Impact of Contrast Modulation on Retinal and Neural Processes in Myopia

DISSERTATION

der Mathematisch-Naturwissenschaftlichen Fakultät
der Eberhard Karls Universität Tübingen
zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)

vorgelegt von
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aus Plauen

Tübingen
2025

Gedruckt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Eberhard Karls Universität Tübingen.

Tag der mündlichen Qualifikation: 28.05.2025

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Acknowledgements

The completion of this doctoral thesis represents not only years of dedicated research but also the culmination of support, guidance, and encouragement from numerous individuals and institutions who have profoundly influenced this journey.

First and foremost, I would like to express my deepest gratitude to my supervisor, Prof. Dr. Siegfried Wahl, for providing the opportunity to undertake this thesis and for his support, guidance, and invaluable advice throughout my doctoral studies. I am also profoundly grateful to my second supervisor, Prof. Dr. Frank Schäffel, whose expert insights and constructive feedback have significantly elevated the quality and scope of this work.

My sincere thanks go to my colleagues at the ZEISS Vision Science Lab for fostering an environment of academic excellence and collaborative research. Their technical expertise, constructive discussions, and collegial support have greatly contributed to this work.

I would also like to acknowledge the essential contribution of all study participants, whose time and dedication made this research possible.

I am indebted to my family for their continued support throughout my academic pursuits. Special appreciation goes to my husband for his understanding and encouragement during the course of this work.

This thesis represents the culmination of support from all these individuals who have contributed to its completion.

Contents

Abbreviations

cpd cycles per degree

CSF contrast sensitivity function

D diopters

DIMS defocus incorporated multiple segments

DOT diffusion optics technology

ipRGCs intrinsically photosensitive retinal ganglion cells

LCA longitudinal chromatic aberration

L-cones long-wavelength sensitive cones

logMAR logarithm of the minimal angle of resolution

M-cells magno ganglion cells

M-cones middle-wavelength sensitive cones

MTF modulation transfer function

NTF neural transfer function

ONH optic nerve head

P-cells parvo ganglion cells

S-cones short-wavelength sensitive cones

SER spherical equivalent refractive error

Summary

Myopia, characterized by an excessively long axial eye length or an overly strong refractive power, has emerged as a global public health concern. From an individual perspective, uncorrected myopic refractive errors can reduce the quality of life and increase the risk of developing sight-threatening eye diseases, especially in high myopia. Furthermore, from a societal view, myopia prevalence is increasing worldwide, raising the need to counteract progressive myopia. Therefore, myopia and its associated complications are a high priority for research.

Current myopia management is based on environmental, behavioral, pharmacological, and optical control strategies. This dissertation seeks to understand the underlying mechanisms of an optical myopia control strategy that utilizes scattering, which induces image contrast reduction. Although a clinical trial of this approach has shown promising results, the mechanisms behind the strategy and its effectiveness remain unclear. Therefore, this dissertation examines short-term adaptation to scattering on contrast sensitivity, neural contrast sensitivity, choroidal thickness, axial length, and visual acuity. These short-term effects indicate a hint of long-term changes, which would be decisive for controlling progressive myopia.

In the first study, it was investigated how short-term exposure to peripherally induced scattering (Bangerter foil 0.4 and 0.8) affected central chromatic and achromatic contrast sensitivity. No contrast adaptation, defined by an increase in supra-threshold contrast sensitivity, was observed after exposure to both levels of peripherally induced scatter. Instead, there was a reduction in contrast sensitivity after 90 minutes of exposure to Bangerter foil 0.8. In the second study, it was tested how 30 minutes of adaptation to full-field scattering (Bangerter foil 0.8) determined neural contrast sensitivity and compared it with imposed positive defocus of +0.5 diopter. The dioptric power of defocus was matched to the scattering condition by a visual acuity reduction of 0.1 logarithm of the minimal angle of resolution. Neural contrast adaptation was found only for the scattering condition but not for defocus. Finally, the effects of peripheral and full-field scattering using sandblasted lenses of medium and high levels on choroidal thickness, axial length, and visual acuity were measured. Choroidal thickening was found after 60 minutes of adaptation to medium peripheral scattering, most pronounced in the superior peripheral retina, and to medium full-field scattering in the nasal central retina. Axial length and visual acuity were not affected by any of the scattering conditions.

The study results provide new insights into short-term adaptation to optically induced scattering on contrast sensitivity, choroidal thickness, axial length, and visual acuity. In the second and third studies, contrast adaptation was observed; however, not in the first study. Contrast adaptation effects would be sensitive enough to provide a signal for eye growth and therefore, refractive development, which could be useful in controlling myopia.

Zusammenfassung

Die Myopie, welche durch eine übermäßige Augenlänge oder Brechkraft gekennzeichnet ist, hat sich zu einem weltweiten Gesundheitsproblem entwickelt. Unkorrigierte myope Refraktionsfehler können einerseits die Lebensqualität beeinträchtigen und das Risiko der Entwicklung von Augenkrankheiten insbesondere bei hoher Myopie erhöhen. Andererseits ist aus gesellschaftlicher Sicht eine Zunahme der Myopieprävalenz weltweit zu beobachten, sodass ein dringendes Handeln erforderlich ist. Daher haben die Myopie und die damint verbundenen Komplikationen eine hohe Priorität für die Forschung.

Aktuell beruht die Myopiekontrolle auf umweltbedingten, verhaltensbezogenen, pharmakologischen und optischen Strategien. Ziel dieser Dissertation ist es, die zugrundeliegenden Mechanismen einer optischen Myopiekontrollstrategie zu verstehen, die auf der Reduktion des Bildkontrastes durch Streuung basiert. Obwohl eine klinische Studie vielversprechende Ergebnisse gezeigt hat, bleiben bezüglich der Funktionsweise dieser Strategie Unklarheiten bestehen. In dieser Arbeit wird daher untersucht, welche Auswirkungen eine kurzfristige Adaptation an die Streuung auf die Kontrastempfindlichkeit, neuronale Kontrastempfindlichkeit, Aderhautdicke, Achsenlänge und Sehschärfe hat. Diese Erkenntnisse sind wichtig, da sie Hinweise auf langfristige Veränderungen liefern können, die für die effektive Kontrolle der Myopieprogression von entscheidender Bedeutung sind.

In der ersten Studie wurde untersucht, wie sich eine kurzeitige Adaptation an peripher induzierte Streuung (Bangerter Folie 0.4 und 0.8) auf die zentrale chromatische und achromatische Kontrastempfindlichkeit auswirkt. Es wurde keine Kontrastadaptation, definiert durch die Zunahme der überschwelligen Kontrastempfindlichkeit, nach Adaptation an beide Level der peripher induzierten Bildstreuung beobachtet. Stattdessen nahm die Kontrastempfindlichkeit nach 90-minütiger Anpassung an die Bangerter Folie 0.8 ab. In der zweiten Studie wurde die neuronale Kontrastempfindlichkeit unter dem Einfluss einer 30-minütigen Adaptation an eine Vollfeldstreuung (Bangerter Folie 0.8) untersucht, und zu einer Defokussierung in Höhe von +0.5 Dioptrien verglichen. Die dioptrische Stärke der Defokussierung wurde so gewählt, dass die Sehschärfe in gleichem Maße reduziert wird wie bei der Streuung, um 0.1 Logarithmus des Minimalwinkels der Auflösung. Hier wurde eine neuronale Kontrastadaptation für die Streuung, jedoch nicht für die Defokussierung festgestellt. Schließlich wurden in der dritten Studie, die Auswirkungen der peripheren und der Vollfeldstreuung durch sandgestrahlte Gläser mittlerer und hoher Stärke auf die Aderhautdicke, Achsenlänge und Sehschärfe gemessen. Eine Verdickung der Aderhaut wurde nach 60-minütiger Adaptation an die mittlere periphere Streuung festgestellt, die in der oberen peripheren Netzhaut am stärksten ausgeprägt war. Die Adaptation an eine Vollfeldstreuung führte dabei zur kurzzeitigen Verdickung im Bereich der nasalen zentralen Aderhaut. Die Achsenlänge und Sehschärfe wurden durch keine

der Streuungsbedingungen beeinflusst.

Die vorliegenden Studien liefern neue Erkenntnisse über die kurzzeitige Adaptation an optisch induzierte Streuung in Bezug auf die Kontrastempfindlichkeit, Aderhautdicke, Augenlänge und Sehschärfe. In der zweiten und dritten Studie, wurden Kontrastadaptationseffekte beobachtet, jedoch nicht in der ersten Studie. Die Effekte der Kontrastadaptation sind möglicherweise ausreichend, um ein Signal für das Augenwachstum und damit die refraktive Entwicklung bereitzustellen, was potenziell zur Kontrolle der Myopieprogression beitragen kann.

List of publications

Accepted publications

[1] Neumann, A., Leube, A., Nabawi, N., Sauer, Y., Essig, P., Breher, K., & Wahl, S. (2022). Short-term peripheral contrast reduction affects central chromatic and achromatic contrast sensitivity. *Photonics, Mdpi*, *9*(3), 123. https://doi.org/10.3390/photonics9030123

[2] Roth, A., Breher, K., Domdei, N., & Wahl, S. (2024). Foveal neural adaptation to optically induced contrast reduction. *Journal of Vision*, *24*(9), 13. https://doi.org/10.1167/jov.24.9.13

[3] Roth, A., Breher, K., Gisbert, S., Arias, A., Clement, S. P., & Wahl, S. (2024). Peripheral contrast reduction optically induced by scattering lenses thickens peripheral choroid. *Translational Vision Science & Technology*, *13*(10), 32. https://doi.org/10.1167/tvst.13.10.32

Related publications, conference contributions and talks

Related reviewed publications

[1] Breher, K., Neumann, A., Kurth, D., Schaeffel, F., & Wahl, S. (2023). ON and OFF receptive field processing in the presence of optical scattering [Publisher: Optica Publishing Group]. *Biomedical Optics Express*, *14*(6), 2618–2628. https://doi.org/10.1364/BOE.489117

Conferences

[1] Neumann, A., Breher, K., & Wahl, S. Visual adaptation to different levels of peripheral optical scattering. In: *63*. (7). The Association for Research in Vision; Ophthalmology, 2022, 2564–F0518

[2] Neumann, A., Domdei, N., Breher, K., & Wahl, S. Short-term neural adaptation to optically induced scattering. In: *64*. (8). New Orleans, USA: The Association for Research in Vision; Ophthalmology, 2023, 1488–1488

Talks

[1] Neumann, A. Einfluss von peripherer Kontrastreduktion auf die zentrale Kontrastempfindlichkeit und auf die Akkommodation. In: Aalen, Germany: Arbeitskreis Ophthalmische Optik, 2021

Personal contribution

Publication 1: Short-term peripheral contrast reduction affects central chromatic and achromatic contrast sensitivity

Neumann, A., Leube, A., Nabawi, N., Sauer, Y., Essig, P., Breher, K., & Wahl, S. (2022). Short-term peripheral contrast reduction affects central chromatic and achromatic contrast sensitivity. *Photonics, Mdpi*, *9*(3), 123. https://doi.org/10.3390/photonics9030123

Contribution of the first author: Conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing — original draft preparation, writing — review, editing, and visualization.

Contribution of the other authors: Conceptualization, A.L., N.N., K.B. and S.W.; methodology, A.L., and K.B.; software, P.E. and Y.S.; formal analysis, K.B.; resources, S.W.; writing — review and editing, A.L., N.N., Y.S., P.E., K.B. and S.W.; visualization, K.B.; supervision, A.L., K.B., and S.W.; project administration, S.W.; funding acquisition, S.W.

Publication 2: Foveal neural adaptation to optically induced contrast reduction

Roth, A., Breher, K., Domdei, N., & Wahl, S. (2024). Foveal neural adaptation to optically induced contrast reduction. *Journal of Vision*, *24*(9), 13. https://doi.org/10.1167/jov.24.9.13

Contribution of the first author: Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing — original draft preparation, writing — review and editing, and visualization.

Contribution of the other authors: Conceptualization, K.B. and S.W.; methodology, K.B. and N.D.; software, N.D.; resources, S.W.; writing — review and editing, K.B., N.D., and S.W.; visualization, N.D.; supervision, K.B. and S.W.; project administration, S.W.; funding acquisition, S.W.

The authors express their gratitude to Augusto Arias for the optical characterization system provision and for conducting the corresponding tests.

Publication 3: Peripheral contrast reduction optically induced by scattering lenses thickens peripheral choroid

Roth, A., Breher, K., Gisbert, S., Arias, A., Clement, S. P., & Wahl, S. (2024). Peripheral contrast reduction optically induced by scattering lenses thickens peripheral choroid. *Translational Vision Science & Technology*, *13*(10), 32. https://doi.org/10.1167/tvst.13.10.32

Contribution of the first author: Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing — original draft preparation, writing — review and editing and visualization.

Contribution of the other authors: Conceptualization, K.B., S.G. and S.W.; methodology, K.B.; software, K.B., S.C. and A.A.; resources, S.W.; writing — review and editing, K.B., S.G. and S.W.; supervision, K.B. and S.W.; project administration, S.W.; funding acquisition, S.W.

1 Introduction

Myopia, defined by an excessively axial eye length or refractive power, has emerged as a global public health concern. In particular, uncorrected myopic refractive errors can reduce quality of life and increase the risk of developing sight-threatening eye diseases, especially in cases of high myopic refractive errors and extensive eye growth. In addition to the progression of myopia, the prevalence of this refractive condition is rising worldwide [Agarwal et al., 2020]. The need to counteract this increasing prevalence and the progression of myopia is a high priority for research. The following sections provide background information on the visual system and perception, refractive development, myopia control strategies, and their underlying mechanisms.

1.1 Visual system and perception

This section describes essential components of the human visual system and visual processing relevant to the dissertation topic.

1.1.1 Ocular structures

The eye is one of five sensory organs of the human body, surrounded by a bony structure [Sachsenweger, 2003]. Anatomically, it is divided into anterior and posterior segments of the orbit. The anterior part of the eye includes the eyelids, conjunctiva, cornea, anterior chamber, pupil, crystalline lens, zonular fiber, and ciliary body. The posterior eye segment contains the vitreous body, optic nerve head (ONH), and retina. The retinal pigment epithelium is surrounded by two additional layers: the choroid, which supplies blood to the retina, and the sclera, which serves as the protective covering of the eye [Lang and Lang, 2015; Sachsenweger, 2003]. To align with the objectives of this thesis, the primary focus will be on the retina and choroid.

The retina comprises the following layers, each with specific functions. These layers include the internal limiting membrane, which separates the retina from the vitreous body; the retinal nerve fiber layer, containing axons of ganglion cells forming the optic nerve; the ganglion cell layer, which consists of ganglion cells; the inner plexiform layer, enables contact between ganglion cells, bipolar cells, and amacrine cells; the inner nuclear layer, containing the cell nuclei of amacrine cells, bipolar cells, and horizontal cells; the outer plexiform layer, connecting horizontal and bipolar cells to rods and cones; the outer nuclear layer, including cell nuclei of rods and cones; the photoreceptor layers, comprising the outer and inner segments of rods and cones; and retinal pigment epithelium, which acts as the outer blood-retina barrier [Masland, 2001]. The adjoining Bruch's membrane separates the retina from the choroid.

The choroid is a sponge-like network of different blood vessels and stroma, which gives the fundus a red color due to its abundance of blood. The choriocapillaris, the network of choroidal blood vessels, supplies the retinal cells and the pigment epithelium with nutrients and oxygen. It also aids in removing waste products generated by photoreceptors and the retinal pigment epithelium, regulates retinal temperature, and absorbs excess light passing through the retina while reducing light scatter and enhancing image clarity [Sachsenweger, 2003].

The macula and ONH are two distinctive anatomical features of the retina. The macula is located slightly temporal to the eye's optical axis because of the angle κ. It has the highest density of cones, which decreases toward the periphery. The fovea centralis, at the center of the macula, consists only of middle-wavelength sensitive cones (M-cones) and long-wavelength sensitive cones (L-cones). In contrast, short-wavelength sensitive cones (S-cones), bipolar, and ganglion cells are shifted to the side. The ONH lacks vision-forming photoreceptors, but ganglion cell axons converge here to form the optic nerve. This area, also known as the blind spot, is only sensitive in the short-wavelength spectrum due to the photopigment melanopsin [Saito et al., 2018; Uhl et al., 2020].

1.1.2 Visual pathways

Light enters the eye and passes through several optical components before focusing on the retina, as summarized by Foley [2019]. The light initially passes through the cornea, crosses the anterior chamber with the aqueous humor, and enters the pupil. The crystalline lens refracts light, directing it into the vitreous chamber, which converges on the retina, ideally minimizing the point spread function to produce a sharp and detailed image. Light is converted from electromagnetic radiation into nerve signals within the retina. This process begins with the absorption of light by the outer segments of the photoreceptors, which are sensitive to wavelengths between 380 and 760 nm.

There are two main classes of photoreceptors: rods and cones. Rods containing the photopigment rhodopsin are abundant in the peripheral retina and sensitive to low light conditions (scotopic vision, $<$0.01 cd/m^2). Both rods and cones are involved in visual processing in medium light levels (mesopic vision, 0.01 to 3 cd/m^2). At the same time, cones, concentrated in the fovea, are responsible for vision under bright light conditions (photopic vision, $>$3 cd/m^2). Cones are further classified into three distinct types based on their spectral sensitivity: S-cones, $\sim$380 to $\sim$540 nm (peak at 420 nm); M-cones, $\sim$400 to $\sim$650 nm (peak at 534 nm); and L-cones, $\sim$400 to $\sim$700 nm (peak at 563 nm) [Bowmaker and Dartnall, 1980]. This trichromatic arrangement of cones allows the brain to interpret a wide range of colors by comparing the varying levels of cone activation across the visible spectrum. A third category of photoreceptors, the intrinsically photosensitive retinal ganglion cells (ipRGCs), contains the opsin melanopsin and has spectral sensitivity in the

short-wavelength range, peaking at 480 nm [Hankins et al., 2008]. Melanopsin percepts light unconsciously and synchronizes diurnal light cycles to the circadian rhythm in the body. It further depolarizes the membrane potential in contrast to rhodopsin.

Light absorption initiates a phototransduction cascade involving photoreceptor-specific opsins, transforming light into changes in membrane potential. The photoreceptors synapse onto ON or OFF bipolar cells via horizontal cells. Bipolar cells synapse with amacrine cells and ganglion cells. Action potentials are generated in the ganglion cells and propagated along their axons. In this process, signals of 125 million photoreceptors are converged to 1 million ganglion cell fibers, which form the optic nerve and extend to the visual processing centers of the brain. As the optic nerve fibers cross the optic chiasm, they become separated, with fibers from each retinal hemisphere crossing to the opposite hemisphere of the brain. The visual signals travel via the optic tracts to the lateral geniculate nucleus, which consists of layers of magno ganglion cells (M-cells) and parvo ganglion cells (P-cells). M-cells are sensitive to luminance differences and have higher temporal but lower spatial resolution, while P-cells are responsible for spatial resolution and color. From there, the information is relayed to the visual cortex, where it is processed and interpreted as an image [Mannu, 2014].

The retinal ganglion cells are arranged into distinct structures that form receptive fields. The receptive field of one cell refers to a specific region in space that elicits either excitation or inhibition in response to stimulation [DeAngelis et al., 1995]. Receptive field sizes are the smallest in the fovea and grow larger with distance from the center of the retina. This leads to the highest sensitivity to fine details in the fovea, which decreases as retinal eccentricity increases [Eysel, 2006]. Two types of receptive fields exist with either an ON or OFF structure. ON-center receptive fields increase their firing rate with increasing light in the center and dark in the OFF-surrounding and reduce it with decreasing light in the center. OFF-center receptive field with ON-surrounding act oppositely [Hashimoto et al., 2013]. Therefore, receptive field processing enables the perception of luminance differences and serves as a fundamental mechanism for contrast vision.

1.1.3 Visual function and contrast sensitivity

The ability to detect luminance differences can be determined by measuring contrast thresholds across spatial frequencies. Contrast is defined by differences in luminance between an object and its surroundings (Weber contrast, Equation 1) or by spatial variations in luminances, e.g., gratings (Michelson contrast, Equation 2). In these equations, I_{min} represents the minimum luminance intensity, and I_{max} corresponds to the maximum luminance intensity.

$$C_{\text{Weber}} = \frac{I_{\text{max}} - I_{\text{min}}}{I_{\text{min}}} \qquad (1)$$

$$C_{\text{Michelson}} = \frac{I_{\text{max}} - I_{\text{min}}}{I_{\text{max}} + I_{\text{min}}} \qquad (2)$$

The ability to identify a difference in brightness is referred to as the contrast threshold, while contrast sensitivity is the inverse of the contrast threshold [Pelli and Bex, 2013]. Contrast sensitivity can be characterized as a function of spatial frequency, known as contrast sensitivity function (CSF), and varies with the size, brightness, motion, and flicker of the test target [Kelly, 1977]. Spatial frequencies are specified in cycles per degree (cpd), whereby one cycle corresponds to a sine wave period within a one degree's visual angle. Sinusoidal patterns are commonly used as contrast stimuli [Kelly, 1977].

The visual system can be described as a bandpass filter, being most sensitive to contrasts between 2 and 5 cpd, with sensitivity decreasing for lower or higher spatial frequencies [Kelly, 1977]. Spatial frequency sensitivity depends on photoreceptor activation, density, and arrangement (associated with receptive field sizes), pupil size (affecting depth of focus), and accommodation (image focus) [Campbell and Green, 1965; Ohzu and Enoch, 1972], as these factors refer to the ability to perceive spatial details. Optical aberrations further influence contrast sensitivity by degrading image quality [Barten, 1999]. The optical modulation transfer function (MTF) can assess optical aberrations, which reflects an optical system's ability to reproduce object details in an image based on the contrast ratio over spatial frequencies. It is limited by the optics of the eye, such as the cornea, crystalline lens, straylight in the ocular media, and pupil diameter [Barten, 1999]. The MTF is the absolute value of the optical transfer function, derived from the Fourier transform of the pupil function. Photoreceptor arrangement, lateral inhibition, spatial summation, and cortical processing influence the neural component of the contrast sensitivity function [Elliott et al., 1996]. This function is also known as the neural transfer function (NTF), which can be assessed psychophysically using laser interferometry. This method circumvents the optical properties of the eye, directly stimulating the retina through a Maxwellian view configuration [Campbell and Green, 1965; Suchkov et al., 2021]. Here, a spatial light modulator uses a phase mask to split a coherent light source into two wavefronts, which are focused in the pupil plane and diverge to create interference fringes on the retina [Suchkov et al., 2021]. The neural contrast sensitivity peaks around 6 cpd, decreasing at lower and higher spatial frequencies [Michael et al., 2011], and is influenced by neural processing from the retina to the brain [Barten, 1999].

Consequently, the CSF comprises two components. The neural (NTF) and an optical (MTF) component, as described in Equation 3.

$$CSF = NTF * MTF \tag{3}$$

Psychophysical procedures are typically used to assess (neural) contrast sensitivity, which describes the relationship between a physical stimulus, e.g., Michelson contrast, and its perception by the sensory system [Fechner, 1860; Gescheider, 2013]. There are three main psychophysical methods [Gescheider, 2013]: the method of limits, constant stimuli,

and adjustment. In the method of limits, stimuli are presented in ascending (from invisible to visible) or descending (from visible to invisible) directions. The contrast threshold is defined as the mean of the ascending and descending limits. In interval-based procedures, the observer selects the interval containing the target stimulus from temporally different intervals of different stimulus categories. Alternative forced-choice involves presenting a specified number of alternatives simultaneously. The method of constant stimuli presented randomly preselected contrast values within an adaptive staircase procedure while the observer indicated if the stimuli were visible. The contrast threshold is determined by fitting the psychometric function using a maximum likelihood procedure, which records the response probability for each stimulus value ('visible' or 'not visible' contrast). In the adjustment method, the non-forced-choice contrast threshold is the minimum contrast that an observer can detect by initiating adjustment of the stimuli contrast above the expected threshold (invisible contrast stimuli) until the stimulus is barely seen. This method is quick but may be influenced by the observer's decision to identify a stimulus as visible. A high criterion shifts the threshold correspondingly higher, indicating low sensitivity, and vice versa [Lu and Dosher, 2013; Pelli and Bex, 2013].

Assessing contrast sensitivity helps to evaluate vision, detect visual impairments or changes in vision, and assess the efficacy of treatments.

1.2 Refractive development and myopia control

This section focuses on the definition and development of refractive errors, emphasizing myopia and strategies for controlling it.

1.2.1 Refractive errors of the eye

A refractive error occurs when the eye's refractive power and axial length do not align to focus an image on the retina. Three types of refractive errors are most common: myopia (nearsightedness), hyperopia (farsightedness), and astigmatism. In myopia, the eye is too long or has too much refractive power, causing light to focus in front of the retina. Hyperopia occurs when the eye is too short or has too little refractive power, causing the light to focus behind the retina. An irregular corneal curvature causes astigmatism and can occur together with hyperopia and myopia. Another type of refractive error is presbyopia, which results from the loss of accommodation and excludes short vision at close distances in emmetropic eyes. All these refractive errors can be corrected using conventional spectacles or contact lenses to refocus the incoming light on the retina to produce a sharp image. However, while these corrective methods improve vision, refractive errors, particularly myopia, can worsen over time. As discussed in the following sections, conventional methods do not address this issue.

1.2.2 Myopia onset, development, and structural changes

The eyes of vertebrates undergo the process of emmetropization during childhood and youth. Generally, humans are born with a hyperopic refractive error of around +2.00 diopters (D) [Wolffsohn et al., 2019]. As the eye grows from birth, it aims to reduce this refractive error and achieve a balance between its axial length and refractive state, known as emmetropia. However, if the emmetropization process fails, refractive errors such as hyperopia or myopia can result, primarily due to variations in axial eye length. Myopia usually develops from excessive axial eye growth, typically starting at 6 years of age and continuing until it stabilizes in the teenage years or early adulthood [Verkicharla et al., 2020]. The exact age of stabilization varies, ranging from 14 [Goss and Winkler, 1983] to 18 years [Goss and Winkler, 1983]. However, there may be further progression or even adult-onset myopia after the age of 20 [Bullimore et al., 2023; Goss and Winkler, 1983]. The age of myopia onset also determines the rate of progression. Earlier onset in childhood leads to faster progression, resulting in higher endpoint refractive errors and increased axial elongation, which raises the risk of developing eye diseases [Ohno-Matsui et al., 2021].

The reasons for myopia onset and progression include environmental and genetic factors. Preventive environmental factors for normal refractive development include spending more time outdoors, associated with higher illuminances, broader spectral composition, and its downstream effects such as dopamine-mediated growth regulation [Goldschmidt and Jacobsen, 2014]. Contrarily, indoor time is associated with lower illuminances and contrasts, which have been shown to contribute to myopia development [Walline et al., 2020]. A recent review showed that near-work accommodation does not play a role in this [Gajjar and Ostrin, 2022]. Exposure to visual stimuli triggers a signal cascade in the retina, involving retinal neurons and spatial frequency analysis. This process induces biochemical changes in the retinal pigment epithelium and choroid, reaching the fibroblasts in the sclera. By regulating the activity of scleral fibroblasts, the synthesis and degradation of the extracellular matrix can be controlled, leading to changes in the depth of the vitreous chamber. An increased vitreous chamber depth will lead to myopia development [Takkar et al., 2019]. Genetic factors are based on inheritance of parental myopia [Jones et al., 2007; Lopes et al., 2009], which may include mutations of middle- and long-wavelength cone opsins (OPN1MW or OPN1LW) [Hagen et al., 2019], and further genes associated with myopia as identified in genome-wide association studies [Hysi et al., 2014]. The latter offer insights into the molecular pathways that underlie this condition and show that genetic factors contribute to over half of the variation in refractive errors within populations [Lopes et al., 2009].

Challenges in preventing myopia onset and progression extend beyond conventional refractive error correction. This thesis focuses solely on axial myopia and axial elongation

as the primary drivers of progressive myopia without addressing lenticular changes, as the lens only changes in pathologies.

High myopia is clinically classified by a spherical equivalent refractive error of -6.00 D or less [D. I. Flitcroft et al., 2019]. It is associated with an enhanced risk of developing various eye diseases due to excessive axial elongation and structural changes in the posterior segment of the eye. Changes are induced in the retinal pigment epithelium, Bruch's membrane, choroid, ONH, peripapillary area, optic nerve, and sclera. These changes can lead to pathologies such as myopic macular degeneration, maculopathy, retinal detachment, choroidal neovascularization, cataracts, and glaucoma [Gilmartin, 2004; Ohno-Matsui et al., 2021], all of which pose a risk of irreversible blindness.

Monitoring changes in refractive error [Pan et al., 2012], contrast sensitivity [Liou and Chiu, 2001], axial length, and choroidal thickness [Ang et al., 2019; Breher et al., 2023; Nickla and Wallman, 2010; Ostrin et al., 2023; Sankaridurg et al., 2023] is crucial for determining the likelihood of developing myopia. In the choroid, a blood vessel containing tissue, thickness changes occur rapidly and precede long-term alterations in axial length. Choroidal thinning causes reduced oxygen and nutrient supply to the retina and sclera, which can lead to scleral hypoxia [H. Wu et al., 2018]. This triggers the upregulation of hypoxia-inducible factor 1-α [W. Wu et al., 2022], which in turn promotes axial elongation and contributes to progressive myopia.

1.2.3 Myopia control strategies

Current myopia control strategies are based on environmental, behavioral, pharmacological, and optical approaches [Gifford et al., 2019; Németh et al., 2021; Wolffsohn et al., 2023], which are explained in the following. Additional short-term adaptation studies supporting the understanding and potential effectiveness of these approaches are presented.

The environmental strategy of spending more time outdoors aims to prevent myopia onset and slow its progression [French et al., 2013; Xiong et al., 2017]. Research in humans indicates that spending 2 to 3 hours outdoors each day provides protective benefits [French et al., 2013; Jones et al., 2007]. Concurrently, cohort studies demonstrated that a lack of outdoor light exposure is associated with an increased risk of myopia progression [French et al., 2013]. Studies in chicken showed that the development of deprivation myopia was delayed when raised in high illuminance levels ($\sim$15000 or $\sim$30000 lux) compared to those raised under normal laboratory illumination ($\sim$500 lux) [Ashby et al., 2009]. The underlying mechanisms were attributed to retinal dopamine release resulting from light stimulation [Feldkaemper et al., 1999; Megaw et al., 1997; Witkovsky, 2004]. Other proposed mechanisms of time outdoors with limited experimental support include relaxed accommodation due to greater viewing distances [McBrien, Moghaddam, New,

and Williams, 1993], a more uniform dioptric range [D. I. Flitcroft, 2012], smaller pupil diameters due to enhanced pupil constriction [Ashby et al., 2009], exposure to ultraviolet light [Ashby et al., 2009; Hammond and Wildsoet, 2012], alterations in the spectral composition [Long et al., 2009] and increased physical activity [Ashby et al., 2009].

Low-dose atropine eye drops, available in different concentrations and formulations, are the major pharmacological interventions. Atropine inhibits the action of the neurotransmitter acetylcholine, which causes pupil dilation (mydriasis) and prevents the ciliary muscle from contracting [Chua et al., 2006] without affecting the accommodation mechanism [McBrien, Moghaddam, New, and Williams, 1993]. The exact mechanism atropine slows down myopia progression is not fully understood [Barathi and Beuerman, 2011; Barathi et al., 2009]. Dopamine, a retinal neurotransmitter, plays an essential role in myopia research as it is involved in the signal cascade that controls eye growth. The intravitreal application of dopamine agonists and the injection of dopamine have been demonstrated to inhibit experimentally induced myopia in several studies [Ashby et al., 2007; Q. Gao et al., 2006; Iuvone et al., 1991; McCarthy et al., 2007; Stone et al., 1989]. Another pharmacological strategy is the oral 7-methylxanthine application, a caffeine metabolite, which has been shown to slow eye growth in Danish children [Trier et al., 2023a]. This is reflected by a shortened vitreous chamber depth and increased choroidal thickness in rhesus monkeys [Hung et al., 2018; Smith et al., 2021; Tran et al., 2022].

Optical myopia control strategies include spectacle and contact lenses of different lens designs. The acceptance and tolerance of myopia control spectacles for children are high [Bao et al., 2022; Chamberlain et al., 2022; Lam et al., 2020], as they are non-invasive, allow clear central vision, and alter peripheral image characteristics [Y. Gao et al., 2021]. The hypotheses behind the current spectacle strategies are as follows:

(1) Mutations in either the middle- or long-wavelength cone opsins (OPN1MW or OPN1LW) result in abnormally high contrast signals at the retinal level [Hagen et al., 2019], affecting lower spatial frequency detection, as lower spatial frequencies control emmetropization [E. L. Smith et al., 2007; Swiatczak and Schaeffel, 2021]. A novel lens design, ”diffusion optics technology (DOT)” (SightGlass Vision Inc., USA), uses peripheral scattering while maintaining a clear central zone of 5 mm to reduce the peripheral retinal image contrast and consequently contrast signaling on the retinal level. The CYPRESS clinical trial (NCT03623074) reported reduced axial elongation and refractive development in 6- to 7-year-old children wearing DOT lenses when compared to a control group wearing single-vision lenses [Chalberg et al., 2023; Laughton et al., 2023]. Two different designs of the DOT lenses were tested; test 1 (commercially called DOT 0.2) featured a microscopic diffuser spacing of 0.365 mm, while test 2 lens had a diffuser spacing of 0.240 mm. The test 1 lens has prevailed, and the test 2 lens has been dropped [Chalberg et al., 2023]. The following report refers to the test 1 DOT lens, demonstrating promising results in controlling myopia progression [Chalberg et al., 2023]. After 36 months, children

treated with DOT lenses showed less myopia progression than the control group wearing single-vision lenses (axial length difference: 0.24 mm, p=0.01, spherical equivalent refractive error (SER) difference: 0.56 D, p=0.003) [Laughton et al., 2023]. From 36 to 42 months, the treated group showed a difference of 0.04 mm in axial length (p=0.013) and 0.09 D in SER (p=0.051) compared to the control group, indicating less myopia progression within the treated group [Chalberg et al., 2023].

Initial experiments on animal models, such as tree shrews, rhesus monkeys, guinea pigs, and chickens, showed that retinal image contrast degradation causes excessive axial eye growth and, thus, myopia development [Bowrey et al., 2015; Sherman et al., 1977; Wallman et al., 1978; Wiesel and Raviola, 1977]. In an attempt to restore a focused image, additional eye growth is triggered, but it caused increased blurriness in an open-loop fashion. The eye continues to elongate without a mechanism to stop it. The reduction in contrast of the retinal image is believed to cause deprivation myopia with a dose-response relationship [Bartmann and Schaeffel, 1994; Smith III and Hung, 2000]. Reduced image contrast can contribute to myopia development, making the analysis of retinal image quality essential. The question remains as to how humans respond to contrast reduction.

Image contrast reduction by a diffuser represents an open-loop condition for emmetropization. No matter which direction the eye grows, the retinal image does not improve [Schaeffel and Howland, 1991]. Further studies have shown that locally induced retinal image degradation triggers eye growth and causes deprivation myopia [Wallman et al., 1987]. Peripheral imposed defocus induced central refractive errors [Pierro et al., 1992; Radhakrishnan et al., 2013; E. L. Smith et al., 2005; Wallman and Winawer, 2004], making the retinal periphery a focus of interest in myopia research and management [Seidemann and Schaeffel, 2002; E. L. Smith et al., 2005]. A recent study found the near peripheral retina (6-10°) is most sensitive to blur [Swiatczak et al., 2024]. This does not rule out that the fovea is involved in the emmetropization process, although it is less sensitive to induced changes. These contradictory findings in animal models and humans highlight a gap in understanding the underlying mechanisms.

(2) Degradation of the retinal image caused axial eye growth and myopia development in animal experiments [Sherman et al., 1977; Wallman et al., 1978; Wiesel and Raviola, 1977]. Consequently, it has been hypothesized that focusing the light onto the retina improves the contrast and sharpness of the retinal image, providing a signal to stop axial eye growth [Norton and Siegwart, 1995; Read et al., 2010]. In line with this hypothesis, the required optical strategy involved imposing peripheral positive defocus using spherical or aspherical lenslet designs (e.g., defocus incorporated multiple segments (DIMS) lenses) while maintaining a clear central aperture. This intervention aims to reduce the axial growth rate by inducing positive defocus [Chakraborty et al., 2013; Read et al., 2010].

Imposed positive defocus represents a closed-loop system, while eye shortening improves

image quality in myopic eyes [Read et al., 2010] because a closed-loop system uses retinal image blur as an error signal for eye growth. In contrast, induced hyperopic defocus, achieved by negative lenses, in which the focal plane is placed behind the retina, induces myopia in animal models [Wallman et al., 1978].

(3) Reducing the lag of accommodation to reduce hyperopic defocus during near work, thereby slowing myopia progression [Charman, 1999], e.g., with progressive addition lenses as evaluated in the COMET clinical trial (NCT00000113). The hypotheses indicate that an increase in retinal defocus contributes to myopia progression. In animal models, continuous exposure to defocus is linked to myopia development [Gwiazda et al., 1993; Norton and Siegwart, 1995; Wildsoet, 1997]. Also, high accommodation lag at near vision is associated with myopia in humans [Abbott et al., 1998; Gwiazda et al., 1993]. The success of the lenses is measured by the vital outcome parameters SER and axial length.

Orthokeratology is another optical treatment that uses special rigid contact lenses worn overnight to reshape the cornea. This temporarily flattens the central cornea, correcting refractive errors for clear daytime vision without lenses, and creates a peripheral myopic defocus that helps slow axial elongation of the eye [Cho and Tan, 2019].

1.2.4 Retinal ON and OFF pathways

The ON and OFF pathways contribute to the emmetropization process, although they exert selective effects on eye growth and myopia development. It has been demonstrated that the stimulation of the ON pathways is linked to choroidal thickening and retinal dopamine release, which may reduce the gain of excessive eye growth [Aleman et al., 2018]. Disruptions in the ON pathway lead to deficits in visual function and dopamine signaling [Aung et al., 2022]. The level of retinal dopamine, in turn, is considered necessary in controlling eye growth, while increased levels are associated with reduced eye growth [Feldkaemper and Schaeffel, 2013]. On the contrary, the stimulation of the OFF pathway leads to choroidal thinning and axial elongation [Aleman et al., 2018; Wang et al., 2019].

A decrease in retinal image contrast leads to reduced firing rates of ON- and OFF-bipolar cells [M. Neitz et al., 2022], as well as to a reduction in abnormal high retinal contrast signaling caused by mutations in cone opsins (OPN1MW and OPN1LW) [Hagen et al., 2019]. Clinical trials of the contrast-reducing DOT lens have indeed reported slowed axial elongation [Chalberg et al., 2023; Rappon et al., 2023]. Although several studies have shown that retinal image contrast might be involved, the underlying mechanisms are inconclusive [Breher et al., 2023; Ohlendorf and Schaeffel, 2009].

Understanding retinal image contrast modulation and further processing related to contrast adaptation, axial length, and choroidal thickness can provide insights into underlying mechanisms. This understanding can be used to evaluate existing optical myopia control strategies and develop new interventions.

2 Objectives and expected outcomes

Available publications on the effect of contrast reduction induced by scattering on contrast sensitivity, axial length, or choroidal thickness are limited. Most studies are based on animal models with ex-vivo analysis or short-term human experiments. In these studies, contrast adaptation, defined as a spatial frequency-selective increase of supra-threshold contrast sensitivity, was measured centrally after central adaptation or peripherally after peripheral adaptation to retinal image contrast reduction. With short-term contrast adaptation, axial length shortening and choroidal thickening may serve as promising biomarkers to predict the long-term effects on myopia progression. Given the lack of conclusive information regarding retinal and cortical processing when image contrast is reduced, further studies were performed to evaluate short-term exposure to contrast reduction via scattering regarding contrast adaptation and structural changes.

(1) In the first study, the effect of peripheral-only contrast reduction, induced by Bangerter foils of different levels (0.4 and 0.8), was investigated on central chromatic and achromatic contrast sensitivity. The psychophysical findings provide a basis for future research, as contrast adaptation was measured in the retinal center, following central adaptation, or in the retinal periphery after peripheral adaptation to contrast reduction. However, it has not been measured centrally after peripheral contrast reduction. This research aims to understand peripheral retinal image contrast on central cone-specific contrast sensitivity and contrast adaptation, where stimuli are designed to align with the peak sensitivity of specific cone types (S, M, or L) using the silent substitution method.

(2) In the second study, neural processing in terms of neural contrast sensitivity was examined in response to short-term adaptation to a full-field contrast reduction, induced by scattering (Bangerter foil 0.8) and positive defocus (+0.5 D). Optically induced scattering causes light to scatter and reduces image contrast. Defocus conditions, achieved with e.g. spherical lenses, result in light rays focusing either in front of or behind the retina, leading to contrast reduction due to blurred vision. This study aims to identify changes in neural contrast sensitivity following exposure to scattering or defocus, which are relevant to optical strategies for myopia control. The findings may provide valuable insights into the neural mechanisms involved in ocular growth regulation.

(3) The objective of the third study was to explore changes in central and peripheral choroidal thickness, foveal axial length, and visual acuity following exposure to full-field and peripheral-only contrast reduction conditions, induced by scattering via sandblasted lenses of two different levels. The results can help deduce possible regional changes, highlight the importance of specific retinal areas for myopia research, and determine the necessary amount of contrast reduction.

3 Results and discussion

The main objective of this dissertation was to explore the mechanisms behind short-term adaptation to contrast modulation, both in peripheral-only and full-field scenarios, induced by scattering. Three studies were conducted to investigate the effect of optically induced scattering on 1) contrast sensitivity, 2) neural contrast sensitivity, and 3) choroidal thickness, axial length, and visual acuity to further characterize fundamental structures and signal cascades related to myopia progression. The findings and results of this research have been published in three publications, which are included in the appendix. The following sections present and discuss contributions to existing research and the potential of this approach as a future myopia control strategy.

3.1 Summary of publications

The following sections provide a summary of findings, described in the three publications.

3.1.1 Publication 1: Short-term peripheral contrast reduction affects central chromatic and achromatic contrast sensitivity

The underlying mechanisms of contrast reduction optically induced by scattering on contrast sensitivity are mostly unclear and partly contradictory. The primary objective of the first study was to determine whether varying levels of peripheral-only contrast reduction caused by scattering impact on central visual performance. Specifically, it was investigated how the short-term adaptation of peripheral contrast reduction induced by scattering affects central chromatic and achromatic contrast sensitivity at the spatial frequencies of 3 and 12 cpd. On the one hand, an increase in contrast sensitivity (contrast adaptation) would indicate the potential success of the applied lens design [Ghosh et al., 2017; Ohlendorf and Schaeffel, 2009]. On the other hand, a difference in contrast adaptation between the cone-specific stimuli would suggest that particular cones are more or less responsive to scattering [Hagen et al., 2019].

Peripheral contrast reduction was achieved using light-scattering Bangerter foils of densities 0.4 and 0.8 while preserving a clear central zone of 8 mm diameter and compared to a clear lens control condition. Bangerter foils were inserted into a trial frame containing the individual's sphero-cylindric correction using a plane lens and were worn for 90 minutes each. The achromatic and chromatic contrast sensitivity (peaking at S-, M- and L-cone sensitivity) was measured after 0, 30, and 90 minutes of lens wear using a self-designed two-interval forced-choice psychophysical test. Cone-specific contrast stimuli were created using the silent substitution method [Estévez and Spekreijse, 1982; Taylor et al., 2018] by modulating red, green, and blue channels of the presentation screen to selectively target

a specific cone type corresponding to their peak sensitivity [Stockman et al., 1993, 1999; Taylor et al., 2018].

The two tested scattering levels similarly influenced chromatic and achromatic contrast sensitivity, with a significant contrast sensitivity reduction after 30 and 90 minutes of lens wear, independently of the spatial frequencies tested. However, the lower level of induced scattering (Bangerter foil 0.8) led to an elevated reduction in contrast sensitivity compared to the high scattering condition (Bangerter foil 0.4) and clear control condition. The results show that a low scattering condition impacts the contrast sensitivity more. However, a reduction in contrast sensitivity was found rather than an increase.

Significant differences between cone-specific contrast sensitivity were found, as expected, due to the retinal topography of the photoreceptors, except for the achromatic and L-cone types. However, the responses of M- and L-cones to M- and L-cone type stimuli cannot be separated due to their large spectral overlap [Stockman and Sharpe, 1999; Stockman et al., 1993].

3.1.2 Publication 2: Foveal neural adaptation to optically induced contrast reduction

Recent studies focused on the optical characterization of myopia control lenses. DOT and DIMS lenses were investigated, whereby a reduction versus an increase in contrast and sharpness (gradient magnitude) was found, respectively [Arias et al., 2023]. This helps to understand which image properties are generated through the lenses. However, it is not completely clear how the optical properties further limit the image quality and how this influences the neural part of the contrast sensitivity function.

In addition to the optical characterization by Arias et al. [2023] and to the current first study, the second study aimed to investigate the effect of full-field retinal contrast reduction optically induced via scattering (Bangerter foil 0.8) and defocus (+0.5 D) on neural contrast sensitivity at the spatial frequency of 6 cpd. The dioptric power of defocus was matched to the scattering condition by a visual acuity reduction of 0.1 logarithm of the minimal angle of resolution (logMAR), but the MTFs remained unmatched. The additional optical characterization, measured in terms of the MTF of the scattering and defocus conditions, allows for the evaluation of the impact on spatial frequency information. The experimental conditions and a clear control condition were applied binocularly to the individual sphero-cylindric correction.

The measurement of neural contrast sensitivity was performed with an interferometric system that allowed for aberration-free stimulus generation at the level of the retina. Consequently, the optics of the eye are bypassed. The psychophysical test procedure was based on the adjustment method, with six stimulus presentations required for each measurement run. A measurement session was performed before and after

each 30 minutes of lens wear to calculate changes in neural contrast sensitivity. The findings enable the evaluation of differences in neural processing, the relationship between scattering and defocus, and whether using such strategies could benefit myopia control. The changes in neural contrast sensitivity were analyzed over time to determine the time course of adaptation.

The results showed a significant change in neural contrast sensitivity from baseline after exposure to scattering, based on the average of the first three measurements after lens wear, which was also significantly increased compared to the control condition. The adaptation effect observed did not persist in the average of the last three post-adaptation measurements. Furthermore, the changes in neural contrast sensitivity between the control and defocus lens conditions were found to be non-significant. Time-dependent measurements showed that neural contrast sensitivity significantly increased 25 ± 12.5 seconds after exposure to scattering, compared to the control condition. Although the increase in neural contrast sensitivity was most pronounced with scatter, these aftereffects were short-lasting.

3.1.3 Publication 3: Peripheral contrast reduction optically induced by scattering thickens peripheral choroid

Short-term changes in choroidal thickness and axial length, two key biomarkers in myopia research, are assumed to predict long-term eye growth regulation and, thus, the success of myopia control strategies. Choroidal thickening and the axial length's shortening may reduce myopia progression in the long term, whereas choroidal thinning and axial elongation reflects myopia progression [Swiatczak et al., 2024].

Therefore, the third study aimed to investigate changes in choroidal thickness, axial length, and visual acuity after short-term exposure to scattering induced by sandblasted spectacle lenses, which reduce retinal image contrast, in young adults. Additionally, regional changes in choroidal thickness were explored in response to peripheral-only and full-field scattering induced by sandblasted lenses, each with medium and high scattering levels. The findings may explain whether scattering related to retinal image contrast modulation can influence choroidal thickness, axial length, and visual acuity.

Clear single-vision spectacle lenses incorporating the sphero-cylindrical correction of the participants were sandblasted in a specified facility (Sigg Strahltechnik GmbH, Lauchingen, Germany) to generate scatter. A medium scattering condition was established by sandblasting these lenses for 25 seconds, while the high scattering condition involved sandblasting for 30 seconds. A clear central zone of 8 mm diameter was implemented to create peripheral conditions, compared to full-field conditions without a clear aperture. The four types of scattering and the additional clear lens control condition were optically characterized, and the levels aligned in terms of the modulation transfer function using

spatial light modulation. The point spread function of each lens condition was generated using a laser of 532 nm wavelength and an artificial pupil of 6 mm diameter. The Fast Fourier Transformation was then applied to the point spread function to calculate the radial MTF. The experimental lenses were placed in front of the right eye, while the left eye was covered by a full-field sandblasted lens that only allowed light perception.

All experimental lenses were tested on separate days in random order at the same daytime (between 8 and 11 A.M.) to avoid that diurnal factors confounding the results. Choroidal thickness, axial length, and visual acuity were measured before and after each 60-minute lens wear phase to calculate subsequent changes. It was found that choroidal thickening in the angular region between 28° and 39° was most pronounced in the superior part after exposure to medium peripheral scattering compared to the control condition. In the central choroid (angular region up to 21° viewing angle), significant thickening was observed only in the nasal part after exposure to the medium full-field scattering condition compared to the control condition. High peripheral and full-field scattering conditions did not alter choroidal thickness significantly.

Axial length and visual acuity were not significantly affected by the 60-minute wear of the experimental lens conditions. Due to the resolution limitations of the axial length measurement device and the expected standard deviation of visual acuity of 0.1 logMAR, assessing small changes is challenging, which may have resulted in non-significant outcomes.

In the third study, the dose-response relationship was examined to determine if the scattering level is directly related to the change in choroidal thickness and axial length. The results did not support a dose-response relationship based on two included scattering levels, as only the medium scattering condition affected choroidal thickness. At the time of the investigation, this was the first study investigating the effect of scattering conditions, both with and without a clear central zone, on these parameters. Specifically, a general peripheral choroidal thickening was found after exposure to the medium peripheral scattering condition, with the most pronounced effect in the superior retina. The nasal central choroid also thickened after exposure to the medium full-field scattering condition, without affecting the superior, temporal, and inferior central retina. Therefore, the findings indicate that a local retinal contrast detection mechanism signals the choroid to thicken, particularly in the peripheral retina. This aligns with current optical myopia control designs, which target the peripheral retina while leaving the central retinal image unobstructed.

3.2 Contribution to science and prospects

The three projects presented in this thesis contribute to understanding myopia control strategies. They describe the role of contrast modulation on visual performance and ocular structures. The following paragraphs detail the specific contributions of the work.

3.2.1 Impact of peripheral contrast reduction induced by scattering on central contrast sensitivity

Optical myopia control strategies are designed to influence the retinal periphery, leaving the central retina, the fovea, unstimulated. Their effectiveness is supported by animal and human studies [Chakraborty et al., 2013; Chalberg et al., 2023; Q. Gao et al., 2006; Laughton et al., 2023; Read et al., 2010; Swiatczak et al., 2024; Wallman and Winawer, 2004; Wildsoet et al., 2019]. One possible explanation for this assumption is that more neurons exist in the retinal periphery, which could overlay the signals from the fovea and thus affect overall eye growth [Smith III and Hung, 2000; Wallman and Winawer, 2004]. Another consideration is that if there is a local signal from the retina to the underlying sclera, stimulating the fovea would result in a localized change in scleral growth [Wallman et al., 1987].

The myopia control lens designs induce either scattering, as in the DOT lens, or myopic defocus, such as in the DIMS lens. A significant slowing in progressive myopia has been reported for both strategies [Jonas et al., 2021]. While visual responses to defocus are extensively researched, the effects of scattering on visual performance are less explored. Previous studies on human eyes have shown bidirectional results to defocus: imposed myopic defocus leads to contrast adaptation (increase in supra-threshold contrast sensitivity), whereas hyperopic defocus had no effect [Ohlendorf and Schaeffel, 2009]. Contrast adaptation to scatter was previously measured centrally following central adaptation [Blakemore and Campbell, 1969; J. M. Foley and Boynton, 1993; Y. Gao et al., 2019; Greenlee et al., 1991; Teoh et al., 2020, 2021; Villa-Carpes et al., 2021; D. W. Williams et al., 1982] or peripherally following peripheral exposure [Y. Gao et al., 2019; Greenlee et al., 1991; Sharpe and Tolhurst, 1973; D. W. Williams et al., 1982] but not centrally after the peripheral exposition.

The first study addressed this gap by investigating the effect of peripheral contrast modulation induced by Bangerter foils 0.4 and 0.8 with a clear central zone of 8 mm on central chromatic contrast sensitivity at the spatial frequencies of 3 and 12 cpd. The scattering conditions were aligned with the DOT lenses used in the CYPRESS study, based on visual acuity through the scattered part of the lenses [Rappon et al., 2023]. In the current study, the Bangerter foil 0.8 corresponded to less dense scattering (matched to test 1 DOT lens), while the Bangerter foil 0.4 induced a denser scattering (the test 2 DOT lens) [Rappon et al., 2023]. One difference between the DOT lens and the Bangerter

foils is the size of the clear central zone, which is 5 mm for the DOT lens and 8 mm for the Bangerter foils. The aperture size of 8.0 mm was selected to prevent crosstalk at the peripheral pupil area, ensuring no scattering occurs within this region.

The results revealed an inverse contrast adaptation defined by a reduction in contrast sensitivity after 90 minutes of lens wear of the Bangerter foil 0.8 compared to the control lens. However, there was no effect following adaptation to the Bangerter foil 0.4, which does not suggest a dose dependence.

The 12-month data of the CYPRESS study reported less beneficial effects in controlling myopia for the test 2 than the test 1 DOT lens, also suggesting no dose-response relationship [Rappon et al., 2023]. Later on, test 2 lens groups were crossed over to test 1 lens [Chalberg et al., 2023], while test 1 lens groups still reported a treatment effect when compared to the single-vision lens control group, up to 42 months [Chalberg et al., 2023]. These results contradict the findings from animal models, where exposure to scattering induced, rather than reduced, myopia progression, leading to form-deprivation myopia in rhesus monkeys [Smith III and Hung, 2000] and other animal models [Bowrey et al., 2015; Sherman et al., 1977; Wallman et al., 1978; Wiesel and Raviola, 1977].

Additionally, after the 30-minute exposure period, neither Bangerter foil level showed any significant impact. This outcome contrasts with previous short-term studies, where full-field induced scattering enhanced contrast adaptation in some studies [Pérez et al., 2009; Villa-Carpes et al., 2021] and reduced contrast sensitivity in another experiment [Teoh et al., 2020]. However, as adaptation time plays a crucial role, the decrease in contrast sensitivity after 90 minutes might be attributed to factors such as fatigue and concentration loss [Foster and Hankins, 2007; Tassi and Pins, 1997].

The findings suggest a more complex relationship between peripheral-induced scattering and central visual performance. While no evidence was found of peripheral contrast information transmission to the fovea in the first study by measuring contrast sensitivity, local retinal mechanisms may still be involved. A recent study found the near-peripheral retinal area between 6 and 10° most responsive to induced defocus, suggesting this retinal area is a target for myopia treatment [Swiatczak et al., 2024]. However, peripheral contrast sensitivity was not directly measured in the first study, leaving room for further exploration.

3.2.2 Effects of peripheral scattering on achromatic, cone-specific contrast sensitivity

The DOT strategy is based on the theory that abnormal high contrast signaling at the retinal level, due to mutations in M- or L-cone opsins, signals the eye to grow, potentially leading to myopia [Hagen et al., 2019]. These mutations can be identified by genetic analysis and amplified by polymerase chain reaction. Hagen et al. [2019] used a full-field

flicker electroretinogram to estimate the ratio of M- to L-cones, concluding that this ratio, along with opsin mutations, is involved in the susceptibility of developing myopia. This hypothesis lacks a direct link to the clinical trial evaluating DOT lenses. Nevertheless, it remains to be determined whether differences in contrast sensitivity using cone-type specific contrast stimuli can be assessed and how they might change after exposure to peripheral contrast reduction induced by scattering.

The first study additionally addressed this uncertainty by implementing achromatic, cone-type specific contrast stimuli based on silent substitution [Taylor et al., 2018]. This method selectively targets the stimulation of either S-, M- or L-cones by modulating the red, green, and blue channels of the presentation screen, based on CIE x- and y-coordinates corresponding to the peak sensitivities of each cone type [Stockman and Sharpe, 1999; Stockman et al., 1993; Taylor et al., 2018].

The results showed that the level of contrast reduction induced by Bangerter foil 0.4 and 0.8 had no significant effect across the cone-type specific contrast stimuli. However, differences in contrast sensitivity between the cone types were observed, independent of the degree of contrast reduction. As reported in previous studies, these differences align with cone density and topography expectations [Kraft et al., 2019; Taylor et al., 2018].

Furthermore, a difference in cone-specific contrast sensitivity was not found between myopes and non-myopes. This finding questions the hypothesis that mutations in M- or L-cone opsins would result in abnormally high cone-specific contrast sensitivity [Hagen et al., 2019]. The lack of a significant difference might be attributed to factors such as external noise, the silent substitution procedure used in the stimuli, stimulus presentation on a liquid crystal display, overlapping sensitivity of M- and L-cones, or the characteristics of the study population, which did not include individuals with high myopia. In addition, not all myopes have M- or L-cone opsin mutations, and it is uncertain whether the myopic participants included were affected by this mutation. Compared to investigations in chicken eyes, L-opsin expression is reduced after exposure to diffusers compared to the response to neutral density filters [Gisbert et al., 2023]. In such studies, it is possible to extract the retina and analyze gene expression, allowing for a deeper understanding of the underlying mechanisms, an approach not feasible in human eyes.

3.2.3 Neural contrast sensitivity and its response to scattering exposure

The second study extends the information into neural adaptation processes in response to contrast reduction induced by scattering. Previous studies focused on optical characterization, specifically contrast modulation, or general visual performance, leaving the neural response underexplored. By employing an interferometric system to bypass the optics of the eye [Campbell and Green, 1965; Suchkov et al., 2021], this study introduces a novel approach to assess neural contrast sensitivity at the spatial frequency of 6 cpd,

reducing the effects typically masked by noise [Pelli and Bex, 2013].

Building on the first project's findings, where the Bangerter foil 0.8 significantly impacted contrast sensitivity, the second study used the same foil in a full-field application. The results explored a significant increase in neural contrast sensitivity after 30 minutes of wearing the Bangerter foil 0.8 compared to the clear lens control condition. The finding of a short-lasting increase in neural contrast sensitivity following scattering exposure suggests that the visual system can temporarily compensate for degraded retinal image contrast. However, the absence of sustained adaptation raises essential questions about the limits of neural plasticity and wear time in response to image contrast modulation.

The findings of the first and second projects cannot fully explain the differential influence of peripheral versus full-field contrast reduction, respectively. No contrast adaptation effect was observed in the first study, whereas significant neural contrast adaptation was found in the second study. This underscores the importance of minimizing the influence of the optical properties of the eye that contribute to noise and masking effects. Consequently, the neural contrast sensitivity test demonstrated excellent repeatability compared to contrast sensitivity testing, which exhibited higher variability between measurements. Although different test procedures were used, two-interval forced-choice (study 1) and method of adjustment (study 2), which might have influenced the results, this factor is likely negligible [Lu and Dosher, 2013; Pelli and Bex, 2013]. Another factor is spatial frequency, as the first study measured contrast sensitivity at 3 and 12 cpd, at peak sensitivity and mid-spatial frequency, respectively [Kelly, 1977]. The second study measured neural contrast sensitivity at 6 cpd, at the peak of the neural contrast sensitivity function [Blakemore and Campbell, 1969; Michael et al., 2011]. The peak of the neural contrast sensitivity function is slightly shifted to higher spatial frequencies, which is explained by bypassing the eye's optical aberrations. Due to the receptive field structure, lower spatial frequencies, including peak spatial frequencies, are important for refractive development.

3.2.4 Neural contrast adaptation in response to scattering and defocus

Scattering and defocus represent two main optical strategies for myopia control. The optical characterization of myopia control lenses revealed that scattering (DOT lenses) reduced retinal image contrast while imposed defocus (DIMS lenses) increased it [Arias et al., 2023]. To explore potential differences in neural adaptation mechanisms, the second study investigated neural contrast adaptation following exposure to scattering (Bangerter foil 0.8) and defocus (+0.5 D). The defocus lens was matched to the scattering condition by equalizing the reduction in high-contrast visual acuity to one line on a letter vision chart (+0.1 logMAR), a method previously applied in related research [Teoh et al., 2020].

The study found that after 30 minutes of lens wear, neural contrast sensitivity increased significantly to the scattering condition. The responses to the control and defocus lens

conditions remained statistically non-significant at a sensitivity of 6 cpd. Previous human studies explored that adaptation to myopic defocus (positive lenses) results in contrast sensitivity improvement [Ohlendorf and Schaeffel, 2009; Teoh et al., 2020] and shortening of axial length [Teoh et al., 2020], suggesting that contrast adaptation may play a beneficial role in myopia control and indicate a potential success for the respective strategy. However, studies on scattering revealed mixed results, with reporting improvement [Villa-Carpes et al., 2021] and reduction in visual performance [Breher et al., 2023; Castro-Torres et al., 2021; Teoh et al., 2020]. Experiments on stronger diffusers exhibited axial elongation in both human eyes [Teoh et al., 2020] and animal models [Smith III and Hung, 2000].

The adaptation effect could be attributed to either the level of image contrast reduction or to distinct neural processing mechanisms for scattering and defocus. If specific spatial frequency channels are essential in myopia control mechanisms, the spurious resolution occurring with defocus leads to less suppression of these channels than with Bangerter foils. Imposing defocus can produce a phase shift, causing increased contrast in the defocused image, while Bangerter foils tend to generate a more uniform grey image [Pérez et al., 2009].

Furthermore, distinct mechanisms might be due to eye growth signals to receive a sharp image on the retina. Defocus might use a vergence cue that changes the axial length until the retinal image is resolved as sharp, using retinal image blur as a stop and error signal for eye growth, which can be described as a closed-loop system [Schaeffel and Howland, 1991]. Studies found bidirectional changes in contrast sensitivity, but also in axial length in response to myopic (axial shortening) and hyperopic defocus (axial elongation) [Chakraborty et al., 2012, 2013; Read et al., 2010]. Scattering, conversely, is referred to as an open-loop system since no feedback is produced to the direction of eye growth due to the retinal image remaining blurred when the eye is longer or shorter [Schaeffel and Howland, 1991; Wallman and Winawer, 2004]. Consequently, the mechanisms behind neural adaptation processes in response to scattering remain unclear and require further research.

3.2.5 Impact of scattering-induced contrast reduction on ocular structures

Choroidal thickness and axial length are key biomarkers in myopia research, with choroidal thickening and reduced axial elongation beneficial in slowing myopia progression. Conversely, choroidal thinning and axial elongation are associated with myopia progression. Previous findings suggest that the choroid is involved in eye growth regulation by altering its thickness to adjust the focal plane of the eye and by releasing growth factors signaling the sclera [Harper and Summers, 2015]. While short-term choroidal thickening and thinning have been observed in response to myopic and hyperopic defocus in animal studies, respectively [Schaeffel and Howland, 1991], the effects of short-term adaptation to

scattering on ocular structures, particularly choroidal thickness, have not been previously investigated in humans.

The third study focused on choroidal thickness and axial length changes in response to contrast reduction through induced peripheral and full-field scattering, examining both central and peripheral effects.

The results of the third study exhibited that the medium peripheral scattering condition induced significant peripheral choroidal thickening, most pronounced in the superior peripheral retina. The medium full-field scattering condition only led to central nasal thickening of the choroid without the general central retina being unaffected. These effects were significantly different from the responses of the clear lens control condition. High peripheral and full-field scattering conditions and the clear control lens did not impact choroidal thickness, suggesting again no dose-response relationship. The results rather indicate that a lower level of contrast reduction affects choroidal thickening, which is in line with a recently published study, showing choroidal thickening after 30 minutes of DOT lens wear in emmetropic children [Jabeen et al., 2024].

The four scattering conditions and the control condition showed no significant changes in axial length after 60 minutes of lens wear. These findings contradict a previous short-term investigation, which found axial elongation [Teoh et al., 2020]. Additionally, animal models have exhibited axial elongation and the development of form-deprivation myopia [Smith III and Hung, 2000]. However, these previous studies used stronger diffusers and not weak diffusers. The amount of induced scattering might be relevant to trigger measurable changes in axial length.

When studying choroidal changes, it's crucial to consider thickness, blood flow, and oxygen saturation in future investigations. Research has shown that increased blood flow and oxygen saturation are associated with choroidal thickening in response to imposed positive defocus [Swiatczak et al., 2023]. Choroidal blood flow or oxygen level responses to induced scattering have not yet been investigated and require further research.

3.2.6 Effects of peripheral and full-field scattering on visual acuity

In addition to investigating choroidal thickness and axial length, the third study explored the effect of peripheral and full-field contrast reduction via induced scattering on high-contrast visual acuity. This complements the findings of the first and second studies, which focused on visual performance following short-term exposure to retinal image contrast reduction induced by Bangerter foils.

This study revealed a reduction in visual acuity under full-field scattering conditions, with the high scattering condition causing a more significant decrease than the medium scattering condition, as expected. In contrast, medium and high peripheral scattering conditions and the clear single vision control lens did not impact visual acuity. After

60 minutes of lens wear, there was neither a reduction nor an improvement in visual acuity in any of the five lens conditions, which contradicts earlier findings that reported an improvement in visual acuity after 40 minutes of full-field adaptation to scattering induced by the Bangerter foil 0.6 [Villa-Carpes et al., 2021]. The differences in scattering conditions and adaptation time between this study and previous research might account for this discrepancy.

3.2.7 Duration of exposure and scattering strategies in myopia control research

Another factor in contrast adaptation is the duration of exposure. The first study showed that effects on contrast sensitivity became noticeable after 90 minutes of adaptation, while the second study focused solely on effects after 30 minutes. These adaptation periods of 30 to 90 minutes align with previous investigations [Rajeev and Metha, 2010; Venkataraman et al., 2015; Villa-Carpes et al., 2021]. Although short-term contrast sensitivity changes are assumed to predict long-term changes in eye growth, they do not provide insight into long-term refractive development or eye growth patterns. Contrary to contrast sensitivity changes, short-term choroidal thickness changes were suggested to predict future eye growth changes, which is supported by recent long-term studies [Liu et al., 2025; H. Wu et al., 2024]. The results of the third study showed choroidal thickening in response to induced scattering after 60 minutes, suggesting beneficial long-term effects on myopia control. However, further long-term investigations are still necessary to fully evaluate the effectiveness and underlying mechanisms of the applied strategy. Clinical trials investigating the efficiency of optical myopia control strategies typically span several years, with results reported at 6- to 12-month intervals, which is the minimum duration required for meaningful comparisons.

Another question for the future is whether long-term full-time exposure to myopia control strategies is necessary or if daily short-term exposure is enough to have a treatment effect. An animal study found that a 3-hour interruption of inducing -3 D did not lead to myopia development [Zhu et al., 2022]. However, there have been no investigations on humans, so further research is needed.

Scattering is naturally experienced by cataract patients, decreasing low-contrast visual acuity and contrast sensitivity being influenced [de Waard et al., 1992; Elliott et al., 1996], with the central region being less impacted than the peripheral region [van den Berg, 2017]. These previous findings could explain why no improvement in contrast sensitivity was found after adaptation to peripheral scattering by Bangerter foils in the first study. In animals, cataracts were also found to increase the axial length variability, while form-deprivation myopia was found to cause axial elongation following exposure to strong diffusers [Bartmann and Schaeffel, 1994; Smith III and Hung, 2000]. This finding could be related to the location of the scattering source - mounted outside the

eye in animal models versus cataracts inside the human eye near the nodal point - or to differences in the interaction between retinal, in particular, foveal development, poor image quality, and eye growth in humans compared to other animals. These aspects still need to be apparent and require further research.

As mentioned earlier, Bangerter foils and sandblasted lenses were chosen as scattering sources to mimic DOT lenses. Bangerter foils and diffusers, similar to sandblasted lenses, are commonly used in myopia research to induce scattering in animal or human eyes. Bangerter foils are typically employed to treat amblyopia by covering the non-amblyopic eye, allowing the amblyopic eye to improve visually. A long-term study revealed enhanced visual acuity in both the amblyopic and covered non-amblyopic eyes after 6 and 12 weeks of treatment [Rutstein et al., 2011]. Although this study was not conducted in the context of myopia, it provides valuable insights into visual processing under the application of Bangerter foils, helping to contextualize the results. Diffusers, such as sandblasted lenses, are frequently employed in animal models due to the enhanced ease of application compared to foils, which may slip or fog. The results obtained from animal models also assist in contextualizing the present findings. Nevertheless, further research is needed to determine which scattering strategy offers the most effective approach for myopia control.

3.2.8 Optical characterization and design considerations for myopia control lenses

The experimental lenses were chosen to match the DOT test 1 and 2 lenses according to the reduction in visual acuity. For the primary test 1 DOT lens, the Bangerter foil 0.8 (study 1 and 2) and medium scattering sandblasted lens (study 3) were chosen. In contrast, the Bangerter foil 0.4 (study 1) and the high scattering sandblasted lenses (study 3) were selected for the dropped test 2 DOT lens. Although the reduction in visual acuity was similar between the experimental and the DOT lenses, the characterization of the experimental lenses revealed detailed information on the respective retinal image quality.

Through optical characterization of the experimental lenses, this thesis' research demonstrated a reduction in image contrast across spatial frequencies for all tested lenses, as expected from previous studies [Arias et al., 2023]. The results show that while the Bangerter foil 0.8 closely matches the characteristics of the DOT lens (test 1 lens), the sandblasted lenses revealed different MTF profiles [Arias et al., 2023; Gantes-Nuñez et al., 2023]. This distinction highlights the importance of lens design, particularly the arrangement of scattering elements.

The Bangerter foils' widely spaced microbubble structures resulted in less image contrast degradation than the sandblasted lenses' uniform scattering surface. This resulted in contrast reduction predominantly at higher spatial frequencies for the Bangerter foils, and across a broader range of low to high spatial frequencies for the sandblasted

lenses. Consequently, denser scattering elements lead to greater forward scattering, increased negative vergence, more pronounced image contrast reduction, and a greater loss of spatial frequency information. These findings align with previous research, which demonstrated that retinal responses are highly dependent on the magnitude of blur [Panorgias et al., 2021].

Optical characterization in terms of contrast, sharpness, scattering properties, and the ratio of clear to scattered areas of the applied strategy is required. Since, on the one hand, previous studies have revealed inconsistent results in the scattering properties of different types of Bangerter foils [Castro-Torres et al., 2021; Pérez et al., 2010]. On the other hand, information about image modulation of different interventions or specific lenses is unavailable. Also, to investigate adaptation differences between scattering and defocus, matching MTFs is necessary to draw definite conclusions. Consequently, naming the strategy no longer seems enough to understand visual responses better. Further to this requirement, a gold standard setup for optical characterization should be implemented to make the findings comparable.

The loss of contrast in the retinal image is expected to predict the degree of contrast adaptation, providing insights into underlying mechanisms. Since contrast reduction induced by scattering varies with spatial frequencies, understanding its relationship across frequencies is crucial. A previous study found that axial shortening occurred after exposure to defocus at spatial frequencies between 2 and 8 cpd, but not at frequencies above 10 cpd [Swiatczak and Schaeffel, 2021]. This raises the question of how contrast adaptation can occur at the high spatial frequencies associated with visual acuity, typically above 10 cpd. It suggests that specific spatial frequencies are necessary to induce axial shortening or are less affected by adaptation. To clarify this, contrast sensitivity in response to contrast reduction at different spatial frequencies must be compared.

Another factor of myopia control lens designs is the presence and size of a clear optical zone on the lens surface. The DOT lenses incorporated a 5 mm clear zone, while the experimental lenses of study 1 and 3 had an 8 mm aperture. A survey on different myopia control strategies revealed that the treatment zone size had varying effects on visual acuity [Rani et al., 2024]. This outcome and the findings of this research suggest that the aperture size is an essential parameter in the lens design and efficacy of myopia control strategies.

An aperture size greater than the pupil size may explain the lack of improvement in contrast sensitivity (study 1). The second study examined the effect of full-field scattering on neural contrast sensitivity to determine whether a clear optical aperture is beneficial or necessary. Improved neural contrast sensitivity following full-field adaptation to scattering was reported, suggesting a beneficial effect on myopia control and questioning the benefit of a clear aperture. The third study reported significant effects after adaptation to the medium peripheral scattering condition, which included a clear optical zone of 8 mm. The

results leave room for further research. Any investigation with the DOT lens itself was not possible, as a DOT lens was not available when the study was conducted. Therefore, the aim was to mimic the DOT lens as closely as possible.

3.2.9 Impact of pupil size, lighting, and retinal location on scattering effects

In addition to exploring different scattering conditions, factors such as pupil size and lighting conditions should also be examined, as they play a crucial role in scattering intensity, as established in previous optical characterizations [Arias et al., 2023]. Greater pupil diameter and higher illuminance both lead to an increase in forward scattering within the eye. In the first study, pupil diameter was monitored, revealing only minimal variation among the participants. The first, second, and third studies were conducted in similar and usual indoor conditions, under photopic lighting, to imitate familiar situations for all participants. Consequently, the pupil size was not further examined in the second and third studies. However, future studies should consider monitoring the pupil size or controlling it with, for example, cycloplegia. Furthermore, the effect of scattering should be investigated under different light levels ranging from scotopic to photopic.

As discussed in the manuscript of study 2, peripheral-induced defocus lenses, such as the DIMS lenses (+3.5 D in the periphery), create a similar blurred point spread function across the ganglion cells, as indicated by the full-width at half maximum, to the full-field imposed defocus of +0.5 D. This could be related to the increase in receptive field sizes with retinal eccentricity, raising the question of whether the input stimulus needs to be scaled accordingly with eccentricity. Furthermore, the possibility exists that the transmission of overall contrast reduction, which can be quantified by the area under the MTF, may be limited by the bandwidth of neurons or the cortical processing capacity. Despite varying levels of contrast reduction in the periphery, the visual system might have a limit in processing these changes, ensuring a consistent impact on image quality across the retina. On the other hand, receptive fields are concatenated by subset and may, therefore, be able to respond locally.

Transferred to the scattering conditions, study 2 revealed a significant effect in neural contrast adaptation following exposure to full-field applied Bangerter foil 0.8. However, in study 1, no improvement in contrast sensitivity was found when the Bangerter foil 0.8 was applied only peripherally. This finding suggests that the peripheral retina might need a more pronounced contrast reduction than the fovea due to the receptive field structure. Contrast sensitivity results after adaptation to the Bangerter Foil 0.4, however, contradict this suggestion, as no contrast adaptation effect was found. It is also possible that an effect was not measurable via the contrast sensitivity test. Furthermore, in the third study, the high level of scattering did not significantly impact choroidal thickness compared to the medium scattering conditions. This finding suggests again, that there is no clear

dose-response relationship for scattering, though specific image characteristics may still benefit myopia control.

3.2.10 Retinal contrast processing and its role in emmetropization

Contrast vision generally begins at the first synapse, where photoreceptor cell output is split into ON and OFF bipolar cells. The retina's task is to compress the output of 125 million photoreceptors to 1 million ganglion cells. Consequently, information about absolute differences is discarded, and only differences in spatial and temporal contrasts are transmitted. The ganglion cells, also structured in ON (ON center, OFF surrounding) and OFF (OFF center, ON surrounding) receptive fields, are barely stimulated by homogenous contrasts.

The DOT lenses reduce retinal image contrast evenly. Subsequently, the fire rate in both ON- and OFF-bipolar cells in the periphery leads to scarce stimulation of the ganglion cells [M. Neitz et al., 2022]. However, ON- and OFF- signals are important for emmetropization and show selective effects on ocular growth. A previous study found that ON channel activation is linked to choroidal thickening and OFF channel activation to choroidal thinning [Aleman et al., 2018], potentially leading to control myopia or myopia progression, respectively. Stimulation of the ON pathway has also been found to trigger the release of dopamine at the retinal level [Wang et al., 2019]. Similarly, increased dopamine levels are correlated with reduced eye growth [Feldkaemper and Schaeffel, 2013; Zhou et al., 2017], while low dopamine levels are related to myopia [Stone et al., 1989].

A human study showed that the psychophysical examination of ON and OFF contrast sensitivity discriminates between myopes and emmetropes for direct measurements without an adaptation period [Breher et al., 2023]. However, the psychophysical measurement of ON and OFF channel responses combines the retinal and cortical output, and the assumption of retinal mechanisms cannot be drawn. Considering psychophysical examinations, conclusions about retinal and cortical mechanisms remain restricted. The findings allow further experiments, including a short- or long-term adaptation phase and assessing ON and OFF channel responses.

To guide emmetropization, retinal contrast adaptation should be utilized [Diether et al., 2001]. One possible mechanism for retinal contrast adaptation is the bipolar pathway [Brown and Masland, 2001; Kim and Rieke, 2000]. It was also found, that contrast adaptation occurs more in the pathway of M-cells than of P-cells [Hohberger et al., 2011; Solomon et al., 2004]. The challenge is that the adaptation process can occur simultaneously across multiple levels, making it impossible to isolate or measure a single mechanism.

3.2.11 Impact of age and refractive state on visual processing and emmetropization

The population of the experiments presented differs from those included in clinical studies. While clinical trials typically involve children still undergoing refractive development and vision-forming processes [Verkicharla et al., 2020], all three performed studies include young adults who primarily completed their refractive development. The stabilization of the refractive state occurs in the late teenage years or early adulthood [Goss and Winkler, 1983; Verkicharla et al., 2020]. The question arises as to whether the modulation of image contrast has a more significant impact on children whose refractive state is not yet stabilized than on adults who have already completed their refractive development.

A further factor in testing responses of adult eyes is the refractive state itself. Participants of all three studies were either hyperopic, emmetropic, low- or moderate myopic, whereby one of the participants had high myopia (study 2). Genetic cone deficiencies were not examined. No significant difference was found between the refractive groups in all three studies. High myopic eyes could develop eye diseases and alter visual and physiological processing in advance, which might have been visible during the investigation. As the studies lacked high myopes, potential differences in visual processing, such as changes in contrast sensitivity, neural contrast sensitivity, axial length, or choroidal thickness, could not be observed. A previous investigation found differences in visual processing in emmetropes and myopes. While emmetropic eyes became shorter after short-term stimulation with myopic defocus (+2.5 D), myopic eyes became longer, suggesting that myopes have a limited ability to inhibit eye growth [Swiatczak and Schaeffel, 2021]. This may be related to retinal image processing in terms of image contrast and defocus detection or poor signal transmission to the choroid, sclera, and visual cortex. It is crucial to understand what changes occurred in the myopic retina and when these changes began, whether before or after the onset of myopia. In contrast, other studies did not find this difference between emmetropes and myopes under similar testing conditions [Chiang et al., 2015; Read et al., 2010], which aligns with the current research.

Further research is needed to understand the reasons and mechanisms behind the development of myopia and the timing of the error signal in emmetropization. It's still unclear whether the error signal occurs before or after refractive changes, which can be investigated by including non-myopic children in the study population. Other factors for further study in children or adults include the relationship between refractive state, genetic predisposition, age, and the eye's response to induced contrast reduction.

4 Conclusion

This thesis demonstrated the potential of optically induced scattering as a myopia control strategy, as scattering seems to mediate contrast adaptation. The findings provide valuable foundations and insights into the effects of peripheral and full-field contrast reduction induced by scattering on chromatic and achromatic contrast sensitivity, neural contrast sensitivity, choroidal thickness, axial length, and visual acuity.

Newly developed psychophysical contrast sensitivity tests and interferometric technologies are introduced to identify contrast adaptation effects following exposure to scattering. The additional optical characterization of contrast modulation under different lens conditions emphasizes the need to analyze retinal image characteristics to understand visual and structural responses. The findings further highlight the importance of considering the exposure of the peripheral retinal area and receptive field structures, which may play a crucial role in signal processing and the emmetropization processes.

It is clear that visual feedback controls the emmetropization process, however, the mechanisms are not fully understood. Therefore, further research is necessary to explore the underlying retinal mechanisms of contrast reduction induced by scattering, to evaluate existing myopia control strategies, and to guide the development of new approaches, with the overall aim of slowing progressive myopia.

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Appendix: Accepted publications

Publication 1:

Short-Term Peripheral Contrast Reduction Affects Central Chromatic and Achromatic Contrast Sensitivity

photonics

MDPI

Article

Short-Term Peripheral Contrast Reduction Affects Central Chromatic and Achromatic Contrast Sensitivity

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Abstract: Peripheral retinal contrast reduction is suggested as a potential myopia control strategy. However, the underlying mechanism is yet unknown. Therefore, this study investigated the influence of peripheral contrast reduction on central chromatic and achromatic contrast sensitivity (CS). A total of 19 participants were included. Peripheral contrast reduction was induced via Bangerter foils of 0.4 and 0.8 density, each with a clear central zone of 8.0 mm diameter. Central achromatic and chromatic (for S-, M-, and L-cone types) CS was measured at 3 and 12 cpd in a 2-IFC psychophysical procedure. CS was tested monocularly at 0, 30, and 90 min of adaptation time, while the fellow eye was covered by an infrared filter. With the filter in place, pupil size was controlled to be smaller than the clear central aperture. Data were analyzed using linear mixed models. Cone-type CS showed significant differences among each other (all $p < 0.05$), except for the achromatic and L-cone type ($p = 0.87$). The minimum sensitivity was found with the S-cone type and the maximum with the M-cone type. Central achromatic and chromatic CS were equally affected by diffusion. The level of peripheral diffusion also influenced CS, while the 0.8 Bangerter foil led to a higher reduction in CS compared to the 0.4 Bangerter foil ($p = 0.0008$) and the control condition ($p = 0.05$). A significant reduction in CS occurred between 30 and 90 min of adaptation time ($p < 0.0001$). The current study found that peripheral contrast reduction impacted central achromatic and chromatic CS equally. It further showed that the amplitude of reduction was influenced by the level of diffusion, with the reduction becoming more pronounced over time.

Keywords: contrast adaptation; scattering; diffusion; contrast reduction; peripheral contrast reduction; contrast sensitivity; visual adaptation; refractive development; myopia

Citation: Neumann, A.; Leube, A.; Nabawi, N.; Sauer, Y.; Essig, P.; Breher, K.; Wahl, S. Short-Term Peripheral Contrast Reduction Affects Central Chromatic and Achromatic Contrast Sensitivity. *Photonics* **2022**, *9*, 123. https://doi.org/10.3390/photonics9030123

Received: 1 February 2022
Accepted: 19 February 2022
Published: 22 February 2022

1. Introduction

Physiological ocular refraction changes during early life are known as refractive development. While hyperopia is common in newborns, it reduces during childhood, also called emmetropization. If the emmetropization process is disturbed, hyperopia may persist or myopia and/or astigmatism may occur [1,2]. Moreover, emmetropization processes depend on multiple factors including the balance of central and peripheral visual experiences [3–5]. Here, the peripheral retina might be of importance in the ability to derive blurred and diffused contrast signals [5], as well as in contrast adaptation processes [6–13].

Retinal contrast reduction is associated with retinal image degradation, based on various optical factors, such as defocus, astigmatism, higher order aberration, or scattering [12,14]. The role of peripheral contrast reduction and the related contrast adaptation processes in refractive development have not yet been fully clarified.

Contrast adaptation is a form of cortical neuroplasticity, where the visual response is re-calibrated to compensate for variations in sensitivities [12]. Previously, improved visual performance was shown to occur in response to blurred and diffused stimuli [11,12,15].

Along this line, a novel spectacle lens design for myopia control was developed to reduce peripheral contrast via diffusion while maintaining clear central vision by a clear aperture [16,17]. In the related non-peer-reviewed article, reduced axial elongation was reported and a protective effect regarding myopia progression was proposed, based on the strategy of reduction in abnormal high contrast signaling in the retinal periphery [16,17].

The impact of contrast reduction in the retina including the separate stimulation of photoreceptors is still unknown, while the sensitivity of cones themselves has already been established. Short-wavelength light sensitive cones (S-cones) exhibit a decreased sensitivity compared to middle-wavelength light sensitive cones (M-cones) and long-wavelength light sensitive cones (L-cones) [18,19].

Achromatic and chromatic contrast adaptation to diffusion was measured centrally after central adaptation [6,7,12,20–24] or peripherally after peripheral adaptation so far [6,7,22,25], however, not centrally after peripheral adaptation. Therefore, this study aimed to investigate the short-term influence of different levels of peripheral contrast reduction in central cone-specific CS, in order to evaluate a potential mechanism that explains the novel myopia control strategy.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria

This prospective study was carried out at the Institute for Ophthalmic Research at the University of Tübingen. The study protocol followed the Declaration of Helsinki and data protection regulations. Approval was obtained by the ethics committee of the Faculty of Medicine of the University of Tübingen. Before the measurements, participants signed a written informed consent form after the content and possible consequences of the study had been explained. Inclusion criteria were self-reported ocular health, visual acuity of $\leq$0.1 logMAR, and normal color vision. Participants were excluded with present self-reported systemic and ocular abnormalities, anisometropia of $>$1 D, a history of orthokeratology wear or corneal refractive surgery, and age $<$18 and $>$40 years.

2.2. Apparatus

The objective refraction was measured with wavefront aberrometry (i.Profiler plus, Carl Zeiss Vision GmbH, Aalen, Germany) and was confirmed with subjective refraction using ZEISS VISUSCREEN 500 and ZEISS VISUPHOR 500 (Carl Zeiss Vision GmbH, Aalen, Germany). For the psychophysical experiment, the individual's sphero-cylindrical correction using trial lenses (Oculus BK 1/T, Oculus GmbH, Wetzlar, Germany) was mounted into a trial frame (Oculus B5, Oculus GmbH, Wetzlar, Germany) with a vertex distance of 12 mm in front of the right eye. The participants right eyes were fully corrected according to the subjective refraction. Bangerter foils (Breitfeld & Schliekert GmbH, Karben, Germany) with a density of 0.4 and 0.8, each with a 8.0 mm clear central aperture were additionally applied to the right eye to induce the desired peripheral contrast reduction. The 0.4 Bangerter foil reduces the visual acuity by five lines (e.g., from 1.0 to 0.4 decimal visual acuity) and the 0.8 Bangerter foil by one line (e.g., from 1.0 to 0.8 decimal visual acuity). For clarification reasons, the naming remains at 0.4 and 0.8 Bangerter foil in the following sections. Each of the Bangerter foils were pasted and centered on a plano lens and then mounted into the backside of the trial frame, see Figure 1. Subsequently, the clear central aperture was centered in front of the individual's pupil. The slots at the front of the frame were reserved for the sphero-cylindrical correction. The participants pupillary response was assessed on the left eye with infrared photorefraction, using the PowerRefractor [26]. Therefore, an additional infrared filter was mounted into the trial frame in front of the participants left eyes, see Figure 1. Head position was stabilized with a chin and forehead rest. To verify normal color vision respective the inclusion criteria, the Ishihara test (Kanehara Trading Inc., Tokyo, Japan) was conducted prior to the actual experiment.

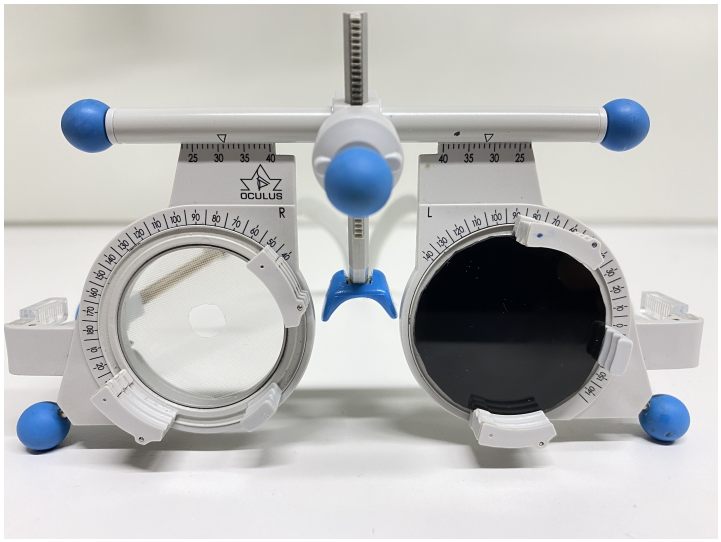

Figure 1. Trial frame example with the 0.4 Bangerter foil pasted on a plane lens, while the clear central aperture is centered to the lens, inserted at the back side of the trial frame—in front of the right eye. The slots on the front side were reserved for the individual sphero-cylindrical correction and the near compensation lens. The infrared filter on the left eye was used to measure the pupil size.

All psychophysical test procedures were programmed in MATLAB (MATLAB R2020a, MathWorks Inc., Natick, USA) using the Psychtoolbox [27,28], Palamedes toolbox [29], and DataPIXX toolbox (VPixx Technologies Inc., Saint-Bruno, QC, Canada) extensions. An LCD display (VIEWPixx, VPixx Technologies Inc., Saint-Bruno, QC, Canada) with a mean luminance of 40 cd/m², a resolution of 1920 × 1200 pixels, and a 12 bit graylevel resolution was used for stimuli presentation in a distance of 75 cm. The luminance nonlinearity of the screen was corrected by using a color lookup table computed for gamma correction.

2.3. Stimuli

The cone-type-specific stimuli were created using the silent substitution method [18,30]. This method elicits changes in a specific cone type only, after modulation of the red, green, and blue screen channels, to present the desired cone-type-specific color direction. The respective Gabor patch was produced using the CIE x- and y-coordinates of the peak modulations of the cone type stimuli, as described elsewhere in more detail [18,31,32]. The Gabor patch was produced with a size of 1.7° of visual angle, spatial frequencies of 3 and 12 cpd, and a 2-D Gaussian envelope of $\sigma = 0.1°$. The color properties of the sinusoidal pattern of the Gabor patch were modified to represent an achromatic, as well as the three cone-specific stimuli for S-, M-, and L-cones, see Figure 2. The test stimulus was presented randomly in four different orientations (0°, 45°, 90°, 135°) against a constant gray background field. Moreover, the size and spatial frequencies of the stimuli were corrected for image magnification artifacts resulting from the participants lens corrections.

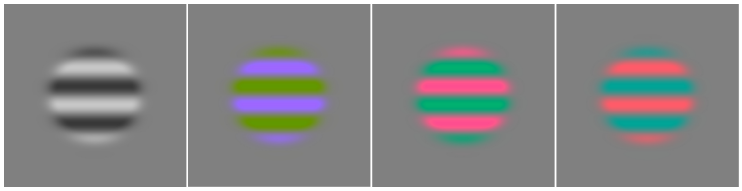

Figure 2. High-contrast versions of the achromatic, S-, M-, and L-cone type Gabor patches with a spatial frequency of 3 cpd.

2.4. Study Protocol

The Tuebingen CS Test [33] was taken as a basis and subsequently modified to a two-interval forced-choice (2IFC) psychophysical test method. An adaptive staircase procedure

was used to automatically select the contrast level on each trial as the search for the contrast threshold was performed. Here, the CS values have been obtained as the reciprocal of the contrast threshold. One experimental session contained 8 different blocks, each consisted of 30 trials while the order of the cone-type-specific stimuli (achromatic, S-, M-, and L-cone) and spatial frequencies (3 and 12 cpd) were presented randomized. One trial consists of two 153 ms intervals separated by a 400 ms inter-stimulus break with a sound, whereas one interval contained the stimulus, and the other interval was blank (gray screen), as depicted in Figure 3. The orientation of the Gabor patches was randomized for each trial. According to the 2IFC psychophysical procedure, the participants had to respond with a key press at which interval the target was presented. During the response time, a gray circle around the stimulus location with the double diameter of the grating served as a fixation point on the gray background. The same test procedure was performed at the initial T_0 session, after 30 min (T_{30}) and 90 min (T_{90}) for each of the three conditions—control (clear vision, without diffusion) and 0.4 and 0.8 Bangerter foil. The conditions were randomized and took place on three different days, however, at the same time of the day to eliminate diurnal variations of vision and attention. An additional +1.25 D lens was implemented in front of the right eye as accommodation compensation to the screen distance during measurements, which took around 8 to 9 min. For all participants, CS testing was conducted monocularly by the right eye and pupil size investigation by the left eye, based on the arrangement possibilities of the test setup. Between the sessions, the participants were advised to watch a standard movie from a distance of 2 m, to avoid accommodation.

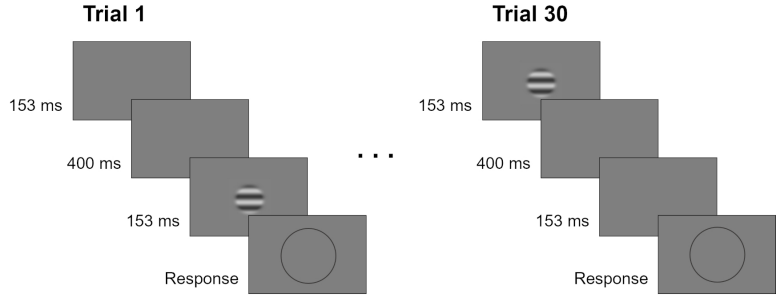

Figure 3. Two-interval forced-choice sequence for one achromatic test block. This sequence was repeated for eight randomized blocks in total: the achromatic block and three chromatic blocks for spatial frequencies of 3 and 12 cpd.

2.5. Statistical Data Analysis

Statistical analysis was conducted using linear mixed models with the statistics software RStudio (RStudio Version 1.4.1717, R Core Team 2021) to identify influencing factors separately on CS measured in log(CS). Before statistical analysis, the data underwent outlier detection. Thereby, data points that were more than three interquartile ranges (IQR) outside of the median were removed. Within the model, CS figured as dependent variable, with participants as random factor and four within-subject factors: spatial frequency (3 and 12 cpd), stimuli type (S-, M-, L-cone, achromatic), adaptation time (T_0, T_{30}, and T_{90}), diffusion level (control, 0.4 BF, and 0.8 Bangerter foil, each with a clear aperture of 8.0 mm). For every possible factor combination with and without interactions, a linear mixed model was designed. All final models were compared by the value of the Akaike information criterion (AIC) to find the most suitable model (AIC comparison, see Table S1). The model with the lowest AIC was selected for further analysis for each parameter CS. Significant effects underwent subsequent post hoc testing using estimated marginal means (least-squares mean and standard error). The significance level was set to $\alpha = 0.05$ and significant effects were defined by $p < 0.05$.

3. Results

3.1. Participant Data

A total of $n = 19$ adults were included in the study (16 females and 3 males). The mean age was age 24.21 ± 3.68 years (ranging from 19 to 31 years). The right eye's subjective refraction resulted in a spherical equivalent of −1.61 D ± 2.16 D with a minimum of −6.25 D and a maximum of 0.75 D. Eye biometry examination revealed an axial length of 24.28 ± 1.18 mm and a pupil size of 4.73 ± 0.68 mm.

3.2. Contrast Sensitivity

The averaged log(CS) values for the different time points T_0 to T_{90} separated for the diffusion condition are presented in Table 1 and Figure 4. CS was influenced significantly by all model factors. However, no significant interactions between these factors were found ($p = 0.86$).

Table 1. Log(CS) (median ± IQR) for the different measurement conditions ($n = 19$ participants).

		Control			0.4 Bangerter Foil			0.8 Bangerter Foil		
		T_0	T_{30}	T_{90}	T_0	T_{30}	T_{90}	T_0	T_{30}	T_{90}
3 cpd	Achromatic	1.60 ± 0.13	1.55 ± 0.23	1.58 ± 0.07	1.58 ± 0.28	1.59 ± 0.19	1.58 ± 0.11	1.62 ± 0.07	1.58 ± 0.11	1.60 ± 0.24
	S-cone	0.95 ± 0.11	0.95 ± 0.15	0.90 ± 0.19	0.92 ± 0.32	1.01 ± 0.32	0.96 ± 0.09	0.98 ± 0.37	0.92 ± 0.25	0.87 ± 0.28
	M-cone	1.64 ± 0.30	1.67 ± 0.22	1.64 ± 0.27	1.78 ± 0.12	1.68 ± 0.30	1.66 ± 0.13	1.54 ± 0.51	1.67 ± 0.24	1.55 ± 0.36
	L-cone	1.62 ± 0.19	1.62 ± 0.48	1.61 ± 0.15	1.68 ± 0.12	1.63 ± 0.16	1.49 ± 0.22	1.66 ± 0.24	1.59 ± 0.20	1.50 ± 0.31
12 cpd	Achromatic	1.06 ± 0.47	1.20 ± 0.22	0.94 ± 0.56	1.34 ± 0.40	1.14 ± 0.38	1.16 ± 0.71	0.84 ± 0.80	1.30 ± 0.53	0.94 ± 0.74
	S-cone	0.47 ± 0.36	0.51 ± 0.30	0.45 ± 0.45	0.51 ± 0.34	0.57 ± 0.35	0.43 ± 0.59	0.41 ± 0.45	0.44 ± 0.31	0.32 ± 0.46
	M-cone	1.30 ± 0.30	1.32 ± 0.36	1.15 ± 0.61	1.31 ± 0.49	1.33 ± 0.46	1.16 ± 0.88	1.22 ± 1.14	1.09 ± 0.91	0.94 ± 0.77
	L-cone	1.13 ± 0.22	1.04 ± 0.71	1.00 ± 0.96	1.26 ± 0.31	1.26 ± 0.76	0.96 ± 1.15	1.26 ± 0.67	1.21 ± 0.29	1.01 ± 0.67

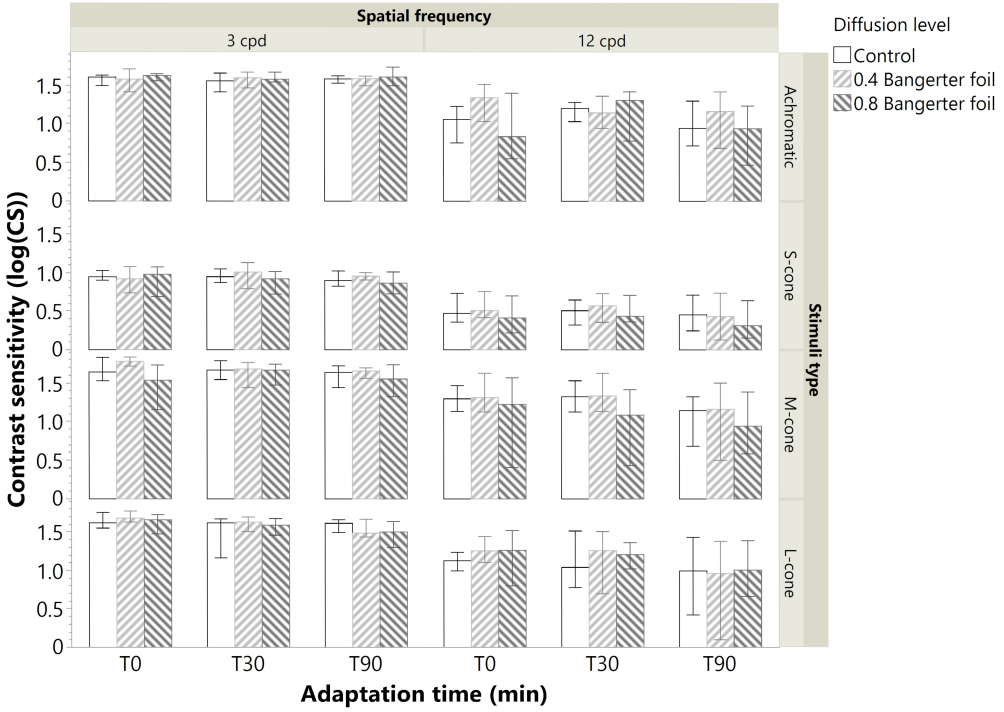

Figure 4. Median ± IQR in log(CS) for the different diffusion levels, spatial frequencies, stimuli types, and adaptation times ($n = 19$ participants).

3.2.1. Spatial Frequency

As expected, CS was significantly higher at 3 cpd (1.33 ± 0.06 log(CS)) than at 12 cpd (0.91 ± 0.06 log(CS)) over all conditions ($p < 0.0001$). Moreover, CS at 12 cpd revealed slightly higher inter-subject variations than at 3 cpd. Interactions with the other factors were not found; consequently, no effects of cone types, the level of diffusion, or adaptation time were exhibited.

3.2.2. Cone Type Specific Contrast Sensitivity

The S-cone type exhibited the lowest CS of 0.67 ± 0.06 log(CS) for both spatial frequencies, whereas the M-cone revealed the highest CS values of 1.32 ± 0.06 log(CS). L-cone type (1.26 ± 0.06 log(CS)) and achromatic type (1.24 ± 0.06 log(CS)) were found closer to the maximum than the minimum. However, significant effects were found for CS in all cone types ($p < 0.05$), except for the comparison of the achromatic and L-cone type (-0.02 ± 0.02 log(CS); $p = 0.87$). Furthermore, L- and M-cone type differed less significantly (-0.06 ± 0.02 log(CS); $p = 0.01$) than achromatic and M-cone type (-0.08 ± 0.02 log(CS); $p = 0.001$) and the comparisons of the achromatic, M- and L-cone type with the S-cone type (achromatic 0.57 ± 0.02 log(CS) vs. M-cone 0.65 ± 0.02 log(CS) vs. L-cone 0.59 ± 0.02 log(CS); all $p < 0.0001$). Achromatic and chromatic cone types were equally influenced by diffusion, as no interaction was found between the factors.

3.2.3. Level of Diffusion

Slight differences were found in the results between the diffusion conditions. Averaging over all adaptation times, cone types, and spatial frequencies, the condition of 0.8 Bangerter foil showed reduced CS values (1.09 ± 0.06 log(CS)) compared to the 0.4 Bangerter foil condition (1.15 ± 0.06 log(CS)) and control condition (1.13 ± 0.06 log(CS)). Statistical analysis exhibited significant effect for the 0.8 Bangerter foil separately compared to the control CS (-0.04 ± 0.02 log(CS); $p = 0.05$) and 0.4 Bangerter foil CS (-0.06 ± 0.02 log(CS); $p = 0.0008$). However, no significant effect was found between control and 0.4 Bangerter foil condition (0.02 ± 0.02 log(CS); $p = 0.40$). The level of diffusion did not show significant interactions with spatial frequency, cone type, and adaptation time.

3.2.4. Contrast Adaptation

Differences in CS were found at the different measuring points, while the adaptation time significantly influenced CS ($p < 0.0001$). Here, post hoc testing showed effects between the single levels, see Figure 5. Significant outcomes were found between 0 and 90 min (0.12 ± 0.02 log(CS); $p < 0.0001$) of adaptation and between 30 and 90 min of adaptation (0.08 ± 0.02 log(CS); $p < 0.0001$), but not between 0 and 30 min (0.03 ± 0.02 log(CS); $p = 0.14$). However, CS was slightly reduced over the time (T_0 1.17 ± 0.06 log(CS), T_{30} 1.14 ± 0.06 log(CS) and T_{90} 1.06 ± 0.06 log(CS)). As no interactions were found between adaptation time and the other factors, no significant influence of Bangerter foil density or of the cone types were revealed.

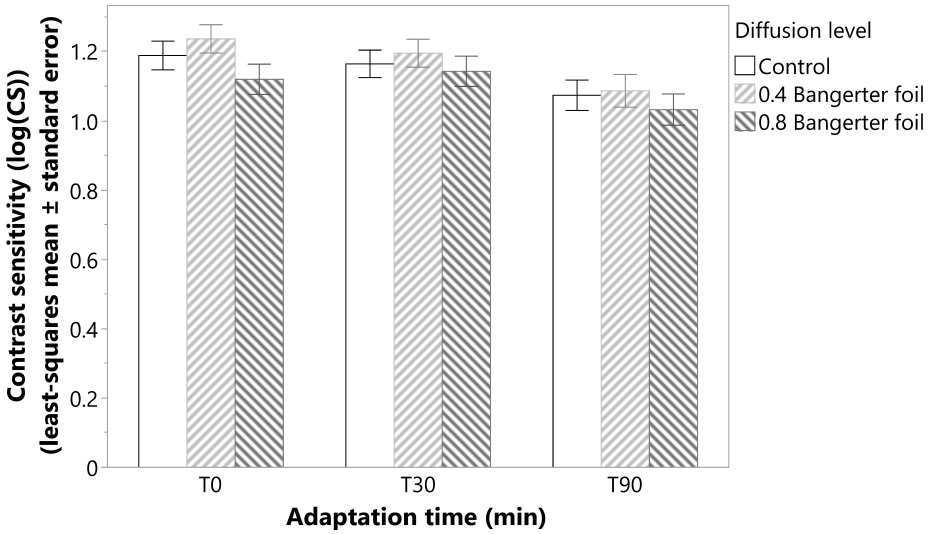

Figure 5. Least-squares mean ± standard error in log(CS) for the different diffusion levels over the adaptation time in min ($n = 19$ participants).

4. Discussion

The current study investigated the effect of different levels of peripheral contrast reduction in central achromatic and cone type specific CS to show if there is a retinal signal alteration or interaction from periphery to center. All influence factors (spatial frequency, cone type, diffusion level, and adaptation time) showed a significant effect on CS, without revealing relevant interactions. The following findings contributed to further understandings of processing and adaptation mechanisms.

The higher spatial frequency of 12 cpd produced lower CS compared to 3 cpd among all conditions compared to 3 cpd. This is already known from previous literature in context of the CS function, while there is an expected sensitivity peak at 2–5 cpd and sensitivities at smaller or greater frequencies than the peak frequency are lower [34]. Moreover, CS at 12 cpd exhibited higher deviations, which might be explained by the fact that contrast at higher spatial frequencies is harder to detect [33]. Furthermore, the results of this study showed lower sensitivities compared to the previous literature of Taylor et al. and Schilling et al. [18,33], although the participants wore their individual correction and an accommodation addition lens to reduce accommodation fluctuations. These discrepancies of previous and current CS results are due to different test procedures (e.g., two- or four-alternative forced-choice, 2IFC, method of adjustment) [33,35,36] and stimulus types (e.g., optotypes, sinusoidal pattern, silent substitution) [18,33,35,36]. Here, the four-alternative forced-choice Tuebingen CS Test figured as the basis for use in this study [33], as well as the stimulus types based on silent substitution. [18]

Differences in cone type CS were found in this study as well, which is in accordance with Taylor et al. [18]. In both studies, the S-cone type exhibited the lowest CS compared to the M-cone, L-cone, and achromatic conditions, which is explained by the filtering of short-wavelength light by crystalline lens and macular pigment [37], lacking in central fovea and lower distribution among the retina [38,39], as well as decreased spatial resolution compared to M- and L-cones [19]. Achromatic, M-, and L-cone type showed similar sensitivities since stimuli are detected by a highly sensitive pathway mechanism [18].

Furthermore, longitudinal chromatic aberration, a color signal, can shift the focal plane, which in turn can produce blur [12,18]. On the one hand, chromatic aberration is associated with adaptation phenomena [12], and on the other hand, contrast adaptation was found to be independent from longitudinal chromatic aberration [9]. Consequently, the chromatic effect was not controlled in the current study and thus could not be ruled out, although the stimulus time was limited to 153 ms. Another limitation is that cone types can be silenced at the level of phototransduction, but not on the output level [40]. Consequently, the silenced cones will still respond with a decreased signal, whereas the targeted cone type

recognizes a light intensity increase [40]. Furthermore, the standard luminosity function $v(\lambda)$ figured as the baseline for the described monitor calibration. This function was not individually obtained for each study participant. Consequently, this could lead to a slight imbalance among subjects in the brightness perception of the different test stimuli.

Surprisingly, the exposure to the 0.8 Bangerter foil condition revealed a higher impact in CS compared to the higher Bangerter foil of 0.4 density. The latter did not show any significant effect compared to the control condition. Consequently, the influence on visual performance depends on the level of the diffusion. Previous studies found similar results for different densities of Bangerter foils [12,41,42]. Especially, 0.4 and 0.8 Bangerter foil found to perform similarly [42]. Moreover, Bangerter foils demonstrated variations in quality, scattering characteristics, and impact in vision as the foils do not always comply with the manufacturer's specifications [41,42]. Therefore, the same Bangerter foil was used for all participants in this study. Furthermore, the Bangerter foils reduced visual acuity by always 0.1 logMAR steps (0.8 Bangerter foil) and 0.5 logMAR steps (0.4 Bangerter foil). Therefore, it did not create the same resulting visual acuities among participants, as this is dependent on the individual baseline acuity. To the authors best knowledge, the current approach is more meaningful, as it is also used in the myopia control spectacles [16,17].

So far, CS was only measured centrally after central adaptation [6,7,12,20–24] or peripherally after peripheral adaptation [6,7,22,25], but not its translation from the peripheral to the central retina. Regarding full-field imposed Bangerter foils, previous studies found an improvement of the visual performance after short-term adaptation to diffusion [12]. However, Villa-Carpes et al. did not find a lasting effect as the visual acuity was restored after removing the 0.6 Bangerter foils [12]. Teoh et al. found contrary results, as the visual acuity was reduced during exposure to Bangerter foils [23]. Investigations of spatial visual performance also found a reduction in CS in addition with diffusion [43]. Other studies focused on the effect on axial length, which is one important metric parameter in refractive development. Therefore, no beneficial changes of Bangerter foils were found in context of myopia treatment, consequently a reduction in axial length [23,24]. Moreover, in a primate study, it was found that Bangerter filter induced form deprivation myopia due to retinal image degradation [44]. According to a novel spectacle lens design including peripheral diffusion with a clear central zone, an early and non-peer-reviewed clinical study showed beneficial effects on refractive error reduction and reduced axial length progression [16,17]. Consequently, the results of the animal study [44] and the preliminary results of the human clinical study [16,17] are conflicting. The underlying technology of diffusion between the novel lens design and Bangerter foils probably differ from each other [45]. It is also worth mentioning that a clear central aperture smaller than the pupil size affects vision of the pupil periphery, as the pupil is a critical factor for adaptation processes [12,15,46]. Therefore, a clear central zone of 8.0 mm was chosen in this study to avoid crosstalk at the peripheral pupil area and no scattering can occur in this way. After all, previous findings are somehow contradictory and retinal mechanisms based on contrast reduction are still unclear, especially in the context of refractive development and its regulation. This study aimed to add information in adaptation procedures regarding peripheral contrast reduction. Additionally, comfort and compliance are maintained for the wearer due to a clear central aperture.

Contrast adaptation was not found neither for the 0.4 nor for the 0.8 Bangerter foil condition in the current study but a reduction in CS over the time. Main changes exhibited between 30 and 90 min of adaptation, while in the first 30 min no significant effect was found in CS. As mentioned above, Villa-Carpes et al. found an adaptation to 0.6 Bangerter foil after 40 min of adaption, except when exposed to full-field diffusion [12]. Nevertheless, contrast adaptation was found to be a signal for eye growth [44,47]. Long-term adaptation processes to retinal contrast reduction need to be investigated to evaluate lasting effects in refractive development. Furthermore, as peripheral contrast reduction imposed by 0.4 Bangerter foil affected central CS in this study, there might be a retinal translation from periphery to center—although contrast adaptation was associated with cortical processes,

so far [12,15,48]. Moreover, Maniglia et al. suggest cortical interactions between fovea and periphery [49], while contrast sensitivity can be modulated by effects of surround suppression [50], lateral masking [51], and other complex network interconnections [52]. This study, however, cannot distinguish, based on its psychophysical procedure, whether these findings underlie retinal and/or cortical interactions. Consequently, further studies are required to investigate optical, retinal, and neural adaptation mechanisms.

5. Conclusions

The study investigated central achromatic and chromatic CS for different peripheral contrast reduction levels with up to 90 min of adaptation time. Here, the lower diffusion levels affected central CS more than higher diffusion levels compared to the control condition. However, a reduction instead of increase in CS was found over time. These psychophysical findings figure as a basis for future research and clinical purposes to fully understand retinal and cortical adaptation mechanisms behind the potential myopia control strategy using peripheral contrast reduction.

Supplementary Materials: The following supplementary material is available online at https://gin.g-node.org/antonia.neumann/photonics-1601950.git, Table S1: Akaike information criterion (AIC) comparison of linear mixed model analysis. Within the model analysis, contrast sensitivity (CS) figured as numeric dependent variable, with participants (subjects, $n = 19$) as random effect and four within-subject factors: Refractive group (Group; non-myopes with a refractive spherical equivalent >-0.5 D and myopes with a refractive spherical equivalent ≤ -0.5 D), stimuli type (ST; Achromatic, S-, M- and L-cone), spatial frequency (SF; 3 cpd and 12 cpd), diffusion level (D; control/without diffusion, 0.4 and 0.8 Bangerter foil each with a clear aperture of 8.0 mm) and adaptation time (Time; T0 – 0 min, T30 – 30 min and T90 – 90 min).

Author Contributions: Conceptualization, A.N., A.L., N.N., K.B. and S.W.; methodology, A.N., A.L. and K.B.; software, A.N., P.E. and Y.S.; validation, A.N.; formal analysis, A.N. and K.B.; investigation, A.N.; resources, S.W.; data curation, A.N.; writing—original draft preparation, A.N.; writing—review and editing, A.N., A.L., N.N., Y.S., P.E., K.B. and S.W.; visualization, A.N. and K.B.; supervision, A.L., K.B. and S.W.; project administration, S.W.; funding acquisition, S.W. All authors have read and agreed to the published version of the manuscript.

Funding: Funding was received from Eberhard Karls University Tübingen (ZUK 63) as part of the German Excellence initiative from the Federal Ministry of Education and Research (BMBF). Further funding was received from Deutsche Forschungsgemeinschaft and Open Access Publishing Fund of University of Tübingen. The funders did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Institutional Review Board Statement: This prospective study was carried out at the Institute for Ophthalmic Research at the University of Tübingen. The study protocol followed the Declaration of Helsinki and data protection regulations. Approval was obtained by the ethics committee of the Faculty of Medicine of the University of Tübingen.

Informed Consent Statement: Written informed consent was obtained from all participants after the content and possible consequences of the study had been explained.

Data Availability Statement: Data available on request.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CS	Contrast sensitivity
L-cones	Long-wavelength light sensitive cones
M-cones	Middle-wavelength light sensitive cones
S-cones	Short-wavelength light sensitive cones

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Publication 2:

Foveal neural adaptation to optically induced contrast reduction

Foveal neural adaptation to optically induced contrast reduction

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Contrast processing is suggested to interact with eye growth and myopia development. A novel contrast-reducing myopia control lens design decreases image contrast and was shown to slow myopia progression. Limited insights exist regarding neural visual processing following adaptation to image contrast reduction. This study investigated foveal neural contrast sensitivity in 29 young adults following a 30-minute adaptation to scattering using a Bangerter occlusion foil 0.8, +0.5-diopter defocus, and a clear lens control condition. Neural contrast sensitivity at its peak sensitivity of 6 cycles per degree was assessed before and after adaptation to the lens conditions, employing a unique interferometric system. Pre-adaptation measurements were averaged from six replicates and post-adaptation measurements by the first and last three of six replicates. The change in neural contrast sensitivity was largest for scattering across the first and last three post-adaptation measurements (+0.05 ± 0.01 logCS and +0.04 ± 0.01 logCS, respectively) compared with control and defocus (all +0.03 ± 0.01 logCS). For scattering, the observed increase of neural contrast sensitivity within the first three measurements differed significantly from the pre-adaptation baseline ($p = 0.04$) and was significantly higher compared with the control condition ($p = 0.04$). The sensitivity increases in the control and defocus conditions were not significant (all $p > 0.05$). As the adaptation effect diminished, no significant differences were found from baseline or between the conditions in the last three measurements (all $p > 0.05$). When post-adaptation neural contrast sensitivities were clustered into 25-second sequences, a significant effect was observed between the conditions, with only a significant relevant effect between control and scattering at 25 seconds ($p = 0.04$) and no further significant effects (all $p > 0.05$). The alteration in neural contrast sensitivity at peak sensitivity was most pronounced following adaptation to the scattering condition compared with defocus and control, suggesting that induced scattering might be considered for myopia control.

Introduction

Myopia is one of the most common ocular disorders (Holden et al., 2016) based on the imbalance of the ocular axial length and the refractive power of the cornea and lens (Atchison, Schmid, & Pritchard, 2006). Greater eye growth corresponds to an elevated risk of developing various eye diseases (e.g., choroidal thinning, retinal detachment, glaucoma, myopic maculopathy), ultimately resulting in visual impairment (Ohno-Matsui et al., 2021; Vera-Diaz, Bex, Ferreira, & Kosovicheva, 2018).

A need to control myopia progression exists. Thus, myopia control strategies aim to minimize abnormal axial elongation of the eye. Among environmental and pharmacological strategies, various optical strategies exist (Kaiti, Shyangbo, Sharma, & Dahal, 2021). The latter can be divided into contact lenses and spectacle lenses, where spectacles present a non-invasive myopia treatment solution. Current spectacle lenses are designed based on three hypotheses: (a) a mutation in either the L- or M-cone opsin results in an abnormally high contrast signal, which in turn interferes with the eye growth control loop (Hagen et al., 2019; Rappon et al., 2022a); (b) imposed peripheral myopic defocus

Citation: Roth, A., Breher, K., Domdei, N., & Wahl, S. (2024). Foveal neural adaptation to optically induced contrast reduction. *Journal of Vision*, *24*(9):13, 1–17, https://doi.org/10.1167/jov.24.9.13.

https://doi.org/10.1167/jov.24.9.13 Received November 9, 2023; published September 17, 2024 ISSN 1534-7362

slows axial elongation (Berntsen, Barr, Mutti, & Zadnik, 2013; Walline et al., 2020); and (c) decreasing the lag of accommodation minimizes hyperopic defocus and slows myopia progression (Logan et al., 2021; Seidemann & Schaeffel, 2003). These three hypotheses collectively suggesting that altering retinal image quality induced by myopia control lenses might reset the growth control loop (Rappon, Neitz, & Neitz, 2020; Rappon, Neitz, Neitz, & Chalberg, 2022b; Rappon, Neitz, Neitz, Chung, & Chalberg, 2022c).

A recent study investigated parameters such as sharpness and contrast via optical characterization of scattering lenses (diffusion optics technology [DOT]) and defocus lenses (defocus incorporated multiple segments [DIMSs]). For the scattering lens, a decrease in peripheral contrast and sharpness was found, related to hypothesis (a) (Arias, Ohlendorf, Artal, & Wahl, 2023; Pérez, Archer, & Artal, 2010). For the defocus lens, an increase in peripheral contrast and sharpness was found, referred to as hypothesis (b) (Arias et al., 2023). Hypothesis (c) is applied centrally and improves the foveal but not peripheral image quality, which is achieved via progressive addition lenses. This suggests distinct underlying mechanisms for each lens strategy.

Thus, current myopia research is focused on understanding the central and peripheral retinal processes involving scattering and defocus, whereby myopia control lenses are designed to influence the retinal periphery. A clinical trial investigating induced scattering through DOT lenses (SightGlass Vision, Inc., 2023) has shown promising results, reporting reduced progression in myopic refractive error and axial elongation (Rappon, Neitz, & Neitz, 2020; Rappon et al., 2022c). In contrast, animal studies found form-deprivation myopia after adaptation to scatter lenses or diffusers (Bowrey, Metse, Leotta, Zeng, & McFadden, 2015; Fitzgerald, Wildsoet, & Reiner, 2002; Flitcroft, Harb, & Wildsoet, 2019; Smith & Hung, 2000; Smith et al., 2007; Tran, Chiu, Tian, & Wildsoet, 2008). Investigating DIMS lenses, a human clinical trial also exhibited a reduction in myopia progression (Lam et al., 2020). In general, previous literature has shown that full-field-of-view exposure to positive lenses slows myopia progression (Berntsen et al., 2013; Logan et al., 2021; Seidemann & Schaeffel, 2003; Walline et al., 2020), as the peripheral image is focused on the retina, whereas negative lenses, focusing the image behind the retina, promote myopia progression (Leube, Ohlendorf, & Wahl, 2016; Ohlendorf & Schaeffel, 2009; Thibos, Bradley, Liu, & López-Gil, 2013).

The visual system is, among others, able to adapt to alterations in contrast and blur, which has been the subject of recent extensive myopia research (Sankaridurg et al., 2023; Vera-Diaz et al., 2018). Contrast adaptation, defined by an altered contrast sensitivity, occurs due to the recalibration of spatial frequency channels and therefore changes the sensitivity of the visual system (Blakemore & Campbell, 1969b). Insufficient and contradictory information is available about short-term adaptation processes to scattering in humans. The literature to date shows that short-term adaptation to scattering leads, on the one hand, to an improvement in visual performance (Villa-Carpes, Bueno, & Fernández, 2021), whereas, on the other hand, eye lengthening (Teoh, Collins, Read, & Pieterse, 2021) and a decrease in contrast sensitivity (Breher, Neumann, Kurth, Schaeffel, & Wahl, 2023; Neumann et al., 2022) have been reported. Furthermore, the underlying mechanisms are not yet clear and require further investigation.

Contrast adaptation to myopic defocus is associated with thickening of the choroid and thus controlling myopia by slowing down the lengthening of the eye (Sankaridurg et al., 2023). In this context, short-term adaptation is thought to provide a hint regarding the success of the applied myopia control strategy (Ghosh, Zheleznyak, Barbot, Jung, & Yoon, 2017; Ohlendorf & Schaeffel, 2009). The increase in sensitivity of the contrast channels due to the adaptation process plays a crucial role in the signal cascade in regulating eye growth (Diether, Gekeler, & Schaeffel, 2001; Mon-Williams, Tresilian, Strang, Kochhar, & Wann, 1998).

However, studies investigating contrast sensitivity are limited by the influence of the optical properties of the eye (Ghosh et al., 2017), altering the individually perceived stimulus contrast. This limitation can be circumvented via laser interferometry, which allows for an aberration-free stimulation by bypassing the optics of the eye and therefore assessment of the neural contrast sensitivity (Campbell & Green, 1965; Suchkov, Kurian, Schwarz, Leube, & Wahl, 2021).

The purpose of this study was to investigate how neural contrast sensitivity adapts to reduced retinal image contrast caused by scattering or defocus at the sensitivity peak (Blakemore & Campbell, 1969a; Michael, Guevara, de la Paz, Alvarez de Toledo, & Barraquer, 2011). The study aims to identify changes in neural contrast sensitivity following exposure to these conditions, which are relevant strategies in myopia control. To elaborate the persistence of potential effects, these changes are analyzed over time. The results can provide insights into neural processing after adaptation to the lens conditions. In addition, it allows the evaluation of potential differences in neural processing between the scattering and defocus and whether the use of such strategies could be beneficial in controlling myopia progression.

Material and methods

Study participants

This prospective study was conducted at the Institute for Ophthalmic Research at the University of Tübingen. The study protocol followed the tenets of the Declaration of Helsinki and data protection regulations. Approval was obtained from the ethics committee of the Faculty of Medicine of the University of Tübingen. Before the measurements, participants signed a written informed consent form after the content and possible consequences of the study had been explained. Inclusion criteria were self-reported systemic and ocular health, corrected visual acuity of $\leq$0.1 logMAR, and age between 18 and 40 years. Participants were excluded who had astigmatism $>$ 2 diopters (D), anisometropia of $>$1 D, or a history of orthokeratology wear or refractive surgery. Additional measurements were conducted to confirm inclusion criteria. Here, screening for corneal and retinal abnormalities was performed using wavefront aberrometry (ZEISS i.Profiler^{plus}; Carl Zeiss Vision, Aalen, Germany), biometry (ZEISS IOLMaster 700; Carl Zeiss Meditec, Jena, Germany), and optical coherence tomography (ZEISS PLEX Elite 9000; Carl Zeiss Meditec, Dublin, USA). Subjective refraction was carried out using ZEISS VISUSCREEN 500 and ZEISS VISUPHOR 500 (Carl Zeiss Vision) to fully correct the subjective spherical and astigmatic refractive errors with a trial frame (Oculus B5; Oculus, Wetzlar, Germany) and trial lenses (Oculus BK 1/T; Oculus) in a vertex distance of 12 mm.

Neural contrast adaptation assessment

Neural contrast sensitivity was psychophysically assessed with an interferometric system that enables projecting aberration-free gratings directly on the retina (Campbell & Green, 1965; Williams, 1985). The setup is described in detail elsewhere (Breher, Gottschalk, Domdei, & Wahl, 2022; Suchkov et al., 2021). In brief, the key element of the system, a spatial light modulator, splits the light of a coherent light source via phase mask into two laterally separated wavefronts. These two beams are focused on the pupil plane of the eye, diverge behind, and form interference fringes on the retina. The advantage of this test procedure is that optical aberrations of the eye can be neglected due to the Maxwellian view configuration, and tonic accommodation does not need to be controlled. In the study procedure, a 1.5° narrowband stimulus grating with a wavelength of 550 $\pm$ 5 nm (300 Td) was used, containing horizontal fringes with a spatial frequency of 6 cycles per degree (cpd) (Figure 1). To avoid adaptation

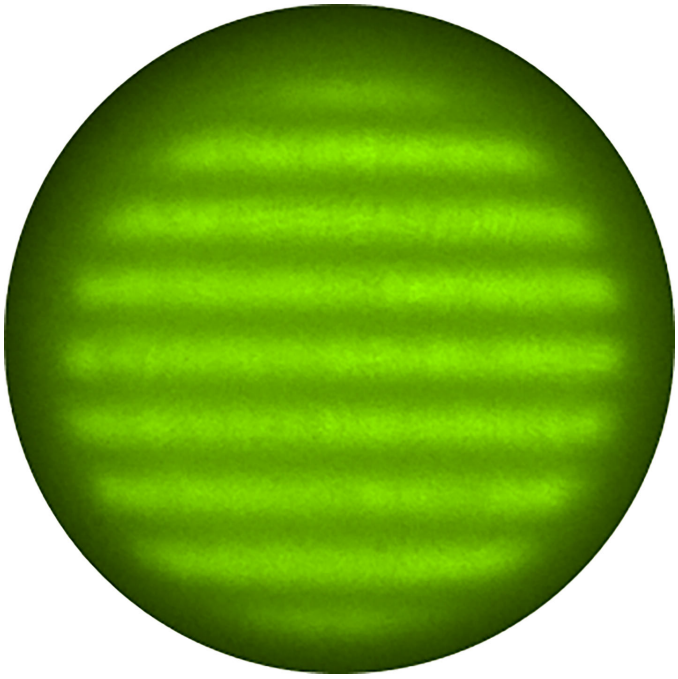

Figure 1. The high-contrast 1.5° stimulus (550 $\pm$ 5 nm, 300 Td) containing horizontal fringes at a spatial frequency of 6 cpd.

to the stimulus during the adjustment procedure, the stimulus was flashed with a flickering frequency of 1 Hz. The psychophysical testing procedure was based on the method of adjustment programmed in MATLAB R2022a (MathWorks, Natick, MA). Each trial of the neural contrast sensitivity test began with a subthreshold contrast setting of $-$2.5 log. The contrast threshold was determined by the participants, who adjusted the contrast so that the stimulus was just visible, from subthreshold contrast (not seen) to threshold contrast (barely seen). Two possible contrast adjustment step sizes were implemented: 0.05 log and 0.20 log. This study included six stimulus presentations per measurement run. An individual bite bar was prepared to align the participant's eye with the pupil plane of the system. An on-axis pupil camera (DMK 27AUP031; The Imaging Source Europe, Bremen, Germany) was used to monitor the ideal position of the participant's eye, which, if necessary, was corrected to ensure a stable stimulus formation on the central retina during testing.

Adaptation conditions

The following lens conditions were applied binocularly to degrade the retinal image: Bangerter foil with a density of 0.8 (Breitfeld & Schliekert, Karben, Germany), referred to as "scattering," and a spherical defocus of +0.5 D, referred to as "defocus." The

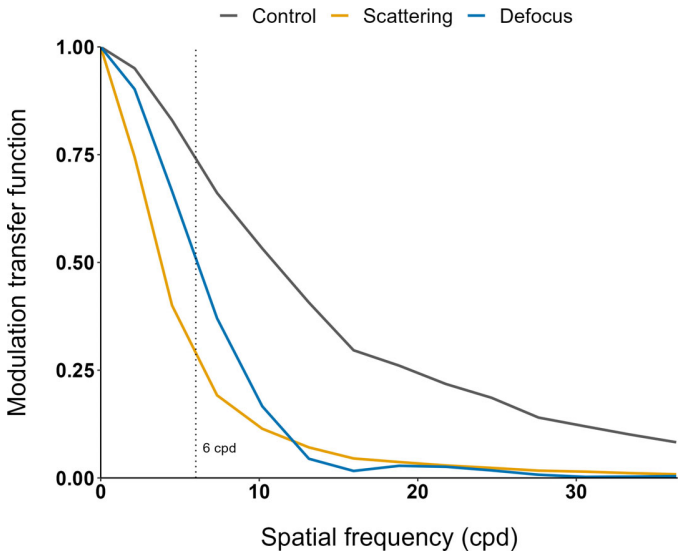

Figure 2. MTF in the range of spatial frequencies from 0 to 36 cpd for the different adaptation lens conditions (control, scattering, and defocus) for the average human eye (Watson, 2013). The dashed line indicates the tested spatial frequency of 6 cpd.

dioptric power of defocus was matched to the scattering condition by a visual acuity reduction of one line on the letter vision chart (+0.1 logMAR), comparable to a recent study investigating DOT lenses (Rappon et al., 2022b). Both image degrading conditions were compared to a clear lens control condition. For a more detailed comparison, the lens conditions were optically characterized by a novel system based on the technology of spatial light modulation (Arias et al., 2023). The system had a 532-nm-wavelength laser light source and captured images of the respective point spread function under central illumination. The modulation transfer function (MTF) was given by the absolute value of the Fourier transform of the point spread function. Subsequently, the MTF data for the lens was multiplied pointwise by the averaged human MTF values for a pupil diameter of 5 mm (Watson, 2013). The MTF results for the lens conditions in the human eye are presented in Figure 2.

Study procedure

The effect of each condition on neural contrast sensitivity was investigated on separate days at the same time of the day to avoid diurnal fluctuations in vision or fatigue (Foster & Hankins, 2007; Tassi & Pins, 1997). To account for daily variabilities in visual performance, for each lens condition a baseline was recorded before adaptation, which was then compared to the measurements after exposure to this lens. The conditions were randomized to minimize any training effects due to the unusual stimulus presentation method. The respective test lenses were mounted in the aforementioned trial frame in addition to the individual's spherocylindrical correction. The study procedure involved a 10-minute rest adaptation, where the participants sat relaxed in a mesopic lighted room without any visual or physical task. The relaxation phase was followed by a neural contrast sensitivity test training round to ensure equal starting conditions for the primary investigation among the participants. Following this, the baseline was determined by pooling across six pre-adaption neural contrast sensitivity measurements. Subsequently, the participants underwent a 30-minute adaptation to the respective lens condition. During the adaptation phase, the participants watched a movie that mimicked indoor scene viewing in a room with 350-lux lighting from a distance of 5 meters with a field of view of 3.66° to avoid accommodation. The mean pupil diameter of the participants under these conditions was similar across the lens conditions, measuring 4 mm on average when assessed prior to adaptation. Finally, six post-adaptation neural contrast sensitivity measurements were performed to determine possible changes as a result of the adaptation to the lens condition. The neural contrast adaptation reported in the following was defined by the difference in neural contrast sensitivity between the baseline and the respective post-adaption dataset. Neural contrast sensitivity measurements were taken on the dominant eye of each participant without any lens in front of the eye. The dominant eye was determined by having each participant look through the small aperture between their interlaced fingers. The visible eye from the examiner's side through the aperture constituted their dominant eye, following a standard clinical procedure (Crider, 1944; Fink, 1938; Mapp, Ono, & Barbeito, 2003; Porac & Coren, 1976).

Statistical analysis

Data were analyzed using R (R Core Team, 2020). Participant information regarding refractive error and axial length is described as mean and standard deviation (*SD*). Neural contrast sensitivity and neural contrast adaptation (determined by changes in post-adaptation neural contrast sensitivity from pre-adaptation neural contrast sensitivity) are reported as mean and standard error (*SE*) in logarithmic scale units (log contrast sensitivity [logCS]). Before statistical analysis, datasets underwent outlier removal using a boxplot analysis, with data points < 1.80 logCS and > 2.55 logCS excluded. The datasets were then grouped separately for the performed measurement number (1–6), time (pre- or post-adaptation), and condition (control, scattering, or defocus) across the participants. Pre-adaptation data points 1.5 interquartile ranges (IQRs) outside of the median were removed. To allow for differences in

neural contrast sensitivity after adaptation to the lens condition, a larger outlier range was selected for the post-adaptation results. Therefore, data points 3 IQRs away from the median were excluded from further analysis. Furthermore, pre-adaptation data points were averaged across the six consecutively performed contrast sensitivity measurements (per condition and for each participant). Post-adaptation data points were grouped for the first three (1–3) and the second three (4–6) measurements. The change of post-adaptation data (for each measurement group) was calculated from the averaged pre-adaptation neural contrast sensitivity. The repeatability, the 95% repeatability limit (McAlinden, Khadka, & Pesudovs, 2011), and the time efficiency of the testing procedure were analyzed based on the neural contrast sensitivity results prior to adaptation. Furthermore, the reproducibility was assessed by Bland–Altman analysis (Euser, Dekker, & le Cessie, 2008) and as the intraclass correlation coefficient (ICC) based on the pre-adaptation neural contrast sensitivity values across the three lens conditions. The ICC is interpreted as excellent between 0.75 and 1.00, as good between 0.60 and 0.74, as fair between 0.40 and 0.59, and as poor for values smaller than 0.40 (Cicchetti, 1994). Normal distribution of the data was verified with the Lilliefors test. Statistical analysis was then conducted using repeated-measures analysis of variance (ANOVA) with sphericity correction by Mauchly's sphericity test, as well as post hoc testing of pairwise *t*-tests with Bonferroni correction and pairwise Friedman rank-sum test. The following factors were analyzed according to neural contrast sensitivity and adaptation: three levels of condition (control, scattering, and defocus) and two levels of time (pre- and post-adaptation). Additionally, adaptation in dependence on testing time was analyzed by comparing the post-adaptation neural contrast sensitivity from baseline. Because the average trial duration was about 25 seconds (Figure 5), the data were clustered into 25 ± 12.5-second sequences as follows: ≤12.5 seconds, >12.5 to ≤37.5 seconds (referred to as "25 seconds"), >37.5 to ≤62.5 seconds (referred to as "50 seconds"), and so on through >150 seconds (referred to as ">150 seconds"). The clustered data points were analyzed using a linear mixed model and the post hoc test of estimated marginal means, with the dependent variable of neural contrast adaptation, the random effect of participants, and two fixed effects of condition (control, scattering, and defocus) and time (25, 50, 75, 100, 125, 150, and >150 seconds). To note, data for ≤12.5 seconds were removed due to too few data points. The significance level set for all types of analysis was $\alpha = 0.05$ and significant effects were defined by $p < 0.05$.

Results

Participant data

A total of 29 participants were included in the study (22 females) with a mean age of 26 ± 5 years (range, 18–35). The subjective refraction of the dominant eye revealed a spherical equivalent of −1.00 ± 1.82 D (range, −5.25 to 3.88). Biometrical measurements revealed an axial length of 23.90 ± 0.91 mm for the dominant eye.

Effects on neural contrast sensitivity

Neural contrast sensitivity results are presented in Table 1 and Figure 3. Pre-adaptation neural contrast sensitivity was similar among all lens conditions with 2.16 ± 0.02 logCS. A significant increase in neural contrast sensitivity was found in the first three measurements compared with baseline neural contrast sensitivity after exposure to the scattering condition (2.20 ± 0.02 logCS; $F = 3.26$, $p = 0.04$, ANOVA) but not for control (2.18 ± 0.02 logCS) or defocus (2.19 ± 0.02 logCS; both $p > 0.05$, ANOVA). The largest difference was found after adaptation to scattering (+0.05 ± 0.02 logCS), followed by defocus (+0.03 ± 0.02 logCS), and finally after adaptation to control (+0.02 ± 0.02 logCS). A comparison of the change in neural contrast sensitivity across the lens conditions revealed a significant sensitivity increase in the scattering condition compared with the control ($F = 4.17$, $p = 0.04$, Friedman test) for the first three measurements. No effects were

Measurement	Control	Scattering	Defocus
Pre-adaptation	2.16 ± 0.02	2.16 ± 0.02	2.16 ± 0.02
Post-adaptation (measurements 1–3)	2.18 ± 0.02	2.20 ± 0.02	2.19 ± 0.02
Change, pre- vs. post-adaptation (measurements 1–3)	+0.02 ± 0.02	+0.05 ± 0.02	+0.03 ± 0.02
Post-adaptation (measurements 4–6)	2.19 ± 0.02	2.19 ± 0.02	2.18 ± 0.02
Change, pre- vs. post-adaptation (measurements 4–6)	+0.03 ± 0.01	+0.04 ± 0.01	+0.03 ± 0.01

Table 1. Pre-adaptation (averaged across all six measurements) and post-adaptation (averaged across the first three measurements and the second three measurements) neural contrast sensitivity and the differences (mean ± *SE*) in logCS for the control, scattering, and defocus conditions ($n = 29$ participants).

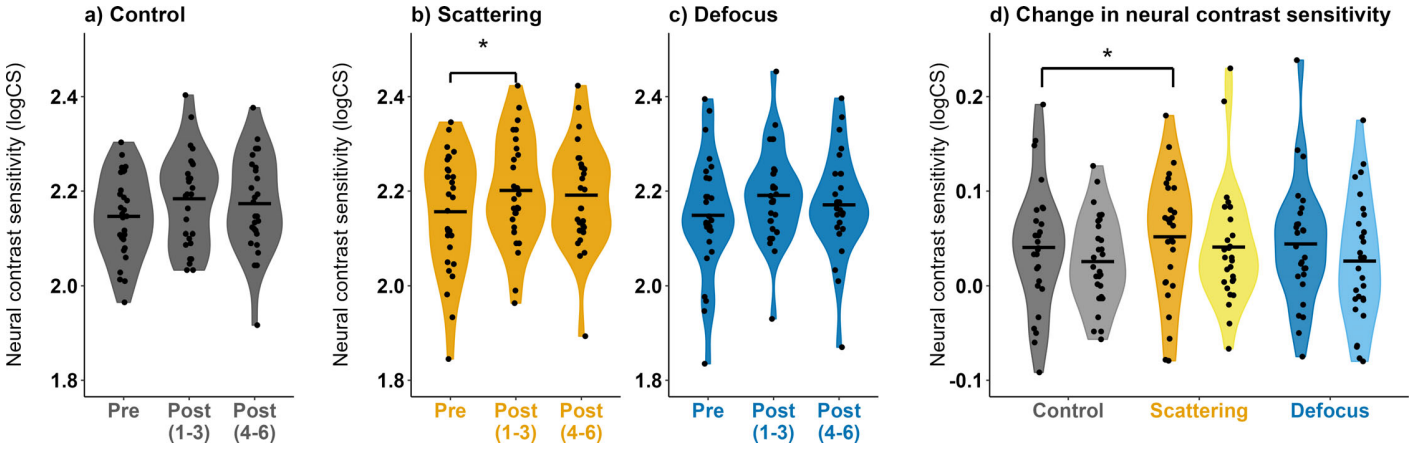

Figure 3. Mean pre- and post-adaptation neural contrast sensitivity values (in logCS; black crossbar) and their distribution for individual lens conditions: (**a**) control, (**b**) scattering, and (**c**) defocus. (**d**) Changes in neural contrast sensitivity to the conditions, averaged for the initial three and last three measurements after removal of the lens condition ($n = 29$ participants).

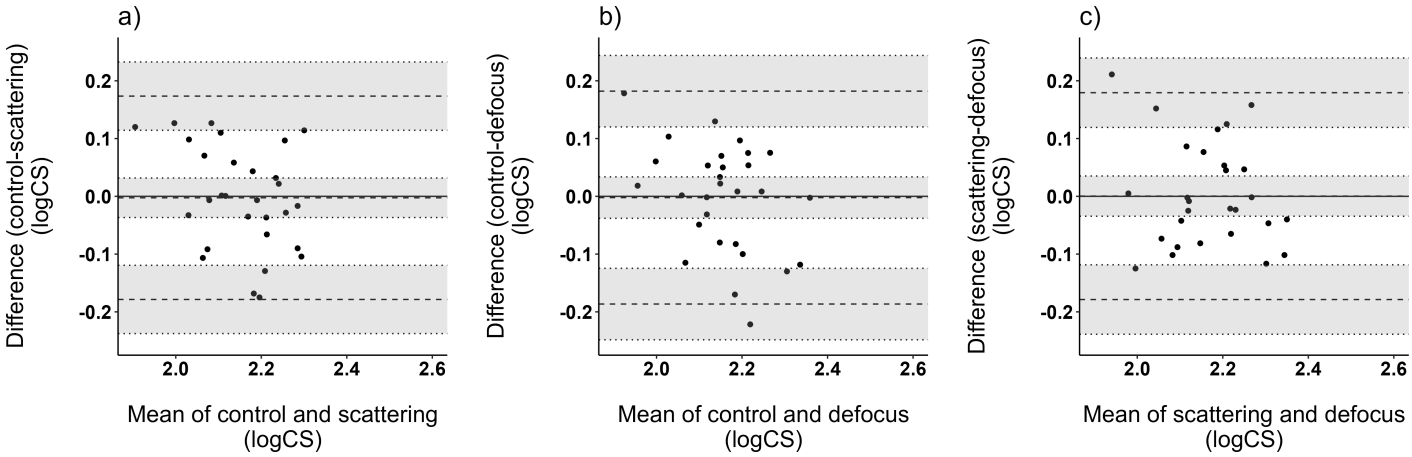

Figure 4. Bland–Altman plots of pre-adaptation neural contrast sensitivity (in logCS) of the lens conditions (**a**) control versus scattering and (**b**) control versus defocus and (**c**) scattering versus defocus, showing the mean differences and 95% confidene intervals as dashed lines ($n = 29$ participants).

found between scattering and defocus or defocus and control (all $p > 0.05$, Friedman test). For the last three post-adaptation measurements, neural contrast sensitivity was less than for the first three post-adaptation measurements (2.19 ± 0.02 logCS for both control and scattering; 2.18 ± 0.02 logCS for defocus), and no longer significantly increased compared with baseline ($F = 0.62$, $p = 0.61$, ANOVA). The differences in the observed changes for the last three post-adaptation measurements across the lens conditions were not significant (+0.04 ± 0.01 logCS, +0.03 ± 0.01 logCS, and +0.03 ± 0.01 logCS, for scatter, control, and defocus, respectively; $F = 0.42$, $p = 0.66$, ANOVA).

Analysis of pre-adaptation neural contrast sensitivity measurement repetitions showed repeatability for the method of adjustment procedure of ±0.01 logCS (95% repeatability limit of ±0.03 logCS). The reproducibility calculated by the ICC between averaged pre-adaptation measurements of the lens conditions resulted in 0.87, with a mean difference of −0.008 logCS (95% confidence interval, −0.22 to 0.21). Additionally, the difference in pre-adaptation neural contrast sensitivity between the lens conditions was compared by Bland–Altman analysis. A mean difference of −0.002 logCS was found between control and scattering (95% limits of agreement [LoA], −0.18 to 0.17) (Figure 4a). The comparison of control and defocus revealed a mean difference in pre-adaptation contrast sensitivity of −0.002 logCS (95% LoA, −0.19 to 0.18) (Figure 4b). Figure 4c shows the agreement of pre-adaptation neural contrast sensitivity between scattering and defocus with a mean difference of 0.0003 logCS (95% LoA, −0.18 to 0.18). The

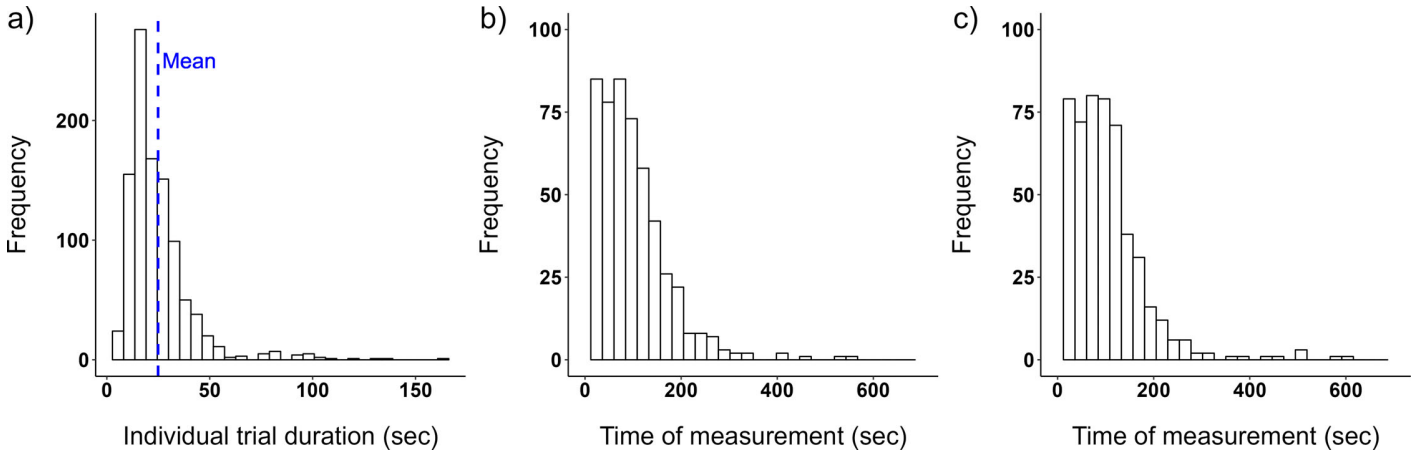

Figure 5. (**a**) The distribution of the individual adjustment trial duration (in seconds). (**b**, **c**) The response time (in seconds) across the six performed measurements before adaptation to a lens condition (**b**) and after adaptation to the lens condition (**c**) ($n = 29$ participants).

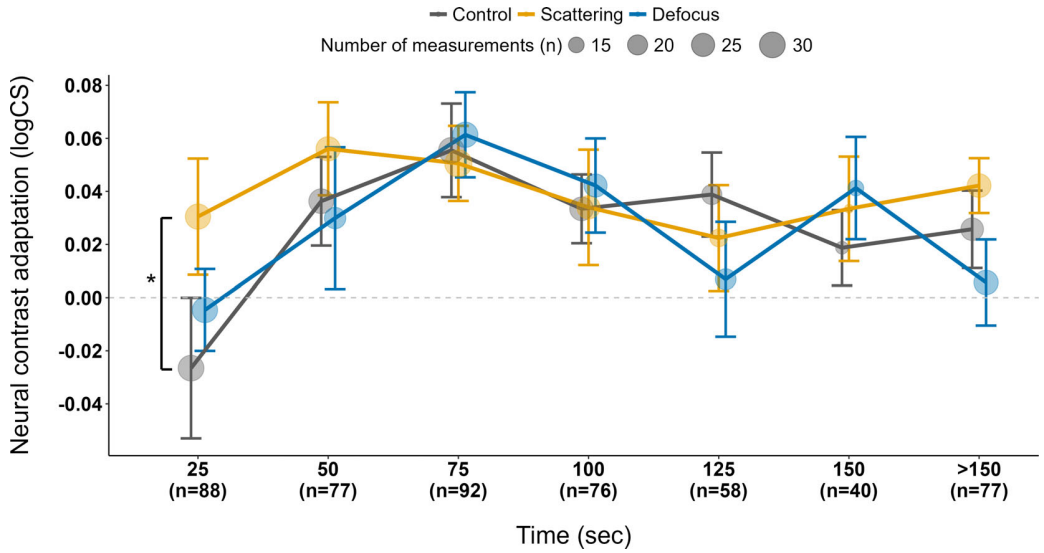

Figure 6. Change in neural contrast sensitivity of pre- versus post-adaptation (mean ± *SE*) grouped by the time of the performed measurement with a range of ±12.5 seconds for the adaptation lens conditions of control, scattering, and defocus ($n = 29$ participants).

results show excellent agreement among the lens conditions.

Time course of adaptation

The individual trial duration was on average 25 ± 16 seconds (minimum, 6 seconds; maximum, 164 seconds) (Figure 5a). The response time across the six performed measurements before adaptation to the lens condition is presented in Figure 5b and after adaptation in Figure 5c. The first three post-adaptation measurements were finished within 88 ± 53 seconds, and the second three at 171 ± 82 seconds.

Neural contrast sensitivity alterations in dependence on the testing time are displayed in Figure 6. Adaptation to the scattering condition shows quantitatively the greatest improvement in neural contrast sensitivity across the testing time when compared to the control and defocus conditions, except between 75 ± 12.5 seconds and 150 ± 12.5 seconds of measurement time. At 25 ± 12.5 seconds, the change in neural contrast sensitivity from baseline observed for scattering was significantly higher compared with the control

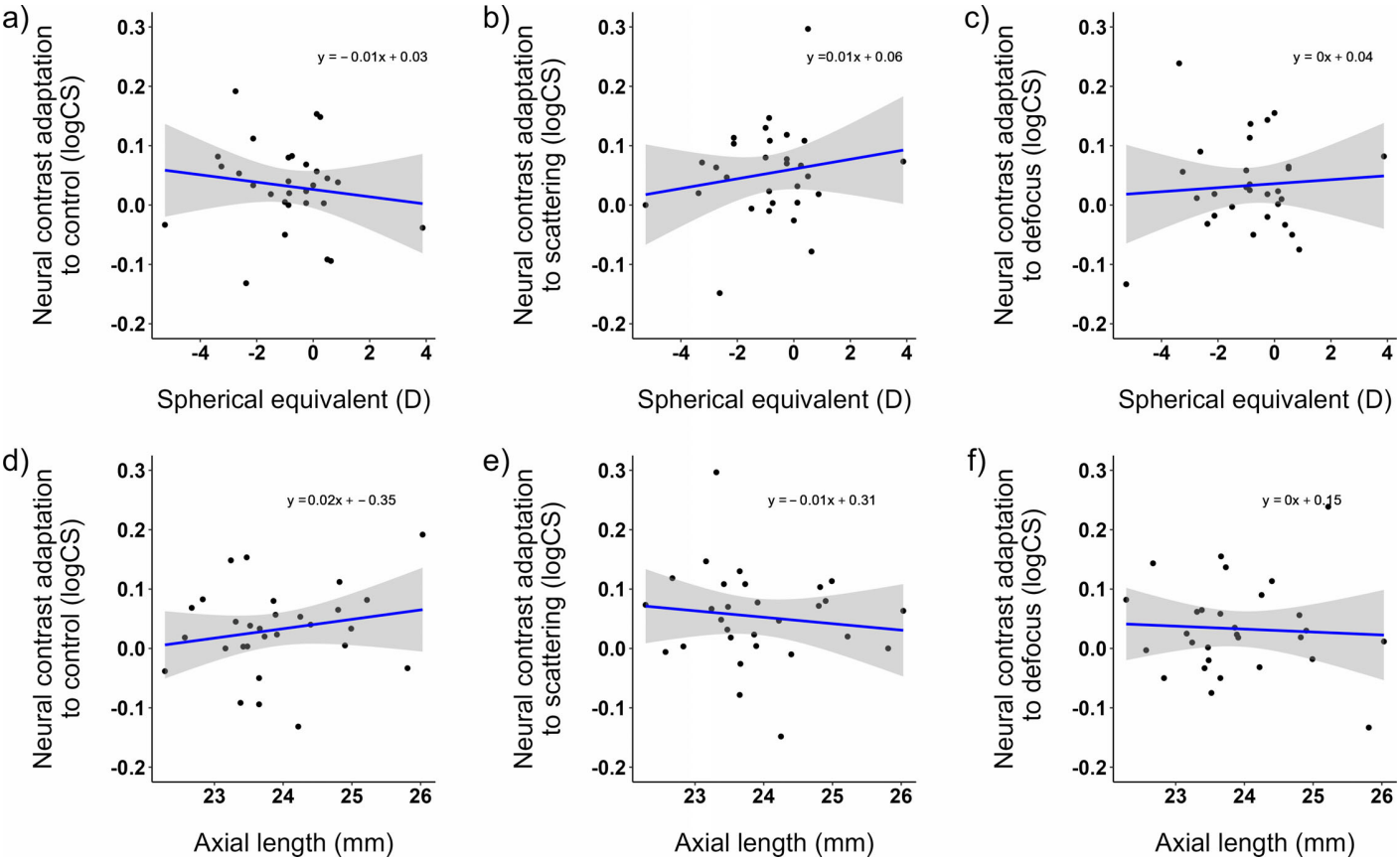

Figure 7. (**a**–**c**) Correlation of neural contrast adaptation to the conditions of control (**a**), scattering (**b**), and defocus (**c**) for the initial three measurements (in logCS) and spherical equivalent refractive error (in diopters). (**d**–**f**) Correlation of neural contrast adaptation to the conditions of control (**d**), scattering (**e**), and defocus (**f**) for the initial three measurements and axial length ($n = 29$ participants). Gray shaded areas show the 95% confidence intervals for the linear correlations.

($+0.03 \pm 0.03$ logCS vs. -0.03 ± 0.02 logCS; $F = 4.17$, $p = 0.04$, Friedman test). At all other time sequences, no statistically relevant effect was found among the lens conditions (all $p > 0.05$).

Refractive status as a covariate

To test, if the refractive status of the eye influences adaptation, the measured neural contrast adaptations for the control, scattering, and defocus conditions were correlated with the individual spherical equivalent refractive errors (Figures 7a to 7c) and axial length (Figures 7d to 7f). No significant correlation was found across the conditions (all $p > 0.05$).

Discussion

This study investigated changes in neural contrast sensitivity after short-term adaptation to scattering and defocus. A significant change of neural contrast sensitivity from baseline was found after scatter adaptation in the first three post-adaptation measurements, as it was significantly increased compared to the control condition. The adaptation effect did not last over the last three post-adaptation measurements. Neural contrast sensitivity changes were not significant for the control and defocus lens conditions. Neural contrast sensitivity depending on the measurement time revealed a significant sensitivity increase after adaptation to scattering compared with the control at 25 ± 12.5 seconds. The observed gains in neural contrast sensitivity tend to be quantitatively highest for scatter; however, these results indicate that the after-effects do not last long.

Neural contrast sensitivity effects

The size of the effect of scattering (+0.05 logCS) was marginally larger than the step size of the neural

contrast sensitivity test, based on the condition-related pre-adaptation neural contrast sensitivity; however, the adaptation effect to scattering was significantly different from the control condition. With the exhibited effect size and given the number of participants (29), a power of 84% was achieved. Pre-adaptation neural contrast sensitivity showed similar means and variations among the conditions, as shown in the Bland–Altman plots (Figure 4). Thus, a bias between the exhibited effects related to the pre-adaptation measurement can be excluded and the found changes were persistent independent of the separate measurement days.

The observed absolute, non-significant changes in relation to the control condition might be explained best by a perceptual learning effect, which was also evident in previous studies (Sagi, 2011). Notably, the change in neural contrast sensitivity following adaptation to scattering was even greater and significantly increased compared with the control condition, indicating a meaningful effect and ruling out a pure learning effect. Although neural contrast adaptation to scattering has not been investigated so far, previous studies have found contradictory contrast sensitivity results regarding adaptation to optically induced scattering using Bangerter foils. Including a clear central zone in the middle of the lens, no central contrast adaptation to a Bangerter foil of density 0.8 was found in another study (Neumann et al., 2022). Villa-Carpes et al. (2021) found an increase in visual acuity after a 40-minute adaptation period to Bangerter foils with a density of 0.6. In other studies measuring regular contrast sensitivity directly after the application of Bangerter foils (without any adaptation phase to the foils), a direct decrease was found in contrast sensitivity over a spatial frequency range of 1.5 to 12 cpd (Breher et al., 2023; Neumann, Breher, & Wahl, 2021; Pérez et al., 2010; Perez, Manzanera, & Artal, 2009) and in visual acuity (Pérez et al., 2010; Villa-Carpes et al., 2021). Furthermore, the current study found no neural adaptation to induced defocus. Adaptation to defocus has extensively been studied in the past, with reports of increases in contrast sensitivity in the mid-spatial frequency range (Venkataraman, Winter, Unsbo, & Lundström, 2015), such as at 3.22 cpd after a 10-minute adaptation to +4 D defocus (Ohlendorf & Schaeffel, 2009) and at 8 cpd and 12 cpd after a 30-minute adaptation to +2 D defocus (Rajeev & Metha, 2010). In this study, a spherical defocus of +0.5 D was applied to achieve the same visual acuity reduction as the applied scattering condition, near a depth of focus of 0.5 D (Vinas, Dorronsoro, Cortes, Pascual, & Marcos, 2015). In comparison with defocus-based optical myopia control strategies, the defocus lens applied in the current study was low in dioptric power. However, it must be taken into account that myopia control strategies are currently applied in the periphery, whereas this study aimed to investigate effects within the fovea. To translate peripheral lens characteristics into requirements for a central lens design having a similar impact on the perceived image, the structure of retinal receptive fields must be considered. At an eccentricity of 8° (roughly the onset of the blurred region for a lens with a 9-mm clear zone), the midget ganglion cell receptive field size is 4.4 arcmin (Watson, 2014). Peripheral-induced defocus lenses, such as the DIMS lenses, with a defocus power of +3.5 D generate a point spread function with a full width at half maximum (FWHM) of 67 arcmin. Thus, the point spread function of the DIMS corresponds to the 17-fold receptive field size. In the foveola, the receptive field size of midget ganglion cells corresponds directly to cone diameter (0.5 arcmin) due to a 1:1 connectivity. If the blurred point spread function should spread comparably across the ganglion cells in the fovea, the FWHM of the point spread function must be 8.5 arcmin. This requirement is quite accurately met when using a defocus of +0.5 D (FWHM = 8.6 arcmin). A low impact of the applied lens conditions on visual acuity is relevant, as visual acuity is an important parameter not only with regard to the quality of life (Brown, 1999) but also for school-aged children in education and normal ocular development (Ikeda, 1980).

The absence of an adaptation effect for spherical defocus can be explained by the lower impact on image contrast when compared to scattering. Considering the whole range of spatial frequencies, contrast is reduced differently by scattering and defocus between 0 and 20 cpd, before it aligns for spatial frequencies greater than 20 cpd. At the tested spatial frequency of 6 cpd, optical scattering reduced the MTF amplitude by approximately half compared with defocus ($MTF_{scattering} = 0.29$ vs. $MTF_{defocus} = 0.51$) (Figure 2). Furthermore, it is worth noting that a slight contrast modulation was also present in the clear control condition at 6 cpd compared with an aberration-free environment, which is negligible compared to the scattering and defocus conditions. Another possible explanation of the observed adaptation effects is a distinct retinal and neural processing of scattering and defocus. However, this could not be addressed within the current study and requires further experiments. In previous investigations, optical characterization of scattering and defocus lenses revealed differences in retinal image contrast (Arias et al., 2023; Pérez et al., 2010). Here, scattering led to a reduction in retinal image contrast and defocus to retinal image sharpening and contrast increase (Arias et al., 2023).

In this study, the participants received input from a wide range of spatial frequencies during the 30 minutes of adaptation. This approach has been used in past studies (Ohlendorf & Schaeffel, 2009;

Ohlendorf, Tabernero, & Schaeffel, 2011; Venkataraman et al., 2015). According to previous literature, indoor scenes, including movies played on a display, range from 0 to 100 cpd (Bex, Solomon, & Dakin, 2009; Flitcroft et al., 2019). However, no detailed frame-by-frame analysis of the video material has been carried out, and no over- or under-representation of certain spatial frequencies or orientations has been determined. The contrast reduction caused by the adaptation conditions in the current study affected the spatial frequency channels differently over the entire range. The found adaptation effect to scattering at 6 cpd is best explained by the amount of contrast reduction over the range of spatial frequencies. An additional explanation for these adaptation effects to scattering and defocus is a required minimum amount of contrast reduction to adjust the contrast gain of underlying neural mechanisms (DeAngelis, Ohzawa, & Freeman, 1995). With adjustment of the contrast gain, the best possible image is perceived. In the present study, this enhancement of neural contrast sensitivity persisted shortly after the lenses were removed. These aftereffects were also found in previous studies (Magnussen & Greenlee, 1985; Ohlendorf & Schaeffel, 2009). The human eye is sensitive to lower spatial frequencies of natural scenery, as low or medium spatial frequencies up to 6 cpd are necessary to identify natural scenes (Bex et al., 2009). In addition, low spatial frequencies are more rapidly processed in the cortex compared with higher spatial frequencies (Kauffmann, Chauvin, Guyader, & Peyrin, 2015). Therefore, this study was performed at a spatial frequency of 6 cpd, the peak sensitivity of the contrast sensitivity function (Blakemore & Campbell, 1969a; Michael et al., 2011), where any potential changes would be mostly visible (Campbell & Green, 1965). Furthermore, neural contrast sensitivity of only one spatial frequency was tested due to time restraints regarding the relatively short aftereffects (Greenlee, Georgeson, Magnussen, & Harris, 1991; Ohlendorf & Schaeffel, 2009).

Time course of contrast adaptation

This study investigated short-term adaptation after 30 minutes. Adaptation periods in past studies range from minutes to weeks (Khan, Dawson, Mankowska, Cufflin, & Mallen, 2013; Rutstein et al., 2011; Villa-Carpes et al., 2021). Contrast adaptation to scattering has been found after 40 minutes (Villa-Carpes et al., 2021) and to defocus already after 4 minutes (Khan et al., 2013). One study that investigated visual acuity after 6 and 12 weeks of wearing Bangerter foils during the daytime reported a significant increase in visual acuity (Rutstein et al., 2011). Further research is required on beneficial time periods to enhance visual performance and possibly beneficial effects on structural changes. In the current study, a significant adaptive aftereffect compared to control was found for scattering at 25 ± 12.5 seconds. A negative, but not significant, aftereffect was exhibited for the control condition at this specific time, as neural contrast sensitivity increased after 25 ± 12.5 seconds. The negative shift in the control condition could be explained by the adaptation process itself (Blakemore & Campbell, 1969a), despite the flickering stimulus to minimize adaptation effects. This difference in the scatter to the control condition did not last long, which is consistent with previous investigations, which have reported aftereffects of short duration (2–5 minutes) (Greenlee et al., 1991; Magnussen & Greenlee, 1985; Ohlendorf & Schaeffel, 2009).

Contrast adaptation in the context of emmetropization

Contrast adaptation and processing are assumed to play a role in myopia development based on eye growth (Aleman, Wang, & Schaeffel, 2018; Diether et al., 2001; Ohlendorf & Schaeffel, 2009; Smith & Hung, 2000; Stoimenova, 2007). Adaptation to induced myopic defocus seems to benefit myopia control by reducing axial length progression and increasing choroidal thickness, accompanied by an improvement in contrast sensitivity, whereas imposed hyperopic defocus causes the opposite (Jonas, Ohno-Matsui, & Panda-Jonas, 2019; Ohlendorf & Schaeffel, 2009). Interestingly, adapting to a low induced defocus of +0.5 D, also known as under-correction of myopia, has shown absolute myopia progression, albeit not statistically significant myopia (Adler & Millodot, 2006; Chung, Mohidin, & O'Leary, 2002; Lin et al., 2015; Vasudevan, Esposito, Peterson, Coronado, & Ciuffreda, 2014). Literature is inconclusive with respect to the effect of scattering on myopia control. The use of scattering-inducing Bangerter foils is also prevalent in animal studies and has led to form-deprivation myopia (Smith & Hung, 2000). However, in a current human clinical trial, scattering lenses resulted in a slowing of myopia progression (Neitz, Wagner-Schuman, Rowlan, Kuchenbecker, & Neitz, 2022). In a clinical study, a novel myopia control lens was used based on the hypothesis that abnormal high contrast signaling, caused by genetic cone mutations, would lead to myopia (Hagen et al., 2019). Here, it has been suggested that the reduction of retinal image contrast rebalances ON and OFF receptive field processing of the retinal ganglion cells, which controls myopia development. Asymmetric receptive field processing was not demonstrated in a previous study (Breher et al., 2023) and was not investigated in the current study.

Further to this theory, a difference between emmetropic and myopic neural contrast adaptation would be expected; however, in the current study, no significant correlation was found between neural contrast adaptation and refractive error or axial length. Consequently, the refractive status did not influence the adaptation effect. This might be explained by the level of ametropia. In addition to one highly myopic and one hyperopic participant, only emmetropic or low myopic participants took part in this study. To investigate neural adaptation effects in more detail, more high myopic participants should be included in future studies. Furthermore, only the combined retinal and cortical response was measured within the psychophysical approach of the current study. Previous studies have reported the sole responsibility of the retina for emmetropization (Aleman et al., 2018; Carrillo-Aleman, Wang, & Schaeffel, 2019; Hoseini-Yazdi, Read, Alonso-Caneiro, & Collins, 2021; Swiatczak & Schaeffel, 2022; Wallman & Winawer, 2004; Wang, Aleman, & Schaeffel, 2019). Even though it was not possible to trace the adaptation effect back to the retina, it is essential to understand that such an effect exists.

Neural contrast sensitivity assessment

The baseline (pre-adaptation) results found in the current study are comparable with previous measurements of the neural contrast sensitivity (Campbell & Green, 1965; Suchkov et al., 2021). In addition to these qualitative results, repeatability was also tested in the current study, resulting in a repeatability of ±0.01 logCS (95% repeatability limit of ±0.03 logCS). Previous studies showed poorer repeatability ranging from 0.15 to 0.40 logCS at 6 cpd for regular contrast sensitivity forced-choice procedures (Schilling, Ohlendorf, Leube, & Wahl, 2017). Another type of adjustment contrast sensitivity test reported a coefficient of repeatability of 0.13 logCS at 6 cpd (Neumann et al., 2021). The neural contrast sensitivity results measured by the interferometric system showed excellent reproducibility with an ICC of 0.87. The measurements included in the reproducibility evaluation were performed on different days, so natural daily fluctuation in visual performance could have occurred (Tassi, Pellerin, Moessinger, Hoeft, & Muzet, 2000; Tassi & Pins, 1997), which may not result in an ICC of 1.00. This is in alignment with previous test procedures showing good and excellent reproducibility (Schilling et al., 2017). Hence, the test procedure for the current study can be considered highly repeatable and having excellent reproducibility. The adjustment test method in this study showed a time duration of 25 ± 16 seconds per single run, which is similar to a regular adjustment contrast test reporting 18 seconds (Neumann et al., 2021). Forced-choice procedures have resulted in longer duration times, ranging from approximately 1 to 2 minutes (Schilling et al., 2017). Time efficiency was a goal in the current study, so that fast (de-)adaptation effects could be observed. Further, it is known that long testing procedures lower the attention of the participant (Dietze, 2008; Schilling et al., 2017). According to the current study results, the method of adjustment, newly introduced as a psychophysical procedure in combination with the system, has the potential to be a repeatable and fast test procedure, despite being time unlimited per se (Pelli & Bex, 2013; Pelli & Farell, 1995; Wier, Jesteadt, & Green, 1976). It is noteworthy that the method of adjustment involves an individual criterion to set the contrast threshold (Gescheider, 2013); therefore, the results might be systematically affected by the individually defined criterion from each participant (Lu & Dosher, 2013). To mitigate the potential bias, all participants were required to undergo all test conditions, and changes in neural contrast sensitivity were calculated individually. To monitor an eventual bias, the adaptation period to a clear control condition was implemented, as well as baseline measurements before adaptation. Analysis of pre-adaptation neural contrast sensitivity across all conditions (see Bland–Altman plots in Figure 4) revealed that the pre-adaptation neural contrast sensitivity was stable for each participant, and the changes in neural contrast sensitivity can be assigned to post-adaptation neural contrast sensitivity. In summary, the analysis of repeatability, reproducibility, and agreement showed that the individual criterion was maintained across the study. Furthermore, the interferometric system eliminated optical aberrations of each participant and therefore ruled out the possibility of any impact on neural contrast sensitivity, which is an important advantage of the test procedure.

The method of adjustment has been used before for measurements of regular contrast sensitivity (Burr & Ross, 1982; Neumann et al., 2021; Norton, Corlis, & Bailey, 2002; Wier et al., 1976). It is one of the simplest psychophysical procedures for threshold estimation; however, due to adaptation during the adjustment of the stimulus (Werner, Sharpe, & Zrenner, 2000), thresholds tend to be higher compared with forced-choice procedures (Wier et al., 1976). To avoid this limitation, the stimulus had a 1-Hz flicker. The measurements were also averaged, following recommendations from previous literature suggesting averaging when using the method of adjustment (Lu & Dosher, 2013; Pelli & Bex, 2013; Pelli & Farell, 1995). It has been suggested that the interference technique used in this study is more direct than calculation of the neural transfer function out of the contrast sensitivity function and the modulation transfer function (Leube et al., 2018). Another advantage of assessing the neural contrast sensitivity in comparison with the regular

contrast sensitivity is that the visual performance is not limited by the optics of the eye, especially higher order aberrations (Ghosh et al., 2017). Furthermore, neural contrast sensitivity is not affected by pupil size, as optical aberrations are eliminated by the measurement procedure (Campbell & Green, 1965; Dressler & Rassow, 1981; Suchkov et al., 2021). This differs from the regular contrast sensitivity metric, as the pupil here influences the optics and thus aberrations of the eye (Michael et al., 2011; Sanz Diez, Wahl, Schaeffel, & Ohlendorf, 2019; Strang, Atchison, & Woods, 1999). Furthermore, clinical measurements of the neural transfer function have already been used for perceptual training (Artal et al., 2004; Sabesan, Barbot, & Yoon, 2017; Vohnsen, 2021). Direct measurement of neural processes might be also useful not only in understanding physiological visual–neural processes but also in the detection of neural disorders. However, the amount of contrast reduction, illuminance, and intraocular scattering on the retinal level is dependent on pupil size (Arias et al., 2023; Castro-Torres, Martino, Casares-López, Ortiz-Peregrina, & Ortiz, 2021; Vohnsen, 2021), which was measured in the current study before adaptation but not controlled during the adaptation period. Similar pupil sizes can be assumed, as the participants were of similar age and ethnicity (Guillon et al., 2016; Heine, Yazdani, & Wilhelm, 2013).

Additionally, the same room lighting was ensured for all participants during the adaptation period. Effects of pupil diameter on neural contrast sensitivity itself were likely negligible, as the optical aberrations were bypassed (Watson & Yellott, 2012). The lack of a strong effect rather than just a tendency after adaptation to optical scattering might have been caused by the relatively short adaptation period. Thus, long-term effects in the range of weeks to years cannot be explained with it. By using the same Bangerter foil among the participants, differences in manufacturing of the foils and thus differences in contrast reduction levels were controlled for (Perez et al., 2009). Moreover, a Bangerter foil with microbubble patterns aligns with the novel myopia lens featuring microdiffusers. Although their manufacturing methods differ, both aim to scatter light, thus reducing visual acuity and contrast. Furthermore, this study investigated the effect of contrast reduction at the peak of the contrast sensitivity function of 6 cpd (Blakemore & Campbell, 1969a; Michael et al., 2011). The impact on lower or higher spatial frequencies was not examined. Also, higher contrast reductions and long-term effects were not included in the current study.

In summary, the alteration of neural contrast sensitivity at peak sensitivity after adaptation to optically induced scattering might be an underlying mechanism for ocular growth regulation. The question remains, then, how the mechanism controls eye growth.

Conclusions

Short-term adaptation to reduced retinal image contrast induced by scattering and defocus was psychophysically assessed at the contrast sensitivity function peak in young adults. A significantly higher increase in neural contrast sensitivity was found after adaptation to scattering in the first three measurements after lens removal compared with the control condition. Observed increases in neural contrast sensitivity from baseline after exposure to defocus and control were not significant, most likely related to the impact on contrast reduction at the tested spatial frequency of 6 cpd. Furthermore, neither axial length nor spherical equivalent was correlated with the observed alteration in neural contrast sensitivity after adaptation in any of the lens conditions and therefore did not influence the adaptation effect. Our findings indicate that scattering affected neural contrast sensitivity at peak sensitivity more than in the control and defocus conditions and therefore might be suitable as a myopia control strategy. Further research is required to determine the impact of optically induced scattering and defocus on a wide range of spatial frequencies and to define the minimal contrast reduction necessary to induce a beneficial effect in ocular growth regulation.

Keywords: contrast adaptation, neural processing, contrast sensitivity, scattering, contrast reduction

Acknowledgments

The authors express their gratitude to Augusto Arias for providing the optical characterization system and for conducting the corresponding tests.

Funding was received from Eberhard-Karls-University Tübingen (ZUK 63) as part of the German Excellence initiative from the Federal Ministry of Education and Research (BMBF). Further funding was received from Deutsche Forschungsgemeinschaft and the Open Access Publishing Fund of the University of Tübingen. The funders did not have any additional role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Commercial relationships: A. Roth, None; K. Breher, Carl Zeiss Vision International (E); N. Domdei, Carl Zeiss Vision International (E); S. Wahl, Carl Zeiss Vision International (E).
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Publication 3:

Peripheral contrast reduction optically induced by scattering lenses thickens peripheral choroid

tvst

Retina

Peripheral Contrast Reduction Optically Induced by Scattering Lenses Thickens Peripheral Choroid

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Received: March 25, 2024
Accepted: September 2, 2024
Published: October 22, 2024

Keywords: contrast reduction; scattering; choroidal thickness; axial length; visual acuity

Citation: Roth A, Breher K, Gisbert S, Arias A, Clement SP, Wahl S. Peripheral contrast reduction optically induced by scattering lenses thickens peripheral choroid. Transl Vis Sci Technol. 2024;13(10):32, https://doi.org/10.1167/tvst.13.10.32

Purpose: The mechanisms underlying a myopia control strategy using scattering lenses are unclear. Therefore, this study investigates the short-term effects of scatter lenses on central and peripheral choroidal thickness and axial length, which serve as a biomarker in myopia progression research.

Methods: In total, 23 participants underwent a 60-minute lens wear phase each to five lens conditions: medium peripheral scattering, high peripheral scattering, medium full-field scattering, high full-field scattering and control (clear lens). Central and peripheral choroidal thickness, foveal axial length, and central visual acuity were measured before and after each lens wear condition.

Results: Peripheral choroidal thickening was found after the lens wear phase of the medium peripheral scattering condition ($+3.91 \pm 5.37$ µm, $P = 0.04$), revealing a significant difference to the control lens condition ($P = 0.004$), most pronounced in the superior peripheral retina ($+1.95 \pm 10.74$ µm, $P = 0.02$). In the central retina, significant choroidal thickening was only found in the nasal part after exposure to medium full-field scattering ($+3.91 \pm 11.72$ µm) compared to the control condition ($P = 0.001$). High peripheral and full-field scattering conditions did not significantly affect central or peripheral choroidal thickness. Visual acuity was significantly reduced in the full-field scattering conditions compared to control and peripheral scattering lenses, with no improvement after 60-minute lens wear. Axial length did not differ significantly after 60-minute exposure to any scattering lens condition or when compared to the control lens.

Conclusions: The results indicate a local retinal contrast detection mechanism signals the choroid to thicken peripherally after adaptation to medium peripheral scattering but not high peripheral scattering or full-field scattering at all, while central thickening was only significant nasally after exposure to medium full-field scattering. This emphasizes the importance of the peripheral retina and the level of contrast reduction in the context of myopia research.

Translational Relevance: This finding gives insight into the mechanism behind the myopia control strategy inducing peripheral scattering.

Introduction

Retinal image quality and image contrast processing are suggested to regulate eye growth.[1–3] The deterioration of the retinal image quality leads to a disruption of the normal growth patterns of the eye, resulting in extensive ocular elongation.[2] This abnormality in eye growth can cause the development of myopic refractive error.[1,2] Myopia is a growing public health concern worldwide due to its increasing prevalence.[4,5] The development of myopia is influenced by a combination of environmental and genetic factors.[6] Exposure to higher illumination levels, wider spectral composition, higher contrast levels, and higher spatial frequencies are thought to underlie the

protective effect of outdoor activity against myopia development.[7,8] Conversely, near-work is thought to contribute to myopia development, potentially due to accommodative demand, reduced illumination, and lower contrast levels that accompany near-work.[9] Genome-wide association studies have identified multiple genes associated with myopia, shedding light on the molecular pathways underlying this condition.[10] Moreover, the robust correlation between myopia and parental history,[11] along with consistent findings from heritability studies,[12] shows that over half of the variability in refractive errors among populations is influenced by genetic factors.

The interaction of genetics and lifestyle factors is thought to trigger excessive ocular elongation, as well as myopia development and progression. This excessive elongation is oftentimes accompanied by degenerative changes in the retina, choroid, and sclera,[13] which can lead to pathologic conditions that may irreversibly reduce vision such as maculopathy, retinal detachment, choroidal neovascularization, cataracts, and glaucoma.[13,14]

Given the severe risks associated with pathologic myopia, slowing down the rate of myopia progression during childhood has become a key goal. Numerous approaches have been described in the literature to slow the progression of myopia, such as pharmaceutical interventions (e.g., atropine eye drops),[15,16] light therapy,[17–19] and optical strategies, which are applied as spectacle lenses, contact lenses, or orthokeratology.[20,21] Current optical approaches are designed to induce peripheral defocus (such as defocus incorporated multiple segments[22] and highly aspherical lenslet lenses),[23] diminish the lag of accommodation (e.g., progressive addition lenses),[24] and decrease retinal image contrast as utilized by diffusion optics technology lenses.[25] Several studies have remarked on the importance of the peripheral retina as a crucial area, in the strategy to control myopia.[26–29]

Previous literature shows that a mutation affecting mid- or long-wavelength cone opsins (OPN1MW or OPN1LW, respectively) results in a deficiency or an absence of opsin function in all cones harboring the mutation. This is thought to produce abnormally high contrast signaling between the affected and nonaffected cones, which may be a signal for eye growth.[25,30] It has been suggested that through a reduction in retinal image contrast, the ON- and OFF-bipolar cell channel pathways, which are responsible for processing image contrast, may reduce their firing rate and the stimulus to eye growth, effectively slowing ocular elongation.[31] The reduced contrast response in the ON and OFF channel pathways is suggested to slow axial elongation. The diffusion optics technology lens design is characterized by integrating light-scattering elements on the peripheral spectacle lens surface while maintaining clear vision with a central aperture of 5 mm.[25,32] The concept aims to reduce peripheral retinal image contrast and thus abnormal high contrast signaling.[25] A clinical trial study reported reduced axial elongation of −0.13 mm in myopic children when wearing diffusion optic technology spectacle lenses compared to myopes wearing single-vision lenses—after 36 months of lens wear.[25,33] Numerous studies have been conducted in animal models to elucidate the mechanisms that regulate eye growth, providing insights into human myopia. It is widely demonstrated that by covering eyes with positive or negative lenses, the eye compensates for the imposed defocus by adjusting its axial growth rate and choroidal thickness.[34–36] As in different animal models, eyes exposed to a spatially low-pass filtered retinal image using frosted diffusers developed abnormal elongation of the eye, subsequently resulting in myopia.[37–40] Nevertheless, nonsignificant axial elongation was found in humans after short-term, full-field-of-view adaptation to diffuse blur induced by Bangerter foils.[41] The mechanisms that underlie the eye's response to low-contrast stimuli remain unclear. However, there is evidence to suggest that the choroid is actively involved in the emmetropization process by changing its thickness to place the retina on the focal plane of the eye as well as releasing growth factors that ultimately lead to changes in the scleral extracellular matrix, altering eye size and refraction.[42]

The primary objective of this study is to investigate changes in choroidal thickness and axial length following short-term wear of spectacle lenses that scatter light and reduce retinal image contrast in young adults. Any regional choroidal thickness alterations are examined in response to full-field scattering lenses versus periphery-only scattering lens wear. The aim of this research is to provide insights into whether retinal image contrast modulation can influence choroidal thickness and axial length and potentially play a future role in slowing myopic ocular growth.

Materials and Methods

Study Participants

The prospective study was approved by the Medical Faculty of the University of Tübingen ethics committee and complied with the Declaration of Helsinki and data protection regulations. Before data collection, all participants signed a written informed consent after receiving an explanation of the study's procedure and potential consequences. The inclusion criteria included self-reported systemic and ocular health,

corrected visual acuity of ≤0.1 logarithm of the minimum angle of resolution (logMAR), and age between 18 and 40 years. Participants with astigmatism >2.00 diopter cylinder (DC), anisometropia of >1 diopters (D), and a history of orthokeratology wear or refractive surgery were excluded. The following measurements were conducted to confirm the inclusion criteria: screening for corneal and retinal health was performed using wavefront aberrometry (i.Profiler plus; Carl Zeiss Vision GmbH, Aalen, Germany), biometry (ZEISS IOLMaster 700; Carl Zeiss Meditec AG, Jena, Germany), optical coherence tomography (OCT) (ZEISS PlexElite 9000; Carl Zeiss Meditec Inc., Dublin, CA, USA), and the assessment of subjective refraction and visual acuity (ZEISS VISUSCREEN 500 and ZEISS VISUPHOR 500; Carl Zeiss Vision GmbH). Twenty-three participants aged 19 to 35 years (mean age 25 ± 4 years) completed this study, with a group mean spherical equivalent refractive error of −1.54 ± 1.65 D, best-corrected visual acuity of −0.20 logMAR, and baseline axial length of 23.92 ± 0.93 mm.

Scattering Lens Conditions

To reduce retinal image contrast, single-vision spectacle lenses incorporating the participant's spherocylindrical correction were sandblasted in the designated facility (Sigg Strahltechnik GmbH, Lauchingen, Germany). The effect of the scattering lenses was compared to a clear single-vision distance lens—one design involved a clear 8-mm aperture with the participant's full distance correction with the surrounding peripheral lens areas being sandblasted to produce a light-scattering effect, and the other design was entirely sandblasted, giving a full field of light scattering. Each of these two designs was made with two different amounts of light scatter: a medium level, in which the lenses were sandblasted for 25 seconds, and a high level, in which the lenses were sandblasted for 30 seconds. Glass beads ranging in size from 50 to 105 µm were blasted with a pressure of 6 bar (600 kPa) onto the lens surface, which was positioned 30 cm away in consistent circular motions, and the timing of the sandblasting was controlled with millisecond accuracy.

The scattering level was determined and aligned through optical characterization, based on spatial light modulation.[32] Images of the point spread function for each experimental lens condition were captured using a camera unit. For this purpose, a laser source of 532 nm wavelength and an artificial pupil with a diameter of 6 mm were utilized. The radial modulation transfer function of each lens was calculated by performing a fast Fourier transformation of the corresponding point spread function. The characterization involved measurements of lens sets of five participants. These lens sets were chosen with either no spherocylindrical lens power or only spherical power, as cylindrical power would have distorted the results. The determined modulation transfer function is depicted in Figure 1.

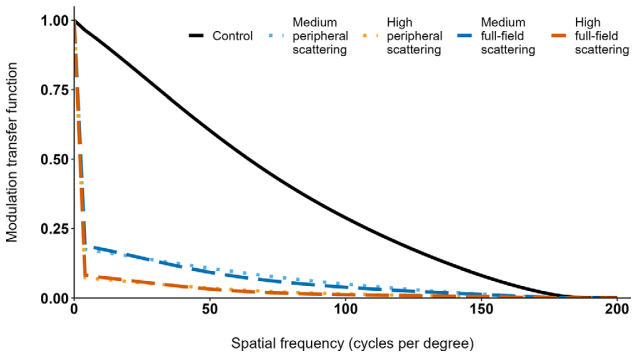

Figure 1. Radial modulation transfer function across the spatial frequencies of 0 to 200 cycles per degree.

The effects of scattering experimental lens conditions were compared with a clear lens control condition. During the experiment, the right eyes were treated with the experimental lenses, while the left eye was covered with a sandblasted single-vision lens without refractive power, with the entire lens surface sandblasted for 1 minute beforehand. Visual acuity in the left eye was tested in all participants, with only light perception being reported. The lenses for both eyes were ground into shape and mounted into a spectacle frame. Before the grinding process, the individual pupil distance and mounting height were measured to place the clear central zone of the peripheral scattering lenses to the optical center (see Figs. 2a–d). The spectacle frame was chosen between a smaller or larger size according to the participant's anatomic characteristics of the head (Figs. 2e–f).

Study Procedure

The four experimental lens conditions and the control condition were tested on different days in random order at the same time each day (between 8 and 11 AM) to avoid diurnal fluctuations in vision,[43,44] axial length, and choroidal thickness.[45] The order of the experimental lenses to be worn was randomized. The same procedure described in the following was carried out for each lens condition. The room lighting was maintained at 20 lux during the experiment, and all measurements were conducted in the same room. Before any study measurement, the participants underwent a 10-minute rest without perform-

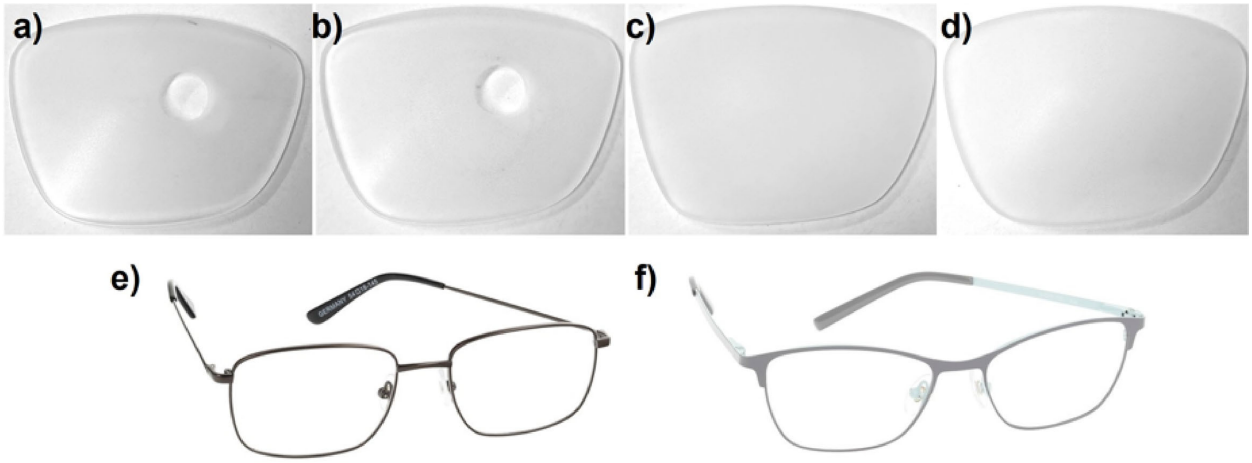

Figure 2. Sandblasted, scattering experimental lens conditions reducing retinal image contrast: (**a**) medium peripheral scattering, (**b**) high peripheral scattering, (**c**) medium full-field scattering, and (**d**) high full-field scattering and frames to mount the experimental lenses: (**e**) smaller frame and (**f**) larger frame.

ing any task to avoid accommodation and change in heart rate and blood flow.[46,47] After the washout phase, baseline measurements of choroidal thickness using OCT (ZEISS PlexElite 9000; Carl Zeiss Meditec Inc.), axial length (ZEISS IOLMaster 700; Carl Zeiss Meditec AG), and letter visual acuity were conducted in the same room. The OCT scans were performed between 1040 nm and 1060 nm, with a frequency of 200 kHz and a pattern of 512 × 512 A- and B-scans covering 12 × 12 mm^2 at the retina. After assessing the baseline measurements, the participants completed a 60-minute lens wear phase to the respective lens condition. During the lens wear phase, the participants were asked to watch a movie at a 4.5-m distance to avoid near-accommodation. Measurements of choroidal thickness, axial length, and visual acuity were then repeated to investigate changes from baseline. For the post–lens wear OCT scan, tracking and follow-up modes were set to capture the same retinal area as in the baseline scan. The changes in choroidal thickness, axial length, and visual acuity after lens wear were subsequently calculated based on the condition- and day-dependent baseline. All measurements were carried out on the treated right eye. The lens was removed for choroidal thickness and axial length measurements but remained in place during visual acuity testing.

Data Computing

Axial length and visual acuity values were derived from the device used. Choroidal thickness was calculated from the OCT scans as follows: Bruch's membrane and choroido-scleral junction were segmented using a validated automated multilayer segmentation from the Advanced Research and Imaging Network (Carl Zeiss Meditec Inc.).[48] The utilized segmentation software reported a strong correlation and good agreement with manual segmentation of the choroid. The automatically generated segmentation was then manually corrected using MATLAB (version: 9.12.0, R2022a; The MathWorks Inc., Natick, MA, USA; see Fig. 3). The area of the optic nerve head was excluded from further processing. Based on the translation of the experimental lens' clear zone of 8 mm in diameter onto the retinal level, angular calculations were performed to determine the central (within the clear central zone) and peripheral (outside of the clear zone) retinal areas to be analyzed regarding the choroidal thickness. Therefore, the visual angle of the clear aperture in the nodal plane was calculated from the distance of the back vertex of the lens (standardized at 12 mm for all participants) to the nodal point and then projected onto the retina. The clear aperture covered a viewing angle of 23° on the retinal level. The viewing angle of the clear zone

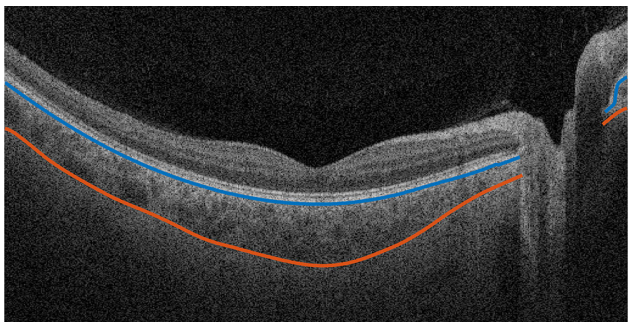

Figure 3. Multilayer segmentation of the choroid (Bruch's membrane in *blue* and choroido-scleral junction in *red*).

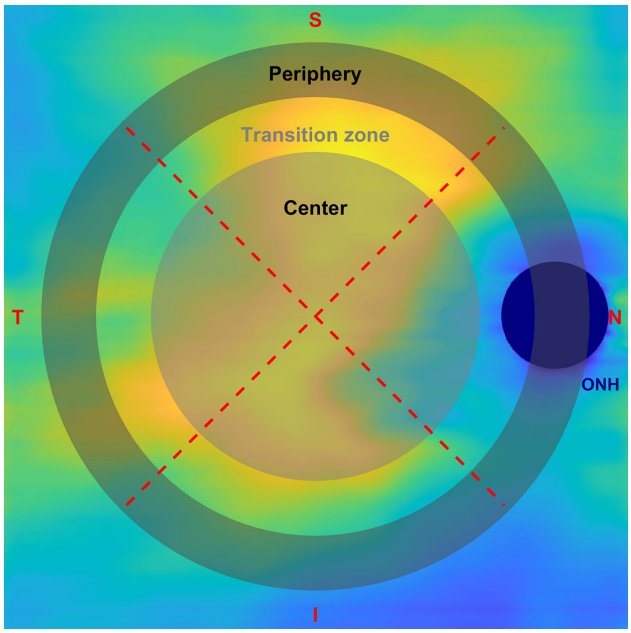

Figure 4. Central and peripheral masks to define retinal areas to analyze choroidal thickness, subsequently subdivided into four quadrants: nasal (N), temporal (T), superior (S), and inferior (I), excluding the area of the optic nerve head (ONH).

was then transformed into pixel values, resulting in 298 pixels in diameter. This zone is defined as the central zone, while the area outside is referred to as the peripheral zone. To ensure a well-defined clear zone on the retinal level, a transition zone between the clear central zone and the peripheral zone was defined. Subsequently, the diameter of the central retinal area was set to a visual angle of 21° and the inner diameter of the peripheral retina to 28°. The peripheral retinal area was further defined as a ring section and adjusted for its outer diameter to keep an equal number of data points as the central area and thus set to a 39° viewing angle. The central and peripheral zones were subsequently subdivided into four quadrants: nasal, temporal, superior and inferior, see Figure 4.

Repeatability of Choroidal Thickness Results

The intraoperator repeatability of central choroidal thickness segmentation was 4.75 ± 13.18 µm, and the intraclass correlation coefficient (ICC) was 0.99 with a mean difference of 1.40 ± 6.74 µm (95% confidence interval [CI], −1.67 to 4.46 µm). Peripheral choroidal thickness analysis reported an intraoperator repeatability of 4.20 ± 11.64 µm, an ICC of 0.99, and a mean difference of 1.86 ± 5.78 µm (95% CI, −0.77 to 4.49 µm). Test and retest axial length measurements reported an intraoperator repeatability of 7.10 ± 9.70 µm and an ICC of 0.99, with a mean difference of 4.46 ± 8.84 µm (95% CI, 0.64–8.28 µm).

Statistical Analysis

Data were analyzed using R/RStudio (version 2022.07.2; RStudio Team, PBC, Boston, MA, USA) and MATLAB (version 2022a; The MathWorks Inc., Natick, Massachusetts, USA). Visual acuity results are presented as mean and standard deviation. Data for axial length and choroidal thickness are reported as median ± interquartile range (IQR) since normal distribution was refuted by the Lilliefors test. Subsequently, data underwent outlier detection by removing data points located beyond 1.5 IQRs from the median. Statistical analysis was then conducted using a linear mixed model and the post hoc test of estimated marginal means. The analyzed model is defined by either central or peripheral choroidal thickness, central axial length or central visual acuity as the dependent variable, participants as a random effect, and two fixed effects: condition (five levels: control, medium peripheral scattering, high peripheral scattering, medium full-field scattering, and high full-field scattering) and time (two levels: pre– and post–lens wear). The choroidal thickness evaluation included the analysis of chorioretinal locations by eccentricity (two levels: central and peripheral) and quadrant (four levels: nasal, temporal, superior, and inferior). Furthermore, changes in choroidal thickness, axial length, and visual acuity were analyzed by calculating the differences between post– and pre–lens wear values. Subsequently, the linear mixed model was specified by the mentioned change (dependent variable), participants (random effect), and the experimental lens condition (fixed effect).

Results

Choroidal Thickness

There was no significant effect found either between pre– and post–lens wear on central choroidal thickness, and no significant differences were exhibited among the lens conditions (all $P > 0.05$; see Fig. 5). Central choroidal thickness decreased; however, this change was not statistically significant for any of the test lens conditions, except for the medium full-field scattering condition, which showed an absolute, nonsignificant choroidal thickening on average compared at 60 minutes (+1.95 ± 5.86 µm, $P = 0.21$). The highest reduction of central choroidal thickness was observed in the control condition (−5.86 ± 9.28 µm, $P = 0.07$), followed by the high peripheral scattering condition (−1.95 ± 12.70 µm, $P = 0.10$) and high full-field scattering condition (−1.95 ± 7.81 µm, $P = 0.06$). The least

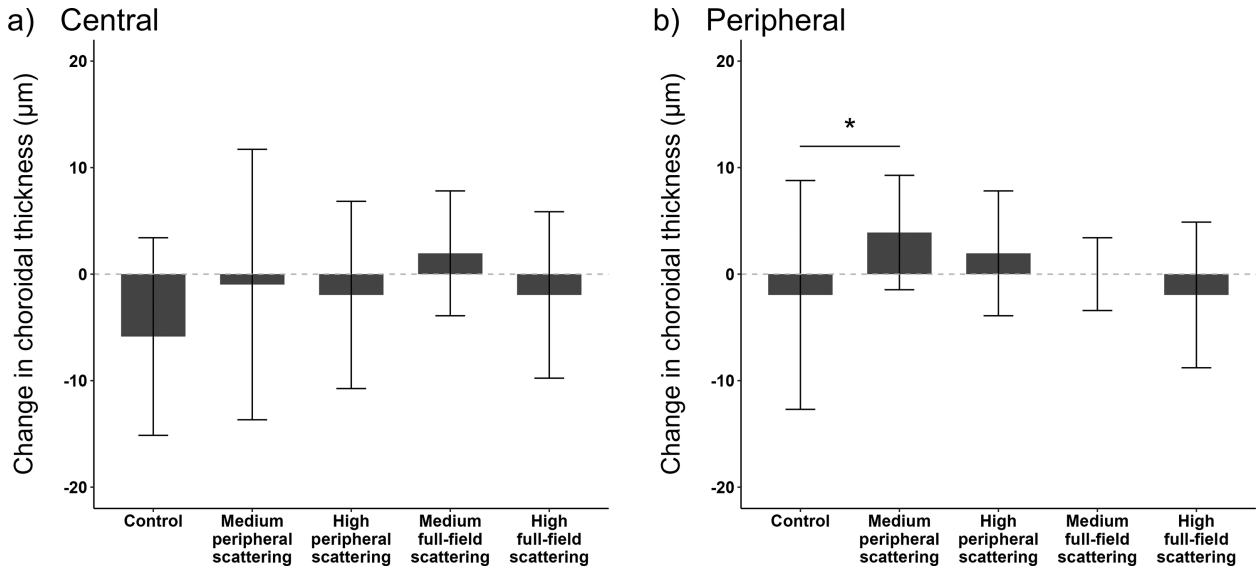

Figure 5. Central and peripheral choroidal thickness (in µm) pre– and post–lens wear of the experimental lens conditions (n = 23 participants).

Table 1. Nasal, Temporal, Superior, and Inferior Central and Peripheral Choroidal Thickness Changes (Median ± IQR) After Lens Wear to the Clear Control Condition, Medium Peripheral Scattering, High Peripheral Scattering, Medium Full-Field Scattering, and High Full-Field Scattering (n = 23 Participants)

	Central Choroidal Thickness				Peripheral Choroidal Thickness			
	Nasal	Temporal	Superior	Inferior	Nasal	Temporal	Superior	Inferior
Control	–3.91±5.86	–3.91±9.28	–5.86±13.18	–5.86±11.72	–3.91±9.77	–1.95±9.28	–1.95±15.14	–1.95±10.74
Medium peripheral scattering	1.95±9.77	–2.93±16.11	0.00±7.81	–0.98±16.11	0.00±8.30	–1.95±9.77	1.95±10.74	1.95±10.74
High peripheral scattering	1.95±13.18	–1.95±9.77	–1.95±7.81	–1.95±10.74	0.00±5.86	–0.98±5.86	1.95±5.86	1.95±7.81
Medium full-field scattering	3.91±11.72	1.95±9.77	0.00±3.91	–0.98±7.81	1.95±9.77	0.00±1.95	–2.93±12.94	–0.98±7.81
High full-field scattering	–1.95±5.86	–1.95±4.88	-4.88±7.81	–3.91±3.91	–1.95±3.91	–1.95±5.37	0.00±7.81	–1.95±5.86

* $P < 0.05$.
** $P < 0.01$.

reduction was noted in the medium peripheral scattering condition (−0.98 ± 12.70 µm, $P = 0.93$).

Statistical analysis revealed a significant increase in peripheral choroidal thickness after lens wear to the medium peripheral scattering condition (+3.91 ± 5.37 µm, $P = 0.04$; see Fig. 5). Peripheral choroidal thickness increased nonsignificantly following short-term exposure to high peripheral scattering (+1.95 ± 5.86 µm, $P = 0.21$) and medium full-field scattering (+0.01 ± 3.41 µm, $P = 0.99$). A not significant decrease was found in peripheral choroidal thickness following lens wear to control (−1.95 ± 10.74 µm, $P = 0.15$) and high full-field scattering (−1.95 ± 6.84 µm, $P = 0.58$). When comparing choroidal thickness changes after exposure to experimental lens conditions, the thickness of the peripheral choroid differed significantly between control and medium peripheral scattering ($P = 0.004$).

The quadrant-specific changes in the central and peripheral choroid following lens wear are shown in Table 1. A significant effect was exhibited between the medium full-field scattering and the control condition at the central nasal part ($P = 0.001$). In the superior periphery, a significant difference between the medium peripheral scattering and control condition ($P = 0.02$) was exhibited. No further effects were found between

Table 2. Mean and Standard Error of Foveal Axial Length Changes Before and After Lens Wear of the Experimental Lens Conditions Control, Medium Peripheral Scattering, High Peripheral Scattering, Medium Full-Field Scattering, and High Full-Field Scattering ($n = 23$ Participants)

	Control	Medium Peripheral Scattering	High Peripheral Scattering	Medium Full-Field Scattering	High Full-Field Scattering
Axial length changes (µm)	$+1.29 \pm 0.47$	-5.48 ± 0.72	-0.66 ± 0.69	-4.93 ± 0.68	$+1.97 \pm 0.54$

the retinal areas and experimental lens conditions (all $P > 0.05$).

Axial Length

The axial length (see Table 2) did not reveal significant changes after wearing the given experimental lens, and no variations were observed among the different lens conditions (all $P > 0.05$).

Visual Acuity

Foveal visual acuity was measured each time with the experimental lens in place, through the optical center of the lens. Baseline (before the lens wear phase) visual acuity was -0.16 ± 0.06 logMAR for control, -0.16 ± 0.06 logMAR for medium peripheral scattering, -0.17 ± 0.05 logMAR for high peripheral scattering, $+0.03 \pm 0.12$ logMAR for medium full-field scattering, and $+0.13 \pm 0.10$ logMAR for high full-field scattering. Visual acuity was noticeably reduced for the full-field scattering conditions. After the lens wear phase, no significant change was found in visual acuity: 0.00 ± 0.02 logMAR for control, 0.00 ± 0.05 logMAR for medium peripheral scattering, $+0.01 \pm 0.04$ logMAR for high peripheral scattering, $+0.04 \pm 0.06$ logMAR for medium full-field scattering, and $+0.03 \pm 0.08$ logMAR for high full-field scattering. There was no improvement in visual acuity after 60 minutes of lens wear (all $P > 0.05$).

Discussion

The study investigated changes in central and peripheral choroidal thickness, axial length, and visual acuity after short-term lens wear, of peripheral and full-field experimental scatter lenses across medium and high levels. Peripheral choroidal thickness significantly increased after lens wear of the medium peripheral scattering condition maintaining clear central vision, while the change was significantly increased compared to the control condition. The analysis divided into quadrants showed a main increase in superior peripheral choroidal thickness after exposure to medium peripheral scattering compared to the control condition, while the central nasal choroid was significantly thicker for the medium full-field scattering condition compared to the control condition. The clear lens control condition, as well as the high peripheral and full-field scattering conditions, did not show any significant changes in the central or peripheral choroidal thickness. Choroidal thickness results were compared within each quadrant and not between quadrants, as the latter would not be meaningful and could be misleading. This is because previous literature has reported an asymmetry in nasal and temporal choroidal thickness.[49,50] The choroid is nasally thinner than temporally due to the presence of the choroidal watershed area in the nasal region.[49,50]

Prior research in animal models has explored compensatory choroidal changes in response to optical defocus, resulting in choroidal thickening by wearing positive lenses and choroidal thinning when negative lenses or diffusers were worn.[36,51–54] In humans, short-term adaptation to myopic (positive lenses) and hyperopic defocus (negative lenses) produces results similar to those observed in animal models.[55–57] However, short-term choroidal thickness changes in response to diffusers or scattering lenses have not yet been investigated; this study is the first to explore this. Several studies have identified a correlation between choroidal thickness and refractive error, indicating that the choroid tends to be thinner in individuals with higher degrees of myopia.[58–60] Additionally, the relationship between choroidal thickness and axial length has been explored, revealing that longer eyes typically exhibit a thinner choroid.[61–64] These valuable insights have suggested that variations in the choroidal thickness are associated with future growth rates, making it a significant biomarker for predicting the efficacy of myopia control strategies. Changes in choroidal thickness occur rapidly and prior to long-term changes in axial length.[42,52] Therefore, choroidal thickness can be considered an appropriate indicator to assess how the

eye responds to visual stimuli. Short-term effects of diffused or scattering lenses on the human choroid and its regional changes have not yet been investigated. However, other investigations of choroidal thickness in response to visual stimuli revealed more prominent changes in choroidal thickness than in the present study.[3,65] Reading black text on a white background for 1 hour and vice versa resulted in changes of 16 µm and 10 µm, respectively.[3] A 60-minute adaptation to +3 D defocus produced regional choroidal thickness changes up to 7 µm.[65] Previous studies determining choroidal thickness with ZEISS PlexElite, which has been used in the current study, found similar or smaller changes in choroidal thickness in response to visual stimuli as in the present study. One study investigated choroidal thickness responses to 30-minute wear of multifocal contact lenses of +2.5 D and found changes of 2 µm.[66] Another study examined 20-minute light stimulation on choroidal thickness and found changes of 3 µm.[67]

In the current study, a significant difference in the peripheral choroidal thickness was found after lens wear of the medium peripheral scattering condition (+3.91 ± 5.37 µm, $P = 0.04$) compared to the control condition (−1.95 ± 10.74 µm), with a rounded difference of 6 µm ($P = 0.004$). A stronger reduction in retinal image contrast by exposure to the high peripheral scattering condition did result in an absolute increase in peripheral choroidal thickness (+1.95 ± 5.86 µm) but was not a significant effect ($P = 0.21$). It is assumed that the retina can adjust the choroidal thickness by altering the blood flow based on the amount of peripheral contrast reduction.[68] The retinal ON and OFF channels play a crucial role in retinal contrast signaling. It is assumed that the activity of both channels is altered when image contrast decreases. Additionally, it is suggested that these ON and OFF channels, specifically their receptive fields, transmit a signal to the choroid to adjust its thickness.[69]

Lens wear of medium or high peripheral scattering lenses with clear apertures did not affect central choroidal thickness ($P > 0.05$). The obtained results highlight a localized regulatory mechanism of the choroidal thickness in response to visual stimuli, consistent with previous findings in both human[65] and animal studies.[51,70–75] These findings align with research suggesting that variations in peripheral image quality have a considerable impact on refractive development.[27,69,76,77] A possible underlying explanation is that the absolute number of neurons in the periphery is greater than in the fovea, and therefore, the signals of the retinal periphery might overlay foveal signals, affecting general ocular growth.[27,28] Another reason could be that selective, critical elements in the signal cascade regulating axial elongation are distributed in the periphery.[28]

Medium and high full-field scattering conditions did not change general central or peripheral choroidal thickness following short-term lens wear (all $P > 0.05$). Consequently, it might be beneficial to maintain a clear central aperture, providing the participants' comfort and compliance when wearing and, at the same time, increasing choroidal thickness in the periphery. Breher et al.[66] found nonsignificant choroidal thickening at the nasal part after 30 minutes of multifocal contact lens wear. In the current study, changes in the nasal part were found as well after 60 minutes of wear of the medium full-field scattering condition, suggesting that the nasal central retina might be able to detect changes in image contrast compared to superior, inferior, and temporal. Another study investigated the influence of hemifield defocus on superior and inferior choroidal thickness after 60 minutes of lens wear and exhibited an increased superior choroidal thickness after superior exposure without influencing the inferior choroidal thickness and vice versa.[65] However, greater changes in choroidal thickening were found in the superior retina.[65] In the current study, changes in the peripheral superior choroidal thickness were found after lens wear of the medium peripheral scattering condition. The previous and current findings suggest a pattern of regional sensitivity in the retina to changes by image contrast. This study extends existing findings by investigating choroidal thickness responses to lens wear of medium and high peripheral and full-field scattering conditions. This supports the idea that different retinal regions have distinct responses to visual stimuli, such as scattering, with the peripheral superior retina and nasal central retina showing significant differences in medium full-field scattering and medium peripheral scattering, respectively.

In comparison to the scattered lens conditions, the clear lens control condition did not degrade retinal image quality, but an absolute, nonsignificant thinning of the choroid was found in the center (−5.86 ± 9.28 µm) and periphery (−1.95 ± 10.74 µm). The control condition was included in the study design to elaborate changes in choroidal thickness, which cannot be attributed to a visual stimulus (e.g., diurnal fluctuations, blood pressure, and hydration status, all of which can influence the choroidal blood flow and therefore choroidal thickness). The slight, nonsignificant choroidal thinning observed following exposure to the control condition is likely due to residual diurnal variation[45,46] or dim room lighting.[78,79] Previous literature has documented similar slight choroidal thinning occurring between 9 and 11 AM.[45] As the choroid undergoes diurnal variations, all measurements were

conducted at the same daytime to eliminate diurnal effects on this study's investigations. Moreover, we conducted baseline measurements before each experimental lens wear phase to keep the fluctuations small and calculated the postadaptation change from the respective condition-dependent baseline. However, due to time constraints and participant availability, it was not possible to keep the number of rest days constant for each participant.

It is worth mentioning that all scattered lens conditions did not reach the amount of central choroidal thinning after lens wear to the clear control condition. As previously shown, visual-induced choroidal changes impact the diurnal rhythm of thickness fluctuations.[80–82] This study could not prove a complete diurnal rhythm impact in exposure to scattering and needs further investigation. Possible confounders related to participant positioning and eye movement during the imaging process were controlled using the tracking mode of the OCT imaging system and therefore can be ruled out. To identify changes in choroidal thickness after exposure to scattering different from the control condition, a pairwise analysis against the control condition was performed. However, the OCT system's capability must be considered in terms of the effect size. While the OCT demonstrated a repeatability of 4 µm and thus falls below the effect size between the control condition and medium scattering condition, the repeatability of the IOLMaster for axial length was 7 µm. Given the resolution limitations of this biometer, accurately assessing small axial length responses is challenging, which led to nonsignificant variations observed in the current study.

A human study observed an elongation in axial length following short-term full-field-of-view exposure (10, 20, and 30 minutes) to a high-level scattering condition using the Bangerter foil of density 0.2.[41] Significant changes in axial length were not found in the current study. However, the level of scattering was not as high as used by Teoh et al.,[41] where the image degradation in terms of visual acuity was 0.8 logMAR. This study reached a maximum degradation in terms of visual acuity of 0.5 logMAR for the high full-field scattering condition. Therefore, the results of this study cannot draw any definitive conclusions regarding the relationship between axial length and choroidal thickness, as the axial length was measured at the fovea while macular choroidal thickness was assessed with a wider field of view. Another study shows axial elongation after short-term exposure to calculated low-pass filtered movies. However, when matching the contrast modulation of calculated low-pass filtered movies and real positive defocus of +2.5 D, the latter led to axial shortening in emmetropes. In myopes, no differentiation between real and calculated defocus was found as both conditions led to axial elongation.[83] Subsequently, previous literature results suggest that myopes have a reduced ability to distinguish between various strategies to reduce retinal image contrast.

Further previous studies reported enhanced visual acuity following both long-term (6 and 12 weeks) and short-term exposure (40 minutes) to full-field scattering induced by Bangerter foils.[84,85] The full-field scattering conditions reduced visual acuity in the current study, while the control condition and the peripheral scattering conditions did not affect visual acuity. Visual acuity remained the same for the respective conditions before and after the lens wear phase. An adaptation effect in visual acuity was not found in the current study after full-field lens wear or peripheral-only exposure to scattering (all $P > 0.05$). Other visual performance assessments found a decrease in contrast sensitivity after short-term adaptation (30 and 90 minutes) to peripherally induced scattering by Bangerter foils. [86]

The literature shows different time durations for adapting to scattered lenses, extending from minutes to weeks.[84–87] In general, contrast adaptation processes are to be distinguished into short-term changes and long-term changes. Both mechanisms are based on a form of cortical neuroplasticity, recalibration of the visual response to compensate or boost for variations in spatial contrast.[85,88] The compensation and boost signal process and its relation to choroidal thickness modulation need further investigation. Regarding the choroid, visually induced differences in its thickness have been observed previously in the literature after minutes[89] to an hour.[56,57,65,81,90–92] Furthermore, it is crucial to explore the long-term effects of reduced contrast in the peripheral retinal image on both central and peripheral choroidal regions. This assessment will provide clarity on the potential of short-term choroidal effects as predictors of long-term consequences.

Scattered lenses reduce contrast over all spatial frequencies, thereby affecting vision at any time. Previous studies found selective channel activation affects the choroidal thickness. It was discovered that ON channel activation increases the thickness of the choroid, while OFF channel stimulation results in choroidal thinning.[3,93] The ON and OFF channel receptive fields, structured in a center-surround system, might be concatenated by subsets and therefore be able to respond locally.[65]

This study observed that the peripheral retinal area exhibited choroidal thickening after exposure to medium peripheral scattering. Conversely, the central retinal area did not show a response in choroidal thickness. Additionally, it is noteworthy that only a specific peripheral scattering condition influenced peripheral

choroidal thickness in our study, as the high peripheral scattering condition did not affect choroidal thickness. The central choroidal thickness was also only influenced nasally by the medium full-field scattering condition and not by the high full-field scattering condition. This suggests that the regional exposure and the degree of reduction in retinal image contrast may play a crucial role in the subsequent signaling cascade. Based on the regional changes, it could be assumed that only the periphery is affected by peripheral scattering and that the center is favored over the periphery by full-field scattering. However, more research is needed to give a clear answer. Regarding the degree of scattering, there is no literature available that specifically addresses the influence of different levels of scattering on human choroidal thickness. Therefore, the reason for the current study's finding is unknown, whereas it can be speculated that a determined level of scattering is needed to trigger changes in choroidal thickness. Still, short-term adaptation in dependence on axial length changes has been studied. In a previous study, 10- to 30-minute adaptation to strong diffusers, such as light-perception Bangerter foils or Bangerter foils of density 0.2, led to axial elongation.[41] Considering that an increase in axial length is related to choroidal thinning, a high level of scattering might be suggested to promote rather than counteract myopia progression. Moreover, the current study cannot provide information on whether the ON or OFF channel was activated concerning choroidal thickening. In a previous study, the psychophysical assessment of ON and OFF receptive field processing showed differences in contrast sensitivity between emmetropes and myopes, but it was not affected by contrast reduction induced by Bangerter foils.[94] Previous and current findings do not shed light on the mechanism by which contrast reduction prevents the development of myopia.

An essential aspect of understanding changes in contrast produced by each experimental lens condition lies in the analysis of the radial modulation transfer function (see Fig. 1). When comparing the modulation transfer function of the medium scattering lens condition used in this study with the diffusion optics technology lenses, previously reported in the literature,[95] it becomes apparent that contrast modulation occurs similarly for spatial frequencies above 40 cycles per degree but differs for lower spatial frequencies. This difference can likely be attributed to variations in lens design and manufacturing processes. The significant effects found in the current study are relatively small. This could be attributed to the contrast modulation of the experimental lens design across different spatial frequencies, as well as the short duration of lens wear. Due to the contrast modulation created by the lens design, it might be essential that low spatial frequencies are not affected or that very low and middle or high spatial frequencies differentiate not too strongly. It is also worth noting that any long-term effects cannot be explained and transferred by the results of this study.

In animal studies, exposure to scatter lenses led to myopia development.[28,96–99] Ambient lighting is another crucial factor that influences the scattering affecting retinal image quality and, therefore, must be considered in our results. Previous optical evaluations have shown that intense light conditions increase scattering, significantly reducing contrast in the retina.[32] Consequently, ambient light levels fluctuate throughout the day, while research studies are typically conducted under constant lighting conditions. Furthermore, the pupil size affects the degradation of the retinal image by induction of diffused lenses. In the current study, pupil size was not controlled, as the intention was to replicate natural conditions. The same applies to eye and head movements. Moreover, natural accommodation was also not controlled. However, participants were instructed to watch a movie at a far distance during the adaptation period to avoid near-accommodation. Previous literature found axial elongation and choroidal thinning linked to accommodation.[47] However, the present study did not reveal a significant modulation in axial length, and no thinning of the choroid was observed. The level of scattering accompanied by contrast reduction, lens design, and exposure duration are, however, crucial factors in predicting the potential success of slowing down myopia progression.

Conclusions

Peripheral choroidal thickening was found after short-term lens wear of the medium peripheral scattering condition, most expressed in the superior peripheral retina, compared to the control condition. Nasal central thickening was explored after exposure to the medium full-field scattering condition in comparison to control. Neither central nor peripheral choroidal thickness was affected by the high peripheral scattering condition or high full-field scattering lens condition. The results indicate local retinal contrast detection mechanisms that signal the choroid to thicken. This finding gives insight into the mechanism behind the myopia control strategy using peripheral scattering and the importance of the peripheral retina in myopia research. Further research is required to evaluate choroidal thickness changes after exposure to scattering lenses concerning the lens design, level of

contrast reduction, lens wear time, lighting conditions, ON and OFF channel activation, and long-term effects on refractive development.

Acknowledgments

Supported by Eberhard-Karls-University Tübingen (ZUK 63) as part of the German Excellence initiative from the Federal Ministry of Education and Research (BMBF) (AR and SW). Further funding was received from Deutsche Forschungsgemeinschaft and the Open Access Publishing Fund of the University of Tübingen. The funders did not have any additional role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Disclosure: **A. Roth**, None; **K. Breher**, Carl Zeiss Vision International GmbH (E); **S. Gisbert**, Carl Zeiss Vision International GmbH (E); **A. Arias**, None; **S.P. Clement**, None; **S. Wahl**, Carl Zeiss Vision International GmbH (E)

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