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Lens-based technologies to study accommodation and refraction

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Author:

CARLES OTERO MOLINS

Supervisors:

Dr. JAUME PUJOL RAMO

Dr. MIKEL ALDABA ARÉVALO

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“Food and studies is on me, anything else is on you”.

Rosa Molins (my mother).

“Un plato en la mesa y los estudios nunca faltarán, el resto corre de tu cuenta”.

Rosa Molins (mi madre).

“Un plat a taula i els estudis mai faltaran, la resta va pel teu compte”.

Rosa Molins (la meva mare).

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As the secretary of the examination committee, I hereby state that the thesis was partly (at least the abstract and the conclusions) defended in a language commonly used in scientific communication in the field that is not an official language of Spain. This does not apply if the stay, report or expert is from a Spanish-speaking country.

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SUPERVISORS' CERTIFICATE

Dr. **Jaume Pujol Ramo**, professor at the Universitat Politècnica de Catalunya (UPC), and Dr. **Mikel Aldaba Arévalo**, senior researcher at the Universitat Politècnica de Catalunya

CERTIFY

that the work reported in the thesis entitled

Lens-based technologies to study refraction and accommodation

which is submitted by Carles Otero Molins in fulfilment of the requirements for the degree of Doctor by the Universitat Politècnica de Catalunya (UPC) has been carried out under our supervision within the framework of the PhD program in Optical Engineering of the same university.

Jaume Pujol Ramo	Mikel Aldaba Arévalo
Terrassa, 2017	Terrassa, 2017

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CONTENTS

List of figures

List of tables

1. Introduction

The visual system involves all the processes that are present from the observation of a stimulus through the optical system of the eye until its perception.[1] Along this image formation and perception, three sequential stages can be considered: the first one is the most concerned with optics and is the formation of an optical image on the retina. The light enters the eye (Figure 1) through the cornea and is refracted by its two main optical elements that are the cornea and the crystalline lens, having the cornea on average 40 D of power and the crystalline lens 20 D of power.

The second stage occurs in the retinal layers and consists on transforming the light input into an electrical output, and finally, the third stage sends the electrical information from the retina to the visual areas of the brain. During this journey, visual perception is specially degraded if the eye forms a suboptimal retinal image, a common situation given the presence of refractive errors, high order aberrations or scattering. Notice that diffraction effects on the eye are typically negligible provided that normal values of pupil diameter are much larger than the wavelengths of the visible spectrum.[2]

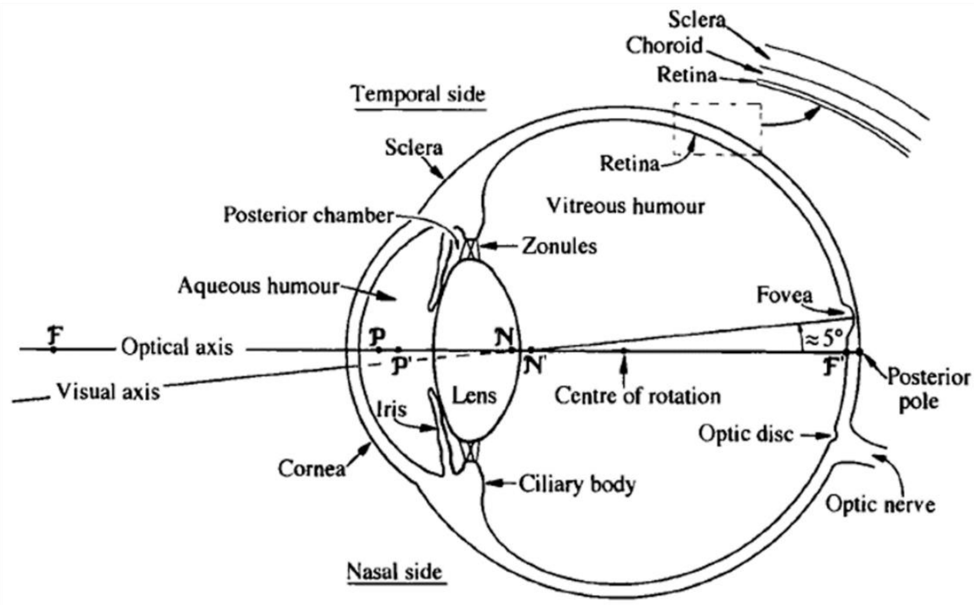

Figure 1. The horizontal section of the right eye as seen from above. Image taken from the book *Optics of the Human Eye*.[2]

Refractive errors are amongst the major contributors to a deteriorated visual performance and they are simply classified as myopia, hyperopia and astigmatism.[3] A myopic eye is characterized by having the focal image plane in front of the retina (in the unaccommodated eye). It is also known as a nearsightedness condition and is usually due to an unbalance between the axial length and the refractive power of its optical lenses, being the axial length the component that better correlates with the overall refractive error,[2] therefore the myopic eye is usually larger (bigger) than the non-myopic eye. Contrary, in hyperopic eyes the focal image plane is behind the retina (in the unaccommodated eye), it is also known as a farsightedness condition and it usually has a shorter axial eye length rather than less optical power of the lenses compared to non-hyperopes. However, in the case of hyperopia the crystalline lens might adjust its power to focus on the retina, a process called *accommodation*. Finally, astigmatism is characterized by having at least two meridians with different optical power, it is present in both the crystalline and the cornea (mainly in the cornea)[2] and it affects when fixating in both far and near distances.

Accommodation is tightly related to the spherical eye's refraction and it is the capability of the eye to focus targets whose ocular image fall behind the retina. It progressively decreases with age leading towards presbyopia and it can also significantly affect the visual performance of the eye when not focusing properly.[4] In such cases, subjects will most likely report blurred vision ('most likely' since the brain can compensate for certain amounts of defocus),[5,6] which in turn might lead to an important visual discomfort. Especially interesting are those situations where the eye has to look through optical instruments and focus on virtual targets in a relatively closed-field environment.[7–9] Examples of this environment can be found in new optical systems within the fields of visual simulators[10,11] and stereoscopic virtual reality displays,[12] which can be encompassed within lens-based technologies.

Visual simulators are instruments that allow the psychophysical testing of certain wavefront profiles. Based on active and adaptive optics, they use electro-optical lenses,[11] spatial light modulators[10,13] or deformable mirrors[14] to shape the wavefront profile. They provide great applications in the field of intraocular lenses, in which it is now possible to experience beforehand -before surgery- how one could perceive with a certain intraocular lens implanted in the eye. However, these devices have also the potential for other applications as they can be used as computer-controlled phoropters. For instance, they could be used as automated subjective refractometers, which is perhaps the application with greatest potential impact on society. According to the most recent estimates from the World Health Organization (WHO), the uncorrected refractive error is the main cause of visual impairment, affecting 43% of the global population.[15] The largest prevalence of visual impairment is found in developing countries, for which there is evidence that one of the leading causes for uncorrected refractive error is the insufficient eye care personnel and massive imbalance in the distribution of eye care services in these countries.[16,17] Automated and portable technology capable of performing accurate refractions could help to reduce this problem.

Besides refraction, computer-controlled phoropters could also be used in accommodation measurements, for example, the automatization of the accommodative facility test.[18,19] This test is typically used in clinics as a measure of visual fatigue and consists on measuring the number of times per minute that an observer can clear 2 different accommodative demands.[19,20] Taking advantage of the capability to computer-control the focal plane of the stimulus, it is possible to think of a new accommodative facility test with more than 2 accommodative demands that are presented in a randomized fashion. This protocol not only would provide more comprehensive information about the visual system performance (as more accommodative demands would be tested) but it would also allow to test the effects of stimulus unpredictability on accommodation.[21–23]

In regards to stereoscopic virtual reality systems, it is an emerging technology with many important applications[12] in the fields of video games, military and vision science (indeed, visual simulators can be considered specific types of virtual reality systems). Despite there are different stereoscopic optical designs, none of them are yet able to perform 3D scenes as in natural viewing conditions. The fundamental problem of these systems is the way in which focus cues are displayed.[24,25] This is an issue difficult to address since it depends on multiple factors such as the field of view, luminance of the stimuli, depth perception and even the way in which vergence is stimulated (e.g., Badal system[26–28] vs real targets). Typically, the anomalous accommodative response of the visual system when looking through closed-field optical instruments is termed *instrument myopia* or *instrument accommodation*.[7,9] A concept that has been studied since the 1950’s although it is not fully resolved yet. It has been reported many times in the past that some subjects are unable to accommodate appropriately when they are optically stimulated.[29–31] Up to date there is not a clear answer why this occurs and it is relevant since nowadays it is becoming more and more common to look at computerized stimuli (i.e., shown on an electronic display and controlled by a computer) through an optical system.[32] Having all this in mind, there are open questions that can help to improve lens-based systems to overcome the abovementioned limitations. First of all, how the accommodative system responds to optical stimulation? How can we improve the response? What are the most important factors and their interactions that affect the response under optical stimulation?. Of course the study of these issues will not only provide further understanding of all the mechanisms that drive accommodation under closed-field optical environments (such in a stereoscopic virtual reality system or visual simulators) but also in balancing the accommodative response of the eye in these systems with respect the natural-viewing conditions.

In essence, this thesis will work under two basic concepts: 1) it will focus on those issues that have not been clarified yet and are related with the accommodative response of the visual system when looking at a stimulus through an optical system and 2), it will focus on new methodologies related to automated subjective refraction and the accommodative tests. The following two sections will detail the goals of this thesis as well as its structure throughout this document.

2. Goals of this thesis

The objective of this thesis is to apply lens-based technologies (from computer-controlled electro-optical lenses to Badal systems) to study accommodation and refraction. This objective is split in the following two main objectives:

1. The study of the accommodative response when stimulated by optical means (a Badal optometer). This general goal has three specific objectives that will lead towards three different studies:

   1.1. To analyze the usefulness of a Badal optometer for accommodative stimulation (study 1).

   1.2. To investigate simple ways of improving the stimulation of accommodation in a Badal optometer (study 2).

   1.3. To investigate what are the main factors (and their interactions) that affect the accommodative response in a Badal optometer (study 3).

2. Investigation of new methodologies related to the automated subjective refraction and the accommodative tests taking advantage of a computer-controlled electro-optical systems. Concretely, this general goal is split in two specific objectives that will lead towards three different studies:

   2.1. To propose and validate a new algorithm to perform an automated non cycloplegic refraction (study 4).

   2.2. To propose and validate a new accommodative facility test in which the accommodative demand is randomly changed (study 5) and investigate the effect of stimulus predictability on accommodation dynamics (study 6).

3. Structure of this thesis

The methodology of this thesis is structured in **6 studies**. Each study comprises one unique section and is written in a paper-like format with the following subsections: introduction, methods, results and discussion.

The first three studies investigate the response of the accommodative system when optically-stimulated with a Badal optometer. Concretely, **the first study** investigates how accommodation is stimulated in a Badal optometer. **The second study** investigates the stimulation of accommodation in a Badal optometer when a two-dimensional stimulus with apparent depth cues that include rendered out-of-focus blur is used and, **the third study** analyzes the effect of field of view, stimulation method (either a real target in free space viewing or a target presented through a Badal optometer), depth of the stimulus (either a flat or a volumetric stimulus), and their interactions, on the accommodative response in observers from different refractive error groups.

The remaining 3 studies take advantage of electro-optical varifocal systems to investigate new methodologies related to the automated subjective refraction and the accommodative facility test. Concretely, **the fourth study** is a clinical validation of a new automated refraction algorithm (implemented on a computer-controlled phoropter) and is the only study that works specifically on eye's refraction. **The fifth study** validates a new accommodative facility test that integrates both the far and near accommodative facility test with random changes of accommodative stimulus. **The sixth study** explores how the predictability of a stimulus affects the accommodation dynamics and could influence the conventional facility test.

After the methodology, a summary of all the studies follows in the conclusions section as well as some related future works are suggested. After that, a list of all the references and also all the papers and conferences communications in which parts of this thesis have been disseminated is provided.

4. State of the art

This thesis evolves around the linkage of lens-based technologies with both refraction and accommodation. The following sections will review the most important aspects of each of these fields that are relevant to this thesis.

4.1. Accommodation

Accommodation could be defined as the capability of the eye to focus targets (usually near targets) whose image falls behind the retina. In terms of physiology, it has been shown that during this process the most important change occurs in the crystalline lens, due to the lens and capsule’s elasticity, the crystalline lens is capable of changing its shape and increasing its power during accommodation. Concretely, the ciliary muscle contracts doing a movement anteriorly and towards the optical axis that allows the anterior zonular fibers, which are attached in the equator of the lens, release its tension to the crystalline lens so it can take its accommodated form (Figure 2). This process of accommodation ends up having the crystalline lens axially thicker, with both the anterior and posterior radius of the lens shorter, with the lens slightly displaced to a more anterior position and with a smaller diameter.[4,33]

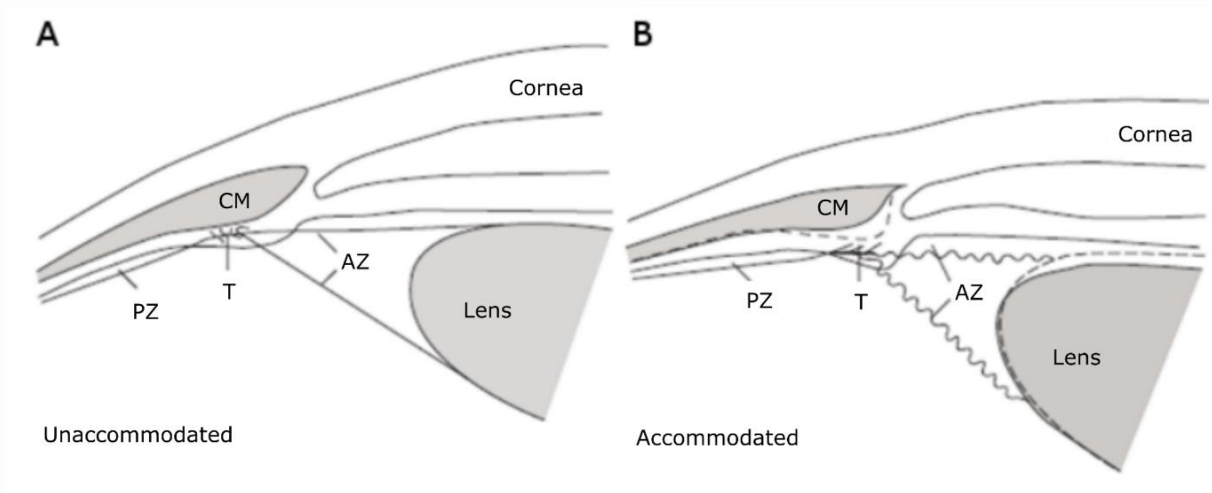

Figure 2. Transverse section of the eye in: A) unaccommodated state, B) accommodated state. CM: Ciliary muscle, PZ: Posterior Zonular fibers. AZ: Anterior Zonular fibers. Adapted from Charman.[4]

Neurologically, accommodation is related with convergence and pupil constriction (miosis) to form the so-called near triad. It can be shown that any time accommodation is activated, there is some convergence and a certain degree of pupil constriction. This also applies when the eyes converge, producing some accommodation and miosis. However, this relationship does not always hold for pupil constriction, since it can be driven independently from convergence and accommodation, i.e., the pupil might constrict without leading the eyes towards convergence and accommodation, for instance that would be the case for the pupil light reflex.[34,35] In Figure 3 it is shown a schematic representation of the afferent (*input*) and efferent (*output*) pathways involved in the neural control of accommodation. The afferent pathway goes through the optic tract to the midbrain (visual cortex) whereas the efferent pathway is mainly done by the parasympathetic fibers of the 3rd cranial nerve originated in the Edinger-Westphal nucleus (Figure 3). Although the sympathetic system plays a role in this process, it is an issue not fully resolved yet.[4]

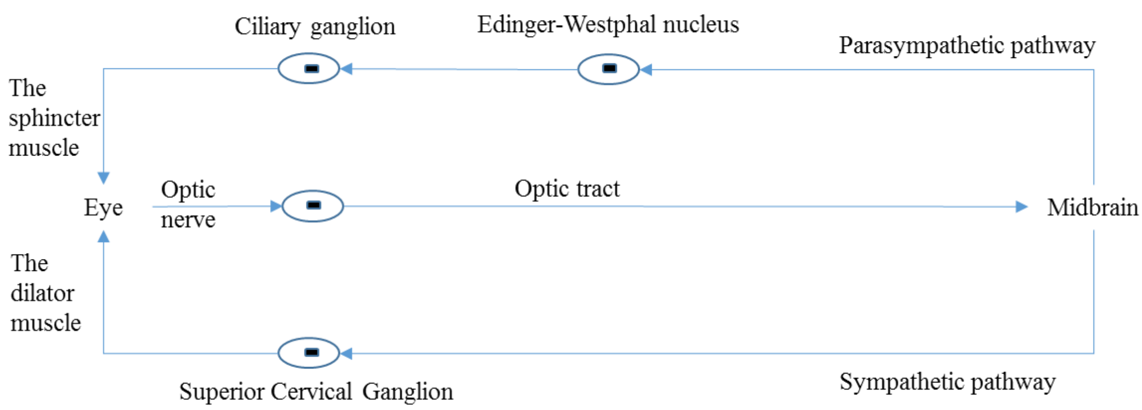

Figure 3. Schematic representation of the afferent and efferent pathways in the visual system. The afferent pathway involves the photoreceptors in the retina, the optic nerve and the optic tract up to the midbrain. The two efferent pathways are shown: the parasympathetic and the sympathetic. The parasympathetic goes from the midbrain, the Edinger-Westphal nucleus, the ciliary ganglion and the sphincter muscle. The sympathetic involves the midbrain, the superior cervical ganglion and the dilator muscle. Adapted from Szczepanowska-Nowak *et al*.[36]

4.1.1. Components of accommodation

It is widely accepted the classification of accommodation in four additive components:[4,37] the reflex accommodation, which is activated to maintain a sharp-retinal image; the proximal accommodation, which is triggered by a knowledge or a belief of knowledge of the object distance; the convergence accommodation, which appears as a consequence of fusion disparity vergence; and finally, the tonic accommodation that occurs when there is not a stimulus.

Actually, the reflex accommodation is the most noticeable component, in other words, accommodation reacts basically in response of blur, which means that the remaining components of accommodation have little impact in comparison to blur and can be easily masked by the reflex accommodation. Related to this, when the accommodative system is blur-driven is said to be under closed-loop conditions. When this component of accommodation is removed (or controlled) the system is said to operate under open-loop conditions, which is useful to study the remaining components of accommodation.[38] Recent findings showed that the main component of accommodation is not blur but vergence-driven,[39] which leads to a blurred retinal image (see section 4.1.5 for more information).

The proximal accommodation can be estimated when no visual feedback is obtained through monocular and binocular vergence, it is mixed up with tonic accommodation and it is stimulated by perceptual cues.[38] The convergence accommodation is related to the AC/A ratio, which is the amount of accommodative convergence in prism diopters (Δ) for 1 D of accommodation response. The normal values of AC/A range from 4 to 6 Δ/D. With respect the tonic accommodation, it has been related to the resting state of the eye, which is the focusing state of the eye when there is no stimulus of accommodation and which is around 1-2 diopters.[4] It is currently accepted the hypothesis that when the stimulus for accommodation is inappropriate (i.e., sufficiently degraded) the eye tends towards this resting state position.[7,9] Those situations in which there is an inappropriate accommodative stimulus are known as dark-field myopia (closely related to night myopia), empty-space myopia (also known as Ganzfeld myopia) and instrument myopia (more appropriately termed as instrument accommodation).[4] It is surprising that it still remains unclear why the eye has a tendency towards this myopic (accommodated) refractive state under these circumstances, which suggests that the most comfortable focus position of the eye is not the optical infinity (often defined from the 6 meter distance on) but an intermediate position. Interestingly, when the accommodative response is compared with the accommodative stimulus it can be shown that there is over-accommodation or accommodative lead for distance objects and under-accommodation or accommodative lag for near objects.[40] This is in agreement with the resting state of the eye.

4.1.2. Accommodative stimulus-response function

The accommodative stimulus-response function relates the accommodative response with the accommodative stimulus demand. It provides a quantitative description of the steady-state accommodative performance of the eye. This function can be classified into 5 non-linear regions and 1 linear region (Figure 4).[3]

The hyperopic nonlinear defocus region (number 6 shown in Figure 4) is the region when the accommodative stimulus is theoretically *beyond* the optical infinity. This produces the accommodative system to shift towards the tonic state (actually, to the resting state of accommodation, which correlates with the tonic accommodation).[7,38]

The initial non-linear region shows a lead of accommodation of about +0.3 D at far distance that is due to the tonic level of ciliary muscles and also to the depth of focus/ depth of field. Thus, at far distance the accommodative system is slightly accommodated (number 1 shown in Figure 4).[41] This is consistent with the far refraction and its rule of maximum plus power with visual acuity.[3]

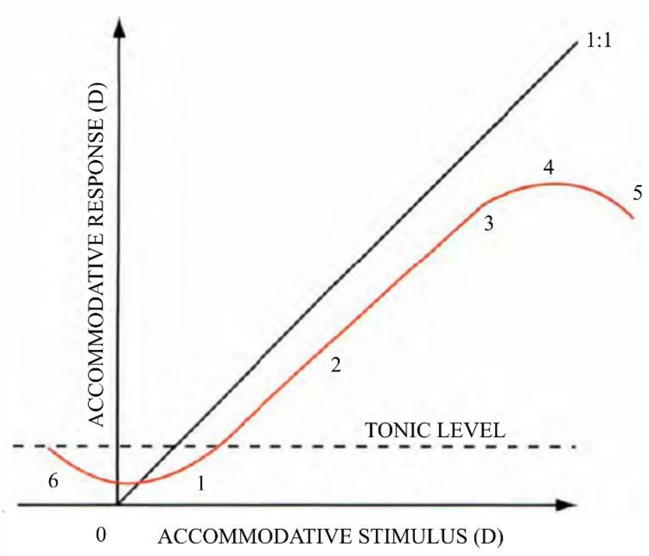

Figure 4. Accommodative response/stimulus function. Figure 4-4 of Borish's clinical refraction.[3]

The linear region (number 2 shown in Figure 4) covers the midrange of the amplitude of accommodation and it typically has a constant slope between 0.7 and 1.0.[42] The concept of amplitude of accommodation is referred to the maximum eye's accommodative range in diopters. In this range there is a direct, positive relation between the accommodative stimulus and response. Generally, the response is less than the accommodative stimulus demand, this is called the lag of accommodation, normal values range from +0.25 D to +1.25 D and it can be measured objectively (e.g., dynamic retinoscopy and autorefractor or wavefront sensor with the capability to stimulate accommodation). The accommodative lag theoretically should be within the limits of the depth of focus in order not to perceive blur.[43]

The non-linear transitional zone goes after the linear region (number 3 shown in Figure 4). The accommodative response progressively saturates with increasing accommodative demands. The non-linear latent zone goes after the non-linear transitional zone and it is the region in with the break point of the maximum accommodative response test occurs (number 4 shown in Figure 4). That is, further increases in accommodative stimulus does not produce an increase in the accommodative response.

Myopic nonlinear defocus zone goes after the non-linear latent zone (number 5 shown in Figure 4) and is the region in which accommodative stimulus of about 2 D greater than the maximum amplitude of accommodation produces a response towards the tonic level (in fact, to the resting state of accommodation).

4.1.3. Dynamic aspects of accommodation

The accommodative system can respond reasonably quickly and accurately to a variety of dynamically changing stimuli such as a step (or square wave), sinusoidal and ramp inputs.[21–23,44]

Both eyes have normally similar dynamic and static accommodative responses, suggesting a common neural origin.[4] As happens with the pupillary system, there are fluctuations of accommodation (also known as focusing tremor) that have values around 0.5 D[4] and have a frequency spectrum up to about 5 Hz.[45–47] Moreover, the reaction time (latency) of accommodation is around 300 msec and the response time to reach the steady state is around 1 second.[4,48] As it was shown in posterior studies, the accommodative response and some parameters of its dynamics (e.g., latency) are affected by both age,[49,50] refractive error[51] and the task instructions given to participants.[27]

The dynamic accommodative stimulus may have the property of ‘predictability’ if the pattern driving the stimulus is constant. The pattern can be characterized with the relationship among changes in magnitude, direction and time of the accommodative stimulus. Most of accommodation dynamic studies have used either predictable sinusoids or predictable square wave inputs and have assumed the presence of anticipation effects.[49,51,52] Only 3 studies investigated the anticipation effects in accommodation,[21–23] all of them agreed with the presence of a prediction operator, although they were limited in sample size and difficult to reproduce due to the lack of information about the typology of participants or the explicit task instructed to them. Interestingly, one of these 3 studies was unable to explain why a subject did not always succeed in following the stimulus optimally despite it was predictable.[21] This thesis will further investigate the prediction operator as it can potentially affect the clinical outcomes of the accommodative facility test (see section 4.1.6 for more information).

4.1.4. Development of accommodation and presbyopia

The accommodative capability is not stable along time.[4,50] Despite the challenge to measure biometric parameter on infants and kids, some studies have assessed the accommodative amplitude in infants and found that during the first 2 months of life infants tends to over-accommodate 2-3 D at far distance targets[53–56] and after that they approach adult-like behavior. With respect the dynamics, it has been reported that by the third postnatal month infants are able to respond with latencies within a factor of two of adults'.[57]

Within the age range from 3 to 14 years old Chen and O'Leary found that the slope of the accommodative stimulus-response function remains relatively constant with age in young emmetropic subjects.[58] Within the age range from 5 to 10 years old, a gradual reduction of the amplitude of accommodation with age was reported[59,60] and also a gradual improvement of accommodative facility test performance,[61] from 12 years of age on, subjects respond similarly as normal young adults during the accommodative facility test.[18]

In adulthood, the accommodative capability decreases linearly with age[4,50] and related to this, presbyopia is the condition defined for little enough accommodative amplitudes that do not allow the eye to focus a near target (30-40 cm from the eye).[4,62] The age at which presbyopia is symptomatic in humans is around 45 years. Beyond forties, the steady-state response/stimulus slope starts to decrease markedly.[4] It is widely accepted the Duane-Hoffstetter formula for probable amplitude of accommodation as a function of age:[63]

$$Maximum\ Amplitude = 25.0 - 0.40 \cdot Age \quad \text{(eq.1)}$$

$$Average\ Amplitude = 18.5 - 0.30 \cdot Age \quad \text{(eq.2)}$$

$$Minimum\ Amplitude = 15.0 - 0.25 \cdot Age \quad \text{(eq.3)}$$

However, the age related changes that underlie presbyopia are not fully understood, there are different theories of presbyopia and the most supported ones are those related with changes in the crystalline lens (more concretely those related with the mechanical changes) rather than the age related changes in the ciliary muscle, ciliary body or choroid (also known as extra-lenticular theories).[2] Within the lenticular theories (crystalline lens related), there were historically two theories equally supported: the Hess-Gullstrand and the Duane-Fincham.

On the one hand, the Hess-Gullstrand theory of presbyopia says that the amount of ciliary muscle contraction remains constant with age. Therefore, the maximum amplitude of accommodation for a given age is not determined by the maximum capability of contraction of the ciliary muscle. On the other hand, the Duane-Fincham model assumes that the ciliary muscle weakens with age and that the maximum amplitude of accommodation is reached when the ciliary muscle is maximally contracted. The latter theory is supported by the increase in the response AC/A ratio with age[2,4] which might indicate greater efforts for a given change in accommodation with age. Although contrary, Ciuffreda *et al*.[64] claimed there is not a significant change in the AC/A ratio and supported the Hess-Gullstrand theory, which has recently become more accepted since Kasthurirangan and Glasser[65] showed that there is an increase in the amount of pupil constriction per diopter of accommodative response, but not per diopter of stimulus amplitude, which suggested that the near effort per se does not increase with age. Also in the same line of thought are the findings of Tabernero *et al*.[66] who indirectly showed that the accommodative ciliary muscle function is preserved in older humans.

4.1.5. Factors that affect accommodation

There are different kinds of inputs to the accommodative system, which can be divided into three main groups: stimulus (to), cues (for) and influences (upon) accommodation.[67]

The stimulus to accommodation is referred mainly to blur, which provides the accommodative system with an estimation of the magnitude of the accommodative adjustment required to sharpen the image, but not with the direction of this adjustment. However, an important finding related to the stimulus to accommodation has been published recently. Del Águila-Carrasco *et al*.[39] showed that the stimulus to accommodation is not blur but vergence and that the accommodative system detects the direction of a pure-vergence stimulus (i.e., regardless of directional cues). What still remains unknown is how the sign of defocus is detected under a pure vergence-driven stimulus of accommodation, it is suggested that this mechanism should be present in the retina itself. There are two hypothesis for that, one is that photopigment bleaching is different for positive than for negative defocus and that it informs the retina which is the direction of vergence and the alternative hypothesis is that blood vessels produce some shadows on the retina that it tells subjects about the appropriate direction.[68]

Regarding the accommodative cues, before the recent findings of Del Águila-Carrasco *et al*.[39] it was claimed that they provide the essential directional information about the blur pattern but now it is more likely that their role is secondary (although important for accurate responses) in the sense that cues just help in guiding the accommodative system to more accurate responses. These cues could be divided into optical cues and non-optical cues. Optical cues involve directional information derived from changes in the optical quality of the retinal image. Among the most important there are: chromatic aberration, spherical aberration, astigmatism, microfluctuations of accommodation and fixational eye movements. With respect the non-optical cues, the most remarkable are: size, proximity, disparity vergence, overlap, texture, gradient, linear perspective and optical flow patterns. Notice that most of the non-optical cues for accommodation are also cues for depth perception, which points out the tight relationship between both concepts.[3] It is important to remark that cues for accommodation are especially relevant when stimulating through lens-based technologies. As mentioned in the introduction, it is very difficult to replicate exactly the same cues present in a natural viewing environment than in a virtual (optically stimulated) one.[24,25] The lack of appropriate cues can significantly alter the overall accommodative response when stimulating by optical means (e.g., when using a Badal optometer).[7,9] This issues are addressed in this thesis in the first 3 studies and have important implications since previous studies have found poorer accommodative responses when accommodation is stimulated with lenses compared to free space targets.[29,30,69]

Finally, the influences upon accommodation are referred to any other factor, mainly cognitive-based factors, that can alter the accommodative response, such as for instance mood, voluntary effort or prediction of the stimulus position.[21–23,27]

4.1.5.1. Depth-of-focus/depth-of-field

Depth-of-focus can be defined as the amount of defocus that can be tolerated without incurring an objectionable lack of sharpness of an image.[70] Projected into free space, this dioptric interval defines the depth-of-field of the eye.

The average values for depth-of-focus are typically between ±0.4 to 0.6 D.[70] It comprises values larger in infants and in presbyopes than in the rest of the population.[70] The large values in infants are due to a neurological development process and in presbyopes are due to normal anatomically pupillary miosis with age.[3,70] Typically, depth-of-focus increases with eccentricity, approximately 0.11 D per diopter of eccentricity up to 8 degrees has been reported.[43]

It is inversely proportional to the pupil diameter and the focal length of the eye. Contrary, it is directly proportional to the just detectable retinal blur circle. Thus, depth-of-focus can also affect the overall accommodative response. It is used by the accommodative system to exert the minimum effort on the ciliary muscles. In other words, the typical values of the lag of accommodation (from 0.25 to 1.25 D) are similar to normal values of depth-of-focus, thus, despite the eye can be optically defocused in accommodation, it does not perceive blur because it is within the range of tolerated depth-of-focus. Moreover, it has been reported that with accommodation there exists some degree of pupillary miosis (0.25 mm/D of accommodation), which in turn increases depth-of-focus.[3]

4.1.5.2. Optical aberrations

The relationship among acommodation and aberrations has been extensively studied in many different ways and for different purposes. Briefly, there are several studies that showed that longitudinal chromatic aberration is a cue for accommodation.[71–73] There are studies that showed that the main change of high order aberrations during accommodation occurs for the spherical aberration which shifts towards negative values.[74,75] In this sense, Gambra *et al*.[14] showed that the presence of negative spherical aberration reduces accommodative lag. Other studies suggest that the presence of high order aberrations may decrease accommodation accuracy due to an increase of depth of focus,[76] which is also consistent with Gambra *et al*.[14] who also found that overall, correcting high order aberration improves accommodative accuracy and decrease fluctuations of accommodation. Although Chen *et al*.[77] did not find that correcting high order aberration improves accommodative accuracy. Finally, it has been recently shown that the eye's monochromatic aberrations are not necessary to track dynamic sinusoidal accommodative stimuli.[78]

4.1.6. Dysfunctions of the accommodative system

The accommodative system may have a consistent, non-pathological, anomalous response, which is described as an accommodative dysfunction. The non-pathological accommodative dysfunctions are accommodative insufficiency, accommodative excess and accommodative infacility. Accommodative dysfunctions has been reported to occur in 60 to 80 percent of patients with binocular vision problems.[79]

Accommodative insufficiency occurs when the amplitude of accommodation is lower than expected for the patient's age and is not due to sclerosis of the crystalline lens. Patients with accommodative insufficiency usually demonstrate poor accommodative sustaining ability and its main symptom is asthenopia after sustained near work. It has been reported an approximated prevalence of 9% in non-presbyopic subjects.[19] Accommodative excess is the inability to relax accommodation readily and its main symptom is blurred vision at distance after near work. There is an approximated prevalence of 5%. Accommodative infacility occurs when the accommodative system is slow in making a change and its main symptom is difficulty changing focus to various near and far distances, the prevalence is around 2.5%.[19,79]

In all of these dysfunctions it has been shown that vision training can alleviate the symptoms and improve the accommodative performance. The accommodative system can be improved in terms of precision and accuracy (i.e., less variability of the response and reduced lag of accommodation)[20,80] and dynamics (i.e., reduced latency and increased response amplitude).[81,82] Training the accommodative system involves different kinds of visual exercises, being the accommodative facility test the most common and effective,[18,83,84]. This test can be used for both training and diagnosis purposes. It consists on measuring (in cycles per minute) the ability of the eye to accurately and repeatedly change the accommodative state between two focal planes during a period of time. This test is usually performed either at far distance (i.e., the fixation target is at 6 m distance) or at near distance (i.e., the fixation target is at 0.4 m distance). The accommodative demand for each focal plane is typically lens-induced: at near distance it is typically used a pair of ophthalmic lenses with power of +2 D and -2 D, which stimulates, respectively, +0.50 D and +4.50 D, and at far distance, it is only used a lens of -2 D, which is used to stimulate an accommodative demand of +2.17 D and +0.17 D (the latter one would correspond to a lens of zero power). This test is performed in children and in young adults. For children between 6 and 12 years old, 6 cpm is the expected finding when the test is performed monocularly.[85] Analogously, between 13 and 30 years old, the expected finding is 11 cpm.[18] There is no normative data for pre-presbyopic adults (between 30 and 40 years old).[86] As previously mentioned in section *Dynamic aspects of accommodation*, the predictability of the stimulus given the repeated sequence of changes between two accommodative demands could affect all these normative values. This will be one of the aspects specifically addressed in this thesis.

4.2. Refraction

The refractive error of an eye is typically defined by three parameters: sphere power in diopters, cylinder power in diopters and axis orientation in degrees. All of them together characterize how the focal stimulus plane is axially positioned relatively to the retina once imaged through the eye.[2] There are three fundamental refractive error types: myopia, hyperopia and astigmatism. The methods for obtaining the refractive error can be classified in two groups according to their independence with regard the observer's response: subjective and objective. The basic aspects of each method as well as their advantages and limitations are explained in the following sections.

4.2.1. Objective Refraction

An objective refraction method is considered when the refractive status of an observer's eye is obtained without the observer's response. If the refractive status is obtained with minimum input from the clinician, the method is said to be automated. Retinoscopy, autorefraction and wavefront refraction are considered objective methods. Nowadays, most of the autorefractometers and wavefront sensors are automated, but retinoscopy is still highly dependent on the clinician skills. Objective refraction techniques are typically used as starting point of subjective refraction.

4.2.1.1. Retinoscopy

A retinoscope is a small, handheld device that emits a stripe of visible white light toward the pupil of the eye being analyzed and allows the operator to view the red reflex of light reflected and scattered back through the pupil from the ocular fundus. It is the operator who moves (rotates) the retinoscope to sweep the stripe across the pupil in a certain meridian (Figure 5).[3,87]

According to the direction, speed of motion, brightness and width of the red reflex of light the clinician can neutralize (i.e., there is no appreciable motion of the light reflected back) the refractive error by adding lenses in front of the measured eye while the contralateral eye is fixating at a distant target under fogging conditions (i.e., over-plused) (Figure 5A). The distant target is typically a high contrast large optotype and the room is darkened.

This technique is said to be the closest to clinician subjective refraction and repeatable.[88] One reason is due to a better control of accommodation than other objective techniques given the clinician can observe the patient's pupil diameter and the reflected light features, which change with accommodation, thus, the clinician can act accordingly to be sure that accommodation is not significantly fluctuating so the final result is more robust.

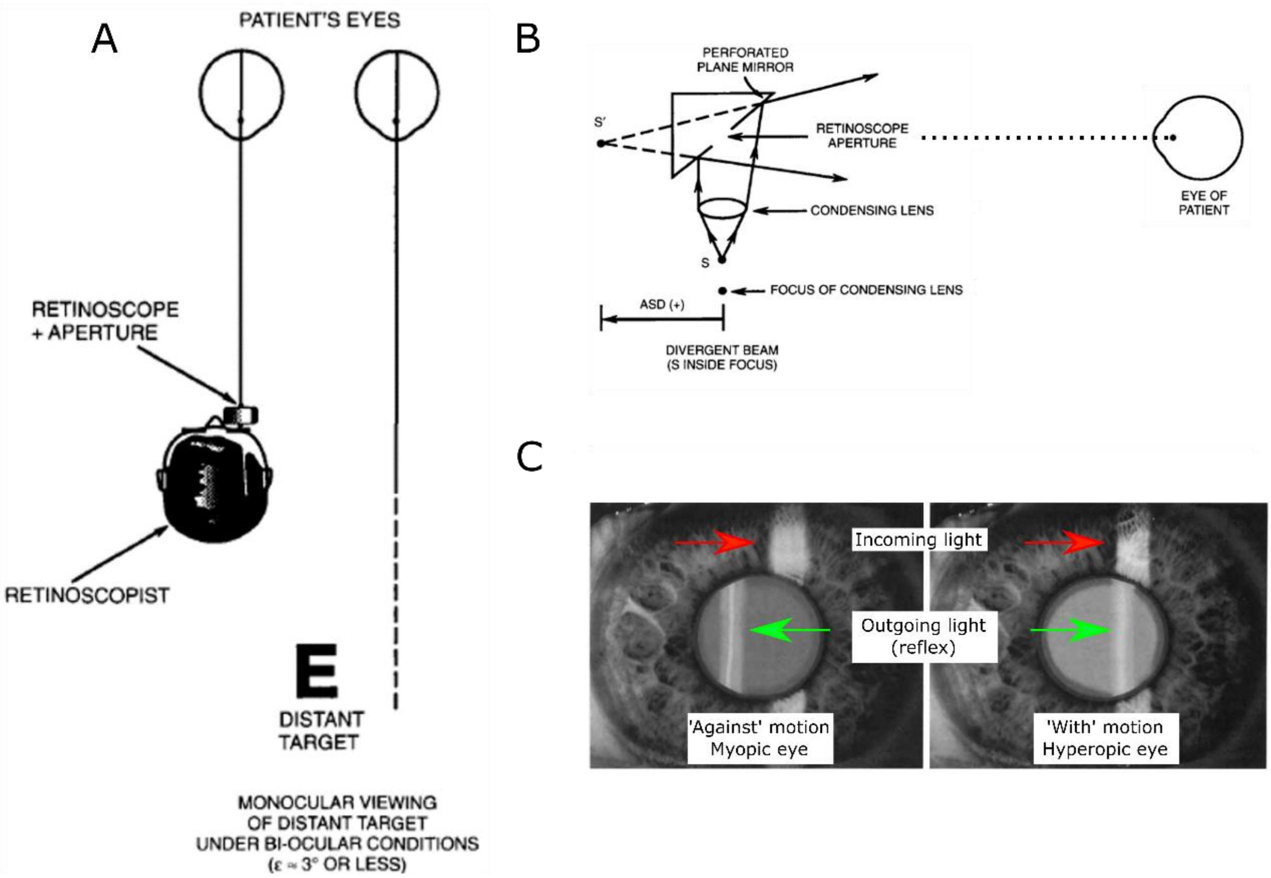

Figure 5. A: Typical position of the retinoscopist, patient and fixation test. B: Optical system of a typical (divergent) retinoscope. C: The fundus reflex (green arrows) obtained in a myopic and in a hyperopic eye when illuminated with a streak retinoscope (red arrows). Adapted from Borish's clinical refraction.[3]

Old studies reported repeatabilities of retinoscopy between ±0.25 D and ±0.50 D in each meridian and ±5º for axis cylinder.[89,90] A recent study found that 80% of intra- and inter-examiner measures fell within ±0.50D for spherical and cylindrical components of cycloplegic retinoscopy in young children.[91] Another recent study reported 95% limits of agreement for 2 repeated measures of ±0.33 D for the spherical equivalent using retinoscopy in young adults.[92]

4.2.1.2. Autorefraction

An autorefractometer (or autorefractor) is a computer-controlled optical system that measures the refractive error of an eye analyzing how light is reflected and scattered back of the eye.[40] The first commercial autorefractor appeared in the fifties and was marketed by Bausch and Lomb.[93] Since then, many different companies have commercialized autorefractors based on different optical principles and with different specifications.[94–97]

It is worth to remark that most of them have used near infrared radiation (NIR) as the light source (instead of visible light) to increase the reflectance from the fundus and also to avoid measurement artifacts given by subject's photophobia, pupil constriction or accommodation. In contrast, using NIR light has an important disadvantage: refraction must be compensated with a correction offset of around 0.7 D – 1.0 D. This is due to two main reasons. Firstly, the NIR penetrates deeper into the retina than the visible light. Secondly, there is a chromatic aberration provided by the difference in refractive indices between NIR and visible light, Llorente *et al.*[98] found an average focus shift between 787 nm and 543 nm of 0.72 D.

Autorefractors can be classified in two categories: those that use a nulling process to find the refractive error of the eye and those that use an open-loop measurement process. An instrument using a nulling principle changes its optical system until the refractive error is neutralized. Contrary, the open-loop autorefractors do not correct the refractive error, they just analyze the properties of the backscatter light from the fundus. Nulling autorefractors can be more accurate and precise whereas open-loop autorefractors are faster and usually easier to assemble, i.e., they are not required to have moving optical systems and often require less components. There are 5 different general optical principles for autorefraction: the Scheiner principle;[99] the retinoscopic principle;[100] the best-focus principle;[101] the knife-edge principle;[102] and the image-size principle.[96]

Accommodation control imposes a challenge in autorefraction. Most autorefractors are monocular measurement devices and use a spherical fogging technique to blur the fixation target (up to +2.0 D) while measuring in order to minimize fluctuations or spasms of accommodation.[103,104] This is typically done by means of a Badal optometer. However, spherical fogging does not perform well in people with high astigmatic errors or people who is overly sensitive to the perceived nearness of the device during measurements as well as the closed-field of view provided by the device. These two latter conditions, which bias the refractive error measurement into the minus direction, are known as proximal accommodation and instrument accommodation artifacts,[7] respectively. When accommodation artifacts are present during the measurement, it is recommended to instilled cycloplegic agents before measurement. This is an alternative of the fogging technique especially recommended in young subjects below 20 years of age.[105]

Most autorefractors sample a central pupil area of 2.5 to 3 mm, thus monochromatic aberrations, especially spherical aberration, is of little concern under these circumstances.[3] Although if all pupil area were sampled, the effect of spherical aberration would be larger and refraction could be more accurate if included in the refractive error computation.[106,107]

Autorefractors are, in general, very repeatable since they do not depend on the patient's response or the clinician's skills. For instance, Pesudovs *et al*.[108] compared the repeatability (test-retest) of two well-known autorefractors (Topcon KR-8000, Nidek AR-800) and found standard deviations for the spherical equivalent of ±0.04 D and ±0.07 D, respectively. In terms of agreement, Sheppard *et al*.[96] compared autorefractor readings of the WAM-5500 (Grand Seiko Ltd., Japan) with the subjective refraction and found limits of agreement for the spherical equivalent of ±0.75 D. In addition, older studies[109,110] that compared autorefractor measurements with subjective refraction found limits of agreement around ±0.95 D.

4.2.1.3. Wavefront refraction

This technique estimates the wavefront aberration function of the eye. It does not only provide the sphere, cylinder and axis orientation but also information on more subtle eye imperfections, namely high order aberrations. This is the main reason why this technique is not embedded within autorefraction.

There are two main approaches to estimate the wavefront aberration function of the eye: the Hartmann-Shack technique[111,112] and the ray tracing technique.[112,113] On the one hand, the Hartmann-Shack measures the shape of the wavefront that is reflected and scattered out of the eye from a point source on the fovea. An array of microlenslets is used to subdivide the outgoing wavefront into multiple beams which produce spot images on a video sensor. The displacement of each spot from the corresponding non-aberrated reference position is used to determine the shape of the wavefront (Figure 6). On the other hand, the ray tracing technique consists on projecting a thin laser beam into the eye, parallel to the visual axis and determines the location of the beam on the retina by using a photodetector. Once the position of the first light spot on the retina is determined, the laser beam is moved to a new position, and the location of the second light spot on the retina is determined. This process is repeated several times and analogously to the

Hartmann-Shack technique, the displacement of each spot from the corresponding non-aberrated reference position is used to determine the shape of the wavefront.

Once displacements of each sampled point is obtained by any of these two techniques, the wavefront aberration function can be retrieved. It should be mathematically expressed -according to the international standards[114] with the Zernike polynomial expansion, which is a weighted sum of functions that are orthogonal over the unit cercle, which means that each mode or polynomial is independent from each other; thus, when one mode or polynomial is modified the rest remain unaltered.[115] These functions are particularly useful in visual optics due to its similarity with the ocular aberrations and due to the eye's pupil is almost circular. The lower order terms piston, tip and tilt are usually neglected and computed as a zero value. On the contrary, the remaining low order terms -i.e., second order- are the most important and can be expressed as the common sphere and cylinder notations used in optometric fields, they are easily corrected using, for example, spectacles or contact lenses.[116] The higher order Zernike polynomials -third order or more- are traditionally not correctable by such methods, although nowadays adaptive optics systems makes it possible.[117]

Wavefront sensors are typically quite repeatable in comparison to subjective refraction. For instantce, Otero *et al*.[118] analysed the repeatability (averaging 3 measurements) of a wavefront sensor (AOVA, Voptica S.L., Spain) and obtained within-subject standard deviations for the sphere of ±0.17 D. In terms of agreement, Cooper *et al*.[119] found better agreement between a wavefront sensor and subjective refraction than an autorefractor. Although in both cases, astigmatism was found to be overcorrected, which precluded them to base a spectacle prescription based solely on their readings.

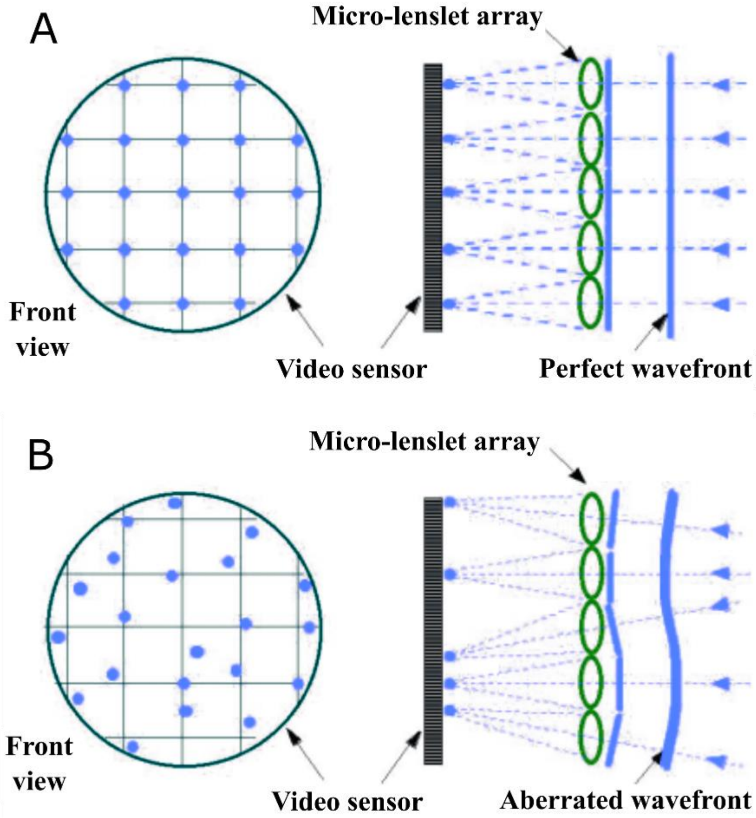

Figure 6. A: Schematic view of the multiple spots generated by the micro-lenslet array of the Hartmann-Shack technique over the video sensor in A, perfect wavefront and B, aberrated wavefront. Adapted from Thibos.[111]

4.2.2. Subjective Refraction

Subjective refraction is based on comparing different dioptric lenses (i.e., spherical and cylindrical lenses) and measuring changes in visual acuity to arrive at the dioptric lens combination that maximizes it.[40] It is considered the gold standard of refraction[3] (i.e., the most accurate method) and it is dependent on both the clinician skills and the observer's response. There exists two basic approaches to obtain the subjective refraction of an observer: the monocular and the binocular subjective refractions.

4.2.2.1. Monocular subjective refraction

The basic procedure of monocular subjective refraction comprises six sequential steps. Most of them also apply to binocular subjective refraction: 1) starting point, 2) fogging, 3) astigmatic correction, 4) monocular spherical endpoints, 5) spherical equalization and 6) binocular spherical endpoints. Steps 5 and 6 are bi-ocular and binocular, respectively.

1) Starting point

Despite monocular subjective refraction can be initiated without any knowledge on prior refractions, it is often not the case. The objective refraction acts usually as the starting point of refraction. In case the objective refraction is not accessible (for any reason) the current spectacle prescription may be used as the starting point of refraction.

2) Fogging

This step aims to maintain accommodation relaxed during the subjective examination. Accommodative spasms and fluctuations in accommodation can bias the observer's response to certain sphero-cylindrical refraction and fogging is the technique typically used to avoid these issues. It consists on leaving the observer myopic in all meridians (e.g., by incrementing the spherical plus power of the refraction that is being tested) until the observer's visual acuity decays to certain level (e.g., 20/100 or 0.7 logMAR is suggested for eyes capable of attaining 20/20 vision with correction).[3] The magnitude of the fogging is often about 1.00 D but under certain subjects (e.g., young hyperopic subjects) this should be incremented up to 2.00 D to significantly minimize fluctuations or spasms of accommodation. More than 2 D of fogging is not recommended due to potential accommodation artifacts, i.e., accommodation may return to its resting state.[103] Once the observer's visual acuity has decayed, the added plus power is reduced in steps of 0.25 D until the visual acuity is improved sufficiently for astigmatic discrimination (typically 20/30 or 0.18 logMAR). This process is called unfogging and astigmatic discrimination is the next sequential step. Notice that it is recommended for children and young adults in which spasm of accommodation or latent hyperopia is suspected to use cycloplegic drugs to temporally paralyze accommodation.[105]

3) Astigmatic correction

There are several stimulus specifically designed to determine the astigmatic correction of the eye. Among them, the clock-dial (Figure 7A) is widely used due to its simplicity. The observer is just required to indicate which line/meridian (if there is any) appeared 'sharper' or 'brighter' and then the clinician needs to adjust the cylinder power and axis until the observer reports an equal level of sharpness in all meridians. Another widespread approach to determine the astigmatic correction is to use the Jackson crossed-cylinder (JCC) technique.[120,121] The JCC has two principal meridians, one with a positive power and one with a negative power. They are typically of ±0.12, ±0.15 or ±0.50 D in magnitude. The JCC procedure comprises two sequential steps: the first step is used to obtain the axis orientation and the second step is used to obtain the cylinder power. Notice that while the clock-dial is typically used under fog, the JCC procedure it is not, thus if the JCC method is chosen, the unfogging from the previous step should be continued until maximum visual acuity.

In the first step, the axes of the JCC are placed at angles 45 degrees to the axes of the starting point of refraction (Figure 7B). Then, the JCC axes positions are reversed (rotated 90º) and the observer need to identify in a forced-choice manner in which axes position the stimulus target is seen clearer. The clinician should change the JCC axes positions in the negative direction (it can be clockwise or counterclockwise, it is the direction where the most negative meridian is) and ask the observer again. The iterative process finishes when the observer reports 'equal sharpness' in both astigmatic options. At this moment the cylinder axis is determined.

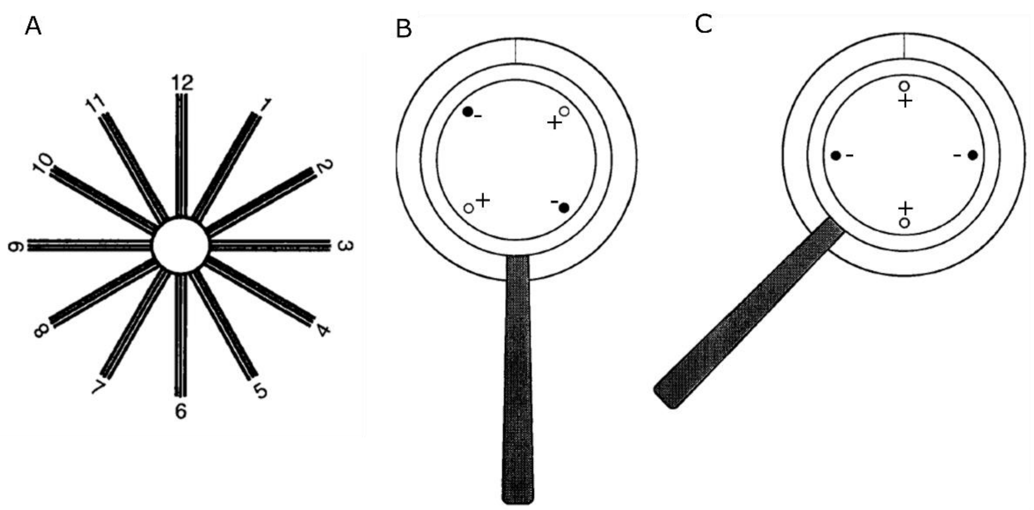

Figure 7. A: Clock-dial test. B: the meridional orientation of Jackson cross-cylinder lens (JCC) in this case can be used to assess the cylinder axis of an eye with-the-rule (the most myopic meridian is vertical) or against-the-rule astigmatic error. C: the meridional orientation of JCC lens in this case can be used to assess the cylinder power.

In the second step, the axes of the JCC lens are placed coincident with the axes of the previously determined cylinder axis (Figure 7C). Analogously to the previous step, the clinician flips the JCC between the two axes positions and asks the observer which option he or she sees clearer. The clinician reduces or increments (in 0.25 D-step) the cylinder power depending on the observer's answer, i.e., the observer compares when the minus axis of the JCC is aligned with the axis of the minus correcting cylinder to when the JCC is flipped such that the plus axis of the JCC coincides with the axis of the minus correcting cylinder. If addition of minus-cylinder power is preferred, the minus power of the correcting cylinder is increased, usually by an increment of -0.25 DC. If subtraction of minus-cylinder power is preferred (white dots aligned), the minus power of the correcting cylinder is reduced in steps of 0.25 DC. The forced-choice tests are repeated and the power of the correcting cylinder adjusted accordingly until the observer reports ‘equal sharpness’ in both astigmatic options, in other words, the interval of Sturm is the shortest possible (in Figure 8 a subject would choose the option B). If a point of equal sharpness is not achieved, it is a general recommendation to consider the weaker of the cylinder powers under choice.

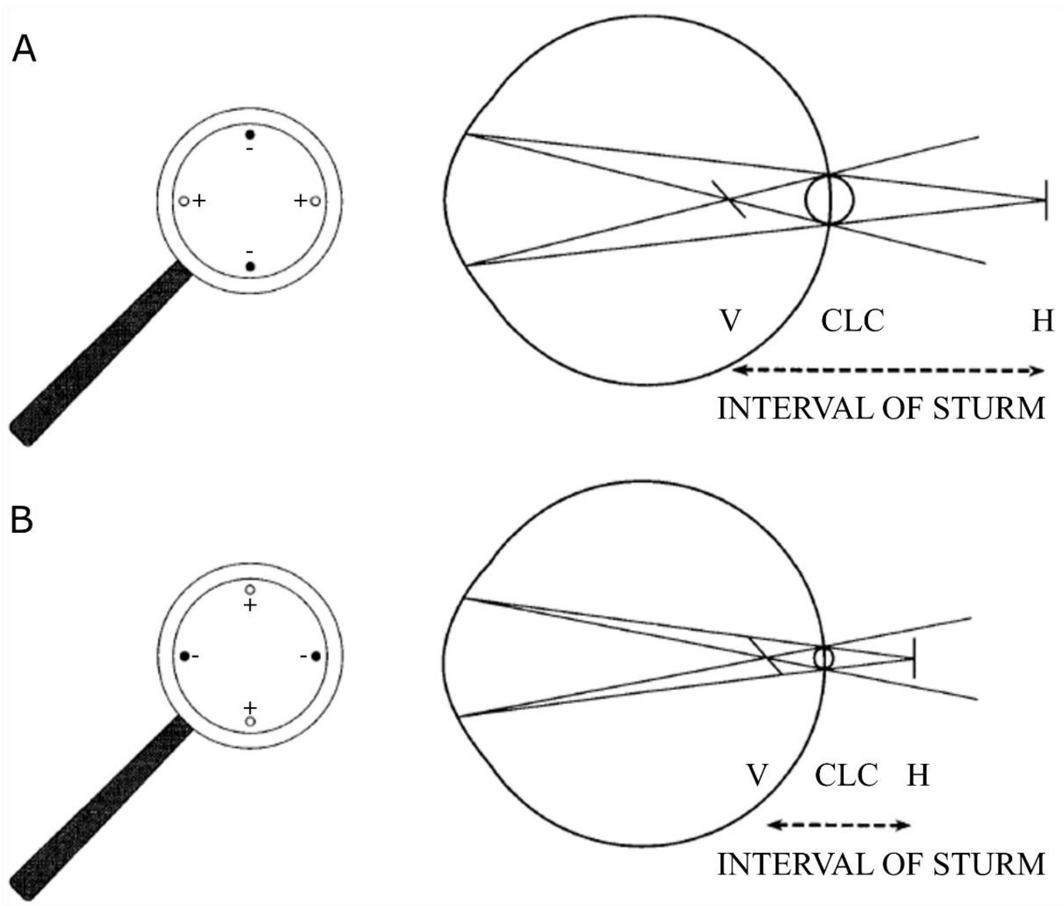

Figure 8. An eye with-the-rule astigmatism (the most myopic meridian is vertical). A: the Jackson cross-cylinder lens with the plus axis (white dots) aligned with that of the minus-cylinder axis of the astigmatic error. B: the Jackson cross-cylinder lens with the negative axis (black dots) aligned with that of the minus-cylinder axis of the astigmatic error. V: vertical meridian. H: Horizontal meridian. CLC: circle of least confusion. Adapted from Figure 20-22 of Borish’s clinical refraction.[3]

4) Monocular spherical endpoints

Once the astigmatic correction is obtained, the eye is fogged by an amount of approximately +1.00 D and then it is unfogged until reaching the maximum plus power with best visual acuity. There are other methods to achieve the monocular spherical endpoints such as the Duochrome or the method of the reduced contrast.

5) Spherical equalization

The purpose of this step is to balance the accommodative efforts required for the two eyes. The classical procedure consists on dissociating (e.g., by means of a vertical prism) and asking the observer to compare the same right and left eye visual acuity line (that is seen bi-ocularly). The clinician should add +0.25 D to the observer's eye that sees the stimulus clearer. This process is repeated two times at the most. If more than 0.50 D is needed to equalize, it is recommended to start again the monocular spherical endpoints. Traditionally, this procedure is only performed when equal visual acuities are obtained in the monocular spherical endpoint determination. If monocular visual acuities are different in both eyes or the observer does not have binocular vision this step is either avoided or more elaborated procedures should be performed.[3]

6) Binocular spherical endpoints

The same methods of the monocular spherical endpoints can be applied to this step to find the maximum plus power with best binocular visual acuity.

4.2.2.2. Binocular subjective refraction

The binocular subjective refraction procedure is the same as that described for monocular testing, except that both eyes here remain unoccluded during all the steps and a dichoptic stimulus is used (each eye sees a different stimulus).

The binocular subjective refraction testing provides some advantages with respect the monocular testing. Accommodation, convergence and light adaptation are more constant under binocular subjective refraction which provide a more realistic way of testing.[122,123] Clinical conditions in which binocular refraction may be advantageous are hyperopic anisometropia, latent hyperopia, pseudomyopia or amblyopia among others.[124]

4.2.2.3. Automated subjective refraction

The automated subjective refraction aims to obtain the subjective refraction without the need of a clinician. As mentioned in the introduction, this can be especially useful in developing countries where a primary eye care service is not accessible for many people[16,17] and also in high-volume practices to reduce costs and time.

In the past some companies looked forward an automated subjective refraction instrument. Just to mention some of them, there were the Humphrey Vision Analyzer,[125,126] the American Optical SR-IV,[127–129] the Bausch and Lomb Integrated Vision Examination System[130,131] and the Topcon BV-1000.[132,133] None of them where a commercial success: the hesitancy in which practitioners accepted that the automated device could eliminate the role of the refractionist and also the high costs of these automated devices limit the penetration of automated subjective refraction methods in the market.[3] The most recent device was the Topcon BV-1000, it replicated almost all of the monocular subjective refraction steps. In terms of accuracy, limits of agreement for the spherical equivalent of ±0.69 D and ±0.82 D were reported.[132,133]

4.3. Lens-based technologies to study refraction and accommodation

Lens-based technologies is a broad term that can describe almost all types of technologies used in vision science. However, for the purpose of this thesis there are a couple of optical elements that deserve a specific mention: the Badal optometer and the electro-optical varifocal system.

4.3.1. Badal optometer

The Badal optometer has been used widely in ophthalmic instruments and in vision research as tool for presenting fixation targets at different stimulus vergences.[26,28] Its basic configuration is a target and a lens, the latter being placed at its focal length from the eye (Figure 9). This simple system has two characteristics that make it useful in visual optics, accommodation, visual simulators or virtual reality displays: there is a linear relation between target position and vergence and there is angular size constancy of the target. Limitations of the basic configuration are reduced negative vergence range, target resolution and proximal accommodation effects (also called instrument myopia).[7] Some optical design approaches have been proposed to minimize the first two limitations.[28]

Interestingly, some previous studies have reported poorer accommodative responses when accommodation is stimulated with lenses compared to free space targets, which is more pronounced in myopes.[29–31] None of these studies have provided a definite answer of whether the Badal optometer stimulates accommodation similarly to real space targets.

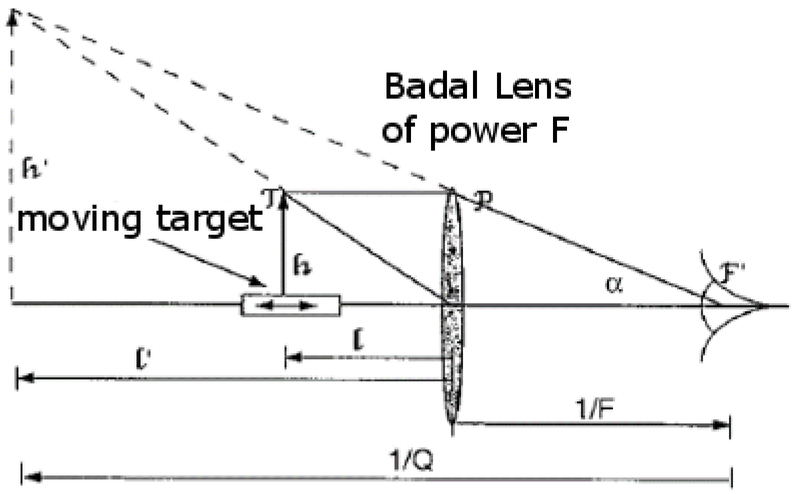

Figure 9. The simple Badal optometer. From Atchison *et al*.[28]

4.3.2. Electro-optical varifocal system

An electro-optical varifocal system is a computer-controlled optical system capable of changing the stimulus vergence automatically and repeatedly. This can be considered an emerging technology since it is now becoming more and more available for research purposes but also for industrial applications.[11,118,134,135]

There are different technologies within this category, even a motorized phoropter could be considered an electro-optical varifocal system. On the one hand there exists the electro-optical lenses that can change spherical profile of the incoming wavefront by means of applying voltage to the lens.[11,135] On the other hand there exists the well-known spatial light modulators[10,13,136] and the deformable mirrors[14,117] that can change not only the sphero-cylindrical profile of the incoming wavefront but also they can achieve much more complicated profiles. Both the spatial light modulators and deformable mirrors are commonly used in adaptive optics systems to correct or induce certain high order aberrations.[117] Of course, due to its simpler design and functionality, electro-optical lenses are much cheaper than deformable mirrors or spatial modulators. Thus, when only control over pure-spherical profiles are needed, electro-optical lenses might be a more appealing choice.

It is worth mentioning that electro-optical varifocal optical systems have important applications in the field of visual simulators[10,11] and stereoscopic virtual reality systems.[134,137] On the one hand, visual simulators are typically used to psychophysically test certain wavefront profiles such as those experienced with multifocal intraocular lenses,[10,11] but, they can have (with some limitations and modifications) the potential to perform optometric tests such as the subjective refraction or the accommodative facility test since they are somewhat computer-controlled phoropters, however, it is interesting to note that these applications are not fully explored yet.

On the other hand, stereoscopic virtual reality systems are important for gaming purposes[12] and for some ophthalmic applications (in fact, visual simulators can be considered a specific type of virtual reality/augmented reality systems), but they still have a fundamental limitation, which is the accommodation-convergence mismatch.[137] That is, the plane of convergence is not coincident with the plane of accommodation (Figure 10). The convergence plane is typically controlled by the binocular disparity induced, for instance, in two screens (one for each eye) and the accommodation plane is determined by the distance at which the screens are placed. This mismatch lead to poor visual performance, fatigue and visual discomfort.[138] Despite that, it can be ‘removed’ or at least controlled if the stereoscopic system integrates an electro-optical varifocal system in each eye-path that conjugates each screen with the convergence plane. This optical system must be synchronized with the convergence plane, thus it is necessary to know at which part of the scene the patient is looking at. It can be done by just assuming where the viewer is fixating at in the scene or by adding an eye-tracker that maps the intersection of both pupillary axis onto the scene.[137]

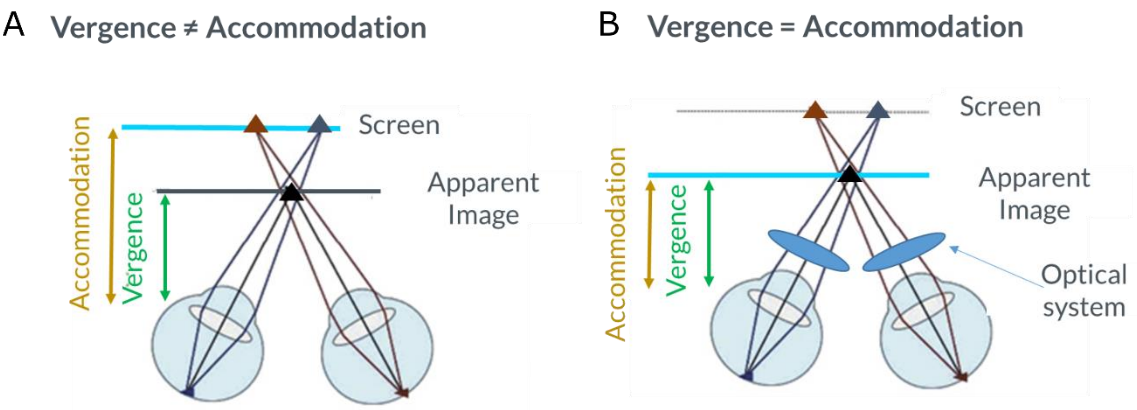

Figure 10. Schematic representation of the accommodation-convergence mismatch (panel A) and how with an optical system it can be compensated (panel B).

However, there is another fundamental limitation, real scenes comprise peripheral depth cues at different focal planes.[25] Even though the fixation object is displayed in a virtual reality system at correct convergence and accommodation planes, the peripheral objects will be displayed at the same accommodation plane, therefore as along as the viewer properly focus in the fixation object, all objects in the scene will be seen sharp, which is not analogous to what happen in a real environment.

We shall recall that all the objects that are at different planes with respect the focused one must be seen blurred by the viewer. This blurring depends mainly on the relative distance between objects, refractive error and aberrations of the viewer's eye. To minimize this limitation, it can be applied some computational blurring to the peripheral objects of the scene in order to simulate peripheral objects at different distances although it increases the setup complexity. An alternative to a stereoscopic display with an electro-optical varifocal system and an eye-tracker, there are the so-called volumetric systems, which can be spatially multiplexed[139] or time multiplexed.[140] In the case of time multiplexed systems they require as well very fast electro-optical varifocal systems capable of changing the focal position fast in order not to perceive flickering (the temporal resolution of the electro-optical system must operate at a frequency equal or above the number of focal planes multiplied by 60 Hz).[140]

5. Methodology

5.1. Study 1. Does the Badal optometer stimulate accommodation accurately?

PREVIOUS NOTE: The following text in this section corresponds to the article: Aldaba M, **Otero C**, Pujol J, Atchison D. Does the Badal optometer stimulate accurately? *Ophthalmic Physiol Opt.* 2017;37(1):88-95.

5.1.1. Introduction

The Badal optometer has been used widely in ophthalmic instruments and in vision research as a tool for presenting fixation targets at different stimulus vergences. Its basic configuration is a target and a lens (Figure 11), the latter being placed at its focal length from the eye.[26,28] This simple system has two characteristics that make it useful in visual optics: there is a linear relation between target position and vergence and there is angular size constancy of the target. Limitations of the basic configuration are reduced negative vergence range, target resolution and proximal accommodation effects (also called instrument myopia).[7,28] Some approaches have been proposed to minimise the first two limitations.[28]

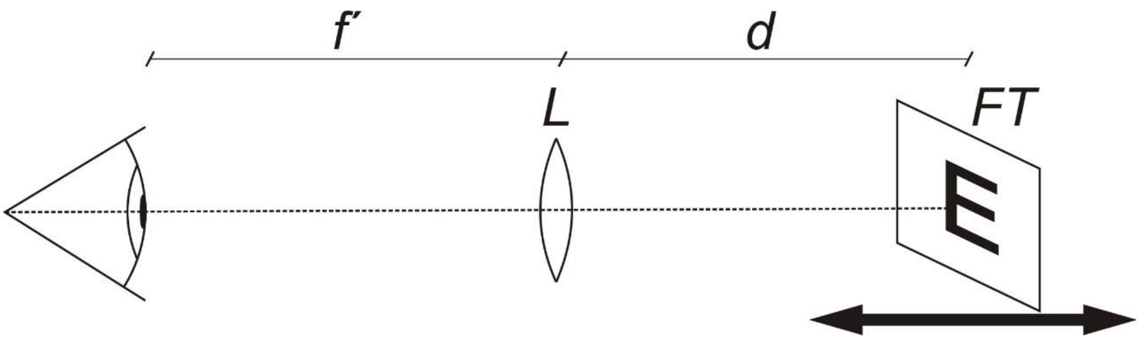

Figure 11. Scheme of the Badal optometer, consisting of lens L and moveable fixation test FT. The distance f ' from the eye to the lens is the focal length of the lens and the distance d from the lens to the fixation test determines the stimulated vergence at the eye.

One application of the Badal optometer is the study of accommodation.[14,69,141–144] However some authors have reported difficulties accommodating to Badal targets. Some studies have found poorer responses to lens-induced than to pushup stimulation, which is more pronounced for myopes than for emmetropes.[29–31] Stark & Atchison[27] studied whether the Badal optometer leads to accommodative responses different from targets in real space and concluded that responses were generally equivalent, but some participants had difficulty accommodating to the Badal optometer.

The Badal optometer system affects a number of parameters that might contribute to accommodation response. It removes or alters monocular depth cues to accommodation.[27] It maintains a constant angular size image, while in natural viewing this changes with object distance.[145–147] In a Badal system the scene is restricted to two dimensions, while under natural viewing conditions there is often a peripheral interposition of objects in depth, such as the examiner, the rod for near targets and the background. The lens size of the Badal optometer may reduce the field of view.[148] In addition to effects on monocular depth cues, instrument 'accommodation' may occur due to the awareness of instrument proximity.[7,148]

From our understanding, the question of whether the Badal optometer stimulates accommodation similarly to real space targets remains unanswered. The objective of this study was to analyse the usefulness of a Badal optometer for accommodative stimulation. This was done by comparisons of accommodative responses with those for real space targets. Parameters that might contribute to differences in response were systematically isolated: stimulation method (real space targets vs targets viewed through a Badal lens), field of view, instrument's cover proximity, the looming effect, and the peripheral interposition of objects in depth.

5.1.2. Methods

Participants

The study was approved by the Ethics Committee of Hospital Mutua de Terrassa (Terrassa, Spain), it followed the tenets of the Declaration of Helsinki, and all participants gave informed written consent. Participants were recruited from staff and students of the Faculty of Optics and Optometry at the Technical University of Catalonia (UPC, Terrassa, Spain). They were untrained in the use of the Badal optometer and thus can be considered to be naïve. Criteria for inclusion were best spectacle-corrected visual acuity of 0.10 logMAR (Snellen 6/7.5 or 20/25) or better and no history of any ocular condition, surgery and/or pharmacological treatment. Participants wearing spectacles were excluded to avoid measurement artefacts caused by reflections from lens surfaces. Consequently, only emmetropes and contact lens wearers were included, with spherical and cylindrical components of over-refractions within ±0.25 D. The upper age limit was set at 27 years old to help ensure good amplitude of accommodation. Mean age ± standard deviation of 28 participants was 24.3 ± 2.1 years (range 18–27 years). One eye of each participant was included, with mean corrected visual acuity of -0.14 ± 0.06 logMAR (range -0.20 to +0.02 logMAR; mean Snellen ~6/4.5 or 20/15) and mean subjective amplitude of accommodation of 9.5 ± 1.9 D (range 7.1 – 15.4 D).

Instrumentation

The Grand Seiko WAM-5500 autorefractometer projects a target through a 2.3 mm diameter annulus onto the retina and determines refraction by measuring size and shape after reflection from the retina through the optics of the eye.18 Subjective refraction with high contrast targets, even in presence of spherical aberration, is mainly driven by the central part of the pupil[149] and thus the small annulus of the instrument seems reasonable for measurements of refraction. It can measure in static mode (i.e. single shot) and in dynamic mode at a frequency of 5 Hz. The WAM-5500 allows binocular accommodative stimulation through an open-view, and it has been used for measuring accommodation.[150]

The setup consisted of the WAM-5500 autorefractometer and different configurations to stimulate accommodation. There was opaque black paper (2 x 2 m) surrounding the autorefractometer at 50 mm from the participant's pupil plane. The fixation target was a 2.0° black Maltese cross, which is suitable for accommodation studies due to its wide frequency spectrum,[151] surrounded by a white background of luminance 31 ± 3 cd/m^2, which provided the field of view. The color temperatures of light sources were approximately 6500 K. Autorefractometer measurements were taken at target distances, or equivalent positions in a Badal system, of 6 m, 50 cm and 20 cm, corresponding to accommodation stimuli of 0.17 D, 2.0 D and 5.0 D, respectively. The refractions were converted to spherical equivalent refractions. Eight different configurations were used to investigate effects of stimulation method, field of view, instrument's cover proximity, looming effect and interposition of objects in depth. The configurations are summarized in Table 1.

Configuration 1 provided a closed-view autorefractor with a Badal optometer (Figure 12A). The Badal optometer consisted of a 150 mm focal length, 42 mm diameter lens and a moveable fixation target, both attached to a calibrated rod mounted on the WAM-5500. The field of view was limited to 2.5° by a 6.5 mm diameter aperture at the front of the Badal lens. The first surface of the autorefractometer was covered with opaque black cardboard, called the ‘instrument cover’, with a 22.5 mm diameter circular aperture at 50 mm from the participant’s pupil plane. The instrument cover was used to study the possible effect of instrument ‘accommodation’ due to the awareness of instrument proximity.

Configuration 2 was similar to Configuration 1, but the aperture at the front of the Badal lens was removed so that the field of view increased from 2.5° to 15.6° as limited by the Badal lens diameter. Comparison between Configurations 1 and 2 isolated the field of view as a variable.

In Configurations 3–8, the Badal lens was absent, but Configurations 3–7 retained some characteristics of a Badal system. Configuration 3 was similar to Configuration 1, but the Badal lens was removed from the system (Figure 12B) and accommodation was stimulated by real space targets. As in Configuration 1, the field of view was 2.5° by means of the aperture where the Badal lens had been, the angular size of the Maltese cross was constant for all the accommodative stimulations (2.0°) and the instrument cover was retained. Comparison between Configurations 1 and 3 isolated stimulating method (Badal optometer or real space targets) as a variable.

Configuration 4 was similar to Configuration 3, but field of view was increased from 2.5° to 15.6° by changing aperture size to 42 mm. Comparison between configurations 2 and 4 isolated the stimulating method as a variable, and comparison between Configurations 3 and 4 isolated field of view as a variable.

Configuration 5 was similar to Configuration 4, but the instrument cover was removed so that the participant saw through the WAM’s window. Comparison between Configurations 4 and 5 isolated instrument cover as a variable.

Configuration 6 was similar to Configuration 5, but the Maltese cross’s angular size was increased 2.5 times and testing was only for 5.0 D stimulation. Unlike previous configurations, the participant saw the fixation test moving towards the eye (push-up method) from 2.0 D to 5.0 D stimulation. Comparison between Configurations 5 and 6 isolated the looming effect as a variable.

Configuration 7 was similar to Configuration 6, but the aperture was removed so that the field of view was limited by the WAM-5500 window of ≈33.0°.

Configuration 8 was the control condition. It mimicked a conventional open-view accommodation measurement by means of a push-up target (Figure 12C). This configuration was similar to Configuration 7, but with objects at different distances from the accommodative stimulation plane: a coat rack (at 1.50 m from the observer's pupil plane and 8° leftwards), back of a chair (0.33 m, 9° rightwards) and a pen (0.18 m, 15° rightwards). Comparison between Configurations 7 and 8 isolated interposition of objects in depth.

Table 1. The eight setup configurations.

Config.	Stimulation method	Field of view	Instrument cover?	Looming effect?	Interposition of objects?	Accommodation stimuli (D)	Angular size of the test (º)
1	Badal target	2.5º	Yes	No	No	0.17/2.0/5.0	2/2/2
2	Badal target	15.6º	Yes	No	No	0.17/2.0/5.0	2/2/2
3	Real space target	2.5º	Yes	No	No	0.17/2.0/5.0	2/2/2
4	Real space target	15.6º	Yes	No	No	0.17/2.0/5.0	2/2/2
5	Real space target	15.6º	No	No	No	0.17/2.0/5.0	2/2/2
6	Real space target	15.6º	No	Yes	No	-/-/5.0	-/-/5
7	Real space target	33.0º (WAM limited)	No	Yes	No	0.17/2.0/5.0	2/2/5
8	Real space target	33.0º (WAM limited)	No	Yes	Yes	0.17/2.0/5.0	2/2/5

Examination protocol

An optometric examination was performed. The refraction was measured by streak retinoscopy and subjective refraction, with the endpoint criteria of maximum plus power consistent with best vision. Monocular visual acuity with the usual correction was measured and the eye with better visual acuity was selected. Monocular amplitude of accommodation was measured by the push-up method. The fixation test was moved towards the participant at an approximate speed of 5 cm/s with the endpoint criteria of reported blurred vision.

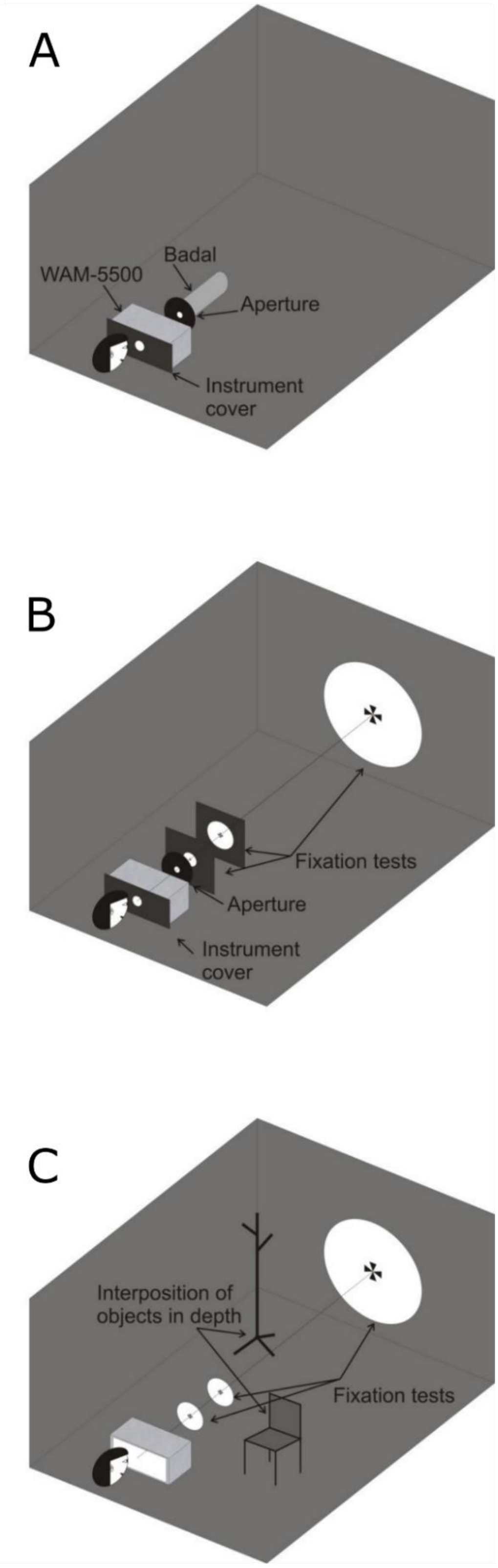

Figure 12. A: Configuration 1 in which the Badal lens is used for stimulating accommodation with small field of view, instrument cover and no depth cues; B: Configuration 3 with real space targets, but with small field of view, the instrument cover kept in place, and the angular size keep constant by varying physical size for different object distances; C: Configuration 8 with real targets in free space and with interposition of peripheral objects in depth.

The participant was blindfolded and moved to the dark experimental room. The participant was not aware of the dimensions of the setup nor the room, which could have biased the accommodative response as suggested elsewhere.[38,152] The blindfold remained in place for 5 min after being seated. In each configuration, the examined eye was uncovered (while the contralateral eye was occluded) and the refraction measured in ascending level of accommodative stimulation (i.e. 0.17 D, 2.0 D and 5.0 D) to minimise difficulties relaxing accommodation.13 The participant was instructed to look at the centre of the cross and carefully focus it. The participant was blindfolded between different accommodative stimuli in order to avoid accommodative cues, except for Configurations 6 and 8 when the participant was allowed to watch while the target distance was changed. For the same reason, the examiner paid special attention to not interfere in the field of view of the participant, except for Configuration 8. The WAM-5500 was used in static mode, 10 consecutive readings per measurement were taken, the sensitivity was set at 0.01 D and vertex distance was set at 0.0 mm. The average of the spherical equivalent of the 10 consecutive readings per measurement for each fixation test distance were considered as the autorefractometer refractions. The accommodation responses for 2.0 D and 5.0 D stimuli were determined by subtracting the refractions for the 0.17 D stimulus from the refractions for these stimuli. The accommodation responses were thus negative, in order to be consistent with refractions. Configurations were randomised except for Configurations 7 and 8 that were performed at the end. That was to avoid participant awareness of room and setup dimensions, which could influence the accommodative response.[38,152]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM; Armonk, NY). Normality of each variable was checked by applying the Shapiro–Wilk test and comparing the skewness and kurtosis statistics to the standard error.

Two different analyses of variances were conducted. On the one hand, a three-way repeated measures ANOVA was performed for the lead/lag of accommodation with the following three factors: field of view (2.5° or 15.6°), stimulation method (Badal or real space targets) and accommodative stimulus (0.17, 2.00 or 5.00 D). This analysis corresponds to the first four configurations and provides straightforward information about interaction effects among these three variables. On the other hand, since the remaining factors (i.e., interposition of objects in depth, instrument cover and looming effect) are not fully permutated, one-way repeated measures ANOVA to compare the eight configurations were conducted for each of the three refractions and two accommodation responses.

In all cases significance was set at $p < 0.05$ and where the assumption of sphericity was violated, the Greenhouse-Geisser correction was used. Where significance was obtained, post-hoc comparisons of configurations were made by paired t-tests incorporating a Bonferroni correction given by the number of pairwise configuration comparisons, with significance $p < 0.05/n$ (for refraction n = 21 for 0.17 and 2.00 D, and n = 28 for 5.00 D of accommodative stimulation; for accommodative response n = 21 for 2.00 D and n = 28 for 5.00 D of accommodative stimulation).

5.1.3. Results

Table 2 gives descriptive statistics of refractions for 0.17 D, 2.0 D and 5.0 D stimuli. The three-way repeated measures ANOVA showed significant effects for the field of view ($F_{1,27} = 9.0$, $p < 0.01$), stimulation method ($F_{1,27} = 5.7$, $p = 0.02$) and accommodative stimulus ($F_{1.1,29.7} = 65.8$, $p < 0.01$). None of the interactions were statistically significant. The post-hoc test performed for each factor showed statistically significant differences in all pairwise comparisons. The stimulation method and field of view showed close to zero effects for 0.17 D of stimulation, while for 2.0 and 5.0 D of stimulation the Badal optometer (vs real space) and smaller (vs larger) field of view induced an approximate reduction in the response of 0.10 D. The one-way repeated measures ANOVA for refractions showed highly significant differences between configurations ($p < 0.001$) for all accommodation stimuli: 0.17 D stimulus, $F_{4.3,116} = 6.5$; 2.0 D stimulus, $F_{3.9,104.6} = 5.0$; 5.0 D stimulus, $F_{7,189} = 5.9$. Also, the analyses of variance for accommodative responses showed highly significant differences between configurations ($p < 0.001$): 2.0 D stimulus, $F_{6,162} = 10.9$; 5.0 D stimulus, $F_{7,189} = 10.0$.

Table 2. Means ± standard deviations of the refractions of different accommodation stimuli for different configurations.

Configuration	0.17D stimulus	2.0 D stimulus	5.0 D stimulus
1	–0.22 ± 0.47	–1.11 ± 0.36	–3.75 ± 0.39
2	–0.17 ± 0.46	–1.25 ± 0.38	–3.83 ± 0..37
3	–0.19 ± 0.46	–1.27 ± 0.35	–3.82 ± 0.39
4	–0.22 ± 0.44	–1.32 ± 0.24	–3.97 ± 0.35
5	–0.14 ± 0.40	–1.37 ± 0.30	–3.98 ± 0.37
6			–3.87 ± 0.35
7	–0.08 ± 0.41	–1.35 ± 0.30	–3.89 ± 0.31
8	+0.03 ± 0.35	–1.37 ± 0.28	-4.08 ± 0.31

Table 3 shows several post-hoc comparisons of configurations, with the differences being the values for the second specified configuration being subtracted from that of the first specified configuration. For 0.17 D stimulus, the refraction of Configuration 8 was significantly more positive (one-way ANOVA) that of the other configurations (except for Configuration 7), indicating more relaxed accommodation for the former. For 2 D and 5 D accommodation stimuli, the accommodation response of Configuration 8 was significantly greater than that of most other configurations (negative values in Table 3).

The other comparisons shown in Table 3 are the ones isolating stimulation method, field of view, instrument's cover and looming effect: none were significant. Of the 60 comparisons not shown in the table, the only ones with significance were the refraction comparisons of 5 vs 1 ($p = 0.001$) at 2.0 D stimulus and 4 vs 1 ($p = 0.001$) at 5.0 D stimulus and the accommodation response comparisons of 5 vs 1 ($p = 0.001$) and 7 vs 1 ($p < 0.001$) at 2.0 D stimulus.

In Figure 13, the Bland and Altman[153] plots are shown comparing the refraction of each configuration against the reference configuration (Configuration 8). The differences in the plot are calculated as the refraction for Configuration 8 minus the refraction of each configuration in the comparison. Thus, as in Table 3, negative differences correspond to greater accommodations for *Configuration 8*. As can be seen, there is a clear tendency to shift from positive to negative differences as the accommodative stimulation is increased.

Table 3. Differences between configurations for the three refractions and two accommodation responses.

Comp.	Parameter studied	0.17D stimulus	2.0 D stimulus		5.0 D stimulus	
		Refraction Mean ± SD (D)	Refraction Mean ± SD (D)	Accommodation response Mean ± SD (D)	Refraction Mean ± SD (D)	Accommodation response Mean ± SD (D)
8 vs 1		+0.25 ± 0.26*	–0.25 ± 0.33*	–0.50 ± 0.43*	–0.33 ± 0.35*	–0.58 ± 0.53*
8 vs 2		+0.20 ± 0.28*	–0.12 ± 0.23	–0.32 ± 0.35*	–0.25 ± 0.27*	–0.45 ± 0.38*
8 vs 3		+0.22 ± 0.28*	–0.09 ± 0.32	–0.31 ± 0.33*	–0.25 ± 0.39*	–0.47 ± 0.41*
8 vs 4		+0.25 ± 0.21*	–0.04 ± 0.21	–0.30 ± 0.31*	–0.11 ± 0.25	–0.36 ± 0.36*
8 vs 5		+0.16 ± 0.15*	–0.00 ± 0.20	–0.17 ± 0.26*	–0.10 ± 0.24	–0.26 ± 0.28*
8 vs 6					–0.21 ± 0.24*	–0.37 ± 0.29*
8 vs 7	IOD	+0.10 ± 0.24	–0.01 ± 0.18	–0.12 ± 0.30	–0.18 ± 0.25*	–0.29 ± 0.36*
3 vs 1	SM	+0.04 ± 0.29	–0.16 ± 0.40	–0.19 ± 0.45	–0.07 ± 0.43	–0.11 ± 0.48
4 vs 2	SM	–0.05 ± 0.31	–0.07 ± 0.32	–0.02 ± 0.40	–0.14 ± 0.27	–0.09 ± 0.39
2 vs 1	FOV	+0.05 ± 0.24	–0.13 ± 0.36	–0.19 ± 0.39	–0.08 ± 0.35	–0.13 ± 0.44
4 vs 3	FOV	–0.03 ± 0.31	–0.05 ± 0.33	–0.02 ± 0.38	–0.14 ± 0.35	–0.11 ± 0.41
5 vs 4	IC	+0.09 ± 0.17	–0.04 ± 0.17	–0.13 ± 0.24	–0.01 ± 0.30	–0.09 ± 0.38
6 vs 5	LE				+0.11 ± 0.33	–0.11 ± 0.33

IOD: Interpositions of Objects in Depth. SM: Stimulation Method. FOV: Field Of View. IC: Instrument Cover. LE: Looming Effect. * Statistically significant. Com.: Comparison.

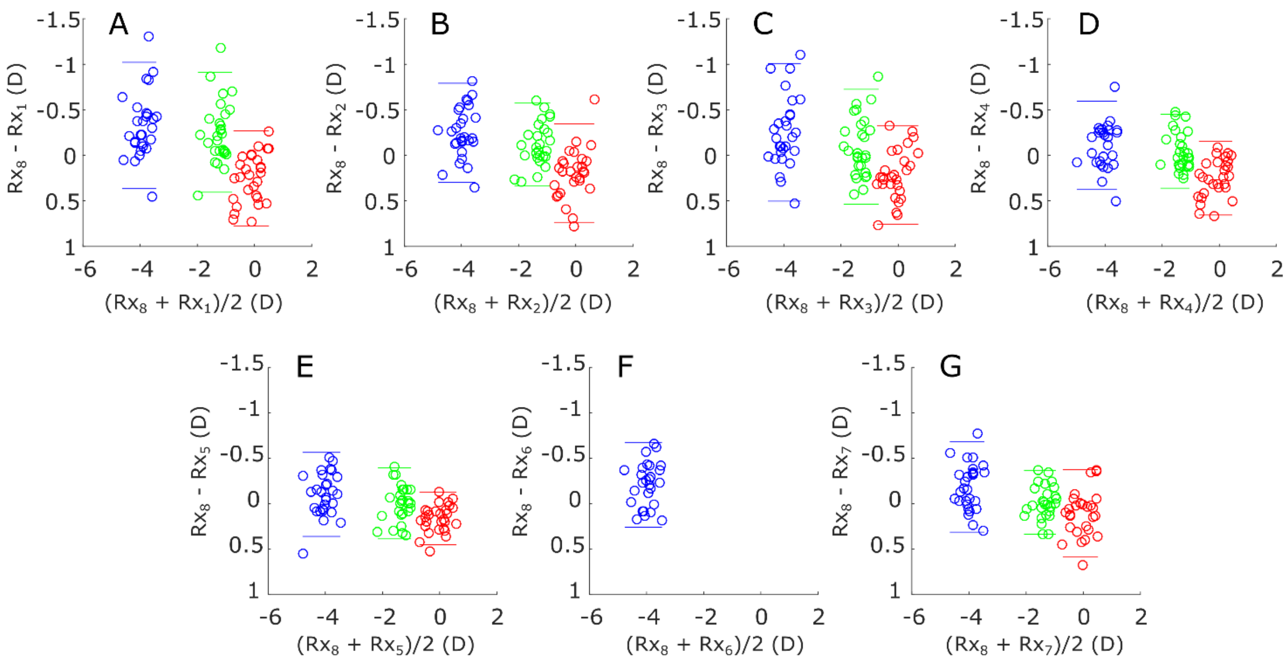

Figure 13. Bland and Altman plots of refractions (Rx) when the different configurations are compared with configuration 8: A) configuration 1, B) configuration 2, C) configuration 3, D) configuration 4, E) configuration 5, F) configuration 6 and G) configuration 7. Refractions corresponding to accommodative stimulation of 0.17 D are in red, those for 2.00 D are in green and those in blue are for 5.00 D. The 95% confidence limits are shown by straight lines.

5.1.4. Discussion

The Badal optometer is widely used for stimulating accommodation. We investigated whether accommodation can be similarly stimulated by means of Badal optometers and real space targets. Two variables were studied: the refraction obtained for each accommodation stimulation and the accommodative response, with the latter calculated as the near refraction minus the far refraction. We investigated the parameters that could contribute to accommodation differences, including stimulation method, field of view, instrument's cover proximity, looming effect, and interposition of objects in depth. The refractions and accommodation responses obtained when stimulated in closed-view with a Badal optometer (Configuration 1) differed from those obtained for an open-view real space stimulation (Configuration 8; Table 3). Interposition of objects in depth was the 'stand-alone' parameter to induce more pronounced differences.

The binocular viewing is the natural viewing condition, including some cues, as vergence and disparity, which are missing in monocular condition.[31] In this study, which only considered monocular vision, Configuration 8 was considered as the closest to natural viewing condition since accommodation was stimulated by means of push-up targets in real space, in open-view and with depth cues.

Despite the participants being in front of the WAM-5500 instrument, Rosenfield & Ciuffreda[152] stated that the open field design of such instruments avoid any extraneous stimuli to proximal induced accommodation. Configuration 1 can be considered as the situation found in closed-view autorefractors. When comparing these extremes for 0.17 D stimuli (Table 3), there was a myopic bias of 0.25 D in the Configuration 1 relative to Configuration 8. This is consistent with studies that have found the eye tends to overaccommodate when looking through closed-view optical instruments.[7,154] However, the accommodation response to 2.0 D and 5.0 D stimuli for Configuration 1 lagged behind those of Configuration 8 by 0.50 D and 0.58 D (Table 3). As previously mentioned, several authors have highlighted accommodative difficulties when stimulating with Badal optometers.[31,155,156] In contradiction with our results, Stark & Atchison[27] found that accommodation for real space and Badal targets is equivalent for practical purposes, but the only difference in their study was the stimulation method (real space or Badal lens) whereas we included other parameters. Some of these studies have referred to accommodation difficulties with Badal targets in a few participants,[155,156] and Stark &

Atchison[27] found that some participants were unable to accommodate to Badal targets. We had no participants who were unable to accommodate. As can be seen in Figure 13, there is a general trend to poorer responses (negative differences) and this is not due to few participants unable to accommodate.

While the stimulation method (real space or Badal targets) might be considered to be the main difference between Configurations 8 and 1, when isolated in the comparisons 3 vs 1 and 4 vs 2 (Table 3), it did not explain by itself those differences. This suggests that there are factors beyond the Badal lens that affect accommodation response. Of the isolated parameters, the interposition of objects in depth was the one which induced more pronounced differences. These findings support the suggestion that a peripheral surround, at a different distance than the fixation target, provides a cue for appropriate accommodation.[152] As there are few other effects of individual parameters, it is likely that Badal optometers affect accommodation through a combination of some or all of limited field of view, cover proximity, lack of looming effect and lack of peripheral interposition of objects in-depth.

The interposition of objects in depth has been the parameter with more marked effects and thus it could be used to improve accommodation response with Badal optometers. This could be further investigated by considering the relative depth at which the peripheral targets allow the most accurate responses. Using wider fields of view could also be a simple way to improve the accommodative response in Badal optometers.

In summary, this study investigated whether the accommodation response to Badal optometer is equivalent to real space targets. We conclude that accommodation stimulated by a Badal optometer embedded in an instrument is not as accurate as under the natural viewing condition. The Badal lens itself does not explain the differences. Introducing peripheral targets, at different distances away from participants than that of fixation targets, has limited influence on response. In isolation, neither field of view, instrument's cover, nor the looming effect, affects accommodation. It is probable that Badal optometers affect accommodation through a combination of some or all of these parameters.

5.2. Study 2. Effect of apparent depth cues on accommodation in a Badal optometer.

PREVIOUS NOTE: The following text in this section corresponds to the article: **Otero C**, Aldaba M, Martínez-Navarro B, Pujol J. Effect of apparent depth cues on accommodation in a Badal optometer. *Clin Exp Optom*. 2017 Mar 21. doi: 10.1111/cxo.12534.

5.2.1. Introduction

In a previous study the closed-loop, steady-state accommodation response (AR) to a Badal optometer was found significantly inaccurate when compared to real space targets.[157] Contributing factors of the Badal lens that could explain the differences are the field of view (FOV), the instrument's cover proximity, the angular size of the stimulus and the peripheral interposition of objects in depth. However, only the interposition of objects in depth significantly affected the response to accommodation, suggesting that a peripheral surround at a different distance than the fixation target might provide an important cue for appropriate accommodation.[152]

Usually the accommodative stimulus in Badal optometers comprise only a fixation target (for instance, a Maltese cross) on an even background in a 2-dimensional surface.[69,158,159] In the context of a specific FOV, an important difference between this configuration and natural viewing conditions is the lack of peripheral depth cues. Two methods can be used to address this dissimilarity. On the one hand, a volumetric (multiplane display) Badal optometer[160] has been recently developed for stereoscopic virtual reality applications. This novel system creates multiple focal planes that theoretically allow real depth representation of objects and thus a 3-D reconstruction of scenes.[139] In these systems the contents of scenes that are in different planes than the fixation target are defocused relatively to the fixation plane. The out-of-focus contents of a scene is optically blurred, i.e., blur arises from the optics of the observer's eye similarly to what occurs in natural viewing conditions. However, these systems are generally difficult to implement and significant technological limitations exist in the number of focal planes that can be displayed.[161,162] In consequence, they are still only used for research purposes. A Badal optometer with a 2-dimensional stimulus comprising apparent depth cues that include rendered out-of-focus blur presents an alternative to volumetric systems. Apparent depth cues influence accommodation in closed-loop conditions. Busby *et al*.[163] analyzed the effect of pictorial images on 3 D of accommodation stimulation and found mean differences of 0.28 D between two positions of a picture with different apparent depth perceptions. Similarly, Takeda *et al*.[164,165] found mean accommodative differences of 0.68 D (for 4 D of AS)[165] and even 0.77 D (for 3 D of AS).[164] In addition, rendered out-of-focus blur may enhance depth perception,[25,166,167] with a potential effect also on accommodation.

To our knowledge, the concepts of apparent depth and rendered out-of-focus blur have not been studied in the context of objective measurements of accommodation stimulated with a Badal optometer. A better understanding of the role of these concepts on the AR may lead to improved lens-based methods to stimulate accommodation in virtual reality. The purpose of this study is to investigate the stimulation of accommodation in a Badal optometer when a 2-dimensional stimulus with apparent depth cues that include rendered out-of-focus blur is used.

5.2.2. Methods

Subjects

The study was approved by the Ethics Committee of Hospital Mutua de Terrassa (Terrassa, Spain). It followed the tenets of the Declaration of Helsinki and all subjects gave informed written consent. Criteria for inclusion were best corrected visual acuity of 0.10 logMAR or better and no history of any ocular condition, surgery and/or pharmacological treatment. Only one eye of each subject was included in the analysis and corrected with spherical and cylindrical components of over-refractions within ±0.25 D. The upper age limit was set at 27 years to ensure good amplitude of accommodation. Mean age ± standard deviation of 28 subjects were 24.6 ± 2.4 years (20 to 27 years) with mean corrected logMAR visual acuity of –0.10 ± 0.08 (–0.20 to +0.10) and mean subjective amplitude of accommodation of 11.8 ± 2.0 D (8.3 to 16.6 D).

Instrumentation and setup

The binocular open field autorefractor PowerRef II (Plusoptix Inc., USA) was used in all measurements. It is based on dynamic infrared retinoscopy and it measures the spherical equivalent, pupil size and gaze position at a sampling frequency of 25 Hz.[97] Alignment between the PowerRef II and the patient's eye was achieved by means of a 50-mm squared Hot Mirror (reflects IR, transmits visible) placed 25 mm from the patient's pupil plane (Figure 14).

The setup consisted of the PowerRef II autorefractometer and different configurations to stimulate accommodation. Autorefractometer measurements were taken at target distances of 6 m and 20 cm or equivalent positions in a Badal system, corresponding to accommodation stimuli of 0.17 D and 5.0 D, respectively. In all cases, luminance of the stimulus was constant (white region: 54 cd/m^2; black region: 2.33 cd/m^2), the field of view of the scene was limited to 25.0º and the fixation target was a black Maltese cross subtending 2.0º.

The *first configuration* consisted of stimulating accommodation with free 3-dimensional space targets. The scene displayed included the fixation target; it was also designed to provide some peripheral depth cues at different focal planes, including three well-known objects: two mannequins of the same height at a distance of 5.5 and 0.7 meters, respectively, and a stool at a distance of 4 meters (Figure 14) in relation to the eye's pupil plane. In this study, this configuration is the closest to natural viewing conditions. However, in the present study subjects were accommodating monocularly, with the other eye occluded, whereas binocular viewing, which includes cues such as vergence and disparity that are missing in monocular conditions, is more appropriately referred to as 'natural viewing'

The *second configuration* consisted of a Badal optometer (Badal lens f'=100 mm, diameter=49 mm). The stimulus was a photograph of the real scene shown in the first configuration for each AS. These pictures were taken to closely approximate human sight. As shown in Figure 15A and B, each photograph focused on the Maltese cross plane and therefore the remaining contents of the scene appears blurred in relation to the relative distance to the Maltese cross plane.

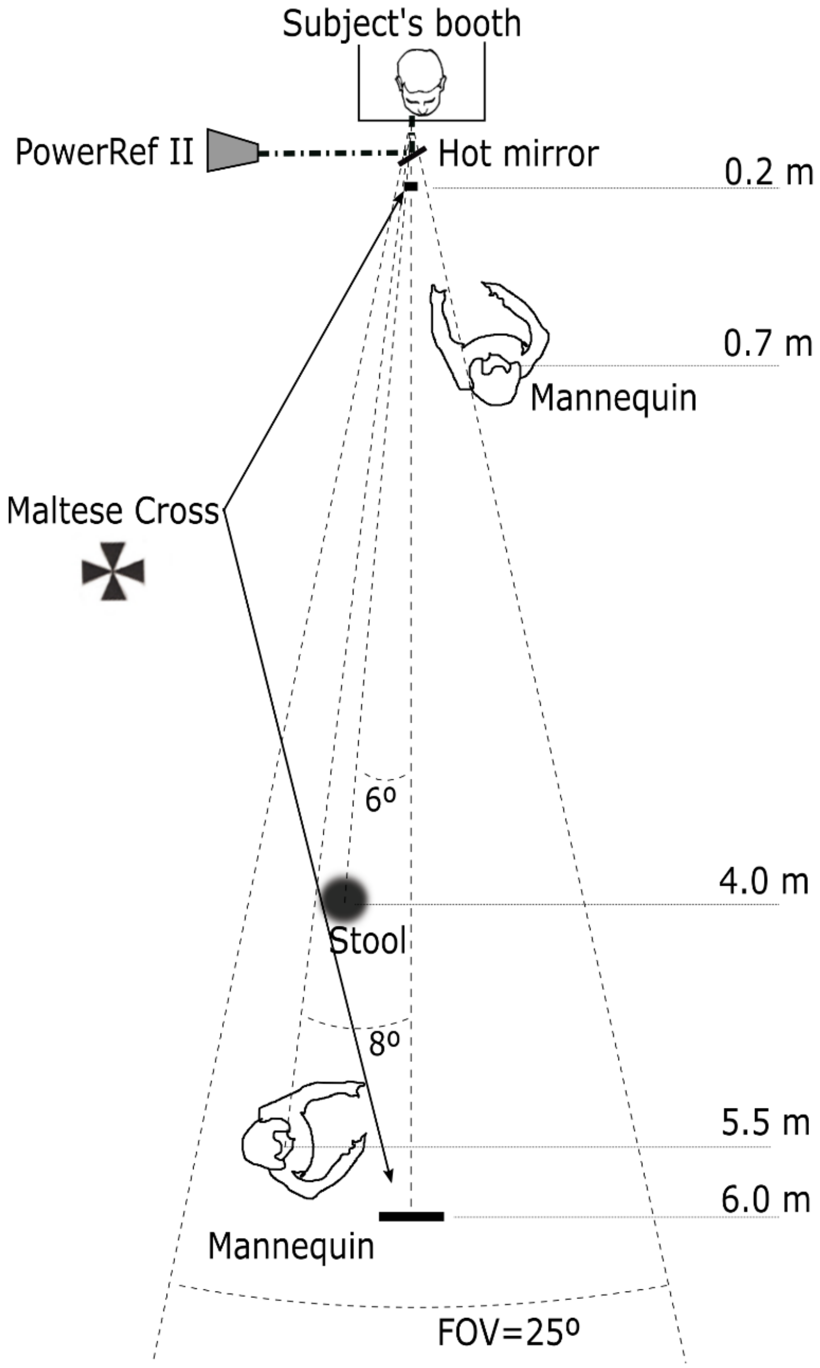

Figure 14. Top-view of the real 3-dimensional space setup (Configuration 1). Distances are shown in meters (m) in relation to the eye's pupil plane.

The *third configuration* consisted of the same previous Badal optometer, but using only the photograph taken at far distance for all accommodative stimulations. In this case, the photograph was computationally rendered with an infinite depth of focus and thus the whole scene looked sharp, even those objects that in the real scene were at different focal planes from the fixation target (Figure 15C and D).

The *fourth configuration* consisted of the same previous Badal optometer with a black Maltese cross on a white even surrounding (Figure 15E and F), a configuration often used in accommodation studies.[69,159,168,169] A summary of each configuration can be found in Table 4.

Table 4. Summary of the 4 setup configurations.

Config.	SM	FOV [°]	Scene (label)	OoFB	AS
1	Real target	25	Real (Real)	Yes	0.17 & 5.00 D
2	Badal target	25	Picture of the real scene (OoF Blur)	Yes	0.17 & 5.00 D
3	Badal target	25	Picture of the real scene rendered with DOF to infinity (OoF Sharpness)	No	0.17 & 5.00 D
4	Badal target	25	White uniform background (White)	No	0.17 & 5.00 D

SM: Stimulation Method, FOV: Field Of View, OoFB: Out-of-Focus Blur, AS: Accommodation Stimulation. Config.: Configuration.

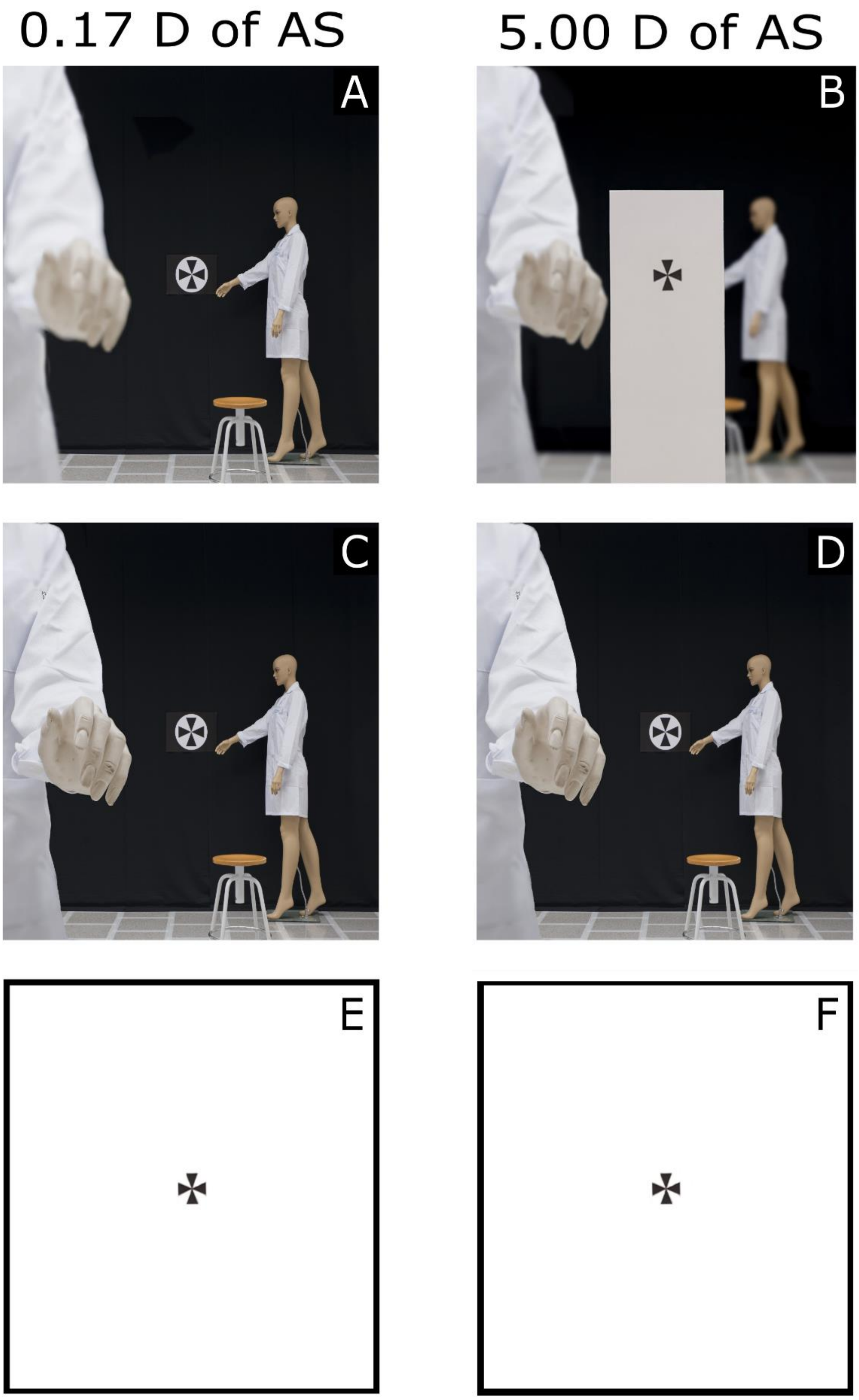

Figure 15. Accommodative stimulus used at 0.17 D (A, C, E) and 5.00 D (B, D, F) in the Badal optometer. Configuration 2 (A, B), Configuration 3 (C, D) and Configuration 4 (E, F).

Characteristics of the Photographs

All images were taken with a Nikon D700 camera and a 60-mm Micro Nikkor lens (Nikkon Inc., Japan). The same light source of the real scene was used to illuminate the photographs, adjusting the white balance of the camera to the corresponding color temperature. Once the images were captured, they were processed with a luminance transition curve akin to that of the human vision.[170]

In the second configuration, a depth of focus (DoF) of ±0.30 D was considered to obtain a picture with a DoF similar to a healthy human subject under standard room lighting conditions (500 lux).[70] The camera's f-number used was f/8. This configuration is potentially limited since depth of focus is variable across subjects and its inter-subject variability can be affected by the accommodative demand.[73]

For the third configuration, the image with an infinite depth of focus was captured with the same equipment and settings as the images of the second configuration. The infinite depth of focus was obtained using image-processing techniques. Several images at different focal planes were captured. Magnifications were unified and stacked with the focus-stacking tool of Adobe Photoshop CS4 (Adobe Systems Inc., USA).

Finally, all images were printed using a sublimation printing system with a resolution of 5 lp/mm (line pairs per millimeter) that is shown to elicit accurate accommodation.[171]

Examination Protocol

Firstly, an optometric examination was performed. Monocular subjective refraction was measured with the endpoint criteria of maximum plus power consistent with best vision. The eye with best visual acuity was chosen for the measurements and the push-up method provided the monocular amplitude of accommodation.

Next, subjects were blindfolded and moved to the measurement room. During all measurements they remained inside a booth and were not aware of the real dimensions of the setup nor the room to avoid biases in the accommodative response.[152] Once the participants sat in front of the chin rest, they remained blindfolded for another 5 minutes to ensure that all started from the same baseline accommodative level (wash-out accommodation procedure).[152] Afterwards, the spherical equivalent refraction was measured in one eye (the contralateral eye was occluded) for the previously described configurations and in ascending level of accommodative stimulation (0.17 D and 5.00 D) to minimize difficulties in relaxing the accommodation. The subjects were instructed to look at the centre of the cross and carefully focus it. The four configurations were randomized and the spherical equivalent of the eye was recorded over a period of 5 seconds in each case. The accommodation responses for the 5.00 D stimulus were determined by subtracting the refractions for the 0.17 D stimulus from the refractions for the 5.00 stimulus. The resulting accommodation response was negative in order to be consistent with refraction.

Statistical analysis

The significance was set at 0.05 and the statistical analysis was performed using SPSS v22 (IBM Corp., USA). Normality of each variable was verified with the Shapiro-Wilk test and comparing skewness and kurtosis to the standard error. The repeated measures ANOVA was used to analyze within-participant effects (i.e., the overall significant difference between each configuration). When significance was obtained, pairwise comparisons were examined by t-tests with the Bonferroni correction. In addition, to further assess individual differences in the accommodative ability of observers, regression and correlation coefficients are also provided.

5.2.3. Results

The post hoc power analysis carried out with the open source G*Power 3.0.10 showed a mean power effect of 0.9 for a sample size of 30 subjects.

The descriptive statistics (mean, standard deviation and within-subject standard deviation) of far refraction (AS at 0.17 D), refraction at 5.00 D of AS and accommodative response at 5.00 D of AS are shown in Table 5 for each configuration. The descriptive statistics of pupil size and gaze position (with respect to the optical axis of the PowerRef II) are also shown.

The repeated measures ANOVA for far refraction was not statistically significant ($F_{3.0, 87.0} = 2.00$ and $p = 0.12$); in contrast, ANOVA was significant for refraction ($F_{3.0, 87.0} = 6.40$ and $p < 0.01$) and accommodative response at 5.00 D of AS ($F_{3.0, 87.0} = 5.24$ and $p < 0.01$). The pairwise comparisons between configurations are shown in Figure 16.

The pupil size differences among configurations were not statistically significant in any case: $F_{3.0, 87.0} = 1.12$ and $p = 0.35$ for stimulus at 0.17 D and $F_{2.3, 61.6} = 3.98$ and $p = 0.02$ for stimulus at 5.00 D (the Bonferroni post-hoc test did not show statistical significance). Similarly, the gaze position was not significantly different among configurations: $F_{2.1, 64.0} = 0.45$ and $p = 0.64$ for stimulus at 0.17 D and $F_{2.2, 68.6} = 0.91$ and $p = 0.41$ for stimulus at 5.00 D.

Table 5. Descriptive statistics of the far distance measurements, near distance measurements and the Accommodative Response (AR) at 5.00 D in all configurations.

	Stimulus at 0.17 D			Stimulus at 5.00 D			AR at 5 D
Config.	Mean SE ± SD (Sw)	Mean PS ± SD (Sw)	Mean GP ± SD (Sw)	Mean SE ± SD (Sw)	Mean PS ± SD (Sw)	Mean GP ± SD (Sw)	Mean SE ± SD (Sw)
Real (1)	0.15 ± 0.81 (0.17)	5.38 ± 1.12 (0.29)	2.96 ± 1.87 (1.61)	-3.61 ± 1.03 (0.39)	4.67 ± 0.92 (0.28)	4.64 ± 3.47 (2.35)	-3.76 ± 0.96 (0.43)
OoF blur (2)	0.00 ± 0.82 (0.13)	5.60 ± 0.94 (0.25)	3.30 ± 1.89 (1.57)	-3.51 ± 0.90 (0.28)	4.96 ± 1.04 (0.32)	4.23 ± 2.51 (2.65)	-3.51 ± 1.08 (0.31)
OoF sharpness (3)	-0.09 ± 1.00 (0.16)	5.47 ± 1.08 (0.29)	3.07 ± 1.99 (1.60)	-3.42 ± 0.92 (0.47)	4.97 ± 1.00 (0.28)	4.78 ± 2.94 (2.44)	-3.33 ± 1.01 (0.49)
White (4)	0.05 ± 0.76 (0.27)	5.74 ± 0.98 (0.29)	3.31 ± 2.40 (1.75)	-3.06 ± 1.05 (0.53)	4.67 ± 1.01 (0.33)	4.19 ± 2.55 (2.66)	-3.11 ± 1.04 (0.59)

SE: Spherical Equivalent in diopters. PS: Pupil Size in millimeters. GP: Gaze Position in degrees. SD: Standard deviation. Sw: Within-subject standard deviation.

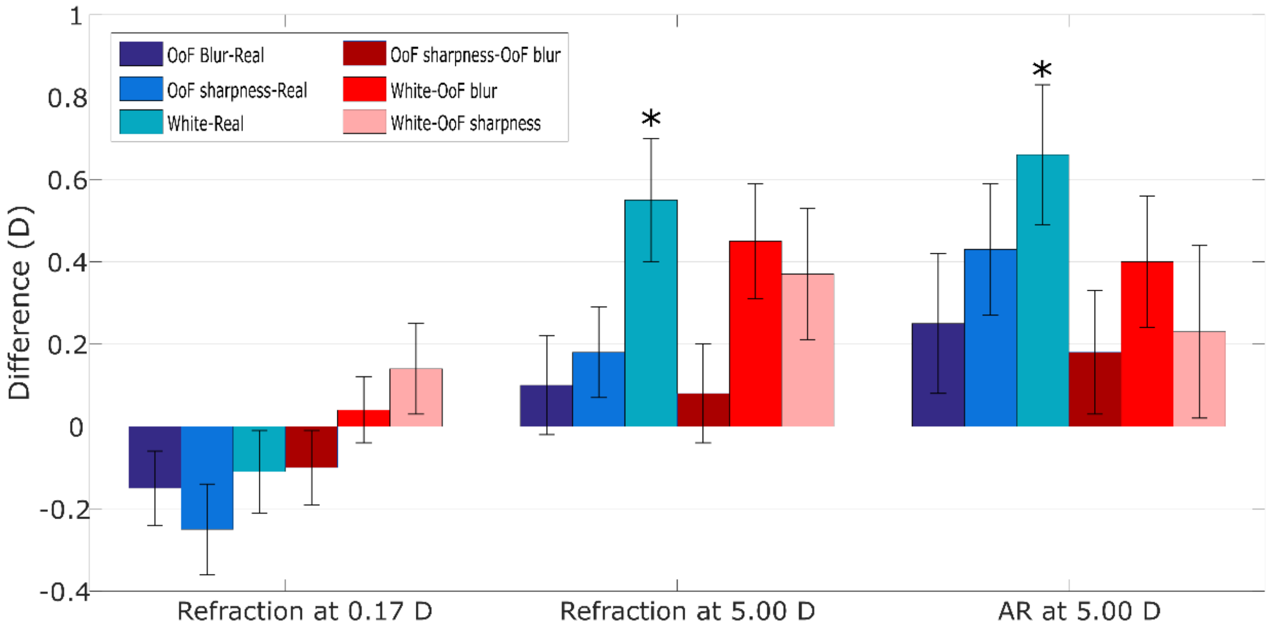

Figure 16. Differences between configurations for refraction (stimuli at 0.17 D & 5.00 D) and the accommodation response (AR) at 5 D. Error bars correspond to the standard error of the mean. *Statistically significant.

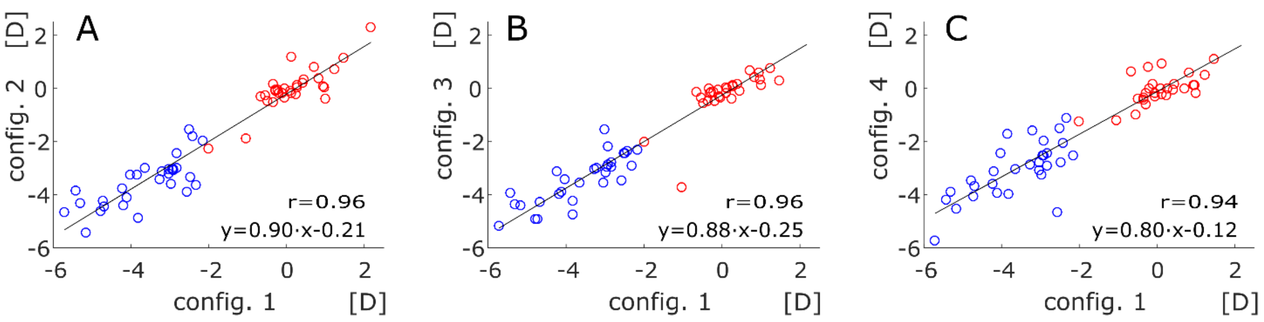

Figure 17. Correlation and regression coefficients for all configurations with respect the reference configuration 1 and for far and near refraction. Red dots refer to far distance refraction (0.17 D of AS) and blue dots to near distance refraction (5.00 of AS). All correlations are statistically significant ($p<0.05$).

5.2.4. Discussion

The effect of apparent depth when stimulating accommodation by means of a Badal optometer was investigated. Two main variables were studied: the refraction and the accommodation response at 5.00 D, with the latter calculated as the near minus the far refraction.

In the case of refractions, a tendency toward higher lag and lead is observed at near and far distance targets, respectively, in Configurations 2, 3 and 4 than in natural viewing conditions (Config. 1). The highest lag is obtained when using the Badal target with no apparent depth cues (Config. 4). In this case, the mean difference with respect to the natural viewing configuration is -0.66 D (Figure 16), which agrees with the mean difference of -0.58 D obtained in a previous study under similar conditions but with a different autorefractometer.[157] This result showed that, due to the real depth stimulus, the response may be influenced by the Mandelbaum effect[7] (i.e., the out-of-focus information in the retinal periphery may behave as a conflicting stimulus and therefore bring the visual system towards its resting state of accommodation). However, when the central fixation target is appropriate to elicit accommodation (e.g., a Maltese cross) the peripheral depth cues (either real or apparent) contribute -on average- to more accurate AR responses.

Configuration 2 with apparent depth cues and simulated out-of-focus blur has the smallest mean AR difference (-0.25 D) with respect to the reference Configuration 1 at 5.00 D of AS. This mean difference is less than half the statistically significant difference obtained when comparing the white background configuration with the natural viewing condition (-0.66 D). Moreover, Configuration 2 has the best regression and correlation coefficients among all configurations compared with Configuration 1 (Figure 17A, B and C). These results suggest a significant improvement when stimulating accommodation in a Badal optometer using realistic stimulus with peripheral apparent depth cues.

Interestingly, this improvement seems to be affected by the consistency between the simulated depth and the real distance of the fixation target. The mean AR difference at 5 D of AS between the apparent depth cues condition with simulated out-of-focus sharpness (Config. 3) and the natural viewing condition is -0.43 D. In this case, the picture used at 5 D of AS in Configuration 3 was not consistent with the real scene since a depth cue was missing (the white cardboard in which the Maltese cross was printed). In consequence, the whole scene appeared sharp as if all the objects were at the same distance, which was unrealistic considering the size of both mannequins. Even if this consistency is not critical at far distances and in the periphery of the field of view since in these conditions the overall blur sensitivity decreases,[70,172] it contributes to a more inaccurate accommodation response according to our results. As shown in Figure 17A and B, the regression coefficients when comparing Config. 3 (OoF sharpness) with Config. 1 (natural viewing) are slightly worse than when comparing Config. 2 (OoF blur) with natural viewing.

We found a rather large inter-subject variability in all pairwise comparisons. Even though inter-subject variability is similar in magnitude to other accommodation studies that used the PowerRef,[173,174] it is important to disclose potentially important sources of variability when considering the results for individual subjects. Variability can be partially explained by fluctuations of accommodation (they can be of about 0.5 D for large AS[47]) and by the precision of the device.[97] These factors can be quantified by the within-subject standard deviation (Sw) shown in Table 5, which ranges from 0.31 to 0.59 D for the AR at 5 D. They represent, respectively, the 28% and 57% of the standard deviation of the differences found for the same variable.

Another factor that might have increased the variability found in all pairwise comparisons relates to peripheral refraction differences among subjects. All patients were corrected in fovea but not in the retinal periphery. It seems thus appropriate to infer that the peripheral refraction affected the amount of perceived out-of-focus blur and eventually the AR. Hartwig *et al*.[175] confirmed that the peripheral retina is sensitive to optical focus and found some evidence for less effective peripheral accommodation in myopes than emmetropes. In our study there were 19 myopes (spherical equivalent from -7.00 D to -0.50 D) and 11 emmetropes (spherical equivalent from 0.00 D to +0.75 D). To test the refractive error as a potential confounding factor, we calculated a mixed ANOVA considering the accommodation response as a dependent variable, the configuration type as a within-subject's factor (with 4 levels: Real, OoF blur, OoF sharpness and White) and the refractive error as a between-subject's factor (with 2 levels, Myopes or Emmetropes). We obtained only a significant effect for the configuration factor ($F_{3, 84} = 4.67$, $p < 0.01$). The refractive error ($F_{1, 28} = 0.86$, $p = 0.36$) and the interaction *Configuration*RefractiveError* were not statistically significant ($F_{3, 84} = 0.35$, $p = 0.79$). While it has been suggested that accommodation inaccuracies associated with myopia may be better analyzed in terms of age of onset (early-onset or late-onset) or progression (stable or progressing),[176,177] these results indicate that under the conditions of the study myopes accommodated similarly to emmetropes.[69,159,168]

Finally, pupil size differences and gaze position differences among configurations (Table 5) were not statistically significant in far and near distance. In consequence, refraction differences among configurations are unlikely to be explained by a change in depth of focus due to a change in pupil size and by instabilities of gaze.[178,179]

To summarize, for near targets seen through an optical system such as a Badal optometer, the accuracy of the accommodation response generally improves with a 2-dimensional stimulus with apparent depth cues and simulated out-of-focus blur in a relatively large field of view. Even though these conditions may not be adequate for all individuals, they can improve the overall visual comfort in those virtual reality systems that use a varifocal optical system to change the focal plane of a 2-dimensional surface.

5.3. Study 3. Effect of experimental conditions in the accommodation response.

PREVIOUS NOTE: The following text in this section corresponds to the article: **Otero C**, Aldaba M, Vera-Diaz FA, Pujol J. Effect of the experimental conditions in the accommodation response in myopia. *Optom Vis Sci.* 2017 Oct 19. doi: 10.1097/OPX.0000000000001140.

5.3.1. Introduction

Accommodation is stimulated in laboratory or clinical settings either by changing the viewing distance of free space targets[30,58,168,174,176,180–184] or by optical means, i.e., Badal,[69,158,159,169,185] or ophthalmic positive[29,30] or negative lenses.[29,30,58] Free space targets usually offer a more naturalistic method of stimulating accommodation. On the other hand, lens-based methods are especially useful when applied to ophthalmic instruments. One important practical advantage of using lenses to stimulate accommodation is that this can be achieved in a compact space, which is of interest in emerging technologies such as stereoscopic virtual reality systems that demand optical solutions to overcome the convergence-accommodation mismatch.[186]

Previous studies have found poorer accommodative responses when accommodation is stimulated with lenses compared to free space targets.[30,69,176] Recently, Aldaba *et al*.[157] reported significantly more inaccurate accommodative responses to a Badal lens viewing when compared to free space. They suggested that the use of the Badal lens itself did not explain these differences and it was rather a combination of factors associated with closed-view Badal systems. They also suggested that the volumetric stimulation (i.e., interposition of objects in depth) and the size of the field of view could be important factors in controlling and providing accurate accommodative responses.

In most studies accommodation is stimulated with fixation targets smaller than 2º field, on a 2-dimensional uniform background.[29,30,58,158,159,168,169,174,180–184] The overall field of view available to the subject is not usually reported, even when using open-field autorefractors that allow for larger field of view (30º or larger horizontally) than the fixation target size. This means that the peripheral scene around the fixation target is not specified nor controlled, which can lead to one of three different conditions: 1) the overall field of view may be restricted to the size of the fixation target reported in the study; 2) the overall field of view may be much larger than the fixation target with a uniform background in the same 2-dimensional plane than the fixation target; or 3) the overall field of view may be much larger than the fixation target used in the study but the peripheral scene has spatial information at multiple focal planes, being this latter condition the one closest to a naturalistic environment.

The accommodative response may be affected by all the previously mentioned experimental conditions, but also by the observer's refractive error. A large number of studies have attempted to disentangle the possible effect of refractive status in accommodative response (see Schmid and Strang[176] for a recent review). Some studies concluded that myopes accommodate significantly different than emmetropes[29,30,169,174,180,181,183,185] while others did not find a clear association between accommodation and refractive error.[69,158,159,168,173,182,184] Whether myopes accommodate more accurately than emmetropes or vice versa differed greatly among studies, especially when the myopic group was sub-classified as stable myopes or progressing myopes,[29,158,159,181,184] or more often, as early-onset myopes (EOM) or late-onset myopes (LOM).[29,69,168,169,173,180,182,183] Interestingly, the size of the fixation target was different in each of these studies, it ranged from 1' to 15º field. Also, most of these studies used only real targets in free space[168,173,174,180–183] or optical means,[69,158,159,169] but not both.

A better understanding of the role of the experimental conditions on the accommodative response would help clarify the causes of inaccurate accommodative responses when accommodation is stimulated optically. By extension this may lead to improved lens-based methods to stimulate accommodation. Moreover, a study that includes an analysis of different refractive error groups and experimental conditions may help understand the causes of discrepancies among previous studies. The purpose of this study was to analyze the effect of field of view, stimulation method (either a real target in free space viewing or a target presented through a Badal lens), depth of the stimulus (either a flat, 2D, or a volumetric, 3D, stimulus), and their interactions, on the accommodative response in observers from different refractive error groups.

5.3.2. Methods

Subjects

The study, approved by the Ethics Committee of Hospital Mutua de Terrassa (Terrassa, Spain), followed the tenets of the Declaration of Helsinki and all subjects gave informed consent. Criteria for inclusion were: 1) best-corrected visual acuity of 0.10 logMAR (20/25 Snellen equivalent) or better in each eye, 2) between 13 and 28 years of age, to ensure good ability to accommodate, 3) spherical equivalent error measured with subjective refraction between -6.50 and +0.75 D, 4) amplitude of accommodation above the minimum given by Hofstetter's formula for Minimum Accommodation[19] (Amplitude = 15 – 0.25*Age), 5) no strabismus or amblyopia, and 6) no history of any ocular disease, surgery and/or pharmacological treatment that may have affected vision at the time of the study. Subjects with myopia were contact lens wearers and used their own disposable soft contact lenses for the study. The contact lenses prescription were within ±0.25 D of the subject's best correction in each meridian, determined by subjective refraction as explained below.

Subjects were divided into three refractive groups according to the classification suggested by McBrien and Millodot:[180] early-onset myopia group (self-reporting as becoming myopic before 15 years old), late-onset myopia group (self-reporting as becoming myopic at or after 15 years old) and emmetropia group. Emmetropia was defined as subjective refraction spherical equivalent between -0.25 and +0.75 D in each eye. Myopia was defined as subjective refraction spherical equivalent less than -0.25 D.

Instrumentation and setup

A binocular open field autorefractor, PowerRef II (Plusoptix Inc., USA), was used to measure accommodation responses. This autorefractor is based on the principle of dynamic infrared retinoscopy and it measures monocular spherical equivalent, pupil size and gaze position at a sampling frequency of 25 Hz.[100,187] Alignment between the PowerRef and the subject eye was achieved through a 50-mm squared IR hot mirror placed 2.50 cm from the subject's pupil plane (Figure 18).[50] Accommodation responses were measured for target distances, or equivalent positions in a Badal system, of 6 m, 0.4 m and 0.2 m, corresponding to accommodative stimulus of 0.17 D, 2.50 D and 5.00 D, respectively. These stimuli represent typical every day accommodation demands within 2/3 of the subjects' amplitude of accommodation.

Each subject observed a fixation target (Maltese cross) under 60 different conditions. These conditions were the result of permuting the following factors: 1) stimulation method (two configurations: free space or Badal lens viewing), 2) stimulus depth (two configurations: flat or volumetric stimulus), 3) field of view (five configurations, 2.5º, 4º, 8º, 10º and 30º) and level of accommodation stimulation (three configurations, 0.17 D, 2.50 D and 5.00 D).

The volumetric stimulus configurations were achieved by manipulation of three independent sections of the stimulus: left periphery, fixation target and right periphery (Figure 18D). The fixation target section comprised only the black Maltese cross, which subtended, in all configurations, 2º field. The positions of the fixation cross were related to the peripheral sections to determine the various accommodation stimulation levels (0.17 D, 2.50 D or 5.00 D). Both the right and the left periphery sections were composed of randomized phase spectra images of the black Maltese cross in the Fourier domain (Figure 18B, C, E and F). The peripheral stimulus was therefore an abstract image with the same spatial frequency content than the fixation target.[188]

When the three sections of the stimulus were in the same focal plane, a flat, 2-dimensional, stimulus was presented (Figure 18A). The volumetric, 3-dimensional, stimuli were achieved by moving at least one peripheral section to a different focal plane than that of the central fixation target. Notice that for all volumetric stimuli, the dioptric distance between the defocused peripheral plane and the fixation target was always 2.50 D. Luminance of the stimulus was constant (3.7 cd/m^2 for the fixation black Maltese cross, 56.2 cd/m^2 for the central white area and 31.9 cd/m^2 for the grey area) for all configurations.

The field of view sizes chosen for this experiment (2.5º, 4º, 8º, 10º and 30º) aimed to stimulate differentiated regions of the retina (fovea, parafovea, perifovea and far periphery). A scaled version of the target for two field of view sizes in both flat and volumetric stimuli can be seen in Figure 18B, C, E and F. The field of view size was controlled by circular apertures positioned between the hot mirror and the Badal lens.

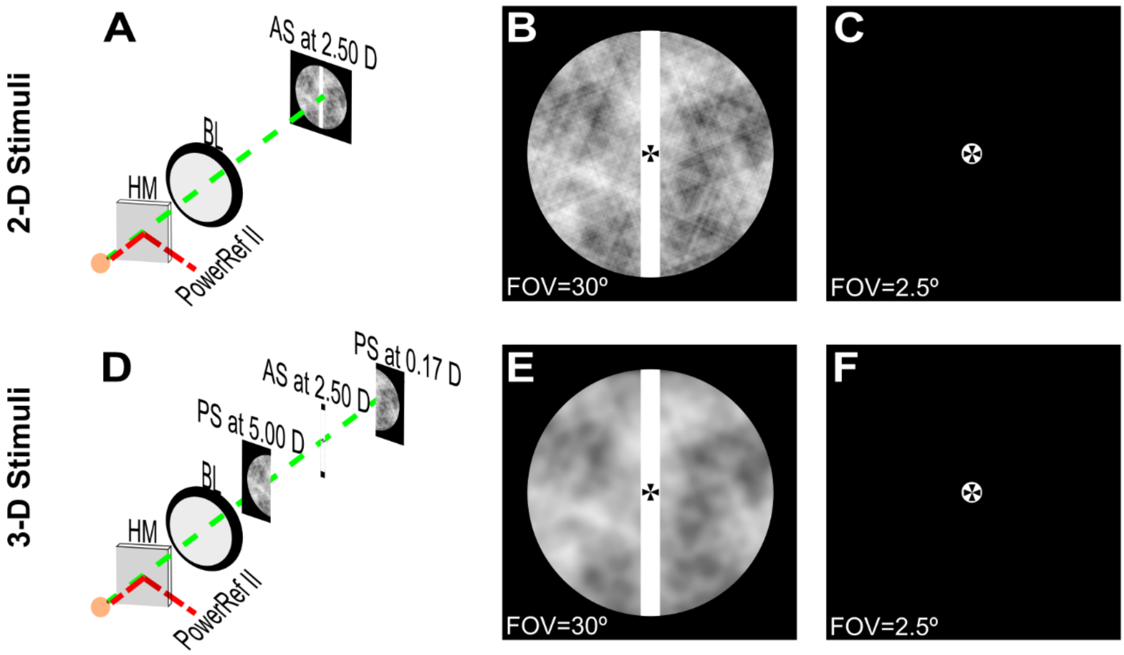

Figure 18. A: schematic representation of the setup for the flat, 2-dimensional, Badal stimulation for the accommodative stimulus of 2.50 diopters and FOV of 30º. Panels B and C: subject's point of view for flat, 2-dimensional, stimuli for a FOV of 30º and 2.5º respectively. Similarly, panels D, E, F represent the same conditions but for a volumetric, 3-dimensional, Badal stimulation. FOV: Field of view. BL: Badal lens. HM: Hot mirror. PS: Peripheral stimulus. Note that the size of the diaphragm is scaled proportionally to the size of the fixation target (black Maltese cross) and that the blur shown in the peripheral stimulus of panel D is an approximation.

Examination Protocol

A monocular subjective refraction with endpoint criteria of maximum plus power that provides best visual acuity was performed to determine best optical correction. The dominant eye was chosen for the measurements and it was obtained with the distance hole-in-the-card test.[189] Monocular amplitude of accommodation was evaluated by averaging the values of two push-up and two push-down trials, to compensate for the bias of push-up to overestimate and push down to underestimate accommodation amplitude.[190]

Accommodative responses were recorded in the dominant eye (the contralateral eye was occluded with an eye patch) for a period of at least 5 seconds for each of the previously described 60 configurations randomly presented. All conditions were measured in one session that took approximately 45 minutes, including breaks. Subjects were allowed to take breaks as needed, although there was no systematic method to provide rests during the measurements. Randomization of configurations was rigorously applied to minimize potential learning or fatigue biases. During the accommodation measurements subjects were inside a booth with a chin rest and a viewing aperture (that did not limit the field of view for any of the configurations) allowed them to see outside. The targets were placed outside the booth. The viewing aperture was closed in between trials so that subjects were not aware of the exact changes made from one configuration to another.

Statistical analysis

The main analysis consisted on a mixed Analysis of Variance (with 3 within-subject factors and 1 between-subject factor) that was conducted for the accommodative response of 2.50 D and 5.00 D. The statistical analysis chosen allowed us, without losing statistical power, to investigate the interactions among factors and at the same time to include fewer participants than other experimental designs (e.g., direct pairwise comparisons). The accommodative response for the 2.50 D and 5.00 D stimuli were determined by subtracting the PowerRef measures for these stimuli from the measures for the 0.17 D stimulus.

The refractive group category (emmetropes, early onset and late onset myopes) was used as a between-subjects' factor. The three within-subject factors were: stimulation method (with two configurations, free space or Badal lens viewing), stimulus depth (with two configurations: flat or volumetric) and field of view (with five configurations: 2.5º, 4º, 8º, 10º or 30º). Where significance was obtained, a Bonferroni post-hoc test was made. Significance was set at $p < 0.05$.

A secondary analysis was used to evaluate whether changes in pupil diameter, fluctuations of accommodation and fluctuations of gaze position played a role in the main analysis (for 5.00 D stimuli). The same statistical methodology described above was used for this purpose, but using as dependent variables the pupil diameter, the within-subject standard deviation of refraction and the within-subject standard deviation of the horizontal gaze position.

Statistical power was assessed with the free open source G*Power 3.0.10.[191] Data from a similar previous study[157] was used to compute the required sample size for a statistical power of 0.8. Considering a significance of 0.05 and an Analysis of Variance model with 20 repetitions and 3 groups the required sample size is 6 for both the accommodative response at 2.50 D and at 5.00 D.

5.3.3. Results

A total of 26 subjects were included in the analysis (n = 9 emmetropes, n = 9 early onset myopes, n = 8 late onset myopes). The mean age ± standard deviation (24 ± 3 years) were not significantly different between the three refractive groups (one-way Analysis of Variance F = 3.26, p = 0.06). Although the difference approached significance because one subject within the emmetropic group was 13 years of age; most of the subjects were between 22 and 26 years of age. The statistical analysis was performed with and without this subject and results did not significantly change. In order to keep the statistical power as high as possible the 13 year old subject was included in the final analysis described below. The descriptive statistics for age in each group are shown in Table 6.

Table 6. Descriptive statistics of each refractive error group.

Refractive Error	SS (n)	Mean Age ± SD [min;max]	Mean Age MO ± SD [min;max]	SE ± SD (D) [min;max]
Early-Onset Myopes (EOM)	9	24.4 ± 2.7 [21;28]	8.8 ± 2.9 [4;12]	-4.07 ± 1.71 [-6.5;-0.75]
Late-Onset Myopes (LOM)	8	26.1 ± 2.1 [21;28]	20.7 ± 3.1 [15;24]	-1.01 ± 0.74 [-2.5;-0.50]
Emmetropes (EMM)	9	22.1 ± 4.2 [13;27]	--	0.05 ± 0.19 [-0.25; 0.25]

SS: Sample Size. MO: Myopia Onset. SE: Spherical Equivalent in diopters. SD: Standard Deviation. Min: minimum value. Max: Maximum value.

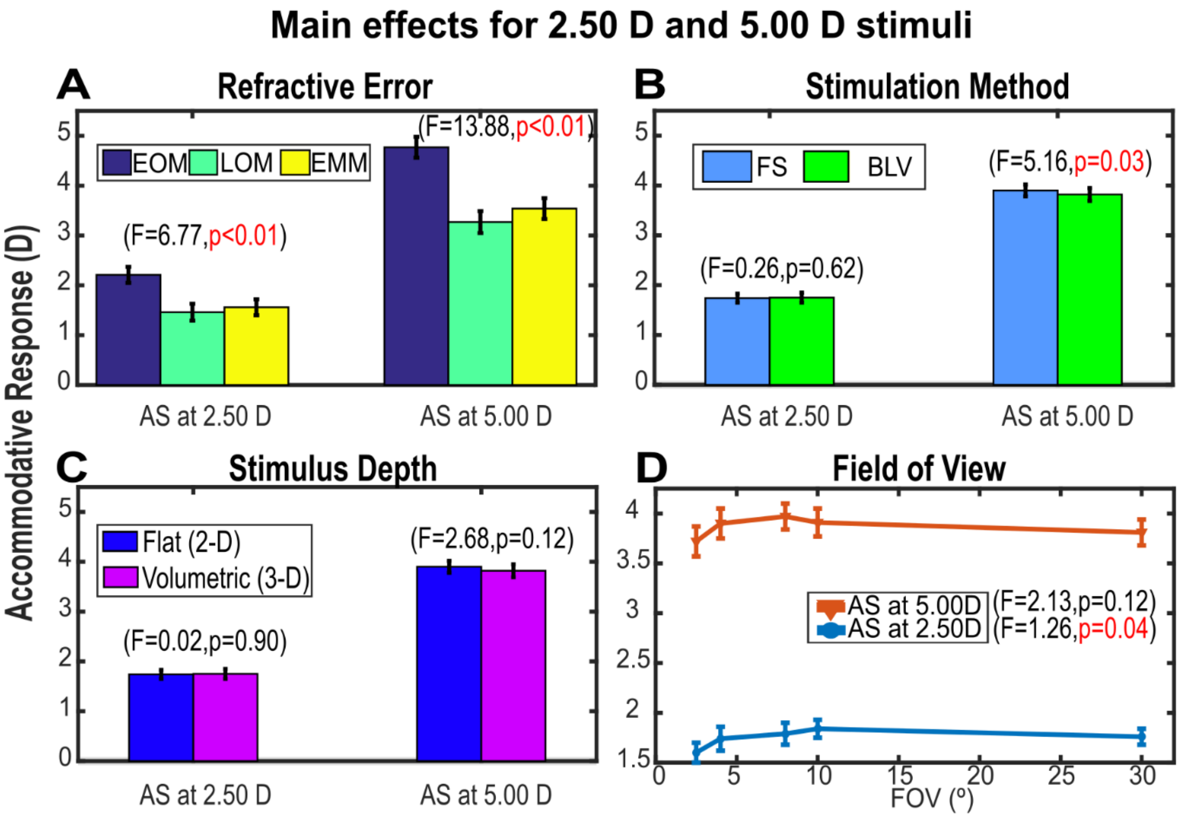

Figure 19. Mean accommodation response effect of each factor for the 2.50 D and 5.00 D accommodative stimuli. Panel A: main effects of refractive error (independently of the stimulation method used, field of view or depth of the stimulus). Panel B: main effects according to the stimulation method used (averaging all subjects, independently of the refractive error group, field of view or depth of the stimulus). Analogously, panel C and D: main effects of stimulus depth and field of view independently of the other of variables. Error bars correspond to the standard error of the mean. AS: Accommodative stimulus. EOM: early onset myopes. LOM: late onset myopes. EMM: emmetropes. FS: free space. BLV: Badal lens viewing. FOV: field of view.

Primary analysis: accommodative response for 2.50 D and 5.00 D stimuli

Figure 19 shows the main effects of each variable for the 2.50 D and 5.00 D accommodative stimuli. Mixed Analysis of Variance for the accommodative stimulus of 2.50 D resulted in a significant main effect of: 1) refractive group ($F = 6.77$, $p < 0.01$), with smaller accommodative lags for early onset myopes compared to late onset myopes and emmetropes (Figure 19A); and 2) field of view ($F = 1.26$, $p = 0.04$), with greater lags for a field of 2.5º (Figure 19D). There were not significant differences for stimulus depth ($F = 0.02$, $p = 0.90$, Figure 19C) or stimulation method ($F = 0.26$, $p = 0.62$, Figure 19B) when considered in isolation.

A significant interaction between field of view and stimulus depth (*Field of view*Depth*, F = 2.73, p = 0.03, Figure 20) was found for the 2.50 D accommodative stimuli. Figure 20 shows mean accommodative responses for the 2.50 D stimulus for each field of view and for both flat and volumetric stimuli. To determine the nature of this interaction, the estimated marginal means (pairwise comparisons adjusted with Bonferroni correction) were computed and the statistically significant comparisons are shown in Table 7. Accommodative responses followed a similar trend across the different field of view sizes used, although for the 8 and 10º fields the accommodative responses appear significantly more accurate than for the 2.5º field in both the volumetric and flat stimuli.

Table 7. Simple main effects of stimulus depth and FOV (interaction FOV*Depth) for 2.50 D stimulus. Paired t tests (with Bonferroni correction) are applied to all pairwise comparisons.

Factor 1, Level	Factor 2, Pairwise Comparison	Mean difference (±SEM) [D]	p-value
FOV, 4º	Stimulus Depth, Flat - Volumetric	0.18 (±0.07)	0.03
Stimulus Depth, Flat	FOV, 10º-2.5º	0.23 (±0.07)	0.02
Stimulus Depth, Volumetric	FOV, 8º-2.5º	0.24 (±0.06)	0.01

SEM: Standard error of the mean. FOV: Field of view.

Analogously, there was an interaction among stimulation method, field of view and refractive group (*Method*Field of view*RefractiveError*, F = 2.42, p = 0.02, Figure 21) for the 2.5 D accommodative stimuli. Figure 21 shows mean accommodative responses for each field of view separated by stimulation method and refractive error group. As described above, we computed pairwise comparisons adjusted with Bonferroni correction to determine the nature of this interaction. The statistically significant comparisons are shown in Table 8. Early onset myopes showed again more accurate accommodative responses compared to emmetropes and late onset myopes independently of the size of the field of view and the stimulation method used. The accommodation responses appear again to be more accurate for the 8 and 10º fields of view than a 2.5º field (particularly for free space viewing and early-onset myopes).

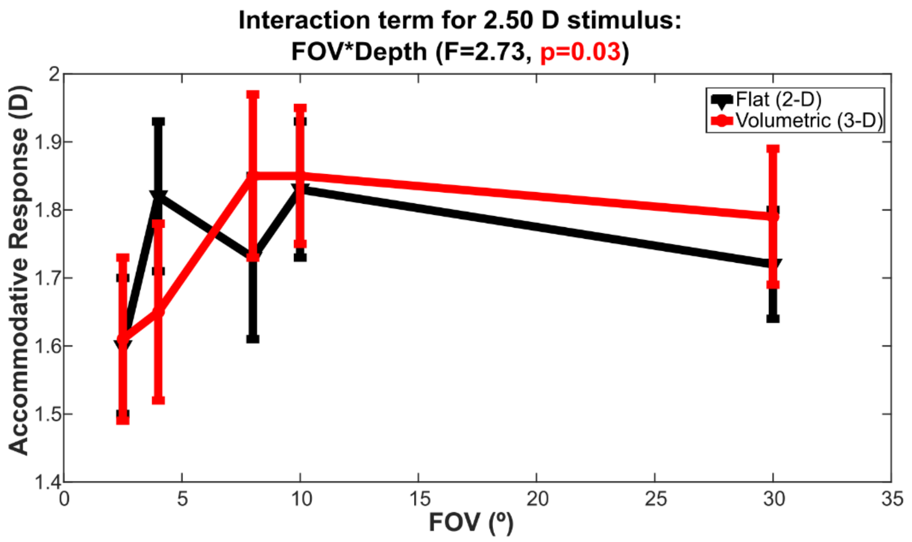

Figure 20. Group data accommodative response for the 2.50 D stimulus when observed with different fields of view (FOV) sizes. Black data points represent accommodation responses to 2-D flat stimuli and red data points represent 3-D volumetric stimulus (depth). Error bars correspond to the standard error of the mean.

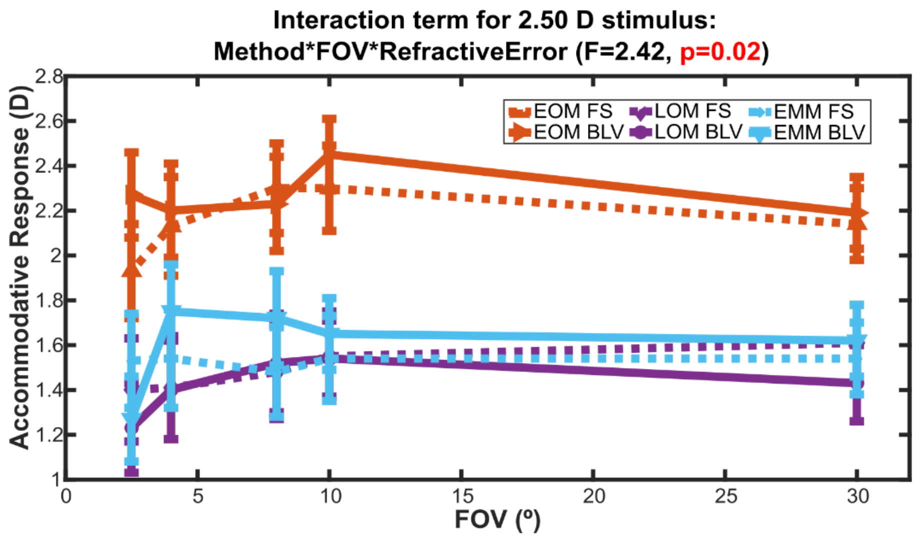

Figure 21. Group data accommodative response for the 2.50 D stimulus when observed with different fields of view (FOV) sizes. Orange lines represent data for the early onset myopes group (EOM). Purple lines represent data for the late onset myopes group (LOM). Blue lines represent data for emmetropes (EMM). Solid lines represent Badal lens viewing (BLV) and dotted lines represent free space (FS) viewing. Error bars represent the standard error of the mean.

Table 8. Simple main effects of stimulation method, FOV and refractive group (interaction Method*FOV*RefractiveError) for 2.50 D stimulus. Unpaired t tests are applied to pairwise comparisons of refractive error groups and paired t tests for any other pairwise comparisons. In all cases Bonferroni correction is applied.

Factor 1, Level	Factor 2, Level	Factor 3, Pairwise Comparison	Mean difference (±SEM) [D]	p-value
Stimulation Method, FS	FOV, 30º	Refractive Error, EOM-EMM	0.60 (±0.23)	0.04
Stimulation Method, FS	FOV, 10º	Refractive Error, EOM-LOM	0.75 (±0.27)	0.03
Stimulation Method, FS	FOV, 10º	Refractive Error, EOM-EMM	0.76 (±0.26)	0.02
Stimulation Method, FS	FOV, 8º	Refractive Error, EOM-LOM	0.81 (±0.29)	0.03
Stimulation Method, FS	FOV, 8º	Refractive Error, EOM-EMM	0.82 (±0.28)	0.02
Stimulation Method, BLV	FOV, 30º	Refractive Error, EOM-LOM	0.76 (±0.23)	0.01
Stimulation Method, BLV	FOV, 10º	Refractive Error, EOM-LOM	0.91 (±0.23)	<0.01
Stimulation Method, BLV	FOV, 10º	Refractive Error, EOM-EMM	0.79 (±0.22)	<0.01
Stimulation Method, BLV	FOV, 4º	Refractive Error, EOM-LOM	0.80 (±0.30)	0.04
Stimulation Method, BLV	FOV, 2.5º	Refractive Error, EOM-LOM	1.04 (±0.27)	<0.01
Stimulation Method, BLV	FOV, 2.5º	Refractive Error, EOM-EMM	1.00 (±0.26)	<0.01
Refractive Error, EOM	Stimulation Method, FS	FOV, 10º-2.5º	0.38 (±0.09)	<0.01
Refractive Error, EOM	Stimulation Method, FS	FOV, 8º-2.5º	0.37 (±0.09)	<0.01

SEM: Standard error of the mean. FS: Free space. BLV: Badal lens viewing. FOV: Field of view. EOM: Early onset myopes. EMM: Emmetropes. LOM: Late onset myopes.

Similarly to the analyses reported for the 2.50 D stimulus, mixed Analysis of Variance for the accommodative stimulus of 5.00 D resulted in a significant main effect of: 1) refractive group ($F = 13.88$, $p < 0.01$, Figure 18A), with smaller accommodative lags for early onset myopes compared to late onset myopes and emmetropes (Figure 18A); 2) and stimulation method ($F = 5.16$, $p = 0.03$, Figure 18B), with significantly smaller lags for free space viewing. There were not significant differences for stimulus depth ($F = 2.68$, $p = 0.12$, Figure 18C) or field of view ($F = 2.13$, $p = 0.12$, Figure 18D) when considered in isolation.

For the 5.00 D stimuli, there was only a significant interaction of stimulation method, stimulus depth and refractive group (*Method*Depth*RefractiveError*, $F = 4.08$, $p = 0.03$, Figure 22). Figure 22 shows mean accommodative responses for each stimulation method, stimulus depth and refractive group for accommodative stimulus of 5.00 D. The statistically significant comparisons are shown in Table 9.

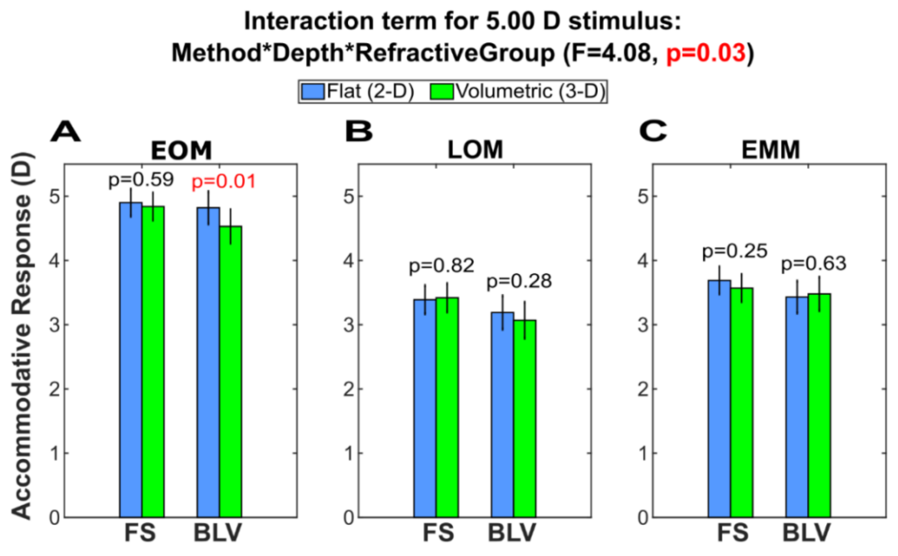

Figure 22. Group data accommodative response for the 5.00 D stimulus when observed with different Stimulation Methods (free space: FS, or Badal lens viewing: BLV) for both flat (2-D) and volumetric (3-D) stimulus (depth). Error bars correspond to the standard error of the mean. Panel A: shows data for early onset myopes (EOM), panel B for late onset myopes (LOM) and panel C for emmetropes (EMM).

The group of early onset myopes showed more accurate accommodative responses than late onset myopes and emmetropes, independently of the stimulation method and depth of the stimulus. The accommodative response for flat stimuli was significantly larger in the early onset myopes group when using the Badal lens viewing method only. There were no significantly differences for stimulation methods across all conditions.

Secondary analysis: pupil diameter and fluctuations of accommodation and gaze position

There was no significant effect and no interactions among the secondary factors: fluctuations of accommodation or gaze position. Pupil diameter was significantly associated only with the stimulation method ($F = 13.25$, $p < 0.01$), stimulus depth ($F = 5.16$, $p = 0.03$) and field of view ($F = 31.81$, $p < 0.01$) for all subjects. There was no association of pupil size with refractive error ($F = 3.36$, $p = 0.06$). Pupils were on average 0.30 mm (standard error = ±0.08) larger for free space targets than Badal lens viewing; 0.08 mm (standard error = ±0.04) larger for flat than volumetric stimuli; and a maximum pupil difference of 0.86 mm (standard error = ±0.08) for a field of 2.5^{o} when compared to 30^{o} (being at 30^{o} larger). Interactions among these factors were not statistically significant. The effect of pupil differences in the main analysis' results found in our study can be considered insignificant.[141,179,192,193]

Table 9. Simple main effects of stimulation method, stimulus depth and refractive group (interaction Method*Depth*RefractiveError) for 5.00 D stimulus. SEM: Standard error of the mean. Unpaired t tests are applied to pairwise comparisons of refractive error groups and paired t tests for any other pairwise comparisons. In all cases Bonferroni correction is applied.

Factor 1, Level	Factor 2, Level	Factor 3, Pairwise Comparison	Mean difference (±SEM) [D]	p-value
Stimulation Method, FS	Stimulus Depth, Flat	Refractive Error, EOM-LOM	1.50 (±0.30)	<0.01
Stimulation Method, FS	Stimulus Depth, Flat	Refractive Error, EOM-EMM	1.20 (±0.29)	<0.01
Stimulation Method, FS	Stimulus Depth, Volumetric	Refractive Error, EOM-LOM	1.42 (±0.30)	<0.01
Stimulation Method, FS	Stimulus Depth, Volumetric	Refractive Error, EOM-EMM	1.27 (±0.30)	<0.01
Stimulation Method, BLV	Stimulus Depth, Flat	Refractive Error, EOM-LOM	1.63 (±0.36)	<0.01
Stimulation Method, BLV	Stimulus Depth, Flat	Refractive Error, EOM-EMM	1.39 (±0.35)	<0.01
Stimulation Method, BLV	Stimulus Depth, Volumetric	Refractive Error, EOM-LOM	1.46 (±0.39)	<0.01
Stimulation Method, BLV	Stimulus Depth, Volumetric	Refractive Error, EOM-EMM	1.04 (±0.37)	0.03
Refractive Error, EOM	Stimulation Method, BLV	Stimulus Depth, Flat-Volumetric	0.30 (±0.11)	0.01

SEM: Standard error of the mean. FS: Free space. BLV: Badal lens viewing. EOM: Early onset myopes. EMM: Emmetropes. LOM: Late onset myopes.

5.3.4. Discussion

This study investigated accommodative response accuracy as a function of the stimulation method used, as well as the depth and field of view of the stimulus, and the interactions of these three factors for subjects in different refractive error groups.

Effect of refractive error

In this study, accommodative response was significantly affected by refractive error group. Late onset myopes showed larger lags of accommodation at near than emmetropes and early onset myopes. Although significant interactions were found between refractive error and stimulus depth, field of view and stimulation method used, when controlling for stimulus depth, field of view and stimulation method, accommodative response differences among refractive error groups were still significant. However, from our results we cannot provide a definitive explanation for these differences among refractive error groups and a longitudinal study would be necessary to establish the mechanism. Our study aimed to determine how the experimental conditions may affect (or interact with) the accommodative response.[176] It is likely that the rate of myopia progression[29,159] (which was unknown in this study) might have biased the differences among refractive error groups. In addition, given that late onset myopes were in our study an average of 3.00 D less myopic than early onset myopes and that subjects with low myopia (less than |1.00| D) often use correction only for certain activities (e.g., driving), we speculate that the relationship between the magnitude of the refractive error and whether subjects wore correction during all day or just during some specific activities might have also been a confounding factor in our results.

Effect of field of view

When a higher accommodative stimulus was used (5.00 D), the effect of the field of view size was relatively small and not statistically significant, in agreement with the results of Yao *et al*,[194] who did not find significant differences in the accommodative response gradients (from 0 to 5.0 D stimuli, 1-D step) obtained for three different visual fields (2º, 8º and 44º) and using a flat, black Maltese cross.

For an accommodative stimulus of 2.50 D, representative of most near vision tasks, the accuracy of accommodative responses appeared to improve as the target's field of view increased from 2.5º to 10º, but no differences were found when the field of view increased to 30º. These results lead to an interesting question: Is there an optimum retinal image size for accommodation stimulation? Physiologically, the macula is the zone richest in cone density with a sharp peak at the foveola and rapid decline up to about 10º to 15º eccentricity.[2] It is not known from our results how accommodative responses behave between this area of 10º to 30º eccentricity, but we can suggest that under photopic conditions the accommodation system appears to only use information from the visual field comprised within the perifovea.

This finding may have important implications in the development of myopia progression treatments such as novel multifocal contact lenses or orthokeratology in which there is an optical correction in the retinal periphery different to that in the foveola. The extent of the annular peripheral corrections may be optimized in these methods.

Effect of stimulus depth

When a subject is asked to look at a stimulus that comprises a range of spatial focal planes in the periphery (i.e., a volumetric stimulus), the accommodation system may respond two different ways. On one hand, peripheral blur provided by the out-of-focus plane may be used to better estimate the focal position of the fixation target.[25] On the other hand, the out-of-focus information in the retinal periphery may provide a conflicting stimulus and therefore bring the visual system towards its resting state of accommodation.[7]

There was no effect of the type of stimulus depth (flat or volumetric display) in the overall accommodative responses for 2.50 D or 5.00 D stimuli in our study. However, we did find that for 2.50 D stimuli, for a field of view of 4º and when using Badal lens viewing, volumetric stimuli resulted in larger lags than flat stimuli. Also, for 5.00 D stimuli, early onset myopes showed larger lags when using volumetric stimuli and Badal lens viewing. These specific conditions suggest that the extent of the effect of a volumetric stimulus in accommodative responses is yet to be determined. It is possible that decreasing the distance between the viewing planes, using more focal planes, or using additional peripheral depth cues besides blur may help to better disentangle the influence of volumetric stimuli in accommodation responses. Our results do show that flat and volumetric stimuli are equivalent if the fixation target is rich enough to stimulate accommodation, as the Maltese cross used in this study. If there was an effect of depth in the accommodative response, a defocused plane in the periphery (with blur-only cues) could behave as a (weak) conflicting stimulus that brings the accommodative system towards less accurate responses. This is consistent with Hartwig *et al*.[175] results as they showed that retinal periphery is sensitive to defocus.

Effect of stimulation method

When an accommodative stimulus of 5.00 D was presented, larger accommodative lags were found for the overall group when using Badal lens viewing compared to free space stimulation conditions. However, no differences were found between the two methods when a 2.50 D stimulus was used. This result is in agreement with some previous studies in myopia that found larger accommodative lags when increasing the accommodative demand[29,30,169] and larger lags when stimulating accommodation by optical means (negative lenses) than when using free space conditions.[29,30,157]

The type of method used to stimulate accommodation showed a statistically significant interaction with the subject's refractive error group and size of the field of view for accommodation stimulation of 2.50 D and with the subject's refractive error group and depth of the stimulus for accommodation stimulation of 5.00 D. Interestingly, when controlling for refractive group, size of the field of view and depth of the stimulus, there were not statistically significant differences between the Badal lens viewing and free space viewing methods for either accommodation demand used. These results agree with Aldaba *et al*.[157] and may explain why previous studies have found significant differences between optically-induced and free space viewing accommodation. Aldaba *et al*. concluded that the differences between Badal lens viewing and free space could potentially (they did not measure in all conditions with a Badal lens) depend on the size of the field of view, the proximity of the instrument's cover, the angular size of the stimulus and the peripheral interposition of objects in depth. If one or more of these factors (field of view, depth or refractive error group) were not controlled for in previous studies, differences in accommodative response between Badal lens and free space viewing could be explained if, for instance, myopes were more sensitive to flat stimuli and smaller fields of view than emmetropes.

In summary, we show that previously reported differences in accommodative response when using lens-based methods compared to free space viewing may be explained by the effect of other factors such as the field of view or the depth of the stimulus, rather than the method to stimulate accommodation. The most accurate accommodative responses were obtained for fields between 8º and 10º, which suggests that there may be an optimum peripheral retinal image size for accommodation stimulation. The only factor that in isolation significantly affects the accuracy of the accommodative responses is the type of refractive error. According to these findings, the stimulation method, the depth of the stimulus and field of view should be controlled factors when measuring the lag of accommodation. In addition, it would be advisable in further studies of the lag of accommodation to include the refractive error as a covariate in all measurements to minimize the variability across subjects, which may mask some important findings.

5.4. Study 4. Automated non-cycloplegic binocular subjective refraction algorithm in adults.

PREVIOUS NOTE: The following text in this section corresponds to the article: **Otero C**, Aldaba M, Pujol J. Automated non-cycloplegic binocular subjective refraction algorithm [submitted].

5.4.1. Introduction

According to the most recent estimates from the World Health Organization (WHO), the uncorrected refractive error is the main cause of visual impairment, affecting 43% of the global population.[15] The largest prevalence of visual impairment is found in developing countries, for which there is evidence that one of the leading causes for uncorrected refractive error is the insufficient eye care personnel and massive imbalance in the distribution of eye care services in these countries.[16,17] Automated and portable technology capable of performing accurate non-cycloplegic refractions could help to reduce this problem.

Eye's refraction can be obtained both objectively and subjectively. Objective refraction measurements can be currently determined fast and easily with autorefractors and wavefront aberrometers and they are often used as a starting point for conventional subjective refraction.[96,195,196] Several studies have reported that most modern objective refractometers are reliable and accurate with regard to subjective refraction.[108,119,197] However, prescribing from objective findings alone achieves limited patient satisfaction and visual acuity does not improve sufficiently.[96,119,198]

Subjective refraction is considered the gold standard of refraction.[3] It is based on comparing different dioptric lenses (i.e., spherical and cylindrical lenses) and measuring changes in visual acuity to arrive at the dioptric lens combination that maximizes it.[40] In contrast to objective refraction, subjective refraction relies on the response of the patient and on the examiner's skills. These two factors may be the reason why some authors found more variability in subjective refraction than in objective refraction outcomes.[108,199] However, Rosenfield and Chiu[200] found no differences in variability, they obtained mean standard deviations for the subjective and objective techniques of ± 0.15 D and ± 0.14 D, respectively.

Despite the goal of subjective refraction seems simple, it is a challenging procedure especially when not using cycloplegia to minimize accommodation artefacts in non-presbyopes, who may sometimes require to accommodate to achieve the maximum visual acuity.[3] This is the case of pseudomyopes[201] or latent hyperopes.[202] Pseudomyopes is the term used for negative subjective spherical refractions whereas latent hyperopes is the term for positive subjective refractions in the presence of excessive accommodation,[63] in both situations a cycloplegic refraction to obtain the full refractive error is recommended and spectacle prescription should be based on careful consideration of the patient's individual visual needs.[63,201,202] It is likely that an automated non-cycloplegic refraction algorithm will not substitute cycloplegic refractions under these circumstances but it can be useful as a screening automated method if embedded in a cost-efficient device. Recently, new technologies have appeared with the aim of approaching eye's refraction to general population in a more affordable way[92,203,204] although none of them include the patient's psychophysical response, which limit their applicability for screening purposes or spectacles prescription. Having all this in mind, the purpose of this study is to propose an algorithm to perform an automated non-cycloplegic refraction in adults.

5.4.2. Methods

Instrument

The proposed method to obtain the subjective refraction of the eye can be generalized and implemented in any optical system capable of changing the sphero-cylindrical refraction of both eyes according to the patient's psychophysical response. For a 'proof-of-concept' of the algorithm a manual phoropter was converted into a motorized system. A commercial manual phoropter (VT-10, Topcon Co. Ltd., Japan) was partially disassembled and 8 motors (4 for each eye) were introduces that allowed to control the sphere power, cylinder power, cylinder orientation and the occluder of each eye independently. All motors were connected to the drivers which in turn were connected to a computer with a USB wire and controlled via Matlab R2015b (MathWorks, Inc., USA). A display connected to the computer was placed at 6 meter distance from the observer and was used as the stimulus display. We used the monitor Philips 246V with 24 inches and 1920x1080 pixel resolution, which could display optotypes from 1.5 to less than -0.3 logMAR. A wireless keyboard was used by the observers to provide feedback to the algorithm. A picture of the setup is shown in Figure 23.

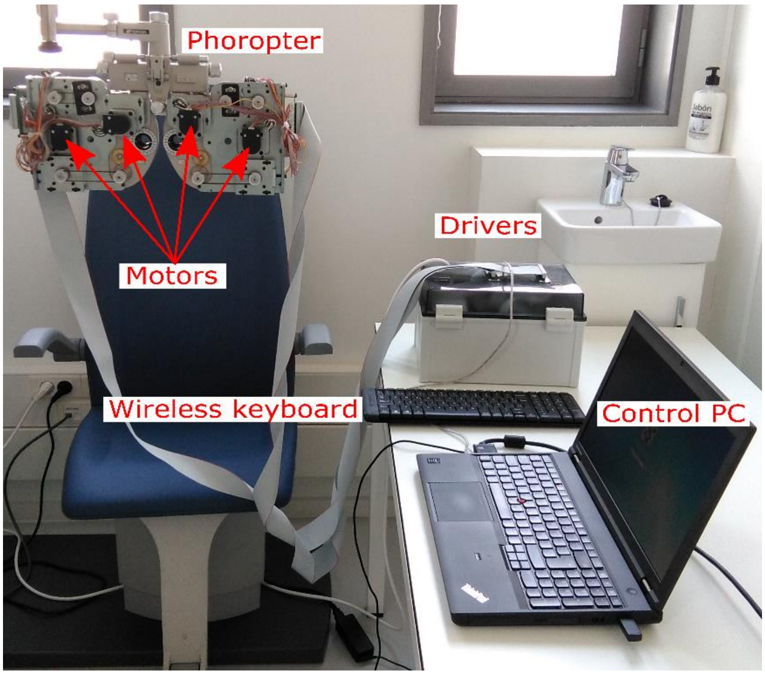

Figure 23. Picture of the clinical setting with the custom-made motorized phoropter. Four motors were attached in the anterior surface and 4 motors were attached in the posterior surface of the phoropter. Motors are connected to the drivers and a USB wire connects the drivers to the control PC. The wireless keyboard is used by the observer to respond (e.g., to respond to stimulus orientation: up, down, left or right).

New method algorithm

The automated subjective refraction algorithm receives two inputs: the current objective refraction and the previous spectacle prescription. The former is referred to the sphere, cylinder and axis of the right and left eye obtained with an autorefractometer or wavefront sensor. The latter is obtained either with the last prescription record or measuring the sphero-cylindrical power (with a fronto-focimeter) of the current spectacles worn by the observer. If the observer has never been prescribed any corrective glasses, we considered a 0 value for the sphere, cylinder and axis in both eyes despite the observer may not be necessarily emmetrope. If the observer does not wear spectacles at the time of the examination and the last prescription record is not available a NULL value was considered for sphere, cylinder and axis in both eyes. Once the two inputs are obtained, the algorithm goes through a sequence of 6 functions (Figure 24) detailed in order as follows:

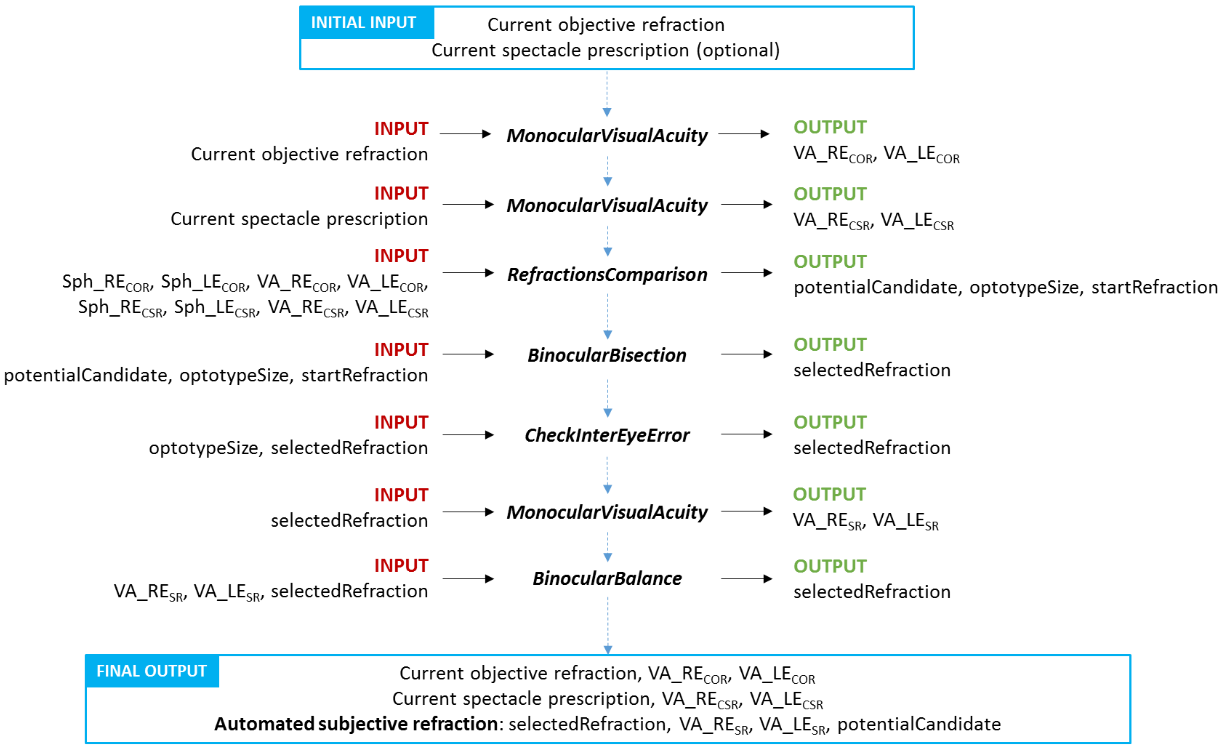

Figure 24. Flowchart of the automated subjective algorithm with all input and output variables for each function. VA: Visual Acuity. RE: Right Eye. LE: Left Eye.

1. *MonocularVisualAcuity* function:

This function receives as an input 6 values: the sphere, cylinder and axis values of the right and left eye of the current objective refraction or current spectacle correction. This function tests the observers' monocular visual acuity in a four-alternative force-choice task (4AFC). A black Snellen optotype is displayed at a visual acuity of 0.1 logMAR and the observer is required to select the correct orientation of the letter by pressing the arrows of a computer keyboard (i.e., up, down, left, right). This process is repeated 3 times to reduce the guess rate while the orientation of the Snellen 'E' randomly changes each time. If the observer selects 2 out of the 3 times correctly, the optotype size is decreased in steps of 0.1 logMAR, otherwise the optotype size is increased in steps of 0.1 logMAR until the observer reports 2 out of the 3 orientations correctly.

2. *RefractionsComparison* function:

This function receives as an input 8 values: the sphere of the right and left eye from both the current objective refraction and current spectacle prescription as well as the corresponding visual acuities measured at the beginning of the method (Figure 24). The aim of this function is: 1) to detect potential pseudomyopes or latent hyperopes; 2) to determine the starting point of refraction and the optotype size used in the next functions.

If the sphere of the current objective refraction minus the sphere of the current spectacle prescription is equal or more than 0.75 D (signed difference) the observer is considered a potential pseudomyope or latent hyperope. The cut-off value of 0.75 D is based on the precision of subjective refraction, as suggested by Rosenfield and Chiu,[200] a change of 0.50 D or more should be adopted as the minimum significant shift in refractive status. It is also important to remark that this way of detecting pseudomyopes or latent hyperopes assumes that the non-cycloplegic autorefraction will be as accurate as measured in a cyclopleged eye, which is not true for infants and teenagers but it is true for young adults once they reach approximately 20 years of age.[105] This is the main reason why we will not consider subjects younger than 20 years of age in this study.

The starting point of refraction to be used in the next function is determined as the refraction (either the current objective refraction or current spectacle prescription) with the best visual acuity, which is computed as the average between the right and left eye's visual acuity. We assume that the best visual acuity average corresponds to a refraction that is closer to the optimum subjective refraction. Notice that in case both averages are equal, the current objective refraction is chosen as starting point of refraction. In addition, there are two situations in which the current objective refraction is chosen by default as the starting point of refraction: one is when the current spectacle prescription input is NULL, the other is when a potential pseudomyope (or latent hyperope) has been detected. In this latter situation, despite the current objective refraction may not provide a better visual acuity than the current spectacle prescription, the algorithm makes this decision for specific reasons explained below in *BinocularBisection* function. The optotype size for the next functions is computed as the maximum visual acuity between the right and left eye's starting point of refraction.

The output of this function is a variable named *potentialCandidate* that can only have three values: *true*, *false* or NULL. *True* is for potential pseudomyopes or latent hyperopes, *false* for observers that are not, and NULL is the output in the case the values from current spectacle refraction are NULL. Other outputs of this function are the optotype size (in logMAR units) and the starting point of refraction.

3. *BinocularBisection* function:

This function receives as input the output of the previous function *RefractionsComparison*. *BinocularBisection* starts setting a range of refractions which assumedly comprise the final subjective refraction and over which the algorithm will test the subject's blur perception. This range is calculated according to the input refraction (current objective refraction or current spectacle prescription) and the *potentialCandidate* variable (an estimation of a potential pseudomyope or latent hyperope).

On the one hand, when *potentialCandidate* equals to *false* (i.e., the observer is presumably not a pseudomyope or latent hyperope) the algorithm considers a range for the sphere (R_S) that goes from -0.50 to +1.50 D with respect the input sphere (R_S = 2.00 D). If the input sphere comes from the current objective refraction, since autorefraction and wavefront sensors tend to result in more minus correction than the subjective refraction,[109,119] a longer positive range than a negative one increases the odds to find the optimum subjective refraction. In the case the input sphere corresponds to the current spectacle prescription, it would not be necessary to have such an asymmetric range but in fact, it strengthens a more positive power which is consistent with the end-point criterion of subjective refraction:[3] maximum plus power with best visual acuity.

On the other hand, when *potentialCandidate* equals to *true*, the starting point of refraction comes from autorefraction or wavefront sensing by default. In this specific situation the algorithm flips the spherical range, i.e., it considers a range that goes from -1.50 to +0.50 D. As expected for a pseudomyope or latent hyperope, observers will likely choose more myopic refractions to achieve the best visual acuity. And finally, if *potentialCandidate* equals to NULL, the spherical range goes from -0.50 to +1.50 D with respect the input sphere. In this case, pseudomyopes or latent hyperopes may not converge properly to the optimum subjective refraction, this is a limitation of the method that is discussed below (see last paragraph of 5. *BinocularBalance* function).

Regarding the cylinder power, the algorithm considers a range that goes from the input cylinder to +1.00 D with respect the input cylinder power (R_C = 1.00 D). For axis orientation, the algorithm does not consider any set of different possible axis orientations (R_A = 0 º). It is important to take into account that R_C and R_A are theoretically bounded quantities, i.e., the axis range is limited to 179º and the cylinder can range from any negative value up to 0 D (considering that all input refractions are in negative cylinder notation). The arbitrary decisions of these ranges can limit the accuracy of the algorithm significantly (specially the fact of not considering any change in axis orientation). But, as we explain below this new methodology can easily include a set of different axis orientations or include larger spherical and cylindrical ranges at the cost of efficiency. Our initial implementation is based on multiple previous pilot studies which sought the best balance between efficiency and accuracy.

Next, the step size (i.e., precision) for each variable must be established. The algorithm considered a step size of 0.25 D for both sphere (SS_S) and cylinder (SS_C). For axis orientation, a step size (SS_A) of 1º could have been considered. Once the six free parameters have been determined (R_S, R_C, R_A, SS_S, SS_C and SS_A), all possible combinations of refractions comprised within the ranges and with the specified step sizes are computed. At this point, all the generated sphero-cylindrical refractions for each eye are transformed into power vector notation (M, J_0 and J_{45}) using equations 4, 5 and 6. This transformation allows algebraic operations on the eye's refraction in an orthogonal 3-D base (M, J_0 and J_{45}). Consequently, even if the three variables sphere, cylinder and axis are not independent from one another, they become theoretically independent when transformed into M, J_0 and J_{45}.

$$M = S + \frac{C}{2} \quad \text{(eq.4)}$$

$$J_0 = -\frac{C}{2} cos2\alpha \quad \text{(eq.5)}$$

$$J_{45} = -\frac{C}{2} sin2\alpha \quad \text{(eq.6)}$$

The next step is to compute for each eye all the Euclidean distances (ED, equation 7) between all the generated refractions (M_i, $J0_i$, $J45_i$, for i=1..N_{ref}) and the most negative refraction (M_1, $J0_1$, $J45_1$) as follows

$$ED = \sqrt{(M_i - M_1)^2 + ({J_0}_i - {J_0}_1)^2 + ({J_{45}}_i - {J_{45}}_1)^2} \, . \quad \text{(eq.7)}$$

Notice that the most negative refraction is that with the smallest spherical equivalent (M). Next, all the generated refractions are sorted in ascending order of Euclidean distances (Figure 25). The maximum number of possible refractions depends on the parameters

R_S, SS_S, R_C, SS_C, R_A and SS_A. Notice that the cylinder value is an inferior bounded quantity (Figure 25A).

Once this computation is completed, a two-interval force-choice task (2IFC) is performed inspired on the mathematical root finding bisection algorithm: an interval is repeatedly halved and in each partition the subinterval in which a root is considered to lie is selected as the next interval. A black Snellen optotype is shown during 4 seconds with a refraction given by one end of the sequence of refractions previously computed for each eye (e.g., M_1, $J0_1$, $J45_1$), and then the same Snellen optotype is again shown during 4 seconds with the opposite extreme refraction (e.g., M_{Nref}, J_{0Nref}, J_{45Nref}). The decision to present a certain refraction firstly or secondly is randomized.

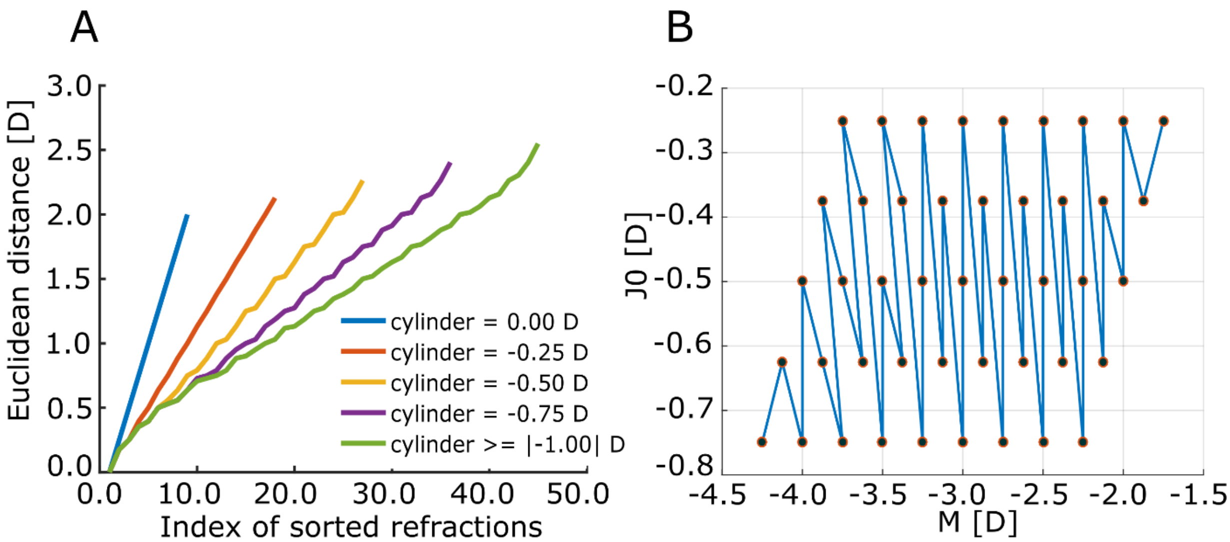

Figure 25. A: Dependence of the Euclidean distances and number of possible refractions according to the amount of cylinder of the most negative refraction (M_1, J_{01}, J_{451}). The specific case of R_S=2.00 D, R_A=0º and SS_S=SS_C=0.25 D is shown. The number of possible refractions (N_{ref}) are (in ascending order): 9, 18, 27, 36 and 45. B: 2-Dimensional representation of all possible power vector refractions considering the specific case of R_S=2.00 D, R_C=1.00 D, R_A=0º, SS_S=SS_C=0.25 D and a starting point of refraction of -3.00-1.50x90º. Each dot represents one refraction. The blue line connects each refraction in ascending order of Euclidean distances from the most negative refraction.

At this point the observer is required to choose which image (i.e., refraction) was the clearest. Once the observer has selected one image, in the next test the unselected refraction is changed by the refraction corresponding to the mean index refraction rounded to the nearest integer. That is, in the first pair selection, refractions correspond always to indices i_{min}=1 and i_{max}=N_{ref} respectively, whereas in the second selection i_{min} or i_{max} correspond to round((N_{ref}+1)/2), depending on whether the patient selected the refraction with index i_{max}=N_{ref} or i_{min}=1. This procedure is repeated until i_{min}=i_{max} and it is performed under binocular conditions. In order to decrease the guess rate, each 2IFC trial is repeated 3 times and the selected refraction is the one chosen at least 2 times out of the 3 repetitions. The output of this function is the selected refraction (sphere, cylinder and axis of both eyes).

4. *CheckInterEyeError* function:

This function receives as input the output of the *BinocularBisection* function. This function aims to reduce the inter-eye measurement error that may come from the starting point of refraction when there is a difference in refraction (either in cylinder or sphere) of 0.75 D or more between the right and left eye's refraction. If differences between right and left eye's sphere or cylinder are less than 0.75 D the algorithm jumps directly to the next function without doing any change.

By way of example, let us assume that the best-corrected spherical subjective refraction is -2.75 D and -2.00 D for the right and left eye, respectively, and the starting point of refraction is -3.00 D and -2.00 D. Let us imagine that after *BinocularBisection* the starting point of refraction is changed for -2.75 D and -1.75 D. In this specific example there is an inter-eye error in sphere of 0.25 D that presumably comes from the starting point of refraction. The function *CheckInterEyeError* addresses this issue as follows: all possible combinations of refractions comprised between the right and left eye's refraction using the same step sizes SS_S and SS_C are computed. Then, all generated refractions are organized according to the Euclidean distances with respect to a reference refraction (e.g., the left eye's refraction) and a 2IFC task repeated three times is performed three times (9 trials).

The procedure is conducted similarly to *BinocularBisection,* where each 2IFC task compares (binocularly) the refraction obtained with *BinocularBisection* with a refraction that reduces the inter-eye difference in at least one Euclidean distance. In the first three comparisons the left refraction is changed one Euclidean distance closer to the right refraction, which remains completely unmodified. In the following three comparisons the right refraction is changed while the left remains unmodified. Finally, in the last three comparisons both the left and right eye refractions are changed one Euclidean distance from each other so the distance between refractions is reduced two steps. After all these trials, the refractions of both eyes are changed according to the observer's response. Notice that when contradictory answers from the observer occur no change is produced. A change in the left eye's refraction occurs only when the observer selects a refraction that reduces the measured inter-eye difference from left to right eye. Analogously happens for the other two conditions.

5. *BinocularBalance* function*:*

This function receives as input the values of sphere, cylinder and axis of both eyes obtained in *BinocularBisection* or *CheckInterEyeError* function and the values of monocular visual acuity obtained in the previous function. The aim of this function is to look for the maximum plus power with the same visual acuity obtained in the previous function. It is added an arbitrary value based on previous pilot studies of +0.50 D to the sphere of the right and left eye. Then, the Snellen 'E' optotype is presented, binocularly, with a size corresponding to the best monocular visual acuity obtained in the previous step. The observer is required to answer the orientation of the letter in the same way it is done in the *MonocularVisualAcuity* function. If the observer answers incorrectly in 2 out of the 3 times, the miopization is decreased 0.25 D, otherwise the algorithm is finished and the final subjective refraction is the last refraction tested.

The final output of the algorithm comprises the sphere, cylinder and axis of both eyes and the monocular visual acuities of the automated subjective procedure, the current objective refraction and (when available) the current spectacle prescription. In addition, the outcome of the algorithm also includes the variable *potentialCandidate* which may advice the patient to look for a cycloplegic refraction with a professional in case it is *true* or NULL.

Examination protocol

The study was approved by the Ethics Committee of Hospital Mutua de Terrassa (Terrassa, Spain). The study follows the tenets of the Declaration of Helsinki and all subjects gave informed written consent.

Non-cycloplegic binocular subjective refraction was obtained twice in 50 healthy adults (none of which suffered from ocular disease) with the new automated method and with the conventional clinician subjective refraction procedure performed in a manual phoropter. All measurements were obtained in two sessions within one week. The objective refraction was obtained with the WAM-5500 (Grand Seiko Co. Ltd., Japan) and was used as starting point of refraction for both the automated and the clinician subjective refractions. One clinician performed all subjective refractions and was blinded to the refraction results obtained with the automated method. The clinician was a graduated Spanish optometrist with 3 years of working experience and was specifically told to follow a refraction protocol of maximum plus power for best visual acuity. All clinical subjective refractions followed a monocular refraction plus biocular and binocular balance. Cylinder and axis orientation were refined with Jackson cross-cylinders. The duochrome test was not used in any case and all refractions were performed under the same room lighting conditions.

Data analysis

Statistical significance was set at 0.05 and the statistical analysis was performed using MATLAB R2015b (MathWorks, Inc., USA). Normality of each variable was verified with the Shapiro-Wilk test. Repeatability of the new method and repeatability of the clinician were analysed by means of the within-subject standard deviation (Sw). The repeatability of the autorefraction (i.e., Grand Seiko WAM-5500) has been evaluated before, the interested reader is referred to previous published articles about it.[92,96,205] Agreement between the automated and the clinician subjective refraction was assessed with Bland and Altman plots for each eye and parameter, as well as the agreement between autorefraction and the clinician subjective refraction. Additionally, paired t-tests are applied for repeatability analysis and repeated measures ANOVA are applied for the agreement analysis among the three methods. Statistical power was assessed with the free open-source G*Power 3.0.10. A pilot study with 25 subjects was conducted to calculate the sample size needed for a statistical power of 0.95 and it resulted in 40 subjects.

5.4.3. Results

The mean age ± standard deviation of the 50 observers were 30 ± 8 years (20 to 57 years) with a mean spherical equivalent refractive error of -1.74 ± 2.28 (-7.25 to 2.13) D and with mean corrected logMAR visual acuity of -0.06 ± 0.07 (-0.1 to 0.2). The starting point of refraction for the automated method was the current spectacle prescription 36% of the times and 0% of the subjects were considered potential candidates for pseudomyopia or latent hyperopia. On average, the new proposed method took 4 minutes and 16 seconds (± 44 seconds) and the conventional standard procedure took 4 minutes and 37 seconds (± 50 seconds). The time difference was statistically significant (paired sample t-test, $p=0.02$).

Repeatability analysis

The mean difference ± standard deviation (SD) between both sessions (test-retest), the within-subject standard deviation (S_W) and the p-values obtained with the paired sample t-test are shown in Table 10 for each eye, parameter and method (i.e., automated subjective refraction and clinician subjective refraction).

Table 10. Repeatability (test-retest) for each eye, parameter and method.

	Repeatability CSR method			Repeatability ASR method		
	Mean Diff. ± SD [D]	S_W [D]	p-value	Mean Diff. ± SD [D]	S_W [D]	p-value
M_{RE}	0.02±0.19	0.13	0.48	-0.07±0.23	0.17	0.04
$J0_{RE}$	0.01±0.05	0.04	0.24	<0.01±0.05	0.03	0.88
$J45_{RE}$	-0.02±0.07	0.05	0.01	<0.01±0.10	0.07	0.81
M_{LE}	0.03±0.18	0.12	0.21	-0.06±0.28	0.20	0.13
$J0_{LE}$	<0.01±0.06	0.05	0.98	<0.01±0.06	0.04	0.83
$J45_{LE}$	<0.01±0.08	0.05	0.86	<0.01±0.11	0.08	0.61

CSR: Clinician Subjective Refraction. ASR: Automated Subjective Refraction. Diff.: difference. SD: standard deviation. S_W: within-subject standard deviation.

Agreement analysis

The Bland and Altman plots comparing the automated subjective refraction with the clinician subjective refraction for each eye and parameter are shown in Figure 26. Analogously, the Bland and Altman plots comparing between autorefraction and the clinician subjective refraction is shown in Figure 27. The results of the repeated measures ANOVA considering the three methods and applied to the right eye parameters are: $F=26.46$, $p<0.01$ for M; $F=2.67$, $p=0.07$ for J_0; and $F=1.37$, $p=0.26$ for J_{45}. Analogously, the results for the left eye are: $F=1.74$, $p<0.01$ for M; $F=0.14$, $p=0.87$ for J_0; and $F=2.05$, $p=0.14$ for J_{45}.

Only the repeated measures ANOVA applied to the spherical equivalent of both eyes results in statistically significant differences among methods. The Bonferroni post-hoc test for the right and left eye shows that differences between autorefraction and clinician subjective refraction are statistically significant (p<0.01) as well as the differences between autorefraction and automated subjective refraction (p<0.01).

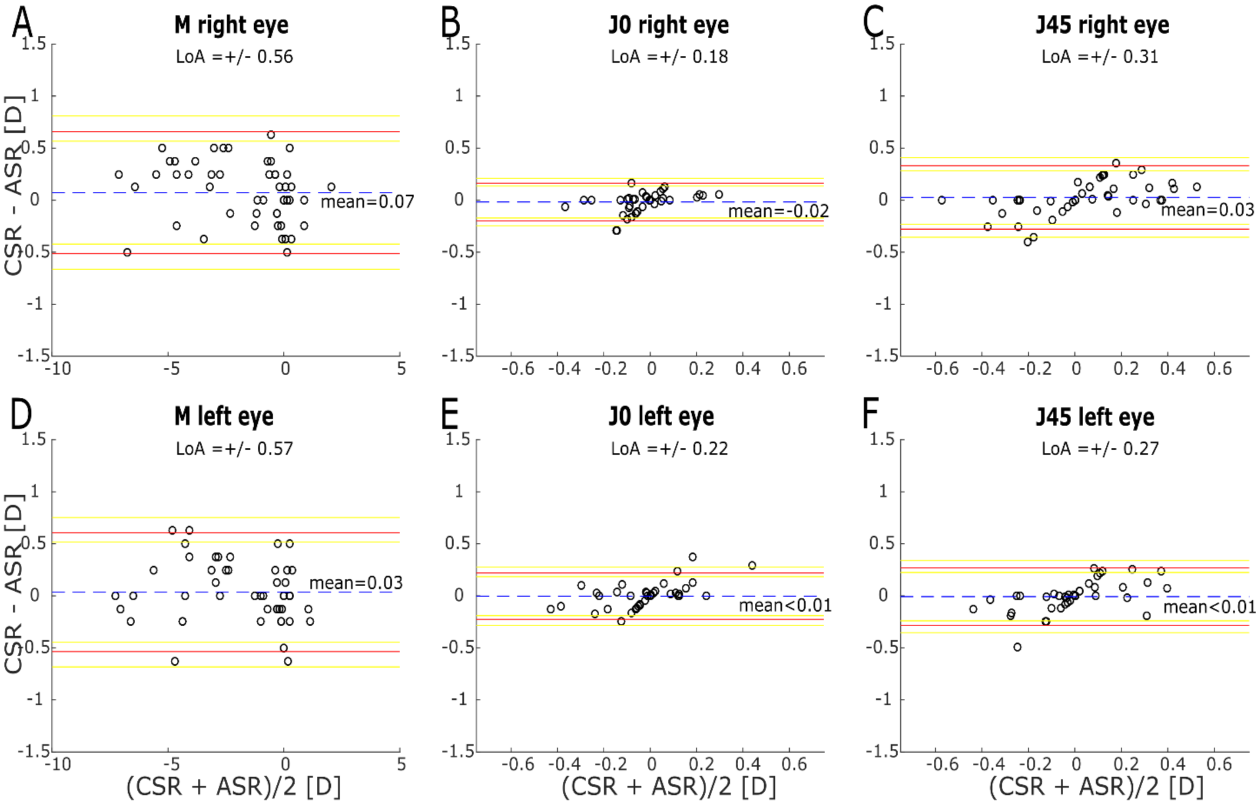

Figure 26. Bland and Altman plots. A, B, C: right eye data. D, E, F: left eye data. The top and bottom red lines indicate the superior and inferior 95% limits of agreement (LoA), respectively. The yellow lines indicate the superior and inferior 95% confidence interval for each limit of agreement. The dashed, blue lines indicate the mean difference. CSR: Clinician Subjective Refraction. ASR: Automated Subjective Refraction.

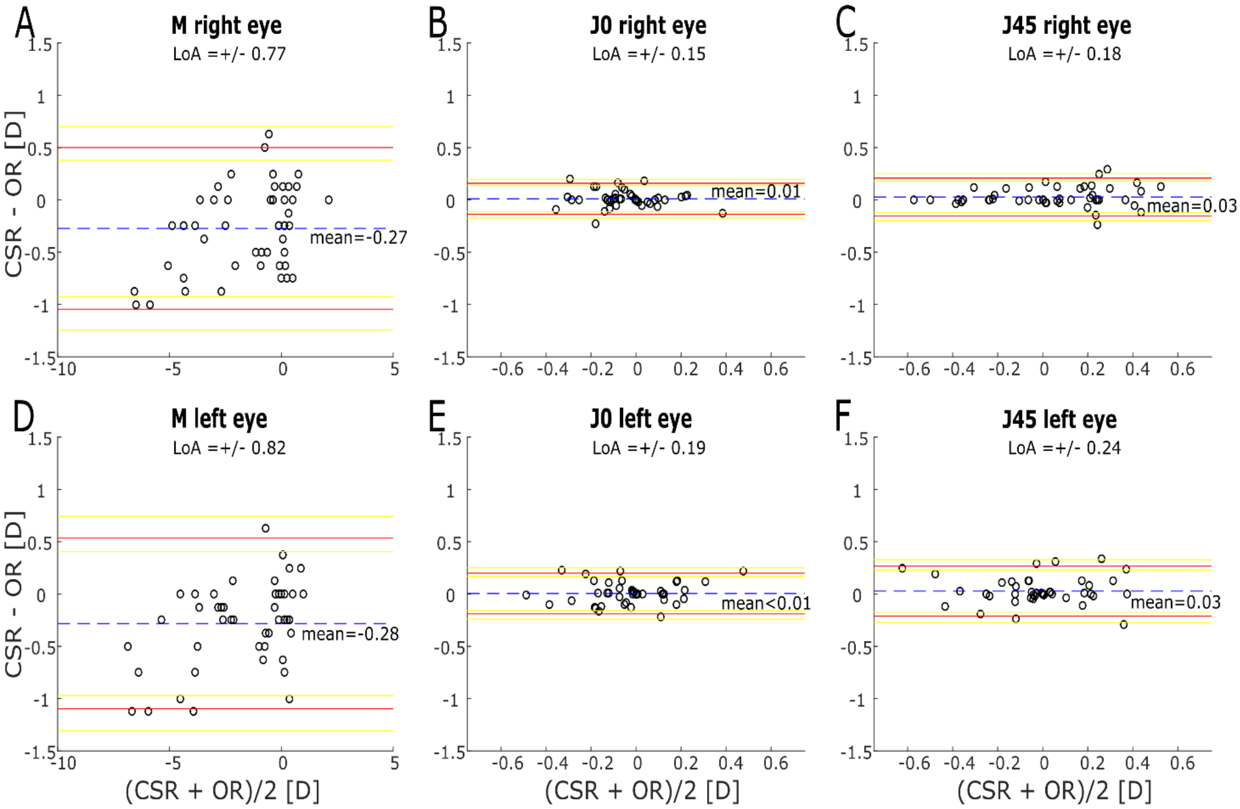

Figure 27. Bland and Altman plots. A, B, C: right eye data. D, E, F: left eye data. The top and bottom red lines indicate the superior and inferior 95% limits of agreement, respectively. The yellow lines indicate the superior and inferior 95% confidence interval for each limit of agreement. The dashed, blue lines indicate the mean difference. CSR: Clinician Subjective Refraction. OR: Objective Refraction (Grand Seiko WAM-5500).

5.4.4. Discussion

A new method to perform non-cycloplegic binocular subjective refraction without the support of a clinician was investigated. Repeatability (test-retest) and agreement of this new method in relation to the conventional clinical procedure was assessed in 50 subjects. A total of 6 variables were analysed: the power vectors components (M, J_0 and J_{45}) of both eyes.

Repeatability analysis

The within-subject standard deviations found for the automated method are comparable to those found for the clinician subjective refraction for all three components (M, J_0 and J_{45}). In all cases we obtained within-subject standard deviations below 0.25 D, which is the limit of clinical significance. The worst-case within-subject standard deviation (S_w) is ±0.20 D for the spherical equivalent M and for the automated subjective refraction (Table 10, left eye). It is consistent with previous studies where standard deviations between ±0.15 D and ±0.38 D were reported between and within clinicians.[108,200,206,207] Autorefractors and wavefront sensors are, in general, more repeatable since they do not depend on the patient's response or the clinician's skills. For instance, Pesudovs *et al*.[108] compared the repeatability (test-retest) of two well-known autorefractors (Topcon KR-8000, Nidek AR-800) and found standard deviations for the spherical equivalent of ±0.04 D and ±0.07 D, respectively. Otero *et al*.[118] analysed the repeatability (averaging 3 measurements) of a wavefront sensor (AOVA, Voptica S.L., Spain) and obtained within-subject standard deviations for the sphere of ±0.17 D.

Agreement analysis

For the spherical equivalent M, the automated method showed lower Limits of Agreement (±0.57 D) than the objective method (±0.80 D), an average difference of roughly 0.25 D. Moreover, the ANOVA post-hoc analysis highlighted no statistically significant differences between the reference method (clinical subjective refraction) and the automated refraction, while statistical differences were found when compared to objective refraction. Regarding the cylinder, the Limits of Agreement obtained for the automated and the objective refraction can be considered equal and no statistical significant differences were found in any case. Thus, on average the automated refraction improves the agreement with the gold standard in comparison with objective refraction and its Limits of Agreement are close to the limit (±0.50D) suggested by Rosenfield and Chiu[200] as the minimum significant shift in refraction status.

In comparison with other studies, on the one hand there are 3 relatively recent studies[132,133,205] that compared the agreement of an automated subjective refraction methods with the conventional clinical subjective refraction. Two of them used the same device (Topcon BV-1000, no longer commercially available) and they reported limits of agreement for the spherical equivalent of ±0.69 D and ±0.82 D.[132,133] The third study was performed in our lab, the automated method was implemented on a stereoscopic virtual reality system and limits of agreement of ±0.88 D were obtained for the spherical equivalent.[205] On the other hand, Sheppard *et al*.[96] compared autorefractor readings of the WAM-5500 (Grand Seiko Ltd., Japan) with the subjective refraction and found limits of agreement for the spherical equivalent of ±0.75 D. In addition, older studies[109,110] that compared autorefractor measurements with subjective refraction found limits of agreement around ±0.95 D.

Limitations of the automated method

Although objective refractions are faster and much more precise than subjective refractions (whether or not automated), our results suggest that the new proposed method is reasonably equivalent to the conventional clinical subjective refraction in time duration, accuracy and precision. It incorporates two important novel factors: it does not require clinician support and it has better agreement than most objective refractometers. However, this new method still needs some improvements before it can be widely used.

In terms of the astigmatic determination, an unexpected systematic linear error in the Bland and Altman plots for the J_0 and J_{45} in both eyes was observed (Figure 26B, C, E and F). We cannot entirely explain the source of these errors and interestingly, other studies that compared a handheld wavefront sensor to subjective refraction obtained as well these systematic errors.[92,203] It is also important the decision to set the axis orientation as a fix parameter. This was chosen for efficiency and considering the following: the precision of cylinder axes determined subjectively is around ±10º;[200] and between 80% and 95% of the cylinder axes determined with an autorefractor are within 20º (or less) of those found subjectively.[96,109,198] Thus, while in most cases we found that the axis determined objectively is within clinically acceptable values, it might not be appropriate for some subjects and the new proposed method should be able to effectively include them in future improvements (for instance, by introducing some pairwise comparisons of refractions with different cylinder orientations in a 2IFC task).

In terms of accommodation control, the automated method does not control it. Especially in the *BinocularBisection* function where observers simply chose the clearest image in each pair of refractions regardless the chosen refraction could make subjects accommodate. However, our results suggest that the automated method was not significantly affected by accommodation artefacts which is likely due to: 1) only healthy adults (without accommodative anomalies) were tested; 2) the short negative ranges that were established in the *BinocularBisection* function limited the potential negative shift; and 3) the objective refraction was a reasonably good starting point of refraction in most of the cases. Thus, from our results we cannot conclude anything about the performance of the algorithm in children, people with ocular pathologies or accommodative anomalies. In these cases a cycloplegic refraction with a professional is advised.

Overall, it has been shown that the automated method is precise enough and more accurate than autorefraction and wavefront sensing in healthy adults, which makes it valuable not only as a preliminary step in subjective refraction but also as a refraction method where it takes place outside a clinical setting and clinicians cannot be present. This latter point is especially important in developing countries where this automated method in conjunction with appropriate lens-based technologies could significantly contribute to overcome the lack of primary eye care services.[16,17] Additionally, we believe that another possible advantage of the method is the possibility to adjust all the free parameters of the method individually when optimization of these parameters can be adapted to, for instance, the subjects' age and prior refraction or initial visual acuity. Consequently, the new automated method can potentially offer a more flexible and controlled way of performing subjective refraction.

Conclusions

The first implementation of the algorithm has shown a potential novel method of performing non-cycloplegic subjective refraction in adults without clinician support. Although it presents some limitations that warrant further research and it still should be tested in a wider population in terms of age, refraction and different ocular conditions, this method can contribute to improve the access to primary eye care services in developing countries.

5.5. Study 5. Random changes of accommodation stimuli: an automatic extension of the flippers accommodative facility test.

PREVIOUS NOTE: The following text in this section corresponds to the article: **Otero C**, Aldaba M, López S, Díaz-Doutón F, Vera-Diaz FA, Pujol J. Random changes of accommodation stimuli: an automatic extension of the flippers accommodative facility test [submitted].

5.5.1. Introduction

The ability of the eye to accurately and repeatedly change its accommodative state when changing focus between two focal planes during a certain period of time is clinically measured using the flippers accommodative facility test.[18] This test is usually performed either at far distance (i.e., the fixation target is at 6 m distance) or at near distance (i.e., the fixation target is at 0.4 m distance), and the accommodative demand for each focal plane is lens-induced with an accommodation flipper. At near distance a pair of ophthalmic flipper lenses of +2.00 D and -2.00 D, which stimulate, respectively, +0.50 D and +4.50 D. At far distance, a lens of -2.00 D is used to stimulate an accommodative demand of +2.17 D, and +0.17 D with no lens. The accommodative facility test is often performed in children[85] and young adults when accommodation abnormalities are suspected.[18] For children six to 12 years old, the expected (norm) finding is 6 cycles per minute (cpm) or more, when the test is performed monocularly in healthy subjects.[85] For teenagers and young adults 13 to 30 years old, the expected finding is 11 cpm or more.[18] The accommodative facility results depend on the individual's amplitude of accommodation, e.g., prepresbyopic subjects from 30 to 42 years of age shown worse results than the previously cited normative values.[86]

Clinical accommodative facility tests are typically used as a measure of visual fatigue,[208] which can be caused by accommodative (if used monocularly) and/or binocular vision (if used binocularly) dysfunctions.[19] The tests are also used to evaluate the treatment effect of accommodation vision training. However, these tests measure accommodation responses under repeated and therefore predictable conditions for the patient, which is not what occurs in natural conditions. During normal daily activities, we are required to change focus within nearly infinite focal planes, and in a random or pseudo-random fashion.

To our knowledge, accommodative facility tests have not been evaluated using more than two predictable accommodative demands, and for a specific viewing distance. Traditional measures of accommodative facility involved repeating the same accommodation demand change over a period of time, therefore are predictable for the subject and do not consider more than two accommodation planes. Emerging technologies such as computer-controlled focus-tunable lens (electro-optical systems)[135] allow to include more (as many as desired) levels of accommodative demands and automatic randomization among these accommodative demands so that they are not predictable. These features may be useful because: (1) they allow automatization of the test, (2) study the potential effect of anticipation (due to stimulus' predictability),[21–23,51] and (3) a more comprehensive examination of the patient's accommodation ability as several different accommodative demands may be measured. In addition, a focus-tunable automated lens can be used to further understand the dynamics of accommodation when optically stimulated. This latter point is especially relevant since it has been shown that the steady-state accommodative response stimulated with lens-based systems is affected by many factors such as the refractive error or the field of view when compared to free space stimulation.[157,176,209] Finally, a better understanding of the dynamics of accommodation under optical stimulation would provide insight into the visual discomfort that some individuals may experience in virtual reality systems.[210]

The purpose of this study is dual, first, we will compare the conventional manual flipper accommodative facility test with an automated test performed in a computer-controlled electro-optical system, and secondly, we will study accommodation dynamics with a new accommodative facility test that changes among various accommodative demands in a unpredictable manner.

5.5.2. Methods

Subjects

This research was performed with full informed consent by each subject, and followed the tenets of the Declaration of Helsinki. Criteria for inclusion were: (1) best-corrected visual acuity of 0.00 logMAR (20/20 Snellen equivalent) or better in each eye, (2) amplitude of accommodation above the average given by Hofstetter's formula for accommodation[19] (Amplitude = 15 – 0.25*Age), (3) between 18 and 25 years of age, to ensure that the amplitude is not a confounding factor in the accommodative facility test, (4) spherical equivalent refractive error measured with subjective refraction between -6.50 and +0.50 D in each eye, (5) no strabismus, amblyopia, binocular or accommodative anomalies, and (6) no history of any ocular disease, surgery and/or pharmacological treatment that may have affected vision at the time of the study. Subjects with myopia wore their own disposable soft contact lenses for the study. All contact lenses prescriptions were within ±0.25 D of the subject's best correction in each meridian, determined by subjective refraction, as explained below.

Instrumentation and methods

The five different experimental conditions of this study that were randomly presented to each subject are summarized in Table 11. The first two conditions were manual clinical monocular accommodative facility tests, for far and near distances, respectively. The specific procedures for these two conditions were as follows: the examiner held accommodation/disaccommodation flipper glasses placed in front of the subject's eye at the eyeglasses plane while the subject tried to clear the accommodative target described below. As soon as the subject reported clarity of the target, the examiner flipped the lenses to induce a change in the accommodative demand. Monocular accommodative facility was tested during 60 seconds for each condition. The remaining three experimental conditions were conducted using an electro-optical system with and open-field autorefractor as described in Figure 28 and explained in detail below. For each of these three conditions, the subject was asked to report clarity of the accommodative target by pressing a key on a keyboard. At that point, the accommodative demand was automatically changed to the next accommodative level. Conditions 3 and 4 replicated the standard clinical far and near distance accommodative facility tests of condition 1 and 2, thus the accommodative demand changed between 0.17 and 2.17 (far distance condition) or 0.50 and 4.50 D (near distance condition). Finally, in condition 5, we integrated the far and near accommodative facility tests into one hybrid test that comprised four possible accommodative demands pseudo-randomly chosen. The pseudo-random sequence forced eight times each possible transition between two demands (e.g., eight times the transition 0.17 to 2.17 D, eight times the transition 4.50 to 2.17 D, etc.). There were six possible transitions for accommodation and six possible transitions for disaccommodation in condition 5, therefore the test finished once the subject cleared 96 transitions (8x6x2=96). This design allowed us to ensure the same accommodative demand changes (or '*overall effort'*) was induced in all subjects. In order to compare the dynamics measured with the autorefractor among conditions 3, 4 and 5, conditions 3 and 4 finished as well once the subject cleared 96 transitions (48x1x2), note that in these two conditions there was only one possible transition: either 0.17/2.17 D or 0.50/4.50 D.

A binocular open field autorefractor, PowerRef II (Plusoptix Inc., USA), was used to measure accommodation responses for conditions 3, 4 and 5. This autorefractor is based on the principle of dynamic infrared retinoscopy and it measures spherical equivalent, pupil size and gaze position at a sampling frequency of 25 Hz.[100,211] In order to align the PowerRef and the subject's eye while allowing the target viewing, a 50 mm squared IR hot mirror was placed 40 mm from the subject's pupil plane. Subjects look at the accommodative stimulus through an optical system comprised by three lenses (Figure 28A). The first lens (L1, diameter of 50 mm, focal length of 100 mm) was placed 200 mm from the subject's pupil (twice f_{L1}). In this way, a pupil conjugate plane was created 200 mm away from the lens, without magnification. The active module that performed the accommodation stimulation was placed in that plane and was composed by an electro-optical lens[135] (EOL, EL-16-40-TC, Optotune Switzerland AG, Switzerland) and a second lens (ophthalmic type) attached to it (L2, diameter of 25 mm, power of +3 D). The EOL had a spherical power range from -10 to +10 D, with a reproducibility of ± 0.05 D and a power settling time of 25 ms (according to manufacturer's specifications). The EOL power was controlled by a current driver, which was connected to a PC and controlled by means of a software application specifically developed for this study that synchronized the accommodative demand changes (for conditions 3, 4, and 5) with the PowerRef. In order to avoid possible thermal drifts on the EOL response, it was warmed up to 28 °C before beginning the measurement sessions, and kept in that temperature throughout the procedures. Moreover, the EOL response at that temperature was calibrated before its integration on the system by means of a digital lensometer CL-300 (Topcon, Japan), including the calibration curve in the software application.

The target was placed 6 meters away from the EOL. This design ensured both the linearity and the 1:1 relationship between the power applied by the EOL and the accommodation stimulated to the subject, as well a constant size of the stimulus when changing in the accommodative demand. The role of lens L2 was to shift 3 D the working power range of the EOL in order to avoid its operation limits (far vision corresponds to an EOL power of +7 D, instead of +10 D), thus guaranteeing its best performance. The overall system can accurately measure an accommodative range up to 10.00 D, with a constant field of view of 14.25° in diameter. The response time for each step change of accommodative demand was approximately 40 ms (response time of the electronics + settling time of the EOL).

The accommodative target for all 5 conditions was a high contrast black Maltese cross on a white uniform background (Figure 28B). Even though this stimulus does not have peripheral depth cues, which could have improved the accommodative response,[157,212] it was chosen because it is easily reproducible and allows direct comparisons of our results with previous dynamic accommodation studies.[50,78,213]

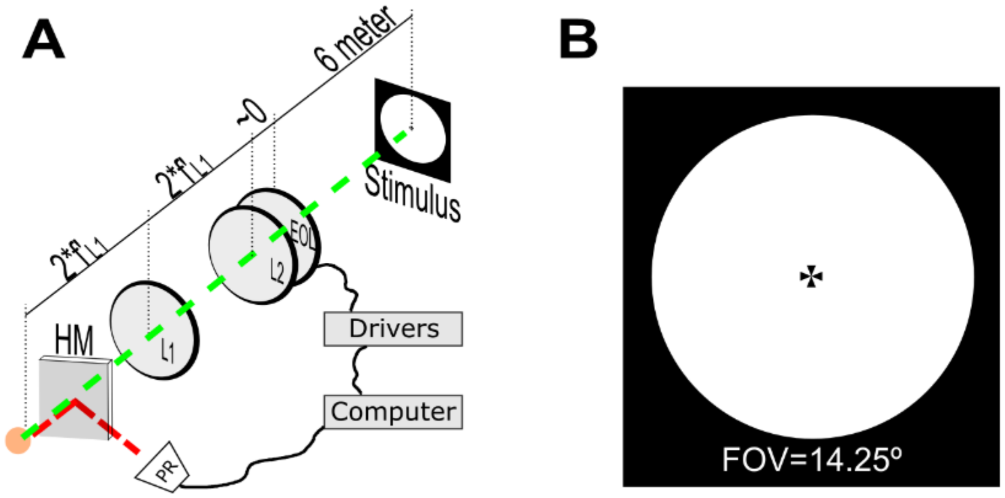

Figure 28. A: schematic view of the setup. B: accommodative stimulus used in the experiment. HM: Hot mirror. EOL: Electro-optical lens. PR: PowerRef II. f': focal length.

Table 11. Summary of the experimental conditions.

Condition	Method	Distance	Accommodative Transitions [D]	Response variables
1	Manual Flippers	Far	0.17 / 2.17	Cycles/minute
2	Manual Flippers	Near	0.50 / 4.50	Cycles/minute
3	Automated (EOL system)	Far	0.17 / 2.17	Cycles/minute Latency Accommodative response Response time
4	Automated (EOL system)	Near	0.50 / 4.50	Cycles/minute Latency Accommodative response Response time
5	Automated (EOL system)	Far & Near (hybrid approach)	0.17 / 0.50 / 2.17 / 4.50	Latency Accommodative response Response time

EOL: Electro-optical liquid system

Examination Protocol

Monocular subjective refraction with endpoint criteria of maximum plus power that provides best visual acuity was performed to determine best optical correction for each subject. Monocular amplitude of accommodation was evaluated by averaging the values of two push-up and two push-down trials, to compensate for the bias of push-up to overestimate and push down to underestimate accommodation amplitude.[190]

The five experimental conditions previously described were measured in two different sessions (test-retest, same day) that took approximately 30 minutes each, including breaks. Subjects were allowed to take breaks as needed, although there was no systematic method to provide rests during the measurements. Randomization of configurations was rigorously applied to minimize potential learning or fatigue biases. The time between the two sessions was 15 minutes. For all experimental conditions, the accommodation response was measured monocularly with the contralateral eye occluded with an eye patch.

Data analysis

From each accommodation response, three parameters were obtained. Accommodation response *Latency* is the time period (in seconds) between the start of the accommodative stimulus change and the start of the response of the subject. *Latency* was computed as described by Kasthurirangan *et al*.[214] To automatically find the start of the response an algorithm searched for three consecutive increasing data values, followed by four consecutive data values in which no two consecutive decreases occurred. When these criteria were met, the first data point in the sequence was selected as the start of the response. The inverse algorithm was used to determine the start of the disaccommodative response. Accommodation *Response Time* was computed as the time period (in seconds) between the start of the accommodative stimulus change and the moment the subject reported clarity and pressed a key. The *accommodative response* at each accommodative demand (half-cycle) was computed as the difference in diopters between the median refraction of the last four samples and the median refraction of the first four samples. Being the last sample the moment in which the subject reported clarity and the first sample the start of the accommodative stimulus change. Notice that for the hybrid condition, only accommodation changes between 0.17 and 2.17 D and between 0.50 and 4.50 D were considered for the analyses.

Data was processed using Matlab R2015b (MathWorks, Inc., USA). Repeatability of the far and near accommodative facility for the manual conditions 1 and 2, and automated experimental conditions 3 and 4 were analyzed using within-subject standard deviation and paired t-tests. Agreement between the manual flippers and the automated tests at both target distances were analyzed using the 95% limits of agreement and paired t-tests. In both of these analysis (repeatability and agreement), the response variable was the number of cycles per minute.

The differences between the hybrid accommodative facility test (condition 5) and the conditions 3 and 4, all performed in the EOL system, were analyzed using a repeated measures ANOVA with 3 within-subjects' factors (two levels each) conducted for the *latency, response time and accommodative response*. The within-subjects' factors were: test {*conventional or hybrid*}, distance {*far or near*} and direction {*accommodation or disaccommodation*}.

Analogously, the accommodative dynamics of each possible change in accommodative demand within the hybrid condition was analyzed using a repeated measures ANOVA with two within-subjects' factors: change in accommodative demand and direction. Changes in accommodative demands could occur for one of the following six levels (in increasing order of magnitude): {*0.17/0.50*, *0.50/2.17*, *0.17/2.17*, *2.17/4.50*, *0.50/4.50*, *0.17/4.50*}. This analysis was conducted for the *latency*, *response time and accommodative response* parameters.

Statistical power was assessed with the free open source G*Power 3.0.10.[191] Data from a pilot study with 6 subjects was used to compute the required sample size for a statistical power of 0.8. Considering a significance of 0.05 and a paired t-test the required sample size was 14 subjects.

5.5.3. Results

A total of 17 subjects that met the inclusion criteria were tested and included in the analyses. Subjects had a mean age ± standard deviation of 23 ± 2 years, a mean monocular subjective amplitude of accommodation of 11 ± 3 D, and a mean subjective spherical equivalent of -1.73 ± 1.68 D (n=6 subjects had emmetropia and n=11 subjects had myopia). Most of the subjects in our sample had myopia, which is a limitation of the study addressed in the discussion.

Repeatability and agreement between manual flippers and the automated test

Repeatability of accommodation responses for each condition (1, 2, 3 and 4):

The mean difference ± standard deviation (SD) between both sessions (test-retest), the within-subject standard deviation (S_W) and the p-values obtained with the paired sample t-test are shown in Table 12, described by method and test distance (i.e., conditions 1, 2, 3 and 4).

Table 12. Repeatability (test-retest) for each method and accommodative distance.

	Manual Flippers			Automated (EOL system)		
Test distance	Mean diff. ± SD [cpm]	S_W [cpm]	p-value	Mean diff. ± SD [cpm]	S_W [cpm]	p-value
Near	-1±1	1	<0.01*	-3±4	3	0.02*
Far	-1±1	1	<0.01*	-5±4	4	<0.01*

diff.: difference. SD: standard deviation. S_W: within-subject standard deviation. cpm: cycles per minute. *Statistically significant (p<0.05).

Agreement of accommodation responses between conditions (1 vs 3 and 2 vs 4):

The comparison between the accommodative facility test performed with the manual flipper and the automated method performed with the EOL system is shown in the Bland and Altman plots of Figure 29 for each target distance. As it can be appreciated in this figure, the mean difference is increased for near distance for both methods, and subjects were able to complete more cycles per minute in the automated than in the manual flippers tests. Both methods were also statistically compared with paired t-tests, p-values also shown in Figure 29.

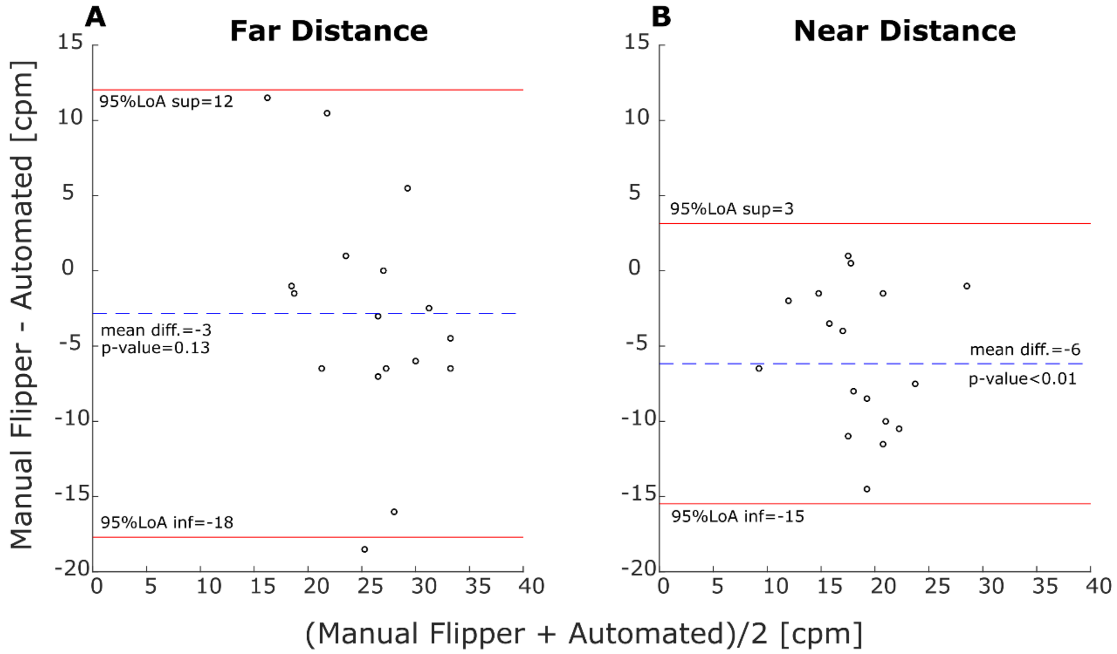

Figure 29. Bland and Altman plots with the 95% Limits of Agreement for far and near distance tests.

Hybrid accommodative facility test

Accommodation response dynamics within condition 5:

The results of the repeated measures ANOVA applied to *latency, response time and accommodative response* are shown in Figure 30 and summarized as follows:

For *latency* of the accommodation/disaccommodation responses, neither the factors (direction and amount of change of the accommodative demand) nor the interaction (*direction*change in accommodative demand*) resulted in statistically significant differences (Figure 30A).

For the accommodation/disaccommodation *response times*, a statistically significant ($p<0.05$) main effect of direction, change in accommodative demand and also the interaction *direction*change in accommodative demand* was obtained. When controlling for the direction, the Bonferroni post-hoc test showed statistically significant pairwise comparisons when comparing any of the first three levels against any of the remaining three levels for accommodation, and also when comparing the last level against the level four and five for disaccommodation. When controlling for change in accommodative demand, significant pairwise comparisons were obtained in three cases (marked with an asterisk in Figure 30B). The interaction term *test*distance* was also significant and the post-hoc showed significant differences between far and near regardless of the test (conventional or hybrid).

For *accommodative response*, a statistically significant main effect of direction of accommodation, change in accommodative demand, and also the interaction *direction* change in accommodative demand* was obtained. In all cases with p-values smaller than 0.01. When controlling for direction, the Bonferroni post-hoc test showed statistically significant pairwise comparisons in all cases except in the following four cases: 1) between the level two and three for accommodation; 2) between the level five and six for accommodation; 3) between the level two and four for disaccommodation; and 4) between the level three and four for disaccommodation. When controlling for accommodative transition, significant pairwise comparisons were obtained only in 2 cases that are marked with an asterisk in Figure 30C.

Accommodation dynamics differences among conditions 3, 4 and 5:

The results of the repeated measures ANOVA with 3 within-subjects' factors (with 2 levels each) conducted for the *latency, response time and accommodative response* are summarized in Table 13.

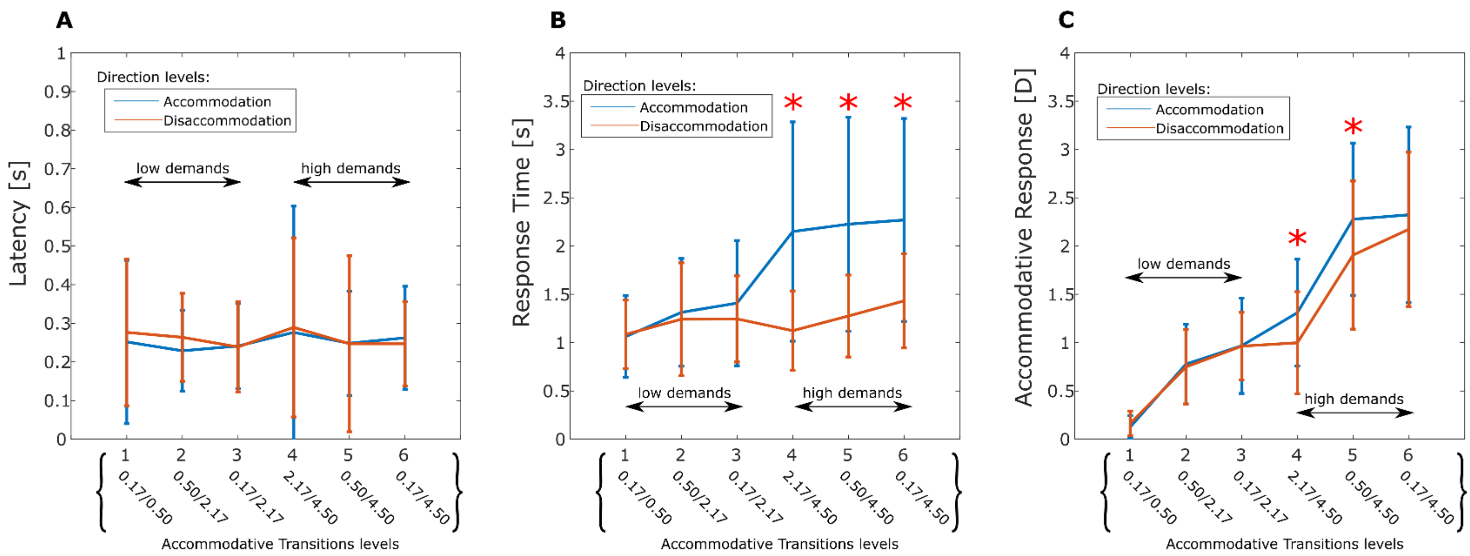

Figure 30. Accommodation dynamics within condition 5. Latency, response time and accommodative response as a function of the accommodative demand factor controlling for direction. Red asterisk indicates statistically significant differences (p<0.05). Error bars are standard deviations.

Table 13. P-values obtained with the repeated measures ANOVA.

Factor	Latency [s]	Response Time [s]	Accommodative Response [D]
Test	0.96	0.98	0.22
Distance	0.93	<0.01*	<0.01*
Direction	0.68	0.01*	<0.01*
*Test*Distance*	0.69	0.04*	0.49
*Test*Direction*	0.36	0.21	0.91
*Distance*Direction*	0.65	<0.01*	<0.01*
*Test*Distance*Direction*	0.57	0.07	0.17

*Statistically significant (p<0.05).

Latency is not affected by the predictability of the stimulus, the direction of accommodation, the accommodative demand and any of the interactions amongst these variables. Contrary, there is a main effect and interaction of distance and direction in both response time and the accommodative response, the Bonferroni post-hoc tests for the interaction term are shown in Table 14. Additionally, there is a statistically significant difference in the interaction term *Test*Distance* for response time. The Bonferroni post-hoc test is shown in Table 15.

Table 14. The Bonferroni post-hoc test of the significant interaction Distance*Direction for response time and the accommodative response.

		Response Time		Accommodative Response	
		Mean diff. ± SD [s]	p-value	Mean diff. ± SD [D]	p-value
Distance	Direction				
Far	Acc.-Disacc.	0.26 ± 0.77	0.18	0.05 ± 0.19	0.27
Near	Acc.-Disacc.	0.75 ± 0.88	<0.01*	0.33 ± 0.28	<0.01*
Direction	Distance				
Accommodation	Far-Near	-0.56 ± 0.57	<0.01*	-1.31 ± 0.38	<0.01*
Disaccommodation	Far-Near	-0.07 ± 0.29	0.33	-1.03 ± 0.51	<0.01*

*Statistically significant (p<0.05).

Table 15. The Bonferroni post-hoc test of the significant interaction *Test*Distance* for response time.

		Response Time	
		Mean diff. ± SD [s]	p-value
Distance	Test		
Far	Conventional-hybrid	0.11 ± 0.27	0.12
Near	Conventional-hybrid	-0.11 ± 0.28	0.14
Test	Distance		
Conventional	Far-Near	-0.21 ± 0.37	0.03*
Hybrid	Far-Near	-0.42 ± 0.32	<0.01*

*Statistically significant (p<0.05).

5.5.4. Discussion

This study compared the repeatability and agreement of clinical manual flippers accommodative facility test with an automated accommodation test performed in a computer-controlled electro-optical system. In addition, a new method for automated accommodative facility tests that presents one of four accommodative demands in an unpredictable manner is presented and analyzed.

Repeatability and agreement between manual flippers and the automated accommodation facility test

The agreement level between the manual flipper accommodation facility test and the automated test performed in a computer-controlled electro-optical system is poor for both target distances. The within-subject standard deviation, i.e., repeatability, obtained for both accommodative facility methods is consistent with the 3 cpm previously reported[215] in subjects 8 to 12 years of age. There are a number of differences between the manual and automatic methods that likely account for the poor agreement found. The most plausible explanation is that the response time of an examiner changing the flipper lenses is much larger, the order of 0.6 seconds/transition,[51] to that of the automated test (approximately 40 ms). Given that young healthy subjects can easily perform 15 to 25 cycles per minute (as shown in Figure 29), the total time spent by the examiner flipping the lenses may add to up to 15 seconds (e.g., 25x0.6=15). Given that the average response time per accommodation change is between 1 and 2.5 seconds (as shown in Figure 30B and previously described),[51] the number of potential cycles 'gained' in one minute due to automatization would be between 2 to 8 cycles (e.g., 9/(2x2.5)≈2). This range accounts for the mean absolute difference in cycles found between the manual and automated (3 and 6 cpm for far and near) accommodative facility tests.

According to these results, accommodative facility measurements obtained from either automatized or manual flippers are not comparable and should not be interchanged. The automated accommodative facility measures represent more accurate information on the individual's ability to accommodate.

The effect of a hybrid, unpredictable, accommodative facility test

In the hybrid approach both far and near accommodative facility tests are automated and integrated into only one test that randomizes among the accommodative demands. One interesting and unexpected outcome was a lack of effect of predictability of the accommodation demand. We initially expected that *latency* of the accommodation response would be larger for unpredicted than predicted stimuli, but no effect was found. Our initial rationale was originated in a small number of studies carried out more than 40 years ago that concluded a prediction operator in accommodation has a small but considerable impact in latency.[21–23] However, after a more thorough review of these few manuscripts, it came to light that the results did not warrant the conclusions due to either their very limited sample size (1 to 4 subjects) or the use of non-naïve subjects (authors were subjects). In addition, the studies are difficult to reproduce due to a lack of specific information about the subjects' characteristics and the instructions they received. Phillips *et al.*[23] measured in 1972 the monocular accommodative response in square wave inputs in 4 subjects and found a mean reduction response latency of 204 ms when using a predictable square wave stimulus compared to an unpredictable one. As the authors acknowledge in their discussion, the distributions obtained were highly skewed, and the mode difference between the two conditions was minimal, only 49 ms. Two years later, Van der Wildt *et al*.[21] investigated the presence of a prediction operator using sinusoid inputs and concluded that even though the effect was small, it was not negligible. They had no explanation as to why subjects did not always succeed in following the stimulus optimally despite its predictability, and noted significant differences in the accommodative response when instructions were changed from 'try to fixate the target' to 'try to clear the target'.

Posterior studies have shown that the accommodative response and some parameters of its dynamics (e.g., latency) are affected by age,[49,50] refractive error[51] and the task instructions given to participants.[27] Our hypothesis is that predictability does not affect accommodation responses *per se* but that specific training using a consistent stimulus and conditions, latency may shorten. Further studies are required to disentangle the isolated effect of stimulus' predictability in time, magnitude and direction, as well as the interactions of these parameters, on accommodation dynamics.

The second interesting outcome was that accommodation response times and accommodative response levels were affected by the direction of accommodation only for high accommodative demands, not for disaccommodation and not for low accommodation demands. For disaccommodation, the mean response time was around 1 second regardless of the accommodative demand, however, for accommodation, the response time was around 1 second for low accommodative demands and it increased abruptly up to 2.5 seconds for higher demands. Similarly, the differences in accommodation response between accommodation and disaccommodation seemed to increase with the amount accommodative demand. Despite of a large variability across subjects in both responses time and accommodative responses, the previously mentioned effects are statistically significant. The results are also consistent with previous studies.[51,214] Moreover, a linkage between accommodative demand and direction of accommodation also appeared when comparing the hybrid unpredictable test with the automated predictable far and near accommodative facility tests. There was a significant interaction between the test distance and the direction of accommodation in both response time and accommodative response. Significantly larger responses were obtained for near viewing distances than for far distances during accommodation regardless of the test type (conventional or hybrid). Radhakrishnan *et al*.[51] also found significantly larger response times for accommodation than disaccommodation at near distances although this difference was only found in subjects with myopia in their study. Thus, it may be possible that the differences found in our study are also larger due to the number of subjects with myopia in our sample (65% of the sample). Indeed, the accommodative response is affected not only by experimental conditions[209] but also by the observer's refractive error.[176] In conclusion, our results show that a hybrid unpredictable approach is able to provide a more comprehensive examination of the accommodative capability to change focus over time than the conventional accommodative facility test. Despite its potential advantage, it will be necessary to replicate these results in future studies that include accommodative dysfunctions and refractive error as covariates, in order to determine whether the current normative values of accommodative facility should be redefined in the context of the hybrid unpredictable approach.

5.6. Study 6. Effect of stimulus unpredictability in time, magnitude and direction on accommodation.

PREVIOUS NOTE: The following text in this section corresponds to the article: **Otero C**, Aldaba M, Díaz-Doutón F, Vera-Diaz FA, Pujol J. Effect of stimulus unpredictability in time, magnitude and direction on accommodation [submitted].

5.6.1. Introduction

The accommodative system can respond reasonably quickly and accurately to a variety of dynamically changing stimuli such as a step (or square wave), sinusoidal and ramp inputs.[21–23,44] All these types of dynamic accommodative stimulus may have the property of predictability if the pattern driving the stimulus is constant. The pattern can be characterized with the relationship among changes in magnitude, direction and time of the accommodative stimulus.

In 1968, Stark[216] mentioned for the first time the capacity of the human accommodative system to anticipate future stimulus changes in sinusoidal inputs. He suggested the presence of a prediction operator that basically reduces response latency in comparison to random accommodative stimulus. This concept was further developed by Phillips *et al.*[23] in 1972, who measured the monocular accommodative response in square wave inputs in 4 subjects and found a mean reduction response latency of 204 ms when using a predictable square wave stimulus instead of a nonpredictable square wave. They obtained highly skewed distributions and when they computed the mode difference they obtained a reduction of only 49 ms. In the next two years, Krishnan *et al.*[22] and Van der Wildt *et al*.[21] investigated the presence of the prediction operator in predictable sinusoid inputs and concluded that its effect is small although not negligible. Interestingly, Van der Wildt *et al.*[21] were not able to explain why a subject did not always succeed in following the stimulus optimally despite it was predictable. Moreover, they also noticed differences in the accommodative response when task instructions given to the subject were changed from ‘try to fixate the target’ to ‘try to clear the target’.

All these studies agreed with the presence of a prediction operator, although they were limited in sample size and difficult to reproduce due to the lack of information about the typology of participants or the explicit task instructed to them. As it was shown in posterior studies, the accommodative response and some parameters of its dynamics (e.g., latency) are affected by both age[49,50] and refractive error.[51,209] The task instructions given to participants in an experiment can also significantly affect the accommodative response as shown by Stark and Atchison.[27] Therefore it is fair to think that when these factors are not controlled they could mask or bias some findings.

After these previous studies, carried out nearly 40 years ago, little has been investigated about the prediction operator. Most of accommodation dynamic studies have used either predictable sinusoids or predictable square wave inputs and have assumed the presence of anticipation effects.[49,51,52] To our knowledge, there are at least a couple of questions related with the prediction operator that are not fully clear yet: 1) How long does it take to the accommodative system to know the pattern behind the predicted stimulus dynamics in order to start predicting the next focus position? and 2) Is the accommodative system capable to predict a stimulus that is predictable only in time, regardless of the magnitude and direction changes, or contrary, it is only capable to predict focus position when magnitude, direction and time are predictable altogether?.

The effect of these factors in insolation has never been studied in the context of accommodation and the answers to these couple of questions do not only provide a much better understanding, at a fundamental level, of the role that the prediction operator has in the models of oculomotor control[217] but also the role that anticipation has in clinical tests such as the accommodative facility,[51] in which predictable stimuli are used to estimate the visual fatigue to focus changes.[208] Having in mind all this, the purpose of this study is to investigate the isolated effect of stimulus' predictability in time, magnitude and direction, as well as their interactions, on accommodation latency and accommodative response.

5.6.2. Methods

Subjects

The research was performed according to institutionally approved human subject's protocols with full informed consent by each subject, and followed the tenets of the Declaration of Helsinki. Criteria for inclusion were: (1) best-corrected visual acuity of

0.00 logMAR (20/20 Snellen equivalent) or better in each eye, (2) between 21 and 28 years of age, to ensure good ability to accommodate, (3) spherical equivalent error in each eye as measured with subjective refraction between -6.50 and +0.50 D, (4) amplitude of accommodation above the value given by Hofstetter's average formula for accommodation[19] (Amplitude = 15 – 0.25 * Age), (5) no strabismus, amblyopia, binocular or accommodative anomalies, and (6) no history of any ocular disease, surgery and/or pharmacological treatment that may have affected vision at the time of the study. Subjects with myopia wore their own disposable soft disposable contact lenses for the study. All contact lenses prescriptions were within ±0.50 D of the subject's best correction spherical equivalent, determined by subjective refraction as explained below.

Instrumentation and methods

A binocular open field autorefractor, PowerRef II (Plusoptix Inc., USA), was used to measure accommodation responses. This autorefractor is based on the principle of dynamic infrared retinoscopy and it measures spherical equivalent, pupil size and gaze position at a sampling frequency of 25 Hz.[100,211] The PowerRef II refractor was calibrated for each subject as described by Radhakrishnan *et al*.[51] In short, while the measured eye fixated the stimulus at 0.17 D viewing distance, trial lenses (from +4.00 to -1.00 D, in 1-D steps) were randomly placed in front of the eye for 4 seconds. The slope and intercept of the linear regression obtained from this calibration were used as a correction factor for that subject's measurements.

In order to align the PowerRef and the subject's eye while allowing the target viewing, a 50 mm squared IR hot mirror was placed 40 mm from the subject's pupil plane. Subjects look at the accommodative stimulus through an optical system comprised by three lenses (Figure 31A). The first lens (L1, diameter of 50 mm, focal length of 100 mm) was placed 200 mm from the subject's pupil (twice f_{L1}). In this way, a pupil conjugate plane was created 200 mm away from the lens, without magnification. The active module that performed the accommodation stimulation was placed in that plane and was composed by an electro-optical lens[135] (EOL, EL-16-40-TC, Optotune Switzerland AG, Switzerland) and a second lens (ophthalmic type) attached to it (L2, diameter of 25 mm, power of +3 D). The EOL had a spherical power range from -10 to +10 D, with a reproducibility of ± 0.05 D and a power settling time of 25 ms (according to manufacturer's specifications).

The target was placed 6 meters away from the EOL. This design ensured both the linearity and the 1:1 relationship between the power applied by the EOL and the accommodation stimulated to the subject, as well a constant size of the stimulus when changing in the accommodative demand. The role of lens L2 was to shift 3 D the working power range of the EOL in order to avoid its operation limits (far vision corresponds to an EOL power of +7 D, instead of +10 D), thus guaranteeing its best performance. The overall system can accurately measure an accommodative range up to 10.00 D, with a constant field of view of 14.25° in diameter. The response time for each step change of accommodative demand was approximately 40 ms (response time of the electronics + settling time of the EOL). The EOL power was controlled by a driver connected to a PC and controlled by means of a software application specifically developed for this study that synchronized the accommodative demand changes with the PowerRef. In order to avoid possible thermal drifts on the EOL response, it was warmed up to 28 °C before beginning the measurement sessions, and kept in that temperature throughout the procedures. Moreover, the EOL response at that temperature was calibrated before its integration on the system by means of a digital lensometer CL-300 (Topcon, Japan), including the calibration curve in the software application.

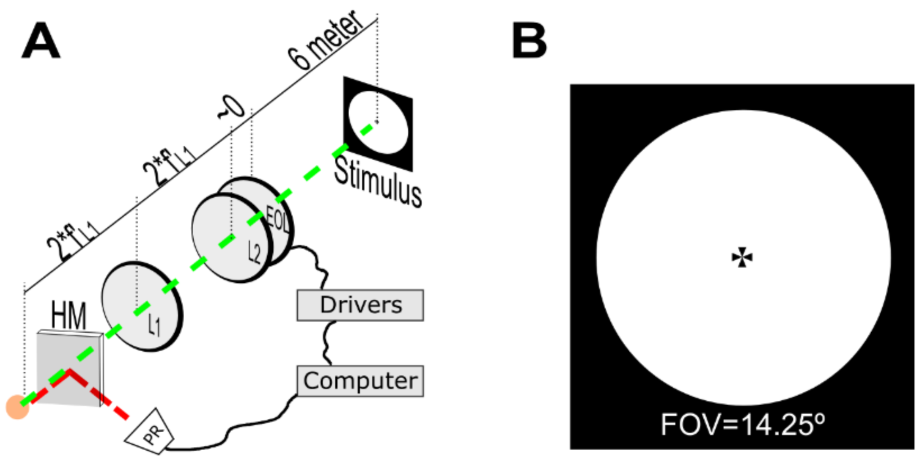

Figure 31. A: schematic view of the setup. B: accommodative stimulus used in the experiment. HM: Hot mirror. EOL: Electro-optical lens. PR: PowerRef II. f': focal length.

Examination protocol

A monocular subjective refraction with endpoint criteria of maximum plus power that provides best visual acuity followed by binocular balance was performed to determine each subject's best optical correction. The dominant sensory eye (resistance to +1.50 D blur)[218] was chosen for the measurements. Monocular subjective amplitude of accommodation was evaluated by averaging the values of two push-up and two push-down trials[190] to determine eligibility.

Accommodative responses were recorded in 9 conditions (randomly presented) where the stimulus accommodative demand changed several times in a step-like fashion for a period of 120 seconds. Each change in accommodative demand (i.e., trial) could have different time duration (i.e., 1, 2 or 3 seconds), magnitude (1, 2 or 3 D) and/or direction (i.e., accommodation or disaccommodation) depending on the condition. Thus, all conditions were created permuting the factors time, magnitude and direction with two levels each: random and not random. The default values for not random time and magnitude were 2 seconds and 2 Diopters, respectively. For direction, the default value was accommodation until the demand reached 4 D, at that moment the direction was reversed to disaccommodation until it reached 0 D accommodation demand. Figure 32 shows the nine testing conditions used in the study.

Notice that when time, magnitude and direction were not random, the input signal followed a well-defined staircase going from 0 to 4 D and from 4 to 0 D in steps of 2 D and staying a period of 2 seconds in each accommodative demand (Figure 32B). This condition with three accommodative states was considered a baseline reference for analysis. However, this baseline condition was different to the signals used for many accommodation dynamic studies in which only 2 accommodative states were considered.[51,52,57,211] To potentially extrapolate our results to other dynamic accommodation studies such as those previously cited, we included one extra baseline condition: a step signal going from 0 to 2 D in steps of 2 D and staying a period of 2 seconds in both accommodative demands (Figure 32A).

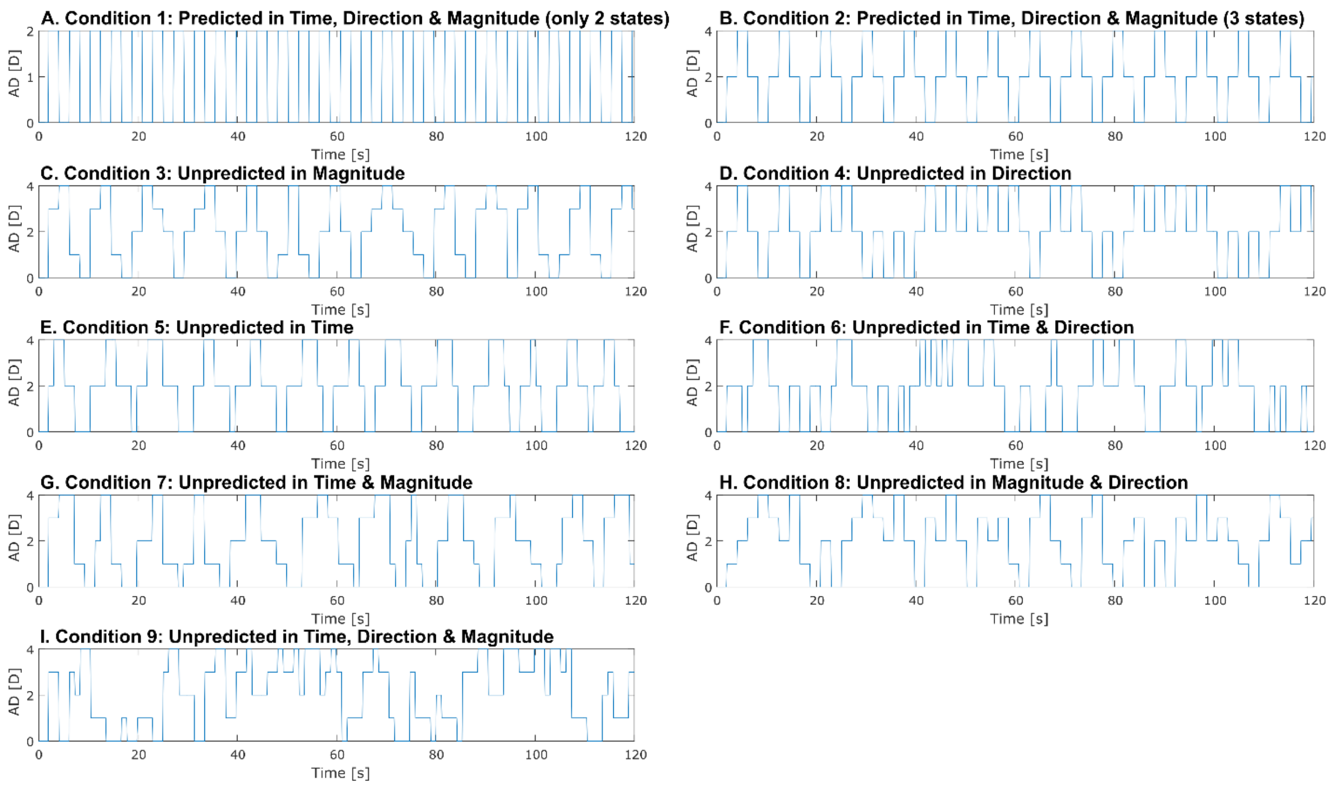

Figure 32. Examples of each accommodation step changes (nine conditions) tested in the experiment. AD: Accommodative Demand. A: the simplest and most predictable condition (baseline). I: the most unpredictable condition (totally unpredictable in time, direction and magnitude).

In addition, each subject was asked to rank on a 5-point scale their subjective perception of predictability after each condition, with level '1' indicating that the accommodation level was fully predictable and level '5' indicating that it was totally unpredictable. The examiner recorded these subjective responses. All subjects were naïve to the purpose of the study, but they were trained at the beginning on what constitutes a predictable condition. All conditions were measured in one session that took approximately 30 minutes, including breaks. Subjects were allowed to take breaks as needed, although there was no systematic method to provide rests during the measurements. Randomization of configurations was rigorously applied to minimize potential learning or fatigue biases.

Data analysis

Data was processed and analyzed using Matlab R2015b (MathWorks, Inc., USA). Since the dynamics of accommodation and disaccommodation are dependent on amplitude,[214] the only two accommodative changes ('transitions') that were considered for the analysis were from 0 to 2 D (accommodation) and from 2 to 0 D (disaccommodation). In each transition both latency and accommodative response were computed. Subsequently, a repeated measures ANOVA was computed for both latency and accommodative response with two within-subjects' factors: *condition* (with nine levels) and *direction of accommodation* (with two levels).

Latency was defined as the time period (in seconds) between the start of the accommodative stimulus change and the start of the accommodative response by the subject, computed as described by Kasthurirangan *et al*.[214] To determine the start of the accommodative response, a custom algorithm was created to search for three consecutive increasing data values, followed by four consecutive data values in which no two consecutive decreases occurred, the first data point in this sequence was recorded as the start of the response. The inverse algorithm was used to determine the start of the disaccommodative response. The *accommodative response* at each accommodative transition was computed as the difference in diopters between the median response of the last four samples, defined as the moment in which the subject reported clarity, and the median response of the first four samples, defined as the start of the accommodative stimulus change.

The perceived predictability scores given by the participants for each condition were analyzed using Friedman tests and with Wilcoxon tests with Bonferroni correction, to determine which pairwise comparisons were significant. Statistical power was determined using a free open source G*Power 3.0.10.[191] Data from a pilot study with four subjects was used to compute the required sample size for a statistical power of 0.8. Considering a significance of 0.05 and an Analysis of Variance model with nine repetitions, the required sample size was seven subjects.

5.6.3. Results

A total of 12 subjects that met the inclusion criteria were tested and included in the analyses. Subjects had a mean age ± standard deviation of 25 ± 2 years, a mean monocular subjective amplitude of accommodation of 11 ± 2 D, and a mean subjective spherical equivalent of -1.45 ± 1.89 D.

Perceived predictability analysis

The Friedman test conducted on the perceived predictability of each condition resulted in statistically significant differences between the conditions (χ^2=56.57, p<0.01). However, Bonferroni post-hoc tests did not show statistically significant differences for any pairwise comparison (all p-values were above 0.05/36, being 36 the number of possible pairwise comparisons). Descriptive statistics of each condition are shown in Figure 33.

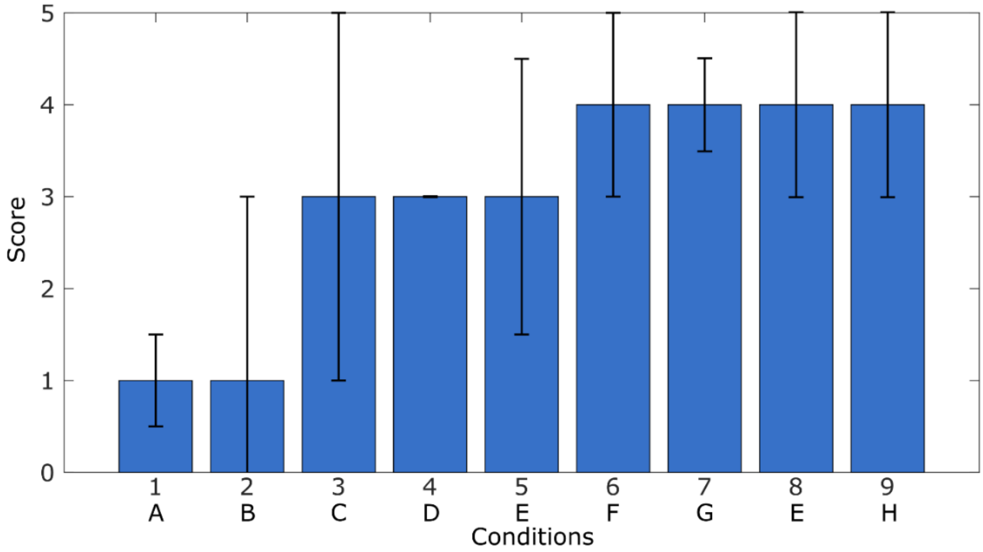

Figure 33. The median and interquartile range of the perceptual predictability scores given to each condition.

Latency analysis

Repeated measures ANOVA applied to latency for the nine conditions tested (Figure 34A) did not show significant effects for either direction of accommodation (accommodation or disaccommodation, F=3.15, p=0.10), condition (F=0.94, p=0.49), nor the interaction *direction*condition* (F=1.20, p=0.31). In addition, no correlation was found between the perceived predictability scores and latency responses for the nine conditions tested (average |r|<=0.21, p>0.05). The scatterplots of the two most predictable conditions (1 and 2) and the less predictable condition (9) are shown in Figure 35A, B and C, respectively.

Accommodative response analysis

Repeated measures ANOVA applied to accommodative response for the nine conditions tested (Figure 34B) did not showed significant effects for either direction of accommodation (F=0.37, p=0.56), condition (F=0.48, p=0.75), nor the interaction *direction*condition* (F=1.39, p=0.25). Analogously to latency analysis, no correlation was found between the perceived predictability scores and the accommodative response. The scatterplots of the two most predictable conditions (1 and 2) and the less predictable condition (9) are shown in Figure 35D, E and F, respectively.

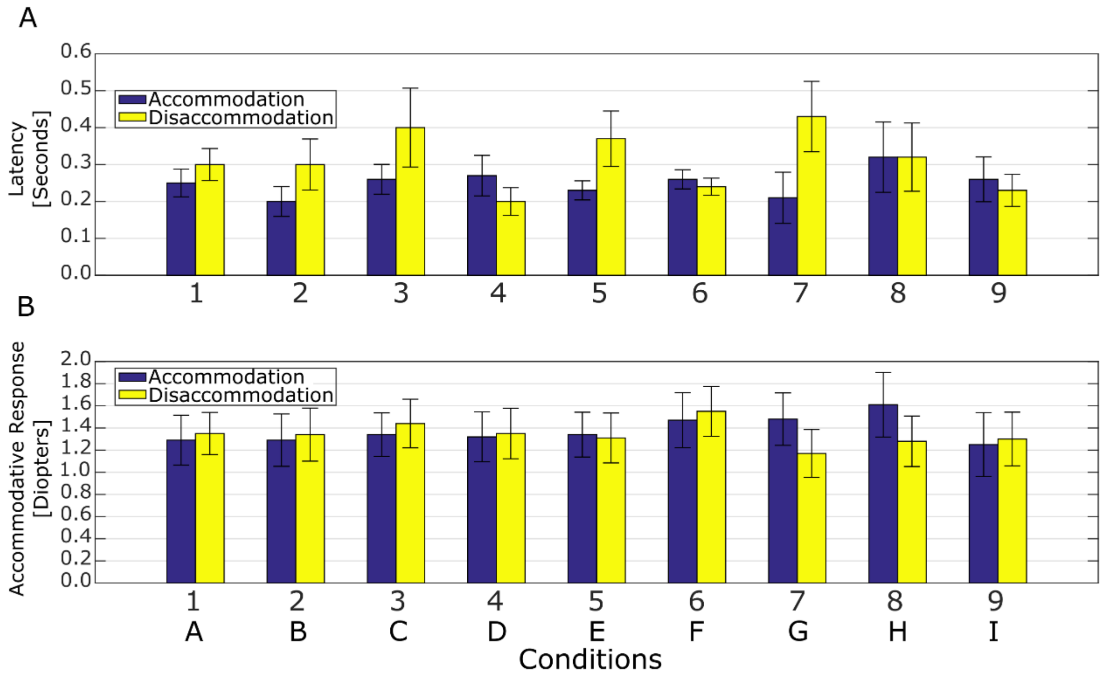

Figure 34. The mean and standard errors obtained for each condition and direction of accommodation for both the variables: A) Latency and B) Accommodative response.

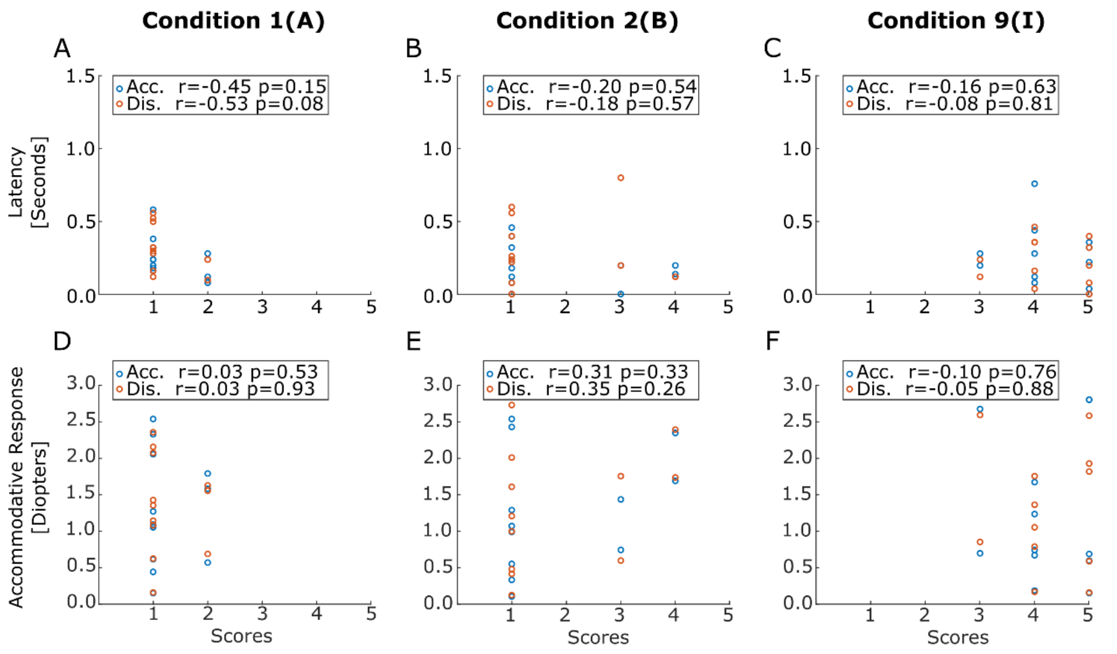

Figure 35. Scatter plots between Latency and Scores and Accommodative Response and Scores for conditions 1, 2 and 3 and accommodation (Acc., blue dots) and disaccommodation (Dis., orange dots). The correlation coefficient as well as the p-value for each correlation is shown in the legends.

5.6.4. Discussion

In 1968, Stark[216] suggested that subjects might anticipate subsequent changes in accommodation demand. This idea was further tested during the following five years by Krishnan,[22] Phillips,[23] and Van der Wildt.[21] They concluded that, when repeatable stimuli (e.g., sinusoidal) are used, latency can be shortened and the accommodative response accuracy can be enhanced. In this study, we investigated the isolated effects of stimulus' predictability in time, magnitude and direction of the accommodative change, as well as the interactions between these factors, on the accommodation response latency and its magnitude.

Our results indicate no significant effect of stimuli predictability on either the accommodation latency or its magnitude. According to the previously described studies, we initially expected that accommodation latency would be larger for unpredicted stimuli. However, no effect was found, at least no effect larger than the 40 milliseconds detectable by the PowerRef II autorefractor. But, after a more thorough review of these previous studies, it came to light that their results were obtained with a limited sample size (4 subjects[23] or 1 subject[21,22]), they did not report whether participants were naïve or not and also the explicit task instructed to them. Thus, it is difficult to compare our results with these studies since the accommodative response and some parameters of its dynamics (e.g., latency) are affected by age,[49,50] refractive error[51,209] and the task instructions given to participants.[27] We speculate that the fact we did not find an effect of predictability in our study was because: 1) we used a larger sample size, 2) the participants were carefully instructed to 'clear the target' at all times, and 3) all participants were not trained and naïve to the purpose of the study. Our hypothesis is that predictability does not affect accommodation responses *per se* but that specific training using a consistent stimulus and conditions, latency may shorten. In fact, our hypothesis is consistent with Van der Wildt *et al*.[21] apparently surprising results of a subject not been successful at optimally following a predictable stimulus.

Another interesting finding is that subjects in our study appeared to be able to perceptually notice whether the stimulus was predictable or not even though accommodation responses and latency were not associated to predictability. However, the differences between the perceived scores of predictable and unpredictable conditions were not statistically significant after correcting for Bonferroni. Non-significance is probably obtained provided that the Bonferroni procedure ignores dependencies among the data and is therefore much too conservative when the number of tests is large,[219] as it occurs in our study with 36 pairwise comparisons.

Finally, the findings from this study have implications in standard clinical procedures such as the accommodative facility test, where subjects are asked to clear two different accommodative demands (one at a time) repeated over a one minute period. According to our results, the accommodation facility clinical test would not be influenced by the predictability of the stimulus, even though it measures visual fatigue under repetitive conditions, although further studies should specifically address this question.

6. Conclusions and future work

In study 1, 2 and 3 we have shown:

1. Previously reported differences in accommodative response when using lens-based methods compared to free space viewing may be explained by the effect of other factors such as the field of view or the depth of the stimulus, rather than the method to stimulate accommodation.
2. The most accurate accommodative responses were obtained for fields between 8º and 10º, which suggests that there may be an optimum peripheral retinal image size for accommodation stimulation.
3. The only factor that in isolation significantly affects the accuracy of the accommodative responses is the type of refractive error.
4. The accuracy of the accommodation response generally improves with a 2-dimensional stimulus with apparent depth cues and simulated out-of-focus blur in a relatively large field of view. Even though these conditions may not be adequate for all individuals, they can improve the overall visual comfort in those virtual reality systems that use a varifocal optical system to change the focal plane of a 2-dimensional surface.

In study 4 we have shown:

1. The first implementation of a new algorithm of a potential novel method of performing non-cycloplegic subjective refraction in adults without clinician support. Although it presents some limitations that warrant further research and it still should be tested in a wider population in terms of age, refraction and different ocular conditions, this method can contribute to improve the access to primary eye care services in developing countries and it has the potential to be incorporated in novel lens-based technologies.

In study 5 we have shown:

1. The first validation of a new accommodative facility test that integrates both the far and near accommodative facility test with random changes of accommodative stimulus. It is a faster test than performing both the near and far accommodative tests and it provides more information than conventional accommodative facility tests.

In study 6 we have shown:

1. The prediction operator does not exist.
2. The unpredictability of the stimulus does not affect the accommodation dynamics.

Future works:

With respect eye's refraction, it is clear that the automated refraction algorithm requires to be tested in a wider population in terms of age, refraction and ocular conditions such as amblyopia, pseudomyopia, latent hyperopia, keratoconus, among others, before it can be generally accepted and used by clinicians.

In parallel, there are other algorithms that can be explored for automated subjective refraction, for instance, the multidimensional Bayesian adaptive psychometric methods could be applied.[220]

Additionally, it would be useful to test (at a research level) the implementation of these automated algorithms in visual simulators/virtual reality systems before it can go into industrial applications.

With respect accommodation, the way to go could be to explore a 3-dimensional characterization of depth cues in volumetric systems for accommodation stimulation. Additionally, the development and clinical validation of objective and automated optometric tests for accommodation such as the push-up amplitude of accommodation tests are not done yet and could potentially be implemented in visual simulators/virtual reality systems as well.

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8. Dissemination of results

8.1. Journal Publications

Aldaba M, **Otero C**, Pujol J, Atchison D. Does the Badal optometer stimulate accurately? *Ophthalmic Physiol Opt.* 2017;37(1):88-95.

Otero C, Aldaba M, Martínez-Navarro B, Pujol J. Effect of apparent depth cues on accommodation in a Badal optometer. *Clin Exp Optom*. 2017 Mar 21. doi: 10.1111/cxo.12534

Otero C, Aldaba M, Vera-Diaz FA, Pujol J. Effect of the experimental conditions in the accommodation response in myopia. *Optom Vis Sci.* 2017 Oct 19. doi: 10.1097/OPX.0000000000001140..

8.2. Papers in submission

Otero C, Aldaba M, Pujol J. Automated non-cycloplegic binocular subjective refraction algorithm [submitted].

Otero C, Aldaba M, López S, Díaz-Doutón F, Vera-Diaz FA, Pujol J. Random changes of accommodation stimuli: an automatic extension of the flippers accommodative facility test [submitted].

Otero C, Aldaba M, Díaz-Doutón F, Vera-Diaz FA, Pujol J. Effect of stimulus unpredictability in time, magnitude and duration on accommodation dynamics [submitted].

8.3. Oral presentations

Otero C, Aldaba M, Martínez-Navarro B, Pujol J. Peripheral depth cues for accommodation stimulation. ARVO meeting 2016. Seattle, USA.

Otero C, Aldaba M, Vera-Diaz FA, Pujol J. Accommodation in virtual reality. EAOO 2017. Barcelona, Spain.

8.4. Poster presentations

Aldaba M, Pujol J, **Otero C**. Does the Badal optometer stimulate accurately?. ARVO meeting 2016. Seattle, USA.

Otero C, Pujol J. Fast non-cycloplegic binocular subjective refraction without clinician support?. VPO meeting 2016. Antwerp, Belgium.

Otero C, Aldaba M, Alavedra-Ortiz C, Pujol J. Effect of the field of view on accommodation stimulated with a volumetric badal optometer. ECVP 2016. Barcelona, Spain.

Otero C, Pujol J. Quick binocular subjective refraction without clinician support. AAOPT 2016. Anaheim, USA.

Otero C, Aldaba M, Vera-Diaz FA, Pujol J. Effect of the experimental conditions in the accommodation response in myopia. ARVO 2017. Baltimore, USA.

8.5. Patents

Spanish patent application number P201631103: 'MÉTODO Y DISPOSITIVO PARA DETERMINAR LA REFRACCIÓN SUBJETIVA OCULAR DE FORMA AUTOMATIZADA'.

Patent owner: Davalor Salud S.L.

National filing date: August 18th 2016.

Authors: CARLES OTERO MOLINS, JAUME PUJOL RAMO.