these findings suggest that MYOs have a larger NITM (Ciuffreda & Wallis, 1998; Culhane & Winn, 1999; Ciuffreda & Lee, 2002; Vera-Diaz, Strang, & Winn, 2002; Wolffsohn et al., 2003a; Wolffsohn et al., 2003b), which has longer decay characteristics than EMMs (Vera-Diaz et al., 2002; Vasudevan & Ciuffreda, 2008), however this is complicated by issues such as different methodology and refractive group classification in different studies (for a review, see Ciuffreda & Vasudevan, 2008).

The prolonged hyperopic blur caused by this characteristic of the static accommodation response has been implicated in the possible development of myopia (Ciuffreda & Wallis, 1998), although the results of Vera-Diaz and colleagues suggest a greater role during myopia progression (Vera-Diaz et al., 2002). Either way, there seems to be an argument for a link between the presence of NITM and myopia (Ciuffreda & Vasudevan, 2008).

Attempts to eliminate defocus

Recent human studies have aimed to investigate whether hyperopic defocus is a cause for myopia by testing the potential treatments for this using spectacle correction. As described earlier, animal studies show that the eye responds preferentially to no blur (Norton et al., 2006; Kee et al., 2007) and to myopic blur (Winawer & Wallman, 2002; Winawer et al., 2005) over hyperopic blur, even if the hyperopic blur occurs for a much longer period of time (Winawer & Wallman, 2002; Norton et al., 2006; Kee et al., 2007). Attempts to alter the type of blur experienced by human subjects wearing their spectacles for different tasks and lengths of time throughout the day has however shown no effect upon the progression of myopia over a 3 year period (Ong, Grice, Held, Thorn, & Gwiazda, 1999). Further, under-correction of myopia, which would produce myopic defocus during distance viewing, has been reported to produce an increase instead of a decrease in myopia progression (Chung, Mohidin, & O'Leary, 2002; Adler & Millodot, 2006).

Studies using lenses that incorporate a reading addition (add), aim to produce clear distance vision whilst reducing the level of blur during reading. Unfortunately the majority of randomised controlled trials using bifocals have demonstrated no significant difference in myopic progression (Grosvenor, Perrigin, Perrigin, & Maslovitz, 1987; Jensen, 1991; Fulk & Cyert, 1996; Fulk, Cyert, & Parker, 2000), although bifocals have been shown to reduce progression in MYOs with esophorias at near (Fulk & Cyert, 1996).

A reduction in progression rate has been shown when using varifocals in comparison to single vision lenses (Leung & Brown, 1999), although the results have been questioned (Saw, Shih-Yen, Koh, & Tan, 2002b). A second study demonstrated no difference in progression rate between the two methods of correction (Shih, Hsiao, & Lin, 2000). A multi-centre randomised, double masked study of children did report a reduction in progression rate when wearing varifocals in comparison to single vision lenses over the first year, however myopia progressed for both groups: for the varifocal wearers by approximately -0.40 D and for those who wore single vision lenses by approximately -0.60 D in one year (Gwiazda et al., 2003). The difference in progression over the first year was statistically significant but was clinically small (0.18 D) and no further reduction in progression was observed beyond the first year.

One big problem with the above studies is that none of them reported the accommodative state whilst wearing these glasses and therefore the amount and magnitude of any defocus present during reading tasks is unknown. This is important since the basis for the use of near add spectacles is the hypothesis that a near add would reduce or eliminate the myopic defocus produced by a lag of accommodation. This has been recently addressed in a study where subjects wore reading spectacles with a +2.00 D or +3.00 D add and it was shown that subjects over-accommodated for near targets, even after 30 minutes of reading with the lenses (Shapiro, Kelly, & Howland, 2005). This suggests that, at least for 30 minutes of lens wearing, the subjects are exposed to myopic defocus which could theoretically reduce the amount of myopia by encouraging the eye to reduce in length towards the focal point.

It could be suggested that, rather than inducing myopic defocus, the aim of a near add lens should be to reduce the error at near to zero so that the subject would have clear near vision. Rosenfield and Carrel (2001) showed that the optimal near add lens to produce clear near viewing was correlated with the initial accommodation error before the introduction of the near lens, however this add altered the phoria to outside normal limits. A follow-up study not only correlated the near add to the initial accommodation error but also the initial near phoria and proposes that future studies should tailor the add to these two parameters for each individual (Jiang, Bussa, Tea, & Seger, 2008). Future studies are needed using lenses generated using these guidelines.

Peripheral defocus

Evidence for peripheral defocus mechanisms

Until very recently, the theories of myopia concentrated on the presence and effects of defocus at the macula. Interest in the peripheral retinal image and the differences in the magnitude of blur between the fovea and the periphery has resulted from findings that the peripheral eye shape is dependent upon refractive status (Logan et al., 2004; Atchison et al., 2005b; Atchison, 2006; Singh et al., 2006), and a recent theory of myopia development and progression (Flitcroft, 2006). During near work, accommodative lag results in a small amount of blur at the fovea. In contrast, a relatively large amount of blur is present in the retinal periphery. Flitcroft (2006) used a computer simulation of the visual environment to calculate the effect of central and peripheral blur at the retina. He hypothesised that the large amount of peripheral blur experienced during reading, in conjunction with retinal shape, could be the cause of myopia development and progression.

This hypothesis fits with the findings of animal studies that indicate a role of the peripheral retina, including a series of experiments undertaken by Smith and colleagues who have demonstrated that the periphery can control emmetropisation without a functioning fovea (Smith et al., 2005; Smith et al., 2007; Smith et al., 2009b; Smith et al., 2010). These studies not only show that the peripheral blur can induce axial length changes without the fovea, but that the eye can respond to hyperopic defocus in the periphery (Smith, Hung, & Huang, 2009a) and can do this independently in nasal and temporal fields, suggesting a local mechanism (Smith et al., 2010).

In order to put these findings into context in human observers, it is important to understand the role of the periphery on the accommodation system because monitoring the accommodation response is a non-invasive method of determining whether this system responds to peripheral information. A few studies have demonstrated an accommodation response to peripheral targets up to approximately 10 deg eccentricity (Hennessy & Leibowitz, 1971; Bullimore & Gilmartin, 1987; Gu & Legge, 1987; Hung & Ciuffreda, 1992; Duffy, Day, Seidel, Gray, & Strang, 2009). Blur adaptation has also recently been described in the periphery up to 10 deg (Mallen, Hussain, Mankowska, & Cufflin, 2010). These recent studies show an initial insight into the potential for the periphery to influence processes that were previously assumed to be functions of the central macula.

Other studies have measured the peripheral refraction in different refractive groups to test the hypothesis of whether the presence of hyperopic defocus in the periphery could drive axial elongation and development of a central myopic refractive error

Table 1
Summary of previous studies measuring peripheral refraction in emmetropes and myopes for 0.00, 1.00, 2.00 and 3.00 D of accommodation

Peripheral Refraction			Eccentricity (degrees)						
			Nasal			Central	Temporal		
Vergence level (D)	Refractive Group	Study	-30	-20	-10	0	10	20	30
0	EMMs	Calver et al., 2007	-1.31	-0.81	-0.50		-0.25	-0.19	-0.56
		Davies & Mallen, 2009	-0.87	-0.62	-0.50	-0.37	-0.62	-0.87	-1.00
	MYOs	Calver et al., 2007	-0.06	0.00	-0.13		-0.25	-0.38	-0.31
		Davies & Mallen, 2009	0.25	-0.25	-0.45	-0.45	-0.45	-0.45	-0.25
1	EMMs	Davies & Mallen, 2009	-0.50	-0.25	0.00	0.05	-0.10	-0.45	-0.60
	MYOs		0.45	0.25	-0.10	0.00	0.10	0.10	0.25
2	EMMs	Calver et al., 2007	-0.48	-0.19	0.22	0.26	0.06	0.06	0.25
		Davies & Mallen, 2009	-0.10	-0.10	0.05	0.40	0.00	-0.45	-0.55
	MYOs	Calver et al., 2007	0.60	0.52	0.58	0.69	0.75	0.63	0.88
		Davies & Mallen, 2009	0.55	0.30	0.05	0.10	0.10	0.10	0.30
3	EMMs	Davies & Mallen, 2009	-0.12	0.25	0.50	0.50	0.25	-0.12	-0.37
	MYOs		0.75	0.70	0.38	0.30	0.38	0.38	0.63

Note. EMMs = emmetropes; MYOs = myopes

(Millodot, 1981; Mutti, Sholtz, Friedman, & Zadnik, 2000; Seidemann, Schaeffel, Guirao, Lopez-Gil, & Artal, 2002; Atchison et al., 2006a; Calver, Radhakrishnan, Osuobeni, & O'Leary, 2007; Mutti et al., 2007; Davies & Mallen, 2009; Tabernero & Schaeffel, 2009; Sankaridurg et al., 2010b). All of these studies report a relative hyperopic defocus in MYOs that is not present in EMMs, with the exception of one (Calver et al., 2007). In the most extensive study, Mutti et al. (2007) showed that those who become myopic have relative hyperopia in the periphery 2 years before developing the myopia through to 5 years afterwards and that the amount of this peripheral hyperopia remains stable after the onset of myopia. Interestingly, the most rapid change in both central and peripheral refractive error happened in the year leading up to the start of myopia development. These findings suggest that peripheral hyperopia could be involved in the onset of myopia, but since it is present and unchanged for the 5 years after onset, its role at this point is uncertain.

Table 1 and Figure 3 provide a summary of the peripheral refraction measured in a couple of the studies mentioned above (Calver et al., 2007; Davies & Mallen, 2009). Table 1 provides a range of values whilst Figure 3 plots the average peripheral refraction of the results. These particular studies are relevant to this discussion since the subjects were not under cycloplegia and therefore show the true amount of blur present when EMM and MYO subjects view targets at 0.00, 1.00, 2.00 and 3.00 D. Many of the other studies use cycloplegia and/or display their results in terms of peripheral refraction relative to the fovea. Although it is useful to know the relative amount of defocus in the periphery, it is important to know the absolute level of blur experienced by observers at any given eccentricity during real life viewing. Studies investigating the effect of accommodation on the peripheral refractive profile in MYOs and EMMs demonstrate no change in relative peripheral refraction with accommodation, although as seen from Figure 3, the absolute level of blur increases due to an increased accommodative lag.

Further to the hyperopic blur in the periphery experienced by MYOs, recent studies have shown that the amount of peripheral defocus increases when subjects wear single vision lenses to correct central myopic ametropia (Tabernero, Vazquez, Seidemann, Uttenweiler, & Schaeffel, 2009; Lin et al., 2010). If hyperopic defocus is involved in the mechanism underlying myopia development, the increased hyperopic defocus when subjects are corrected with minus lenses could potentially cause the progression of myopia.

The data from these studies can be further analysed with respect to a 3.00 D visual scene. The data can be plotted assuming a typical near vision situation where someone is reading text at a distance of 33 cm in a room where the peripheral stimuli are effectively at infinity (see Figure 4 a). If the text is an A4 sheet of paper held in a portrait orientation, it subtends an angle of 17.5 deg either side of fixation, and the amount of blur experienced by the observer within 17.5 deg is equivalent to the peripheral re-

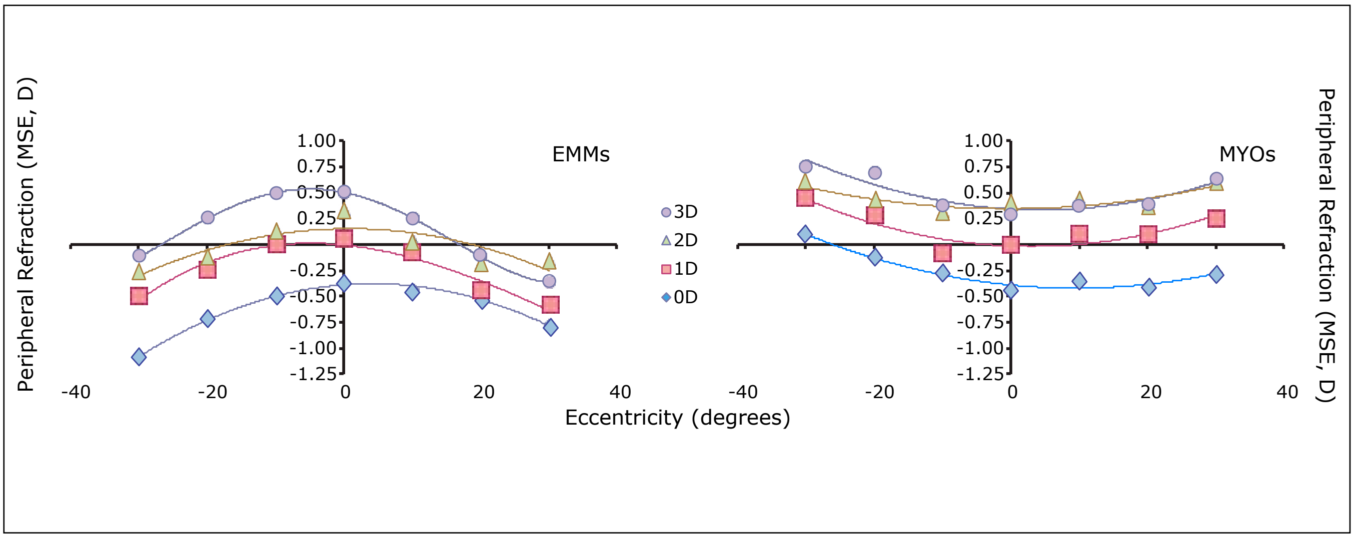


Figure 3. Summary of previous studies measuring residual refraction after correction of the distance prescription in emmetropes (EMMs) and myopes (MYOs) for 0.00, 1.00, 2.00 and 3.00 D of accommodation.

fraction measured for a 3.00 D stimulus. The blur experienced by the observer beyond 17.5 deg will be altered by 3.00 D since the observer is accommodating for a 3.00 D target but the vergence of the peripheral stimuli is 0.00 D. Figure 4 shows the resultant blur experienced by typical EMM and MYO subjects in this situation. It can be seen that within 17.5 deg there is little difference in blur experienced by the EMM and MYO, both being exposed to hyperopic defocus and further out than 17.5 deg both types of observer are exposed to a large amount of myopic defocus. If the situation is changed slightly, where the text extends 15 cm either side of fixation such as when reading a small newspaper, a magazine or using a laptop computer, the angle becomes 25 deg and refractive group differences start to emerge (Figure 4 b). At 20 deg EMMs are exposed to approximately 0.00 D blur while MYOs have approximately 0.50 D of hyperopic defocus. This would be of significance if the retina uses signals for growth at that eccentricity, if this is not overridden by the large magnitude of myopic defocus experienced further out in the periphery and if all of these magnitudes of defocus exceed the peripheral neural threshold for defocus.

Sensitivity to peripheral defocus

As with central defocus, the ability of the peripheral retina to detect defocus is important in understanding the possible threshold for eye growth. To date, investigations of peripheral DoF have been reported out to 50 deg (Ronchi & Molesini, 1975; Wang & Ciuffreda, 2004; Ciuffreda, Wang, & Wong, 2005) and are shown in Figure 5. The results show a linear increase in DoF with increasing eccentricity in all studies. Figure 6 plots the average subjective DoF with eccentricity in Figure 5 as a zone around the horizontal retinal ellipse along with the peripheral refractions for a 3.00 D target from Figure 3. The same DoF has been plotted nasally and temporally and for the EMM and MYO eye since individual measures have yet to be made. By plotting

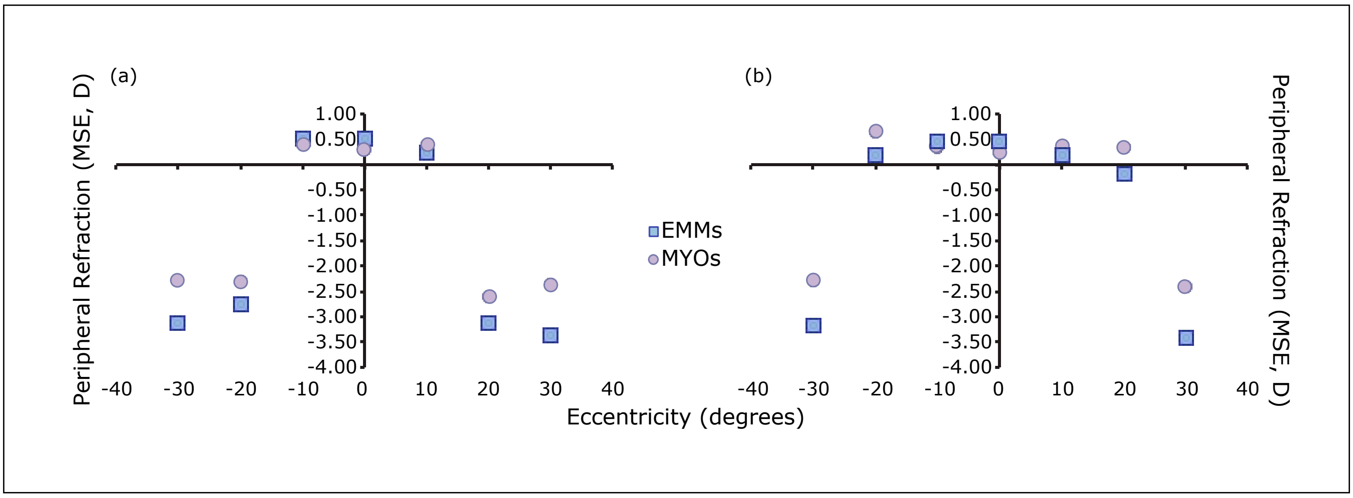


Figure 4. Estimated residual refraction after correction of the distance prescription for emmetropes (EMMs) and myopes (MYOs) while viewing reading text at a distance of 33 cm in a room where the other, peripheral, stimuli are at 0.00 D when the text is (a) an A4 sheet of paper held in a portrait orientation (10 cm or 17.5 deg either side of fixation) and (b) a small newspaper, magazine or laptop computer (15 cm or 25 deg either side of fixation). Peripheral refraction data uses data for 3.00 D accommodation level in Table 1 and Figure 3.

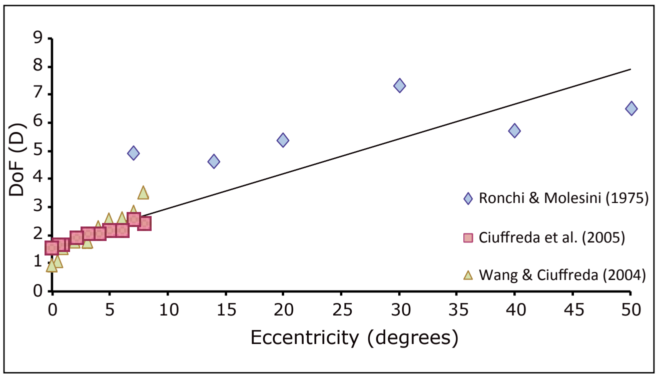


Figure 5. Subjective peripheral depth of focus (DoF) with eccentricity from previous studies and the linear fit for all data.

DoF and peripheral refraction together on an eye with realistic shape characteristics, it is easy to visualise what is happening. It can be seen that while the EMM gets exposure to myopic blur in the periphery, the -5.00 D MYO experiences hyperopic defocus. Any blur shown from the peripheral refraction that is outwith the DoF zone is likely to have the potential of providing a growth signal to the eye. Unfortunately, all of the DoF studies to date have used subjective methods of measurement and they are therefore likely to be larger than the equivalent objective measures that are more appropriate when trying to estimate a threshold for eye growth. This is evident when comparing the DoF at 0 deg on Figure 5 with the central DoF values seen in Figure 2. Further, there have been no measurements of peripheral DoF in different refractive groups thus far and future investigation is needed in this area of research before further conclusions can be made.

Luminance, pupil diameter and peripheral defocus

One counter argument to the association between near work and myopia is that those who spend more time reading spend less time outdoors and it could be that the outdoors acts as a protective effect against myopia. A significant number of papers have now substantiated the protective effect of the outdoors in epidemiological studies showing an association between the length of time spent outdoors and the prevalence of myopia (Mutti et al., 2002; Jones et al., 2007; Onal et al., 2007; Rose et al., 2008a, 2008b; Dirani et al., 2009). There does not seem to be a direct trade-off between the number of hours spent outdoors and reading (Jones et al., 2007; Rose et al., 2008a; Dirani et al., 2009), although this does not eliminate the possibility of an increase in distance viewing tasks when spending time outdoors.

Recent animal studies suggest that the light intensity is an important factor in myopia (Ashby, Ohlendorf, & Schaeffel, 2009; Ashby & Morgan, 2010). These studies show that, at least in chicks, high illuminance environments reduce the ocular growth to negative lenses and diffusers (Ashby et al., 2009; Ashby & Morgan, 2010), which may be produced by the effect of light on the release of dopamine by the retinal cells (Ashby & Morgan, 2010). In addition to affecting the axial length in these animals, the light intensity modulates the corneal curvature (Cohen, Belkin, Avni, & Polat, 2010).

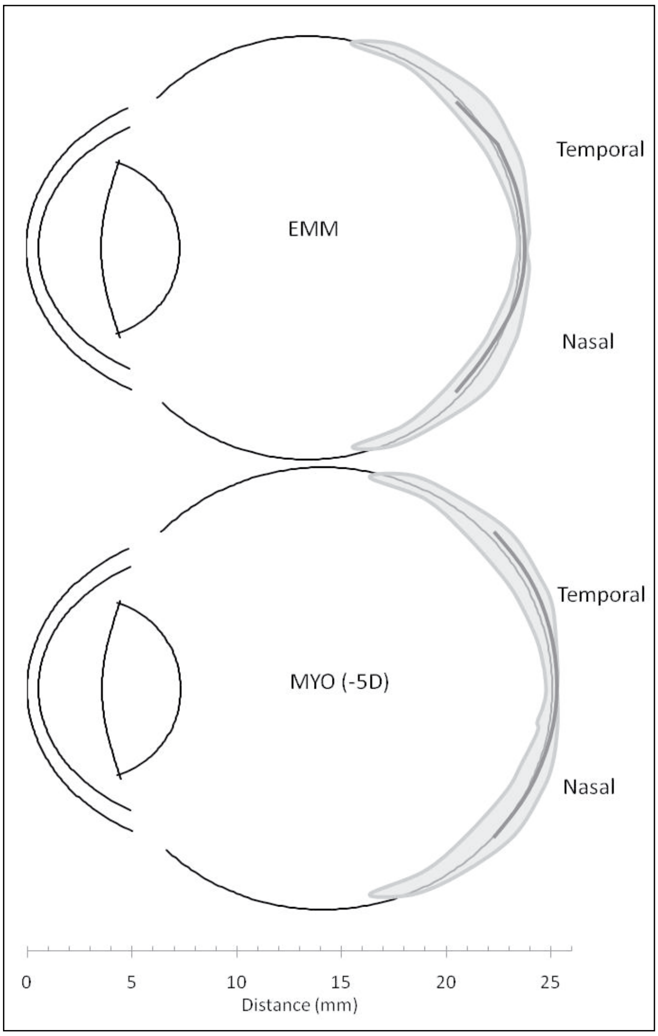


Figure 6. Average subjective peripheral depth of focus zone (from Table 2, Figure 5) and peripheral refraction at 3.00 D (from Table 1, Figure 3) plotted around the horizontal retinal profile of an emmetrope (EMM) and -5.00 D myope (MYO). The same subjective DoF has been used nasally and temporally and for the EMM and MYO eye since individual measures have yet to be made.

The pupil is obviously heavily involved when discussing the light intensity. It is known that the pupil diameter alters the DoF, although only for pupils < 2 mm in diameter (Campbell, 1957; Ogle & Schwartz, 1959; Charman & Whitefoot, 1977; Atchison, Charman, & Woods, 1997). In addition, the area of the retina that is illuminated will be affected, which is important if the amount of blur in the retinal periphery has an influence on myopia.

Attempts to eliminate peripheral defocus

As with central defocus, experimenters have conducted trials with spectacles and contact lenses aiming to reduce myopia by eliminating hyperopic defocus, but this time in the periphery (Tabernero et al., 2009; Ho et al., 2010; Sankaridurg et al., 2010a). Sankaridurg et al. (2010a) compared the effects of three different types of specially designed spectacle lenses with variable sizes of clear central zones and different powers of the peripheral zones with conventional spectacle lenses. Unfortunately they report no significant difference in myopia progression after 12 months in all four spectacle groups. Sankaridurg et al. (2010a) revealed that none of their three peripheral spectacle lenses showed any systematic change in the amount of peripheral hyperopic defocus induced to no lenses, which may explain their unsuccessful results. Similarly, spectacle lenses designed with a 3.00 D base curve either had no effect, or they increased or reduced the

Table 2

Subjective peripheral depth of focus with eccentricity from previous studies

DoF (D)	Eccentricity (degrees)															Linear fit	
Study	0	0.5	1	2	3	4	5	6	7	8	14	20	30	40	50	Formula	R^2
Ciuffreda et al., 2005	1.37	1.49	1.55	1.75	1.9	1.87	2.05	2.05	2.40	2.30						y = 0.12x + 1.44	0.94
Ronchi & Molesini, 1975									4.90		4.60	5.40	7.30	5.70	6.50	y = 0.04x + 4.60	0.46
Wang & Ciufredda, 2004	0.87	1.00	1.48	1.75	1.70	2.20	2.45	2.60	2.80	3.50						y = 0.29x + 0.98	0.96
Wang & Ciufredda, 2005 (detection task)	0.85			1.30		1.20		1.50		1.89						y = 0.11x + 0.89	0.88
Wang & Ciufredda, 2005 (discrimination task)	0.45			0.68		0.82		0.80		0.93						y = 0.05x + 0.52	0.87
Average of studies above	0.89	1.25	1.52	1.37	1.80	1.52	2.25	1.74	3.37	2.16	4.60	5.40	7.30	5.70	6.50	y = 0.12x + 1.71	0.77

Note. DoF = depth of focus. Linear fit equations for each dataset are provided as well as the linear fit for all data.

amount of peripheral hyperopic defocus at various eccentricities across the retina. However, spectacle lenses with an 8.00 D base curve reduced hyperopic defocus at all retinal locations. An additional problem that arises with spectacle lenses is that it is difficult to control the location of the peripheral blur on the retina due to eye movements (Drobe, 2010; Sankaridurg et al., 2010a). Further analysis showed potentially promising results in a subgroup of 6-12 year-olds with parents with myopia, and future studies are needed to consolidate and investigate these initial findings.

In contrast, a couple of studies have shown that contact lenses successfully induce myopic defocus in the periphery (Tabernero et al., 2009; Ho et al., 2010), although Tabernero et al. (2009) expressed concerns about the measurements of peripheral refraction in that study and further noted that the lenses contain peripheral distortion as a result of varying the power of the contact lens. At the recent myopia conference two studies reported initial promising results with contact lenses after 12 months (Holden et al., 2010; Lam, Tang, Tang, Tse, & To, 2010). Holden et al. (2010) reported that those wearing normal contact lenses and those wearing contact lenses to reduce the peripheral hyperopia showed myopic progression of -0.54 ± 0.37 D and -0.84 ± 0.47 D respectively, a -0.30 D difference in progression between these groups. Similarly a mean difference of -0.35 D was reported by Lam et al. (2010). It should be noted that in both cases the MYOs still progressed, but less progression was observed in those wearing the special peripheral contact lenses. In the closing discussions of the conference, Gwiazda pointed out that although these results are encouraging, they are very similar to the results observed with single vision lenses after 1 year (Gwiazda et al., 2003). In this 2003 study, no further reduction in progression was observed beyond the first year and therefore the myopia researchers need to wait with baited breath for future results.

Conclusions

The research summarised in this paper lends a large volume of evidence towards a role of defocus in eye growth. Studies considering central defocus alone have been unable to find a unified theory due to insufficient evidence showing refractive group differences in the amount of central defocus present and unsuccessful attempts to wholely reduce myopia progression using corrective lenses. The researchers in this field have recently turned to the investigation of peripheral defocus in which there is some encouraging evidence regarding increased peripheral blur in MYO observers, however future research measuring peripheral thresholds for defocus, understanding the exact influence of luminance in eye growth and novel ways to correct for the peripheral defocus are all needed before further conclusions can be made. Additionally, future discussions need to consider the potential impact of the periphery in more complex situations of everyday life where the eyes are constantly altering their focus and moving between objects at various distances.

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