Keep Your Eyes above the Ball: Investigation of Virtual Reality (VR) Assistive Gaming for Age-Related Macular Degeneration (AMD) Visual Training

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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Tübingen

2023

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

Tag der mündlichen Qualifikation:	12.10.2023
Dekan:	Prof. Dr. Thilo Stehle
1. Berichterstatter:	Prof. Dr. Siegfried Wahl
2. Berichterstatter:	Prof. Dr. Martin Butz

Acknowledgments

My profound appreciation goes to Professor Dr. Siegfried Wahl for his guidance and support throughout the good, the bad, and the challenging phases of my Ph.D. journey. His constant encouragement and precise interventions have been invaluable – without them, the current work could not have been possible.

I am incredibly grateful to Professor Dr. Martin Butz, my second Ph.D. supervisor, for his time, effort, and valuable feedback. His comments and stimulating discussion points always kept me on my mental toes and provided important intellectual challenges throughout my journey.

This endeavour would not have been possible without the following European fundings: Federal Ministry of Education and Research (BMBF), Deutsche Forschungsgemeinschaft, European Union's Horizon 2020 research and innovation program (under Marie Skłodowska-Curie Grant), and the mini graduate school 'Integrative Augmented Reality (I-AR)'.

Many thanks to the colleagues that started alongside me: Olga, Peter, Yannick, Katha, and to all the others that joined later on. Thank you for all the movie nights, lab dinners, bowling competitions, and in general, for the constant moral support and push and for all the fun we shared these last years. I am also grateful to all the ZEISS Vision Science lab colleagues who inspired and generously provided knowledge and expertise whenever needed. Special thanks to Miguel, who joined my Ph.D. project later on and provided invaluable feedback, support, and helpful guidance.

I gratefully acknowledge all the IDeA project partners for making my Ph.D. journey even more engaging. It has been a pleasure to have worked with you all. Many thanks to Florian, Jesse, and the LMU Human-Centered Ubiquitous Media for being my second scientific home.

I am incredibly grateful to the Augenklinik - Universitätsklinikum Tübingen. Many thanks to David and Alexandra; without your guidance and valuable expertise, this thesis's clinical part would not have been possible.

Special thanks to my boyfriend, Tamás, for closely empathizing with my scientific dream. You have always been a real motivating factor and a patient and valuable guide. Thank you for the scientific contribution and for proofreading this thesis. I am also thankful to Zsuzsa, Aron, Aron Sr., Hilke, Imre, and Dundi. Your kind words and encouragement have always managed to provide invaluable support.

A sincere and big thanks to all my friends who have supported me with patience, understanding, and kindness throughout these years.

To conclude, I'd like to express my deepest gratitude to my parents, Mariana and Vasile. Their unwavering support and unconditional love provided a constant pillar of encouragement. These pages cannot describe the amount of love, gratitude, and respect I have for you.

Contents

Abbreviations

AMD	Age-related Macular Degeneration
VR	Virtual Reality
WHO	World Health Organization
RPE	Retinal Pigment Epithelium
2D	two-Dimensional
LGN	Lateral Geniculate Nucleus
PRL	Preferred Retinal Locus
QALY	Quality-Adjusted Life years
BCVA	Best Corrected Visual Acuity
fMRI	functional Magnetic Resonance Imaging
EEG	Electroencephalogram
AR	Augmented Reality

Summary

Visual perception is one of the most relied-on senses of modern humans. Without functional vision, individuals may have severe difficulties participating in their daily lives. However, with growing age, humans are at higher risk of developing severe visual impairments, such as age-related macular degeneration (AMD), drastically damaging their overall quality of life. AMD describes the phenomena in which individuals lose central vision as they age. To overcome the negative impact of AMD, medical experts suggest training procedures to help patients navigate their environment through eccentric vision. However, effective current methods suffer under the effects of attrition due to the repetitiveness of the exercises. In prior work, researchers suggest digital games and entertainment technology as tools to reduce the impact of attrition in digital interventions. First investigations with screen-based games suggest lower attrition to AMD training, yet potential distractions around the patient may affect the training. However, virtual reality (VR) headsets may help overcome screen-based digital interventions' potential shortcomings.

Therefore, this dissertation investigates whether VR games are feasible as a platform for effective AMD training using immersive games and gaze-tracking technologies. In study 1, we provide an overview of the quantification of the eye-tracking data quality in VR for general gaze-contingent applications. We show that eye-tracking within a VR headset is feasible for peripheral gaze-contingent applications. Further, in study 2, we explore the influence of a salient gaze-contingent peripheral stimulus around a simulated scotoma on eccentric viewing during a VR game. The results of this study showed that such stimuli influence gaze directionality and stimulate eccentric viewing. In study 3, we analysed the effects of salient gaze-contingent spatial cues and optical distortions stimuli for eccentric viewing training during the same VR game. Our results of this study suggest that spatial cues are better at assisting with eccentric viewing. In a final case study, we evaluated whether a spatial gaze-contingent peripheral cue would help the eccentric viewing of an AMD patient while gaming in VR. We showed that the results found in studies 2 and 3 were replicated for the patient. Additionally, we indicate that gaming in VR can be feasibly used for eccentric viewing training in an elderly population.

Overall the results of this dissertation provide new insights about how we may use

VR, and digital gaming in combination with eye-tracking as a platform to develop immersive, playful, and more engaging AMD visual training to help patients to increase their overall quality of life.

Zusammenfassung

Die visuelle Wahrnehmung ist einer der meist genutzten Sinne des modernen Menschen. Ohne ein funktionierendes Sehvermögen stehen Einzelne vor meist sehr schwer überwindbaren Herausforderungen im Alltag. Mit zunehmendem Alter steigt jedoch auch das Risiko, dass sich schwerwiegende Sehstörungen wie die altersbedingte Makuladegeneration (AMD) entwickeln, die das gesamte Leben massiv einschränken. AMD beschreibt eine Erkrankung, die mit zunehmendem Alter zum Verlust des zentralen Sichtbereichs führt. Um die negativen Auswirkungen von AMD zu reduzieren, werden von medizinischen Experten Trainingsverfahren durchgeführt, die den Patienten helfen sollen, ihre Umgebung über die Peripherie erfassen zu können. Allerdings kann es durch die stark repetitive Natur des Trainings dazu kommen, dass die Nutzer die Übungen nicht vollständig durchführen oder gar abbrechen. Um dieses Problem in den Griff zu bekommen, schlagen Forscher digitale Spiele oder Unterhaltungstechnologie vor. Erste Untersuchungen mit bildschirmbasierten Spielen zeigen, dass die Kombination von digitalen Spielen und AMD-Trainings effektiv ist. Allerdings können mögliche Ablenkungen im Umfeld des Patienten das Training beeinträchtigen. Virtuelle Realität (VR) könnte jedoch dazu beitragen, die potenziellen Schwächen bildschirmbasierter Interventionen zu überwinden.

Diese Dissertation untersucht, inwiefern VR mit Unterstützung von Eyetracking Technologien eine effektive Plattform für die Entwicklung eines Spiele-basierten AMD Trainingsansatzes ist. Studie 1 gibt einen Überblick über die Quantifizierung der Datenqualität von Eyetracking-Technologien in VR für allgemeine Blick-abhängige Anwendungen. Die Ergebnisse der Studie zeigen, dass VR mit Unterstützung von Eyetracking-Technologien für periphere blick-abhängige Anwendungen machbar ist. Ferner untersucht Studie 2 den Einfluss eines auffälligen peripheren Stimulus um ein simuliertes Skotom auf das exzentrische Sehen während eines VR-Spiels. Basierend auf den Ergebnissen dieser Studie schlussfolgern wir, dass auffällige periphere Stimuli die Blickrichtung beeinflussen und das exzentrische Sehen stimulieren. Studie 3 untersucht die Auswirkungen von hervorstechenden, blick-abhängigen räumlichen Hinweisen und optischen Verzeichnungen für das Training des exzentrischen Sehens während desselben VR-Spiels. Die Ergebnisse dieser Studie deuten darauf hin, dass räumliche Hinweise

besser geeignet sind, um das exzentrische Sehen zu unterstützen. In einer abschließenden Fallstudie untersuchten wir, ob ein räumlicher, vom Blick abhängiger, peripherer Stimulus das exzentrische Sehen eines AMD-Patienten während eines VR-Spiels unterstützen würde. Wir konnten zeigen, dass die in den Studien 2 und 3 gefundenen Ergebnisse auch mit Patienten repliziert werden konnten. Darüber hinaus weisen unsere Ergebnisse darauf hin, dass VR-Spiele für das Training des exzentrischen Sehens bei älteren Menschen geeignet sind.

Zusammengefasst liefert diese Dissertation neue Erkenntnisse darüber, wie wir VR und digitale Spiele in Kombination mit Eyetracking-Technologien als Plattform nutzen können, um ansprechendere und effektive AMD-Trainings zu entwickeln.

List of publications

Accepted publications

(1) **Sipatchin A.**, Wahl S. & Rifai K. (2020). Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability. Healthcare, 9(2): 180. DOI: 10.3390/healthcare9020180

(2) **Sipatchin A.**, García García M. & Wahl S. (2021). Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR). Applied Sciences 11(15): 7164. DOI: 10.3390/app11157164

(3) **Sipatchin A.**, García García M., Sauer Y. & Wahl S. (2022). Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training. International Journal of Environmental Research and Public Health 19 (15): 9571. DOI: 10.3390/ijerph19159571

Submitted manuscript

(1) **Sipatchin A.***, Merle D.* , Wolfram L., Strudel L.V., Schweig A. & Wahl S. (2023). Real-world feasibility of a Virtual Reality (VR) gaming environment for the training of eccentric vision in age-related macular degeneration (AMD). in review, submitted to British Journal of Ophthalmology.

(* shared authorship)

Related publications, conference contributions and talks

Peer reviewed publications

(1) Sauer Y., **Sipatchin A.**, Wahl S. & García García M. (2021). Assessment of consumer VR-headsets' objective and subjective field of view (FoV) and its feasibility for visual field testing. VR, 1-13. DOI: 10.1007/s10055-021-00619-x

Conference contributions

(1) **Sipatchin, A.**, Wahl, S. & Rifai, K. (2020). Accuracy and precision of the HTC VIVE PRO eye-tracking in head-restrained and head-free conditions. Investigative Ophthalmology Visual Science, 61(7), 5071-5071.

(2) **Sipatchin A.**, García García M. & Wahl S. (2021). VR gaming: visual behavior in simulated conditions. In 3rd International Neuroergonomics Conference. Frontiers Research Foundation.

(3) Grootjen J., **Sipatchin A.**, Wahl S., Machulla T. & Chuang L. (2021). Towards an early diagnostic model of central visual impairments, based on gaze behaviour. In 3rd International Neuroergonomics Conference. Frontiers Research Foundation.

(4) **Sipatchin, A.**, García, M. G. & Wahl, S. (2022). Assistance for macular degeneration (MD): Different strategies for different augmentations. Investigative Ophthalmology Visual Science, 63(7), 714-F0442.

Talks

(1) **Sipatchin A.**, García García M. & Wahl S.(2021). Impact of unconstrained head movements to scotoma and enhanced scotoma simulation in virtual-reality (VR) smooth pursuit gaming. Investigative Ophthalmology Visual Science, 62(8), 1446-1446.

Personal contribution

Publication 1 - Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability.

Sipatchin A., Wahl S. & Rifai K. (2020). Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability. Healthcare, 9(2): 180. DOI:10.3390/healthcare9020180

Contribution of the first author:

I contributed to conceptualizing the study idea, defined the methodology, performed the measurements on the study participants, and analysed the data. I wrote the initial version of the manuscript and improved it in collaboration with the other authors.

Contribution of the other authors:

Prof. Dr. Siegfried Wahl as the second author of the paper provided materials, supervised the work, and edited the manuscript. The last author, Dr. Katharina Rifai, conceived the initial study idea, supervised the study, and helped to improve the manuscript.

Publication 2 - Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR)

Sipatchin A., García García M. & Wahl S. (2021). Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR). Applied Sciences 11(15): 7164. DOI: 10.3390/app11157164

Contribution of the first author:

I developed the initial idea for the study and defined the methodology. I performed the measurements on study participants and analysed the data. I wrote the initial version of the manuscript and improved it based on my ideas and input from the other authors.

Contribution of the other authors:

Dr. Miguel García García as the second author of the paper supported the work with his experience in data analysis and visualization and was involved in the editing of the manuscript. The last author, Prof. Dr. Siegfried Wahl, provided materials, supervised the study, and helped improve the manuscript.

Publication 3 - Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training

Sipatchin A., García García M., Sauer Y. & Wahl S. (2022). Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training. International Journal of Environmental Research and Public Health 19 (15): 9571. DOI: 10.3390/ijerph19159571

Contribution of the first author:

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Contribution of the other authors:

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Case study (non-published work) - Real-world feasibility of a Virtual Reality (VR) gaming environment for the training of eccentric vision in age-related macular degeneration (AMD)

Sipatchin A.*, Merle D.*, Wolfram L., Strudel L.V., Schweig A. & Wahl S. (2023). Real-world feasibility of a Virtual Reality (VR) gaming environment for the training of eccentric vision in age-related macular degeneration (AMD) in review, submitted to British Journal of Ophthalmology.

Contribution of the first author:

I helped develop the initial idea for the experiments and defined the methodology. I performed the measurements on study participants and analysed the data. I wrote the initial version of the manuscript and I improved it based on my thoughts and suggestions from the other authors.

Contribution of the other authors:

Dr. med. univ. David Merle, as the second first shared author of the paper (*), conceived the initial idea for the study, and was involved in the writing of the initial draft and the editing of the manuscript. Dr. med. Lasse Wolfram and Dr. med. Lisa Vanessa Strudel as the third, and fourth authors respectively supported the study with their experience as ophthalmologists offered their support for patient recruitment, and reviewed the manuscript. Dr. med. Alexandra Schweig as the fifth author contributed to the study idea, data visualization, reviewed and edited the manuscript. The last author, Prof. Dr. Siegfried Wahl, provided materials, supervised the study, and helped improve the manuscript.

1 Introduction

1.1 Age-related macular degeneration: the when and where

The World Health Organization (WHO) declared that in 2019 $13\,\%$ of the world's population was older than 60 years, and estimated that this number will double by 2050 (World Health Organization [2022a]). An increase in the ageing population results in a susceptibility rise of age-related diseases (Lu et al. [2022]). Among the elderly, visual impairment has the most common occurrence, with one out of four likely to be affected (Stevens et al. [2013]; Péres et al. [2017]; Amilon and Siren [2021]). Globally, among visual afflictions, age-related macular degeneration (AMD) is the top-leading disease that affects vision permanently and severely (World Health Organization [2022b]).

1.1.1 The three membranes composing the human eye

The descriptions of the eyes' anatomical features were taken from Fischbarg [2005], Mescher [2016] and Remington and Goodwin [2021]. For the purpose of the thesis, the main focus will be on the eye's vascular layer, the choroid, and the inner neural layer, primarily the retina, the main structures affected by AMD.

The eye is a sense organ that responds to a specific stimulus: light. The light information that is gathered gets translated into a signal that the brain can interpret (Schmidt-Rhaesa [2007]). The eye's entire translation process is made of a complex system of structures, each designed to perform a specific function. The eye is made of three membranes or tunics:

(1) Fibrous tunic: forms the sclera, the corneal limbus, and cornea and is made of connective tissue to protect and support the internal structures. The sclera is the white, opaque part of the eye, and the limbus is the part that connects the sclera to the cornea, the structure where a change in curvature and transparency occurs. The variation in translucence permits $80\,\%$ of the light to be focused on the eyes' most inner layer, where light is translated into a neural electrical signal. The lenses placed behind the cornea fine-tune further the light rays (Hejtmancik and Shiels [2015]).

(2) Vascular layer: the eye's middle coating is composed of the iris, ciliary body, and cho-

roid. The iris, controlled by the automatic part of the nervous system, regulates the shape and the diameter of the round central aperture, the pupil, to adjust the light's quantity entering through it. As a continuation of the iris, there is the ciliary body, the one secreting a thin, transparent fluid called aqueous humour that supports and maintains the cornea and the lens. Additionally, thanks to the ciliary muscle, the ciliary body controls the shape of the lens, which changes shape to focus the eyes on a near object. The last structure of the fibrous tunic is the choroid, a thin ($0.10\,\mathrm{mm}$-$0.15\,\mathrm{mm}$) and richly vascularised tissue surrounding the retina and having different types of macromolecules and macrophages, a type of white blood cells, with the task of disposing of unwanted material (Ambati et al. [2013]). The choroid is composed mainly of large and medium vessels and specialized choriocapillaris unique to the choroid. The choriocapillaris comprises tiny capillaries with small pores directed towards the Bruch's membrane, the innermost layer of the choroid, that plays a vital role in supporting structurally and functionally the outer retina (Murali et al. [2020]). This arrangement is typical only for the choriocapillaris, which is hypothesized to bring an advantage to the metabolic exchange between the choroid blood and the retina. The choriocapillaris' primary function is to supply oxygen and nutrients to the inner part of the eye (Ambati et al. [2013]).

(3) Retina: the inner part of the eye is a circular disk of approximately $40\,\mathrm{mm}$ diameter divided into central and peripheral, with the macula being the central retina and extending $6\,\mathrm{mm}$ (Kolb [1995]). It is composed of the outer pigmented layer (retinal pigment epithelium - RPE) and the inner neural layer, formed of photoreceptors. The RPE is a highly organized monolayer that supports the photoreceptor cells and recycles the biomedical products of light transduction processes to chemical signals. Together with the Bruch membrane, they maintain the outer blood-retinal barrier, preventing macromolecules and macrophages from entering the photoreceptor layer (Ambati et al. [2013]). The photoreceptor layer is composed of rods and cones, cell types that convert the incoming light signal, the photons, into action potentials, an electrical signal, which the brain cortices process into three-dimensional vision (Mahabadi and Al Khalili [2021]). The rods and cones have a different distribution across the retina, with the peripheral layer being thinner and mainly composed of rods ($95\,\%$).

In contrast, the central retina, the macula, is thicker and packed densely and mostly with cones (Mahabadi and Al Khalili [2021]; Kolb [1995]). The macula's centre is the fovea containing a highly specialized region, measuring less than a quarter of a millimetre ($200\,\mu m$), the foveal pit, composed only of cones. The high density of cones in the central fovea enables the cortical brain areas to detect the diameter of a strand of hair placed at $20\,cm$ allowing excellent spatial acuity. The acuity is achieved thanks to the cone's convergence ratio being as good as 1-to-1 (Mahabadi and Al Khalili [2021]). The rods' converge proportion decreases further away from the fovea, leading to decreased spatial acuity (Banks et al. [1991]; Mahabadi and Al Khalili [2021]).

1.1.2 Age-related macular degeneration: physiology

AMD damages the macula, and it develops across three distinct stages: early (onset $\approx$ 50 years), intermediate (onset $\approx$ 60 years), and late (onset $\geq$ 60 years) (Sickenberg [2001]).

(1) During the early stages, the Burch membrane starts to thicken, the RPE deteriorates, and small to medium-sized drusen (not more than $123\,\mu m$) begin to form, accompanied by pigmentary abnormalities (Ambati et al. [2013]; Ferris III et al. [2013]; Al Gwairi et al. [2016]; Finger et al. [2019]). Drusen are lipid and protein-based debris that are typically present below the RPE. The normal ageing process leads to their expansion, but only to a particular value ($63\,\mu m$)); with AMD, they become more prominent, increase in number, and accumulate. This change is hypothesized to be due to a malfunction in drusen effective removal (Sarks [1976]; Abdelsalam et al. [1999]). At this stage, symptoms can include mild visual distortion, which can also be accompanied by blurred central vision. However, since initially, the damage occurs in one eye, thanks to the brain's compensation mechanisms, patients may not notice any vision abnormalities yet. If they do, they attribute it to their ageing (Achard et al. [1995]; Schwartz and Loewenstein [2015]).

(2) As the disease advances and AMD reaches its intermediate stage, the drusen become larger and larger (above $123\,\mu m$) and start accumulating more and more; microglia migration starts to occur, choroidal macrophages increase in concentration, and

the Burch's membrane functionality becomes impaired (Ambati et al. [2013]; Al Gwairi et al. [2016]; Finger et al. [2019]). Patients often report difficulties with contrast and low luminance accompanied by glimmer perception and still do not seek consultation yet (Taylor et al. [2018]; Finger et al. [2019]).

(3) Different types can occur at the later stages of AMD: dry, wet, or dry accompanied by wet. For both dry and wet types, the drusen keep enlarging and become more prominent; with dry AMD, cell atrophy and structural clutter occur. The RPE, photoreceptors, and underlying choriocapillaris start degenerating, and choroidal blood vessels start constraining (Ambati et al. [2013]; Al Gwairi et al. [2016]; Waugh et al. [2018]; Ebner et al. [2021]). With wet AMD, on the other hand, abnormal choroidal vessels, accompanied by macrophages, start infiltrating into the neural layer, breaching the Burch membrane and damaging the photoreceptors (Ambati et al. [2013]; Al Gwairi et al. [2016]; Waugh et al. [2018]). The symptoms experienced at this stage include the appearance of grey or black spots and shadows, the appearance of blind spots, and difficulties focusing and reading. It is at this stage that both eyes start to be affected, and most patients start to worry about their vision and start consulting an ophthalmologist (Parfitt et al. [2019]).

1.2 Central vision and foveation: two important aspects of the human daily life

Losing central vision means losing functional activities such as reading, face recognition, and mobility (Colenbrander [2005]; Borkenstein et al. [2021]). As a result, the independence in their daily lives, goal pursuit, and engagement in significant hobbies and social relations of those affected are reduced (West et al. [1997]; Klein et al. [1998]; Hassell et al. [2006]). These influence self-esteem, perceived self-efficacy, and proficiency in return (Rovner and Casten [2002]). More so, the emotional impact AMD has on those affected is significant and, independent of the amount of central visual loss, patients are often experiencing feelings of frustration, depression and anxiety (Hassell et al. [2006]; Casten et al. [2004]; Varano et al. [2016]; Cimarolli et al. [2016]).

The following chapters will give a better overview of the visual and cognitive mechanisms affected and the patients' strategies and cortical adaptation processes implemented to overcome it.

1.2.1 Central vision and visual foveation: interaction of gaze behaviour and goal-directed attention

High visual resolution is restricted to the fovea, the only region that allows for reliable visual information processing. The eyes are, therefore, always moving to align this region with the intended object of interest. Fixational eye movements continuously change the gaze position, a process called foveation, to direct the fovea toward a relevant point in space as rapidly as possible.

Daily life depends on the rapid processing of visual information that switches on and off the focus between essential and non-important information. It is a primitive mechanism with a high evolutionary significance because it allows, for example, rapid detection and identification of danger in the visual world (Bahmani and Wahl [2016]).

The selection of one particular spatial location over another is based on a two-dimensional (2D) model referred to as the saliency-map theory (Koch and Ullman [1987]). The model aims to explain how behavioural eye orientation is controlled and what elements contribute to selecting the next salient position.

In the first step of the model, early visual features are topographically and in parallel order computed, starting from the retinal input. Projections from the retina to the early cortical processing areas (lateral geniculate nucleus, LGN, visual brain areas: V1 till V4) are very well known to follow a retinotopic organization (Wagor et al. [1980]; Horton and Hoyt [1991]; Aine et al. [1993]; Sereno et al. [1994, 1995]; Tootell et al. [1996]; Engel et al. [1997]; Tootell and Hadjikhani [2001]; Brewer et al. [2002]; Motter [2009]). The cortical retinotopic map is first decomposed into orientation, intensity, and colour thanks to linear flirting that extracts these features. Subsequently, a frequency analysis of the map helps isolate those features that are different from their surroundings. Recent developments have proposed an additional level of image analysis that accounts for distortions, altered colour, blurring, altered feature intensity, and contrast. These extra features also align with the eyes' visual distortions that the brain must process (Bahmani and Wahl [2016]). These features have been recently integrated into the saliency map model (Baveye et al. [2012]; Bahmani and Wahl [2016]; Gide et al. [2016]).

The next step of visual processing is a winner-take-all mechanism (Itti and Koch

[2000]) arising from the competition among those neurons encoding the mentioned features that influence the direction of the eyes. The object where the fovea is directed for further accurate interpretation is referred to as the most salient one on the map (White et al. [2017]).

Cognitive science has shown that unique structures, such as parallel lines, lines that converge towards a single point, concentric circles, blur, and distorted images, are being processed rapidly, having the priority in the visual map (Leeuwenberg [1967]; Lowe [1987]; Witkin and Tenenbaum [1983]; Sandon [1990]; Dumoulin and Hess [2007]; Mao and Toyoura [2016]; Oleskiw et al. [2017, 2018]; Mochizuki et al. [2018]; Entezari and Bair [2019]). They attract the eyes' position and are, therefore, referred to as salient. Another salient feature are single eye-of-origin stimuli, meaning stimuli presented monocularly (Zhaoping [2008]).

1.2.2 Disruption of foveation and adaptive behaviour: eccentric viewing behaviour

Macula deterioration means that the main important part of the vision is lost; nonetheless, the remaining part of the retina, away from the macula, remains intact. A new fixation area starts forming naturally to continue daily activities with no specific training (Cheung and Legge [2005]). The literature has agreed on defining the area as the preferred retinal locus (PRL) (Crossland et al. [2011]). The adaptive mechanism adopted by patients that start using the peripheral part of the retina to focus on objects of interest is called eccentric viewing. A mechanism so strong that it has been also observed in participants with a simulated central scotoma.

1.2.2.1 Eccentric viewing: mechanisms and theories behind the selection of a new preferred retinal area

Three different hypotheses have been postulated behind the formation of a new fixation reference point in the healthy peripheral retina (Cheung and Legge [2005]):

(1) Retinotopy-driven selection - According to this hypothesis, a new PRL location depends on the visual brain areas' cortical reorganization processes following the loss

of retinal input. According to the cortical reorganization theory, the lack of incoming sensory information leads to the reorganization of the original cortical map around the damaged area due to spontaneous new pathways forming in the sensory-deprived cortex (Pietrini et al. [2009]; Weishaupt [2017]). Research has shown large-scale reorganization from V1 to V4 following macular degeneration around the site where the sensory input has been lost (Baker et al. [2005]; Dilks et al. [2014]). In terms of the initial development of a new retinal locus, the PRL will be near the border of the damaged area (Cheung and Legge [2005]).

(2) Function-driven - The second hypothesis, states that the PRL position depends on the visual activity at hand; all regions around the scotoma are functionally equivalent, with the PRL more likely to be placed near or in direct paths of the visual target. Research has shown patterns of PRL positions linked to the visual task: for reading, writing, and tracking moving targets, the PRL was mainly positioned below the scotoma since that position was found to be more advantageous for performing these tasks (Sullivan et al. [2005]; Greenstein et al. [2008]; Trauzettel-Klosinski [2009]; Satgunam and Luo [2018]).

(3) Performance-driven - The hypothesis suggests that the location of a PRL will be selected to achieve the best visual performance. From a retinal perspective, the position will be at an intact retinal area and with the highest visual acuity. Specifically, considering the drop in visual acuity in the peripheral regions (Kerr [1971]), the best visual acuity position would be the closest to the scotoma edges. From a visual attention perspective, the PRL would be positioned in those retinal regions with the highest attentional enhancement. The enhancement can occur thanks to facilitatory modulations of the sensory neurons in the striate and extrastriate visual areas (V1 and V2 till V4). Research has shown that attention can boost neural activity in the topographic visual areas, from V1 till V4 (Chawla et al. [1999]; Somers et al. [1999]; Spyropoulos et al. [2018]). Regarding PRL location, attentional facilitatory modulations have shown an asymmetry, preferring the lower visual field over the upper. The reason could be the anatomical difference between the lower and upward visual field, or the higher number of neurons projecting from the lower primary visual cortex to further regions in the brain processing visual information (Maunsell and Newsome [1987];

He et al. [1996]). The evidence of this hypothesis comes from studies showing better attentional enhancement in the lower visual field: PRL, for most participants, was developed in the lower visual field where the attentional resources were at their best (Barraza-Bernal et al. [2017a]).

The proof of one theory prevailing over the others has not yet been confirmed; instead, different studies advanced the hypothesis that there is not one but multiple mechanisms that can be concomitantly implicated in the PRL formation (Barraza Bernal [2018]; Li et al. [2022]).

1.3 Health-care: tools to overcome what patients lost

Living with a severe visual impairment severely impacts one's quality of life. The quality-adjusted life years (QALY) is a metric used to evaluate a person's quality of life when affected by a disease. Patients with severe AMD are known to have a value below 0.5 QALY, meaning the person concerned can live for one year, but their life quality is halved in comparison to healthy subjects Brown et al. [2003, 2005]. Proposing interventions that can improve this number is therefore essential.

Studies indicated that self-management tasks such as the ones that maintain, change, and create strategies to manage the disease in everyday life could effectively improve a patient's well-being (Lorig and Holman [2003]).

Among the strategies proposed by low vision practice for self-management of the disease, the eccentric viewing training technique showed a better potential in maximizing the visual performance of those with impaired central vision compared to other assistive methods (Goodrich and Mehr [1986]; Vukicevic and Fitzmaurice [2005]).

1.3.1 Training methodology: overview and limitations

Research has suggested that efficient eccentric viewing training requires eye-movement training and attentional control of the shift to a peripheral location in the visual field (Raasch [2004]). As presented in the previous chapter, stimulating attention has proven to affect PRL formation; additionally, it has been linked to successful PRL training procedures (Barraza-Bernal et al. [2017a]; Li et al. [2022]).

The salience theory has indeed found its application in the eccentric training technique by modulating visual attention thanks to salient stimuli (Goodrich and Quillman [1977]). Both the parallel and leading lines linked to the saliency theory have been used successfully since the late 70s' emergence of eccentric viewing training for residual vision rehabilitation (Goodrich and Quillman [1977]; Bäckman and Inde [1979]; Goodrich and Mehr [1986]; Fitzmaurice et al. [1993]; Frennesson et al. [1995]; Vukicevic and Fitzmaurice [2008, 2009]). The idea behind the training is simple: parallel or leading lines act as a static peripheral landmark that attracts attention and guides the patient's view toward an eccentric position. When the central part of the vision is guided away, the intended stimulus shown by the training, usually a letter, becomes visible in the periphery. Thanks to this mechanism, the patient gets trained to use a small peripheral part of the vision to acknowledge an intended object.

One first limitation of this approach is that for the training, patients have to go to the ophthalmologist's office; visits that contribute to the disease's strain on the health system, known to allocate a budget between 51.3 and 101.1 million euros yearly (Bonastre et al. [2002, 2003]). Secondly, the training is designed for close-vision tasks, such as reading, and performed in front of a 2D display; thirdly, the sessions are long, with 3 to 5 hours of repetitive daily tasks that must be performed for 2 to 3 weeks (Goodrich and Quillman [1977]; Goodrich and Mehr [1986]; Vukicevic and Fitzmaurice [2009]). They are exhaustive, and tedious, decreasing the subject's motivation (Lumsden et al. [2016]). Fourthly, the peripheral stimuli used are static. According to the Troxler effect, fixed stimuli presented in the periphery fade fast (Bachy and Zaidi [2014]); therefore, after a while, they lose their saliency. Fourthly, it is mainly oriented toward eye-movement coaching, with the primary goal of implementing a single, best-suited PRL. Nonetheless, studies showed the presence of multiple PRLs in patients (Sunness et al. [1996]; Fletcher and Schuchard [1997]; Sullivan et al. [2005]; Greenstein et al. [2008]; Trauzettel-Klosinski [2009]; Satgunam and Luo [2018]), indicating that, realistically, patients do not adopt a single point that is then optimal for all tasks. AMD is a degenerative disease that leads to very irregular damage in the visual field; therefore, a specific one is not feasible throughout the decrease, and constant re-adaptation is required from patients. In addition, forceful stabilization of fixation counteracts fixational eye moments that compensate for peripheral perceptual fading (Deruaz et al. [2004]). For this reason, it has been suggested that rehabilitation procedures should facilitate a relatively larger fixational preferred area. More so, training should be individualized and consider and implement the PRLs spontaneously developed by the patients for better training results (Deruaz et al. [2002]; Sullivan et al. [2005]).

1.4 Background: efforts done to overcome limitations

Even if the training is superior to all assistive methodologies (Goodrich and Mehr [1986]; Vukicevic and Fitzmaurice [2005]), the previous chapter showed that there are still limitations. With new technologies that can be home-based, individualized, and stimulate motivation and engagement, training techniques can become even more efficient cost and usability-wise. New and advanced tools include VR combined with eye-tracking and gaming as part of the rehabilitation methodology (Cameirão et al. [2007, 2010]; Yates et al. [2016]; Janssen et al. [2017]; Fu et al. [2021, 2022]).

1.4.1 Gaze-contingency: VR and eye-tracking

Eye-tracking is an important feature for assistive and training aids, thanks to gaze-contingency paradigms (Danforth et al. [2000]; Tien et al. [2014]; Rosch and Vogel-Walcutt [2013]; Khan and Lee [2019]; Scheiter et al. [2019]; Masnadi et al. [2020]).

A gaze-contingency paradigm is one where an eye-tracker tracks a person's eyes, and a display is updated continuously based on the tracked position. Gaze-contingent studies are built on the principle that the participant is unaware of the constant changing display as long as it happens within the time frame of rapid and very brief eye movements, called saccades (Brooks and Fuchs [1975]; Riggs et al. [1982]). Their duration depends upon the amplitude: for saccades between $5°$ and $20°$, there is a mean duration between 31 and 54 ms (Baloh et al. [1975]; Bahill et al. [1981]; Becker [1989]; Thickbroom et al. [1991]; Behrens et al. [2010]; Gibaldi et al. [2017]). Within this time frame, it is assumed that a person cannot perceive any stimulus (Brooks and Fuchs [1975]; Riggs et al. [1982]); therefore, stimuli presented gaze-contingently are perceived as continuously following the eyes.

The use of gaze-contingency paradigms for assisting eccentric viewing has been suggested to be used since it offers the advantage of real-time individualized assistive intervention Tlapale et al. [2006]. The combination between VR and gaze-contingency offers an additional advantage to the quasi-natural implementation of assistive visual features: neck and body movements are unrestricted and additionally, an independent monocular application is possible (David et al. [2021]).

Therefore, it permits the full use of the advantages of gaze-contingent peripheral stimuli that can be customized to each AMD patient based on their disease and the PRLs spontaneously developed. An additional advantage is that gaze-contingent stimuli can distribute attention more efficiently than static stimuli. Studies have shown that gaze can be quickly and accurately directed towards an intended region when a stimulus is presented gaze-contingently in the periphery (Barth et al. [2006]; De Graef et al. [2009]; Pomarjanschi et al. [2012]).

Gaze-contingency is an essential feature in AMD research because it allows studying, in a standardized manner, the effects of different peripheral assistive stimuli. Patients' various damages around the macula lead to different shapes of their central visual loss. Regular participants can be presented with an equal-to-all gaze-contingent simulated central black dot (called a simulated scotoma) displayed in both eyes. This methodology is a valid alternative to using AMD patients (Brandeis et al. [2008]; Maniglia et al. [2023]).

1.4.2 At home-training: VR and gaming

Traditional approaches to eccentric viewing training have evidenced that the quality of the training programs depends on the intensity, the repeatability, and, what is often missed, the rewarded performance feedback and motivation promotion patients get from such rehabilitation programs. The traditional training programs have been reported to lack stimulation of the patient's motivation (Pijnacker et al. [2011]), a key factor for continuing and persevering with it.

Gaming is known to stimulate the reward feedback neural system (Kühn et al. [2011]; Gleich et al. [2017]; Palaus et al. [2017]) responsible for improved learning (Janssen et al. [2017]).

VR is also a valuable methodology since it enhances patients' autonomy during training and makes redundant the need for an ophthalmologist to supervise the patient's activity (Cameirão et al. [2007]), reducing intervention costs. VR, in combination with gaming, offers an extra advantage since both manipulate motivational factors and extend the period spent to engage with it and perform the training (Fu et al. [2022]). Additionally, it allows better immersion, and it overcomes the disadvantages of display settings that are known to distract participants (Pallavicini and Pepe [2019]).

Recently, combining VR and gamification has been implemented in visual rehabilitation (Jiménez-Rodríguez et al. [2021]), opening the road for at-home potential applications to eccentric viewing training.

It has been found that when gamification is introduced for eccentric viewing training, it is the preferred method for patients (Stelmack et al. [2004]). More so, gaming has been found to stimulate the development of a PRL and improve visual acuity and retinal sensitivity in the peripheral vision (Li et al. [2011]).

2 Objectives

Patients with AMD rely on eccentric viewing training to continue their daily activity. Traditional eccentric viewing approaches have evidenced limitations such as repetitive training with extended ophthalmic visits and rehabilitation procedures implementing mostly reading. Additionally, the peripheral assistive stimuli are static and implement one single PRL. With the emergence of new rehabilitation processes involving gaze contingency assistance and gaming in VR, these limitations can be better addressed.

(1) The first study focused on quantifying eye-tracking data quality — a measure necessary for correctly implementing gaze-contingent applications. The data obtained from the measurements helped correctly implement a gaze-contingent salient peripheral assistance and a standardized scotoma simulation to be used as a proof of concept for the different peripheral assistive stimuli.

(2) The second study implemented the first gaze-contingent peripheral salient stimulus around a gaze-contingent simulated scotoma in the form of a concentric ring. A simple 2D VR PONG game was developed to help eccentric viewing training in participants with normal vision. The study objective was to investigate how a salient peripheral stimulus influences eccentric viewing during a simple VR game.

(3) The third study implemented four more gaze-contingent salient stimuli presented in the periphery around a gaze-contingent simulated scotoma to investigate whatever additional stimuli from the saliency map theory could lead to similar or better effects. The same 2D PONG game was presented with the same task to allow a comparison with the second study. The third study aimed to find the best-suited peripheral augmentations for age-related macular degeneration patients.

(4) The last study applied the best-suited gaze-contingent salient stimulus around a damaged macular area of $\approx 5^\circ$ radius of an age-related macular degeneration case patient. This study aimed to investigate eccentric training using assistive saliency and compare the results from the previous two studies with simulated macular degeneration participants. A secondary objective was to assess the feasibility of a VR game as training in an older population.

3 Discussion

The main goal of the thesis was to develop a more effective type of eccentric viewing training for AMD patients. To achieve the objective, the work presented in this thesis first assessed the data quality of an eye-tracker integrated into an off-the-self VR headset. Afterward, gaze-contingent salient stimuli were tested during a simple 2D VR game as a training possibility for eccentric viewing. The feasibility of such a design was then tested in an older population using a case study.

3.1 Summary of published work and case study

The following section will provide a summary of the publications and the case study that constitute this thesis.

3.1.1 Publication 1

Throughout the thesis, an off-the-shelf VR headset with an integrated eye-tracker (HTC Vive Pro Eye) was used for implementing gaze-contingent scotoma simulation and peripheral assistive stimuli. Precise accuracy measurements of the spatial and temporal eye-tracker's capabilities are essential for this usability. The first term refers to an eye tracker's capability to identify the eyes' location. When presenting a scotoma simulation, it is essential to know that the black dot is centralized with the eyes' position. Temporal accuracy, on the other hand, indicates the time elapsed between the eye tracker's detection of the eye position and the change of the display, a time-lapse that, for gaze-contingent scotoma, must be up until 54 ms (Baloh et al. [1975]; Bahill et al. [1981]; Becker [1989]; Thickbroom et al. [1991]; Behrens et al. [2010]; Gibaldi et al. [2017] and peripheral stimuli, up to 70 ms (Loschky and Wolverton [2007]; Albert et al. [2017]). Both types of measurements were missing from the literature. Thus, the first study investigated the suitability of the HTC Vive Pro Eye for gaze-contingent applications. Results showed good central accuracy but a drop in precision, affected by movement. The temporal accuracy was found to be 58.1 ms.

Given the results, the spatial and temporal measurements revealed some constraints in simulating a gaze-contingent scotoma. To address them, an in-between trials drift correction and a gaze-contingent scotoma large enough to still cover a good part of central vision and successfully simulate AMD (Saunders and Woods [2014]) were developed. For peripheral gaze-contingency applications, the temporal precision was adequate for such implementation (Loschky and Wolverton [2007]; Albert et al. [2017]).

3.1.2 Publication 2

The second study aimed to use an off-the-shelf VR headset as an assistive tool during simple VR gaming. The problem the study aimed to investigate was to study the effects of a peripheral salient gaze-contingent stimulus on eccentric viewing. As presented in the previous chapter, gaze contingency as an assistive method was proposed but not yet implemented. Peripheral salient stimuli developed to attract gaze towards an eccentric position have not yet been studied at the time of the study. Gaming was used to fast-forward the learning process of eccentric viewing behaviour in simulated scotoma participants, since it has been shown to stimulate learning.

The game was a modified version of a 2D PONG game where subjects had to track a moving target. The moving target was necessary for the game because it changed colour at random time intervals so that participants could not predict when a colour change occurred. A correct colour change indication was attributing participants with points.

AMD simulated participants were used as proof of concept, and a concentric circle augmentation around the simulated scotoma was applied in the periphery, gaze-contingent and monocular, to the dominant eye only, to stimulate saliency. Participants were tested in two attentional conditions: one where the saliency was presented before the scotoma simulation alone and one after. The two conditions allowed us to examine the preventive and post-intervention effects of attentional stimulation. The study investigated the impact on gaze behaviour by looking into gaze position and direction. Therefore, the eccentric gaze behaviour was analysed, considering the eye decentralization and gaze position with respect to the moving target. Results indicated that eccentric viewing was implemented during both conditions, with the participants using a decentralized peripheral region close to the simulated scotoma edges to acknowledge the moving target. An upward and more steady gaze direction preference was observed during the condition where the ring augmentation was presented before simulating a scotoma alone. The results indicated that salience stimuli in the periphery could assist eccentric viewing better when presented as a preventive intervention, in accordance with what was suggested by previous literature (Barraza-Bernal et al. [2017a]; Li et al. [2022]).

3.1.3 Publication 3

The third study extended further the assistive methodologies and, besides the previous concentric line augmentation, additional gaze-contingent monocular and binocular effects were tested. The study aimed to conduct a compassion study between the first type of augmentation implemented and other candidates to look for different possible peripheral salient stimuli. The saliency map theory was implemented when considering the new stimuli candidates. The other salient stimuli investigated were: blurred concentric areas applied monocularly and optical distortions shown binocularly, all known to prompt saliency.

Results from the previous study were used, and saliency was applied before the presentation of AMD simulation alone, since it was observed to have better effects on eccentric gaze behaviour. Therefore, all the additional assistive stimuli were presented before the participants experienced an advanced simulated scotoma. The methodology applied was the same as the second study; the 2D VR PONG game was used, and the augmentations were presented concentrically and using a gaze-contingent paradigm.

Results from the concentric ring augmentation were confirmed again: eccentric viewing was achieved, and an upwards direction was observed. More so, the blurred conditions showed some potential for assisting eccentric vision training, but the effects were not as strong as the concentric line. The binocular optical distortion augmentations did not implement an eccentric viewing behaviour, and gaze directionality was directed in the opposite direction, downwards. The results indicated that the ring augmentation would be a better candidate for eccentric viewing training with AMD participants.

3.1.4 Case study - non-published work

The last is a case report applying the best-suited assistive cue to a macular degeneration patient. The best-suited augmentation from the previous studies was revealed to be concentric line augmentation.

The case study presented a foveal geographic lesion to both eyes due to AMD. The extension of the atrophy had a total horizontal radius of approximately $1.5\,\mathrm{mm}$ ($\approx 5^\circ$ visual angle). The total lesion area of the right eye was slightly larger than the left one ($5.46\,\mathrm{mm}^2$ right eye, $4.30\,\mathrm{mm}^2$ left eye). The best corrected visual acuity (BCVA) was 20/400 for the right eye and 20/80 for the left eye. The patient reported a basic knowledge of technological systems (smartphone usage).

The methodology was the same as the two previous studies: a 2D VR PONG game for the training and the concentric line (ring augmentation), presented centralized to the patient's damaged area, monocular, and to the dominant eye. The experiment consisted of three stages: a pre-augmentation condition, where the subject played the game without assistance; one where the peripheral salience augmentation was present on the left (dominant) eye; and the post-augmentation stage, where the peripheral stimulus was removed.

During the baseline condition, the patient showed a downward-right preference. When present, the assistive stimulus implemented the patient's preference. The bias was conserved when removed, as observed in the previous two studies. A stable 7° visual angle gaze distance with respect to the target was also kept across the three stages.

The patient did not report comprehension problems and did not have difficulties completing the task. It was observed that the game scores were comparable to the simulated subjects from the previous two studies and that the gaming sessions did not have to be re-taken. Additionally, the patient reported being highly engaged and rated the experience as enjoyable and entertaining.

The case report demonstrated the feasibility of a VR game for AMD visual assistance intervention. It showed that the technology has the potential to enforce eccentric vision and help develop a new PRL in cases where the initial PRL is no longer usable due to the enlargement of the lesion.

3.1.5 Contextualization in theory

The results will be conceptualized in the theoretical background introduced in the previous chapters in the following two paragraphs.

3.1.5.1 Gaze-contingent stimuli for PRL training: saliency and attention

Eccentric viewing training uses parallel and converging lines to re-distribute the gaze towards an eccentric position. The stimuli used have been associated with the saliency theory. It has been shown that these types of incentives are among the basic features extracted from a visual scene and the ones analysed first. Salient stimuli are selected based on a winner-take-it-all type of cellular brain activation. These stimuli elicit an eye movement towards the salient location, thanks to increased attentional gain (Moore and Armstrong [2003]; Treue [2003]).

Our study used a similar conceptualization of eccentric viewing training and utilized stimuli associated with the saliency theory. In addition, to better stimulate saliency, stimuli were presented gaze-contingently, and the ones used as spatial cues were presented monocularly. Similar to previous literature (Treue [2003]; Menon and Uddin [2010]; Ji et al. [2019]), we observed a connection between saliency and attention in all three studies. The second study's results suggested stimulation of attention as a preventive method before developing a later stage of AMD (Barraza-Bernal et al. [2017a]; Li et al. [2022]). An upwards gaze directionality was observed when the salient stimuli were first shown around a simulated scotoma and then removed. Once removed, the implemented gaze directionality was maintained and increased across time, even when only the central scotoma simulation was present. The same effect was observed in the third manuscript when the ring augmentation was presented again. Similar results were observed for the blur-in and blur-out conditions. The only difference was that the upwards position of the gaze was not as strongly conserved once the augmentation was removed.

Both results from the second and third studies indicate that the concentric line and both blurred conditions elicited a strong response on the saliency map. The simulated participants could have the entire peripheral part of the visual field at their disposal from which to choose; nonetheless, the gaze was directed towards the hemifield, which has been found by multiple studies to be linked with attentional enhancement. Once the attentional gain started to form, the gaze was shifted upwards, since it is known to be the preferred position where the eyes are directed once attention is stimulated.

In the case study, the gaze directionality observed during the baseline condition was downwards. Similar to the second and third studies, once the ring augmentation was introduced, the behaviour was implemented and conserved once the salient assistive stimulus was removed. The results are encouraging, since during the third study it was observed that other peripheral stimuli can interfere with the PRL formation or conservation.

The downward gaze directionality shown by the patient can be explained in terms of subjective preference. Hence, the results suggest that with a ring augmentation, personalized eccentric viewing can be maintained and not disrupted when eccentric viewing is already present.

3.1.5.2 Gamification in VR of eccentric viewing training: effects

Playful behaviour or gaming is favoured by evolution because activities such as social behaviour for humans or hunting skills in the case of animals can be learned in a safe environment, where clear rules are set and clear, quantifiable gains are achieved (Koepp et al. [1998]; Tekinbas and Zimmerman [2003]). It has an adaptive value because the playful behaviour in the early development stages helps train, mature, and master motor and other complex skills essential for survival and reproductive success (Balkaya and Catak [2016]). Gaming additionally stimulates the reward system. The participant is motivated by the game itself to continue, which stimulates the brain's learning structures (Howard-Jones and Jay [2016]).

In the second and third studies, regular participants were presented with a gaze-contingent simulated scotoma, and eccentric viewing was observed. As previous research has shown, normally sighted participants thus formed a similar eccentric behaviour as patients when presented with a simulated disease (Bertera [1992, 1988]; Altpeter et al. [2000]; Pilz et al. [2006]).

What was additionally observed is that there was a fast adaptation to the eccentric viewing behaviour. Previous studies have shown that eccentric viewing can take up to 3 hours to form successfully with gaze-contingent simulated scotoma (Kwon et al. [2013]; Barraza-Bernal et al. [2017a]; Barraza Bernal [2018]). In both our studies, after a 15 minutes-window, participants successfully adapted and could use the peripheral part of their vision, indicating that gaming and VR could have led to faster training of visual skills. The results are in accordance with previous literature (Achtman et al. [2008]).

3.2 Dissertation contributions

The next chapters will present an overview of the significant contributions that the work developed in this thesis gave to the scientific community.

3.2.1 Gaze-contingency rehabilitation: applicability in VR

Implementing eye-tracking into off-the-shelf VR headsets is a new field; the first commercial headset with such technology became available in early 2017 (Fove-0, 2017). As the years went by, more and more models appeared on the market (Varjo VR-1,2,3 and Aero, 2019, 2020, and 2022; HTC Vive Pro Eye, 2019; Pico Neo 2 and 3, 2020 and 2021 and StarVR One, 2020). At the same time, very little information was known about the data quality of the eye-tracking systems embedded into these kinds of devices (Holmqvist et al. [2022]; Schuetz and Fiehler [2022]). Additionally, the information provided by the manufacturer offered little knowledge of how the accuracy and precision measures were conducted. For correct implementation of a simulated scotoma and salient peripheral gaze-contingent application, accurate eye-tracking data quality measures of a VR-integrated eye-tracker were needed.

3.2.1.1 The new field of VR integrated eye-trackers: understanding applicability performance

Two main limitations to integrated eye trackers in an HMD constrain its usability.

(1) Position of the camera that is tracking the eyes.

The cameras that track eye movements are usually positioned in front of the user for better accuracy. Inside the HMD, cameras can be placed outside the HMD optics, obliquely, such as add-on eye trackers, or inside the body of the VR headset, such as the HTC Vive Pro Eye. The positioning highly influences the quality of the correct eye position identification. Eye-front cameras that can film the eye through the headset's optics are known to provide better accuracy than add-ons (Richter et al. [2019]; Adhanom et al. [2023]).

(2) The sampling frequency of the eye cameras.

The sampling frequency or rate refers to how many eye position data points are recorded by the eye-tracker. The camera capturing the eye images can have a high sampling frequency. However, considering that the recorded position has to be displayed for gaze-contingent applications, the sampling rate depends more on the display capacity inside the HMD. If the sampling frequency of the display is lower than the capacity of the eye camera, then there is a discrepancy between the recorded data and the displayed data. The eye camera of the HTC Vive Pro Eye has a sampling frequency of 120 Hz, while the HMD displays have a 90 Hz rate, lowering its temporal accuracy. Therefore, this limits the applicability performance (Loschky and Wolverton [2007]).

The first study, therefore, was necessary since, at the time of the thesis, only one study (Lohr et al. [2019]) had systematically investigated eye-tracking data quality in VR. However, the study considered an add-on system with a different eye-tracking capability than integrated eye-trackers. The first publication added to the growing literature by offering systematic and accurate information about the data capabilities of an eye-tracking system integrated into an off-the-shelf VR headset. Indeed, in the following years, additional studies started focusing on the data capabilities of VR-integrated eye trackers (Stein et al. [2021]; Schuetz and Fiehler [2022]; Adhanom et al. [2023]).

3.2.1.2 Individualized application of VR assistive techniques for visually impaired patients

The combined results of studies focusing on the eye-tracking data quality of HMDs make many implementations, such as gaze-contingent medical assistance devices, possible. Applications using a VR headset with integrated eye-tracking can offer patients more dynamic and individualized support (Tlapale et al. [2006]; Masnadi et al. [2020]).

This type of application is a crucial leap forward from assistive technologies such as magnifiers, contrast, edges, or colour enhancements that modify the entire field of view (Wolffsohn et al. [2002]; Satgunam et al. [2012]; Bittner et al. [2022]), including the healthy parts, leading to an unnatural user experience (Masnadi et al. [2020]). Eye-tracking instead offers the possibility to dynamically assist the user based on the specific characteristics of their disease.

The usage of such assistive systems has indeed started to emerge more and more with promising results (Konrad et al. [2016]; Leotta and Ross [2018]; Reichenberger et al. [2020]), opening the field to individualized rehabilitation techniques. Gaze-contingency for eccentric viewing training has been proposed for eccentric viewing training, but to our knowledge, it has not been implemented and tested. The second, third, and fourth studies contributed to the emerging research showing that gaze-contingency can successfully be implemented as an eccentric viewing training technique in simulated scotoma participants and patients.

3.2.2 Eccentric viewing training: gamification feasibility

Games offer a unique feature for any training because of being highly versatile. The engagement aspect is always present, from the simplest to the more complex game.

3.2.2.1 Eccentric viewing training: the faster, the better

When patients lose their visual landmark, that specific part they always used to orient, an adaptation period to the new way of looking at objects follows. Literature has shown that this period takes a long time, especially considering older patients. The adaptation period can last up until three months. Some patients do not even succeed in adapting to it due to other health conditions compromising their ability to re-learn a visual function (White and Bedell [1990]; Uhlmann et al. [1991]; Crossland et al. [2005]; Berman and Brodaty [2006]; Gehrs et al. [2006]).

Therefore, a system that can help speed up the adaptation period and be, at the same time, in line with the population capabilities the training system is developed for represents a step forward in helping these patients. Gaming, as previously discussed, is a natural part of learning new things quickly and efficiently new concepts. Therefore, investigating gaming as a tool for eccentric viewing training opens the door to faster and more engaging training techniques.

3.2.2.2 AMD and gaming: acceptability of a new form of training

The way we interact with technology highly depends on previous experiences. The elderly did not grow up in a continuous technological advancement environment; therefore, interaction with new innovations is more challenging. It has indeed been shown that the elderly are slower at utilizing newer technology because they use it less intuitively than the younger population (Blackler [2006]).

Therefore, the literature advises, that when designing games or systems meant for an elderly population symbols and games with already-known features are more suitable (Blackler [2006]). For this reason, the current thesis implemented a simple 2D PONG for eccentric viewing training gamification. It is a classical and straightforward game that emerged as one of the so-called 'university games' in a lab research felicity in the 60s. Afterward, it was widely used in the 80s in the arcade game scenario, based on the concept of what is simple is better (Lowood [2009]). The game offers the right combination of competitiveness and simplicity. Therefore, the game was introduced because of these two main features: it would have been simple enough to be understood and competitive enough to create engagement. Additionally, considering the age group, it might have been more familiar, thus, easier to interact with for the targeted population group (Blackler [2006]).

3.2.2.3 Feasibility of gaming as a visual training AMD tool

Gamification of visual training is not a new idea. It has been proposed for other visual diseases, such as amblyopia and retinitis pigmentosa participants (Jiménez-Rodríguez et al. [2021]; Neugebauer et al. [2022]), but best to our knowledge, no gaming was tested for age-related macular degeneration. The case study demonstrated encouraging results, indicating that simple games are feasible for eccentric viewing training in AMD. The participant achieved the goal of understanding, playing, and focusing on the task. The results obtained add up to research showing good acceptance levels from an older population of gaming for rehabilitation (Steinert et al. [2018]; Koivisto and Malik [2021]; White et al. [2022]). Concluding, the thesis showed the feasibility of gamification of eccentric viewing training for AMD patients.

3.3 Future outlooks

In the following chapters, a look into what future work could be explored based on the current thesis's results.

3.3.1 Neuroscientific approach to assistive stimuli and eccentric viewing training

Based on the results obtained, a possible link between salient stimuli, attention, and PRL formation was hypothesized. Neuroscientific techniques can evidence the connection between these stimuli types and brain activity.

3.3.1.1 Advantages of neuroscientific approaches

Neuroscience is a research area that started to get more and more attention as a field of human behaviour research in the 1990s (Casado-Aranda and Sanchez-Fernandez [2022]). The field offers a unique advantage of non-invasive techniques developed to understand human behaviour's neural correlates (Krueger et al. [2008]; Higuchi et al. [2009]; Kohl et al. [2009]; Koch et al. [2016]). Understanding the neural correlates of a particular behaviour provides the benefit of a better intervention, since the core of the problem is being better understood. A deeper understanding of the core problem also makes finding preventive interventions for that affliction possible (Bryck and Fisher [2012]; Hall [2016]).

3.3.1.2 Neuroimaging techniques: unveiling the neural correlates of PRL formation and saliency

For example, functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) studies (Baker et al. [2005]; Versek et al. [2021]) have already been used to look into PRL formation and offer insight into the neural mechanisms behind the consequential adaptive behaviour, as presented in the introduction chapters.

The gaze-contingent stimuli used for the current work were based on the saliency map theory. Studies 2 and 3 showed that these stimuli differently influenced gaze directionality. More so, in study 3, we observed that monocular stimuli implemented an eccentric viewing behaviour, while the binocular distortions did not.

From a neuroscientific point of view, all the stimuli tested have been liked to a particular brain area. Concentric lines, blur, and distortions elicited activity in the V4 visual area (Oleskiw et al. [2017, 2018]; Entezari and Bair [2019]), an area central for visual attention and involved in creating a saliency map (Treue [2003]).

This brain area is particularly interesting because it is known to be little affected by ageing (Roe et al. [2012]; Sciberras-Lim and Lambert [2017]). It has been shown that with ageing, visual attention is still well-preserved in this area since it receives inputs from the topographically organized visual sites as well as from higher brain areas that compensate for possible sensory-reduced activity (Sciberras-Lim and Lambert [2017]). Therefore, stimuli that elicit V4 activation could be more suited for the rehabilitation process, thanks to attentional resources and the plasticity features still present with age.

For instance, concentric lines have been shown to elicit a vigorous V4 activity when compared to simple lines (Treue [2003]). The more robust effect on gaze direction and eccentric viewing observed in studies 2, 3, and 4 from the ring augmentation could be due to a V4 activation. Stimuli, such as blur or distortions, were also related to attentional mechanisms and V4 activation, but the mechanisms involved are more complex than the neural processing of simple concentric lines. For instance, it has been shown that for blur, after the initial processing in the early visual areas, information is sent directly to the higher hierarchical brain regions, such as the prefrontal cortex (Bar [2003]; Katsuki and Constantinidis [2012]). Authors have hypothesized that the prefrontal areas could play an early involvement in saliency representation. A similar mechanism could be behind the neural processing of distortions (Zirnsak et al. [2014]).

Neuroimaging technologies can be utilized to explore and unveil the link between the stimuli used and the brain activation to show if brain areas linked to saliency and attention processing areas are also active when these stimuli are presented. More so, they could permit a better understanding of the effect the stimuli utilized for this work have on PRL formation. The neuroscientific investigation would allow us to understand how they activate the brain and the connected temporal stages of these activations.

Additional neuroscientific testing also offers the opportunity for preventive interventions for when the disease advances and the exploration of more stimuli linked to the saliency map.

For example, literature has proposed a gaze-contingent augmented parallel line for reading (Tlapale et al. [2006]). Additional gaze-contingent stimuli linked to saliency are luminance and contrast increases around scotoma edges (Lei and Schuchard [1997]). An edge detection could be implemented and presented as gaze-contingent around the scotoma. It has been shown that hard edges around the scotoma can contribute to a faster PRL formation (Maniglia et al. [2021]). When the participants become aware of the actual extent of their disease with an edge-detection implementation, they could better place the PRL where needed.

3.3.2 Augmented reality (AR) extensions: training with AR gaming

In addition to gaze-contingency applications in VR, another technological feature emerged as an assistive methodology: AR. AR uses a see-through head-mounted display that adds computer-generated virtual information to a real-world scenario (Carmigniani and Furht [2011]).

3.3.2.1 Advantages of AR interventions

Besides interactivity and engagement, AR offers the additional advantage of permitting a more intuitive interaction with a more realistic environment and a better reality judgement than VR because participants interact with natural objects (Correa et al. [2007]; Chen et al. [2019]). Additionally, when AR is combined with gaming, AR does not need additional gaming input gadgets such as consoles, joysticks, mouses, or keyboards (Correa et al. [2007]), known to be not so intuitive for older populations (Blackler and Hurtienne [2007]). As discussed previously, older people have been associated with slower adaptability to newer technology due to mental models formed around how to interact with objects formed mostly in their youth. For this reason, they require additional effort to learn new technology (Blackler [2006]). AR could offer an even more natural interaction and better help eccentric viewing training while gaming.

3.3.2.2 AR PONG: implementation feasibility

In combination with gaming, AR has already been implemented (Thomas et al. [2002]; Magerkurth et al. [2005]; Kojima et al. [2006]; Kern et al. [2006]; Eishita et al. [2014]) and recent studies have shown the feasibility of AR gaming rehabilitation systems for different diseases (Hayhurst [2018]; Hatzigiannakoglou and Okalidou [2019]; Mubin et al. [2019]; Sun et al. [2023]). The mentioned studies have all cited the motivation and entertainment aspects of the success behind these types of rehabilitative tools.

On the other hand, less research on gaze-contingency applications in AR has been conducted in comparison to VR, but recent studies have evidenced its usability as an assistive visual aid for the visually impaired (Lang et al. [2020]).

Considering that an adapted PONG game has been proposed in AR (Gao et al. [2014]; Salas et al. [2021]), the same methodology shown throughout this thesis work could be implemented using PONG AR. Therefore, for future research, AR gaming could be used for eccentric viewing training for an even more intuitive interaction.

AR gaming training is currently less feasible than VR gaming, since AR technology development is not yet mature enough. AR took longer to develop, since the technical requirements were higher than those for VR (Van Krevelen and Poelman [2010]). Even if there have been breakthrough advancements, the data quality in AR is low, and this technology does not yet permit long recording hours (Parsons and MacCallum [2021]).

These limitations indicate that, as of now, for AR PONG implementations, more technological progress in terms of AR is needed.

3.4 Applicability of results

The present work's main focus was to study interventions in VR that could assist eccentric viewing. Nonetheless, the results obtained from the studies can be applied to further research.

3.4.1 Interdisciplinary research into eccentric viewing training

The results from studies 1-4 offered a bridge between traditional eccentric viewing training and new forms of technology. Given the conventional approach, salient stimuli were designed for eccentric viewing training. Considering the advantage of the latest technology, a new system was developed: salient gaze-contingent stimuli in VR. The efficiency of new technology was tested, meaning the eye-tracking capability for gaze-contingent applications in VR was analysed. Afterward, the new system was examined using a standardized scotoma simulation and finally applied to the target population.

The effects the stimuli had on gaze directionality indicated that cognitive and neuroscientific theories offer a good implementation for eccentric viewing training. These results can be applied to expand eccentric viewing training for AMD toward new horizons. For example, home-based interventions with the newest VR technology combined with portable neuroscientific techniques become a viable possibility.

For instance, portable neuroimaging solutions can detect changes in brain activity whenever salient stimuli are investigated (Straetmans et al. [2022]). Such techniques could be applied to identify if brain activity changes can be identified when comparing periods using the ring augmentation proposed in this thesis and when not. A second step would be to determine precisely the brain area that becomes activated between those two phases.

Studies have analysed the feasibility and the effect such approaches could have when utilized for clinical populations (Teo et al. [2016]; Landowska et al. [2018]; Aspiotis et al. [2022]) and have concluded that neuroscientific approaches combined with VR applications could complement each other and provide more targeted interventions for rehabilitation. The authors have also advised caution and encouraged such studies to be conducted on a large population. The effects observed in VR should be carefully analysed and corroborated in a natural environment (Teo et al. [2016]).

Therefore, as a third step, the ring augmentation could be used in an AR PONG environment, where the link to the real-world scenario is more robust, and then compare the results obtained in VR PONG with the ones observed in AR PONG.

3.4.2 Research into long-lasting effects of eccentric viewing training gamification

Normally sighted participants simulated with a gaze-contingent scotoma developed a fast adaptation, and eccentric viewing was observed after a quarter of an hour. Gamification of the training was hypothesized to play a role in it.

While the case study was not designed to provide information about learning acceleration outcomes associated with VR gaming assistive techniques, the results obtained from healthy participants suggest that such effects can also apply to patients.

As AMD patients frequently experience disease deterioration, the proposed training showed that it does not interfere with their existing adaptation process. This indicates that it can be applied to shift further off the PRL while maintaining the patient's personal preference when the disease advances. More so, a good acceptability of such a game is shown, encouraging further application and investigation in a larger patient group.

Additionally, since gamification permits more extended training periods thanks to its engaging nature, the long-lasting effects of training and gaming can be explored. There is evidence that the duration of coaching plays a crucial role in establishing a PRL: the longer the training period is, the more prolonged the effects are (Barraza-Bernal et al. [2017b]). The time effects of the training are known to last up to four years (Palmer et al. [2010]; Barraza-Bernal et al. [2017c]).

Studies have also suggested boosting sessions, referring to eccentric viewing sessions performed after a training period to reinforce the trained PRL (Alma et al. [2012]; Nastasi [2020]). It has been reported that these sessions significantly affect the frequency of patients engaging in daily activities such as outdoor activities (Nastasi [2020]).

Gamification of AMD training can be applied to all these areas and help have an active role in overcoming the isolation these patients experience as time passes and boost their confidence. More so, such prolonged training can significantly benefit their quality of life.

Evidence shows that VR combined with gaming can significantly improve the QALY when used for training. VR gaming was more effective than traditional training, with the VR gaming doubling the effect on QALY after the time spent in training doubled. Such results were not observed when using conventional training techniques (Fatoye et al. [2022]).

These outcomes are encouraging and suggest that such effects could be observed when VR gaming is used for prolonged periods in AMD patients.

4 Conclusion

The current thesis showed that gaze-contingent salient stimuli in different formats could affect gaze direction differently and be connected to attention. These results opened the door to new approaches for eccentric viewing training based on neuroscientific theories.

Moreover, it showed that new technologies could be implemented and used. The usability of such more user-friendly systems builds up the user's confidence. VR allows an individual user to train in the comfort of their home and independent of an expert present for the training. In this way, patients can retake charge of their disease and, therefore, permit them to take control of their life.

Secondly, gamification is possible for eccentric viewing training. Fast adaptability for participants never exposed to central vision loss and feasibility for an older age group was observed.

Given the current work, we hope that further studies will focus on technology that allows for more independence and uses gamification to help people with visual disorders have valuable training sessions.

5 References

Abdelsalam, A., Del Priore, L., and Zarbin, M. A. (1999). Drusen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation–induced regression. *Survey of ophthalmology*, 44(1):1–29.

Achard, O. A., Safran, A. B., Duret, F. C., and Ragama, E. (1995). Role of the completion phenomenon in the evaluation of amsler grid results. *American journal of ophthalmology*, 120(3):322–329.

Achtman, R. L., Green, C. S., and Bavelier, D. (2008). Video games as a tool to train visual skills. *Restorative neurology and neuroscience*, 26(4-5):435–446.

Adhanom, I. B., MacNeilage, P., and Folmer, E. (2023). Eye tracking in virtual reality: a broad review of applications and challenges. *Virtual Reality*, pages 1–24.

Aine, C., George, J., Ranken, D., Best, E., Tiee, W., Vigil, V., Flynn, E., Wood, C., and Supek, S. (1993). Meg studies of human vision: retinotopic organization of v1. Technical report, Los Alamos National Lab., NM (United States).

Al Gwairi, O., Thach, L., Zheng, W., Osman, N., and Little, P. J. (2016). Cellular and molecular pathology of age-related macular degeneration: potential role for proteoglycans. *Journal of ophthalmology*, 2016.

Albert, R., Patney, A., Luebke, D., and Kim, J. (2017). Latency requirements for foveated rendering in virtual reality. *ACM Transactions on Applied Perception (TAP)*, 14(4):1–13.

Alma, M. A., Groothoff, J. W., Melis-Dankers, B. J., Post, M. W., Suurmeijer, T. P., and Van der Mei, S. F. (2012). Effects of a multidisciplinary group rehabilitation programme on participation of the visually impaired elderly: A pilot study. *Disability and Rehabilitation*, 34(20):1677–1685.

Altpeter, E., Mackeben, M., and Trauzettel-Klosinski, S. (2000). The importance of sustained attention for patients with maculopathies. *Vision Research*, 40(10-12):1539–1547.

Ambati, J., Atkinson, J. P., and Gelfand, B. D. (2013). Immunology of age-related macular degeneration. *Nature Reviews Immunology*, 13(6):438–451.

Amilon, A. and Siren, A. (2021). The link between vision impairment and depressive symptomatology in late life: does having a partner matter? *European Journal of Ageing*, 1:1–12.

Aspiotis, V., Miltiadous, A., Kalafatakis, K., Tzimourta, K. D., Giannakeas, N., Tsipouras, M. G., Peschos, D., Glavas, E., and Tzallas, A. T. (2022). Assessing electroencephalography as a stress indicator: A vr high-altitude scenario monitored through eeg and ecg. *Sensors*, 22(15):5792.

Bachy, R. and Zaidi, Q. (2014). Troxler fading, eye movements, and retinal ganglion cell properties. *i-Perception*, 5(7):611–612.

Bäckman, Ö. and Inde, K. (1979). *Low vision training*. LiberLäromedel/Hermod.

Bahill, A., Brockenbrough, A., and Troost, B. (1981). Variability and development of a normative data base for saccadic eye movements. *Investigative ophthalmology & visual science*, 21(1):116–125.

Bahmani, H. and Wahl, S. (2016). Distorted low-level visual features affect saliency-based visual attention. *Frontiers in Computational Neuroscience*, 10:124.

Baker, C. I., Peli, E., Knouf, N., and Kanwisher, N. G. (2005). Reorganization of visual processing in macular degeneration. *Journal of Neuroscience*, 25(3):614–618.

Balkaya, M. and Catak, G. (2016). Why games are fun? the reward system in the human brain. In *Gamer Psychology and Behavior*, pages 21–38. Springer.

Baloh, R. W., Sills, A. W., Kumley, W. E., and Honrubia, V. (1975). Quantitative measurement of saccade amplitude, duration, and velocity. *Neurology*, 25(11):1065–1065.

Banks, M. S., Sekuler, A. B., and Anderson, S. J. (1991). Peripheral spatial vision: Limits imposed by optics, photoreceptors, and receptor pooling. *JOSA a*, 8(11):1775–1787.

Bar, M. (2003). A cortical mechanism for triggering top-down facilitation in visual object recognition. *Journal of cognitive neuroscience*, 15(4):600–609.

Barraza Bernal, M. J. (2018). *Novel strategies to enhance the visual performance of the visually impaired*. PhD thesis, Universität Tübingen.

Barraza-Bernal, M. J., Ivanov, I. V., Nill, S., Rifai, K., Trauzettel-Klosinski, S., and Wahl, S. (2017a). Can positions in the visual field with high attentional capabilities be good candidates for a new preferred retinal locus? *Vision Research*, 140:1–12.

Barraza-Bernal, M. J., Rifai, K., and Wahl, S. (2017b). A preferred retinal location of fixation can be induced when systematic stimulus relocations are applied. *Journal of Vision*, 17(2):11–11.

Barraza-Bernal, M. J., Rifai, K., and Wahl, S. (2017c). Transfer of an induced preferred retinal locus of fixation to everyday life visual tasks. *Journal of Vision*, 17(14):2–2.

Barth, E., Dorr, M., Böhme, M., Gegenfurtner, K., and Martinetz, T. (2006). Guiding eye movements for better communication and augmented vision. In *International Tutorial and Research Workshop on Perception and Interactive Technologies for Speech-Based Systems*, pages 1–8. Springer.

Baveye, Y., Urban, F., and Chamaret, C. (2012). Image and video saliency models improvement by blur identification. In *International Conference on Computer Vision and Graphics*, pages 280–287. Springer.

Becker, W. (1989). The neurobiology of saccadic eye movements: Metrics. *Reviews of Oculomotor Research*, 3:13–67.

Behrens, F., MacKeben, M., and Schröder-Preikschat, W. (2010). An improved algorithm for automatic detection of saccades in eye movement data and for calculating saccade parameters. *Behavior research methods*, 42(3):701–708.

Berman, K. and Brodaty, H. (2006). Psychosocial effects of age-related macular degeneration. *International Psychogeriatrics*, 18(3):415–428.

Bertera, J. H. (1988). The effect of simulated scotomas on visual search in normal subjects. *Investigative Ophthalmology & Visual Science*, 29(3):470–475.

Bertera, J. H. (1992). Oculomotor adaptation with virtual reality scotomas. *Simulation*, 59(1):37–43.

Bittner, A. K., Yoshinaga, P. D., Shepherd, J. D., Kaminski, J. E., Malkin, A. G., Chun, M. W., Chan, T. L., Deemer, A. D., Ross, N. C., Team, B.-A. S., et al. (2022). Acceptability of telerehabilitation for magnification devices for the visually impaired using various approaches to facilitate accessibility. *Translational Vision Science & Technology*, 11(8):4–4.

Blackler, A. and Hurtienne, J. (2007). Towards a unified view of intuitive interaction: definitions, models and tools across the world. *MMI-interaktiv*, 13(2007):36–54.

Blackler, A. L. (2006). *Intuitive interaction with complex artefacts*. PhD thesis, Queensland University of Technology.

Bonastre, J., Le Pen, C., Anderson, P., Ganz, A., Berto, P., and Berdeaux, G. (2002). The epidemiology, economics and quality of life burden of age-related macular degeneration in france, germany, italy and the united kingdom. *The European Journal of Health Economics*, 3(2):94–102.

Bonastre, J., Le Pen, C., Soubrane, G., and Quentel, G. (2003). The burden of age-related macular degeneration. *Pharmacoeconomics*, 21(3):181–190.

Borkenstein, A. F., Borkenstein, E. M., Persson, S., Muus, G., and Nielsen, N. V. (2021). Improving Outcomes for Patients with Age-Related Macular Degeneration and Cataracts: The Importance of Including an Assessment of Activities of Daily Life (ADL). *Clinical Ophthalmology (Auckland, N.Z.)*, 15:3333.

Brandeis, R., Egoz, I., Peri, D., Sapiens, N., and Turetz, J. (2008). Psychophysical and perceptual performance in a simulated-scotoma model of human eye injury. In *Ophthalmic Technologies XVIII*, volume 6844, pages 266–276. SPIE.

Brewer, A. A., Press, W. A., Logothetis, N. K., and Wandell, B. A. (2002). Visual areas in macaque cortex measured using functional magnetic resonance imaging. *Journal of Neuroscience*, 22(23):10416–10426.

Brooks, B. A. and Fuchs, A. F. (1975). Influence of stimulus parameters on visual sensitivity during saccadic eye movement. *Vision research*, 15(12):1389–1398.

Brown, G. C., Brown, M. M., Sharma, S., Stein, J. D., Roth, Z., Campanella, J., and Beauchamp, G. R. (2005). The burden of age-related macular degeneration: a value-based medicine analysis. *Transactions of the American Ophthalmological Society*, 103:173.

Brown, M. M., Brown, G. C., Sharma, S., and Landy, J. (2003). Health care economic analyses and value-based medicine. *Survey of ophthalmology*, 48(2):204–223.

Bryck, R. L. and Fisher, P. A. (2012). Training the brain: practical applications of neural plasticity from the intersection of cognitive neuroscience, developmental psychology, and prevention science. *American Psychologist*, 67(2):87.

Cameirão, M. S., i Badia, S. B., Zimmerli, L., Oller, E. D., and Verschure, P. F. (2007). The rehabilitation gaming system: a virtual reality based system for the evaluation and rehabilitation of motor deficits. In *2007 Virtual Rehabilitation*, pages 29–33. IEEE.

Cameirão, M. S., Oller, E. D., Verschure, P. F., et al. (2010). Neurorehabilitation using the virtual reality based rehabilitation gaming system: methodology, design, psychometrics, usability and validation. *Journal of neuroengineering and rehabilitation*, 7(1):1–14.

Carmigniani, J. and Furht, B. (2011). Augmented reality: an overview. *Handbook of augmented reality*, pages 3–46.

Casado-Aranda, L.-A. and Sanchez-Fernandez, J. (2022). Advances in neuroscience and marketing: analyzing tool possibilities and research opportunities. *Spanish Journal of Marketing-ESIC*.

Casten, R. J., Rovner, B. W., and Tasman, W. (2004). Age-related macular degeneration and depression: a review of recent research. *Current opinion in ophthalmology*, 15(3):181–183.

Chawla, D., Rees, G., and Friston, K. (1999). The physiological basis of attentional modulation in extrastriate visual areas. *Nature neuroscience*, 2(7):671–676.

Chen, Y., Wang, Q., Chen, H., Song, X., Tang, H., and Tian, M. (2019). An overview of augmented reality technology. In *Journal of Physics: Conference Series*, volume 1237, page 022082. IOP Publishing.

Cheung, S.-H. and Legge, G. E. (2005). Functional and cortical adaptations to central vision loss. *Visual neuroscience*, 22(2):187–201.

Cimarolli, V. R., Casten, R. J., Rovner, B. W., Heyl, V., Sörensen, S., and Horowitz, A. (2016). Anxiety and depression in patients with advanced macular degeneration: current perspectives. *Clinical Ophthalmology (Auckland, NZ)*, 10:55.

Colenbrander, A. (2005). Visual functions and functional vision. *International Congress Series*, 1282:482–486.

Correa, A. G. D., De Assis, G. A., do Nascimento, M., Ficheman, I., and de Deus Lopes, R. (2007). Genvirtual: An augmented reality musical game for cognitive and motor rehabilitation. In *2007 Virtual Rehabilitation*, pages 1–6. IEEE.

Crossland, M. D., Culham, L. E., Kabanarou, S. A., and Rubin, G. S. (2005). Preferred retinal locus development in patients with macular disease. *Ophthalmology*, 112(9):1579–1585.

Crossland, M. D., Engel, S. A., and Legge, G. E. (2011). The preferred retinal locus in macular disease: toward a consensus definition. *Retina*, 31(10):2109–2114.

Danforth, R., Duchowski, A., Geist, R., and McAliley, E. (2000). A platform for gaze-contingent virtual environments. In *Smart Graphics (Papers from the 2000 AAAI Spring Symposium, Technical Report SS-00-04)*, pages 66–70. American Association for Artificial Intelligence Palo Alto, CA, USA.

David, E. J., Beitner, J., and Võ, M. L.-H. (2021). The importance of peripheral vision when searching 3d real-world scenes: A gaze-contingent study in virtual reality. *Journal of Vision*, 21(7):3–3.

De Graef, P., Hamon, G., Dorr, M., and Barth, E. (2009). Virtual navigation training and gaze guidance. *Eye and the auto*, 2009:19–19.

Deruaz, A., Matter, M., Whatham, A., Goldschmidt, M., Duret, F., Issenhuth, M., and Safran, A. (2004). Can fixation instability improve text perception during eccentric fixation in patients with central scotomas? *British Journal of Ophthalmology*, 88(4):461–463.

Deruaz, A., Whatham, A., Mermoud, C., and Safran, A. (2002). Reading with multiple preferred retinal loci: implications for training a more efficient reading strategy. *Vision research*, 42(27):2947–2957.

Dilks, D. D., Julian, J. B., Peli, E., and Kanwisher, N. (2014). Reorganization of visual processing in age-related macular degeneration depends on foveal loss. *Optometry and Vision Science*, 91(8):e199–e206.

Dumoulin, S. O. and Hess, R. F. (2007). Cortical specialization for concentric shape processing. *Vision Research*, 47(12):1608–1613.

Ebner, C., Wernigg, C., Schütze, C., Weingessel, B., and Vécsei-Marlovits, P.-V. (2021). Retinal pigment epithelial characteristics in eyes with neovascular age-related macular degeneration. *Wiener Klinische Wochenschrift*, 133(3):123–130.

Eishita, F. Z., Stanley, K. G., and Mandryk, R. (2014). Iterative design of an augmented reality game and level-editing tool for use in the classroom. In *2014 IEEE Games Media Entertainment*, pages 1–4. IEEE.

Engel, S. A., Glover, G. H., and Wandell, B. A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional mri. *Cerebral cortex (New York, NY: 1991)*, 7(2):181–192.

Entezari, S. and Bair, W. (2019). Artiphysiology reveals visual preferences underlying v4-like blur selectivity in a deep convolutional neural network. *bioRxiv*.

Fatoye, F., Gebrye, T., Mbada, C. E., Fatoye, C. T., Makinde, M. O., Ayomide, S., and Ige, B. (2022). Cost effectiveness of virtual reality game compared to clinic based mckenzie extension therapy for chronic non-specific low back pain. *British Journal of Pain*, 16(6):601–609.

Ferris III, F. L., Wilkinson, C., Bird, A., Chakravarthy, U., Chew, E., Csaky, K., Sadda, S. R., for Macular Research Classification Committee, B. I., et al. (2013). Clinical classification of age-related macular degeneration. *Ophthalmology*, 120(4):844–851.

Finger, R. P., Schmitz-Valckenberg, S., Schmid, M., Rubin, G. S., Dunbar, H., Tufail, A., Crabb, D. P., Binns, A., Sánchez, C. I., Margaron, P., et al. (2019). Macustar: development and clinical validation of functional, structural, and patient-reported endpoints in intermediate age-related macular degeneration. *Ophthalmologica*, 241(2):61–72.

Fischbarg, J. (2005). *The biology of the eye*. Elsevier.

Fitzmaurice, K., Kinnear, J., and Chen, Y. (1993). Eccvue: A computer generated method of training eccentric viewing. *Aust Orthopt J*, 29:13–17.

Fletcher, D. C. and Schuchard, R. A. (1997). Preferred retinal loci relationship to macular scotomas in a low-vision population. *Ophthalmology*, 104(4):632–638.

Frennesson, C., Jakobsson, P., and Nilsson, U. L. (1995). A computer and video display based system for training eccentric viewing in macular degeneration with an absolute central scotoma. *Documenta ophthalmologica*, 91(1):9–16.

Fu, Y., Hu, Y., Sundstedt, V., and Fagerström, C. (2021). A survey of possibilities and challenges with ar/vr/mr and gamification usage in healthcare. In *HEALTHINF*, pages 733–740.

Fu, Y., Hu, Y., Sundstedt, V., and Forsell, Y. (2022). Conceptual design of an extended reality exercise game for the elderly. *Applied Sciences*, 12(13):6436.

Gao, X., Tian, J., Liang, X., and Wang, G. (2014). Arpp: An augmented reality 3d ping-pong game system on android mobile platform. In *2014 23rd Wireless and Optical Communication Conference (WOCC)*, pages 1–6. IEEE.

Gehrs, K. M., Anderson, D. H., Johnson, L. V., and Hageman, G. S. (2006). Age-related macular degeneration—emerging pathogenetic and therapeutic concepts. *Annals of medicine*, 38(7):450–471.

Gibaldi, A., Vanegas, M., Bex, P. J., and Maiello, G. (2017). Evaluation of the tobii eyex eye tracking controller and matlab toolkit for research. *Behavior research methods*, 49:923–946.

Gide, M. S., Dodge, S. F., and Karam, L. J. (2016). The effect of distortions on the prediction of visual attention. *arXiv preprint arXiv:1604.03882*.

Gleich, T., Lorenz, R. C., Gallinat, J., and Kühn, S. (2017). Functional changes in the reward circuit in response to gaming-related cues after training with a commercial video game. *Neuroimage*, 152:467–475.

Goodrich, G. L. and Mehr, E. B. (1986). Eccentric viewing training and low vision aids: current practice and implications of peripheral retinal research. *Am J Optom Physiol Opt*, 63(2):119–26.

Goodrich, G. L. and Quillman, R. D. (1977). Training eccentric viewing. *Journal of Visual Impairment & Blindness*, 71(9):377–381.

Greenstein, V. C., Santos, R. A., Tsang, S. H., Smith, R. T., Barile, G. R., and Seiple, W. (2008). Preferred retinal locus in macular disease: characteristics and clinical implications. *Retina (Philadelphia, Pa.)*, 28(9):1234.

Hall, P. A. (2016). Prevention neuroscience: A new frontier for preventive medicine. *Preventive medicine*, 86:114–116.

Hassell, J. B., Lamoureux, E. L., and Keeffe, J. E. (2006). Impact of age related macular degeneration on quality of life. *The British Journal of Ophthalmology*, 90(5):593.

Hatzigiannakoglou, P. D. and Okalidou, A. (2019). Development of an auditory rehabilitation tool for children with cochlear implants through a mobile-based vr and ar serious game. *International Journal of Online & Biomedical Engineering*, 15(2).

Hayhurst, J. (2018). How augmented reality and virtual reality is being used to support people living with dementia—design challenges and future directions. *Augmented reality and virtual reality: Empowering human, place and business*, pages 295–305.

He, S., Cavanagh, P., and Intriligator, J. (1996). Attentional resolution and the locus of visual awareness. *Nature*, 383(6598):334–337.

Hejtmancik, J. F. and Shiels, A. (2015). Overview of the lens. *Progress in molecular biology and translational science*, 134:119–127.

Higuchi, S., Chaminade, T., Imamizu, H., and Kawato, M. (2009). Shared neural correlates for language and tool use in broca's area. *Neuroreport*, 20(15):1376–1381.

Holmqvist, K., Örbom, S. L., Hooge, I. T., Niehorster, D. C., Alexander, R. G., Andersson, R., Benjamins, J. S., Blignaut, P., Brouwer, A.-M., Chuang, L. L., et al. (2022). Eye tracking: empirical foundations for a minimal reporting guideline. *Behavior research methods*, pages 1–53.

Horton, J. C. and Hoyt, W. F. (1991). The representation of the visual field in human striate cortex: a revision of the classic holmes map. *Archives of ophthalmology*, 109(6):816–824.

Howard-Jones, P. A. and Jay, T. (2016). Reward, learning and games. *Current opinion in behavioral sciences*, 10:65–72.

Itti, L. and Koch, C. (2000). A saliency-based search mechanism for overt and covert shifts of visual attention. *Vision research*, 40(10-12):1489–1506.

Janssen, J., Verschuren, O., Renger, W. J., Ermers, J., Ketelaar, M., and Van Ee, R. (2017). Gamification in physical therapy: More than using games. *Pediatric Physical Therapy*, 29(1):95–99.

Ji, Z., Wang, H., Han, J., and Pang, Y. (2019). Saliency-guided attention network for image-sentence matching. In *Proceedings of the IEEE/CVF international conference on computer vision*, pages 5754–5763.

Jiménez-Rodríguez, C., Yélamos-Capel, L., Salvestrini, P., Pérez-Fernández, C., Sánchez-Santed, F., and Nieto-Escámez, F. (2021). Rehabilitation of visual functions in adult amblyopic patients with a virtual reality videogame: A case series. *Virtual Reality*, pages 1–12.

Katsuki, F. and Constantinidis, C. (2012). Early involvement of prefrontal cortex in visual bottom-up attention. *Nature neuroscience*, 15(8):1160–1166.

Kern, D., Stringer, M., Fitzpatrick, G., and Schmidt, A. (2006). Curball–a prototype tangible game for inter-generational play. In *15th IEEE International Workshops on Enabling Technologies: Infrastructure for Collaborative Enterprises (WETICE'06)*, pages 412–418. IEEE.

Kerr, J. L. (1971). Visual resolution in the periphery. *Perception & Psychophysics*, 9(3):375–378.

Khan, M. Q. and Lee, S. (2019). Gaze and eye tracking: Techniques and applications in adas. *Sensors*, 19(24):5540.

Klein, B. E., Klein, R., Lee, K. E., and Cruickshanks, K. J. (1998). Performance-based and self-assessed measures of visual function as related to history of falls, hip fractures, and measured gait time. The Beaver Dam Eye Study. *Ophthalmology*, 105(1):160–164.

Koch, C., Massimini, M., Boly, M., and Tononi, G. (2016). Neural correlates of consciousness: progress and problems. *Nature Reviews Neuroscience*, 17(5):307–321.

Koch, C. and Ullman, S. (1987). Shifts in selective visual attention: towards the underlying neural circuitry. In *Matters of intelligence*, pages 115–141. Springer.

Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., Brooks, D. J., Bench, C. J., and Grasby, P. (1998). Evidence for striatal dopamine release during a video game. *Nature*, 393(6682):266–268.

Kohl, A. D., Wylie, G. R., Genova, H., Hillary, F. G., and Deluca, J. (2009). The neural correlates of cognitive fatigue in traumatic brain injury using functional mri. *Brain injury*, 23(5):420–432.

Koivisto, J. and Malik, A. (2021). Gamification for older adults: a systematic literature review. *The Gerontologist*, 61(7):e360–e372.

Kojima, M., Sugimoto, M., Nakamura, A., Tomita, M., Nii, H., and Inami, M. (2006). Augmented coliseum: An augmented game environment with small vehicles. In *First IEEE International Workshop on Horizontal Interactive Human-Computer Systems (TABLETOP'06)*, pages 6–pp. IEEE.

Kolb, H. (1995). *Simple Anatomy of the Retina*. University of Utah Health Sciences Center, Salt Lake City (UT).

Konrad, R., Cooper, E. A., and Wetzstein, G. (2016). Novel optical configurations for virtual reality: Evaluating user preference and performance with focus-tunable and monovision near-eye displays. In *Proceedings of the 2016 CHI conference on human factors in computing systems*, pages 1211–1220.

Krueger, F., Grafman, J., and McCabe, K. (2008). Neural correlates of economic game playing. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1511):3859–3874.

Kühn, S., Romanowski, A., Schilling, C., Lorenz, R., Mörsen, C., Seiferth, N., Banaschewski, T., Barbot, A., Barker, G., Büchel, C., et al. (2011). The neural basis of video gaming. *Translational psychiatry*, 1(11):e53–e53.

Kwon, M., Nandy, A. S., and Tjan, B. S. (2013). Rapid and persistent adaptability of human oculomotor control in response to simulated central vision loss. *Current Biology*, 23(17):1663–1669.

Landowska, A., Royle, S., Eachus, P., and Roberts, D. (2018). Testing the potential of combining functional near-infrared spectroscopy with different virtual reality displays—oculus rift and octave. *Augmented Reality and Virtual Reality: Empowering Human, Place and Business*, pages 309–321.

Lang, F., Schmidt, A., and Machulla, T. (2020). Augmented reality for people with low vision: symbolic and alphanumeric representation of information. In *International Conference on Computers Helping People with Special Needs*, pages 146–156. Springer.

Leeuwenberg, E. L. J. (1967). *Structural information of visual patterns: An Efficient Coding System in Perception*. Mouton, The Hague.

Lei, H. and Schuchard, R. A. (1997). Using two preferred retinal loci for different lighting conditions in patients with central scotomas. *Investigative ophthalmology & visual science*, 38(9):1812–1818.

Leotta, A. and Ross, M. (2018). Touring the 'world picture': virtual reality and the tourist gaze. *Studies in Documentary Film*, 12(2):150–162.

Li, R. W., Ngo, C., Nguyen, J., and Levi, D. M. (2011). Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS biology*, 9(8):e1001135.

Li, S., Deng, X., and Zhang, J. (2022). An overview of preferred retinal locus and its application in biofeedback training for low-vision rehabilitation. In *Seminars in Ophthalmology*, volume 37, pages 142–152. Taylor & Francis.

Lohr, D. J., Friedman, L., and Komogortsev, O. V. (2019). Evaluating the data quality of eye tracking signals from a virtual reality system: Case study using smi's eye-tracking htc vive. *arXiv preprint arXiv:1912.02083*.

Lorig, K. R. and Holman, H. R. (2003). Self-management education: history, definition, outcomes, and mechanisms. *Annals of behavioral medicine*, 26(1):1–7.

Loschky, L. C. and Wolverton, G. S. (2007). How late can you update gaze-contingent multiresolutional displays without detection? *ACM Transactions on Multimedia Computing, Communications, and Applications (TOMM)*, 3(4):1–10.

Lowe, D. G. (1987). Three-dimensional object recognition from single two-dimensional images. *Artificial intelligence*, 31(3):355–395.

Lowood, H. (2009). Videogames in computer space: The complex history of pong. *IEEE Annals of the History of Computing*, 31(3):5–19.

Lu, R. J., Wang, E. K., and Benayoun, B. A. (2022). Functional genomics of inflamm-aging and immunosenescence. *Briefings in Functional Genomics*, 21(1):43.

Lumsden, J., Edwards, E. A., Lawrence, N. S., Coyle, D., Munafò, M. R., et al. (2016). Gamification of cognitive assessment and cognitive training: a systematic review of applications and efficacy. *JMIR serious games*, 4(2):e5888.

Magerkurth, C., Cheok, A. D., Mandryk, R. L., and Nilsen, T. (2005). Pervasive games: bringing computer entertainment back to the real world. *Computers in Entertainment (CIE)*, 3(3):4–4.

Mahabadi, N. and Al Khalili, Y. (2021). Neuroanatomy, retina. In *StatPearls [Internet]*. StatPearls Publishing.

Maniglia, M., Visscher, K. M., and Seitz, A. R. (2021). Perspective on vision science-informed interventions for central vision loss. *Frontiers in neuroscience*, 15.

Maniglia, M., Visscher, K. M., and Seitz, A. R. (2023). Consistency of preferred retinal locus across tasks and participants trained with a simulated scotoma. *Vision Research*, 203:108158.

Mao, X. and Toyoura, M. (2016). Saliency map for images with leading lines. In *2016 Nicograph International (NicoInt)*, pages 151–151. IEEE.

Masnadi, S., Williamson, B., González, A. N. V., and LaViola, J. J. (2020). Vriassist: An eye-tracked virtual reality low vision assistance tool. In *2020 IEEE Conference on Virtual Reality and 3D User Interfaces Abstracts and Workshops (VRW)*, pages 808–809. IEEE.

Maunsell, J. H. and Newsome, W. T. (1987). Visual processing in monkey extrastriate cortex. *Annual review of neuroscience*.

Menon, V. and Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain structure and function*, 214(5):655–667.

Mescher, A. L. (2016). *Junqueira's basic histology*. New York: MC GRAW HILL.

Mochizuki, I., Toyoura, M., and Mao, X. (2018). Visual attention prediction for images with leading line structure. *The Visual Computer*, 34(6):1031–1041.

Moore, T. and Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature*, 421(6921):370–373.

Motter, B. C. (2009). Central v4 receptive fields are scaled by the v1 cortical magnification and correspond to a constant-sized sampling of the v1 surface. *Journal of Neuroscience*, 29(18):5749–5757.

Mubin, O., Alnajjar, F., Jishtu, N., Alsinglawi, B., and Al Mahmud, A. (2019). Exoskeletons with virtual reality, augmented reality, and gamification for stroke patients' rehabilitation: systematic review. *JMIR rehabilitation and assistive technologies*, 6(2):e12010.

Murali, A., Krishnakumar, S., Subramanian, A., and Parameswaran, S. (2020). Bruch's membrane pathology: a mechanistic perspective. *European Journal of Ophthalmology*, 30(6):1195–1206.

Nastasi, J. A. (2020). Occupational therapy interventions supporting leisure and social participation for older adults with low vision: a systematic review. *The American Journal of Occupational Therapy*, 74(1):7401185020p1–7401185020p9.

Neugebauer, A., Stingl, K., Ivanov, I., and Wahl, S. (2022). Evaluation of virtual-reality based gaze training for improved visual performance in persons with tunnel vision. *Investigative Ophthalmology & Visual Science*, 63(7):717–F0445.

Oleskiw, T., Nowack, A., and Pasupathy, A. (2017). Joint coding of shape and blur in area v4. *Journal of Vision*, 17(10):31–31.

Oleskiw, T. D., Nowack, A., and Pasupathy, A. (2018). Joint coding of shape and blur in area v4. *Nature communications*, 9(1):1–13.

Palaus, M., Marron, E. M., Viejo-Sobera, R., and Redolar-Ripoll, D. (2017). Neural basis of video gaming: A systematic review. *Frontiers in human neuroscience*, page 248.

Pallavicini, F. and Pepe, A. (2019). Comparing player experience in video games played in virtual reality or on desktop displays: Immersion, flow, and positive emotions. In *Extended Abstracts of the Annual Symposium on Computer-Human Interaction in Play Companion Extended Abstracts*, pages 195–210.

Palmer, S., Logan, D., Nabili, S., and Dutton, G. N. (2010). Effective rehabilitation of reading by training in the technique of eccentric viewing: evaluation of a 4-year programme of service delivery. *British Journal of Ophthalmology*, 94(4):494–497.

Parfitt, A., Boxell, E., Amoaku, W. M., and Bradley, C. (2019). Patient-reported reasons for delay in diagnosis of age-related macular degeneration: a national survey. *BMJ open ophthalmology*, 4(1):e000276.

Parsons, D. and MacCallum, K. (2021). Current perspectives on augmented reality in medical education: applications, affordances and limitations. *Advances in medical education and practice*, pages 77–91.

Péres, K., Matharan, F., Daien, V., Nael, V., Edjolo, A., Isabelle Bourdel-Marchasson, I., Ritchie, K., Tzourio, C., Delcourt, C., and Carriere, I. (2017). Visual loss and subsequent activity limitations in the elderly: The French three-city cohort. *American Journal of Public Health*, 107(4):564–569.

Pietrini, P., Ptito, M., and Kupers, R. (2009). Blindness and consciousness: new light from the dark. In *The Neurology of Conciousness*, pages 393–406. Elsevier.

Pijnacker, J., Verstraten, P., Van Damme, W., Vandermeulen, J., and Steenbergen, B. (2011). Rehabilitation of reading in older individuals with macular degeneration: A review of effective training programs. *Aging, Neuropsychology, and Cognition*, 18(6):708–732.

Pilz, K. S., Braun, C., Altpeter, E., MacKeben, M., and Trauzettel-Klosinski, S. (2006). Modulation of visual stimulus discrimination by sustained focal attention: an meg study. *Investigative ophthalmology & visual science*, 47(3):1225–1229.

Pomarjanschi, L., Dorr, M., and Barth, E. (2012). Gaze guidance reduces the number of collisions with pedestrians in a driving simulator. *ACM Transactions on Interactive Intelligent Systems (TiiS)*, 1(2):1–14.

Raasch, T. (2004). What we don't know about eccentric viewing.

Reichenberger, J., Pfaller, M., and Mühlberger, A. (2020). Gaze behavior in social fear conditioning: An eye-tracking study in virtual reality. *Frontiers in psychology*, 11:35.

Remington, L. A. and Goodwin, D. (2021). *Clinical Anatomy and Physiology of the Visual System E-Book*. Elsevier Health Sciences.

Richter, C., Fromm, C. A., and Diaz, G. J. (2019). Hardware modification for improved eye tracking with the pupil labs virtual-reality integration. *Journal of Vision*, 19(10):147a–147a.

Riggs, L. A., Volkmann, F. C., Moore, R. K., and Ellicott, A. G. (1982). Perception of suprathreshold stimuli during saccadic eye movement. *Vision research*, 22(4):423–428.

Roe, A. W., Chelazzi, L., Connor, C. E., Conway, B. R., Fujita, I., Gallant, J. L., Lu, H., and Vanduffel, W. (2012). Toward a unified theory of visual area v4. *Neuron*, 74(1):12–29.

Rosch, J. L. and Vogel-Walcutt, J. J. (2013). A review of eye-tracking applications as tools for training. *Cognition, technology & work*, 15(3):313–327.

Rovner, B. W. and Casten, R. J. (2002). Activity loss and depression in age-related macular degeneration. *The American journal of geriatric psychiatry*, 10(3):305–310.

Salas, J., Vera, P., Hernández, A., and Meza-de Luna, M.-E. (2021). An augmented reality implementation of the pong game. *IEEE Transactions on Games*, 13(2):216–227.

Sandon, P. A. (1990). Simulating visual attention. *Journal of Cognitive Neuroscience*, 2(3):213–231.

Sarks, S. (1976). Ageing and degeneration in the macular region: a clinico-pathological study. *British Journal of Ophthalmology*, 60(5):324–341.

Satgunam, P. and Luo, G. (2018). Does central vision loss impair visual search performance of adults more than children? *Optometry and vision science: official publication of the American Academy of Optometry*, 95(5):443.

Satgunam, P., Woods, R. L., Luo, G., Bronstad, P. M., Reynolds, Z., Ramachandra, C., Mel, B. W., and Peli, E. (2012). Effects of contour enhancement on low-vision preference and visual search. *Optometry and vision science: official publication of the American Academy of Optometry*, 89(9):E1364.

Saunders, D. R. and Woods, R. L. (2014). Direct measurement of the system latency of gaze-contingent displays. *Behavior research methods*, 46(2):439–447.

Scheiter, K., Schubert, C., Schüler, A., Schmidt, H., Zimmermann, G., Wassermann, B., Krebs, M.-C., and Eder, T. (2019). Adaptive multimedia: Using gaze-contingent instructional guidance to provide personalized processing support. *Computers & Education*, 139:31–47.

Schmidt-Rhaesa, A. (2007). Sensory organs. In *The Evolution of Organ Systems*. Oxford University Press.

Schuetz, I. and Fiehler, K. (2022). Eye tracking in virtual reality: Vive pro eye spatial accuracy, precision, and calibration reliability. *Journal of Eye Movement Research*, 15(3).

Schwartz, R. and Loewenstein, A. (2015). Early detection of age related macular degeneration: current status. *International journal of retina and vitreous*, 1(1):1–8.

Sciberras-Lim, E. T. and Lambert, A. J. (2017). Attentional orienting and dorsal visual stream decline: review of behavioral and eeg studies. *Frontiers in aging neuroscience*, 9:246.

Sereno, M. I., Dale, A., Reppas, J., Kwong, K., Belliveau, J., Brady, T., Rosen, B., and Tootell, R. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science*, 268(5212):889–893.

Sereno, M. I., McDonald, C. T., and Allman, J. M. (1994). Analysis of retinotopic maps in extrastriate cortex. *Cerebral Cortex*, 4(6):601–620.

Sickenberg, M. (2001). Early detection, diagnosis and management of choroidal neovascularization in age-related macular degeneration: the role of ophthalmologists. *Ophthalmologica*, 215(4):247–253.

Somers, D. C., Dale, A. M., Seiffert, A. E., and Tootell, R. B. (1999). Functional mri reveals spatially specific attentional modulation in human primary visual cortex. *Proceedings of the National Academy of Sciences*, 96(4):1663–1668.

Spyropoulos, G., Bosman, C. A., and Fries, P. (2018). A theta rhythm in macaque visual cortex and its attentional modulation. *Proceedings of the National Academy of Sciences*, 115(24):E5614–E5623.

Stein, N., Niehorster, D. C., Watson, T., Steinicke, F., Rifai, K., Wahl, S., and Lappe, M. (2021). A comparison of eye tracking latencies among several commercial head-mounted displays. *i-Perception*, 12(1):2041669520983338.

Steinert, A., Buchem, I., Merceron, A., Kreutel, J., and Haesner, M. (2018). A wearable-enhanced fitness program for older adults, combining fitness trackers and gamification elements: the pilot study fmooc@ home. *Sport Sciences for Health*, 14(2):275–282.

Stelmack, J. A., Massof, R. W., and Stelmack, T. R. (2004). Is there a standard of care for eccentric viewing training? *Journal of Rehabilitation Research & Development*, 41(5).

Stevens, G. A., White, R. A., Flaxman, S. R., Price, H., Jonas, J. B., Keeffe, J., Leasher, J., Naidoo, K., Pesudovs, K., Resnikoff, S., Taylor, H., and Bourne, R. R. (2013). Global Prevalence of Vision Impairment and Blindness: Magnitude and Temporal Trends, 1990–2010. *Ophthalmology*, 120(12):2377–2384.

Straetmans, L., Holtze, B., Debener, S., Jaeger, M., and Mirkovic, B. (2022). Neural tracking to go: auditory attention decoding and saliency detection with mobile eeg. *Journal of Neural Engineering*, 18(6):066054.

Sullivan, B., Jovancevic, J., Hayhoe, M., and Sterns, G. (2005). Use of gaze in natural tasks in stargardt's disease: A preferred retinal region. In *International congress series*, volume 1282, pages 608–612. Elsevier.

Sun, Y., Hunt, C. L., Lamounier, E. A., and Soares, A. B. (2023). Neurorehabilitation with virtual and augmented reality tools. In *Handbook of Neuroengineering*, pages 1859–1899. Springer.

Sunness, J. S., Applegate, C. A., Haselwood, D., and Rubin, G. S. (1996). Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and stargardt disease. *Ophthalmology*, 103(9):1458–1466.

Taylor, D. J., Edwards, L. A., Binns, A. M., and Crabb, D. P. (2018). Seeing it differently: self-reported description of vision loss in dry age-related macular degeneration. *Ophthalmic and Physiological Optics*, 38(1):98–105.

Tekinbas, K. S. and Zimmerman, E. (2003). *Rules of play: Game design fundamentals*. MIT press.

Teo, W.-P., Muthalib, M., Yamin, S., Hendy, A. M., Bramstedt, K., Kotsopoulos, E., Perrey, S., and Ayaz, H. (2016). Does a combination of virtual reality, neuromodulation and neuroimaging provide a comprehensive platform for neurorehabilitation?–a narrative review of the literature. *Frontiers in human neuroscience*, 10:284.

Thickbroom, G., Knezevic, W., Carroll, W., and Mastaglia, F. (1991). Saccade onset and offset lambda waves: relation to pattern movement visually evoked potentials. *Brain research*, 551(1-2):150–156.

Thomas, B., Close, B., Donoghue, J., Squires, J., Bondi, P. D., and Piekarski, W. (2002). First person indoor/outdoor augmented reality application: Arquake. *Personal and Ubiquitous Computing*, 6(1):75–86.

Tien, T., Pucher, P. H., Sodergren, M. H., Sriskandarajah, K., Yang, G.-Z., and Darzi, A. (2014). Eye tracking for skills assessment and training: a systematic review. *journal of surgical research*, 191(1):169–178.

Tlapale, É., Bernard, J.-B., Castet, É., and Kornprobst, P. (2006). *The solaire project: A gaze-contingent system to facilitate reading for patients with scotomatas*. PhD thesis, INRIA.

Tootell, R. B., Dale, A. M., Sereno, M. I., and Malach, R. (1996). New images from human visual cortex. *Trends in neurosciences*, 19(11):481–489.

Tootell, R. B. and Hadjikhani, N. (2001). Where is 'dorsal v4'in human visual cortex? retinotopic, topographic and functional evidence. *Cerebral cortex*, 11(4):298–311.

Trauzettel-Klosinski, S. (2009). Rehabilitation of lesions in the visual pathways. *Klinische Monatsblatter fur Augenheilkunde*, 226(11):897–907.

Treue, S. (2003). Visual attention: the where, what, how and why of saliency. *Current opinion in neurobiology*, 13(4):428–432.

Uhlmann, R. F., Larson, E. B., Koepsell, T. D., Rees, T. S., and Duckert, L. G. (1991). Visual impairment and cognitive dysfunction in alzheimer's disease. *Journal of general internal medicine*, 6(2):126–132.

Van Krevelen, D. and Poelman, R. (2010). A survey of augmented reality technologies, applications and limitations. *International journal of virtual reality*, 9(2):1–20.

Varano, M., Eter, N., Winyard, S., Wittrup-Jensen, K. U., Navarro, R., and Heraghty, J. (2016). The emotional and physical impact of wet age-related macular degeneration:

findings from the wamd patient and caregiver survey. *Clinical ophthalmology (Auckland, NZ)*, 10:257.

Versek, C., Banijamali, S. M. A., Bex, P., Lashkari, K., Kamarthi, S., and Sridhar, S. (2021). Portable diagnostic system for age-related macular degeneration screening using visual evoked potentials. *Eye and brain*, 13:111.

Vukicevic, M. and Fitzmaurice, K. (2005). Rehabilitation strategies used to ameliorate the impact of centre field loss. *Visual Impairment Research*, 7(2-3):79–84.

Vukicevic, M. and Fitzmaurice, K. (2008). Vision rehabilitation and the development of eccentric viewing training: A historical overview. *Australian Orthoptic Journal*, 40(1):13–18.

Vukicevic, M. and Fitzmaurice, K. (2009). Eccentric viewing training in the home environment: Can it improve the performance of activities of daily living? *Journal of Visual Impairment & Blindness*, 103(5):277–290.

Wagor, E., Mangini, N. J., and Pearlman, A. L. (1980). Retinotopic organization of striate and extrastriate visual cortex in the mouse. *Journal of Comparative Neurology*, 193(1):187–202.

Waugh, N., Loveman, E., Colquitt, J., Royle, P., Yeong, J. L., Hoad, G., and Lois, N. (2018). Introduction to age-related macular degeneration. In *Treatments for dry age-related macular degeneration and Stargardt disease: a systematic review*. NIHR Journals Library.

Weishaupt, N. (2017). Cortical plasticity in response to injury and disease. In *The Cerebral Cortex in Neurodegenerative and Neuropsychiatric Disorders*, pages 37–56. Elsevier.

West, S. K., Munoz, B., Rubin, G. S., Schein, O. D., Bandeen-Roche, K., Zeger, S., German, P. S., and Fried, L. P. (1997). Function and visual impairment in a population-based study of older adults. The SEE project. Salisbury Eye Evaluation. *Investigative Ophthalmology & Visual Science*, 38(1):72–82.

White, B. J., Berg, D. J., Kan, J. Y., Marino, R. A., Itti, L., and Munoz, D. P. (2017). Superior colliculus neurons encode a visual saliency map during free viewing of natural dynamic video. *Nature communications*, 8(1):1–9.

White, B. K., Martin, A., and White, J. (2022). Gamification and older adults: Opportunities for gamification to support health promotion initiatives for older adults in the context of covid-19. *The Lancet Regional Health-Western Pacific*, page 100528.

White, J. M. and Bedell, H. E. (1990). The oculomotor reference in humans with bilateral macular disease. *Investigative ophthalmology & visual science*, 31(6):1149–1161.

Witkin, A. P. and Tenenbaum, J. M. (1983). What is perceptual organization for? In *IJCAI*, volume 83, pages 1023–1026.

Wolffsohn, J., Dinardo, C., and Vingrys, A. (2002). Benefit of coloured lenses for age-related macular degeneration. *Ophthalmic and Physiological Optics*, 22(4):300–311.

World Health Organization, W. (2022a). World health organization: Ageing. `https://www.who.int/health-topics/ageing#tab=tab_1`. Accessed: 2022-08-11.

World Health Organization, W. (2022b). World health organization: Blindness and vision impairment. `https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment`. Accessed: 2022-08-11.

Yates, M., Kelemen, A., and Sik Lanyi, C. (2016). Virtual reality gaming in the rehabilitation of the upper extremities post-stroke. *Brain injury*, 30(7):855–863.

Zhaoping, L. (2008). Attention capture by eye of origin singletons even without awareness—a hallmark of a bottom-up saliency map in the primary visual cortex. *Journal of Vision*, 8(5):1–1.

Zirnsak, M., Steinmetz, N. A., Noudoost, B., Xu, K. Z., and Moore, T. (2014). Visual space is compressed in prefrontal cortex before eye movements. *Nature*, 507(7493):504–507.

6 Appendix

6.1 Accepted publications

6.1.1 Study 1

Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability.

healthcare

Article

Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability

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Abstract: Background: A case study is proposed to empirically test and discuss the eye-tracking status-quo hardware capabilities and limitations of an off-the-shelf virtual reality (VR) headset with embedded eye-tracking for at-home ready-to-go online usability in ophthalmology applications. Methods: The eye-tracking status-quo data quality of the HTC Vive Pro Eye is investigated with novel testing specific to objective online VR perimetry. Testing was done across a wide visual field of the head-mounted-display's (HMD) screen and in two different moving conditions. A new automatic and low-cost Raspberry Pi system is introduced for VR temporal precision testing for assessing the usability of the HTC Vive Pro Eye as an online assistance tool for visual loss. Results: The target position on the screen and head movement evidenced limitations of the eye-tracker capabilities as a perimetry assessment tool. Temporal precision testing showed the system's latency of 58.1 milliseconds (ms), evidencing its good potential usage as a ready-to-go online assistance tool for visual loss. Conclusions: The test of the eye-tracking data quality provides novel analysis useful for testing upcoming VR headsets with embedded eye-tracking and opens discussion regarding expanding future introduction of these HMDs into patients' homes for low-vision clinical usability.

Keywords: eye-tracking; head-mounted display (HMD); virtual reality (VR); ophthalmology; usability methods

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Citation: Sipatchin, A.; Wahl, S.; Rifai, K. Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability. *Healthcare* **2021**, *9*, 180. https://doi.org/10.3390/healthcare9020180

Academic Editor: Tin-Chih Toly Chen
Received: 21 December 2020
Accepted: 5 February 2021
Published: 9 February 2021

1. Introduction

Eye-tracking in virtual reality (VR) for ophthalmology practices is a promising emerging field for objective and at-home diagnostic and treatment purposes. Online analysis of eye-tracking data is currently being used in a VR environment for hands-free perimetry testing [1–3] and dynamic VR visual enhancements [4,5].

Online gaze tracking for virtual reality perimetry implements an objective, mobile and portable perimetry where the gaze replaces the patient's response. A perimetry test is usually used to identify the amount of visual loss in the central and peripheral visual field. For example, the standard perimetry test, the Humphrey visual field analyzer (HFA, Carl Zeiss Meditec Inc., Dublin, CA, USA) is used to test a specific point in the visual field. Subjects are asked to press a button whenever they see a light target on a 2D plane extending $\pm 30^\circ$ temporally and nasally. The concept of virtual perimetry [6] has shown increasing potential with multiple studies testing its comparability to the standard HFA [7–11]. Virtual reality perimetry introduces a visual grasp mode, based on eye movements instead of subjective button presses to collect the patient responses. It has the advantage of overcoming long periods of fixation of peripheral stimuli common to standard perimetry [12]. In a visual-grasp modality, eye-tracking data automatically identifies the responses. During central fixation, a stimulus appears at a new fixation area, and it induces an automatic gaze reflex change towards the new target. When the gaze change is consistent with the change in the target position, the test identifies that part of the visual field as being intact. Testing the visual field in a VR environment expands perimetry in the direction of a mobile application that can easily be introduced into the patient's home's comfort.

Virtual reality technology has the additional potential of overcoming the limits of conventional rehabilitative therapy regarding its actual usage in at-home settings thanks to the engaging nature of VR [13]. New up-coming extended reality assistive software techniques have started to use eye-tracking to offer a more reactive user interface. These studies take the gaze input to enhance low vision via a display that continuously and dynamically updates where the subject is looking. The eye-tracking application's main advantage is that it can be customized to each patient's needs with the required enhancement being applied to the damaged visual field uniquely in all of its parts. [4].

For these applications, the eye-tracking data quality has to be accurate, precise, and temporally exact for effective usability. For an objective visual grasp modality in VR, accuracy and precision of fixation are essential for the correct assessment of visual field loss. For visual enhancement usage, eye-tracking temporal precision is important: the actual timing between a shift in the eye-tracking data and a relative change in the VR headset screen should ideally last less than 54 milliseconds (ms), a saccade duration [14–20], so that the applied enhancement remains undetected and a comfortable user interface is maintained. Indeed, this type of study assumes that the participant is not aware of the changing display while performing eye movements such as saccades, since, during a saccade, the stimulus is not perceived [21,22].

The current limitation is that eye-tracking quality varies by software, hardware, and manufacturer. Currently, low vision clinical studies, using virtual reality, have used different hardware and reported information from the manufacturer to indicate eye-tracking hardware capability and usability in their studies [1–5]. No study until now has questioned the reliability and suitability of the available manufacturers' information for online low-vision applications.

For engaging at-home treatments, an empirical assessment of the status-quo of the eye-tracking hardware is needed, so that reliable information can be used for assessing the ready-to-go potentiality of VR headsets with an embedded eye-tracker. Accordingly, the first case study that investigates the status-quo of a commercial head-mounted-display (HMD) with embedded eye-tracking is being proposed. The status-quo of the HTC Vive Pro Eye is tested. The results obtained will provide better guidance for future research using this hardware for clinical studies. The current pilot study describes two new types of methodology to test eye-tracking data quality for low-vision use. For VR online perimetry testing, eye-tracking data quality is investigated at large visual fields up to ±30°, and the influence of different screen regions of the VR headset over data quality is tested. For mobile applications, the current study also tests for data quality during movement. For VR online visual enhancement applications, a Rasberry Pi system, non-expensive, and with an automatic method for temporal precision calculation, is used. These eye-tracking testing tools are essential for future investigation of upcoming and more advanced commercial virtual reality headsets with embedded eye-tracking such as StarVR One (Starbreeze Studios AB, Stockholm, Sweden) and Pico Neo 2 Eye (Pico Interactive, San Francisco, CA, USA) intended for online low-vision assessment.

2. Materials and Methods

2.1. Study Group

Eleven participants took part in the data quality assessment test (six females and five males, mean age 28.73, standard deviation (SD): ±2.49 years) with 11 participating for the head-still and 10 being re-tested for the head-free condition. The direct end-to-end method for latency required no participants.

2.2. Set-Up

For the virtual experiment, the Unity 2019.1.10f1 version was used as a design tool, with C# as a programming language, running on a computer with Windows 10 Home, having a 64-bit operating system, an Intel Core i7 -7700HQ, 2.8 GHz, 16 GB RAM, and an NVIDIA GeForce GTX 1070 GDDR5 graphics card. A single-board computer was used, the Raspberry Pi (Raspberry Pi Foundation, Cambridge, England, UK), model B 2018 [23], controlling a Raspberry Pi camera (Version 2.1 [24] with a capability of 120 Hz,) for the end-to-end direct latency tests. Eye-tracking data was collected in a virtual environment using the HTC Vive Pro Eye [25] with built-in Tobii eye tracker (Core SW 2.16.4.67) with an accuracy estimation of 0.5°–1.1° and a sampling frequency of 120 Hz (HTC Corporation, Taoyuan, Taiwan). Tobii Pro SDK v1.7.1.1081 [26] (Tobii Technology, Stockholm, Sweden) and Vive SRanipal SDK v1.1.0.1 [27] (HTC Corporation, Taoyuan, Taiwan) are used to access non-filtered and filtered eye-tracking data, respectively. The embedded HMD's calibration system is used to calibrate eye-tracking data for each participant.

The HTC Vive headset contains two active-matrix organic light-emitting diode (AMOLED) screens, with a resolution of 2.880 × 1.600 pixels in total with a refresh rate of 90 Hz and a field of view of 110°.

2.3. Study Parameters

2.3.1. Eye-Tracking Accuracy and Precision Measurements: Head-Still and Head-Free Tests

Accuracy is the average angular error between the measured and the actual location of the intended fixation target. Precision is the spread of the gaze positions when a user is fixating on a known location in space [20,28]. Accuracy and precision were tested in a virtual environment where fixation targets (Figure 1a) were two concentric circles, one internal black and one external red circle, with a radius of 0.72 degrees of visual angle, positioned at 1 m in a Unity world coordinate system. To avoid alteration of eye-tracking samples, the Tobii Pro SDK was used to access non-filtered data, and the luminance of the targets was kept constant in the virtual environment to avoid pupil dilatation due to changes in stimulus brightness, which is known to affect eye-tracking data [28–30]. Two separate conditions were investigated: head-still and head-free. Subjects performed the task in both conditions in a seated position on a chair.

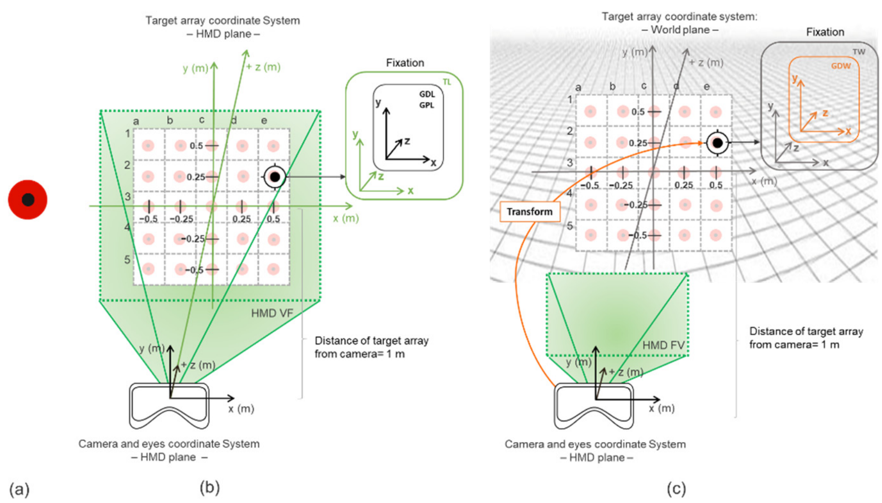

Figure 1. The target (**a**) is a virtual object with two concentric circles. In the head-still condition (**b**) the targets are locally fixed to the head-mounted display (HMD) (referred in the figure as TL), the same as for gaze direction (GDL in the figure) and gaze position (or GPL). In the head-free condition (**c**), precision is tested on the 3D world plane. Fixation is re-referenced (transform), so that target (as in TW) and gaze direction (or GDW) are on a world plane.

In the head-still condition, the target position was fixed to the HMD. As a result, if the headset moved, targets would move along with it. This way, accuracy, and precision could be tested across the headset 2D plane covering a visual field of ± 26.6° (Figure 1b). The target would appear at 25 different sample positions with 5 columns and 5 rows. The target position appearance was randomized, and each target was displayed for 5 s [31] with 5 repetitions (5 sec/target × 25 targets × 5 repetitions = 625 s, approximately 10 min and a half). When a target appeared, the subject had to fixate on it until it disappeared while keeping their head still.

In the head-free condition, targets were positioned in a world-fixed coordinate system, and as a result the targets did not move with the HMD but had a fixed position on the world plane (Figure 1c). The subject had to move their head instead so that precision and data loss could be tested for head-movement effects. As for the head still condition, targets were distributed across 25 different positions at a similarly large visual field. A central fixation target was added (coordinates: [0,0,0]) at the end of each target presentation that lasted 2 s, to make the participates come back to the same referencing point (5 sec/target + 2 sec/central target × 25 targets × 5 repetitions = 875 s, approximately 15 min). During this condition, subjects had to saccade towards the appearing target, fixate on it and then move their head naturally, while fixating, towards the position where it appeared. As soon as the target could be fixated centrally, subjects were instructed to keep the head stable until the target disappeared.

2.3.2. Eye-Tracking Temporal Precision Measurements: Eye-Detection and Gaze-Contingent Tests

Temporal precision is the average end-to-end delay from the tracked eye's actual movement until the recording device signals that the movement has occurred [28]. A new method is described, which uses a low-cost configuration (Figure 2a): a Raspberry Pi single-board computer that controls the output of infrared light-emitting diodes (LEDs) and records, with a Raspberry Pi camera, reflections from the camera and eye-tracking events displayed by the headset produced by these infrared reflections when the LEDs are on (Figure 2a,b). A virtual environment was used, running on a computer that displayed the VR Positioning Guide Prefab, incorporated in the Tobii Pro SDK (Figure 2c, first image) and a similar programmed version of the Prefab SRanipal SDK (Figure 2c, last two images) to display the events. Ten different videos for each SDK were recorded. The Raspberry Pi tested temporal precision using two different scenarios.

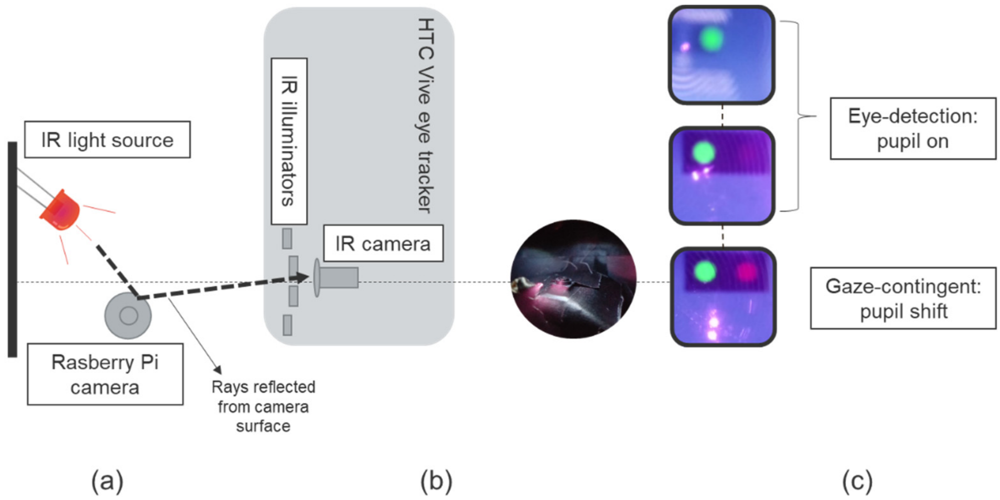

Figure 2. Infrared (IR) light source (orange) illuminates the Raspberry Pi camera: (**a**) schematic and (**b**) picture of the camera. The Rasberry Pi records it as a reflection on the HMD lenses (**c**), pink dot. The IR camera inside the HTC Vive Pro Eye captures the reflected rays by the Raspberry Pi camera as an artificial eye. (**c**) Recorded events: greed dot referring to pupil-on and red dot indicating pupil-shift events.

The eye tracker is firstly tricked into the detection of an eye: the eye-detection scenario. The Raspberry Pi turns on two infrared LEDs for 1 s, leading to a pupil-on event with the appearance of a green dot (Figure 2c, first two images and Figure 3a). Afterward, the LEDs are switched off for 2 s (Figure 3a). A total of 33 infrared LED on and 33 LED off time series are tested. This first scenario is tested both with Tobii Pro SDK and SRanipal SDK to check for differences in latency when identifying an eye appearing between two different SDKs. The second scenario is tested only with the SRanipal. Therefore, when using the Tobii Pro SDK there are 330 repetitions and a recording time of 16.7 min.

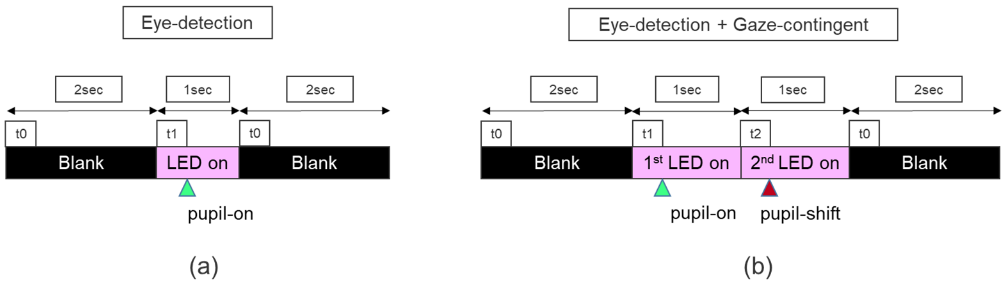

Figure 3. (**a**) The eye-detection scenario was tested both for the Tobii and the SRanipal SKD. The test has two-time series; at t0 the LED is off (2 s) and t1 two pairs of LEDs are turned on (1 s): pupil-on is simulated (green triangle). (**b**) For the SRanipal SDK, an eye-detection scenario is produced followed by a gaze-contingent scenario: the Raspberry system turns on the first pair of LEDs (t1) for 1 sec, then switches off the first one while turning on the second pair (t2): pupil shift is simulated (red triangle).

While recording with the SRanipal, a second scenario is introduced as a modified version of an artificial saccade generator [32]. Secondly, the Raspberry Pi tricks the eye-tracker into an abrupt change in gaze position of the recognized artificial pupil, i.e., the gaze-contingent scenario. For this scenario, two additional infrared LEDs were placed at a 1cm distance from the other two, and the Raspberry Pi turned them on for 1 s, at the same time as it turned off the first two that had previously been used to produce the green dot event (Figure 3b). Turning on the second pair of infrared LEDs simulated an abrupt change in the previously recognized artificial pupil's gaze position. This change was followed by a pupil shift event with a bright red dot (Figure 2c, lower image, and Figure 3b). The pupil shift event did not disrupt the first pupil-on event since the display of this event was programmed such that a green dot would still be shown as long as an eye is being detected. For the SRanipal SDK, each scenario had 33 infrared LED on-off time series; therefore, 660 repetitions were recorded with a total time of 21.2 min.

2.4. Statistical Analysis

2.4.1. Pre-Processing: Eye-Tracking Accuracy and Precision

In the head-still condition, both for the left and right eye separately, the HMD-local gaze position (vector of eye position measured in millimeters from the center of the HMD) and HMD-local gaze direction (a normalized vector referenced in HMD-local's coordinate system pointing from the pupil towards the virtual object) were selected. Local gaze direction (Figure 4, GDL) and local position vector (Figure 4, GPL) were then calculated, with the average of both eyes' coordinates [31]. The local target position was also saved at every sample (Figure 4, TL). For each data sample, the targets were re-referenced to the eye (TL-E) by subtracting the local eye's position vector from the local target's coordinates (target vector (TL)—eye position vector (GPL)).

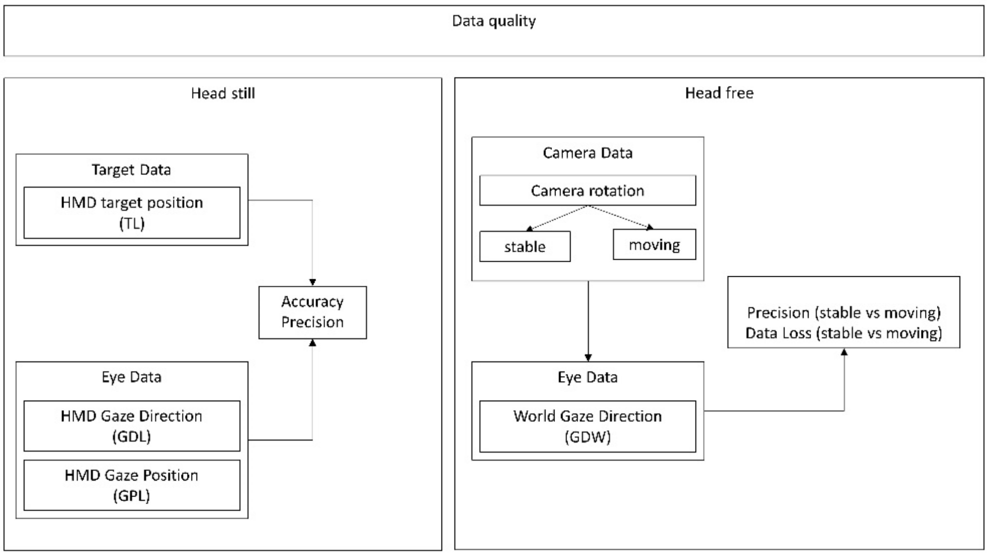

Figure 4. For the head-still condition, the HMD-local target position (TL), HMD-local gaze direction (GDL), and HMD-local gaze position (GPL) are used for accuracy and precision measures. In the head-free condition, camera rotation is used to separate world gaze direction, distinguishing stable head and moving head. The world gaze direction (GDW) is used to investigate precision and data loss between periods of stable fixations and periods of moving fixations.

Afterwards, the angle between the local gaze direction vector (GDL) and the local target-eye vector(TL-E) was calculated using the Formula (1) to estimate the angle between two vectors (angleV) [31].

$$\text{angleV } (^\circ)(\text{Local coordinates}) = \tan^{-1}(\text{norm}((\text{GDL} \times \ \text{TL} - \text{E}), (\text{GDL} \cdot \text{TL} - \text{E}))) \quad (1)$$

Norm normalizes the vector; cross (×), and dot (·) calculate the cross and the dot product, respectively.

In the head-free condition, the world gaze (Figure 4, GDW) was selected as an already averaged vector between the left and right eye as provided by the Tobii Pro SDK Prefab. The world gaze direction provided by the Prefab is calculated as follows: the HMD-local gaze position is used to re-reference the new gaze direction [31]. In the head-free condition, for each data sample, to separate between fixation during head-non-moving (head-free$_{\text{stable}}$) and fixation during head-moving phases (head-free$_{\text{moving}}$), the differential of the speed of the HMD's rotation quaternion was calculated (Figure 4, camera data), rotated around a normalized vector.

For the analysis, the first 500 ms [31] after the target appearance were discarded. That was considered as the time a subject used to direct the gaze. Gaze points where no eye could be tracked were excluded from the analysis both for the left and the right eye in both conditions. For the data loss analysis, gaze points where no eye was detected were kept.

2.4.2. Eye-Tracking Accuracy and Precision

Accuracy is defined as the mean of all the angles (angleV) calculated between GDL and TL-E using the formula described in Equation (1). To calculate the eye-tracker's spatial precision [33] the common practice was used, i.e., the root mean square (RMS) of the inter-sample angular distances between successive gaze directions.

For the head-still condition before averaging between the two eyes, a one-way ANOVA tested for differences in accuracy between the two eyes. To analyze changes in eye data quality across the population, tested percentiles were calculated. An overall average and an average for different percentiles of users for accuracy and precision were computed. A one-way ANOVA way tested how accuracy and precision differ across screen regions with the horizontal line as the independent factor and the vertical lines as levels. Differences observed across the horizontal line might be an indication of the altering of eye-tracking data quality induced by reflections from vision corrections [34]. As an additional precision indicator, a bivariate contour ellipse area (BCEA) for left, right, and the average of the two eyes was also plotted to show the area that encompasses 50% of fixation points around the mean for each given target.

In the head-free condition, the average precision as RMS between the successive GDW was calculated and a one-way ANOVA tested how precision is affected by phases of stable head and moving head while subjects fixated on the target. The data loss percentage [35] was calculated using the Formula (2):

$$\text{Data loss } (\%) = 100 \times \frac{\text{Nsamples} - \text{Nvalid\_samples}}{\text{Nexpected\_samples}} \tag{2}$$

Nsamples represents the number of data samples recorded after excluding the initial 500 ms, and Nvalid_samples are the number of samples during which a valid gaze position was recorded.

2.4.3. Eye-Tracking Temporal Precision

The recorded videos were converted into images frame-by-frame through a converter program (Free Video to JPG Converter, version 5.0.101). A new automatized method was programmed to detect the elapsed frames between the LED's onset and the onset of the different dots. The Color Thresholder app was used from the Matlab Image Processing Toolbox (version 10.4) to manipulate sample frames' color components via a hue, saturation, value (2HSV) color space. Three separate red-green-blue (RGB) 2HSV segmentation masks were created: one for all the LED's reflection on the HMD (Figure 5a, LED; Figure 5b, first LED and second LED), one for the appearance of the green dot (Figure 5a,b, G-D), and one for the appearance of the bright red dot (Figure 5b, R-D). The masks indicated how many pixels in the frame contained the events; this permits automatic identification of events. When using the SRanipal, to differentiate between the first and the second pair of LEDs, for each frame, the script attributed a flag whenever the number of pixels was greater or smaller than given values. This flag is made possible since the second pair of LEDs cause a bigger reflection area, therefore a bigger number of pixels on the resulting mask (Figure 5b, second LED on and second LED mask).

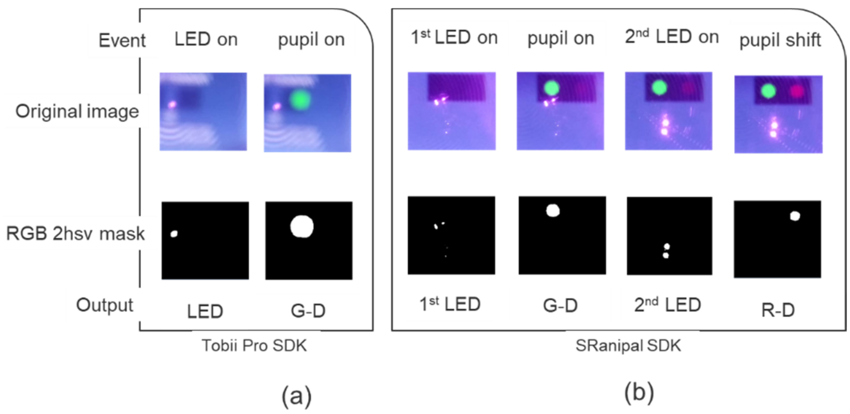

Figure 5. Original image: original frame pictures showing different events for (**a**) the Tobii Pro SDK (event: LED on and pupil on) and (**b**) the SRanipal SDK (event: first LED on, pupil on, second LED on, pupil shift). RGB 2hsv mask: application of Matlab's image segmentation mask to the selected events. The masks indicate how many pixels are in each event for the LED and dot events for (**a**) the Tobii Pro SDK (output: LED, G-D) and (**b**) SRanipal SDK (output: first LED, G-D, second LED, R-D).

For the eye-detection scenario, both when using the Tobii Pro SDK and the SRanipal SDK, the script automatically counted the number of frames between LEDs and the green dot onset. For each frame, the script attributed a flag whenever the generated LED mask or G-D mask had a number of pixels greater than 10. Additionally, when using the SRanipal, the script identified the first LED pair when the first LED mask had a number of pixels greater than 10, but also smaller than 250.

The count started with the second pair of LEDs' onset for the gaze-contingent scenario and ended with the bright red dot appearance. When the bright red dot was on for each frame, the script attributed a flag to the corresponding R-D mask when it contained a number of pixels greater than 10. For the second pair of LEDs, on every frame the script attributed a flag, whenever the number of pixels was greater than 300, to the second LED mask.

For the analysis both for eye-detection and gaze-contingent scenarios a histogram and a boxplot were plotted with the resulting intervals between events and tested for normal distribution with a one-sample Kolmogorov-Smirnov test. Temporal precision was calculated as the median of frame numbers elapsed between the LED and the different dot event multiplied by each video frame's mean duration.

3. Results

3.1. Pre-Processing: Eye-Tracking Accuracy and Precision

After data selection for each target, subjects had a median of 2638 data points in the head-still (Figure 6a) condition. The head-free$_{stable}$ (Figure 6b) condition had a median of 1408, and the head-free$_{moving}$ had a median of 251 points per target (Figure 6c).

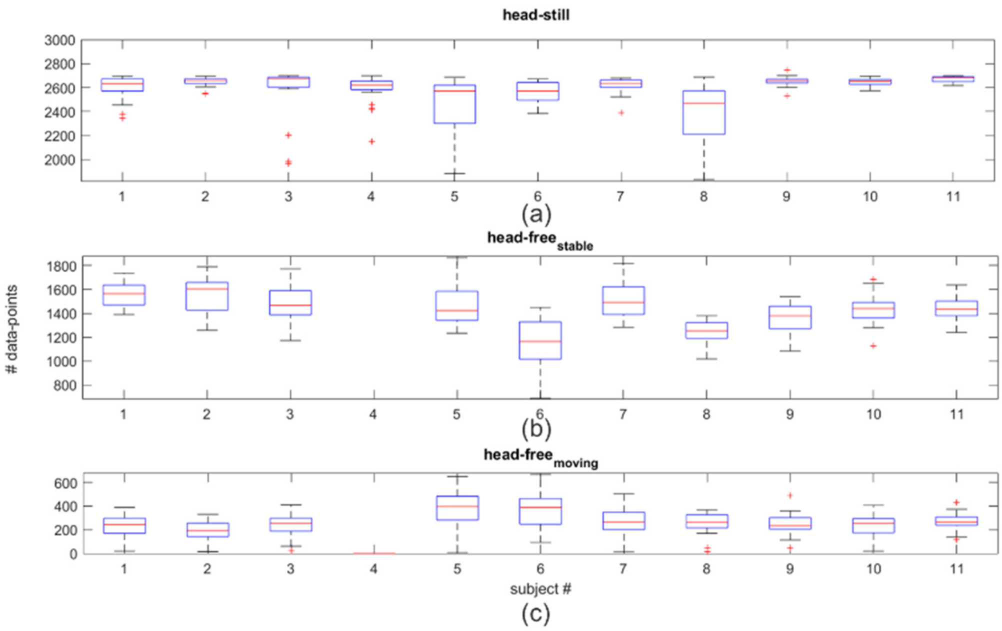

Figure 6. Bar plots with error bars and outliers (red plus dots) represent the median of data point for each subject for the 25 targets after data pre-processing for the head still (**a**) and head-free condition (**b**,**c**). The head-free condition is divided between stable (**b**) and moving head (**c**) periods.

3.2. Eye-Tracking Accuracy and Precision

In the head-still condition, the one-way ANOVA resulted in no significant differences in accuracy between the two eyes (F (1, 20) = 0.81, p = 0.38; mean left eye: 4.16° SD: ±1.49 and mean right eye: 4.75° SD: ±1.63). For this reason, the average across eyes (mean average of both eyes: 4.16°, SD: ±1.40) was used for the analysis. Precision has a mean of 2.17°, SD: ±0.75. The BCEA and mean accuracy angle and precision values per target show that the accuracy and precision of the estimated gaze are worse at the outermost horizontal regions and that the central line has higher accuracy and precision than the most externally positioned targets, with the highest level of accuracy and precision for the central target

(Figure 7a–c and Table 1). Comparing horizontal regions, a one-way ANOVA revealed that there is a significant difference in accuracy and precision (F (4, 50) = 3.35, $p = 0.02$ for accuracy; F (4, 50) = 3.6, $p = 0.01$ for precision). Post-hoc *t*-tests (Bonferroni corrected) show the center as being more accurate than the upper horizontal ($p < 0.03$, central row mean offset: 2.26°, SD: ±0.73; upper row mean offset: 6.16° SD: ±5.50), and as more precise than the lower horizontal ($p < 0.01$, central row RMS mean: 1.63° SD: ±0.30 and the lowest row RMS mean: 3.15°, SD: ±2.00).

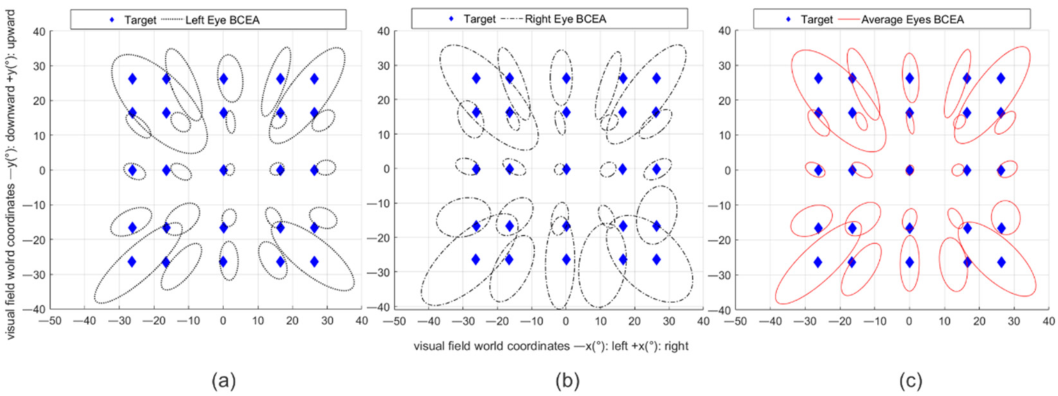

Figure 7. Covariance ellipses (BCEA) are fitted to the left eye's (**a**), right eye's (**b**), and both eyes' (**c**) gaze points corresponding to all fixations of the same target across all subjects. The blue diamonds are the targets.

Table 1. Mean angle accuracy and RMS precision for the 25 different targets across the visual field (VF) tested for left (L), right (R), and left-right average (B).

VF (°)	−27°			−13°			0°			13°			27°		
	L	R	B	L	R	B	L	R	B	L	R	B	L	R	B
27°	10.77	10.09	9.95	5.84	5.16	5.28	3.05	3.63	3.1	5.13	4.53	4.58	8.01	8.6	7.93
	2.64	2.67	2.29	2.27	1.91	1.86	2.84	4.29	2.79	1.9	1.98	1.72	3.18	2.18	2.25
13°	4.21	3.66	3.61	3.8	3.47	3.57	2.87	3.19	2.96	3.28	3.67	3.36	3.08	4.82	3.55
	2.16	2.4	1.94	2.31	2.11	1.87	1.87	2.1	1.67	2.12	2.06	1.75	2.22	2.03	1.88
0°	2.4	2.66	2.2	3.09	3.3	3.11	0.94	1.02	0.74	3.12	2.98	2.87	2.34	3.21	2.37
	1.95	2.08	1.79	1.73	1.81	1.55	1.64	1.8	1.45	1.98	1.95	1.68	1.94	1.95	1.76
−13°	4.05	5.32	4.3	4.14	4.16	4.1	3.27	2.34	2.73	4.78	3.98	4.33	3.49	4.98	3.75
	2.02	3.4	2.35	1.63	3.16	2.03	1.73	3.91	2.31	1.87	2.08	1.67	2.09	2.35	1.92
−27°	6.95	9.44	7.41	4.57	6.68	5.39	2.44	7.13	4.06	4.63	8.12	6.01	5.62	8.7	6.44
	2.02	4.81	2.89	2.51	4.32	2.81	3.12	7.13	4.06	2.87	5.99	3.5	4.13	3.4	2.95

Fixational eye movements of single subjects were plotted that revealed unstable fixation patterns for the upper row (Figure 8a) and deviations for the lower (Figure 8b). Accuracy and precision become worse for different quantiles of users (Table 2). Starting from the third quartile, accuracy and precision dropped. The accuracy passed from a visual angle of 3.21° to 4.88° and 6.06°, and precision passed from 1.63° to 2.51° and 3.55° from the first quartile to the third, and the 90th percentile, respectively.

In the head-free condition, there is an overall average precision of 1.15°, SD: ±0.69. Under head-movement one-way ANOVA revealed a significant difference in precision between head-free$_{stable}$, compared to phases of head-free$_{moving}$ (F (1, 18) = 8.64), $p < 0.01$; RMS mean$_{stable}$: 0.76°, SD$_{stable}$: ±0.39, RMS mean$_{moving}$: 1.54°, SD$_{moving}$: ±0.74) with higher imprecision during periods in which subjects were moving their head. As to data loss, there is a double amount of data slippage in the head-free$_{moving}$ phase compared to when subjects were not moving their head (7.56% of data spillage compared to 3.69% of data spillage).

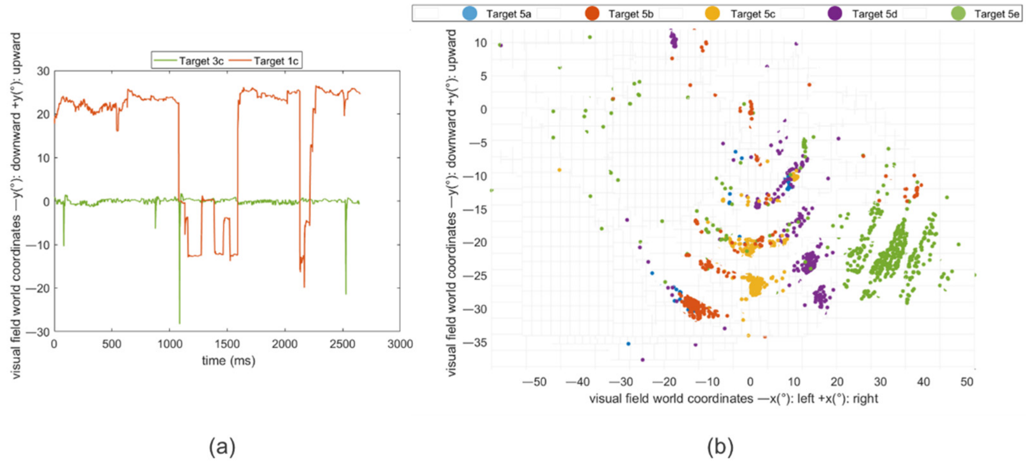

Figure 8. (**a**) Fixations plotted across the time for one subject evidence an unstable fixation of the upper-central target, target 3c, compared to a central one (green), target 1c. (**b**) Starting from left to right, target 5a is the most left target, positioned in the last row, and target 5e is the most right target. Blue, orange, yellow, lilac, and green are the dispersed fixation points belonging to target 5a, 5b, 5c, 5d, and 5e, respectively.

Table 2. Mean accuracy and RMS precision across different percentiles of each target in the head-still condition.

Percentile (Head-Still)	Accuracy (°)	Precision (°)
25%	3.21	1.63
50%	3.98	1.95
75%	4.88	2.51
90%	6.06	3.55

3.3. *Eye-Tracking Accuracy and Precision*

The one-sample Kolmogorov-Smirnov test showed that the intervals between LED and dot onset are not extracted from a standard normal distribution (Figure 9a,c,e), therefore a better indication for comparison between the temporal precision tests is the median (Figure 9b,d,f).

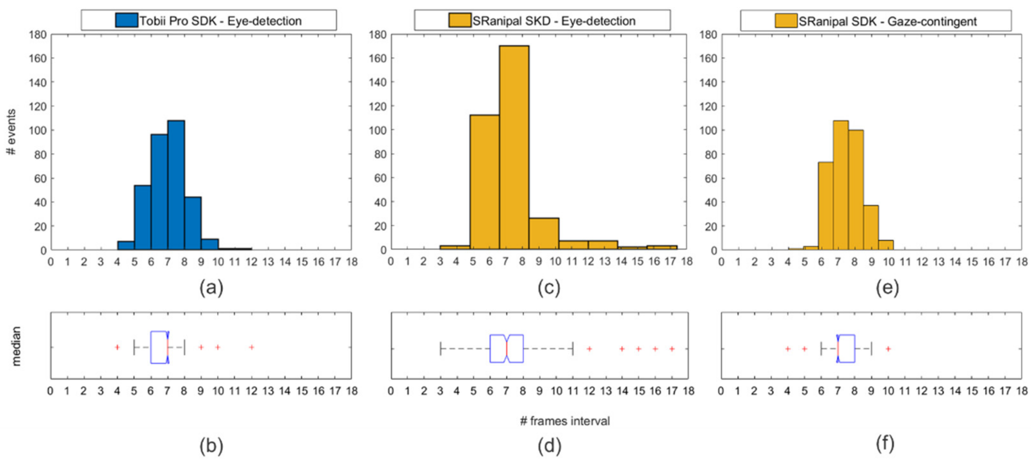

Figure 9. (**a**) The blue histogram indicates the number of the frame distribution when using the Tobii Pro SDK in the eye-detection scenario. (**b**) Box plot of the median inter-frame interval. (**c**) The number of the frame distribution in the eye-detection scenario. (**d**) Box-plot with the median of the eye-detection scenario. (**e**) Number of the frame distribution in the gaze-contingent scenario. (**f**) Box-plot of the median of the gaze-contingent scenario. All box-plots are plotted with error bars and outliers (red plus dots).

In the eye-detection scenario for the Tobii Pro SDK and the SRanipal, a median of 58.1 ms is found. In the gaze-contingent scenario, a median temporal precision of 58.1 ms is also found.

4. Discussion

New research using eye-tracking in VR has seen the emergence of more and more patient-friendly clinical applications intended to investigate and rehabilitate visual diseases. The current pilot study applied tailored data quality and temporal precision methods in VR to better understand how suitable is the manufacture's information for future low vision usability as an online at-home virtual perimetry and enhancement implementation. As a show-case for healthy subjects, the methodology was applied to investigate the status-quo usability of the HTC VIVE Pro Eye. The results obtained opens new discussion relating to online eye-tracking usability in VR for novel at-home ophthalmology applications.

For an online virtual perimetry testing application, two different conditions were tested: head-still and head-free. The head-still was used to test the eye-tracking accuracy and precision data over a large visual field and at different HMD regions. For this purpose, fixational targets were fixed to the VR headset, and accuracy and precision were tested on a 2D plane covering ±26.6° of the visual field of the HMD both horizontally and vertically. The head-free scenario tested the effect of head movement over eye-tracking precision and data spillage. For this purpose, fixation was tested in a 3D environment while keeping the head stable and while moving. Both showed different limitations of the embedded eye-tracker.

The head-still condition evidenced that, in comparison to the manufacturer's claim, spatial accuracy is worse than the reported values. Following previous VR eye-tracking accuracy research [36], eye-tracking data was more than three-time more inaccurate than the commercialized values with an average of 4.16°, SD: ±1.40°. Only the central target's accuracy seems to be within the range of 0.5°–1.1° spatial accuracy reported by the manufacturer. The remaining targets have values outside the range and, as found in previous screen-based eye-tracking studies [31,37], the target position on the HMD screen affected eye-tracking data quality. Compared with the central line, at approximately 25° away from the midline, significant inaccuracy is found for the upper horizontal line and imprecision for the lower one.

The inaccuracy observed at the upper horizontal line indicated that fixations in regions above 25° from the midline are difficult. It is hypothesized that subjective facial configurations, such as the distance of the VR headset from the eyes, is shrinking the visual field and making fixation in that area more challenging. Very recent research has shown that the commercially reported visual field values of the most common VR headsets are the sum of monocular fields for each eye and the actual value that should be used to indicate the visual field extent is the monocular value [38]. It can be hypothesized, therefore, that the actual visual field measurement for the HTC Vive Pro Eye would be only half, ±27.5° horizontally and vertically. The eye-tracking methodology applied therefore tested accuracy at the edge of the VR headset's possibilities in terms of the visual field, and this is reflected by the difficulty in fixating the extreme upper regions. Future studies using upcoming commercial HMDs with embedded eye-tracking should keep these restrictions in consideration.

As to the lower horizontal line, below 25° from the midline, eye-tracking data was found to be significantly more imprecise, and fixational points were more spread compared to the others. The spread of data points at the lowest edge of the HMD indicates effects due to reflections. It is known that reflections due to the surrounding environment, depending upon eye physiology, usage of corrective lenses, or due to the infrared camera position inside the VR headset, can lead to errors in the eye-tracking data [39]. The observed changes in data quality across the population indeed point towards external factors affecting eye-tracking data quality. Therefore, it is hypothesized that the observed deviations could be affected by all three above mentioned effects. Traditional calibration methodology can correct for each user's eye physiological characteristics [40]. Nonetheless, it can still be challenged by light conditions, the eye-correction used, reflections, and head movement [28] and this is what was found in our preliminary study as well.

Novel calibration methodology suitable in moving scenarios for online eye-tracking usage in VR could be used instead [41]. More and more research is being done in that direction. The most promising, which could overcome most of the current study's challenges, uses smooth pursuit to self-calibrate the system while a task is still being performed in VR. Results have shown that smooth pursuit calibration can overcome challenges such as differences in eye physiology, head movement, and problems in keeping a stable fixation [42,43] which are common in patients with visual loss. For a visual grasping mode, instead of using stimuli that change in brightness, limiting eye-tracking data [28], moving stimuli could be used to attract a patient's attention towards a new test area, which can occur in concomitance with self-calibration. Smooth-pursuit tasks in combination with head movements do not influence patients with both binocular and monocular visual loss more than normally sighted participants [44]. Hence, self-calibration systems that use smooth-pursuit for online visual field perimetry testing could overcome problems due to light conditions, patient fixational stability, eye physiology, and head movements. In future studies, a self-calibrating smooth pursuit could be applied both to normal and other patients, and the result could be compared to the current data.

The head-free condition evidenced how precision and data loss can be influenced by head movement: precision is lowest, and a double amount of data loss occurs while moving. The results obtained are pertinent with head-mounted eye tracker studies [28,35,45].

From the data quality analyzed, it can be concluded that the feasibility of the HTC Vive Pro Eye as an online objective visual grasp tool that could detect the early onset of glaucoma at eccentricities above $\pm 25°$ [46] is very restricted. With high inaccuracy and imprecision above $\pm 25°$ from the midline, and eye-tracking imprecision and data spillage during movement, its status-quo usage in online visual field testing is limited. The manufacturer's information shows no indication of these restrictions; therefore, the current pilot study provided additional eye-tracking data information for visual field online low-vision applications.

As to its application for online visual enhancement clinical studies that require a limited temporal precision and lack reliable and direct temporal precision measurements, additional conditions should be kept in mind. The display refresh rate can make a difference between a good or an acceptable latency level [20,47]. The eye tracker used in the HTC Vive Pro Eye has a higher refresh rate than the display, therefore, for this system, one part of the latency's variance can be due to the display's refresh. Additionally, ideally the display should be updated immediately at the end of each saccade. This is limited in practice since a lag always exists between the identification of saccade ending, rendering the new image, transmitting it, and displaying it, due to hardware differences [48]. For example, rendering the image can take from 25 to 150 ms [49–51] and an acceptable level of the system's latency depends on the application.

The new objective and automatic temporal precision tests showed that there is no difference between the detection of an eye and a gaze-contingent scenario. Furthermore, displaying data through the Tobii Pro SDK or the SRanipal SDK makes no difference in terms of temporal precision. For all the tests conducted, the median is a good indicator of temporal precision. The value of 58.1 ms makes the system suitable for patient-friendly visual enhancement applications. Indeed, it has been discussed that for changes in the peripheral areas of vision, latencies between 50 and 70 ms are well accepted because visual loss simulations are applied in the periphery, and they are not usually detected [48,52]. This happens because changes in the post saccade area mostly overlap with changes in the pre-saccadic [47]. If a saccade has a maximum duration of 54 ms and peripheral changes can go undetected up to 70 ms, the HTC Vive Pro Eye's eye-tracker is suitable as a responsive and undetectable online visual enhancement software.

5. Conclusions

In this study, the goal was to assess the preliminary eye-tracking status-quo capabilities of the HTC VIVE Pro Eye in a pilot number of healthy subjects to test its potentiality for future online clinical low-vision applications. Preliminary results indicate that the status-quo of eye-tracking embedded in the HTC VIVE Pro Eye has limitations for online VR perimetry testing and is generally suited as a low vision enhancement software. The results obtained added essential discussion points to be considered for future and upcoming VR headsets that want to use embedded eye-tracking as a virtual perimetry testing. The correctness of the actual reported visual field expansion of the VR headset and its relation to eye-tracking data need to be considered and additionally tested over a more heterogeneous subject population. Furthermore, a more suited smooth pursuit online self-calibration system could be considered for ongoing VR perimetry when considering using VR headsets for patients.

Author Contributions: A.S. contributed to conceptualization, writing—original draft, methodology, investigation, formal analysis, and data curation. K.R. and S.W. contributed to conceptualization, supervision, writing—review, and editing. S.W. was project head. All authors have read and agreed to the published version of the manuscript.

Funding: The work of authors is supported by the Institutional Strategy of the University Tübingen (Deutsche Forschungsgemeinschaft, ZUK 63), the German Excellence initiative from the Federal Ministry of Education and Research (BMBF) in the framework of IDeA (project number 16SV8104). This work was done in an industry on campus cooperation between the University of Tübingen and Carl Zeiss Vision International GmbH. The authors recognize intra-mutual funding of the University of Tübingen through the mini graduate school 'Integrative Augmented Reality (I-AR)'. There was no other additional external funding received for this study.

Institutional Review Board Statement: The Ethics Committee at the Medical Faculty of the Eberhard Karls University and the University Hospital Tübingen approved to carry out the study within its facilities (Institutional Review Board number: 138/2017b02). The study followed the tenets of the Declaration of Helsinki.

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 is available in figshare under HTCProEyeDataQuality&TemporalPrecision_Data. Link: https://figshare.com/s/dee0b7285b98748b512e, accessed on 2 February 2021.

Acknowledgments: The authors acknowledge support by Open Access Publishing Fund of the University of Tübingen.

Conflicts of Interest: Author A.S. declares no potential conflict of interest regarding this study. K.R. and S.W. are employed by Carl Zeiss Vision International GmbH, are scientists at the University of Tübingen, and have no potential conflict of interest regarding this study.

References

1. Wroblewski, D.; Francis, B.A.; Sadun, A.; Vakili, G.; Chopra, V. Testing of visual field with virtual reality goggles in manual and visual grasp modes. *Biomed. Res. Int.* **2014**, *2014*. [CrossRef] [PubMed]
2. Hotta, K.; Prima, O.D.A.; Imabuchi, T.; Ito, H. VR-HMD Eye Tracker in Active Visual Field Testing. In Proceedings of the 2019 IEEE Conference on Virtual Reality and 3D User Interfaces (VR), Osaka, Japan, 23–27 March 2019; pp. 1843–1847.
3. Ogura, K.; Sugano, M.; Takabatake, S.; Naitoh, Y.; Nakaoka, K. VR Application for Visual Field Measurement of Unilateral Spatial Neglect Patients Using Eye Tracking. In Proceedings of the 2019 IEEE International Conference on Healthcare Informatics (ICHI), Xi'an, China, 10–13 June 2019; pp. 1–2.
4. Masnadi, S.; Williamson, B.; González, A.N.V.; LaViola, J.J. VRiAssist: An Eye-Tracked Virtual Reality Low Vision Assistance Tool. In Proceedings of the 2020 IEEE Conference on Virtual Reality and 3D User Interfaces Abstracts and Workshops (VRW), Atlanta, GA, USA, 22–26 March 2020; pp. 809–810.
5. Sayed, A.M.; Abdel-Mottaleb, M.; Kashem, R.; Roongpoovapatr, V.; Elsawy, A.; Abdel-Mottaleb, M.; Parrish II, R.K.; Abou Shousha, M. Expansion of Peripheral Visual Field with Novel Virtual Reality Digital Spectacles. *Am. J. Ophthalmol.* **2020**, *210*, 125–135. [CrossRef] [PubMed]
6. Kasha, J.R., Jr. Visual Field Perimetry Using Virtual Reality Glasses. U.S. Patent 5737060A, 7 April 1998.

7. Hollander, D.; Volpe, N.; Moster, M.; Liu, G.; Balcer, L.; Judy, K.; Galetta, S. Use of a portable head mounted perimetry system to assess bedside visual fields. *Br. J. Ophthalmol.* **2000**, *84*, 1185–1190. [CrossRef] [PubMed]
8. Plummer, D.J.; Lopez, A.; Azen, S.P.; LaBree, L.; Bartsch, D.-U.G.; Sadun, A.A.; Freeman, W.R. Correlation between static automated and scanning laser entoptic perimetry in normal subjects and glaucoma patients. *Ophthalmology* **2000**, *107*, 1693–1701. [CrossRef]
9. Tsapakis, S.; Papaconstantinou, D.; Diagourtas, A.; Droutsas, K.; Andreanos, K.; Moschos, M.M.; Brouzas, D. Visual field examination method using virtual reality glasses compared with the Humphrey perimeter. *Clin. Ophthalmol. (Auckl. Nz)* **2017**, *11*, 1431. [CrossRef]
10. Erichev, V.; Ermolaev, A.; Antonov, A.; Grigoryan, G.; Kosova, J. New visual field testing possibilities (a preliminary report). *Eur. PMC* **2018**. [CrossRef]
11. Mees, L.; Upadhyaya, S.; Kumar, P.; Kotawala, S.; Haran, S.; Rajasekar, S.; Friedman, D.S.; Venkatesh, R. Validation of a Head-mounted Virtual Reality Visual Field Screening Device. *J. Glaucoma* **2020**, *29*, 86–91. [CrossRef] [PubMed]
12. Trope, G.; Eizenman, M.; Coyle, E. Eye movement perimetry in glaucoma. *Can. J. Ophthalmol. J. Can. D'ophtalmologie* **1989**, *24*, 197–199.
13. Coco-Martin, M.B.; Piñero, D.P.; Leal-Vega, L.; Hernández-Rodríguez, C.J.; Adiego, J.; Molina-Martín, A.; de Fez, D.; Arenillas, J.F. The Potential of Virtual Reality for Inducing Neuroplasticity in Children with Amblyopia. *J. Ophthalmol.* **2020**, *2020*. [CrossRef]
14. Baloh, R.W.; Sills, A.W.; Kumley, W.E.; Honrubia, V. Quantitative measurement of saccade amplitude, duration, and velocity. *Neurology* **1975**, *25*, 1065. [CrossRef]
15. Bahill, A.; Brockenbrough, A.; Troost, B. Variability and development of a normative data base for saccadic eye movements. *Investig. Ophthalmol. Vis. Sci.* **1981**, *21*, 116–125.
16. Becker, W. The neurobiology of saccadic eye movements. Metrics. *Rev. Oculomot. Res.* **1989**, *3*, 13.
17. Thickbroom, G.; Knezevic, W.; Carroll, W.; Mastaglia, F. Saccade onset and offset lambda waves: Relation to pattern movement visually evoked potentials. *Brain Res.* **1991**, *551*, 150–156. [CrossRef]
18. Rayner, K.; Foorman, B.R.; Perfetti, C.A.; Pesetsky, D.; Seidenberg, M.S. How psychological science informs the teaching of reading. *Psychol. Sci. Public Interest* **2001**, *2*, 31–74. [CrossRef] [PubMed]
19. Behrens, F.; MacKeben, M.; Schröder-Preikschat, W. An improved algorithm for automatic detection of saccades in eye movement data and for calculating saccade parameters. *Behav. Res. Methods* **2010**, *42*, 701–708. [CrossRef] [PubMed]
20. Gibaldi, A.; Vanegas, M.; Bex, P.J.; Maiello, G. Evaluation of the Tobii EyeX Eye tracking controller and Matlab toolkit for research. *Behav. Res. Methods* **2017**, *49*, 923–946. [CrossRef] [PubMed]
21. Brooks, B.A.; Fuchs, A.F. Influence of stimulus parameters on visual sensitivity during saccadic eye movement. *Vis. Res.* **1975**, *15*, 1389–1398. [CrossRef]
22. Riggs, L.A.; Volkmann, F.C.; Moore, R.K.; Ellicott, A.G. Perception of suprathreshold stimuli during saccadic eye movement. *Vis. Res.* **1982**, *22*, 423–428. [CrossRef]
23. Raspberry Pi 3 Model B. Available online: https://web.archive.org/web/20210203153003if_/https://www.raspberrypi.org/products/raspberry-pi-3-model-b/ (accessed on 2 February 2021).
24. Raspberry Pi Camera Module v2. Available online: https://web.archive.org/web/20210119155729/https://www.raspberrypi.org/products/camera-module-v2/ (accessed on 19 January 2021).
25. Vive Pro Eye. Available online: https://web.archive.org/web/20201111190618/https://www.vive.com/eu/product/vive-pro-eye/overview/ (accessed on 11 November 2020).
26. Tobii Pro SDK. Available online: https://web.archive.org/web/20200622201031/https://www.tobiipro.com/product-listing/tobii-pro-sdk/ (accessed on 22 June 2020).
27. VIVE Eye Tracking SDK (SRanipal). Available online: https://web.archive.org/web/20200923043350/https://developer.vive.com/resources/vive-sense/sdk/vive-eye-tracking-sdk-sranipal/ (accessed on 23 September 2020).
28. Holmqvist, K.; Nyström, M.; Andersson, R.; Dewhurst, R.; Jarodzka, H.; Van de Weijer, J. *Eye Tracking: A Comprehensive Guide to Methods and Measures*; Oxford University Press: Oxford, UK, 2011.
29. Holmqvist, K.; Zemblys, R.; Beelders, T. Magnitude and nature of variability in eye-tracking data. In Proceedings of the European Conference on Eye Movements (ECEM), Wuppertal, Germany, 20–24 August 2017.
30. Orquin, J.L.; Holmqvist, K. Threats to the validity of eye-movement research in psychology. *Behav. Res. Methods* **2018**, *50*, 1645–1656. [CrossRef]
31. Clemotte, A.; Velasco, M.A.; Torricelli, D.; Raya, R.; Ceres Ruiz, R. Accuracy and precision of the Tobii X2–30 eye-tracking under non ideal conditions. In Proceedings of the 2nd International Congress on Neurotechnology, Electronics and Informatics, Rome, Italy, 25–26 October 2014; pp. 111–116. [CrossRef]
32. Reingold, E.M. Eye tracking research and technology: Towards objective measurement of data quality. *Vis. Cogn.* **2014**, *22*, 635–652. [CrossRef]
33. Blignaut, P.; Beelders, T. The precision of eye-trackers: A case for a new measure. In Proceedings of the Symposium on eye tracking research and applications (ETRA '12), Santa Barbara, CA, USA, 28–30 March 2012; pp. 289–292.
34. Dahlberg, J. Eye tracking with eyeglasses. Master's Thesis, Umea University, Umea, Sweden, 2010.
35. Niehorster, D.C.; Santini, T.; Hessels, R.S.; Hooge, I.T.; Kasneci, E.; Nyström, M. The impact of slippage on the data quality of head-worn eye trackers. *Behav. Res. Methods* **2020**, *52*, 1140–1160. [CrossRef]

36. Lohr, D.J.; Friedman, L.; Komogortsev, O.V. Evaluating the Data Quality of Eye Tracking Signals from a Virtual Reality System: Case Study using SMI's Eye-Tracking HTC Vive. *arXiv* **2019**, arXiv:1912.02083.
37. Feit, A.M.; Williams, S.; Toledo, A.; Paradiso, A.; Kulkarni, H.; Kane, S.; Morris, M.R. Toward everyday gaze input: Accuracy and precision of eye tracking and implications for design. In Proceedings of the 2017 Chi Conference on Human Factors in Computing Systems, Denver, CO, USA, 6–11 May 2017; pp. 1118–1130.
38. Lynn, M.H.; Luo, G.; Tomasi, M.; Pundlik, S.; Houston, K.E. Measuring Virtual Reality Headset Resolution and Field of View: Implications for Vision Care Applications. *Optom. Vis. Sci.* **2020**, *97*, 573–582. [CrossRef]
39. Kothari, R.S.; Chaudhary, A.K.; Bailey, R.J.; Pelz, J.B.; Diaz, G.J. EllSeg: An Ellipse Segmentation Framework for Robust Gaze Tracking. *arXiv* **2020**, arXiv:2007.09600.
40. Guestrin, E.D.; Eizenman, M. General theory of remote gaze estimation using the pupil center and corneal reflections. *IEEE Trans. Biomed. Eng.* **2006**, *53*, 1124–1133. [CrossRef] [PubMed]
41. Tripathi, S.; Guenter, B. A statistical approach to continuous self-calibrating eye gaze tracking for head-mounted virtual reality systems. In Proceedings of the 2017 IEEE Winter Conference on Applications of Computer VISION (WACV), Santa Rosa, CA, USA, 27–29 March 2017; pp. 862–870.
42. Blignaut, P. Using smooth pursuit calibration for difficult-to-calibrate participants. *J. Eye Mov. Res.* **2017**, *4*. [CrossRef]
43. Drewes, H.; Pfeuffer, K.; Alt, F. Time-and space-efficient eye tracker calibration. In Proceedings of the 11th ACM Symposium on Eye Tracking Research & Applications, Denver, CO, USA, 25–28 June 2019; pp. 1–8.
44. Shanidze, N.M.; Velisar, A. Eye, head, and gaze contributions to smooth pursuit in macular degeneration. *J. Neurophysiol.* **2020**, *124*, 134–144. [CrossRef]
45. Holmqvist, K.; Nyström, M.; Mulvey, F. Eye tracker data quality: What it is and how to measure it. In Proceedings of the Symposium on eye tracking research and applications (ETRA '12), Santa Barbara, CA, USA, 28–30 March 2012; pp. 45–52.
46. Nouri-Mahdavi, K. Selecting visual field tests and assessing visual field deterioration in glaucoma. *Can. J. Ophthalmol.* **2014**, *49*, 497–505. [CrossRef]
47. Saunders, D.R.; Woods, R.L. Direct measurement of the system latency of gaze-contingent displays. *Behav. Res. Methods* **2014**, *46*, 439–447. [CrossRef] [PubMed]
48. Loschky, L.C.; Wolverton, G.S. How late can you update gaze-contingent multiresolutional displays without detection? *ACM Trans. Multimed. Comput. Commun. Appl. (TOMM)* **2007**, *3*, 1–10. [CrossRef]
49. Thomas, M.; Geltmacher, H. Combat simulator display development. *Inf. Disp.* **1993**, *9*, 23.
50. Ohshima, T.; Yamamoto, H.; Tamura, H. Gaze-directed adaptive rendering for interacting with virtual space. In Proceedings of Proceedings of the IEEE 1996 Virtual Reality Annual International Symposium, Santa Clara, CA, USA, 30 March–3 April 1996; pp. 103–110.
51. Geisler, W.S.; Perry, J.S. Real-time foveated multiresolution system for low-bandwidth video communication. In Proceedings of the Human Vision and Electronic Imaging III, San Jose, CA, USA, 24 January 1998; pp. 294–305.
52. Albert, R.; Patney, A.; Luebke, D.; Kim, J. Latency requirements for foveated rendering in virtual reality. *Acm Trans. Appl. Percept. (TAP)* **2017**, *14*, 1–13. [CrossRef]

6.1.2 Study 2

Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR)

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Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR)

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Abstract: This study addresses the importance of salience placement before or after scotoma development for an efficient target allocation in the visual field. Pre-allocation of attention is a mechanism known to induce a better gaze positioning towards the target. Three different conditions were tested: a simulated central scotoma, a salience augmentation surrounding the scotoma and a baseline condition without any simulation. All conditions were investigated within a virtual reality VR gaming environment. Participants were tested in two different orders, either the salient cue was applied together with the scotoma before being presented with the scotoma alone or the scotoma in the wild was presented before and, then, with the augmentation around it. Both groups showed a change in gaze behaviour when saliency was applied. However, in the second group, salient augmentation also induced changes in gaze behaviour for the scotoma condition without augmentation, gazing above and outside the scotoma following previous literature. These preliminary results indicate salience placement before developing an advanced stage of scotoma can induce effective and rapid training for efficient target maintenance during VR gaming. The study shows the potential of salience and VR gaming as therapy for early AMD patients.

Keywords: AMD; salience; virtual reality; VR; preventive care

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Citation: Sipatchin, A.; García García, M.; Wahl, S. Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR). *Appl. Sci.* **2021**, *11*, 7164. https://doi.org/10.3390/app11157164

Academic Editors: Marco Gesi, Giuseppe Turini, Rosanna Maria Viglialoro, Marina Carbone and Sara Condino

Received: 23 June 2021
Accepted: 28 July 2021
Published: 3 August 2021

1. Introduction

The macula is the human eye's richest area in terms of photoreceptors. This part of the retina is endeavoured to produce a sharp image of the objects we gaze upon. Hence, deterioration of this area may lead to the formation of scotomas or areas with partial or complete diminished visual acuity.

Amid the different conditions that can deteriorate the status of the macula, two are the conditions that appear more often: the myopic macular degeneration, which occurs in the presence of high myopia [1], and the age-related macular degeneration (AMD), which usually appears in the last decades of life [2]. Myopic macular degeneration and AMD combined affect approximately 11% of the world's population [1,3].

Patients with macular degeneration are known to adapt to the central visual loss by modifying the so-called foveated behaviour, i.e., objects of interest will no longer be fixated within the macula. A peripheral behaviour substitutes this foveation, meaning that patients will learn to fixate away from the target of interest so that the target can be positioned on a healthy retinal location, and consequently acknowledged. This technique is called eccentric viewing, and the healthy part of the retina used to look at objects is referred to as the preferred retinal locus (PRL). This peripheral gaze behaviour is known to be the only way that patients have to continue their daily life [4].

However, the peripheral retina has a poor visual resolution [5], and it is not intended to acknowledge details in focused objects. It takes time to adapt and modify the natural foveation behaviour, but in the end, one or more eccentric PRLs develop naturally [6–10]. Correct adaptation and use of the retinal areas with intact visual quality are a key part of safely continuing day-life activities such as safely crossing the street [11,12].

New technologies such as virtual reality (VR) and augmented reality (AR) have recently proposed new assisting tools for patients suffering from macular degeneration [13–15]. These tools aim to improve the quality of life of patients by improving the eccentric viewing and assisting patients specifically during critical tasks.

Embracing these new technologies and applying them to patients can assist them in improving eccentric fixation. Likewise, these technologies can be used with healthy subjects to study improvements in gaze behaviour under simulated visual loss conditions.

Standardised gaze-contingent scotoma simulations can change gaze behaviour in healthy participants in the same way as patients do [16–20] and scotoma simulations can replicate visual loss in a standardised manner with a well-defined area and filling [21–23]. Thanks to this standardization, there is the advantage to overcome the variability of different shapes and positions the scotoma patients bring into studies [16,17] and investigate augmentations in a generalized manner that can get later validated when applied to patients [24].

In this study, a standardised gaze-contingent scotoma simulation was used to occlude the central vision bilaterally to test, for the first time, the effects of gaze placement before and after salience application. The study's purpose was to test the hypothesis according to which preventive attention placement can lead to a better target positioning in relation to scotomas [4,25].

An augmented peripheral cue was designed to be perceived as salient, and induce the eyes to position a moving target outside the central occluded area. The circular cue was applied to the dominant eye only, in the periphery and gaze-contingent. A unique-eye-of-origin stimulus presented in the periphery is known to attract the gaze towards its position; it induces a popping-out effect, known as saliency [26]. Furthermore, the augmentation was gaze-contingent, with a constant position in the peripheral visual field. It is known that peripheral cues have an automatic component of attention allocation that once they have triggered it, its focus is preserved in that location [27,28]. For the present study, this means that once the eyes were attracted towards the peripheral cue, the target would start to be positioned in an annulus area where automatic attention is known to be focused [27].

Traditional tasks used for PRL development studies and therapy can be repetitive, exhaustive, and tedious, ending in a decrease in the subject's motivation [29]. For the current study, a VR game that involved tracking and detecting changes in a moving object was introduced to re-definite these traditional tasks. Gamification, in this context, was intended as a leap from those training sessions to more engaging experiment blocks.

2. Materials and Methods

2.1. Participants

Thirteen participants took part in the study (7 females and 6 males, mean age 29, standard deviation (SD) $\pm$ 3 years, only one subject wearing eye-correction, eye contact lenses).

2.2. Set-Up

For the virtual experiment, the Unity 2019.3.0a5 version was used as a design tool, with C# as a programming language, running on a PC with Windows 10 Home, having a 64-bit operating system, an Intel Core i7 -7700HQ, 2.8 GHz, 16 GB RAM, and an NVIDIA GeForce GTX 1070 GDDR5 graphics card.

The HTC Vive Pro Eye [30] headset was used to present the virtual environment. This headset has an integrated eye tracker with a sampling frequency of 120 Hz and a known latency between 58 ms and 80 ms [31,32]. This HMD also has two AMOLED screens, with a resolution of 1.440 $\times$ 1.600 pixels to each eye (pixel density of 615 pixels per inch (PPI)), and a refresh rate of 90 Hz. Tobii Pro SDK v1.7.1.1081 [33] and Vive SRanipal

SDK v1.0.3.0 [34] were used to save eye-tracking data and to present the gaze-contingent simulations, respectively. A Microsoft Xbox wireless controller was used for subject input.

2.3. Calibration Procedure

An initial semi-automated inter-pupillary distance (IPD) adjustment and a calibration of five points (SRAnipal) was carried out for all participants at the beginning of each condition. The participant sets the IPD through a knob that can be rotated to adjust the lenses distance. Based on the pupil position, the SRAnipal system provides feedback to the subject when the distance has been set correctly. Only after a correct IPD adjustment, the eye-tracking calibration can start. After a correct calibration output offered by the software, the subject could start with each condition type.

2.4. Experimental Procedure

Participants were asked to pursuit a moving target with unrestricted head movement while playing a 2-D Pong game in VR. The playing area covered $\pm 28°$ horizontally by $\pm 26°$ vertically. The moving target consisted of a 3° ball moving at an average velocity of $21.74\,°\,s^{-1}$ (SD: $\pm 0.63\,°\,s^{-1}$) from one side to the other of the screen following a randomised triangular trajectory. The subjects controlled two paddles to keep the moving ball inside the playing area. If the ball left the playing area, the trial was re-started by the participant.

During the Pong game, the ball changed colour at random intervals. Participants were asked to press a button whenever they acknowledged that the ball stimulus changed colour, which, if recognised, it would increase their score. During the session, the participants could move their heads freely. In addition, a head-fixed rectangle of $\pm 14.25°$ horizontally and vertically was presented to motivate the subjects to move their heads.

2.4.1. Conditions

All participants were tested in three (3) conditions: normally sighted, central scotoma, and salience augmentation of scotoma simulation. In the normal condition, no simulation was used while playing the game. During the central scotoma condition, eye-tracking was used to simulate a 12° circular scotoma occluding the central visual field. In the augmented central scotoma condition, a 2° circular augmentation, with a diameter of 27° was implemented around the simulated scotoma and applied to the dominant eye.

Figure 1 shows of how the simulations in the scotoma and augmented condition looked like. Each condition was measured in three blocks of five (5) minutes. Before each block, a manual drift correction had to be performed by the subject.

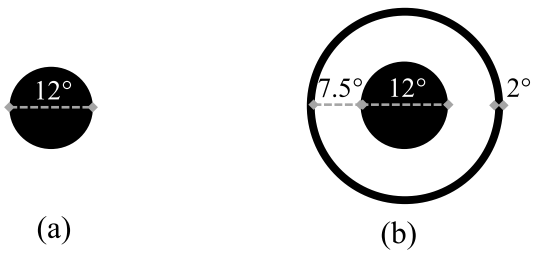

Figure 1. (**a**) Specifications of the central scotoma (CS) and (**b**) augmented scotoma (AS) condition. In the CS condition the scotoma (**a**) had a diameter of 12°. In the AS condition (**b**) there was an concentric augmentation of 2° around the scotoma and an annulus area extending 7.5°.

2.4.2. Manual Drift Correction

A manual drift correction was applied at the beginning of each block for all conditions. The manual drift correction (Figure 2) consisted of a manual scotoma adjustment performed by the participant. Each subject was presented with a scotoma simulation for each eye and a central red dot, attached to the eye camera. The red dot was used as a reference to centre the scotoma. Participants could correct the scotoma position using the Xbox controller. After the scotoma was correctly centred and checked by the experimenter, the experimenter pressed a key to start the next block. These offset values were then applied throughout the block session. The drift correction was designed to compensate for eye-tracking data quality decay in VR due to the movement of the participant, which is known to induce drifts into the precision of the eye tracker [35]. These drifts can influence scotoma positioning.

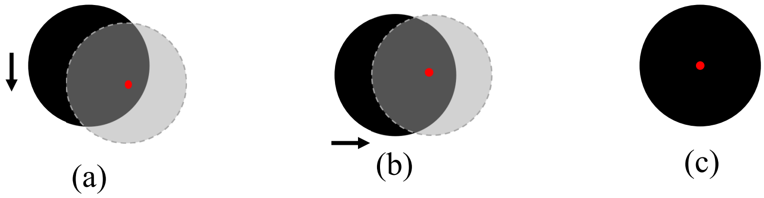

Figure 2. Drift correction was performed manually by the subject to have a centralized scotoma around the red dot at the beginning of each block. In the figure above, a hypothetical example of how a decentralized scotoma (in black) might look like (**a**) and hypothetical stages of position correction (**b**,**c**), black arrows, performed to have a concentric positioning of the scotoma around the red dot (**c**). The grey circle is used as a reference for this figure to indicate where the simulated scotoma should be positioned.

2.5. Groups

The participants were separated into two groups, defined by the order in which the different conditions were presented. Although the augmentation and scotoma conditions were randomized, all subjects started playing the game without any applied simulation first (normally sighted condition) (Figure 3).

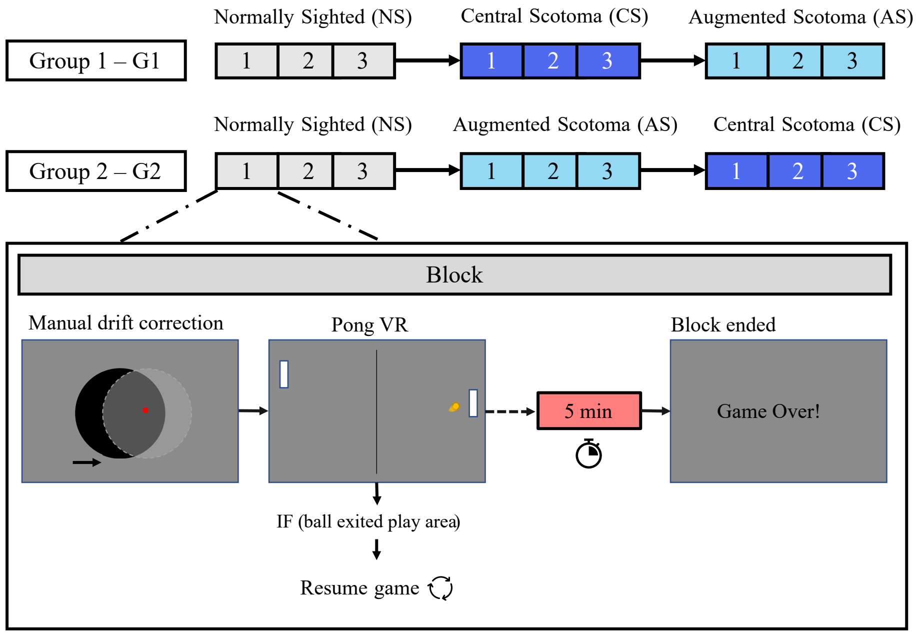

Figure 3. Scheme of the experimental procedure. Participants were divided into two groups (G1 and G2). Both groups initiated playing the Pong game under normal vision conditions (normally sighted, NS). The difference between groups was defined by the order by which the scotoma (CS) and augmented scotoma (AS) simulations were presented. In group 1, the scotoma simulation followed the augmentation, in group 2 the opposite. During each condition, three blocks (1, 2, and 3) were tested. Each block was the same for all conditions. It started with a manual drift correction followed by a 5-min timer playtime. During the game, the ball could have exited the play area. In that case, the timer was frozen and the game re-started. When the timer ended, a new block started.

3. Data Processing

3.1. Data Pre-Processing

3.1.1. Noise Cancellation: Fluctuation in the Sampling Data

Eye-tracking data were first checked for fluctuations in the sampling rate which can lead to noise in the eye-tracking data introducing spurious variation into the eye movements [36,37]. Sampling rate fluctuations were found if the time that passed between two samplings were bigger than the known inter-sample range (8.3 ms, with an error margin of $\pm$0.4 ms). Following common practice [37], when fluctuations were detected, two data points before, and two data points after the identified fluctuation were deleted from the dataset. After this filter, a percentage of total data exclusion was calculated.

3.1.2. Latency Error Correction

All gaze-contingent paradigms are always subject to a lag between where the participant's current eye position is and where the rendering of the scotoma is shown on display. This latency is related to the system's processes to display the image based on the eye position. First, it needs to record the eye position and transmit it to the computer; the computer would receive it and shift the scotoma position, render the new image, and finally, it displays the new image on the headset screen [38]. This delay in the scotoma presentation means for the current experiment that the scotoma might not cover the exact 6° radius of the central vision at all time.

To account for the latency error between the actual eye's position and the actual recording of the eye, the target position was used as an indicator of where the recording of the eye should have been. This error can be approximated in the distance between the gaze and target positions measured during the normal condition.

For every frame, the normalised target (re-referenced to the eye) and the dominant eye's normalised gaze were transformed into two-dimensional Cartesian coordinates. Then, the eye-target distance was calculated using the Pythagorean theorem. For every target data sample, twenty-one eye data points (ten previous to the matching timestamp and ten forward) were registered. The median in the distances between these 21 points and the target position was considered the system standard error.

A mean and the standard deviation [39] for this error were calculated for each subject and assumed as the time delay between the recorded eye position and the actual eye location.

3.1.3. Eye-Tracking Data Filtering

The Nyström and Holmqvist [40] velocity-based algorithm was used to filter the high jumps in eye velocity caused by missing eye data. These jumps occur above the normal velocity of the eye during a saccade ($300\,^{\circ}\,\mathrm{s}^{-1}$). The *sgolay* function in Matlab based on Savitzky and Golay [41] was used over the 3D raw gaze coordinates. Sample-to-sample velocity between two consecutive gaze coordinates in degrees was calculated for the raw and filtered data. These velocities were compared to observe the filtering effect of this algorithm.

3.1.4. Saccades Smoothing: Moving Median Window

As described by Shanidze et al. [42], to calculate the gaze-target distance, saccade information is usually kept. To smooth the saccade's data and look for trends that could otherwise be overlooked due to a high number of saccades that occur during the initial phases of scotoma habituation [43], a moving median window was used. Different sliding windows of 5, 10, 20, and 40 s were compared until saccades smoothing was achieved, and a more clear trend with less volatility in gaze-target distance was observed.

3.1.5. Colour Change Recognition Sub-Task and Scotoma Radius as Cutoff for the Maximum Positive and Negative Predictive Values

Bayes' theorem was applied to test the probability of colour recognition due to scotoma coverage. The distance between gaze and the edge of the target and whether it was above the scotoma's radii were used to indicate seen or not seen, and the colour change detection to determine correct or wrong.

Seen and correctly recognised was defined as true-positive, while non-seen and detected was false-positive. Similarly, if the colour change was not detected but the target was visible, it was considered a false-negative. If it was not visible and not detected, it counted as a true-negative. The probability of the positive and the negative predictive value were then calculated for the group and individually, and can indicate that the central vision might not be correctly occluded due to eye movements such as saccades and blinks [44,45]. Hence, the subject could have seen the target outside the intended radius of occlusion partially or entirely when he/she was not supposed to, influencing the correct and incorrect colour recognition task ratio. To test for possible errors in scotoma occlusion, five different scotoma radii extensions were considered, from 6° to 4°, in steps of 0.5°. Suppose an actual error due to partial occlusion of the central visual field was present. In that case, all subjects should present a low positive predictive value and a high negative predictive value for the 6° scotoma radii.

The lower the margin for the scotoma radii, the higher number of positive predictive values are expected. This increase will occur until the positive predictive value would reach a plateau. The opposite would be observed for the negative predictive value. Furthermore, this test allows us to identify the subjects who performed the task correctly from those who did not. Each subject was looked at individually to observe the trend. If the positive and negative predictive values did not show the same trend as the majority did, they were identified as having a bad performance, not in line with the experiment and therefore excluded.

3.2. Data Analysis

3.2.1. Gaze-Target Distancing: Condition Type Influence over Eye Position

After data pre-processing, the effect of the independent variable, condition type, was investigated over the dependant variable, the median distance between the gaze and the centre of the target. The normality of the sample was tested with the Kolmogorov–Smirnov one-sample test ($p < 0.001$). Given the absence of a normal distribution in our data, the non-parametric Kruskal–Wallis test was used. These results were further compared with an FWER test (Dunn–Šidák).

3.2.2. Gaze-Target Direction: Training Effect across Blocks

To examine whether there was a significant change in gaze behaviour, the gaze-target direction was plotted as a function of different blocks. Re-direction of eye positions in favour of the upper, lower, right, or leftwards hemifield indicated changes of gaze behaviour across time [18,25]. A polar histogram was used to look into the gaze direction and confront it to the target across blocks. Zittrell [46] polar histogram plot based on Berens [47] was used after calculating the wrap angle between gaze and target. Circular statistics were used, and the mean resultant vector (r) and the average direction were calculated for each block. The mean resultant vector values range between 0 and 1, where 0 indicates that data have a large spread while 1 means that the entire dataset is concatenated towards one point. This parameter was used to look into the spread of the gaze direction with respect to the target. The average angle indicates the potential directionality for the tested block.

4. Results

4.1. Data Pre-Processing

4.1.1. Noise Cancellation: Fluctuation in the Sampling Data

Only 0.83% of the data were omitted due to fluctuations in the sampling rate, meaning that these points had a sampling rate outside the normal range of sampling.

4.1.2. Latency Error Correction

The best gaze-target distance was found to be when gaze data points were 3 position updates behind the target data. Considering the sampling frequency of 120 Hz, in terms of latency, this indicates that the recorded eye position and the actual eye position had a delay error of 25 ms (Figure 4).

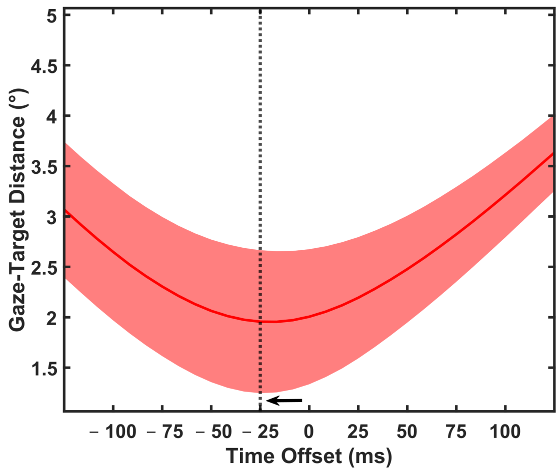

Figure 4. Latency offset for best gaze-target distance across all subjects. The red line indicates the mean tested for all the different time offsets, and the shading red represented the SD around the mean. The black arrow indicates that the best gaze-target distance is at its lowest when gaze data are sifted by 25 ms.

4.1.3. Eye-Tracking Data Filtering

A 24 sample Savitzky and Golay [41]´s algorithm was found to effectively refine the velocity between successive gaze data. This second-order polynomial interpolation smooths the gaze data gaps, where the velocity was above the normal saccades velocity, as reported by Nyström and Holmqvist [40]. The result of the filter can be seen in Figure 5 when comparing filtered data with raw data, sample-by-sample.

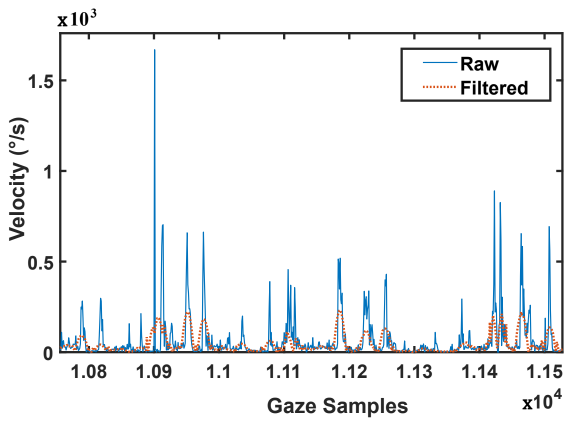

Figure 5. Gaze samples were filtered using the Savitzky–Golay filter, with second-order polynomials and 24 filter length. In the dataset, the effect (red) on simple, raw (blue), sample-to-sample velocity.

4.1.4. Saccades Smoothing: Moving Median Window

Four different moving median windows were tested to the gaze-target distance to de-noise it. In comparison to the original data, every sliding window proved to improve and smooth the gaze-target distance (Figure 6). Out of the four tested ones, the 40 s centred moving average window presented less volatility induced by saccadic behaviour and best smoothing in the data.

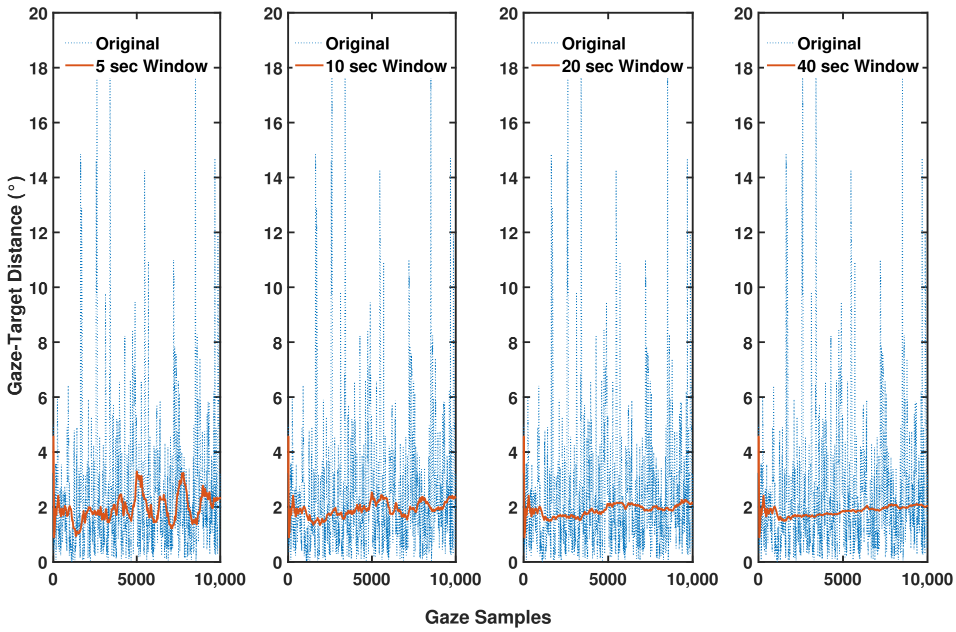

Figure 6. Original gaze samples (blue) and different moving window medians applied to the original data smoothing the saccades (red).

4.1.5. Colour Change Recognition Sub-Task and Scotoma Radius as Cutoff for the Maximum Positive and Negative Predictive Values

The test revealed that indeed there was a big variability when comparing positive and negative predictive values across different scotoma radii, starting already at 5.5° indicating that the actual radius of the coverage area was smaller than 6°. The probability of positive and negative predictive values had less considerable variability when reaching the 5° radius of scotoma coverage and started to reach a plateau (Figure 7). This indicated that the ball could have been perceived when the distance was $\leq$5°, and not 6° from the target.

On the other hand, it was observed that some subjects performed the task correctly across all conditions, while others did not. The probability of positive and negative predictive values did not show the same trend as the majority of subjects, with no plateau reached (Figure 8); those subjects were excluded from the analysis, as a poor performance in the test was suspected. A total of 5 subjects had to be excluded due to this criterion. For the analysis, a total of 8 subjects were included, four from each group.

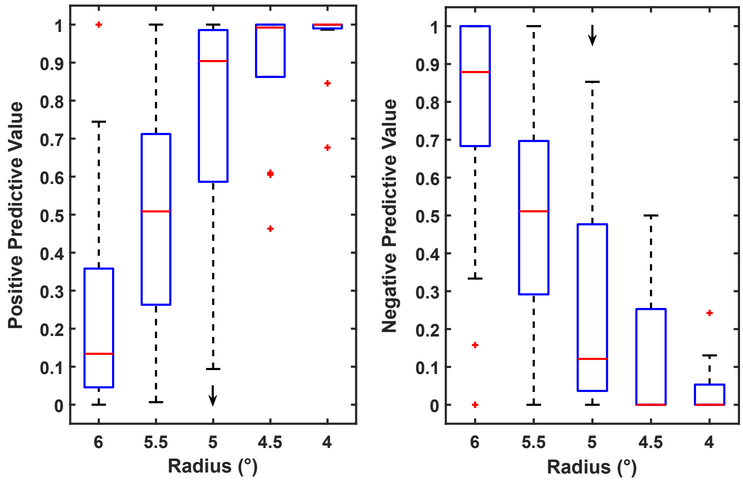

Figure 7. Bar plots of positive and negative predictive values of all subjects across different scotoma radii. The black arrow inside the box plots indicates the point from which a plateau is starting to emerge. The plateau is starting to emerge at 5°.

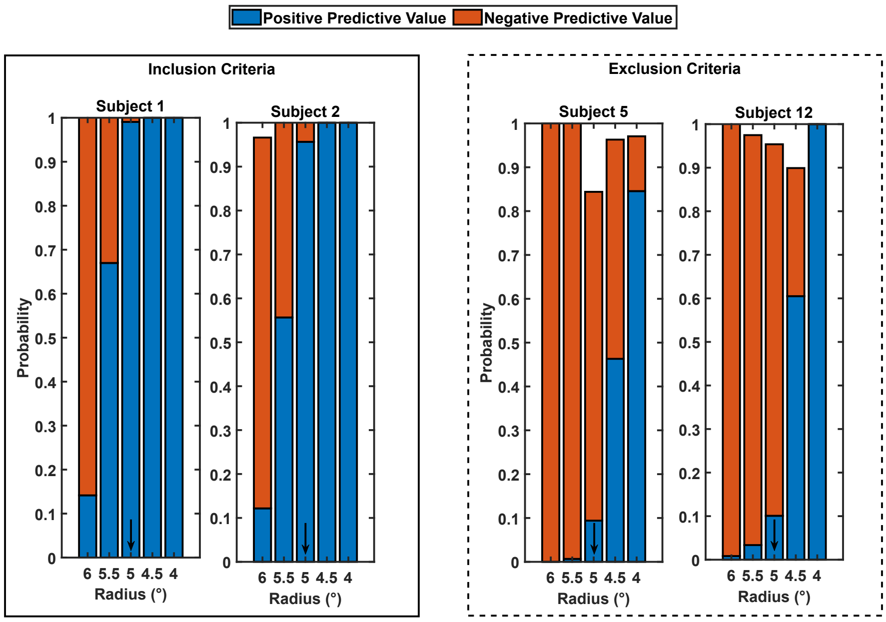

Figure 8. Inclusion and exclusion criteria for different subjects. Positive and negative predictive values were looked at to identify the trend where, irrespective of the scotoma radius, both values reached a plateau (the positive predictive value did not increase and the negative predictive value did not decrease anymore). The black arrow indicates where this plateau was reached for the majority of subjects. In this example, a demonstration is shown for subjects 1 and 2. For those where this trend was not observed, they were excluded. This was the case, for example, for subjects 5 and 12.

4.2. Data Analysis

4.2.1. Gaze-Target Distancing: Condition Type Influence over Eye Position

In the first group, salience was applied after subjects had to adapt for 15 min to an advanced scotoma simulation. The Kruskal–Wallis test found that there is a significant difference between the three conditions (χ^2 (2) = 7.19, p = 0.03) for the distance between gaze and target. The post-hoc Dunn's revealed that the cued scotoma induced significant changes in the gaze-target distance (p = 0.02) compared to the normal condition. No significant difference was found for the scotoma condition compared to the other two conditions (Figure 9, G1).

For the second group, where subjects were presented first with the scotoma simulation together with the cued salience, there was a significant effect between the three conditions as well (χ^2 (2) = 7.20, p = 0.03). The post-hoc Dunn's revealed that compared to the normal condition, the central scotoma changed significantly the gaze-target distance (p = 0.02, Figure 9, G2).

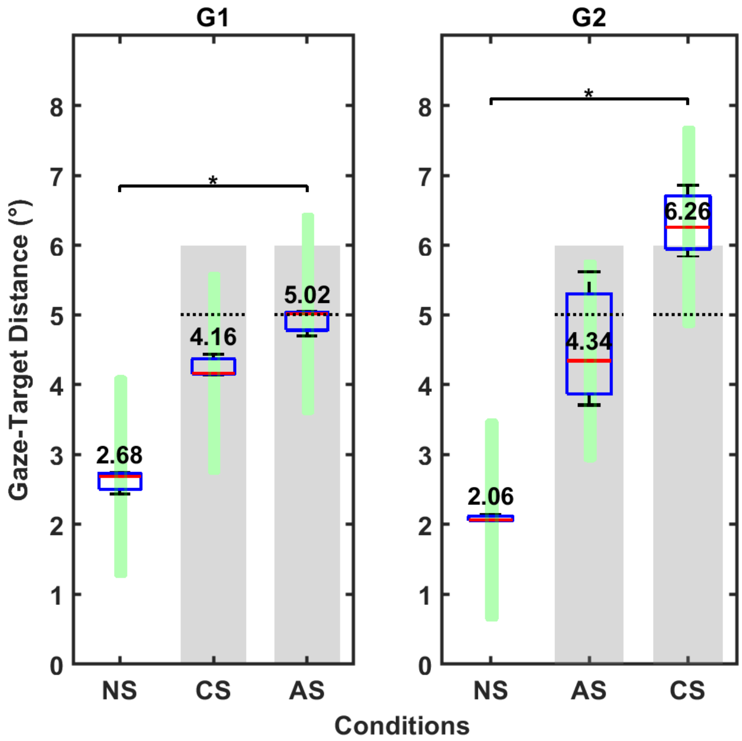

Figure 9. Box plots of the gaze-target distance for the two groups tested. A Kruskal–Wallis test indicated a significant difference between the three conditions for both groups. The post-hoc Dunn's indicated differences in gaze behaviour when comparing the normal condition to the augmented scotoma (AS) for group 1 (**G1**) and the scotoma condition (CS) for group 2 (**G2**). Both p-values were below 0.05 (indicated by the asterisk). The target cover area (in green) is both above the intended scotoma cover area (in gray) and the scotoma area with cover errors (scotoma trailing area, above the dotted lines). The values above the median line (red) of the box plots are the median value of the pre-processed gaze-target distance for all subjects across all three blocks.

4.2.2. Gaze-Target Direction: Training Effect across Blocks

Circular statistics revealed that gaze had a directional tendency above the target in the second group, where subjects started first with the augmented scotoma. For both groups, when the augmentation was present (during the three blocks), the gaze starts showing a preferred direction, with a less homogeneous distribution in the gaze directions, across blocks. For the second group, the gaze shifts upwards, and during the third block, the resultant mean vector doubles its size for the second block, meaning a greater bias in the directionality. An upper direction starts to emerge, with an average angle of 92° ± 2° of gaze with respect to target. This trend is maintained when the augmentation is removed (central scotoma condition), becoming more pronounced across blocks of this new condition, maintaining the gaze-target direction at 89° ± 1° and at 91° ± 1° for the second and third block, respectively (Figure 10). The bias strength also increased across blocks. No such trend was observed for group one.

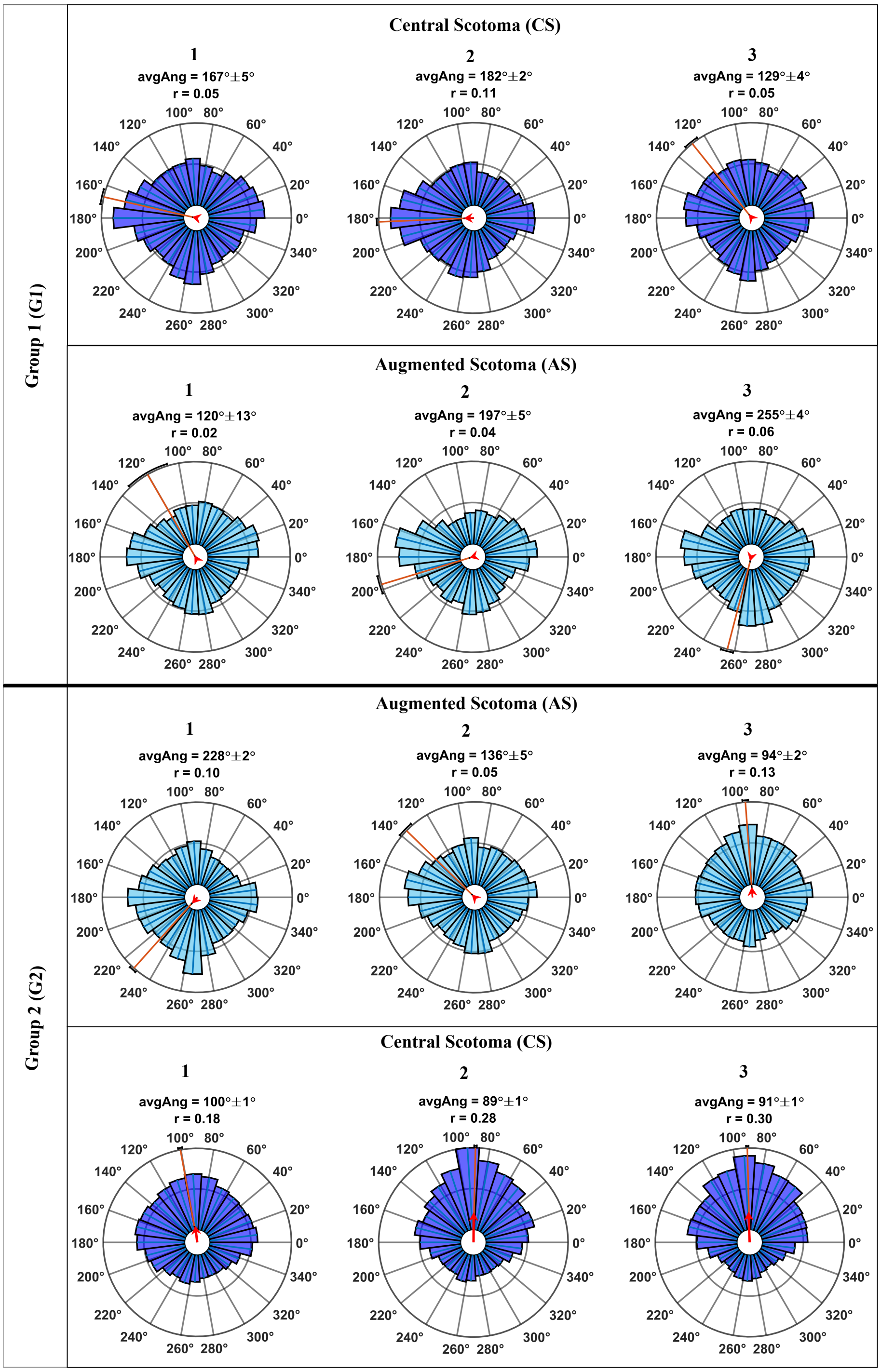

Figure 10. Polar histograms of gaze direction in respect to target for group 1 (**G1**) and group 2 (**G2**) across the blocks (1, 2, and 3). Above each polar histogram, the mean resultant length (r) and the average angle (avgAng) with the corresponding SD of gaze-target direction are represented. The long red line represents the average angle, the black bold semicircle at the end of the red line indicates the SD. The red arrow overlapped on top of the long red line is the mean resultant vector.

5. Discussion

Macular degeneration is a chronic disease that affects central vision; as the macular region deteriorates, it loses the ability to produce clear images of the focused objects. The visual system needs to re-adapt its behaviour to overcome this condition by shifting the gaze away from the object of interest and reallocating it in the periphery (outside the area of visual loss). Quickly developing a new adaptive mechanism is essential for patients suffering from macular degeneration to detect objects of interest, such as incoming cars or bicycles. Most patients with central visual loss take up to three (3) months to adapt, and only one out of three manages to direct their eyes correctly towards the object of interest [9,48].

Other authors have already used VR for rehabilitation and training of this eccentric fixation behaviour using patients [13–15]. However, one of the major challenges for these studies is that patients have different types of scotomas with different shapes and positions, and for this reason, patients require individualized augmentations. The mixed results obtained so far regarding individual augmentation on patients complicate its translation to clinical practice.

The current study investigates gaze behaviour during salience augmentation for standardised central scotoma simulation during tracking of a moving object. Previous studies only looked at changes in normally sighted participants with simulated scotomas without further testing how augmentations might change their behaviours. In our case, a modified version of a VR Pong game was presented to participants where they had to pursue a ball, stopping it from exiting the play area by moving the paddles, and they also had to acknowledge changes in the ball's colour.

The group whose participants initially experienced an advanced scotoma simulation, and only afterwards salience around the scotoma was presented, a significant change in gaze behaviour was observed. In comparison to the normal condition, during the salience augmented scotoma condition, the target was placed above the scotoma edge both when considering 5° as well as 6° radius (Figure 9, G1). Furthermore, the polar histograms show that, even if the mean resultant vector did not increase across blocks, gaze position started to be directed more and more towards the lower hemifield in the augmented condition. On the other hand, no such trend could be observed across blocks for the scotoma simulation condition (Figure 10, G1). The tendency observed for the salient augmented condition is in accordance with previous findings [4] where 57% of macula degeneration patients had better attention preference for the lower hemifield and where most patients with central visual loss direct their gaze [21,48–51].

For the second group, a change in gaze behaviour for both simulated conditions was also achieved. A significant change was observed during the scotoma simulation, with the target being placed further away from the scotoma edge when taking into account 5° and also 6° extension in the coverage range (Figure 9, G2), when compared with the baseline condition (normal). The polar histogram revealed a similar trend for the augmented condition to the one observed by the first group. The gaze's direction started having a specific directionality that was kept throughout the other two blocks. This direction was kept when scotoma simulated participants had to play the game without augmentation, and the value increased even more across the blocks. Additionally, by the end of the third block of the central scotoma condition, the bias strength tripled the value that subjects had when they finished the last block of the augmented condition (Figure 10, G2). The trend that emerged was to position the gaze above the target. However, even if in an uncommon position, the gaze position above the target was still in line with previous studies [25].

Based on the results, we hypothesise that presenting salient cues at the early stages of central visual loss can help build a preferred gaze location. In contrast, prior experiences of wild gazing in the presence of a scotoma may delay this choice. These results also point towards developing a preferred retinal locus (PRL) position for moving targets.

Subjects presented with advanced stages of a central scotoma who have not undergone any training and had not been presented with visual cueing usually develop an unclear and variable preferred gaze positioning. This variability is reduced when augmentation is implemented and the previously adopted positioning changes. However, this behavioural change might take longer due to this previously positioning that the subject already has.

Some potential limitations should be acknowledged, considering the pilot nature of the study. For instance, future studies will need to replicate our findings with greater samples.

Moreover, the present study indicates that different adjustments on the augmentation might be needed depending on the stage of the macular degeneration.

In this study, the HTC Vive Pro Eye, which is known to have an end-to-end latency between 58.1 ms [31] and 80 ms [32] was used. Thanks to the colour recognition subtask and the scotoma radii thresholding, the data were corrected for eye-tracking delays (25 ms). However, this end-to-end latency [31,32,44] is not stable as it can be seen in the results, and therefore may have influenced the scotoma positioning similarly to previous gaze-contingent paradigms [44,45].

After data pre-processing, a 1° error in scotoma coverage for the majority of subjects tested was found. This finding allowed a better understanding of the occluded area and allowed us to correct for it when analysing the results. However, it also decreased the area that was intended to be covered.

An additional limitation of the current system are errors in the IPD estimation. This type of error can lead to a breakdown of binocular fusion, with errors in correctly focusing on a target [52]. However, as calibrations were performed before each condition and manual adjustments of the scotoma were performed on a trial basis, this error can be neglected.

Despite the limitations discussed above, a standardised scotoma simulation of 5° was still achieved for eight subjects. The simulation changed the gaze behaviour compared to normal conditions. In general, our results confirm what was previously published [16–20,24], i.e., standardised scotoma simulations and augmentations help study and train gaze behaviours. Virtual reality gaming proved to be a more entertaining task, resulting in greater participants' engagement and rapid adaptation. The similar results obtained in a VR 2D world to previous literature is the first step for building a model for a future, more complex and immersive reference system. Once a model of PRL development with the key characteristics and behaviours has been established more immersive and realistic virtual scenarios can be used, such as, for example, crossing the street scenarios that involve tracking a moving target in the periphery.

6. Conclusions

Not only salience augmentation to standardised scotoma simulations in normally sighted participants was investigated for the first time in this study, but this study also looked and corrected for the latency effect these paradigms suffer from.

Displaying a gaze-contingent scotoma induces an eccentric gaze behaviour, and a ring augmentation on top of it can modify this behaviour. Early application of this augmentation enhances the gaze positioning and the development of a PRL, similar to what has been reported in the literature. Meanwhile, experiencing a scotoma without any cue can lead to a higher position disparity and may require more extended training periods.

This study needs to be replicated before clinical translation can be applied. Nonetheless, it shows potential for a new type of training for macular degeneration patients.

Author Contributions: Conceptualization, A.S., S.W., M.G.G.; methodology, A.S. and S.W.; formal analysis, A.S. and M.G.G.; investigation, A.S.; data curation, A.S.; writing—original draft preparation, A.S., M.G.G. and S.W.; writing—review and editing, A.S., M.G.G. and S.W.; visualization, A.S. and M.G.G.; supervision, S.W.; project administration, S.W. All authors have read and agreed to the published version of the manuscript.

Funding: The work of the authors is supported by the Institutional Strategy of the University Tübingen (Deutsche Forschungsgemeinschaft, ZUK 63), the German Excellence initiative from the Federal Ministry of Education and Research (BMBF) in the framework of IDeA (project number 16SV8104). This work was done in an industry on campus cooperation between the University of Tübingen and Carl Zeiss Vision International GmbH. The authors recognise intra-mutual funding of the University of Tübingen through the mini graduate school "Integrative Augmented Reality (I-AR)". There was no other additional external funding received for this study.

Institutional Review Board Statement: The Ethics Committee at the Medical Faculty of the Eberhard Karls University and the University Hospital Tübingen approved to carry out the study within its facilities (Institutional Review Board number: 986/2020BO2). The study followed the tenets of the Declaration of Helsinki.

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 are available at the following doi:10.6084/m9.figshare.14810301 (accessed on 23 June 2021).

Acknowledgments: We would like to thank Tamás Borbáth and NMY Mixed-Reality Communication GmbH, Frankfurt am Main for technical assistance. The authors gratefully acknowledge the helpful support of Carl Zeiss Vision International GmbH, Aalen, Katharina Rifai and to all our colleagues for offering their help. We acknowledge support by Open Access Publishing Fund of University of Tübingen.

Conflicts of Interest: Author A.S. and M.G.G. declare no potential conflicts of interest regarding this study. S.W. is a scientist at the University of Tübingen and is employed by Carl Zeiss Vision International GmbH. There is no conflict of interest regarding this study.

References

1. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *Lancet Glob. Health* **2014**, *2*, e106–e116. [CrossRef]
2. Harvey, P.T. Common Eye Diseases of Elderly People: Identifying and Treating Causes of Vision Loss. *Gerontology* **2003**, *49*, 1–11. [CrossRef]
3. Zou, M.; Wang, S.; Chen, A.; Liu, Z.; Young, C.A.; Zhang, Y.; Jin, G.; Zheng, D. Prevalence of myopic macular degeneration worldwide: A systematic review and meta-analysis. *Br. J. Ophthalmol.* **2020**, *104*, 1748–1754. [CrossRef] [PubMed]
4. Altpeter, E.; Mackeben, M.; Trauzettel-Klosinski, S. The importance of sustained attention for patients with maculopathies. *Vis. Res.* **2000**, *40*, 1539–1547. [CrossRef]
5. Curcio, C.A.; Sloan, K.R.; Kalina, R.E.; Hendrickson, A.E. Human photoreceptor topography. *J. Comp. Neurol.* **1990**, *292*, 497–523. [CrossRef] [PubMed]
6. Cummings, R.W.; Whittaker, S.G.; Watson, G.R.; Budd, J.M. Scanning characters and reading with a central scotoma. *Optom. Vis. Sci.* **1985**, *62*, 833–843. [CrossRef]
7. Timberlake, G.T.; Mainster, M.A.; Peli, E.; Augliere, R.A.; Essock, E.A.; Arend, L.E. Reading with a macular scotoma. I. Retinal location of scotoma and fixation area. *Investig. Ophthalmol. Vis. Sci.* **1986**, *27*, 1137–1147.
8. Timberlake, G.T.; Peli, E.; Essock, E.A.; Augliere, R.A. Reading with a macular scotoma. II. Retinal locus for scanning text. *Investig. Ophthalmol. Vis. Sci.* **1987**, *28*, 1268–1274.
9. White, J.M.; Bedell, H.E. The oculomotor reference in humans with bilateral macular disease. *Investig. Ophthalmol. Vis. Sci.* **1990**, *31*, 1149–1161.
10. Schuchard, R.A. Validity and Interpretation of Amsler Grid Reports. *Arch. Ophthalmol.* **1993**, *111*, 776–780. [CrossRef]
11. Hassan, S.E.; Snyder, B.D. Street-crossing decision-making: A comparison between patients with age-related macular degeneration and normal vision. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 6137–6144. [CrossRef] [PubMed]
12. Almutleb, E.S.; Hassan, S.E. The Effect of Simulated Central Field Loss on Street-crossing Decision-Making in Young Adult Pedestrians. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **2020**, *97*, 229–238. [CrossRef]
13. Morales, M.U.; Limoli, P.G.; Limoli, C. Augmented reality eyewear for home-based vision training after biofeedback rehabilitation of eccentric fixation. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 548.
14. Pratt, J.D.; Stevenson, S.B.; Bedell, H.E. Scotoma Visibility and Reading Rate with Bilateral Central Scotomas. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **2017**, *94*, 279. [CrossRef] [PubMed]
15. Deemer, A.D.; Swenor, B.K.; Fujiwara, K.; Deremeik, J.T.; Ross, N.C.; Natale, D.M.; Bradley, C.K.; Werblin, F.S.; Massof, R.W. Preliminary evaluation of two digital image processing strategies for head-mounted magnification for low vision patients. *Transl. Vis. Sci. Technol.* **2019**, *8*, 23. [CrossRef]
16. Bertera, J.H. Oculomotor adaptation with virtual reality scotomas. *Simulation* **1992**, *59*, 37–43. [CrossRef]
17. Bertera, J.H. The Effect of Simulated Scotomas on Visual Search in Normal Subjects. *Investig. Ophthalmol. Vis. Sci.* **1988**, *29*, 470–475.
18. Kwon, M.; Nandy, A.S.; Tjan, B.S. Rapid and persistent adaptability of human oculomotor control in response to simulated central vision loss. *Curr. Biol.* **2013**, *23*, 1663–1669. [CrossRef] [PubMed]
19. Wu, H.; Ashmead, D.H.; Adams, H.; Bodenheimer, B. Using Virtual Reality to Assess the Street Crossing Behavior of Pedestrians With Simulated Macular Degeneration at a Roundabout. *Front. ICT* **2018**, *5*, 27. [CrossRef]

20. Pidcoe, P.E.; Wetze, P.A. Oculomotor tracking strategy in normal subjects with and without simulated scotoma. *Investig. Ophthalmol. Vis. Sci.* **2006**, *47*, 169–178. [CrossRef] [PubMed]
21. Guez, J.E.; Le Gargasson, J.F.; Rigaudiere, F.; O'Regan, J.K. Is there a systematic location for the pseudo-fovea in patients with central scotoma? *Vis. Res.* **1993**, *33*, 1271–1279. [CrossRef]
22. Lewis, J.; Shires, L.; Brown, D.J. Development of a Visual Impairment Simulator Using the Microsoft XNA Framework. In Proceedings of the 9th International Conference on Disability, Virtual Reality and Associated Technologies (ICDVRAT), Laval, France, 10–12 September 2012.
23. Väyrynen, J.; Colley, A.; Häkkilä, J. Head mounted display design tool for simulating visual disabilities. In Proceedings of the ACM International Conference Proceeding Series, Association for Computing Machinery (MUM 2016), Rovaniemi, Finland, 13–15 December 2016; pp. 69–73. [CrossRef]
24. Kwon, M.; Ramachandra, C.; Satgunam, P.; Mel, B.W.; Peli, E.; Tjan, B.S. Contour enhancement benefits older adults with simulated central field loss. *Optom. Vis. Sci.* **2012**, *89*, 1374–1384. [CrossRef] [PubMed]
25. Barraza-Bernal, M.J.; Ivanov, I.V.; Nill, S.; Rifai, K.; Trauzettel-Klosinski, S.; Wahl, S. Can positions in the visual field with high attentional capabilities be good candidates for a new preferred retinal locus? *Vis. Res.* **2017**, *140*, 1–12. [CrossRef] [PubMed]
26. Zhaoping, L. Attention capture by eye of origin singletons even without awareness—A hallmark of a bottom-up saliency map in the primary visual cortex. *J. Vis.* **2008**, *8*, 1. [CrossRef] [PubMed]
27. Warner, C.B.; Juola, J.F.; Koshino, H. Voluntary allocation versus automatic capture of visual attention. *Percept. Psychophys.* **1990**, *48*, 243–251. [CrossRef] [PubMed]
28. Parr, T.; Friston, K.J. Attention or Salience? *Curr. Opin. Psychol.* **2019**, *29*, 1–5. [CrossRef] [PubMed]
29. Lumsden, J.; Edwards, E.A.; Lawrence, N.S.; Coyle, D.; Munafò, M.R. Gamification of Cognitive Assessment and Cognitive Training: A Systematic Review of Applications and Efficacy. *JMIR Serious Games* **2016**, *4*, e11. [CrossRef] [PubMed]
30. Vive Pro Eye, VIVE Pro Eye | The Professional-Grade VR Headset. Available online: https://www.vive.com/eu/product/vive-pro-eye/overview/ (accessed on 11 November 2020).
31. Sipatchin, A.; Wahl, S.; Rifai, K. Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability. *Healthcare* **2021**, *9*, 180. [CrossRef]
32. Stein, N.; Niehorster, D.C.; Watson, T.; Steinicke, F.; Rifai, K.; Wahl, S.; Lappe, M. A Comparison of Eye Tracking Latencies Among Several Commercial Head-Mounted Displays. *i-Perception* **2021**, *12*, 1–16. [CrossRef]
33. Tobii Pro SDK, Tobii Pro SDK v1.7.1.1081. Available online: https://www.tobiipro.com/product-listing/tobii-pro-sdk/ (accessed on 22 June 2020).
34. VIVE Eye Tracking SDK (SRanipal), SRanipal SDK v1.0.3.0. Available online: https://developer.vive.com/resources/vive-sense/sdk/vive-eye-tracking-sdk-sranipal/ (accessed on 23 September 2020).
35. Clay, V.; König, P.; König, S. Eye tracking in virtual reality. *J. Eye Mov. Res.* **2019**, *12*. [CrossRef]
36. Coey, C.A.; Wallot, S.; Richardson, M.J.; van Orden, G. On the structure of measurement noise in eye-tracking. *J. Eye Mov. Res.* **2012**, *5*, 5. [CrossRef]
37. Liu, B.; Zhao, Q.C.; Ren, Y.Y.; Wang, Q.J.; Zheng, X.L. An elaborate algorithm for automatic processing of eye movement data and identifying fixations in eye-tracking experiments. *Adv. Mech. Eng.* **2018**, *10*, 2018. [CrossRef]
38. Loschky, L.C.; Wolverton, G.S. How late can you update gaze-contingent multiresolutional displays without detection. *ACM Trans. Multimed. Comput. Commun. Appl.* **2007**, *3*. [CrossRef]
39. Musall, S. Stdshade, MATLAB Central File Exchange. Available online: https://www.mathworks.com/matlabcentral/fileexchange/29534-stdshade (accessed on 23 June 2021).
40. Nyström, M.; Holmqvist, K. An adaptive algorithm for fixation, saccade, and glissade detection in eyetracking data. *Behav. Res. Methods* **2010**, *42*, 188–204. [CrossRef]
41. Savitzky, A.; Golay, Marcel, J. Smoothing and Differentiation of Data by Simplified Least Squares Procedures. *Anal. Chem.* **1964**, *36*, 1627–1639. [CrossRef]
42. Shanidze, N.; Ghahghaei, S.; Verghese, P. Accuracy of eye position for saccades and smooth pursuit. *J. Vis.* **2016**, *16*. [CrossRef] [PubMed]
43. Whittaker, S.G.; Cummings, R.W.; Swieson, L.R. Saccade control without a fovea. *Vis. Res.* **1991**, *31*, 2209–2218. [CrossRef]
44. Saunders, D.R.; Woods, R.L. Direct measurement of the system latency of gaze-contingent displays. *Behav. Res. Methods* **2014**, *46*, 439–447. [CrossRef] [PubMed]
45. Aguilar, C.; Castet, E. Gaze-contingent simulation of retinopathy: Some potential pitfalls and remedies. *Vis. Res.* **2011**, *51*, 997–1012. [CrossRef] [PubMed]
46. Zittrell, F. CircHist—Circular/Polar/Angle Histogram. Available online: https://de.mathworks.com/matlabcentral/fileexchange/66258-circhist-circular-polar-angle-histogram (accessed on 23 June 2021).
47. Berens, P. CircStat : A MATLAB Toolbox for Circular Statistics . *J. Stat. Softw.* **2009**, *31*, 1–21. [CrossRef]
48. Crossland, M.D.; Culham, L.E.; Kabanarou, S.A.; Rubin, G.S. Preferred retinal locus development in patients with macular disease. *Ophthalmology* **2005**, *112*, 1579–1585. [CrossRef] [PubMed]
49. Sunness, J.S.; Applegate, C.A.; Haselwood, D.; Rubin, G.S. Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology* **1996**, *103*, 1458–1466. [CrossRef]

50. Trauzettel-Klosinski, S.; Tornow, R.P. Fixation behavior and reading ability in macular scotoma. Assessed by Tuebingen manual perimetry and scanning laser ophthalmoscopy. *Neuro-ophthalmology* **1996**, *16*, 241–253. [CrossRef] [PubMed]
51. Fletcher, D.C.; Schuchard, R.A. Preferred retinal loci relationship to macular scotomas in a low-vision population. *Ophthalmology* **1997**, *104*, 632–638. [CrossRef]
52. Hibbard, P.B.; van Dam, L.C.; Scarfe, P. The implications of interpupillary distance variability for virtual reality. In Proceedings of the 2020 International Conference on 3D Immersion (IC3D), Brussels, Belgium, 15 December 2020; pp. 1–7.

6.1.3 Study 3

Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training

International Journal of
Environmental Research and Public Health

MDPI

Article

Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training

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Abstract: The present study investigates the effects of peripheral spatial cues and optically distorting augmentations over eccentric vision mechanisms in normally sighted participants with simulated scotoma. Five different augmentations were tested inside a virtual reality (VR)-gaming environment. Three were monocular spatial cues, and two were binocular optical distortions. Each was divided into three conditions: baseline with normal viewing, augmentation with one of the assistance methods positioned around the scotoma, and one with only the simulated central scotoma. The study found that the gaming scenario induced eccentric viewing for the cued augmentation groups, even when the peripheral assistance was removed, while for the optical distortions group, the eccentric behavior disappeared after the augmentation removal. Additionally, an upwards directionality of gaze relative to target during regular gaming was found. The bias was maintained and implemented during and after the cued augmentations but not after the distorted ones. The results suggest that monocular peripheral cues could be better candidates for implementing eccentric viewing training in patients. At the same time, it showed that optical distortions might disrupt such behavior. Such results are noteworthy since distortions such as zoom are known to help patients with macular degeneration see targets of interest.

Keywords: AMD; eccentric viewing training; virtual reality (VR); gaming; augmentation; salience

Citation: Sipatchin, A.; García García, M.; Sauer, Y.; Wahl, S. Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training. *Int. J. Environ. Res. Public Health* **2022**, *19*, 9571. https://doi.org/10.3390/ijerph19159571

Academic Editors: Toshiaki Tanaka and Atsushi Mitani

Received: 20 July 2022
Accepted: 2 August 2022
Published: 4 August 2022

1. Introduction

The macula is a small region of the retina (~5.5 mm in diameter) responsible for depicting 4% of our visual field [1,2], an even smaller part (~2 mm), the fovea, accounts for about 1% of our visual field [2]. However, the fovea region is the only part of the visual field that allows for the highest visual acuity. It is through it that most of the usual information for daily activities such as reading, driving, and face recognition is acquired [3]. Objects appearing outside this area are also perceived, but there is a constant re-alignment of the eye with the objects of visual focus to resolve them in detail. It is referred to as the fovea-based oculomotor routine [4].

Damage to the macula due to local or entire degeneration leads to a form of central visual loss referred to as scotoma. This visual loss ultimately disrupts the foveal mechanism [2]. Macula's alteration has a highly detrimental impact on the patients' lives, considering its importance for daily life. The prevalence of this condition is steadily increasing [5], with an estimation that by 2040, it will reach pandemic proportions [6], with 288 million people afflicted [7].

Therefore, considering the burden of this condition, it is a pressing matter for the health community to find ways to help patients continue with their daily activities. In general, patients suffering from macular degeneration macular degeneration (MD) can continue being functional individuals as their peripheral visual area remains unaffected by the disease. This area can be used to look at objects. Both patients and even participants with simulated central scotoma [8–11], use an adaptive mechanism where both groups gaze away from the target of interest. They use their peripheral vision to examine the targets by placing the scotoma away from the region of interest. This behavior is called eccentric viewing. Furthermore, the peripheral visual area constantly aligning with the target is referred to as the preferred retinal locus (PRL) [12]. The PRL becomes the new oculomotor reference in the visual field.

When developing the PRL, it is crucial to carefully choose a part of the intact peripheral vision that can maximize visual performance by being the closest to the damaged area and having the highest acuity. The closer the target is to the scotoma, the higher the sharpness and the better the chances of detecting that object's properties. Peripheral vision is known to have a minor visual quality and less of a one-on-one representation of the outside world the further away it is placed from the macula [13]. A correct adaptation to this mechanism allows patients to still detect the needed features of an object during daily activities. Unfortunately, not everyone adapts to it, and some may have an inefficient PRL because it is not far enough or too far away from the affected central vision [2]. Therefore, it is essential to help patients to develop an appropriate PRL by presenting effective assistive training techniques.

Thanks to recent technological advances, extended reality (XR) technology, which includes virtual and augmented reality, has seen a rapid increase in its use as a rehabilitation technique to assist low vision patients [14–19].

Research has shown that peripheral stimuli can influence salience, or where the current focus of visual attention is allocated while viewing eccentrically [20–23]. Assistive tools for patients with macular degeneration have been developed as spatial cueing, meaning attention was drawn to a specific location, and as optical distortions in the periphery in combination with virtual reality [24–27].

Investigating the impact of gaze-contingent peripheral stimuli is essential, considering that information presented in the periphery can affect eccentric viewing. This study aims to test the gazing behavior under the presentation of gaze-contingent peripheral stimuli in the presence of a simulated scotoma. Few studies have investigated how eccentric viewing behavior is affected by different types of stimuli presented in the periphery when a scotoma is present. The current study used different peripheral stimuli in virtual reality to investigate their effects on eccentric viewing training in participants with a gaze-contingent simulated central scotoma. A gaming environment was used to stimulate target tracking.

Five stimuli were tested: three without and two containing distortions. Three were monocular cues applied to the dominant eye as an eye-of-origin singleton stimulus. An eye-of-origin singleton stimulus is known to induce saliency, a type of attention, where the eyes automatically be drawn to [28]. The monocular augmentations were a concentric ring, known to induce salience effectively [24] and an annular area either blurred in or out around the scotoma. Several studies have evidenced that blur applied as a singleton efficiently captures attention [29–31]. The other two augmentations were zoom and fish-eye distortions presented binocularly. Both have been investigated previously as assisting viewing aids [32,33].

In this study, a two-dimensional virtual reality gaming environment was used. Training with virtual reality gamification applications has been substituting more traditional rehabilitation techniques thanks to the engagement and learning effect these technologies offer to patients. Recent surveys have shown that rehabilitation with gamification techniques stimulates reward-related systems in the brain known to facilitate learning [34]. Additionally, it has been shown that gaming in combination with VR offered the advantage of reducing the complexity of a task [35]. Furthermore, combining VR, augmentation, and gamification expanded use frequency [36]. All these factors are necessary features for applications developed for training and extensive use, such as training for eccentric viewing. In the present context, gamification in extended reality was presented to train eccentric viewing.

2. Materials and Methods

2.1. Participants

Thirty participants participated in the study (with a gender balance ratio of 15 females and 15 males, mean age 27, standard deviation (SD) $\pm$ 4 years, with only one subject wearing eye correction: contact lenses). Seventeen participants had a previous experience with a virtual reality headset.

2.2. Set-Up

For the design of the virtual experiment, the rendering engine Unity 2019.3.0, together with the programming language C#, was used. The experiment ran on a desktop PC with Windows 10 Home, having a 64-bit operating system, an Intel Core i5-7500 processor with 3.41 GHz, and random-access memory (RAM) of 16 GB. A NVIDIA GeForce RTX 3080 Ti was used as a graphics card.

The HTC Vive Pro Eye [37] headset was used to present the virtual environment. The headset has an integrated eye tracker with a sampling frequency of 120 Hz and a known latency between 58 ms and 80 ms [38,39]. The HMD has two AMOLED screens, each with a resolution of 1.440 $\times$ 1.600 pixels, meaning a pixel density of 615 pixels per inch (PPI) for each eye, a field of view of 94° $\times$ 91° (horizontally per vertically) [40], a luminance of 116.1 $\mathrm{cd\,m^{-2}}$ [40] and a refresh rate of 90 Hz. The Tobii Pro SDK v1.7.1.1081 [41] was used to save the eye-tracking data. The Vive SRanipal SDK v1.0.3.0 [42] was used for the gaze-contingent scotoma simulation. An Xbox Microsoft wireless controller was used for the subject's input.

2.3. Calibration Procedure and Manual Drift Correction

An inter-pupillary distance (IPD) adjustment and a five point calibration of the eye tracking (SRAnipal), were performed for all participants before the measuring phase started [24]. After calibration and IPD adjustment, subjects could begin with each condition type. At the beginning of each block of each condition type, a manual drift correction was carried out [24]. Each block started after the experimenter checked the accuracy of the manual drift correction.

2.4. Experimental Procedure

Before the experiment started all participants had a first initial trial out session of the VR gaming environment until they felt confident with it. Afterwards participants were asked to play the 2D VR Pong game [24] consisting of a 3° ball moving at an average velocity of 21.74 $^{\circ}\,\mathrm{s^{-1}}$ (SD: $\pm$0.63 $^{\circ}\,\mathrm{s^{-1}}$) and two paddles at the left and right edge of the play area. Whenever the ball hit one of the paddles, it bounced off with the same speed again and moved on straight lines in different (random) directions. The subjects could control the two paddles to maintain the ball inside the play area. Participants had to restart the game if the ball exited the play area.

Additionally, to motivate patients to track the target eccentrically, they were asked to press a button whenever the ball's color changed. The ball changed color at random intervals, and correct identification of color change awarded them points. A time of 2 s was provided to indicate the color change. Moreover, a concentric rectangle, head-fixed, measuring $\pm$14.25° horizontally and vertically, was used to motivate the subjects to move their heads.

2.4.1. Conditions

To each participant, three conditions were presented in the following order (Figure 1): baseline (BS), augmented scotoma (AS), and central scotoma (CS). During the first condition, no simulation nor augmentation was applied to play the game. In the augmentation condition, a monocular or binocular peripheral assistance was presented around a binocular scotoma simulation of 12°. Both augmentation and binocular scotoma were gaze-contingent. For the third condition, only the gaze-contingent binocular scotoma simulation was used to play the game.

Each condition was (15) minutes long and divided into three gaming blocks of 5 min. After each gaming block, there was a break during which subjects had to perform the manual drift correction; after the break, the following block started.

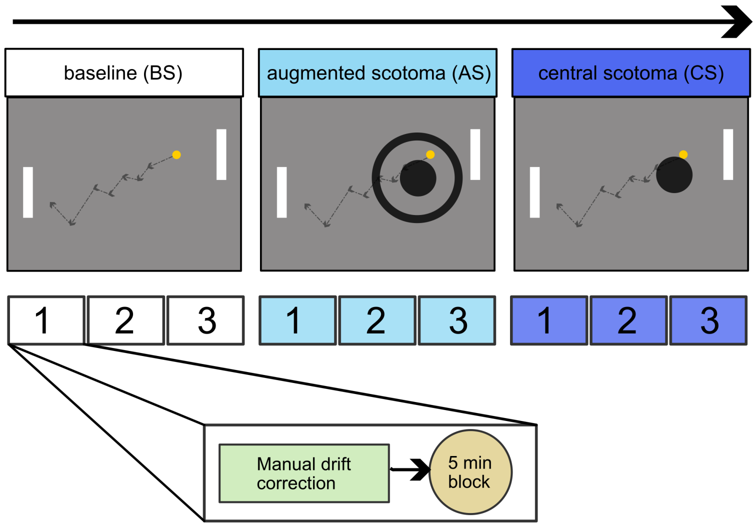

Figure 1. Diagram flow of the study. First, the participants played a baseline (BS) game condition using their normal vision. During gaming, the ball followed a random trajectory (dotted line). Afterward, the augmented scotoma (AS) was presented, showing either a monocular cue or binocular distortion augmentation around the scotoma. The current figure showcases the monocular ring augmentation. The last condition was the central scotoma simulation (CS). Each condition has three repetitions (1, 2, and 3) containing the manual drift correction and a 5 min block.

2.4.2. Groups

Participants were divided into five groups depending on the type of assistance presented during the augmented scotoma condition. The five types of augmentations were three cued and monocular and two binocular and with optical distortions. The monocular ones were applied to the dominant eye and concentrically around the scotoma: one was a 2° broad black ring, 7.5° away from the simulated scotoma's edges and the other two were an area of 7.5° diameter, either blurred in or out (Figure 2a: ring, blur-in, blur-out). The blur had a kernel size of 20 pixels and a sigma value of 5. These values were found to induce changes in gaze directionality when used peripherally [43,44]. The binocular optical distortion augmentations displayed were zoom and fish-eye (Figure 2b: zoom and fish-eye). The magnification applied was 2.11 both for height and width, considered to be a good value and not above a multiple of four as indicated by Goldstein et al. [45,46]. The distortion applied had a power of 2.11 on the height and 1.66 on the width following [33].

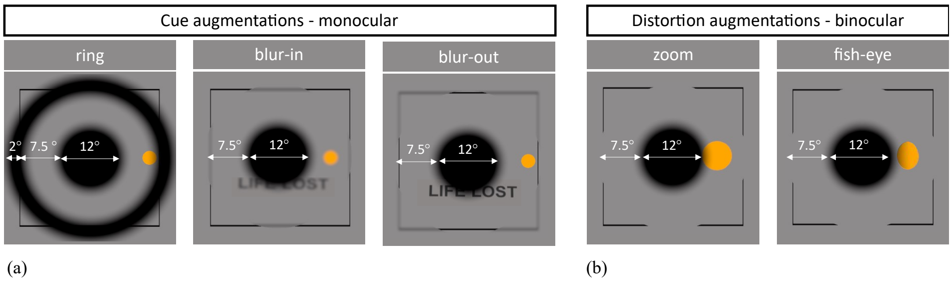

Figure 2. Screenshots and specifications of the monocular (**a**) and binocular augmentations (**b**) as they looked in the VR environment and the different impacts they had on the target. The big black circle is the gaze-contingent scotoma simulation, and the yellow one is the target: the ball. A text is added to show better the bluring effect for the blur-in and blur-out augmentations.

3. Data Processing

3.1. Color Change Task: Decoding Where the Scotoma Was Displayed

Gaze-contingent paradigms are lag sensitive. When presenting certain features based on the position recorded by an eye tracker, there is always a delay between the registered location and the displaying of the wanted feature [47]. For the current study, having such a delay meant that the subject could have seen parts or the entire target outside the designed radius of the simulated scotoma. Such latency fault was causing an error in the correct vs. incorrect recognition task ratio.

Therefore, the subjects' eye position during the color change throughout the scotoma condition was considered. First, Bayes's theorem was used, and the positive and negative predictive values were calculated at different gaze-target distances in the same manner as Sipatchin et al. [24]. A latency error in rendering the central scotoma would be indicated by a sudden increase in the positive predictive value and a decrease in the negative predictive value. The gaze-target distances where this would be observed represented the point from where the scotoma edge was. Additionally, as a further control, the fixation frequency during the time given to respond to the color change was considered. For this analysis, the non-smoothed gaze-target distance data was used. A fixation was defined as the gaze-target distance that was within 1° and kept long enough to process visual information (between 100 ms to 250 ms) [48,49]. The fixation frequency was calculated as the total number of fixations made per second during the time interval subjects could indicate the correct color change. Literature has shown that simple features require one or two eye fixations to be recognized [50–52]. Fixations above two indicate further extraction of visual detail [53,54]. Therefore, a fixation frequency between one and two indicated efficient and rapid information processing. At the same time, further increases above two indicated inefficient processing. Goldberg and Kotval [55] have indeed shown that an increase in fixation frequency translated into a more inefficient search to find the relevant and needed information. During the color change task, different scotoma radii from 7° to 3°, in steps of 1° were tested to identify where would have been detected a fixation rate > 2. If the fixation rate was >2, the eyes needed more fixations because the target could not be perceived immediately, indicating an obstacle and, therefore, the presence of the scotoma.

These two tests additionally allowed for the identification of outliers. Each subject that was not in line with the majority trend and did not show a sudden increase and decrease in the positive and negative predictive value, respectively, and/or a fixation frequency above two was considered an outlier.

3.2. Data Analysis

The eye-tracking data first underwent a pre-processing phase. A noise cancellation filter [56,57], a latency error correction, and saccades smoothing [58] were applied as described in Sipatchin et al. [24].

3.2.1. Gaze-Target Distancing: Influence of Condition Type over the Gaze Distance

Following the pre-processing step, the normality of the data was then tested with the Kolmogorov–Smirnov one-sample test ($p < 0.001$). The data was not normally distributed; therefore, the non-parametric Kruskal–Wallis test was used to test the effect of the condition type (independent variable) over the median distance between the gaze and the center of the target (dependent variable). These results were further processed using a post hoc FWER test (Dunn–Šidák).

3.2.2. Gaze Position in Relation to Target: Directional Change across Conditions

Circular statistics [59] were used to identify changes in gaze position relative to target across the three different conditions between the five groups. First, the data were checked for circular uniformity using the Rayleigh test. The data was a non-uniform distribution; therefore, the inverse Power Batschelet distribution was used to analyze the gaze position relative to the target. More specifically, the modified version of the inverse Power Batschelet with application to eye data was used [60,61]. Four different functions were used to fit the data which represented the four peaks (close to right, left, up and down) [60]. All exemplified directions were where the gaze could have been directed with respect to the target. The gaze direction in relation to the target was plotted on a polar histogram, and the data were fitted using a mixture of the four circular distributions, one for each direction. A non-linear fit square model was used to fit the data, and an R-squared and root mean square error (RMSE) were calculated to identify the model's goodness of fit. For each of the distributions, the fitting function $f(\theta|\mu,\kappa,\lambda)$ given in Equation (1) was used.

$$\begin{aligned} f(\theta|\mu,\kappa,\lambda) &= \frac{1}{\mathcal{N}} t(\theta|\mu,\kappa,\lambda) \\ t(\theta|\mu,\kappa,\lambda) &= \exp\left[\kappa \cos\left(\text{sign}(\theta-\mu)\pi\left(\frac{|\theta-\mu|}{\pi}\right)^{\frac{1-0.405228\lambda}{1+0.405228\lambda}}\right)\right] \end{aligned} \tag{1}$$

where $\mathcal{N} = \int_{-\pi}^{\pi} t(\theta|\mu,\kappa,\lambda)\mathrm{d}\theta$ is a normalisation constant and κ and μ representing, respectively, the concentration and the peak position parameter; λ as the peakedness adapted from the Jones–Pewsey distribution [62] and the Inverse Batschelet distribution [63]. All parameters were normalized across the four distributions.

Each function was summed up with different weights ω constrained to the sum of one since the mixture model of the four directions lies on a simplex. The ω is used as an indication of a directionality bias, and it quantifies the relative importance of all parameters [60,61].

4. Results

4.1. Color Change Task: Decoding Where the Scotoma Was Displayed

As previously [24], for the cued assistive methods (red, Figure 3), the positive and the negative predictive values reached a plateau and evidenced a sudden increase and decrease, respectively, at 5° distance between gaze and target. Additionally, it was observed that a fixation frequency bigger than two for values between 5° to 3°.

During the optical distortions, the positive and negative predictive values did not reach a plateau at 5° distance between gaze and target, but it was sill observed a high number of fixations (Fixation Frequency(s), blue, Figure 3) whenever the gaze-target distance was between 5° to 3°.

Positive and negative predictive values and fixation frequencies showed that some subjects performed the task correctly across all conditions. In contrast, others did not, as evidenced by the violin plots skewed at the edges. For the monocular augmentations, the probability of positive and negative predictive values and the fixation frequency were used to detect divergence from the trends across subjects. At the same time, only the fixation frequencies indicated subjective deviation for the distortions. A total of 6 subjects were excluded, one per each augmentation type; therefore, for the analysis, 25 participants were included, five from each group.

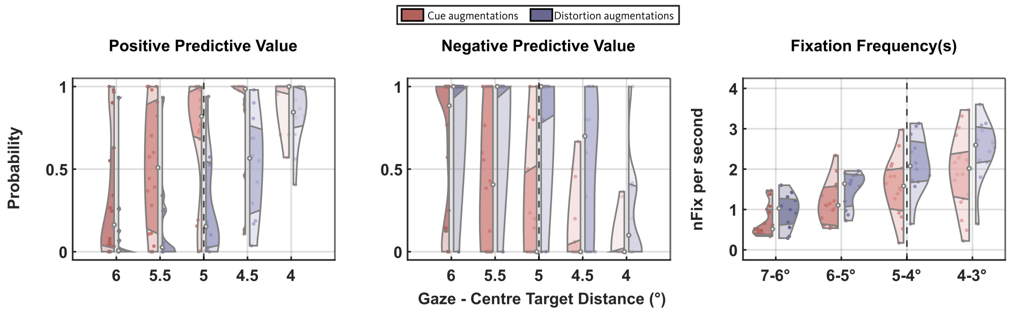

Figure 3. Violin scatter plots for positive and negative predictive values and fixation frequency of all subjects across different distances between gaze and target separated for the cued (red) and optical distortions (blue) augmentations. The black dotted line placed at the value 5° inside the plots indicates the point from which a plateau is starting to emerge for the positive and negative predictive values when considering the monocular augmentations. Furthermore, for the fixation frequency shows where the fixation frequency remains within the two fixations per second range. The plateau and the increase in fixation frequency are starting to emerge below 5°.

4.2. Data Analysis

4.2.1. Gaze-Target Distancing: Influence of Condition Type over the Gaze Distance

Both monocular and binocular augmentations induced a significant change in gaze-target distance between conditions (ring: χ^2 (2) = 9.50, p = 0.01; blur-in: χ^2 (2) = 8.54, p = 0.01; blur-out: χ^2 (2) = 9.78, p = 0.01; zoom: χ^2 (2) = 10.50, p = 0.01; fish-eye: χ^2 (2) = 7.74, p = 0.02). The post hoc Dunn test evidenced that the scotoma condition was significantly different than the normal condition following all augmentations: the ring (p = 0.01), blur-out (p = 0.01), blur-in (p = 0.01), zoom, (p = 0.01), and the fish-eye (p = 0.02) augmentation; and only the ring augmentation induced a significant change following the normal condition (ring, p = 0.04). The monocular augmentations were observed to induce an eccentric viewing behavior that was preserved during the scotoma condition, this was not the case for the binocular ones (Figure 4).

4.2.2. Gaze Position in Relation to Target: Directional Change across Conditions

There was adequate goodness of fit for all augmentations and across all conditions (R-squared $\geq$ 0.94, RMSE = 0.01). The four parameters evidenced changes in the circular distributions across the three different conditions.

For the ring augmentation (ring, Figure 5), during the baseline condition, the right and left directions had the highest concentration around the μ. During the monocular cue condition, the downward distribution was the highest one around its μ value with right and left decreasing. All through scotoma, the right and the down concentration parameters were equally the highest. The peakedness parameter remained mostly unaltered between the baseline, augmentation and scotoma conditions. The ω parameter evidenced a bias for the up direction during all three conditions.

During the baseline condition of the blur-in augmentation group (blur-in, Figure 5), the down direction had the highest concentration around the μ value. Once the blur-in assistance around the scotoma was introduced, the concentration value was the highest for the right directionality, while all the others decreased close to null values. After the assistance removal the concentration of the right distribution decreased. The peakedness parameter was the highest for the right and left direction during baseline, up and left during augmentation, and right and left again throughout scotoma. The bias parameter evidenced an upwards bias during baseline, augmentation and scotoma conditions.

For the blur-out augmentation group (blur-out, Figure 5), during baseline, the concentration value was the highest for the right and down direction distributions and right during augmentation and scotoma, with a slight decrease during the last condition. The λ parameter was the highest for the left direction during baseline, right and left during augmentation and only right during scotoma. An upwards bias during the baseline condition is observed, slightly decreasing with the augmentation and during the scotoma.

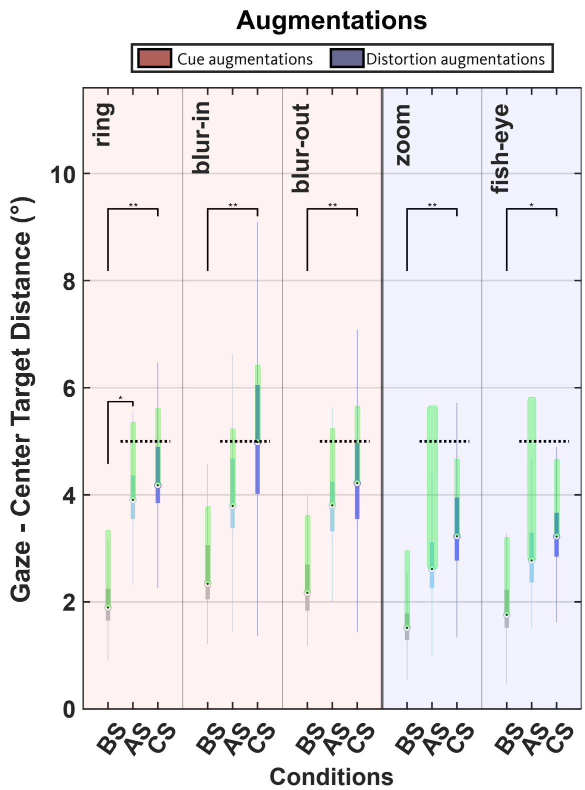

Figure 4. Box plots of the distance between gaze and target center for all the augmentations and all the three conditions (baseline (BS), augmented scotoma (AS), and central scotoma (CS)) tested. The asterisks above the box plots indicate the post hoc Dunn p-values, one for p-values ≤ 0.05 and two for p-values ≤ 0.01. The green rectangles represent the target radius, and the dotted lines are where the edge of the scotoma was considering the latency error. The target is distorted for the zoom and fish-eye during the augmentation condition. Zoom induced a 2.11 multiplication factor on both height and width, while the fish-eye generated a magnification of 2.11 on height and 1.66 on width.

As to the distorted augmentations, for the zoom group (zoom, Figure 5), during the baseline condition, the right (μ: 5.02°) and the left (μ: 190.02°) direction distributions had the highest concentration. During the peripheral optical distortions, the left distribution concentration increased and became the highest, and during scotoma, right, up, and left distributions leveled up, while the down remained the lowest. All through baseline, the peakedness parameter was equally distributed around right, up, and down direction distributions. The up and down directions were the highest during augmentation, while all through scotoma, the down distribution has higher than right, up, and left. During baseline, an upwards bias was observed again. With the optical distortion, the tendency dropped and remained low during the scotoma condition. At the same time, the downwards direction bias increased both when the distortion was present around the scotoma and after its removal.

For the second distorted peripheral augmentation used, fish-eye (fish-eye, Figure 5), the right and left distributions had the highest concentration and low peakedness values during baseline. Throughout the augmentation condition, the concentration decreased, and the peakedness parameter increased for both. During the scotoma condition, the left distribution had the highest concentration for the left and the highest peakedness for the upwards one. Furthermore, for this group, an initial upwards bias was observed, and the bias decreased when the augmentation was introduced. In contrast, the downwards preference increased. During the scotoma condition, the upwards and downwards biases further reduced and intensified, respectively.

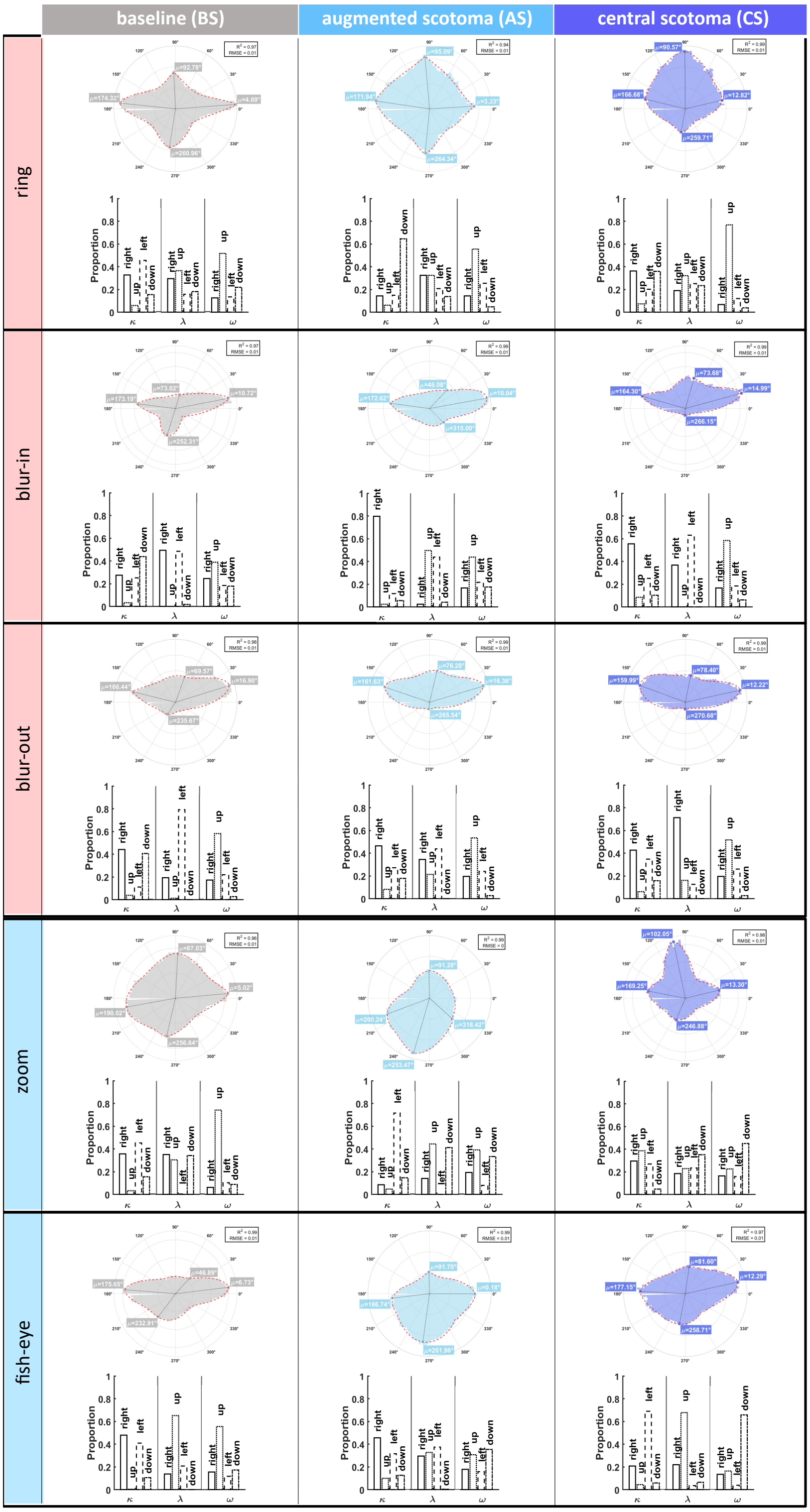

Figure 5. Polar histograms of gaze direction in respect to the target for all the five augmentations (cued monocular, red, and optical distortions binocular, blue) were tested across the three conditions (baseline, augmented scotoma, and central scotoma). The red dotted line represents the outcome of the fitted non-linear square model, with the R-squared and RMSE values plotted above each polar histogram. Additionally, the μ values for the right, up, left, and down directions are plotted. Beneath all polar histograms, an additional histogram representing the κ, λ, and ω parameters for each directionality is also presented.

5. Discussion

Central vision is the most critical part of a person's vision; thanks to it, it is possible to perceive an object of interest with very fine detail. Therefore, a visual disease such as scotoma that leads to central vision loss is very debilitating due to the impossibility of using such a central view. Those affected actively suppress their eyes from looking straight ahead and instead form a PRL in the intact peripheral vision.

Correctly allocating the PRL in the peripheral visual field is connected to maintaining a better or worse ability to see. Attention has been shown to play a crucial role in the influence of the PRL allocation [20,23,64,65].

The present study investigated the effects of a specific type of attention, salience [66,67], and of optically distorted augmentations over eccentric viewing. A VR pong game induced smooth pursuit during a target tracking task in participants with simulated scotoma. Five types of assistive peripheral stimuli, known to generate salience, were presented around the scotoma. Three were peripheral cues presented monocularly, and two induced peripheral distortions.

The study revealed that eccentric viewing was successful during the augmentation for all the peripheral monocular enhancements (red cued augmentations, the target was visible outside the scotoma area, Figure 4). Eccentric viewing was maintained for the scotoma condition after the cues were removed. Additionally, the baseline condition was significantly different from the scotoma condition after removing the augmentation. The fitting of the distribution of gaze relative to target revealed that monocular cued augmentations placed in the periphery could modify the distribution concentration and peakedness values around the four μ direction values. Changes in the concentration and peakedness meant that the distributions were less spread out whenever the κ values were high and less flattened around the μ value with high peakedness values. For the ring group, the concentration values of the right and left directions had more spread-out distributions when the assistance around the scotoma was used, while the down distribution less so. For the blur-in, the concentration value of the right direction was the least outspread one. The λ was more peaked around the up and left directions. As for the blur-out group, the augmentation condition spread out the down distribution. However, no trend emerged across groups, nor were any of the changes induced during the augmentations preserved during the scotoma condition.

Eccentric viewing was carried out successfully also during the distortions but not after removing them (blue distortion augmentation groups, target was not all the time visible outside the scotoma area, Figure 4). Same as for the cued monocular groups, the eyes behavior differed significantly between the baseline and the scotoma condition. However, eccentric viewing was not the strategy used. An efficient fixation frequency was observed during the scotoma condition (blue, Figure 3), indicating that the subjects could acknowledge the target by only directing their eyes at regular intervals to check for changes in the target. The distorted augmentations also induced changes in the distribution values of gaze in relation to target. Throughout the zoom augmentation condition the left distribution was less outspread while the up and down distributions were the most peaked ones. During the fish-eye augmentation the left distribution became more outspread and the peakedness increased. However, as observed for the previous cued monocular augmentations groups, the modifications induced did not have a tendency nor were further implemented during the scotoma condition.

It can be concluded that there is no trend in the distribution changes induced by either the cued or distortion augmentations used.

The weight parameter, an general indicator of a directional bias, evidenced an interesting behavior instead. Without simulated scotoma there was an upwards bias, and each peripheral assistant used further implemented the tendency or decayed it entirely.

The monocular augmentations preserved the bias during presentation and after being removed. The direction tendency further increased for two of the three monocular cues after the removal: ring, with the highest raise in such bias, and blur-in. The blur-out augmentation only preserved the tendency after the cue was removed. Nonetheless, the upwards bias remained the highest directional bias during scotoma simulation for all the groups where the monocular augmentations were used. Additionally, whenever a down bias was present, an increase in the upwards bias corresponded to a decrease in the downwards one during the ring and blur-in augmentation and scotoma conditions.

Distorted augmentations implemented the opposite: the upwards bias observed during the baseline condition decreased during zoom and the fish-eye. The fish-eye had a more substantial effect in reducing such tendency. Furthermore, to a decrease in the upwards direction corresponded an increase in the downwards one during the scotoma condition.

An upwards bias has been previously shown to be present during smooth pursuit [68]. The upwards directional bias implemented with peripheral monocular cues is consistent with previous literature. Attention stimulation mainly focuses the PRL on the lower part of the visual hemifield, where the highest attentional capability is allocated [23,65]. Additionally, an eccentric viewing behavior was preserved once monocular cues were removed. An eccentric viewing was not observed after the presentation of binocular distortions presentation. Additionally, the PRL was allocated in the higher part of the visual hemifield, which is known to have reduced attention capabilities compared to the lower one [65].

Given the current results, there is evidence that monocular cues could be better augmentations than binocular distortions. Eccentric viewing and directional bias are maintained after their removal, suggesting that subjects continue implementing the training they developed while having the scotoma and assistance. The established directional bias was the most efficient since it is where the highest attentional capability is. Once removed, one monocular cue, the ring, increased the directional bias even more so than the other monocular cues. It can be concluded that monocular ring augmentation might employ better attentional resources for eccentric viewing training.

Given the pilot nature of the study, additional studies with more participants are needed to confirm the advanced hypothesis. A further limitation to the study was the HTC Vive Pro Eye. As it was previously observed [38], an error of 1° limited the rendering of a 6° scotoma radii simulation when using the HTC Vive Pro Eye. The color change task provided the information that there was a 1° error in the scotoma radii rendering. As previously [38], a sudden increase in the positive and a decrease in the negative predictive values were observed for the cued augmentation groups when the eyes were $\leq$5° away from the target. Additionally, fixation frequency increased above 2, when the eyes were $\leq$5° away from the target, indicative of inefficient visual processing. For all the peripheral augmentations, only when the eyes were $\geq$5° away from the target did fixation frequency decrease, suggesting the target was visible only when the eyes were 5° away from the target and not 6°. Nonetheless, the identified error remained consistent across the present and previous study. Furthermore, as previously conducted, the error was considered and corrected for.

In general, our study showed that gaming can be used for stimulating eccentric viewing and that monocular cues presented in the periphery can implement the best-suited attention resources. The results obtained for the ring augmentation confirm previous findings [24] where an upwards gaze direction strategy was also observed during and after removing a monocular peripheral concentric ring around a simulated scotoma. These results are encouraging for future patient applications where the VR pong game could be extended with multiple sessions of the augmentation condition applied to train eccentric viewing. Previous research showed that training periods could be extended up to 2.6 h since the duration of the training can play an important role in developing a PRL [69]. The effects seem to last up to 25 months [70]. Additionally, the longer the training period, the more prolonged the effect induced by the exercise will be. Nonetheless, 1 h long training sessions for a one-week-long period gave satisfactory results [71], suggesting a good starting point for future studies.

On the other hand, caution should be used for those studies implementing augmentations with peripheral distortions [22,72–77]. This is the first study to investigate the effects these assistive aids have on eccentric viewing behavior and results showed how peripheral distortions could negatively alter eccentric viewing and attentional resource allocation.

6. Conclusions

For the first time, the eccentric gaze behavior of normally sighted participants presented with monocular cues and binocular distorted peripheral augmentations around a simulated scotoma was investigated.

The study evidenced that monocular cues maintain eccentric viewing and better allocate attentional resources even after removal. The results confirmed previous results, encouraging the study's application to patients to train eccentric viewing. Additional training sessions will need to be utilized for future patient applicability to induce a more long-term bias. The gaming and mixed reality nature of the training offers a perfect combination of engagement, learning facilitation, and frequent use motivation to suggest a successful usage of the system as a future eccentric viewing training tool. Binocular distortions in the periphery, on the contrary, canceled out both attentional resources and eccentric viewing. The negative impact on eccentric viewing behavior is to be considered for studies currently or from this point forward that will want to apply distortions as visual aids to patients.

Author Contributions: Conceptualization, A.S., S.W. and M.G.G.; methodology, A.S. and S.W.; formal analysis, A.S., Y.S. and M.G.G.; investigation, A.S.; data curation, A.S.; writing—original draft preparation, A.S., M.G.G., Y.S. and S.W.; writing—review and editing, A.S., M.G.G., Y.S. and S.W.; visualization, A.S., M.G.G. and Y.S.; supervision, S.W.; project administration, S.W. All authors have read and agreed to the published version of the manuscript.

Funding: The work of the authors is supported by the Federal Ministry of Education and Research (BMBF) in the framework of IDeA (project number 16SV8104), and the Institutional Strategy of the University Tübingen (Deutsche Forschungsgemeinschaft, ZUK 63) in the context of the German Excellence initiative as an industry on campus cooperation between the University of Tübingen and Carl Zeiss Vision International GmbH. The authors recognize also intramural funding of the University of Tübingen through the mini graduate school 'Integrative Augmented Reality (I-AR)', and funding from the European Union's Horizon 2020 research and innovation program (under Marie Skłodowska-Curie Grant agreement No. 734227–Platypus). There was no other additional external funding received for this study.

Institutional Review Board Statement: The Ethics Committee at the Medical Faculty of the Eberhard Karls University and the University Hospital Tübingen approved conducting the study within its facilities (Institutional Review Board number: 986/2020BO2). The study followed the tenets of the Declaration of Helsinki and later amendments.

Informed Consent Statement: Written informed consent was obtained to take part in the study from all participants after the content and possible consequences of the study had been explained. All data were pseudo-anonymized and stored in full compliance with the principles of the Data Protection Act GDPR 2016/679 of the European Union.

Data Availability Statement: Data are available in figshare at the following doi: https://doi.org/10.6084/m9.figshare.20338911, accessed on 19 July 2022.

Acknowledgments: The authors gratefully acknowledge the helpful support of all our colleagues. We acknowledge support by Open Access Publishing Fund of University of Tübingen.

Conflicts of Interest: Authors A.S., M.G.G. and Y.S. declare no potential conflicts of interest regarding this study. S.W. is a scientist at the University of Tübingen and is employed by Carl Zeiss Vision International GmbH. There is no conflict of interest regarding this study.

References

1. Deng, Y.; Qiao, L.; Du, M.; Qu, C.; Wan, L.; Li, J.; Huang, L. Age-related macular degeneration: Epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. *Genes Dis.* **2022**, *9*, 62–79. [CrossRef] [PubMed]
2. Gehrs, K.M.; Anderson, D.H.; Johnson, L.V.; Hageman, G.S. Age-related macular degeneration—Emerging pathogenetic and therapeutic concepts. *Ann. Med.* **2009**, *38*, 450–471. [CrossRef] [PubMed]
3. Poletti, M.; Rucci, M. Active Vision: Adapting How to Look. *Curr. Biol.* **2013**, *23*, R718–R720. [CrossRef] [PubMed]
4. Walsh, D.V.; Liu, L. Adaptation to a simulated central scotoma during visual search training. *Vis. Res.* **2014**, *96*, 75–86. [CrossRef]
5. Jonas, J.B. Global prevalence of age-related macular degeneration. *Lancet Glob. Health* **2014**, *2*, e65–e66. [CrossRef]
6. Gaffney, A.J.; Margrain, T.H.; Bunce, C.V.; Binns, A.M. How effective is eccentric viewing training? A systematic literature review. *Ophthalmic Physiol. Opt.* **2014**, *34*, 427–437. [CrossRef]
7. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *Lancet. Glob. Health* **2014**, *2*, e106–e116. [CrossRef]
8. Fine, E.M.; Rubin, G.S. Reading with simulated scotomas: Attending to the right is better than attending to the left. *Vis. Res.* **1999**, *39*, 1039–1048. [CrossRef]
9. Petre, K.L.; Hazel, C.A.; Fine, E.M.; Rubin, G.S. Reading with eccentric fixation is faster in inferior visual field than in left visual field. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **2000**, *77*, 34–39. [CrossRef]
10. Pidcoe, P.E.; Wetze, P.A. Oculomotor tracking strategy in normal subjects with and without simulated scotoma. *Investig. Ophthalmol. Vis. Sci.* **2006**, *47*, 169–178. [CrossRef]
11. Scherlen, A.C.; Bernard, J.B.; Calabrese, A.; Castet, E. Page mode reading with simulated scotomas: Oculo-motor patterns. *Vis. Res.* **2008**, *48*, 1870–1878. [CrossRef]
12. Crossland, M.D.; Engel, S.A.; Legge, G.E. The preferred retinal locus in macular disease: Toward a consensus definition. *Retina* **2011**, *31*, 2109–2114. [CrossRef]
13. Rosenholtz, R. Capabilities and Limitations of Peripheral Vision. *Annu. Rev. Vis. Sci.* **2016**, *2*, 437–457. [CrossRef]
14. Brulé, E.; Tomlinson, B.J.; Metatla, O.; Jouffrais, C.; Serrano, M. Review of Quantitative Empirical Evaluations of Technology for People with Visual Impairments. In Proceedings of the 2020 CHI Conference on Human Factors in Computing Systems, Honolulu, HI, USA, 25–30 April 2020. [CrossRef]
15. Htike, H.M.; Margrain, T.H.; Lai, Y.K.; Eslambolchilar, P. Ability of Head-Mounted Display Technology to Improve Mobility in People With Low Vision: A Systematic Review. *Transl. Vis. Sci. Technol.* **2020**, *9*, 1–27. [CrossRef]
16. Manjari, K.; Verma, M.; Singal, G. A survey on Assistive Technology for visually impaired. *Internet Things* **2020**, *11*, 100188. [CrossRef]
17. Butler, M.; Holloway, L.; Reinders, S.; Goncu, C.; Marriott, K. Technology developments in touch-based accessible graphics: A systematic review of research 2010–2020. In Proceedings of the 2021 CHI Conference on Human Factors in Computing Systems, Yokohama, Japan, 8–13 May 2021. [CrossRef]
18. Kasowski, J.; Johnson, B.A.; Neydavood, R.; Beyeler, M.; Akkaraju, A. Furthering Visual Accessibility with Extended Reality (XR): A Systematic Review. *arXiv* **2021**, arXiv:2109.04995.
19. Lang, F.; Machulla, T. Pressing a Button You Cannot See: Evaluating Visual Designs to Assist Persons with Low Vision through Augmented Reality. In Proceedings of the 27th ACM Symposium on Virtual Reality Software and Technology, Osaka Japan, 8–10 December 2021; p. 10. [CrossRef]
20. Altpeter, E.; Mackeben, M.; Trauzettel-Klosinski, S. The importance of sustained attention for patients with maculopathies. *Vis. Res.* **2000**, *40*, 1539–1547. [CrossRef]
21. Trauzettel-Klosinski, S.; Dieling, C.; Pietsch, B. The influence of visual field defects and other clinical parameters on reading performance: A retrospective study in a low vision population. *Vis. Impair. Res.* **2003**, *5*, 83–100. [CrossRef]
22. Nguyen, N.X.; Trauzettel-Klosinski, S. Effectiveness of magnifying low vision aids in patients with age-related macular degeneration. *Neuro-Ophthalmology* **2009**, *33*, 115–119. [CrossRef]
23. Barraza-Bernal, M.J.; Ivanov, I.V.; Nill, S.; Rifai, K.; Trauzettel-Klosinski, S.; Wahl, S. Can positions in the visual field with high attentional capabilities be good candidates for a new preferred retinal locus? *Vis. Res.* **2017**, *140*, 1–12. [CrossRef]
24. Sipatchin, A.; García, M.G.; Wahl, S. Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR). *Appl. Sci.* **2021**, *11*, 7164. [CrossRef]
25. Martin-Gonzalez, A.; Kotliar, K.; Rios-Martinez, J.; Lanzl, I.; Navab, N. Mediated-reality magnification for macular degeneration rehabilitation. *J. Mod. Opt.* **2014**, *61*, 1400–1408. [CrossRef]
26. Stearns, L.; DeSouza, V.; Yin, J.; Findlater, L.; Froehlich, J.E. Augmented reality magnification for low vision users with the microsoft hololens and a finger-worn camera. In Proceedings of the ASSETS 2017—19th International ACM SIGACCESS Conference on Computers and Accessibility, Baltimore, MD, USA, 20 October–1 November 2017; pp. 361–362. [CrossRef]
27. de Lange, C. Vision restored with virtual reality. *New Sci.* **2018**, *239*, 4. [CrossRef]
28. Zhaoping, L. Attention capture by eye of origin singletons even without awareness—A Hallmark of a bottom-up saliency map in the primary visual cortex. *J. Vis.* **2008**, *8*, 1–18. [CrossRef]
29. Peterson, J.J. The Interaction between Visual Resolution and Task-Relevance in Guiding Visual Selective Attention. Master's Thesis, Kansas State University, Manhattan, KS, USA, 2012.

30. Peterson, J.; Erickson, G.; Johnson, A.; Dendurent, J.; Loschky, L. The Effects of Blur on Selective Visual Attention. *J. Vis.* **2015**, *15*, 1071. [CrossRef]
31. Peterson, J.; Ringer, R.; Sisco, E.; De La Torre, M.; Talkington, H.; Shanahan, M.; Loschky, L. The Effects of Unique Blur/Clarity Contrast on Visual Selective Attention as Measured by Eye Movements: Strong Clarity Capture and Weak Blur Repulsion. *J. Vis.* **2017**, *17*, 1119. [CrossRef]
32. Bowers, A.R. Eye movements and reading with plus-lens magnifiers. *Optom. Vis. Sci.* **2000**, *77*, 25–33. [CrossRef]
33. Ashmore, M.; Duchowski, A.T.; Shoemaker, G. Efficient Eye Pointing with a Fisheye Lens. In Proceedings of the Graphics Interface, Victoria, BC, Canada, 9–11 May 2005. [CrossRef]
34. Janssen, J.; Verschuren, O.; Renger, W.J.; Ermers, J.; Ketelaar, M.; Van Ee, R. Gamification in physical therapy: More than using games. *Pediatr. Phys. Ther.* **2017**, *29*, 95–99. [CrossRef]
35. Fu, Y.; Hu, Y.; Sundstedt, V.; Fagerström, C. A Survey of Possibilities and Challenges with AR/VR/MR and Gamification Usage in Healthcare. In Proceedings of the 14th International Conference on Health Informatics , Porto Alegre, Brazil, 11–13 March 2021; pp. 733–740. [CrossRef]
36. Fu, Y.; Hu, Y.; Sundstedt, V.; Forsell, Y. Conceptual Design of an Extended Reality Exercise Game for the Elderly. *Appl. Sci.* **2022**, *12*, 6436. [CrossRef]
37. Vive Pro Eye. Available online: https://web.archive.org/web/20201111190618/https://www.vive.com/eu/product/vive-pro-eye/overview/ (accessed on 11 November 2020).
38. Sipatchin, A.; Wahl, S.; Rifai, K. Eye-Tracking for Clinical Ophthalmology with Virtual Reality (VR): A Case Study of the HTC Vive Pro Eye's Usability. *Healthcare* **2021**, *9*, 180. [CrossRef]
39. Stein, N.; Niehorster, D.C.; Watson, T.; Steinicke, F.; Rifai, K.; Wahl, S.; Lappe, M. A Comparison of Eye Tracking Latencies Among Several Commercial Head-Mounted Displays. *i-Perception* **2021**, *12*, 2041669520983338. [CrossRef] [PubMed]
40. Sauer, Y.; Sipatchin, A.; Wahl, S.; García García, M. Assessment of consumer VR-headsets' objective and subjective field of view (FoV) and its feasibility for visual field testing. *Virtual Real.* **2022**, *1*, 1–13. [CrossRef]
41. Tobii AB. Tobii Pro SDK v1.7.1.1081. Available online:https://web.archive.org/web/20200622201031/https://www.tobiipro.com/product-listing/tobii-pro-sdk/ (accessed on 22 June 2020).
42. VIVE Eye Tracking SDK (SRanipal). Available online: https://web.archive.org/web/20200923043350/https://developer.vive.com/resources/vive-sense/sdk/vive-eye-tracking-sdk-sranipal/(accessed on 23 September 2020).
43. Lintu, A.; Carbonell, N. Gaze Guidance through Peripheral Stimuli. *HAL-Inria* **2009**.
44. Hata, H.; Koike, H.; Sato, Y. Visual guidance with unnoticed blur effect. In Proceedings of the Workshop on Advanced Visual Interfaces AVI , Bari, Italy, 7–10 June 2016; pp. 28–35. [CrossRef]
45. Goldstein, R.B.; Apfelbaum, H.; Luo, G.; Peli, E. 37.3: Dynamic Magnification of Video for People with Visual Impairment. *SID Symp. Dig. Tech. Pap.* **2003**, *34*, 1152–1155. [CrossRef]
46. Goldstein, R.B.; Woods, R.L.; Peli, E. Where people look when watching movies: Do all viewers look at the same place? *Comput. Biol. Med.* **2007**, *37*, 957–964. [CrossRef] [PubMed]
47. Duchowski, A.T. Incorporating the viewer's point of regard (POR) in gaze-contingent virtual environments. In Proceedings of the Stereoscopic Displays and Virtual Reality Systems, San Jose, CA, USA, 24–30 January 1998; SPIE: San Jose, CA, USA, 1998; Volume 3295, pp. 332–343. [CrossRef]
48. Wilson, M.; McGrath, J.; Vine, S.; Brewer, J.; Defriend, D.; Masters, R. Psychomotor control in a virtual laparoscopic surgery training environment: Gaze control parameters differentiate novices from experts. *Surg. Endosc.* **2010**, *24*, 2458–2464. [CrossRef]
49. Galley, N.; Betz, D.; Biniossek, C. Fixation durations-Why are they so highly variable? In *Advances in Visual Perception Research*; Heinen, T., Ed.; Nova Science Publishers: New York, NY, USA, 2015; pp. 83–106.
50. Fei-Fei, L.; Iyer, A.; Koch, C.; Perona, P. What do we perceive in a glance of a real-world scene? *J. Vis.* **2007**, *7*, 10. [CrossRef] [PubMed]
51. Larson, A.; Hendry, J.; Loschky, L. Scene Gist Meets Event Perception: The Time Course of Scene Gist and Event Recognition. *J. Vis.* **2012**, *12*, 1077. [CrossRef]
52. Loschky, L.C.; Larson, A.M.; Smith, T.J.; Magliano, J.P. The Scene Perception & Event Comprehension Theory (SPECT) Applied to Visual Narratives. *Top. Cogn. Sci.* **2020**, *12*, 311–351. [CrossRef]
53. Nelson, W.W.; Loftus, G.R. The functional visual field during picture viewing. *J. Exp. Psychol. Hum. Learn. Mem.* **1980**, *6*, 391–399. [CrossRef]
54. Deubel, H.; Schneider, W.X. Saccade target selection and object recognition: Evidence for a common attentional mechanism. *Vis. Res.* **1996**, *36*, 1827–1837. [CrossRef]
55. Goldberg, J.H.; Kotval, X.P. Computer interface evaluation using eye movements: Methods and constructs. *Int. J. Ind. Ergon.* **1999**, *24*, 631–645. [CrossRef]
56. Savitzky, A.; Golay, M.J. Smoothing and Differentiation of Data by Simplified Least Squares Procedures. *Anal. Chem.* **1964**, *36*, 1627–1639._V03. [CrossRef]
57. Nyström, M.; Holmqvist, K. An adaptive algorithm for fixation, saccade, and glissade detection in eyetracking data. *Behav. Res. Methods* **2010**, *42*, 188–204. [CrossRef]
58. Ebisawa, Y.; Minamitani, H.; Mori, Y.; Takase, M. New methods for removing saccades in analysis of smooth pursuit eye movement. *Biol. Cybern.* **1988**, *60*, 111–119. [CrossRef]

59. Berens, P. CircStat : A MATLAB Toolbox for Circular Statistics . *J. Stat. Softw.* **2009**, *31*, 1–21. [CrossRef]
60. Mulder, K.T. Bayesian Circular Statistics: Von Mises-Based Solutions for Practical Problems. Ph.D Thesis, Utrecht University, Utrecht, The Netherlands, 2019.
61. Mulder, K.; Klugkist, I.; van Renswoude, D.; Visser, I. Mixtures of peaked power Batschelet distributions for circular data with application to saccade directions. *J. Math. Psychol.* **2020**, *95*, 102309. [CrossRef]
62. Jones, M.C.; Pewsey, A. A family of symmetric distributions on the circle. *J. Am. Stat. Assoc.* **2005**, *100*, 1422–1428. [CrossRef]
63. Jones, M.C.; Pewsey, A. Inverse Batschelet distributions for circular data. *Biometrics* **2012**, *68*, 183–193. [CrossRef]
64. Mackeben, M. Sustained focal attention and peripheral letter recognition. *Spat. Vis.* **1999**, *12*, 51–72. [CrossRef]
65. Trauzettel-Klosinski, S.; Besch, D.; Mackeben, M. Reading disorders due to visual field defects: A neuro-ophthalmological view. *Neuro-Ophthalmology* **2009**, *27*, 79–90. [CrossRef]
66. Yantis, S. How visual salience wins the battle for awareness. *Nat. Neurosci.* **2005**, *8*, 975–977. [CrossRef]
67. Parr, T.; Friston, K.J. Attention or salience? *Curr. Opin. Psychol.* **2019**, *29*, 1–5. [CrossRef]
68. Lisberger, S.G. Visual guidance of smooth-pursuit eye movements: Sensation, action, and what happens in between. *Neuron* **2010**, *66*, 477–491. [CrossRef]
69. Barraza-Bernal, M.J.; Rifai, K.; Wahl, S. A preferred retinal location of fixation can be induced when systematic stimulus relocations are applied. *J. Vis.* **2017**, *17*, 11. [CrossRef]
70. Barraza-Bernal, M.J.; Rifai, K.; Wahl, S. Transfer of an induced preferred retinal locus of fixation to everyday life visual tasks. *J. Vis.* **2017**, *17*, 2. [CrossRef]
71. Nilsson, U.L.; Frennesson, C.; Nilsson, S.E.G. Patients with AMD and a large absolute central scotoma can be trained successfully to use eccentric viewing, as demonstrated in a scanning laser ophthalmoscope. *Vis. Res.* **2003**, *43*, 1777–1787. [CrossRef]
72. Nilsson, U.L.; Nilsson, S.E.G. Rehabilitation of the visually handicapped with advanced macular degeneration. *Doc. Ophthalmol.* **1986**, *62*, 345–367. [CrossRef]
73. Virtanen, P.; Laatikainen, L. Primary success with low vision aids in age-related macular degeneration. *Acta Ophthalmol.* **1991**, *69*, 484–490. [CrossRef]
74. Cheong, A.M.; Lovie-Kitchin, J.E.; Bowers, A.R.; Brown, B. Short-term in-office practice improves reading performance with stand magnifiers for people with AMD. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **2005**, *82*, 114–127. [CrossRef]
75. Watson, G.R.; Maino, J.; De l'Aune, W. Comparison of low-vision reading with spectacle-mounted magnifiers. *J. Rehabil. Res. Dev.* **2005**, *42*, 459–469. [CrossRef] [PubMed]
76. Nguyen, N.X.; Besch, D.; Bartz-Schmidt, K.; Gelisken, F.; Trauzettel-Klosinski, S. Reading performance with low-vision aids and vision-related quality of life after macular translocation surgery in patients with age-related macular degeneration. *Acta Ophthalmol. Scand.* **2007**, *85*, 877–882. [CrossRef] [PubMed]
77. Gill, K.; Mao, A.; Powell, A.M.; Sheidow, T. Digital reader vs print media: The role of digital technology in reading accuracy in age-related macular degeneration. *Eye* **2013**, *27*, 639–643. [CrossRef] [PubMed]

6.2 Submitted manuscript

6.2.1 Case study: non-published work

Real-world feasibility of a Virtual Reality (VR) gaming environment for the training of eccentric vision in age-related macular degeneration (AMD)

Title:

Real-world feasibility of a Virtual Reality (VR) gaming environment for the training of eccentric vision in age-related macular degeneration (AMD)

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Summary:

Digital games and entertainment technology, such as virtual reality (VR), are rapidly emerging as impactful healthcare technologies substituting non-vital clinic visits characterized by poorly engaging patient rehabilitation techniques. Several studies have shown that VR and gaming can be used for rehabilitation programs, including visual training. No study has investigated whether such interventions could assist patients with age-related macular degeneration (AMD). With the current study, we aimed to examine the feasibility of assistive eccentric viewing training using VR gaming for an AMD patient.

Main text:

AMD is a leading cause of legal blindness among the elderly in developed countries (1). With the progressive accumulation of waste material, commonly known as drusen, and associated processes, the central retinal cells experience increasing levels of molecular stress that may ultimately lead to cell death and outer retinal atrophy. Patients suffering from AMD experience blurred central vision or even central scotomas, i.e., complete loss of central vision. Despite significant visual impairments, AMD does not usually cause total blindness as the degeneration is limited to the macular area, leaving the peripheral retina intact (2). Naturally, after a while, patients with AMD-induced central vision loss start to preferentially use healthy peripheral parts of the retina, a phenomenon known as eccentric vision. Due to the lower photoreceptor density in the periphery, the surrogate vision those patients eccentrically achieve is far inferior to macular vision but largely helps to sustain mobility and independence. While switching to another preferred retinal locus (PRL) is commonly accomplished in younger patients, it typically depicts a challenging task for the elderly. The time it takes patients to achieve it is highly variable, and some patients never correctly learn it despite the availability of clinician-guided training. Here, virtual reality (VR) systems depict a promising alternative to traditional interventions due to their technical versatility.

Additionally, gamification aspects have the potential to improve patient adherence significantly (3). Therefore, VR-based applications offer effective and cost-efficient alternatives to traditional interventions. Accordingly, their potential is increasingly recognized in the medical sector, as reflected by the recent increase in food and drug administration (FDA) approvals for VR applications (4).

In two previous studies (5, 6), we used a VR setup to simulate central scotomas in healthy subjects to test their ability to develop eccentric vision with and without assistive stimuli that aimed to facilitate eccentric viewing. Participants with simulated macular degeneration are known to form the same adaptation to an eccentric viewing as the one observed in patients (7).

Following previous literature, we could show that the subjects were able to learn eccentric fixation and that the training regimen and the use of assistive stimuli significantly accelerated this process. However, it remains unclear whether elderly patients with limited technological experience can adequately use the equipment and the VR-based application. It is known that the elderly interact differently with newer technology, less intuitively, and, consequently, slower than the younger population (8). Therefore, more recent technologies, such as VR gaming, must be tested for their feasibility. Consequently, this study tested a VR gaming setup in a patient with AMD-associated foveal geographic atrophy in both eyes. Best to our knowledge, this is the first study to test the feasibility of assistive eccentric viewing training using salient peripheral augmentation during VR gaming in an elderly patient suffering from AMD.

This case study's subject (Figure 1A, B and C) was an emmetropic 78-year-old male with bilateral foveal geographic atrophy secondary to AMD. He presented with a BCVA of 20/400 in the right eye and 20/80 in the left eye. The lesions in both eyes held a horizontal radius of approximately 1.5 mm (≈5° visual angle; see Figure 1A) with a slightly larger total lesion area in the right eye (5.46 mm^2 right eye, 4.30 mm^2 left eye). The subject reported only a basic technological experience and no previous interaction with a VR headset. For this study, the same training regimen as in the previous two studies (5, 6) was used (Figure 1D).

For the analysis, equivalent to the antecedent research (5, 6), eccentric viewing behaviour was measured using gaze directionality and distance between the new PRL and the foveal center. The measurement was performed for the dominant eye only since it has been shown that the dominant eye is a better indication of preference habit (9) and binocular vision was needed during the experiment since eye tracking is more accurate when both eye are considered (10). During the baseline condition (first block in Figure 1D), the subject showed a stable downward-right preference with a PRL located temporal to the foveal center of the dominant left eye. With the assistive stimulus (concentric ring around the central scotoma; second block in Figure 1D), this preference was maintained and not disrupted (first and second block in Figure 1E). The results are encouraging since previous literature has shown that some stimuli can lead to PRL formation perturbation (6). As observed previously, the PRL remained stable after removing the assistive stimulus (5, 6) (third block in Figure 1E). From a subjective point of view, the patient did not report difficulties understanding and completing the task. In line with this, the obtained game scores were comparable to healthy subjects. Additionally, the patient reported being highly engaged and rated the experience as enjoyable and entertaining.

Given the current results, the case study indicated that our VR setup could be successfully used in elderly patients suffering from AMD despite basic technological expertise. Although the study is not powered to provide a statement concerning accelerated learning of eccentric vision using our VR application, future clinical trials in a larger cohort will provide real-life data concerning the potential acceleration of initial eccentric vision establishment. Additionally, the technology may help to re-establish eccentric vision in cases where the initial PRL vanishes due to enlargement of atrophy by facilitating the finding of a new PRL.

Figure legend:

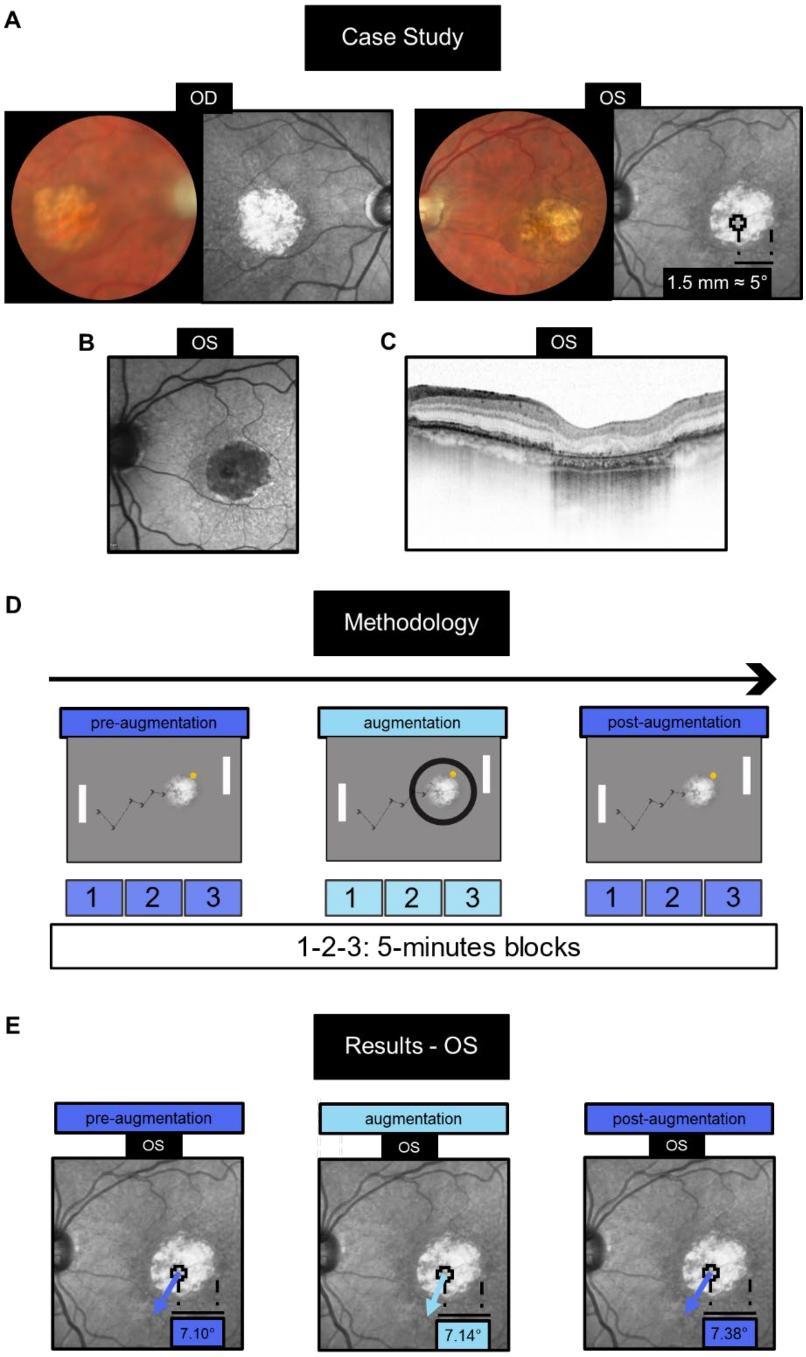
(A) Fundus and infrared pictures of the subject's posterior poles.

(B) Fundusautofluorescence (FAF) picture of the posterior pole of the left eye. The foveal atrophy is visible as a central area of hypofluorescence caused by atrophy of the retinal pigment epithelium (RPE).

(C) Optical coherence tomography (OCT) scan of the macular region of the left eye. In the macular area complete atrophy of the outer retinal layers and the RPE is visible. Due to the RPE atrophy, signal amplification is observed in the structures below the affected area (Bruch's membrane, choroid).

(D) Methodology: The experimental setup consists of a two-dimensional (2D) VR Pong game with a moving ball and two paddles positioned at the edges of the play area (white rectangles). The ball (yellow) follows a random trajectory (indicated by the arrows) that goes from one side to the other of the 2D play area after hitting one of the paddles. The two paddles can be controlled by the subject and be moved upwards or downwards with the goal of keeping the ball inside the play area. An additional task was implemented to motivate patients to keep the target visible via eccentric fixation: press a button whenever the ball changes color. The ball changes color at random intervals, and a correct identification of color change gives points during the game. The sequence of the study: before (pre-augmentation) and after (post-augmentation) the peripheral salience condition, the patient performed the experiment with macular degeneration (schematic representation of the atrophic lesion: the white spot. Only during the peripheral salience condition (augmentation), while playing the game, a salient peripheral augmentation was presented to the dominant eye, OS (black concentric ring around the scotoma). Each condition was tested in three separate 5-minute blocks and the entire experiment was 75 minutes long, with no need of re-takes.

(E) Results: Gaze behavior was analyzed in terms of median gaze directionality and median gaze decentralized position (gaze distance with respect to target). The results of gaze direction (colored arrows) and PRL position (colored boxes) are plotted on the infrared retinal image.



Contributions: Conceptualization: ASi, DAM and ASc; Data Analysis: ASi; Investigation: ASi; Resources: DAM, LW, LVS, ASc and SW; Writing - original draft: ASi and DAM; Writing - review and editing: ASi, DAM, LW, LVS, ASc and SW; Visualization: ASi, DAM, ASc; Supervision: SW; Project administration: SW; Funding acquisition: SW.

Acknowledgments: The authors gratefully acknowledge the helpful support of all our colleagues. We acknowledge support by Open Access Publishing Fund of University of Tübingen.

Conflict of interest: Author ASi, DAM, LW, LVS and ASc declare no potential conflicts of interest regarding this study. S.W. is a scientist at the University of Tübingen and is employed by Carl Zeiss Vision International GmbH. There is no conflict of interest regarding this study.

Funding: The work of the authors is supported by the Institutional Strategy of the University Tübingen (Deutsche Forschungsgemeinschaft, ZUK 63), the German Excellence initiative from the Federal Ministry of Education and Research (BMBF) in the framework of IDeA (project number 16SV8104). This work was done in an industry on campus cooperation between the University of Tübingen and Carl Zeiss Vision International GmbH. The authors recognise intra-mutual funding of the University of Tübingen through the mini graduate school "Integrative Augmented Reality (I-AR)" and funding from the European Union's Horizon 2020 research and innovation program (under Marie Skłodowska-Curie Grant agreement No. 734227–Platypus). There was no other additional external funding received for this study.

Institutional Review Board Statement: The Ethics Committee at the Medical Faculty of the Eberhard Karls University and the University Hospital Tübingen approved conducting the study within its facilities (Institutional Review Board number: 062/2022BO2). The study followed the tenets of the Declaration of Helsinki and later amendments.

Informed Consent Statement: Written informed consent was obtained to take part in the study from all participants after the content and possible consequences of the study had been explained. All data were pseudo-anonymized and stored in full compliance with the principles of the Data Protection Act GDPR 2016/679 of the European Union.

References:

1. Colijn JM, Buitendijk GH, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, et al. Prevalence of age-related macular degeneration in Europe: the past and the future. Ophthalmology. 2017;124(12):1753-63.
2. Merle DA, Sen M, Armento A, Stanton CM, Thee EF, Meester-Smoor MA, et al. 10q26–The enigma in age-related macular degeneration. Progress in Retinal and Eye Research. 2022:101154.
3. Rose T, Nam CS, Chen KB. Immersion of virtual reality for rehabilitation-Review. Applied ergonomics. 2018;69:153-61.
4. Vlake JH, van Bommel J, Riva G, Wiederhold BK, Cipresso P, Rizzo AS, et al. Reporting the early stage clinical evaluation of virtual-reality-based intervention trials: RATE-VR. Nature medicine. 2022:1-2.
5. Sipatchin A, García García M, Wahl S. Target Maintenance in Gaming via Saliency Augmentation: An Early-Stage Scotoma Simulation Study Using Virtual Reality (VR). Applied Sciences. 2021;11(15):7164.
6. Sipatchin A, García García M, Sauer Y, Wahl S. Application of Spatial Cues and Optical Distortions as Augmentations during Virtual Reality (VR) Gaming: The Multifaceted Effects of Assistance for Eccentric Viewing Training. International Journal of Environmental Research and Public Health. 2022;19(15):9571.
7. Whittaker SG, Budd J, Cummings R. Eccentric fixation with macular scotoma. Investigative ophthalmology & visual science. 1988;29(2):268-78.
8. Blackler AL. Intuitive interaction with complex artefacts: Queensland University of Technology; 2006.
9. Ono H, Barbeito R. The cyclopean eye vs. the sighting-dominant eye as the center of visual direction. Perception & Psychophysics. 1982;32(3):201-10.
10. Cui Y, Hondzinski JM. Gaze tracking accuracy in humans: Two eyes are better than one. Neuroscience letters. 2006;396(3):257-62.