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THE STUDY OF THE ACCOMMODATIVE FUNCTION UNDER DIFFERENT AROUSAL AND ATTENTIONAL STATES.

ESTUDIO DE LA FUNCIÓN ACOMODATIVA BAJO DIFERENTES DEMANDAS ATENCIONALES Y NIVELES DE ACTIVACIÓN.

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BEATRIZ REDONDO CABRERA

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Departamento de Óptica, Facultad de Ciencias, Universidad de Granada

Departamento de Pediatría, Facultad de Medicina, Universidad de Granada

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Doctoral Thesis Supervisors (Directores de Tesis):

Dr. Raimundo Jiménez Rodríguez, Profesor Titular de Universidad, Universidad de Granada.

Dr. Antonio Muñoz Hoyos, Catedrático de Universidad, Universidad de Granada.

Doctoral Thesis Committe (Miembros del tribunal):

Dr. Luis M. Jiménez del Barco Jaldo, Catedrático de Universidad, Universidad de Granada.

Dra. Rosario González Anera, Catedrática de Universidad, Universidad de Granada

Dr. David P. Piñero Llorens, Investigador Ramón y Cajal, Universidad de Alicante.

Dra. María Isabel Sánchez Pérez, Profesora Titular de Universidad, Universidad Complutense de Madrid.

Dr. George A. Koulieris, Assistant Professor, University of Durham.

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Porque juntos hacemos el mejor equipo.

CONTENTS

ABSTRACT

Ocular accommodation is a critical mechanism that provides clear vision at different viewing distances and ensures optimal visual performance in daily situations. In normal conditions, the accommodative response is determined by a complex interaction of many factors, which can broadly be divided into optical and non-optical factors. Accommodation is mainly driven by optical factors (e.g., blur), being these factors extensively studied in literature, while the non-optical factors (e.g., attentional state) are not well understood. Several researchers have found that non-optical factors can alter the accommodative system, since ocular accommodation is controlled by the action of the ciliary muscle which is innervated by the autonomic nervous system. However, the direction and magnitude of these changes in the accommodative response are not consistent due to the heterogenous nature of the psychological behaviour, and therefore, it seems reasonable to deeply explore the effects of a variety of non-optical factors on the accommodative response.

The main objectives of the present International Doctoral Thesis were to examine the effects of arousal and attentional state on the accommodative response, as well as to assess whether the dynamics of the accommodative response could be considered as a potential index of changes in the autonomic state. To address these aims, we conducted eight studies, which were divided in two different sections. In section one, we manipulated the arousal state with physical exercise, caffeine intake and cognitive effort, and examined their effects on the accommodative response in healthy young populations (studies I to IV). In section two, we evaluated the behaviour of the accommodative response dynamics when manipulating the attentional state in healthy subjects (study V), as well as the influence of presenting an attentional deficit on the accommodative function by the inclusion of children with attention-deficit/hyperactivity disorder (studies VI-VIII).

The main findings and conclusions derived from the eight studies were: I) Highly demanding physical effort induces a greater lag of accommodation; II) Caffeine consumption decrease the variability of accommodative, but does not influence the lag of accommodation; III) Caffeine consumption improves the stability of the accommodative response in high caffeine consumers, but not in low caffeine consumers, during a sustained attention task; IV) the variability of accommodation is modulated as a function

of time-on-task, with higher values of variability of accommodation over time. The variability of accommodation seems to be a reasonably good predictor of behavioural performance; V) Attention facilitators induce a reduction in the lag and variability of accommodation, while attention distractors promote an increase in the accommodative response at far distance; VI) Children with attention-deficit/hyperactivity disorder exhibit higher lags of accommodation in comparison to an age-matched control group; VII) The higher lags of accommodation in children with attention-deficit/hyperactivity disorder are not dependent on the visual stimulus, and methylphenidate treatment does not restore the accommodative lag to normal values; and VIII) The variability of accommodation could be used as objective physiological marker of behavioural performance since it predicts a significant amount of variance in several indicators of attentional performance in children with attention-deficit/hyperactivity disorder and healthy controls.

The results of this International Doctoral Thesis enhance our understanding about the complex influence of non-optical factors on the accommodative response. These outcomes may be of special relevance when performing near activities (e.g., reading), since some psychological conditions can modify the magnitude and variability of accommodation corresponding to a specific viewing distance. Also, the capacity of the accommodative variability for predicting attentional performance may help to improve the diagnosis of attention-deficit/hyperactivity disorder.

RESUMEN

La acomodación es un mecanismo fundamental que garantiza una visión clara a diferentes distancias para un correcto rendimiento visual en tareas rutinarias. En condiciones normales, la respuesta acomodativa está determinada por interacciones complejas entre factores ópticos y no ópticos. La acomodación es principalmente estimulada por los factores no ópticos (ej. borrosidad), siendo estos factores ampliamente investigados en la literatura científica, mientras que los factores no ópticos (ej. estado atencional) no son completamente entendidos. Numerosos investigadores han observado que los factores no ópticos pueden alterar el sistema acomodativo ya que este es controlado por la acción del musculo ciliar, que es inervado por el sistema nervioso central autónomo. Sin embargo, la dirección de estas alteraciones no es consistente debido a la heterogénea naturaleza del comportamiento psicológico, por lo tanto, es razonable explorar en profundidad los efectos de factores no ópticos en la respuesta acomodativa.

Los objetivos principales de la presente Tesis Doctoral Internacional son examinar los efectos de la activación y la atención sobre la respuesta acomodativa, así como evaluar si la acomodación puede ser considerada como un marcador que muestre cambios en el estado autonómico. Para abordar este objetivo, llevamos a cabo ocho estudios divididos en dos secciones diferentes. En la sección uno, manipulamos el estado de activación mediante ejercicio físico, consumo de cafeína y esfuerzo cognitivo, y medimos su efecto sobre la respuesta acomodativa en sujetos jóvenes sanos (estudios I al IV). En la sección dos, evaluamos el comportamiento de la respuesta acomodativa al manipular la capacidad de atención en sujetos sanos (estudio V), así como la influencia de presentar un déficit atencional en la función acomodativa con la inclusión de niños diagnosticados con trastorno por déficit de atención e hiperactividad (estudios V al VIII).

Los principales hallazgos y conclusiones derivados de los ocho estudios son: I) Un esfuerzo físico elevado aumenta el retraso acomodativo; II) La ingesta de cafeína disminuye la variabilidad de acomodación pero no influye sobre el retraso acomodativo; III) El consumo de cafeína mejora la estabilidad de acomodación en los consumidores altos de cafeína, pero no en los consumidores bajos, durante una tarea de atención sostenida; IV) La variabilidad de acomodación fue modulada en función del tiempo en la tarea, con mayores valores relacionados con un peor rendimiento conductual; V) Los

facilitadores atencionales indujeron una reducción del retraso acomodativo y variabilidad de acomodación, mientras que los distractores atencionales promovieron un aumento del retraso de acomodación pero sólo para distancias lejanas; VI) Niños con trastorno por déficit de atención e hiperactividad mostraron mayores retrasos de acomodación en comparación con niños controles de edades equivalentes; VII) Los altos retrasos de acomodación encontrados en niños con trastorno por déficit de atención e hiperactividad no dependen del estímulo visual. El tratamiento con metilfenidato no restauró los valores de retraso acomodativo a la normalidad; y VIII) La variabilidad de acomodación podría emplearse como un marcador psicológico objetivo del rendimiento conductual ya que predijo una cantidad significativa de cambios en numerosos indicadores de rendimiento atencional en niños con trastorno por déficit de atención e hiperactividad y sujetos sanos.

Los resultados de esta Tesis Doctoral Internacional mejoran nuestro entendimiento sobre la compleja influencia de los factores no ópticos en la respuesta acomodativa. Estos hallazgos son de especial relevancia cuando se llevan a cabo tareas de cerca que requieren de una visión óptima (ej. la lectura), ya que numerosas condiciones psicológicas pueden modificar la magnitud y variabilidad de acomodación congruente a una determinada distancia. Además, la capacidad de la variabilidad de acomodación para predecir el rendimiento atencional podría ayudar a mejorar el diagnóstico del trastorno por déficit de atención e hiperactividad.

CHAPTER 1: INTRODUCTION

INTRODUCTION

FUNDAMENTAL ASPECTS OF THE ACCOMMODATIVE RESPONSE.

An optimal vision at different viewing distances is critical for a wide variety of everyday activities. The ability to keep a sharp image of an object on the retina by adjusting the optics of the eye is defined as ocular accommodation (Millodot, 2014). The dynamic aspects of accommodation are complex, since they involve perceptual, sensory, motor, neurological, anatomical and bio-mechanical factors. In order to maintain clear vision when the viewing distance changes, the accommodative system needs to determine the direction of accommodation (i.e., generate accommodation or disaccommodation) as well as to regulate the magnitude of the accommodative response required. This is ensured by neurological mechanisms that transform physical stimuli such as blur, disparity and proximal cues to neurological codes for driving accommodation (Kaufman, Levin, Adler, & Alm, 2011).

Under normal binocular conditions, accommodation is closely linked to the vergence and pupil systems, which ensures that the eyes converge to bring the images of any object onto the fovea of both eyes and inducing pupil miosis (constriction) at closer distances, respectively. These three physiological functions (accommodation, convergence and miosis) are denoted as the accommodative triad or the near reflex (Glasser, 2006). The afferent impulses travel from the retina to the visual cortex via optic nerve, optic chiasm, optic tract, lateral geniculate nucleus and optic radiation, and the efferent impulses travel from the visual cortex to the pretectal area and then to the parasympathetic nucleus of Perlia, located medial and ventral to the Edinger-Westphal nucleus. Then, these impulses travel to the nuclear area of the medial rectus muscle (ocular convergence) and to the Edinger-Westphal nucleus of the oculomotor nerve, from which they proceed to the ciliary ganglion and muscle (accommodation) and to the pupillary sphincter (pupil miosis) (Sure & Culicchia, 2013) (Figure 1). Although both accommodation and vergence respond independently, a cross-linked reciprocal interaction exists between accommodation and convergence. When disparity is open-loop, blur-driven accommodation elicits convergence which is defined as accommodative convergence, and when blur is open-loop, disparity-driven convergence elicits accommodation which is defined as convergence accommodation (Ciuffreda & Kenyon, 1983).

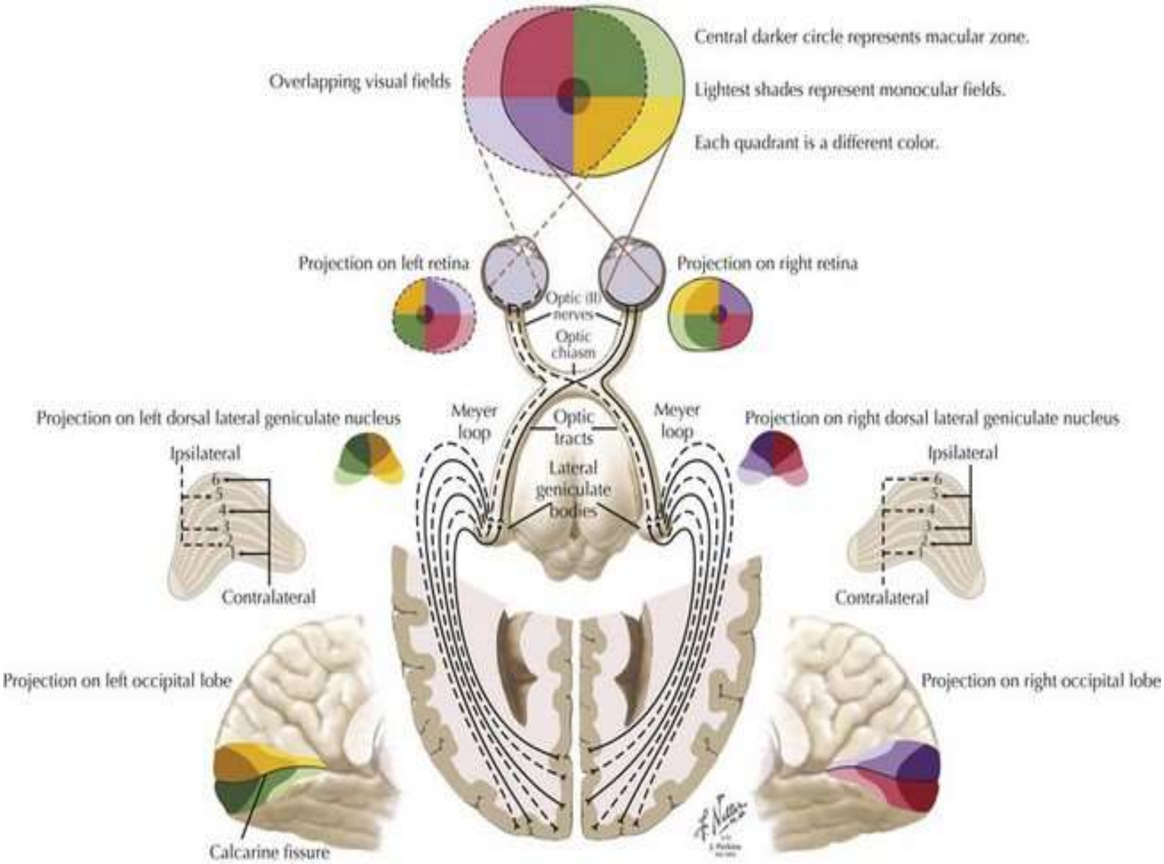

Figure 1. A graphical overview of the visual pathway: Retino-Geniculo-Calcarine Pathway. Retrieved from Felten, O'Banion, & Maida (2015).

In the absence of adequate visual stimuli or by opening the accommodative feedback loop, the accommodative system adopts an intermediate resting position which is termed as 'tonic accommodation', 'dark focus' or 'resting sate' (Bullimore & Gilmartin, 1987). This myopic shift is proportional to the level of background ciliary muscle tone mediated by the autonomic nervous system (Gilmartin, 1986). The amount of accommodation exerted is rarely equal to the dioptric stimulus for accommodation. During distance vision, a small amount of accommodation is generally exerted (lead of accommodation), while as the near demand increases the accommodative system tends to progressively under accommodate (lag of accommodation) (Abbott, Schmid, & Strang, 1988; Schmid & Strang, 1988).

Assessment of accommodation

The functioning of ocular accommodation can be assessed by different procedures including subjective (e.g., push-up, push-down, dynamic retinoscopy, minus lenses) and objective methods (e.g., autorefractors or aberrometers) (Figure 2). Subjective methods are considered as clinical tests to routinely assess accommodation, however, subjective methods tend to overestimate the true accommodative optical change in power of the eye. Objective methods have shown to provide a more reliable and accurate measure of accommodation (Kaufman, Levin, Adler, & Alm, 2011). Most commercially available autorefractors are only valid to measure the distance refractive error and they present internal fixation targets that have shown to affect the magnitude of proximally induced accommodation (Rosenfield & Ciuffreda, 1991). Therefore, the most appropriate autorefractors should permit natural binocular viewing conditions of external fixation targets in open-view, which are the so-called open-field autorefractors (Sheppard & Davies, 2010).

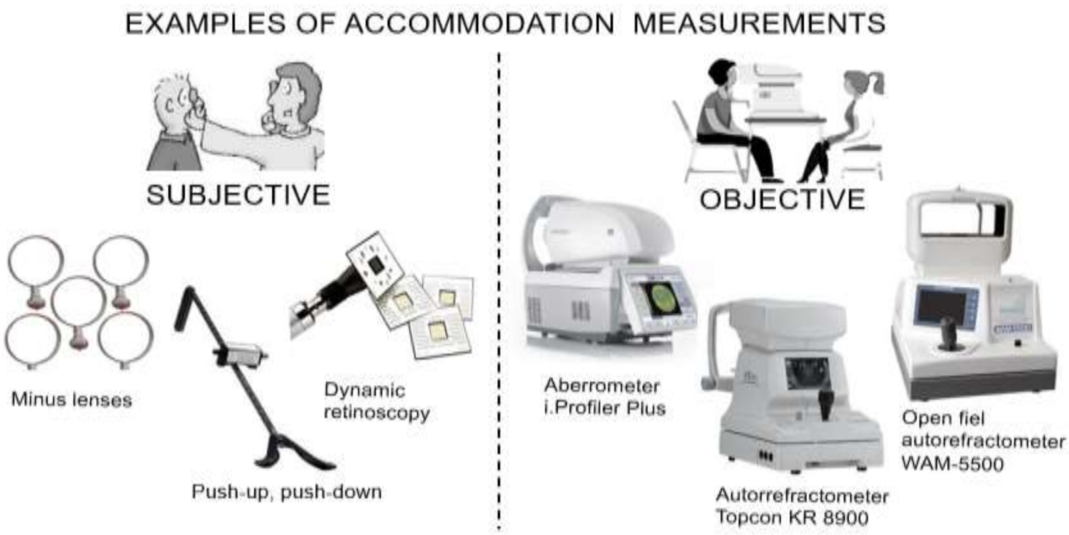

Figure 2. Examples of subjective and objective methods to measure accommodation.

Objective accommodative amplitudes are slightly greater than 7D in children from the age of 3 into the teenage years. However, the ability to accommodate diminishes with age, and especially with the development of presbyopia. The amplitude of accommodation does not begin to decline rapidly until the third decade of life, being completely lost by about 55 years old (Anderson, Hentz, Glasser, Stuebing, & Manny, 2008; Duane, 1922; Mordi & Ciuffreda, 2004).

Accommodation mechanism and innervation

The accommodative system of the eye is anatomically formed by the ciliary muscle, the choroid, the suspensory zonules, and the crystalline lens (Figure 3). To allow the lens to accommodate at different distances, it is necessary that the power of the crystalline lens changes according to the accommodative demand. The first description of the mechanism of ocular accommodation was provided by Helmholtz von, (1909), however, Fincham, (1937) and more recent investigations have helped to enhance its understanding (Plainis, Charman, & Pallikaris, 2014). In the unaccommodated state, resting tension on the elastic zonular fibres at the lens equation pulls outward and the lens rests in a flattened state. The changes in focus of the eye from a distant to a near target are explained by the contraction force from the ciliary muscle leading to anterior movement of the lens surface and a relaxation of the zonules that suspend the crystalline lens in the anterior chamber of the eye. While accommodating, the reduced tension in the zonular fibres allows the crystalline lens to become more curved and thicker, permitting to increase its refractive power (Artal, 2017).

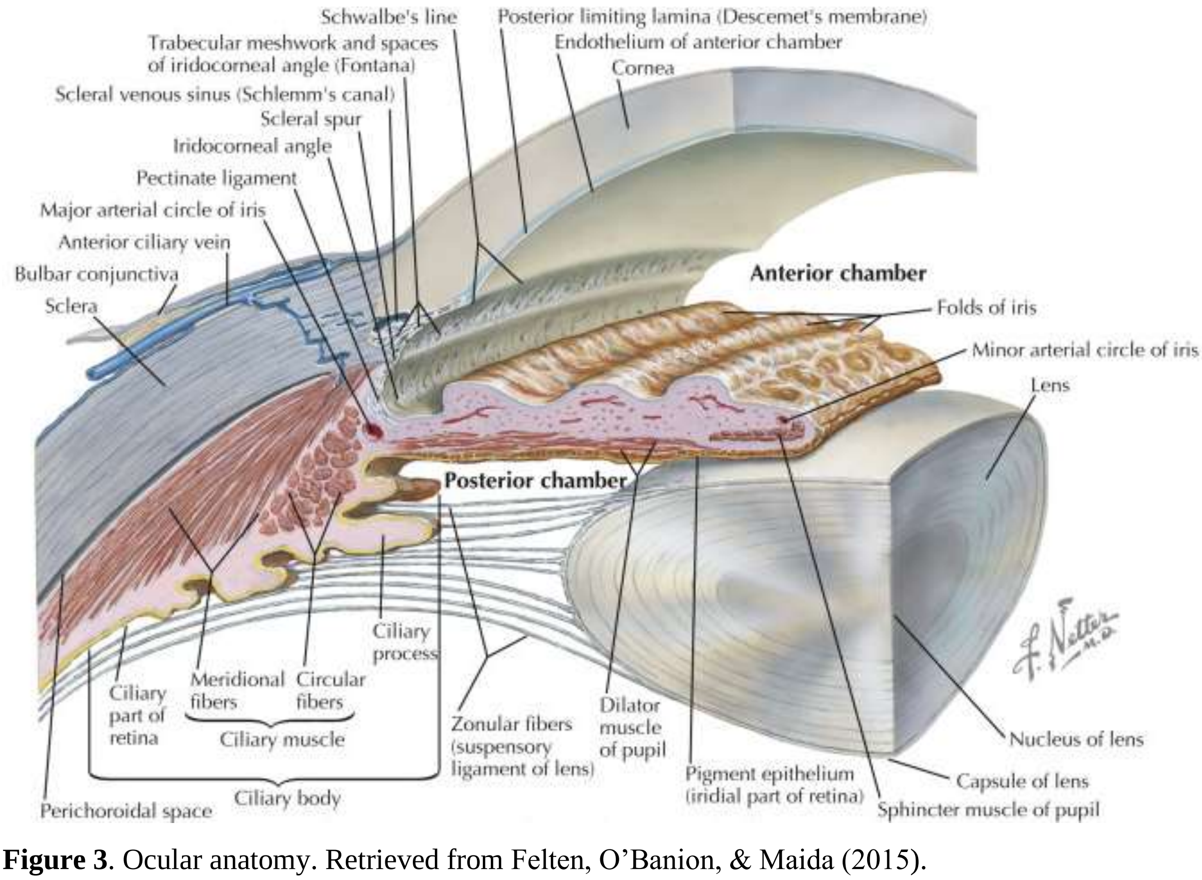

Figure 3. Ocular anatomy. Retrieved from Felten, O'Banion, & Maida (2015).

The accommodative system receives dual innervation from the parasympathetic and sympathetic branches of the autonomic nervous system (Kardon, 2005). The parasympathetic system provides the dominant innervation to the ciliary muscle, being mediated by the action of acetylcholine on muscarinic receptor subtype M3 (Franzén, Richter, & Stark, 2000). Contraction of the ciliary muscle is brought about by the activity of the parasympathetic fibres of third cranial nerve originated in the Edinger-Westphal nucleus in the midbrain, where the fibres travel and synapse in the ciliary ganglion and the postganglionic fibres enter the eye as the short ciliary nerves (Gamlin & Reiner, 1991; Gamlin, Zhang 1994). Increases in parasympathetic innervation act rapidly (~ 1 second) to produce a positive accommodation of up to 20 D. In contrast, the sympathetic system is inhibitory in nature and averages only 1% of ciliary muscle terminals (Tornqvist, 1966). The sympathetic supply to the ciliary muscle initiates in the diencephalon and travels down the spinal cord synapse in the spinociliary center of Budge in the intermediolateral tract of the cord (Figure 4). This innervation is mediated by the action of noradrenaline on two subclasses of postsynaptic receptors (a1- and b2-adrenoceptors) (Chen, Schmid, & Brown, 2003). Notably, the sympathetic system acts with a much slower time course of 10–40 seconds to produce hyperopia of at most 1.5 D, being its contribution only evident when performing prolonged near work (Gilmartin, 1986; McDougal & Gamlin, 2015).

Physiological investigations have described that the midbrain plays an important role on the near response, since it contains premotor neurons that supplies lens-related preganglionic motoneurons in the Edinger-Westphal nucleus (Mays, & Gamlin, 1995). Cells located in the midbrain exhibit tonic activity related to eye position or accommodative drive (May, Billig, Gamlin, & Quinet, 2019), with these premotor neurons being concentrated at the caudal end of the oculomotor nucleus, within the supraoculomotor area (May, Warren, Gamlin, & Billig, 2018). Additionally, electrophysiological studies have proven that certain areas of the cerebral cortex such as the lateral intraparietal, posterior parietal cortex, and frontal eye fields are sensitive to lens accommodation (for more detailed information see Nadel & Barnes, 2003). Specifically, the posterior parietal cortex and the frontal eye fields project to the superior colliculus (Ohtsuka, & Sato, 2000), which is a structure that has demonstrated to be involved in the generation of saccadic eye movements and the control of accommodation, vergences and ocular fixations (Suzuki, 2007). Also, there is scientific evidence that the cerebellum contributes to lens accommodation (Gamlin, 1999).

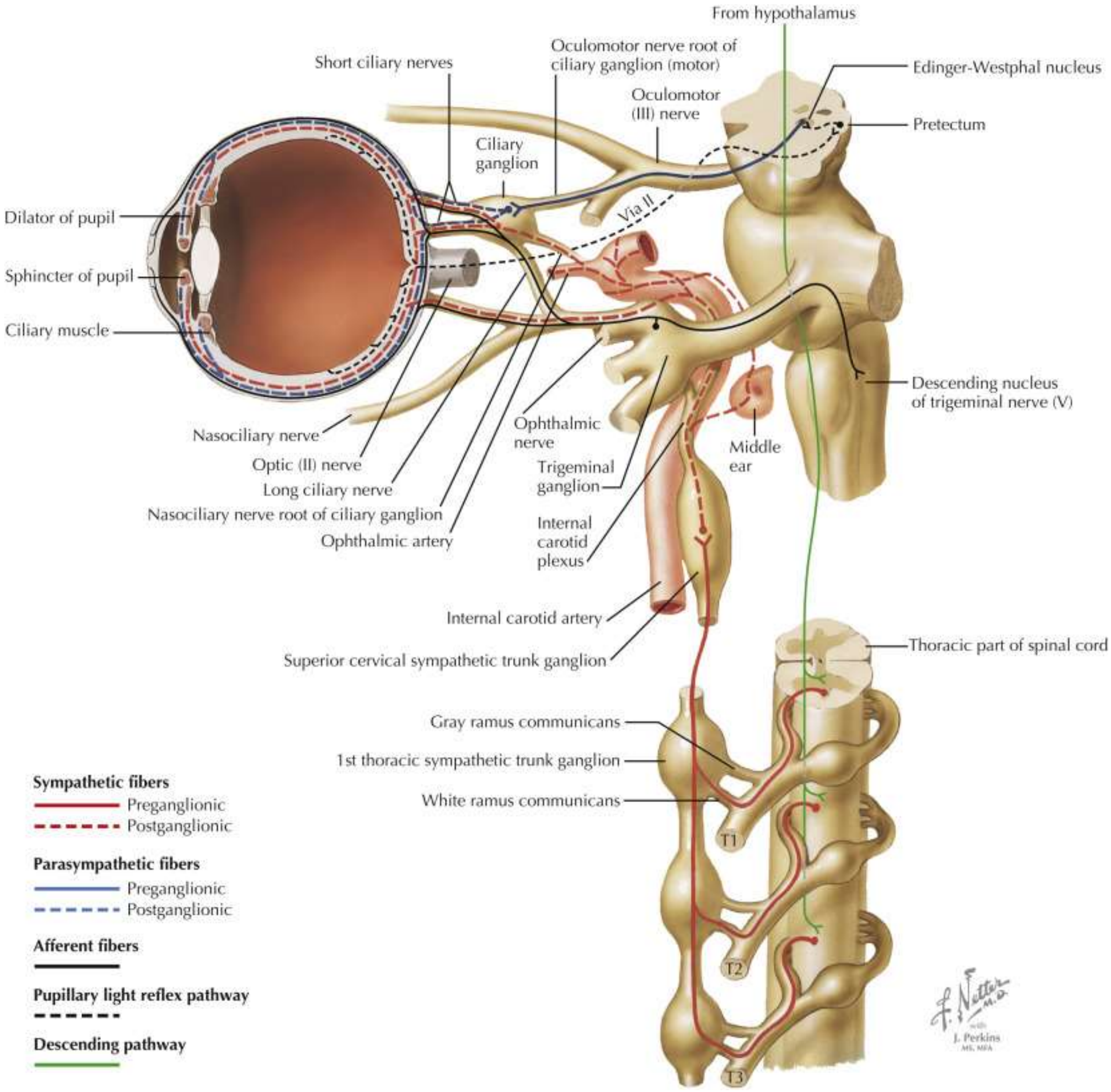

Figure 4. Autonomic distribution of the eye. Retrieved from Felten, O’Banion, & Maida, (2015).

Microfluctuations of accommodation

The accommodation of the eye is not stable throughout time when focusing on a stationary target, showing small fluctuations of approximately 0.5D at a temporal frequency spectrum up to ~5 Hz. These fluctuations or variations of the accommodative response are known as microfluctuations, and they seem to represent a combination of “plant noise" and neurological control (Charman & Heron, 2015). It is hypothesised that the microfluctuations of accommodation generate a blurred stimulus smaller than the ocular depth of focus that is of a sufficient magnitude to provide the required directional information to the accommodation control system allowing maintenance of the steady-state response via negative feedback of retinal image blur (Metlapally, Tong, Tahir, & Schor, 2016; Schor, Alexander, Cormack, & Stevenson, 1992).

Fourier analysis revealed that the microfluctuations of accommodation are divided in a low (<0.6 Hz) and high (1-2 Hz) frequency component. The low frequency component seems to be under neurological control and arises from changes on the surface of the lens, being also related to the respiration frequency and changes in depth of focus (Collins, Davis, & Wood, 1995; Yao, Lin, Huang, Chu, & Jiang, 2010). For its part, the high frequency component reflects noise from blood flow in the ciliary body and orbit (Collins et al., 1995; Winn, Pugh, Gilmartin, & Owens, 1990). Due to these potential mechanisms, rhythmic changes in the parasympathetic/sympathetic balance could result in rhythmic fluctuations of the accommodative response.

FACTORS INFLUENCING THE ACCOMMODATIVE RESPONSE

The accommodative response is determined by a complex integration of optical and non-optical factors. Accommodation can be stimulated from an alteration in the composition of the retinal image (optical factors), but also, it can be independent of the retinal image (non-optical factors) (Mark Rosenfield & Ciuffreda, 1990). The optical factors are primarily associated with the characteristics of the visual stimulus and they are part of a closed-loop system (e.g., blur), while non-optical factors are more influenced by task demands with a cognitive component, as well as individual cognitive and motivational characteristics (see below for further details), and they are denoted as open-loop factors because they do not form a closed-loop feedback system driving the accommodative response (Edgar, 2007).

Blurring of the retinal image can result from a variety of factors including improper focus, diffraction, and different types of optical aberrations including the chromatic aberration (Gambra & Marcos, 2009; Kruger & Pola, 1986). On the other hand, open-loop influences on the accommodative response may include other factors such as perceived distance and target size, proximity, and retinal disparity (Edgar, 2007). The accommodative response is also dependent on the subject (e.g., age [Anderson, Glasser, Manny, & Stuebing, 2010], pupil size [Ward PA, 1985]) and target characteristics (e.g., luminance [Johnson, 1976], spatial frequency [Charman & Tucker, 1977], contrast [Owens, 1980], colour [Charman & Tucker, 1979]).

Regarding ocular microfluctuations, they are also sensitive to factors that induce changes in depth of focus. For example, reductions in pupil size promote a greater depth of focus, leading to an increase in the magnitude of the microfluctuations (Gray & Winn, 1993). Additionally, the magnitude of the microfluctuations has demonstrated to be dependent on the refractive error, with myopes exhibiting greater values due to an increased baseline neural blur detection threshold and perceptual depth of focus (Day, Seidel, Gray, & Strang, 2009; Day, Strang, Seidel, Gray, & Mallen, 2006). The magnitude of microfluctuations is also associated with age (Anderson et al., 2010; Mordi & Ciuffreda, 2004), viewing distance (Charman & Heron, 2015) and target luminance (Gray,Winn, & Gilmartin, 1993).

The ciliary muscle is innervated by the autonomic nervous system (McDougal & Gamlin, 2015) and consequently, the accommodation is not just driven by the previously mentioned factors. Notably, there are other issues such as the arousal state (Vera et al., 2016), mental stress (Westheimer., 1957), mood shifts (e.g., anger, anxiety) (Miller, 1987), attentional state (Edgar, 2007; Poltavski, Biberdorf, & Petros, 2012), motivation (Provine, and Enoch, 1974) and cognitive demands (Edgar, 2007) that should be considered, since they may also influence the resultant magnitude and variability of accommodative response. In the present International Doctoral Thesis, we will focus on the effects of the arousal and attentional states on the dynamics of the accommodative response.

Arousal state

Arousal refers to the combination of autonomic, electrophysiological, and behavioural activity of the subject, ranging from sleep at one extreme to panic or extreme excitement at the other (Dickman, 2002; Gazzaniga, Michael, Mangun, 2014) (Figure 5). Different tasks require different levels of arousal for optimal performance, namely easier tasks require higher levels of arousal than more difficult tasks (Diamond, Campbell, Park, Halonen, & Zoladz, 2007), however the optimal level of activation for the accommodative response remains unclear.

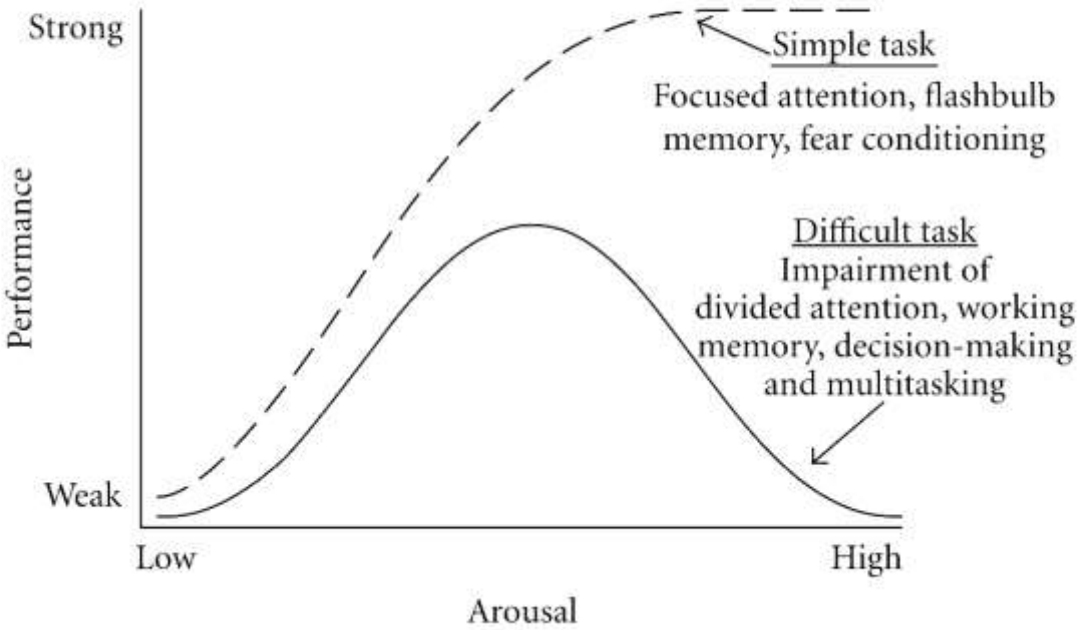

Figure 5. The Yerkes–Dodson law. Retrieved from Diamond, Campbell, Park, Halonen, & Zoladz (2007).

As stated above, the parasympathetic innervation of the ciliary muscle induces an increase in the magnitude of accommodation while the sympathetic innervation inhibits accommodation. Therefore, accommodation may reflect the balance between the parasympathetic and sympathetic branches of the autonomic nervous system, driving changes in the eye's refractive power (McDougal & Gamlin, 2015). Due to the fact that the level of autonomic activation or arousal is modulated by multiple causes (e.g., physical effort, monotonous and predictable activities), and that it promotes autonomic or central nervous system disequilibrium, it is plausible to expect that ocular accommodation may be sensitive to changes in the level of activation or arousal (Miller & Takahama, 1988).

Previous studies have examined the effects of different behavioural manipulations of the arousal state on the accommodative response (Miller, & Takahama, 1988; Ritter, & Huhn-Beck, 1993). These studies have assessed accommodation under open-loop conditions and under conditions where both open- and closed-loop influences are active. Alterations in the level of arousal often, but not always, have shown to induced changes in the accommodative response, being those effects more pronounced in open-loop conditions. Miller and Takahama (1988) observed that the magnitude of accommodation in total darkness was reduced when inducing sympathetic but not parasympathetic activation. Additionally, the accommodative response has proved to be sensitive to emotion-arousing stimulation due to the differences in autonomic activation. Specifically, under stress manipulations (e.g., performance examination, regarding unpleasant images), accommodation showed a heightened response (Miller, 2004; Miller & Robert, 1982). Furthermore, dark focus of accommodation has been evaluated after stimulating the sympathetic nervous system with physical exercise, showing an increased accommodative response (Ritter, & Huhn-Beck, 1993).

Arousal changes are also associated with cognitively demanding tasks, and when mental workload increases the central nervous system provides a greater amount of resources (Reimer & Mehler, 2011). In this regard, previous investigations focused on the accommodative response changes after arousal variations, as a consequence of mental efforts, have reported discrepant findings. Some studies observed that sympathetic activation during mentally demanding activities induces a reduced accommodative response (Davies, Wolffsohn, & Gilmartin, 2005; Malmstrom, 1984; Malmstrom, Angeles, Randle, Bendix, & Weber, 1980; Rosenfield & Ciuffreda, 1990), whereas others have found that it may lead to an increased accommodative response (Bullimore & Gilmartin, 1987; Jaschinski-Kruza & Toenies, 1988; Kruger, 1980; Post, Johnson, & Owens, 1984; Winn, Gilmartin, Mortimer, & Edwards, 1991). Bullimore and Gilmartin (1988) suggested that task distance may influence the direction of accommodative response. They observed that under mental effort the mean accommodative response increased when viewing a dioptric stimulus of 1D and decreased for a stimulus of 5D. Other factors that may also influence that contradictory results are the method of information presentation and the nature of the processing task (Edgar, 2007). Additionally, the accommodative response seems to be more stable (smaller variability of accommodation) under cognitively demanding tasks (Hynes, Cufflin, Hampson, & Mallen, 2018; Roberts, Manny, Benoit, & Anderson, 2018).

Highly demanding physical or mental activities, as well as prolonged time-on-task may lead to fatigue, and it leads to impairments in vigilance and task performance (Lal, & Craig, 2001). Previous studies have suggested that the sustained physiological effort required during near visual work promotes a reduction in the ability of the ciliary muscle to contract, and consequently the magnitude of accommodation decreases, and the variability of accommodation increases. The magnitude of these effects are dependent on the nature of the task and subjects´ initial oculomotor resting tonus, and the changes in the dynamics of accommodation can be also maintained during subsequent distance viewing (transient myopia) (Becker, Warm, & Dember, 1979; Berens, & Sells, 1950; Harb, Thorn, & Troilo, 2006; Hasebe, Graf, & Schor, 2001; Ostberg, 1980; Owens & Wolf-Kelly, 1987; Takeda, Ostberg, Fukui, & Iida, 1988). On the contrary, some studies argue that the accommodative response is robust to fatigue during highly demanding and prolonged near work, since both amplitude and accuracy of accommodation remain constant (Miller, Pigion, Wesner, & Patterson, 1983; Vilupuru, Kasthurirangan, & Glasser, 2005; Wolffsohn, Sheppard, Vakani, & Davies, 2011).

The manipulation of the level of arousal is commonly assessed by subjective reports, however they may not be enough to determine its possible impact on the autonomic nervous system (Tyrrell, Pearson, & Thayer, 2000). There are several non-invasive techniques such as blood pressure, skin conductivity, heart rate variability and pupil light reflex that allow to measure the level of autonomic reactivity (Kahneman, Tursky, & Shapiro, 1969; Pumprla, Howorka, Groves, Chester, & Nolan, 2002). Previous studies have demonstrated a behavioural link between the accommodative and cardiovascular systems, in which changes in cardiovascular balance result in changes on the accommodation function, as well as alterations of the dynamics of accommodation due to near visual work may influence the cardiovascular system (Tyrrell, Pearson, & Thayer, 2000). Indeed, Davies et al., (2005) continuously recorded heart rate with a finger-mounted piezoelectric pulse while measuring the accommodative response. They observed a reduction in accommodation with greater levels of cognitive demand, being associated with a reduction in mean heart period that was attributable to a concurrent reduction in the relative power of the parasympathetic branch. Similarly, Tyrrell et al (1992) observed that accommodation increased more during sympathetic dominance than during parasympathetic dominance. On the other hand, for sustained near work, Davies et al. (2009) and Tyrrell et al. (1994) observed a link between accommodation and the cardiovascular system, which was predominantly attributable to changes in the systemic parasympathetic nervous system. However, Jainta et al. (2008) did not observed a robust link between cognitive demand and accommodative behaviour, suggesting that accommodation is not a good indicator of the autonomic balance.

Attention

Attention can be defined as the appropriate allocation of processing resources to relevant stimuli (Coull, 1998; Zimmermann, & Leclercq, 2004). It has been suggested that attentional factors may mediate and influence the dynamics of ocular accommodation, possibly caused by the interaction of perceived distance and allocation of attention (Edgar, 1997, 2007). Remarkably, Owens et al. (2000) measured dark focus under two levels of visual attentiveness, with their results suggesting that active viewing tasks improves accommodation and reduces fatigue, whereas the accommodative response under passive viewing tasks, using impoverished stimulus conditions, returns to the individuals intermediate dark focus. In the same line, Francis et al. (2003) observed that the accommodative response was more accurate when the observers were instructed to concentrate in comparison to the space-out condition, supporting that an active effort exerts a profound top-down influence on the accommodative behaviour which allows to accurately respond to the target demand. Additionally, Wagner et al. (2016) reported that the accommodative lag can be reduced by improving the attentional state with auditory feedback.

It seems that the influence of attention on the accommodative behaviour is not just related to the task characteristics or the experimental design, but also to the individual's interest. In this sense, Horwood & Riddell (2010) compared the accommodative response in a group of optometry experts and naïve to vision science, showing that the naïve group under-accommodated for a wide range of distances in comparison to the expert group. They suggested that this difference is due to attention, as experts were paying more attention because they were more involved in the task.

The relationship between attention and accommodation has also been assessed in the opposite direction, namely studying the effect of changes in the ability to accommodate on attentional performance. Poltavski et al. (2012) observed that attention, measured by a computerized test of sustained attention commonly used in the diagnosis of attention deficit hyperactivity disorder, was impaired in a normal population when it was evaluated under accommodative stress conditions (wearing -2.00D lenses), increasing a 6% the probability of participants to be diagnosed of attention deficit hyperactivity disorder. The authors suggested that attention controls and optimises the visual system limited resources in the brain by selecting the representation of objects that appears more relevant, so that an added visual effort may limit the attentional reserves.

JUSTIFICATION OF PRESENT DOCTORAL THESIS

The accommodative response is determined by a complex interaction of many factors which can be broadly divided into optical and non-optical factors. The former aspect is better documented, including closed-loop inputs (e.g., blur and chromatic aberration) (Rosenfield & Ciuffreda, 1990). However, the non-optical factors are not fully understood due to the heterogenous influence that cognitive factors such as mental workload or attention may have on the accommodative response (Edgar, 2007). The effects of the previously mentioned non-optical factors on the dynamics of the accommodative response are not consistent, presumably due to a lack a of a clear definition of the accommodative response in the context of psychological knowledge (Francis, Jiang, Owens & Tyrrell, 2003). In applied contexts, some of the above described factors occur simultaneously, with their effects being cumulative (Edgar, 2007). Therefore, it is important to assess the impact of these possible interactions on the dynamics of the accommodative response in closed-loop conditions.

There is scientific evidence that different ocular variables are closely linked to neurocognitive processes (Seligman, & Giovannetti, 2015). Indeed, the magnitude and variability of pupil size have been proposed as potentially useful psychophysiological markers for detecting changes in the arousal and attentional states (Reimer et al., 2016; Van Den Brink, Murphy, & Nieuwenhuis, 2016). Given the considerable evidence supporting that the accommodative system is regulated by the autonomic control (McDougal & Gamlin, 2015), it is plausible to expect that the magnitude and variability of the accommodative response may be able to partially predict any change in the autonomic balance.

Lastly, in a clinical population with inherent problems of attention, as is the case of attention-deficit/hyperactivity disorder, the study of the accommodative response should be crucial since the possibility of suffering accommodative problems may further aggravate their behavioural and visual symptomatology. This neurophysiological disorder has a worldwide prevalence ranging from 5.9% to 7.1% (Willcutt, 2012) and is characterised by developmentally inappropriate degrees of inattention, impulsivity, and hyperactivity (Barkley, 2014). Previous studies have found a wide variety of visual problems associated with attention-deficit/hyperactivity disorder, among which the most investigated ones are visual processing deficits (Lenz et al., 2010), atypical oculomotor behaviour (Mahone, 2012) and the presence of convergence insufficiency (Granet, Gomi, Ventura, & Miller-Scholte, 2005). However, there are no studies analysing whether accommodative deficits are associated with this disorder.

Summing up, in order to elucidate the remaining uncertainties and to better understand the underlying mechanisms that regulate the accommodative response, we aimed to assess the effects of non-optical factors (i.e., arousal and attentional states) in closed-loop conditions on the accommodative response, and also, to determine whether ocular accommodation could be considered as a potential biomarker of the autonomic state. Arousal and attention are multi-dimensional psychological processes, which interact closely with one another (Coull, 1998). However, in order to simplify its relationship with the accommodative response, the present International Doctoral Thesis has been divided into two different sections with a total of eight studies (four in each section). In section one, we focus on the study of the arousal state and the accommodative function. We experimentally manipulate the level of arousal in different ways (i.e., physical exercise [study I], psychostimulants [studies II and III], and sustained attention [study IV]) and measure its effects on the accommodative response (magnitude and variability). In section two, we evaluate the impact of the attentional state on the dynamics of the accommodative response. This section is also subdivided into two parts according to the experimental population, namely a healthy young population which is exposed to attentional distractors and facilitators (study V), and a clinical population of children attention-deficit/hyperactivity disorder (studies VI, VII and VIII).

CHAPTER 2: AIMS/ OBJETIVOS

AIMS

The main objective of the present International Doctoral Thesis is to study the effects of non-optical factors on the accommodative response (magnitude and variability). In particular, we aim to analyse the changes in the accommodative response caused by the manipulation of the sympathetic/parasympathetic balance through changes in the arousal and attentional states. Additionally, we evaluate the accommodative response in a clinical population with an intrinsic attentional deficit as is the case of the attention-deficit/hyperactivity disorder.

The specific objectives of the present Doctoral Thesis are separately described for each of the eight studies.

Section 1: Effects of arousal on the accommodative response.

- Study I. To test the impact of two high-intensity interval training protocols differing in exercise intensity (low intensity and high intensity) on the accommodative response during the execution of a sustained attention task, as well as to evaluate the possible link between changes in ocular accommodation and the autonomic function as measured by heart rate variability.
- Study II. To study the acute effect of caffeine consumption on the accommodative response at six viewing distances.
- Study III. To measure the acute effects of caffeine while performing a sustained attention task, and to determine the possible differences between low and high caffeine consumers.
- Study IV. To assess the time-on-task effect of a sustained attention task on the accommodative response, as well as to establish the possible association between the accommodative dynamics, cardiac autonomic regulation and behavioural performance while performing a cognitive task.

Section 2: Effects of the attention on the accommodative response.

- Study V. To evaluate the effects of attention facilitators (auditory feedback) and distractors (arithmetic task) on the dynamics of the accommodative response at two different levels of complexity (low and high).

- Study VI. To compare the accommodative response at three different accommodative demands between a group of non-medicated children with attention-deficit/hyperactivity disorder and an age-matched control group.
- Study VII. To study the influence of the engagement in the visual stimuli on the accuracy of accommodation in a population of medicated and non-medicated children with attention-deficit/hyperactivity disorder in comparison to age-matched healthy controls.
- Study VIII. To assess the effects of sustained attention on the dynamics of ocular accommodation in a population of non-medicated children with attention-deficit/hyperactivity disorder, and to evaluate the association between the dynamics of the accommodative response and behavioural performance during a continuous performance task of 14 minutes.

OBJETIVOS

El principal objetivo de la presente Tesis Doctoral Internacional es estudiar los efectos de factores no ópticos en la respuesta acomodativa. En concreto, se pretende analizar los cambios en la respuesta acomodativa provocados por manipulaciones en el sistema nervioso simpático y parasimpático induciendo cambios en el nivel de activación y modificando la atención requerida para una determinada tarea. Además, se evaluará la respuesta acomodativa una población clínica con déficit de atención intrínseco como es el caso del trastorno por déficit de atención e hiperactividad.

Los objetivos de la presente tesis se han dividido en dos secciones principales, divididas a su vez en cuatro estudios cada una, formando un total de ocho estudios.

Sección 1: Efectos del nivel de activación sobre la respuesta acomodativa.

- Estudio 1. Examinar el impacto de dos protocolos de entrenamiento físico de intervalos de alta intensidad bajo dos intensidades diferentes (baja intensidad y alta intensidad) sobre la respuesta acomodativa medida durante una tarea de atención sostenida, además de evaluar la posible relación entre los cambios acomodativos y la función autonómica medida a través de la variabilidad de la frecuencia cardiaca.
- Estudio 2. Evaluar el efecto agudo del consumo de cafeína sobre la respuesta acomodativa en seis distancias de fijación.
- Estudio 3. Medir los efectos de la cafeína mientras se realiza una tarea de atención sostenida y comparar las posibles diferencias entre bajos y altos consumidores de cafeína.
- Estudio 4. Estudiar el efecto del tiempo en una tarea de atención sostenida sobre la respuesta acomodativa, establecer la posible relación entre la dinámica acomodativa, la regulación autonómica cardiaca y el rendimiento en la tarea.

Sección 2: Efectos del estado atencional sobre la respuesta acomodativa.

- Estudio 5. Evaluar los efectos de facilitadores (feedback auditivo) y distractores atencionales (tarea aritmética) sobre la dinámica de acomodación bajo dos niveles diferentes de demanda cognitiva (bajo y alto).

- Estudio 6. Comparar la respuesta acomodativa para tres demandas acomodativas diferentes entre un grupo de niños no medicados con trastorno por déficit de atención e hiperactividad y un grupo control de la misma edad.
- Estudio 7. Estudiar la influencia del interés inducido por el estímulo visual sobre la precisión de la respuesta acomodativa en una población medicada y no medicada de niños con trastorno por déficit de atención e hiperactividad en comparación con sujetos sanos de la misma edad.
- Estudio 8. Evaluar la dinámica de acomodación en una población de niños no medicados con trastorno por déficit de atención e hiperactividad, determinar el efecto del tiempo, y evaluar la relación entre la acomodación con el rendimiento en una tarea de rendimiento continuo de 14 minutos.

CHAPTER 3: EFFECTS OF AROUSAL ON THE ACCOMMODATIVE RESPONSE

STUDY I. OCULAR ACCOMMODATIVE RESPONSE IS MODULATED AS A FUNCTION OF PHYSICAL EXERCISE INTENSITY

Introduction

The acute effect of physical exercise on sensory and cognitive performance has been thoroughly addressed due to its relevance in laboratory and applied scenarios (Davranche, Brisswalter, & Radel, 2014; Davranche, Burle, Audiffren, & Hasbroucq, 2005; Lambourne, Audiffren, & Tomporowski, 2010; Mcmorris & Hale, 2015). Most findings have been explained by the arousal theory, which states that an increase in arousal up to a certain point due to physical exercise could promote an enhancement in both sensory and cognitive performance, while highly demanding physical exercise promotes over-arousal and it impairs sensory and cognitive performance (McMorris, Hale, Corbett, Robertson, & Hodgson, 2015). Nevertheless, there are numerous factors such as exercise type, exercise intensity, exercise duration, participants´ fitness level, study population, measured time points, sensory or cognitive processes being assessed that may affect the acute impact of physical effort on sensory and cognitive performance (Zimmer et al., 2017). In general, the effect of physical effort on sensory and cognitive performance seems to be instantaneous and it disappears rapidly when the exercise is terminated (Lambourne et al., 2010; Lambourne & Tomporowski, 2010). However, while there is a large body of knowledge about the effect of physical effort on cognitive performance, the impact of physical effort on sensory functioning has been less studied.

The main channel to gather information in the majority of situations is the visual system, being highly necessary during sports practice (Memmert, Simons, & Grimme, 2008). Physical effort induces physiological changes, which also influence the ocular function. For example, intraocular pressure (Vera et al., 2017), retinal activity (Zwierko, Czepita, & Lubiński, 2010) or neural conductivity in the visual pathway (Zwierko, Lubiński, Lubkowska, Niechwiej-Szwedo, & Czepita, 2011) have been shown to be sensitive to exercise. An important visual ability is the accommodative response, since it allows to see clearly at different distances (Millodot, 2014) and, thus, it is of vital importance in numerous contexts (e.g., reading). Accommodative response has been linked to the cardiovascular system, as measured by heart rate variability, suggesting that both are highly dependent on the balance between the sympathetic and parasympathetic branches of the autonomic nervous system (Davies et al., 2009). Indeed, changes of the level of arousal as consequence of mental fatigue have been demonstrated to alter accommodative response (Davies et al., 2005; Vera et al., 2016) and these variations have been explained by variations of the neural integrator in the accommodation control system (Schor, Kotulak, & Tsuetaki, 1986; Winn et al., 1990). In view of this, it is plausible that changes in the level of arousal induced by physical effort may impact accommodative response, as it has been evidenced with mental effort.

Focusing on the type of physical exercise and in accordance with the arousal theory, high-intensity interval-training has emerged as a time-efficient strategy to improve the health status (Gillen & Gibala, 2014), promoting similar physical and psychological benefits in comparison with continuous exercise (Stork, Banfield, Gibala, & Ginis, 2017). To date, there are limited studies that have examined the effect of high-intensity interval-training on brain function. For example, Hillman & Biggan, (2017) recently suggested that high-intensity interval-training may lead to neural, cognitive and academic enhancements. Therefore, assuming that high-intensity interval-training induces autonomic nervous system changes and modulates the levels of arousal, the assessment of the acute effects of different high-intensity interval-training protocols on the accommodative response would expand our knowledge of the association between physical effort and sensory functioning.

The main objectives of the present study were: (1) to examine the impact of low-intensity and high-intensity protocols on the accommodative response dynamically measured during a task that requires constant attentional demand, and (2) to elucidate whether the ocular accommodation changes are associated with the function of the autonomic nervous system during stimulus processing, as measured by heart rate variability. We hypothesised that (1) following the arousal theory the ocular accommodative response would be enhanced and impaired (i.e., lower and higher lags of accommodation, respectively) after the low- and high- intensity high-intensity interval-training protocols, respectively (McMorris et al., 2015), and (2) the ocular accommodation would be significantly associated with the autonomic function after both high-intensity interval-training protocols, as shown during mentally demanding tasks (Davies et al., 2005).

Methods

Ethical approval and participants

This study followed the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Institutional Review Board. Twenty healthy and physically active university students (9 women; mean age ± SD = 23.9 ± 3.3 years) took part in this study. All participants were free of any general or ocular condition that could affect or mask the dependent variables assessed. Hence, the inclusion criteria were: 1) be free of any ocular disease, as checked by slit lamp and direct ophthalmoscopy examination, 2) not suffering any systemic disease, and not taking any medication that might cause visual alterations, 3) have no history of strabismus, refractive surgery and orthokeratology, 4) achieve a visual acuity with their best refractive correction of ≤ 0 logMAR (20/20 Snellen) in each eye, 5) belong to the asymptomatic group as measured with the Conlon survey (cut off value of ≤ 24) (Conlon, Lovegrove, Chekaluk, & Pattison, 1999), 6) be soft contact lenses users at least for one year, since differences in ocular accommodation have been demonstrated between contact lenses and spectacles (Jiménez, Martínez-Almeida, Salas, & Ortíz, 2011), and 7) present no significant uncorrected refractive error that could affect accommodative and vergence systems (myopia < 0.50 D, astigmatism and anisometropia < 0.50 D, and/or hyperopia < 1.50 D) (Vera et al., 2016). Participants´ refractive errors without optical compensation were: mean spherical equivalent ± SD = -0.61 ± 0.86 D, ranging from -2.27 to +1.56 D. Additionally, participants were asked to avoid alcohol and caffeine-based drinks 24h and 12h before experimental sessions, respectively. Finally, they were instructed to sleep at least 7h the night before testing. The level of alertness across experimental sessions was checked by the Stanford Sleepiness Scale (Hoddes, Zarcone, & Dement, 1972), and a cut off-value <4 was considered as inclusion criteria (Vera et al., 2016).

Subjective questionnaires

The Borg CR10 scale (Borg, 1998) was used to assess the perceived exertion of the three protocols through a numerical scale ranging from 0 (“nothing at all”) to 10 (“extremely strong”). The ratings of perceived exertion were collected before the testing period, after each of the 8 sprints (or every 45 seconds for the Control condition), and after 15 min of rest. Additionally, the Stanford Sleepiness Scale (Hoddes, Zarcone, & Dement, 1972) was used to check the level of sleepiness/alertness before the commencement of each experimental session. This scale ranges from 1 “Feeling active, vital, alert, or wide awake” to 7 “No longer fighting sleep, sleep onset soon, having dream-like thoughts”, and it provides a global subjective measure of the level of alertness.

Ocular accommodation assessment and visual task

The Grand Seiko WAM-5500 open field autorefractor (Grand Seiko Co. Ltd., Hiroshima, Japan), was used to measure dynamic accommodative response values before and after each high-intensity interval-training protocol. This instrument permits the examiner to continuously record the mean spherical equivalent refractive error and pupil size in the dynamic mode with a sensitivity of 0.01D and 0.1mm, respectively. The temporal resolution is ~5 Hz. In order to obtain a robust dynamic accommodative response and following previous recommendations (Poltavski et al., 2012), we measured static refraction at far distance before starting each experimental session, which would be used for data analysis. We considered the average value from ten static accommodative response measurements in each eye. Participants wore their contact lenses when necessary based on exact ocular refraction and were asked to position their chin and forehead on the respective supports. After it, dynamic accommodative response was continuously measured while participants performed a 10-minute visual task (see below) in binocular and free-viewing conditions by using a high-contrast target stimulus displayed at 50 cm from their eyes. Although the WAM-5500 permits binocular viewing, the accommodative response cannot be measured for both eyes simultaneously. In the current study, the dominant eye, which was determined by the hole-in-the card method, was chosen to record accommodative response data (Momeni-Moghaddam, McAlinden, Azimi, Sobhani, & Skiadaresi, 2014). For data analysis and based on previous investigations, values varying more than 3 SD from the mean were considered as blinks or recording errors and, thus, they were excluded from further analysis. Each 10-min task was divided into five temporal blocks of 2-min each in order to investigate the possible changes over time (time-on-task effects; blocks: 1, 2, 3, 4 and 5). For the calculation of the lag of accommodation, we subtracted the accommodative response to the accommodative demand (2D) of the visual task. The accommodative response was considered as the dynamic measure during the Psychomotor Vigilance Task corrected by the baseline static refractive value at far distance to avoid the effects of residual refractive errors (Poltavski et al., 2012; Redondo et al., 2018; Vera et al., 2016).

Accommodative lag (D) = -2 - dynamic accommodative response - residual refractive error at far distance

A modified version of the psychomotor vigilance task (Basner & Dinges, 2011) was used as a standardized procedure to control the presentation of visual stimuli in order to measure the accommodative response in the different experimental conditions. A 15.6″ LCD laptop and the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) were used to control for stimulus presentation and response collection. The centre of the laptop screen was situated at 50 cm from the participants' head and at their eye level. The device used to collect responses was the PC keyboard. The procedure of the psychomotor vigilance task was originally designed to measure vigilance by recording participants' reaction time to visual stimuli that occur at random inter-stimulus intervals (Basner & Dinges, 2011). This procedure was used for two main reasons: first, to standardize the random presentation of visual stimuli between experimental conditions in order to obtain reliable data of accommodative response; second, we tried to match the different experimental conditions in terms of attentional demands with the aim of ensuring that participants were paying appropriate attention to the stimuli presented on the screen. It should be noted that the psychomotor vigilance task requires to maintain the viewer´s attention, however, an accurate accommodation may not be essential for detection of the visual stimuli.

The procedure of presentation of the visual stimuli was as follows (see Figure 6 for a graphical description of the psychomotor vigilance task procedure): each trial began with the presentation of an empty black circle in a blank background, which subtended 6.73° in the horizontal and vertical axes, for 2000ms. Later, in a random time interval (between 2000 and 10000ms), the circle was filled all at once in a black colour. Participants were instructed to respond as fast as they could once they had detected the presentation of the filled circle. The filled circle was presented for 500ms and the participants had a maximum of 1500ms to respond. They had to respond with their dominant hand by pressing the space bar on the keyboard. A reaction time visual feedback message was displayed for 300ms after response, except in case of an anticipated response (‘‘wait for the target'') or if no response was made within 1000ms after target offset (''you did not answer''). Following the feedback message, the next trial began. The task lasted 10 minutes.

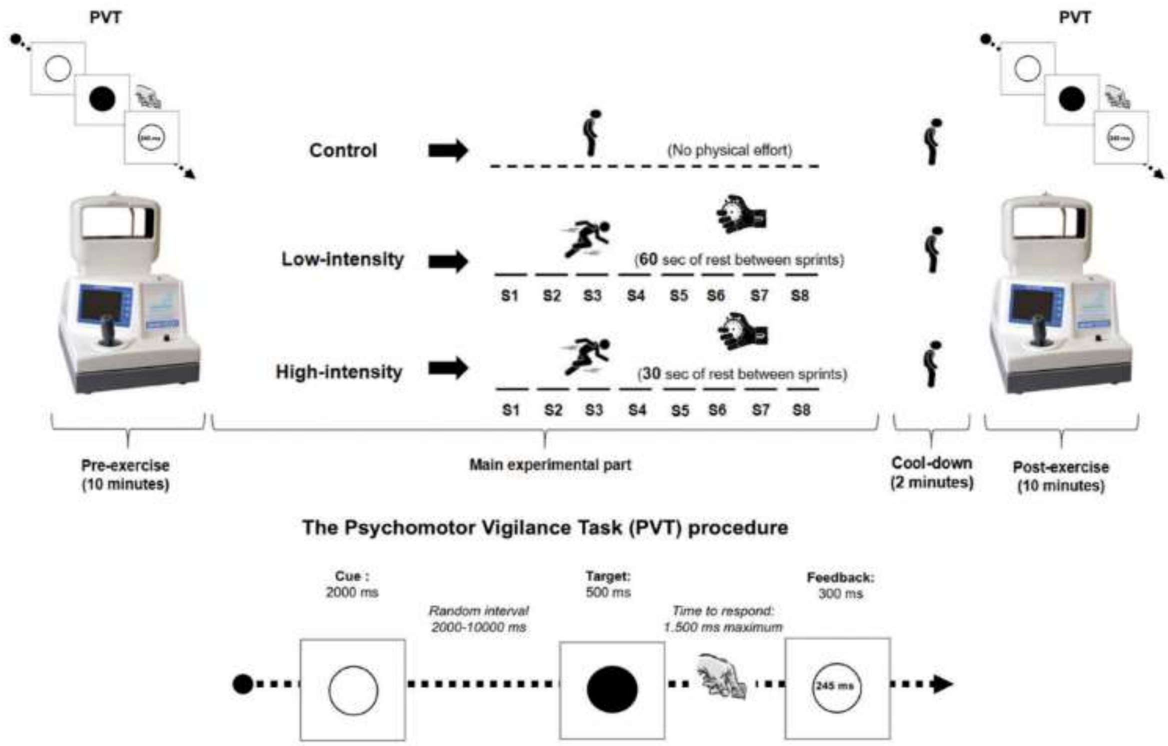

Figure 6. Graphical overview of the experimental design (upper panel) and timeline of the psychomotor vigilance task (lower panel).

Cardiovascular function assessment

Heart rate and heart rate variability were recorded throughout the experimental sessions using a Polar RS800 CX monitor (Polar Electro, Kempele, Finland). The heart rate monitor was placed at the beginning of each experimental session and participants rested for six minutes (the first minute was discarded from the analysis to obtain a more reliable measure) in a supine position to record the baseline heart rate variability. Participants were encouraged to stay as relaxed as possible. Moreover, the average heart rate was calculated for the main part of the testing session (i.e., from the first to the last sprint) to check the cardiovascular demands of the different high-intensity interval-training protocols and heart rate variability was analysed during the stimuli presentation (see *ocular accommodation assessment and visual task* section for details). Subsequently, each R-R interval file was analysed by means of the Kubios heart rate variability Analysis

Software 2.0 (Mika, Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karjalainen, 2009). The recordings were preprocessed to exclude artifacts by eliminating R-R intervals which differed more than 25% from the previous and the subsequent R-R intervals. A detrending procedure based on smoothness priors approach was applied to avoid any distortion in heart rate variability results due to its non-stationary behavior (e.g., slow linear or more complex trends in the heart rate variability signal) (Tarvainen, Ranta-aho, & Karjalainen, 2002). The root-mean-square difference of successive normal R-R intervals (RMSSD) was used to analyse the heart rate variability within the time domain. The denotations and definitions for the heart rate variability analysis in this paper follow the procedure used in previous studies (Luque-Casado, Perales, Cárdenas, & Sanabria, 2016) and the guidelines given in *Task Force of the European Society of Cardiology* and the *North American Society of Pacing and Electrophysiology* (Malik et al., 1996).

Procedure

All participants attended to the laboratory on four different occasions. In the first visit, participants signed the consent form, were checked for their compliance with the inclusion criteria, and were familiarized with the visual task. The next three experimental sessions comprised the main part of the study. Upon arrival to the laboratory, participants completed the Stanford Sleepiness Scale and were fitted with a heart rate monitor. At this point, they rested for six minutes in supine position for baseline cardiovascular assessment. Subsequently, we assessed ocular accommodation while performing the 10-min visual task before any physical effort. Just after it, participants carried out the warm-up and performed the corresponding high-intensity interval-training protocol. The general warm-up for both high-intensity interval-training sessions consisted of 10 min of jogging and dynamic stretching, which was followed by 2 sets of sprints with a 180º change of direction (see details below) performed at 50% and 90% of the maximum intensity. Afterwards, participants rested for 5 min before the initiation of the high-intensity interval-training protocol. Each sprint consisted of running at the maximum possible velocity for 15m, a 180º change of direction, and then running again at the maximum possible velocity until crossing the starting line (total distance: 30m). The time needed to complete each sprint was collected by means of a telemetric photocell (Microgate, Bolzano, Italy) placed on the starting line. The starting position was standardized with the lead-off foot placed 1 m behind the starting line. Participants were instructed to complete each sprint in the shortest possible time. The three exercise protocols were performed on separate occasions and in a randomized order. They were defined as follows: low-intensity interval-training (8 sprints with 60 seconds of rest between sprints), high-intensity interval-training (8 sprints with 30 seconds of rest between sprints), and Control (walking for 8 minutes).

After each of the eight sprints, or every 45 seconds for the control condition, they reported their level of perceived exertion (eight points of measure in each condition), using the ratings of perceived exertion scale. When the high-intensity interval-training protocol was completed, a 2 minutes cool-down protocol (recovery) was carried out to avoid sudden heart rate decelerations as recommended by the American Heart Association for submaximal physical effort (Fletcher et al., 2013), and the accommodative response was evaluated again (see Figure 6 for a graphical description of the experimental design). In order to avoid any circadian effect on arousal levels, all experimental sessions were scheduled at the same time of the day (± 1 hour). Also, the order of the experimental sessions was counterbalanced to avoid potential practice/learning effects. All evaluations were performed under constant environment (~22ºC and ~60% humidity) and illumination (217±12 lx, as measured in the corneal plane [Illuminance meter T-10, Konica Minolta, Inc., Japan]) conditions.

Experimental design and statistical analysis

A repeated measures design was carried out to test the effects of high-intensity interval-training protocols differing in the level of effort on the ocular accommodation and cardiovascular functioning.

To check whether participants attended to the laboratory under similar conditions, we conducted an one-way analysis of variance with the exercise-intensity (control, low-intensity, and high-intensity) as the only within-participants factor, and considering the level of alertness (Stanford Sleepiness Scale) reported by participants at the beginning of each experimental session, baseline heart rate and heart rate variability measures (RMMSD), as well as for the lag of accommodation measured before physical effort as the dependent variables. The success of the experimental manipulation was checked by a repeated measures analysis of variance, considering the exercise-intensity (control, low-intensity, and high-intensity) and the point of measure (sprint 1 to sprint 8) as the within-participants factors, and with ratings of perceived exertion and heart rate as the dependent variables.

The main set of analyses aimed to assess the effect of physical exercise intensity on the dynamic accommodative function (lag of accommodation). To do it, a two-way analysis of variance with the intensity (control, low-intensity, and high-intensity) and the time-on-task (blocks: 1, 2, 3, 4 and 5) as the within-participants factors was carried out for the changes in the lag of accommodation (post-exercise minus pre-exercise) as well as for the changes in the RMSSD component of heart rate variability (post-exercise minus pre-exercise). We also calculated the Pearson product-moment correlation coefficients (Pearson r) to explore the possible associations between the lag of accommodation and the heart rate variability at the different points of measure. The magnitude of the differences was also assessed through the Cohen's d for pairwise comparisons and the partial eta squared (η_p^2) for multiple comparisons. All statistical analyses were performed using JASP software (version 0.8.5.1). Statistical significance was set at an alpha level of 0.05, and post hoc tests were corrected using Holm-Bonferroni procedures.

Results

Firstly, we checked that the level of alertness ($F_{2, 38} = 0.755$, $p = 0.477$), the baseline heart rate variability measure ($F_{2, 38} = 0.408$, $p = 0.668$), and the measures of the main dependent variables obtained before physical effort were not different between the three experimental conditions ($F_{2, 38} = 0.067$, $p = 0.935$ for the lag of accommodation and $F_{2, 38} = 1.370$, $p = 0.266$ for the RMSSD component of heart rate variability). A successful exercise-intensity manipulation was confirmed by the analysis of heart rate and ratings of perceived exertion ($F_{2, 38} = 1596.52$, $p < 0.001$, $\eta_p^2 = 0.99$ for heart rate and $F_{2, 38} = 138.02$, $p < 0.001$, $\eta_p^2 = 0.88$ for ratings of perceived exertion), showing progressively higher values of heart rate and ratings of perceived exertion as the exercise intensity increased (Table 1).

A two-way analysis of variance for the changes in the lag of accommodation revealed significant differences for the intensity ($F_{2, 38} = 7.875$, $p = 0.001$, $\eta_p^2 = 0.293$), whereas the time-on-task and the interaction intensity x time-on-task did not reach statistical significance ($F_{4, 76} = 1.632$, $p = 0.175$; and $F_{8, 152} = 0.751$, $p = 0.646$; respectively). Post-hoc comparisons demonstrated greater lags of accommodation for the high-intensity condition compared to the low-intensity (corrected p-value = 0.006, d = 0.798) and control condition (corrected p-value = 0.007, d = 0.741) after physical effort. However, there was no statistical difference between the control and low-intensity conditions (corrected p-value = 0.598, d = 0.12) (Figure 7 and Table 2).

Table 1. Differences in subjective responses, ocular and cardiovascular measures before and during physical effort across experimental sessions.

	Control	Low-fatigue	High-fatigue	p-value
Baseline				
Level of alertness (SSS)	2.2 ± 0.52	2.15 ± 0.67	2.00 ± 0.56	0.477
HRV (RMSSD [ms])	76.0 ± 12.8	74.9 ± 12.3	75.8 ± 12.7	0.668
Pre-exercise 10-min task				
Lag of accommodation (D)	0.74 ± 0.29	0.72 ± 0.46	0.71 ± 0.39	0.935
HRV (RMSSD [ms])	64.9 ± 38.2	67.0 ± 41.2	61.9 ± 29.2	0.844
During physical effort				
Heart rate (bpm)**	83.2 ± 5.2	141.2 ± 5.3	158.1 ± 4.1	< 0.001
Perceived exertion (RPE)**	0.26 ± 0.3	4.67 ± 1.53	5.34 ± 1.64	< 0.001

Note: ** indicates p-values < 0.001. SSS = Stanford Sleepiness Scale; HRV = heart rate variability; RMSSD = root mean squared successive difference; ms = milliseconds; D = dioptres; bpm = beats per minute; RPE = ratings of perceived exertion.

The RMSSD component of heart rate variability demonstrated a statistically significant effect for the intensity ($F_{2, 38}$ = 38.463, p < 0.001, η_p^2 = 0.669), whereas no statistically significant differences were found for the time-on-task ($F_{4, 76}$ = 1.685, p = 0.162) and the interaction intensity x time-on-task ($F_{8, 152}$ = 1.060, p = 0.394). Post-hoc comparisons exhibited statistically significant differences for the high-intensity vs. control (corrected p-value < 0.001, d = 1.41) and the low-intensity vs. control (corrected p-value < 0.001, d =1.57), whereas no significant differences were found between the high-intensity and low-intensity conditions (corrected p-value = 0.443, d = 0.175) (Figure 8 and Table 2).

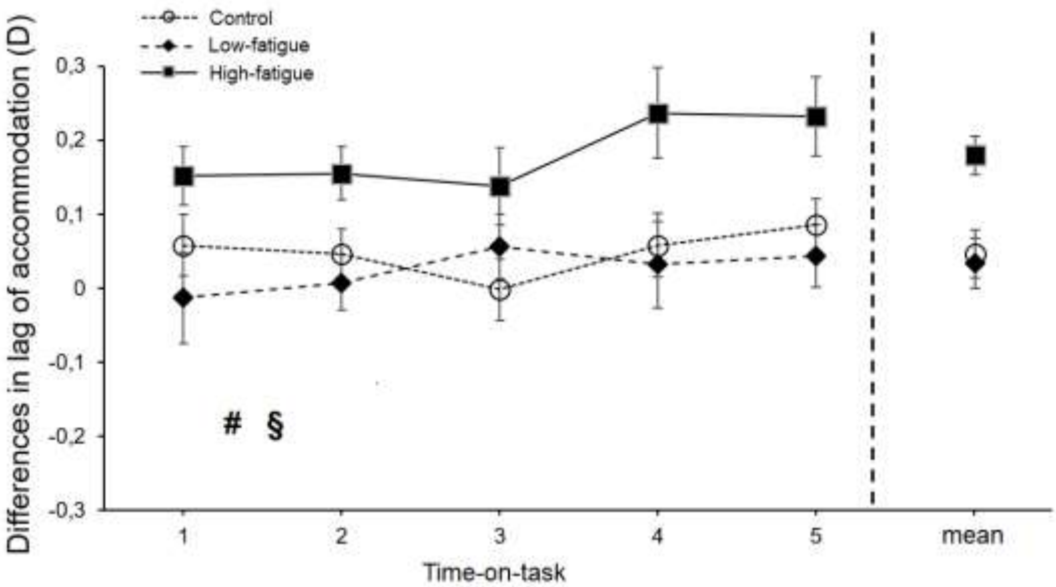

Figure 7. Effects of physical effort on the lag of accommodation in diopters (D). Differences are calculated as post-exercise minus pre-exercise values of accommodative lag at each of the five 2-min blocks from the 10-min visual task and the average value of accommodative lag for the complete 10-min visual task. Error bars represent the standard error. All values are calculated across participants (n = 20).

Finally, we conducted separate Pearson correlations between the values of lag of accommodation and RMSSD measured after exercise, considering the mean value from the 10-min visual task, as well as the five 2-min blocks, however, no statistically significant correlations were found at any point of measure (all p-values > 0.05). Additionally, the same procedure was carried out, but considering the differences between the accommodative response and heart rate variability values obtained before and after each experimental condition. Again, the level of correlation did not reach statistical significance (all p-values > 0.05).

Table 2. Descriptive values (mean ± standard deviation) of lag of accommodation and heart rate variability during the five blocks of 2-minute measured before and after each high-intensity interval-training protocol

			Block 1	Block 2	Block 3	Block 4	Block 5
Lag of accommodation (D)	*Pre-effort*	*Control*	0.66 ± 0.34	0.66 ± 0.31	0.64 ± 0.28	0.64 ± 0.26	0.65 ± 0.27
		Low-intensity	0.73 ± 0.39	0.65 ± 0.36	0.62 ± 0.42	0.65 ± 0.33	0.64 ± 0.31
		High-intensity	0.63 ± 0.29	0.65 ± 0.33	0.66 ± 0.28	0.64 ± 0.27	0.65 ± 0.29
	Post-effort	*Control*	0.71 ± 0.25	0.70 ± 0.27	0.64 ± 0.30	0.70 ± 0.27	0.73 ± 0.30
		Low-intensity	0.71 ± 0.39	0.66 ± 0.40	0.68 ± 0.38	0.68 ± 0.40	0.69 ± 0.38
		High-intensity	0.78 ± 0.36	0.80 ± 0.30	0.80 ± 0.34	0.87 ± 0.41	0.88 ± 0.37
HRV (RMSSD [ms])	*Pre-effort*	*Control*	57.24 ± 29.39	50.87 ± 31.31	54.09 ± 31.37	55.02 ± 23.96	50.93 ± 23.96
		Low-intensity	55.22 ± 29.17	54.12 ± 29.15	53.12 ± 29.97	49.34 ± 28.28	52.70 ± 29.04
		High-intensity	49.09 ± 20.29	48.49 ± 25.73	47.51 ± 24.36	45.66 ± 22.50	44.18 ± 21.53
	Post-effort	*Control*	61.55 ± 31.40	62.73 ± 35.22	58.95 ± 30.78	59.13 ± 33.07	57.31 ± 26.99
		Low-intensity	10.32 ± 5.46	10.55 ± 5.51	10.55 ± 5.99	9.92 ± 4.87	11.52 ± 6.91
		High-intensity	7.46 ± 3.54	7.86 ± 3.66	7.77 ± 3.93	7.12 ± 3.14	8.35 ± 5.18

Note: HRV = heart rate variability; RMSSD = Root mean square of successive R-R interval differences; D = diopters, ms = milliseconds.

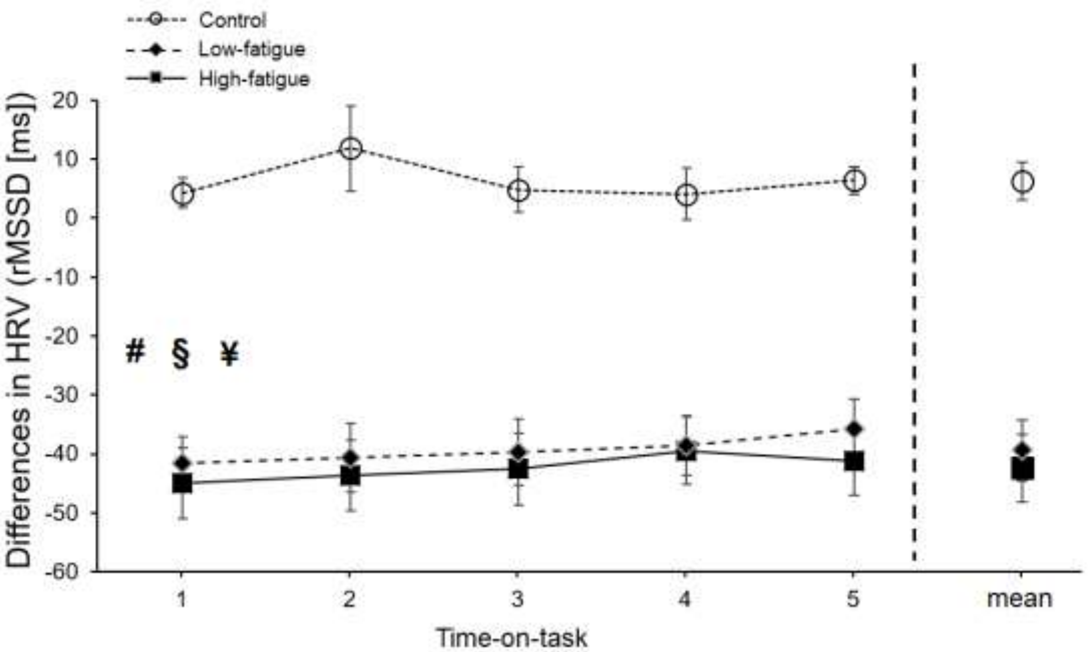

Figure 8. Effects of physical effort on the root mean squared of successive differences (RMSSD) component of heart rate variability (HRV) in milliseconds (ms). Differences are calculated as post-exercise minus pre-exercise values of RMSSDD at each of the five 2-min blocks from the 10-min visual task and the average value of accommodative lag for the complete 10-min visual task. Error bars represent the standard error. All values are calculated across participants (n = 20).

Discussion

We aimed to test the acute impact of two high-intensity interval-training protocols with different physical requirements (low and high-intensity) on dynamic, binocular and free-viewing ocular accommodation, as well as the possible links between ocular accommodation changes and the autonomic function measured by means of the heart rate variability. Our results demonstrated that accommodative response varied as a function of exercise-intensity, with higher lag of accommodation values (lower accommodative response) after the high-intensity interval-training protocol compared to the low-intensity interval-training protocol and control condition. Complementarily, heart rate variability was also sensitive to high-intensity interval-training, showing lower heart rate variability values with higher exercise intensity (high-intensity < low-intensity < control). However, we found that the behaviour of both indices was not significantly correlated. This set of data indicates that highly demanding physical effort impairs ocular accommodation, causing an increased lag of accommodation, which may alter performance in applied settings. These accommodative response changes may be explained by arousal-based effects, as it has been previously evidenced by the variation of individuals' level of activation in mental and driving tasks (Davies et al., 2005; Vera et al., 2016).

First, we checked a successful experimental manipulation by confirming that participants attended the lab under similar conditions (Stanford Sleepiness Scale and baseline heart rate variability), and the pre-exercise measures (accommodative response and heart rate variability) during the 10-min visual task were comparable across experimental sessions. These indices were far from showing any significance, and thus, it permits us to control possible confounding factors. Additionally, exercise-intensity manipulation was controlled by the analysis of heart rate during physical effort, as well as by ratings of perceived exertion values. As expected, both variables increased with higher exercise intensity, demonstrating different physiological and subjective responses depending on exercise intensity (Table 1).

Our first hypothesis was partially confirmed since ocular accommodation changes were dependent on exercise-intensity. This finding converges with the assumption that very demanding physical effort may induce poorer performance than at rest, thus revealing an inverted-J effect, whereas when the stressor is purely psychological promotes an inverted-U effect. The inverted-J and inverted-U effects reveal that performance depends on the level of activation. However, different activities require different levels of activation for optimal performance and, thus, this relationship is task-dependent (e.g., physical, mental or a combination of both) (Dickman, 2002). In particular, the inverted-U theory postulates that certain level of arousal is beneficial for performance, while extreme levels of activation (very low or high) decrease performance. For its part, the inverted-J effect indicates that performance is reduced at very high levels of activation, which has been commonly described for physical tasks (McMorris et al., 2015). The lack of effect on the accommodative response after performing the less physically demanding protocol is somewhat surprising, since moderate physical exercise is known to increase the concentration of dopamine and norepinephrine, moderately raise physiological arousal levels, and improve motor unit coordination and contractile function (Lambourne & Tomporowski, 2010; McMorris et al., 2015), being this last especially relevant for an accurate function of the ciliary muscle, and thus, for ocular accommodation (McDougal & Gamlin, 2015). For example, a recent study by Kujach et al., (2018) demonstrated that sedentary individuals improved their executive function after performing a high-intensity interval-training session at 60% of maximal aerobic power, which was linked with the activation of the left-dorsal-lateral prefrontal cortex. Nevertheless, the previous literature has been mainly focused on cognitive and executive performance (Mcmorris & Hale, 2012), and multiple circumstances such as the lack of individualized exercise intensity, the fact that the effects of high-intensity interval-training exercise on sensory performance has not been investigated to date, or the non-existent evidence of the impact of physical exercise on the ocular accommodation may explain these novel outcomes. The high-intensity condition clearly showed a detrimental effect on the dynamics of ocular accommodation after physical effort, and although its clinical significance may be modest, it may be of relevance in tasks requiring a sustained accurate accommodative functioning, especially at near viewing distances (e.g., occupational settings, viewing a smartphone, etc.). This finding agrees with the related research in the area of cognition, supporting a negative effect of highly intense exercise (Mcmorris & Hale, 2012; McMorris et al., 2015). The changes found for ocular accommodation are important since small increments in the accommodative lag have been linked to visual discomfort (Koulieris, Bui, Banks, & Drettakis, 2017), being these effects more significant at closer viewing distances (Rosenfield, 2011). Relevantly, the execution of highly demanding exercise promotes an excessive concentration of catecholamines and the dysfunction the hypothalamo–pituitary–adrenocortical axis, which are known to play a major role in the control of the ocular dynamics (Arnsten, 2009; Dos Santos Júnior et al., 2015; Neuhuber & Schrödl, 2011). Moreover, we can state from our results that high-intensity interval-training induces an inverted-J effect on the accommodative response, showing no effects of the low-intensity condition whereas the high-intensity protocol caused an acute increase on the lag of accommodation.

The effects of physical effort on the cardiovascular function are well-known, exhibiting higher values of heart rate and lower of heart rate variability as exercise intensity increases and it was corroborated in the present investigation (Kaikkonen, Nummela, & Rusko, 2007). However, heart rate variability was included to explore the association between the ocular accommodation and cardiovascular functioning after performing two high-intensity interval-training protocols differing in the level of effort. Here, we did not find any significant correlation between them. Although these variables have been found to be significantly correlated during cognitive processing (Davies et al., 2005), the lack of association when incorporating physical demands may be explained by the fact that physical effort disrupts the autonomic nervous system balance that is reflected in heart rate variability (Hautala, Kiviniemi, & Tulppo, 2009). Notably, ocular accommodation is directed by the ciliary muscle, which is innervated by the dual action of the sympathetic and parasympathetic branches of the autonomic nervous system and an anomalous autonomic input leads to inaccurate accommodative responses (McDougal & Gamlin, 2015). In this sense, Davies, Wolffsohn, & Gilmartin, (2009) found that the alteration of the accommodative demands modifies the cardiovascular function, and also observed that ocular accommodation correlates with the parasympathetic autonomic innervation during a cognitive task (Davies et al., 2005). A similar result was found by Vera et al., (2017) when considering intraocular pressure, who reported an association between this ocular variable and the autonomic cardiovascular control during the execution of a mental workload task. Physical and mental efforts are known to induce specific physiological changes (Marcora, Staiano, & Manning, 2009). The fatigue induced by physical effort is caused by the complex interaction of multiple peripheral physiological systems and the brain. Particularly, it should be noted that the effects of high-intensity interval-training on the human physiology are still not well understood (Laursen & Jenkins, 2002). The lack of association between ocular accommodation and heart rate variability observed in the present study may be explained by the different physiological mechanisms involved in predominantly physical and mental tasks.

Limitations and future research

The validity of our findings may be limited by several factors that should be acknowledged. First, as we failed to find any association between ocular accommodation and cardiovascular functioning after high-intensity interval-training , the assessment of brain areas, which play a role in controlling ocular accommodation (e.g., extrastriate cortex, parietal cortex, frontal eye fields, cerebellum or midbrain), may help to elucidate possible mechanisms underlying the influence of central nervous system alterations as consequence of physical exercise on ocular accommodation (McDougal & Gamlin, 2015). We assessed ocular accommodation in a pre/post manner, with the post-exercise measure obtained after 2 minutes of recovery. Further studies should explore the impact of physical fatigue during exercise on the ocular accommodation and cardiovascular function, as well as the possible association between them. In the present study, we assessed ocular accommodation while participants were performing a sustained attention task. In this regard it should be noted that the inclusion of tasks with different viewing demands (e.g., size, colour, contrast, attentional requirements, time of presentation, etc.) may also alter the present results. Participants´ characteristics (sex or fitness level), exercise type, variables assessed, or the points of measure may also influence the results of the present study and, therefore, our results must be cautiously interpreted in this regard. The inclusion of other ocular indices may be of interest to elucidate the influence of physical effort on the ocular physiology. For example, the assessment of choroidal thickness, which is the ocular structure with the highest blood flow, could help to clarify the ocular accommodation changes as consequence of physical efforts (Wylegala, 2016). Lastly, previous studies have found that adults with progressing and stable myopia exhibit different accommodative responses at near (Schmid & Strang, 2015), and consequently, future investigations are needed with this population. We consider that the effects of physical effort on the ocular functioning may have an impact on task performance in applied contexts, especially in activities performed at near working distances (e.g., computer work, reading, etc.). It is our hope that the effects of physical effort on visual performance during real-world situations will be tested in future investigations.

Conclusions

In summary, ocular accommodation is sensitive to physical effort depending on exercise-intensity, obtaining a higher lag of accommodation after performing the most demanding high-intensity interval-training protocol. Overall, this finding corroborates and expands the evidence about the effects of exercise on sensory functioning, and particularly on the accommodative function, based on the arousal theory. High-intensity interval-training induces changes on heart rate variability, but these variations are independent of ocular accommodation. Our results incorporate novel insights into the capacity of the visual system to reflect the nervous system´s activation changes caused by physical effort, which may have important applications when performing near tasks after highly demanding physical activities.

STUDY II: ACUTE EFFECTS OF CAFFEINE ON DYNAMIC ACCOMMODATIVE RESPONSE AND PUPIL SIZE: A PLACEBO-CONTROLLED, DOUBLE-BLIND, BALANCED CROSSOVER STUDY.

Introduction

Caffeine is the most widely consumed psychoactive drug (Barone & Roberts, 1996). It is rapidly distributed throughout the body, increasing energy metabolism in the brain at the same time that decreases cerebral blood flow (Einöther & Giesbrecht, 2013). Caffeine predominantly acts on the cerebral circulation as an adenosine antagonist, which is a central nervous system modulator that generates neural and vascular effects (Ferré, 2008). Also, it is well known that caffeine generates also ergogenic effects on cognitive performance (Jarvis, 1993), and has demonstrated to alter human behaviour (Childs & De Wit, 2006). The ingestion of caffeine produces different physiological adaptations such as blood pressure rise as a result of a greater vascular resistance of the vessels, increased myocardial stimulation, and reduced heart rate and tone of smooth muscle (Vural, Kara, Sayin, Pirhan, & Ersan, 2014).

In addition to these physiological responses induced by acute caffeine intake, direct vasoconstriction of several intracranial arteries such as ophthalmic, central retina and short posterior ciliary arteries has been described, altering the ocular physiology(Terai, Spoerl, Pillunat, & Stodtmeister, 2012). Indeed, the acute consumption of caffeine has demonstrated to alter a wide range of ocular indices such as blood flow in the optic nerve head (Okuno et al., 2002), choroidal thickness (Okuno et al., 2002; Vural et al., 2014), intraocular pressure (Li, Wang, Guo, Wang, & Sun, 2011), tear formation (Arita et al., 2012), ocular aberrations (Bardak, Gunay, Mumcu, & Bardak, 2016), eye movements (Connell et al., 2017), visual processing (Coren, 2002), pupil size (Bardak et al., 2016) and accommodative function (Abokyi, Owusu-Mensah, & Osei, 2016) among others. The physiological mechanisms underlying caffeine effects on the visual system have been commonly explained by the bidirectional relationship between ocular functioning and the parasympathetic and sympathetic branches of the autonomic nervous system (McDougal & Gamlin, 2015). In this regard, caffeine as a stimulant of the central nervous system (Nehlig, Daval, & Debry, 1992), promotes physiological variations by the activation of the sympathetic branch (Corti et al., 2002), at which different ocular indices (i.e., intraocular pressure, oculomotor system, accommodative response) have demonstrated to be sensitive (Vera, Jiménez, García, & Cárdenas, 2017).

In relation to accommodative function, Abokyi et al., (2016) found that ingesting a caffeinated drink of 250 mg increased the amplitude of accommodation in comparison to placebo consumption, these effects being probably mediated by the stimulation of the autonomic nervous system (Nehlig et al., 1992). However, these authors analysed the monocular amplitude of accommodation by the push-up technique, and despite this method is widely used in clinical practice, there is no agreement on its accuracy in research settings due to its subjectivity (Anderson & Stuebing, 2014; Antona, Sanchez, Barrio, Barra, & Gonzalez, 2009). In addition, the assessment of the amplitude of accommodation allows to determine the maximum potential increase in optical power terms that an eye can achieve in adjusting its focus to the closest possible target, whereas the accommodative response is a measure of the accuracy of the accommodative system, which is defined as the ocular ability that allows people to perceive clear at different distances as long as the response is gain in ~70% of the demand (Millodot, 2014; Roberts, Anderson, & Stuebing, 2015). The clinical relevance of accommodative response relies on its implication when focusing on all distances, whereas the amplitude of accommodation is only relevant when looking at extremely near targets, and thus, the importance of an increased amplitude of accommodation is somewhat limited. Importantly, the autonomic control of accommodative response is predominately mediated by parasympathetic innervation, but also by the sympathetic activity (Gilmartin, Mallen, & Wolffsohn, 2002; Mallen, Gilmartin, & Wolffsohn, 2005; Winn, Culhane, Gilmartin, & Strang, 2002). An increase in parasympathetic innervation produces a rapid and substantial positive accommodation, while sympathetic innervation acts much slower to produce hyperopia (McDougal & Gamlin, 2015). The balance of the neural integrator of accommodation determines the accuracy of accommodative response (Gilmartin et al., 2002; McLin, Schor, & Kruger, 1988). Also, when focusing on a stationary target accommodative response is constantly varying over time with a temporal instability of about ± 0.5 D, aiming to maintain the accommodative response and obtain directional cues for the dynamic accommodative response (Charman & Heron, 2015). This characteristic is termed accommodation variability, and it is produced as a combination of neurological control and physiological rhythmic variations (Winn, 1992), being termed as variability or microfluctuations of accommodative response (Charman & Heron, 2015). Previous studies have proved that the accommodative response is sensitive enough to suffer alterations under increasing cognitive demand or changes in the level of arousal due to mental fatigue (Bullimore & Gilmartin, 1987; Davies et al., 2005; Francis, Jiang, Owens, & Tyrrell, 2003; Kruger, 1980; Roberts et al., 2018), predominantly attributable to variations of the autonomic nervous system activity (Davies et al., 2005; Vera et al., 2016). Even though it is well established that caffeine stimulates the autonomic nervous system, the potential impact of caffeine intake on the dynamics of the accommodative response remains unclear (Yoon & Danesh-Meyer, 2018).

As stated above, effects of caffeine on autonomic nervous system activity are well known (Corti et al., 2002), and thus, it is plausible to expect that the accommodative response, which is dependent of autonomic nervous system innervation, may be altered by caffeine intake. To assess the possible impact of acute caffeine consumption on accommodative response, we objectively measured the accommodative response after ingesting either a caffeine or placebo capsule using a binocular open-field autorefractometer (WAM-5500 Grand Seiko Co., Ltd., Hiroshima, Japan), which has demonstrated to be an accurate tool for quantifying the accommodative response (Sheppard & Davies, 2010). The main objectives of this placebo-controlled, double-blind, balanced crossover study were to evaluate the acute effect of caffeine consumption on the lag and variability of accommodation (Sheppard & Davies, 2010). In addition, given the accommodation-pupil synkinesis in near response (Kaufman, Levin, Adler & Alm, 2011), we explored the influence of caffeine intake on pupil diameter. To check the effectiveness of caffeine/placebo manipulation, participants reported their subjective levels of activation. Based on the available literature, we hypothesized that lag of the accommodative response and pupil size would increase in the caffeine condition (Abokyi et al., 2016), whereas accommodative variability would decrease as a consequence of a higher sympathetic activation after consuming caffeine (Charman & Heron, 2015). We expect that participants perceive higher levels of activation after caffeine consumption (Nehlig et al., 1992).

Methods

The protocol was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the University Institutional Review Board (IRB approval: 438/CEIH/2017).

Participants

Twenty-two (10 women and 12 men) healthy undergraduate students were recruited to participate in this study. The experimental sample had an age range between 18 and 28 years (mean age ± standard deviation [SD]: 21.68 ± 3 .67 years old) and a weight range between 50 and 84 kg (mean weight ± standard deviation [SD]: 66.70 ± 9.84 kg). The habitual caffeine intake of the participants ranged between 0 and 4 cups of caffeine per day (mean consumption ± standard deviation [SD]: 0.74 ± 1.19 cups per day). At the initial visit, a board certified optometrist performed an optometric examination which included: distance and near monocular and binocular best-corrected visual acuity, objective refraction using the Grand Seiko WAM-5500 autorefractometer (Grand Seiko Co. Ltd., Hiroshima, Japan), monocular and binocular non-cycloplegic subjective refraction, accommodative push-up amplitude, monocular and binocular accommodative facility using ± 2.00D flippers at 40cm, near and distance horizontal and vertical phoria measured by the Thorington's method, negative and positive fusional vergence at 40cm and far using a prism bar, near point of convergence, and near stereoacuity with the Randot Stereotest (Stereo Optical Company, Chicago, Illinois). Binocular and accommodative test procedures and normative values followed the recommendations of Scheiman & Wick (2008). The inclusion criteria considered to participate in this study were: (1) have a corrected visual acuity ≤ 0.00 logMAR (20/20 Snellen) in each eye, (2) present low visual discomfort (cut-off value<24) as measured by the Conlon survey (Conlon et al., 1999), (3) be free of strabismus, amblyopia or any ocular disease, (4) have a near stereoacuity better than 50 seconds of arc, and (5) have an uncorrected spherical equivalent refractive error lower than ±1D. All participants were no smokers and they had no history of cardiac arrhythmia, peptic ulcer disease, liver or kidney damage, allergy to xantic basis, insomnia, pregnancy or breastfeeding (Grosso, Godos, Galvano, & Giovannucci, 2017).

Accommodative response assessment

For the study of dynamic accommodation, we objectively measured the lag and variability of accommodation using the clinically validated Grand Seiko WAM-5500 open field autorefractometer in binocular conditions and hi-speed mode, which offers continuous recording at a rate of ~5Hz (Sheppard & Davies, 2010). Data were recorded in binocular conditions from the dominant eye which was determined by the hole-in-the card method (Momeni-Moghaddam et al., 2014), and the accommodative response and pupil were recorded with a sensitivity of 0.01D and 0.1mm, respectively. Subjects were seated at the instrument with their head stabilized in the chin rest and forehead strap and were aligned with the fixation target which was positioned in the participant's gaze midline. Participants maintained in focus a high-contrast (Michelson=79%) five-point back star on a white background target at six viewing distances (5m, 50cm, 40cm, 33cm, 25cm and 20cm) during a time period of 2 min for each one. The order of the distances measured was randomized, and 3-min breaks between measurements were established in order to avoid the presence of tonic accommodation (Lin, Lin, & Chen, 2016). After 30 minutes of caffeine/placebo ingestion, we first performed a monocular static refractive measure at far in both compensated eyes (baseline refractive value), and subsequently, the assessment of dynamic accommodative response at the differences tested was carried out. The base luminance of the target was 31cdm−2, and the experimental room illuminance was ~ 150lx.

For the elimination of blinking or recording errors, we identified and removed data points of ± 3 standard deviations from the mean spherical refraction value (Tosha, Borsting, Ridder, & Chase, 2009). Then, we obtained the values of pupil size and accommodation from the remaining data. Following the equation proposed by Poltavski et al., (2012), the lag of accommodation was calculated by subtracting the mean value from the dynamic measures and the baseline static refractive value obtained in far distance to the accommodative demand at each distance. The standard deviation during each dynamic AR measurement was considered for the variability of accommodation.

Subjective questionnaires

At the beginning of each experimental session, participants completed the Stanford Sleepiness Scale, which assess the subjective level of alertness/sleepiness (Hoddes, Zarcone, & Dement, 1972). This scale contains seven statements ranging from 1 "Feeling active, vital, alert, or wide awake" to 7 "No longer fighting sleep, sleep onset soon, having dream-like thoughts", and participants have to indicate which statement reflects their actual state. After 30 minutes of caffeine/placebo ingestion, we asked participants to complete a visual analogue scale in order to evaluate their subjective level of activation (0 absolutely not activated and 10 extremely activated).

Procedure

The experiment was conducted in three separate sessions, which were performed on different days and were scheduled at the same time of day (±1h). In the first session, the optometric examination was performed to exclude those participants who did not fulfil the inclusion criteria, and also, we asked participants to report their daily consumption of caffeine. Participants were asked to wear their soft contact lenses when necessary, and they were used in the different experimental sessions. Before attending the laboratory, participants were instructed to sleep at least 7 hours the night prior testing, to avoid the practice of intense physical activity 2 days prior the testing session, as well as alcohol and caffeine-based drinks 24 h and 12 h before each experimental session, respectively.

A pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) prepared the caffeine-containing capsules (caffeine anhydrous and corn-starch) and placebo capsules (corn-starch), the contents of which were certified safe for human consumption. Both capsules (placebo and caffeine) had an identical colour, size and shape, and thus, they were indistinguishable. In the main experimental sessions, a capsule of caffeine (4mg/kg of caffeine plus 20mg of corn-starch) or placebo (300mg of corn-starch) along with 100ml of tap water was orally administrated in a counterbalanced order. Caffeine capsules were available in steps of 20mg, and thus, participant´s weight was rounded up in steps of 5kg in order to choose the amount of caffeine used by each individual. The amount of caffeine given to the participants ranged between 200 mg to 340 mg (mean caffeine ± standard deviation [SD]: 243.18 ± 87.94 mg). Aiming to accomplish the double-blind procedure, the capsules were prepared and coded by a third person. After caffeine or placebo consumption, participants were allowed to rest during 30 minutes in order to reach a considerable plasma concentrations of caffeine (Mort & Kruse, 2008).

Statistical analysis

A Shapiro-Wilk test and Levene's test were performed to assess the normality of data and the equality of variance, respectively (p>0.05). Aiming to check possible differences in the level of alertness/sleepiness at the beginning of both experimental sessions, a t-test for related samples was performed for the Stanford Sleepiness Scale survey. Also, a t-test for related samples with caffeine consumption (placebo, caffeine) as the only within-participants factor was carried out for the perceived level of activation reported by participants after 30 minutes of ingesting either caffeine or placebo. For the main statistical analyses, separate two-ways repeated measures analyses of variance with caffeine consumption (placebo, caffeine) and target distance (far, 50cm, 40cm, 33 cm, 25 cm, y 20 cm) as the within-participant factors, and using the measures of the accommodative response (lag and variability) and pupil diameter as the dependent variables, were performed. Multiple comparisons were corrected using the Holm-Bonferroni procedure. Statistical significance was set at 0.05, and standardised effect sizes were reported by means of the partial η^2 for Fs and the Cohen's d for t tests. All statistical analyses were carried out using the JASP software (version 0.9.0.1).

Results

Manipulation check and caffeine effects on subjective activation

First, we analysed the perceived level of alertness/ sleepiness at the beginning of each experimental session by the Stanford Sleepiness Scale survey. Our analysis revealed no statistically significant differences between both experimental sessions (p=0.815), confirming that participants came to the laboratory under similar conditions. Then, the perceived level of activation demonstrated higher values in the caffeine condition in comparison to the placebo condition (p=0.047, Cohen´s d=0.48) (see Table 3).

Influence of caffeine consumption on pupil size

The main effects of caffeine consumption ($F_{1,21}$=7.812, p=0.011, η^2=0.271) and accommodative distance ($F_{5,105}$=33.305, p<0.001, η^2=0.613) yielded statistical significance, obtaining larger pupil sizes in the caffeine condition in comparison to the control condition, as well as smaller pupil sizes at closer distances. The interaction caffeine consumption x target distance was far from showing any significance ($F_{5,105}$<1) (see Figure 9). Post hoc analysis showed no significant difference between caffeine and placebo comparisons in each target distance (corrected p-value>0.05).

Table 3. Subjective perceived level of arousal and activation response measured before and after the caffeine or placebo intake.

	Placebo Mean (SD)	Caffeine Mean (SD)	p-value
Baseline			
Stanford Sleepiness Scale (1-7)	2.05 (0.90)	2.09 (0.81)	0.815
After 30 min of capsule ingestion			
Level of activation (0-10)	6.64 (1.99)	7.55 (1.84)	0.047*

Note. *SD* = standard deviation, * denotes significant differences between groups (p <0.05).

Influence of caffeine consumption on lag of accommodation

The lag of accommodation shows statistically significant differences for the target distance ($F_{5,105}$=419.780, p<0.001, η^2=0.977), showing higher lags of accommodation at closer distances. However, caffeine consumption and the interaction caffeine consumption x target distance did not reach statistical significance ($F_{1,21}$=1.090, p=0.321; and $F_{5,105}$=0.412, p=0.838; respectively) (see Figure 10). Post hoc analysis showed no significant differences for the lag of accommodation between caffeine and placebo comparisons for each target distance (corrected p-values>0.05)

Influence of caffeine consumption on variability of accommodative response

The analysis of variability of the accommodative response showed statistically significant differences for the main factors caffeine consumption ($F_{1,21}$=5.625, p=0.027, η^2=0.211) and target distance ($F_{5,105}$=101.683, p<0.001, η^2=0.829), as well as for the interaction caffeine consumption x target distance ($F_{5,105}$=4.342, p<0.001, η^2=0.171). Caffeine ingestion provoked a better stability of accommodation (lower variability of accommodation) when compared with the consumption of placebo, and, greater variability of accommodation was found at closer target distances (see Figure 11). No significant differences were found in the post-hoc comparisons (corrected p-value>0.05) between caffeine and placebo conditions at each target distance.

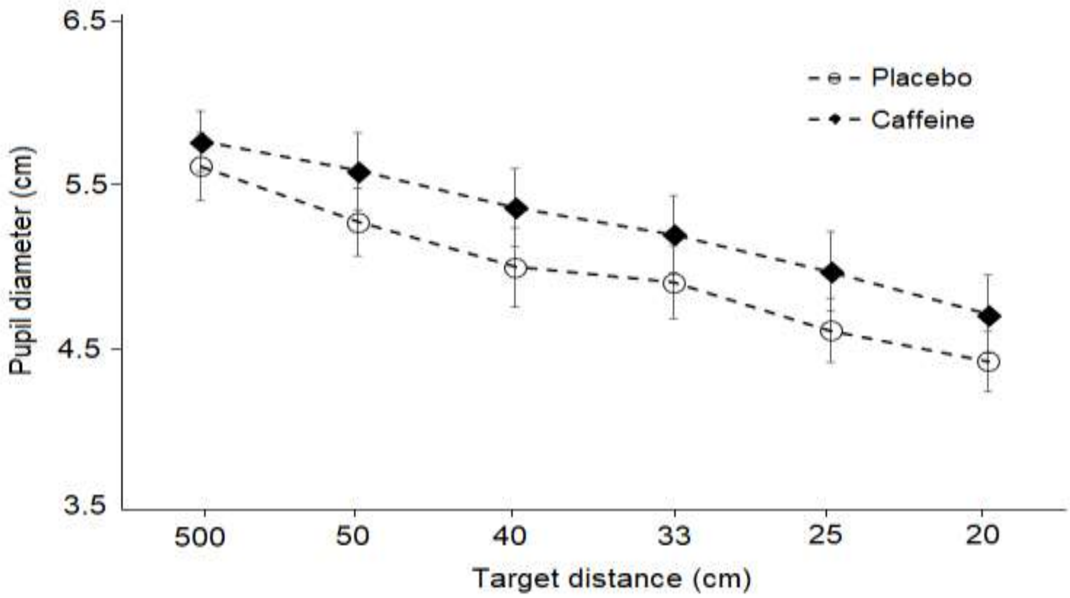

Figure 9. Pupil diameter after caffeine and placebo intake for the different target distances (500 cm, 50 cm, 40 cm, 33 cm, 25 cm, y 20 cm). Error bars show the standard error (SE). All values are calculated across participants (n = 22).

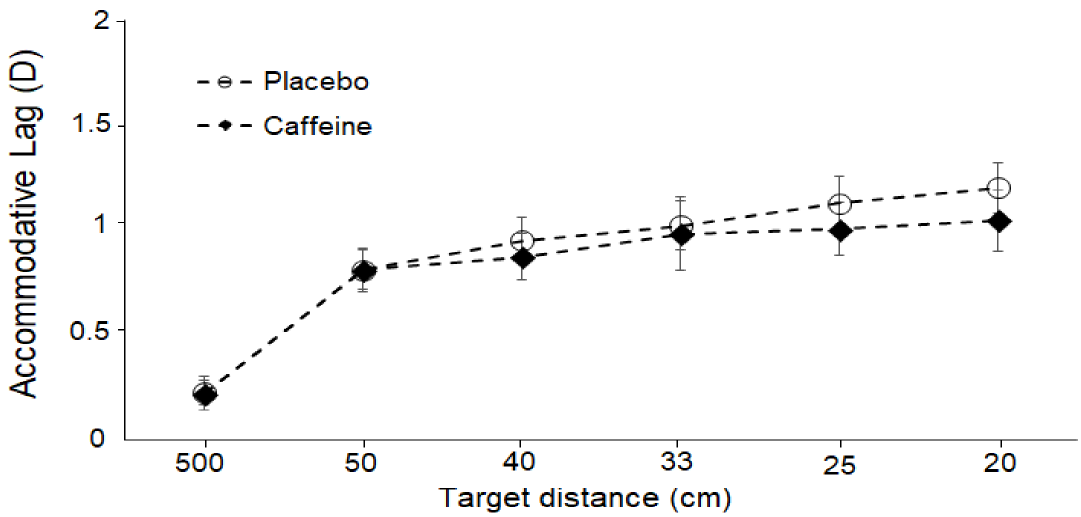

Figure 10. Accommodative lag after caffeine and placebo intake for the different target distances (500 cm, 50 cm, 40 cm, 33 cm, 25 cm, y 20 cm). Error bars show the standard error (SE). All values are calculated across participants (n = 22).

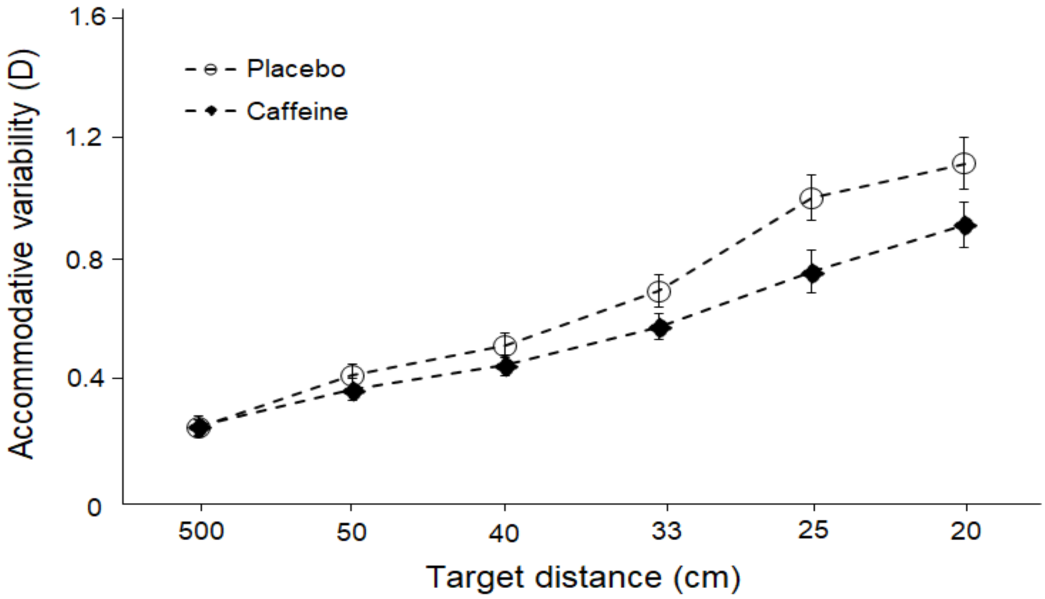

Figure 11. Accommodative variability after caffeine and placebo intake for the different target (500 cm, 50 cm, 40 cm, 33 cm, 25 cm, y 20 cm). Error bars show the standard error (SE). All values are calculated across participants (n = 22).

Discussion

Caffeine induces a variety of cardiovascular and central nervous system alterations, which have implications for human behaviour and performance (Childs & De Wit, 2006; Jarvis, 1993; Nehlig et al., 1992). The present study aimed to assess the acute effect of caffeine consumption on the visual system, specifically on the accommodative response, as well as its impact on pupil size and subjective activation. Our data showed, that under similar pre-experimental arousal conditions, participants reported higher levels of activation after caffeine consumption. We also found that pupil size increased as consequence of caffeine intake. In relation to the accommodative response, the lag of accommodation was insensitive to caffeine ingestion, whereas a more stable accommodative response (lower variability of accommodation) was induced by caffeine intake.

According to the subjective responses with the Stanford Sleepiness Scale, participants reported a similar level of alertness/sleepiness at the beginning of each session, allowing us to confirm an appropriate experimental control. Regarding the effect of caffeine on subjective feelings of activation, there is a general consensus that acute caffeine consumption causes an increase in perceived arousal/alertness (Nehlig et al., 1992). Our result, in accordance with this fact, indicate that the experimental manipulation was effective in inducing feelings of alertness since participants reported higher levels of activation after 30 min caffeine intake in comparison to the placebo condition.

In agreement with the scientific literature, pupil diameter decreased as the accommodative demand increased (Toates, 1972). In addition, we found that caffeine induced a mydriatic effect, with a pupil size increment of 5.12% when participants consumed caffeine in comparison to placebo. Although studies on the effect of caffeine on pupil size are inconsistent, our result is in line with Abokyi et al., (2016), who showed pupil dilation after the consumption of a 250mg caffeine drink. This finding may be explained by the fact that caffeine increases the excitability of the adenosine-sensitive sympathetic nervous system, and thus, heightened sympathetic innervation activity, which results in contraction of the iris dilator muscle, causing pupil dilation (Kardon, 2005). On the contrary, other studies have only found a mydriatic effect of caffeine in non-habitual caffeine consumers (Bolton, Feldman, Null, Revici, & Stumper, 1984), or even, did not find any changes on pupil size (Bardak et al., 2016). However, those studies used low caffeine doses (lower than 110mg of caffeine) or did not adjust the caffeine dose to participant´s weight, as we did in the current study, and thus, results from different studies should be cautiously compared.

Higher lags of accommodation have been linked to reduced attentional resources (Poltavski et al., 2012; Redondo et al., 2018), and since caffeine increases the ability to concentrate and focus attention (Glade, 2010), it seems reasonable to expect that caffeine would induce a higher accommodative response accuracy, namely, lower lags of accommodation. However, we failed to find any effect of caffeine manipulation at the six distances tested (5m, 50, 40, 33, 25, and 20cm) on the lag of accommodation. Our results are partially in contrast with previous studies, where caffeine ingestion induced changes on accommodation, specifically increasing amplitude of accommodation and decreasing the AC/A ratio (Abokyi et al., 2016; Zhai, Goss, & Hammond, 1993). However, despite those previously mentioned variables are related to the accommodative function, they reflect different accommodative skills, and thus, they are not interchangeable (Scheiman, & Wick, 2008). To the best of our knowledge, no studies have analysed the accuracy of accommodation under the effects of caffeine using objectives and valid instruments. Relevantly, we used an objective and validated research tool in the study of ocular accommodation (Sheppard & Davies, 2010), while the above mentioned studies employed subjective techniques, whose validity is limited for research purposes (Antona et al., 2009), and thus, our findings are solid in this regard.

We found preliminary evidence of a reduced variability of the accommodative response caused by caffeine intake. Accommodative variability occurs during steady-state viewing conditions as a result of the combination of central neurological control and physiological rhythmic fluctuations (Winn, 1992), and its function aims to maintain an accurate accommodation and obtain directional cues for dynamic the accommodative response (Charman & Heron, 2015). Numerous factors such as age, monochromatic aberrations, stimulus characteristics, participant´s ametropia, pupil size (e.g. smaller than 4 mm) (Atchison, & Charman, 1997), and mean focus state are known to vary the depth of focus (Le, Bao, Chen, He, & Lu, 2010), which may led to continuous adjustments of accommodation in an attempt to obtain a clearer image (Charman & Heron, 2015). Both pupil size and lag of accommodation have independent effects on the accommodative variability (Metlapally et al., 2016), with larger pupil sizes being associated with reduced variability of accommodation, while greater lags of accommodation are linked to higher variability of accommodation (Stark & Atchison, 1997). The relationship between lag and variability of accommodation is determined by which comparison has been made. Namely, when comparing the variability of accommodation between different accommodative demands, it has shown to increase at greater demands (Roberts, Manny, & Anderson, 2019), and also when comparing this variable at the same level of demand, the variability of accommodation increases when the lag of accommodation yields higher values (Roberts et al., 2018). Our data support previous studies since we found that caffeine ingestion induced higher pupil sizes in comparison to the placebo consumption, which has been associated with both reduced depth of focus and variability of accommodation (Lyle, Gray, & Winn, 1993; Yao et al., 2010). Thus, this mechanism of action may be responsible and justify the decrease found in accommodative variability.

A plausible physiological explanation

In this study, acute caffeine ingestion (~ 4mg/kg) did not modify the lag of the accommodative response, however, the variability of the accommodative response demonstrated to be sensitive to caffeine consumption. These effects may be explained by the impact of caffeine on the autonomic nervous system activity, which is responsible of ocular accommodation control (McDougal & Gamlin, 2015). As previously stated, caffeine blocks the adenosine receptors and stimulates a reflex activation of the sympathetic system (Corti et al., 2002; Einöther & Giesbrecht, 2013). The role of the sympathetic system in the control of accommodation is subtle in comparison to the parasympathetic innervation (Gilmartin, 1986), however, the sympathetic activity seems to complement the reflexive nature of the parasympathetic activity and slightly affects the dynamics of accommodation, having poor effects on the resting level or amplitude of accommodation (Gilmartin et al., 2002). These differences in the role of both autonomic nervous system branches may explain the lack of changes in lag of accommodation after caffeine consumption. Conversely, sympathetic innervation has been described as necessary to provide optimal accommodative gain across all temporal frequencies and attenuate the retention of accommodative tone induced by periods of intense close work (Gilmartin, 1986). It is reasonable to consider that this fact may have important implications on the variability of accommodation and explain why caffeine intake induces a better stability of accommodation.

Limitations and future research

A good knowledge of the physiological and functional effects of caffeine on the eye is crucial due to its widespread use. This study provides evidence on the effects of caffeine on accommodation and pupil, showing that caffeine increases pupil size and induces a more stable accommodative response. The current findings may be of interest in research and applied settings. However, there are several factors that may limit the generalizability of our findings, and they should be acknowledged. First, we have discussed different physiological mechanisms that may explain the present findings, however, future studies are needed to determine the role of caffeine on the human structures responsible of ocular accommodation control. We consider that the use of recent developments in ocular imagining techniques (e.g., anterior segment optical coherence tomography) would help to advance into the knowledge of the caffeine effects on the ocular physiology. Second, some physiological changes induced by caffeine have showed to be dependent on caffeine consumption habits (Corti et al., 2002; Grosso et al., 2017), and thus future studies should compare the impact of caffeine intake on the accommodative response and pupil size in high and low caffeine consumers. Third, visual fatigue is linked to the lag and variability of the accommodative response (Tosha et al., 2009), and we found that the variability of accommodation is sensitive to caffeine ingestion, thus, we consider of interest to test the possible effects of caffeine on visual fatigue by the inclusion of participants with visual discomfort or the design of experiments with prolonged near tasks. Fourth, the impact of caffeine on several physiological indices has showed a dose-response effect (Chen & Parrish, 2009), in which low or intermediate doses of caffeine are associated with positive effects (i.e. increase in arousal, concentration, performance), while high doses induce negative effects (i.e. nervousness, agitation) (Grosso et al., 2017). Additionally, peak plasma caffeine concentration is habitually reached between 15 and 120 min after oral ingestion, with a tendency for slightly faster times when lower doses are administered. Here, we choose an amount of caffeine (~4mg/kg) based on the estimations of mean daily caffeine consumption for United States habitual consumers (Barone & Roberts, 1996), and accommodative measures were assessed between 30-60 min after caffeine ingestion. Different doses of caffeine and time frame could lead to a different behaviour of the ocular variables and therefore, the manipulation of caffeine dose and time in future studies may help deepen the association between caffeine and ocular accommodation.

Conclusions

We found an acute effect of caffeine consumption on pupil size and accommodative function, specifically on variability of accommodative response. Our data showed that the ingestion of caffeine provoked a reduced variability of accommodation and induced a dilator effect on pupil size after 30 minutes of caffeine intake. However, we did not observe any effect of caffeine consumption on the lag of accommodation. These findings are in line with the effects of caffeine consumption mediated by binding adenosine receptors and stimulation of the sympathetic nervous system.

STUDY III. CAFFEINE ALTERS THE DYNAMICS OF OCULAR ACCOMMODATION DEPENDING ON THE HABITUAL CAFFEINE INTAKE

Introduction

Caffeine is considered the most widely consumed psychoactive stimulant (Rall, 1980), which acts on the central nervous system and certain portions of the autonomic nervous system (Barry, Clarke, Johnstone, & Rushby, 2008). Caffeine increases cortical arousal by serving as an antagonist to the inhibitory neurotransmitter of adenosine A1 receptors (Ferré, 2008). Also, it has proved to increase energy availability, decrease fatigue and sense of effort, increase alertness and concentration and enhance physical, motor and cognitive performance (Glade, 2010). Specifically, sustained attention (i.e., the capacity to respond to relevant stimuli and to effectively allocate attentional resources over prolonged periods of time), which is important in multiple cognitive abilities, living skills and responsible professional tasks (e.g., reading [Steinmayr, Ziegler, & Träuble, 2010], driving [Larue, Rakotonirainy, & Pettitt, 2011], performing surgery [Gawande, Zinner, Studdert, & Brennan, 2003]), is highly improved after ingesting a single dose of caffeine (Foxe et al., 2012).

Sustained near visual tasks involve both parasympathetic and sympathetic branches of the autonomic system to maintain a clear image of the target over time, showing a regulatory role on the synkinesis in the near response triad (pupil miosis, convergence and increased accommodation) (Gilmartin, 1986). However, the results of the effect of caffeine on pupil size are inconsistent. A recent study showed that caffeine induces pupil dilation (Abokyi et al., 2016), whereas significant miosis has been found in anesthetized rats when caffeine was topically applied (Kronschläger et al., 2014). Also, these effects have demonstrated to be dependent on the habitual caffeine intake, with greater pupil dilations in non-habitual caffeine consumers (Bolton et al., 1984). Regarding the accommodative-vergence response, the ingestion of caffeine has demonstrated to decrease the AC/A ratio (Zhap, Indian, & Service, 1993), and also, an increase in the magnitude of accommodation has been associated with caffeine intake (Abokyi et al., 2016). In addition, the dynamics of ocular accommodation have evidenced to be sensitive to mental efforts (Davies et al., 2005), in fact, it has been considered as a potential predictor of behavioural performance during sustained attention, since a worse performance has been linked with alterations in the accommodative-vergence system (Poltavski et al., 2012). However, the triangular relationship between caffeine consumption, accommodative response and behavioural performance has not been examined yet.

On the other hand, the habitual caffeine intake seems to modulate the acute behavioural and physiological effects of caffeine, possibly due to increased sensitivity of the subjects to endogenous adenosine (Nehlig et al., 1992). Correspondingly, the effective dosage to enhance cognitive processes depends on the habitual caffeine consumption, being necessary higher caffeine doses to reach substantial dopamine increases in high caffeine consumers (Brunyé et al., 2010). However, there is limited evidence of whether the effects of caffeine consumption on the ocular physiology are subject to tolerance. In this regard, a recent study of Vera et al., (2019) demonstrated a mediating role of caffeine habitual consumption on intraocular pressure, in which high caffeine consumers showed a less accentuated intraocular pressure rise in comparison to low caffeine consumers. To the best of our knowledge, there are no studies analysing the possible differences between low and high caffeine consumers on the accommodative response changes induced by acute caffeine ingestion.

To address the limitations found in the related literature, the main objectives of the present placebo-controlled, double-blind, balanced crossover study were (i) to explore the acute effect of caffeine intake on the dynamics of ocular accommodation (magnitude and variability of the accommodative response) during a sustained attention task, and (ii) to compare the possible differences on these effects between low (≤ one cup of coffee per day) and high (≥ three cups of coffee per day) caffeine consumers. Complementarily, subjective perceptions and behavioural performance were assessed. We hypothesized that (i) the dynamics of ocular accommodation would be more accurate and stable for the caffeine condition in comparison to placebo, as it has been previously demonstrated for the amplitude of accommodation (Abokyi et al., 2016), and (ii) the changes induced by caffeine may be subject to tolerance, as it has been demonstrated for other ocular variables (Vera et al., 2019). These results are expected to expand the knowledge regarding the accommodative response changes induced by caffeine intake, as its possible effects on behavioural performance.

Methods

Participants

Twenty-one young adults (mean age ± standard deviation: 21.6 ± 3.4 years) participated in this study and were divided according to their daily caffeine intake as low caffeine consumers (n = 10 [five women]; one or less cup of coffee per day) and high caffeine consumers (n = 11 [six women]; three or more cups of coffee day) (Kennedy & Haskell, 2011). All participants included in this study accomplished the following inclusion criteria: (i) be free of any systemic or ocular disease and no present history of strabismus, amblyopia or refractive surgery, (ii) not taking any medication, (iii) not presenting allergy to xanthines, (iv) have normal or corrected-to-normal vision (visual acuity of ≤ 0 logMAR in each eye), being compensated with soft contact lenses when necessary (contact lens habitual users with at least one year of experience) (v) have an uncorrected myopia < 0.50 D, hyperopia < 1.00 D, and astigmatism or anisometropia < 1.00 D, (vi) have an accommodative lag < 1.55 D at 20 cm (Wang & Ciuffreda, 2004), (vii) report low visual discomfort symptomatology based on the scores of the Conlon visual discomfort survey (< 24) (Conlon et al., 1999), and (viii) score < 4 on the Stanford Sleepiness Scale, which provides a global measure of sleepiness (Connor et al., 2002). Participants had no adverse symptoms associated with caffeine intake and were neither pregnant nor breast-feeding. The experimental protocol followed the guidelines of the Declaration of Helsinki, and was approved by the Institutional Review Board (IRB approval: 438/CEIH/2017).

Experimental design

The present study followed a placebo-controlled, double-blind, balanced crossover design in order to test the acute effects of caffeine ingestion on the dynamics of ocular accommodation (lag and variability of accommodation) in low and high caffeine consumers during a sustained attention task Psychomotor Vigilance Task. The within-participants factors were the *caffeine consumption* (placebo and caffeine) and *time-on-task* (five 2-min blocks: block 1, block 2, block 3, block 4, and block 5), whereas the between-participants factor was the *habitual caffeine intake* (low-consumers and high-consumers). The dependent variables were accommodative lag, accommodative variability, behavioural performance (reaction time), and subjective measures.

Accommodative response assessment

The Grand Seiko WAM-5500 open field autorefractometer (Grand Seiko Co. Ltd., Hiroshima, Japan) in hi-speed mode was used to assess the accommodative response. This apparatus has been clinically validated and records the dynamic accommodative response (magnitude and variability) in binocular conditions with a temporal resolution of 5 HZ and sensitivity of 0.01D (Sheppard & Davies, 2010). First, the baseline refractive value was obtained by the monocular static refractive measure in both corrected eyes while participants looked at a 5m stationary target, being these measurements used to calculate the lag of accommodation (see below). Then, we recorded the dynamic accommodative response from the dominant eye, evaluated by the hole-in-the card method (Momeni-Moghaddam et al., 2014), while participants performed the Psychomotor Vigilance Task for 10 min. We discarded possible blinking or recording errors by rejecting data points of ± 3 standard deviations from the mean spherical refraction value (Tosha et al., 2009; Vera et al., 2016). The lag of accommodation was calculated from the difference in dioptre units between the target distance, the mean point of focus during dynamic testing and the baseline static spherical equivalent refraction value (Poltavski et al., 2012). For its part, the variability of accommodative response was obtained from the standard deviation of the dynamic the accommodative response recording (Sreenivasan, Irving, & Bobier, 2011).

Sustained attention task

A modified version of the Psychomotor Vigilance Task (Basner & Dinges, 2011) was used as a standardized procedure to control the presentation of visual stimuli while participants are required to maintain attention. A 15.6″ LCD laptop PC and the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) were used to control for stimulus presentation and response collection. The centre of the laptop screen was situated at 50cm from the participants' head and at their eye level. Each Psychomotor Vigilance Task trial procedure began with the presentation of an empty high-contrast black circle (viewing angle of 6.73º) in a blank background for 2000ms. Later, in a random time interval (between 2000 and 10000ms), the circle was filled all at once in a black colour. Participants were instructed to respond, pressing the space bar on the PC keyboard with their dominant hand, as fast as they could once they had detected the presentation of the filled circle. The filled circle was presented for 500ms and the participants had a maximum of 1500ms to respond. A reaction time visual feedback message was displayed for 300ms after response, except in case of an anticipated response (‘‘wait for the target’’) or if no response was made within 1000ms after target offset (‘‘you did not answer’’). Following the feedback message, the next trial began. The entire task lasted 10 minutes.

Subjective measures

At the beginning of each experimental session, participants were asked to complete the Stanford Sleepiness Scale in order to check that the levels of alertness/sleepiness were similar between sessions (Hoddes, Zarcone & Dement, 1973). The Stanford Sleepiness Scale is a self-rating scale that contains seven statements ranging from 1 “Feeling active, vital, alert, or wide awake” to 7 “No longer fighting sleep, sleep onset soon, having dream-like thoughts”. Participants were instructed to indicate which statement described their actual state.

Also, before the commencement of each experimental, after 60 min of caffeine/placebo intake and at the end of the Psychomotor Vigilance Task, participants completed two visual analogue scales in order to evaluate their subjective level of activation and fatigue. These scales range from 1 “absolutely not activated” to 10 “extremely activated” and from 1 “absolutely not fatigued” to 10 “extremely fatigued” respectively.

Procedure

Participants visited the laboratory in two separate occasions on different days, being both experimental sessions scheduled at the same time of the day (± 1 hour) in order to avoid circadian variations. Caffeine or placebo were consumed in different days, and they were administered in counterbalanced order. Participants were asked to abstain from alcohol and caffeine-based drinks 24 and 12h before each experimental session, respectively. Also, we instructed them to sleep at least 7h the night prior the experiment and, when necessary, to attend to the laboratory with their soft contact lenses. In the first session, each participant underwent an optometric examination in order to verify that the inclusion criteria were fulfilled (see the participants subsection for a description of the inclusion criteria). Briefly, they completed the Conlon questionnaire, and we performed a slit lamp and direct ophthalmoscopy examination in order to detect any ocular pathology. Also, subjective refraction was conducted using the end-point criteria were maximum plus sphere and minimum minus cylinder power maintaining the best visual acuity. Charts employing the Bailey–Lovie design were used to measure visual acuity at far distance. Lastly, the accommodative response at 20 cm was assessed using the WAM-5500 autorefractometer while participants viewed a high-contrast Maltese cross. Additionally, the daily consumption of caffeine and anthropometric characteristics for each participant were obtained. From then on, both experimental sessions were identical, except for the content of the capsule (caffeine or placebo). Each placebo capsule contained 300mg of corn-starch and the caffeine capsules (caffeine anhydrous) were dispensed in steps of 20 mg (i.e., 200 mg, 220 mg, 240 mg, etc.), being chosen based on participant´s weight (~ 4 mg/kg) (Mitchell et al., 2014). Both capsules were prepared by a pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) and packaged in opaque gelatin capsules to avoid the identification of contents by colour, taste, or shape. Aiming to accomplish the double-blind procedure, the capsules were coded and prepared by a third person. Prior to the main measurements, participants rested for 60 minutes after capsule (caffeine or placebo) ingestion in order to reach a considerable plasma concentration of caffeine (Mort, & Kruse, 2008).

Statistical analysis

Before any statistical analysis, the normal distribution of the data (Shapiro-Wilk test) and the homogeneity of variances (Levene’s test) were confirmed ($p > 0.05$). Three mixed analyses of variance with *caffeine consumption* (placebo and caffeine) and *time-on-task* (block 1, block 2, block 3, block 4, and block 5) as the within-participants factors, and the *habitual caffeine intake* (low-consumers and high-consumers) as the between-participants factor, were carried out to test the impact of our experimental manipulation on the lag and variability of accommodation, and behavioural performance (reaction time). It should be noted that reaction time data from one participant were excluded due to log system failures during the recording, and thus, twenty participants (10 low and 10 high caffeine consumers) were included for the analysis of behavioural performance. Additionally, two mixed analyses of variance with *caffeine consumption* (placebo and caffeine) and *measurement moment* (baseline, before Psychomotor Vigilance Task, After Psychomotor Vigilance Task) as between-participants factors, and *habitual caffeine intake* (low-consumers and high-consumers) as the between-participants factor were performed for the perceived levels of activation and fatigue. The magnitude of the differences was reported by the partial eta squared (η_p^2) and Cohen's d effect size for *Fs* and *t-tests*, respectively. Statistical significance was set at an alpha level of 0.05, and post hoc tests were corrected with Holm-Bonferroni procedure.

Results

First, we checked that all participants attended to both experimental sessions under similar level of alertness/sleepiness by the analysis of the Stanford Sleepiness Scale ($t_{20} = 0.326$, $p = 0.748$).

For the lag of accommodation, there were no statistically significant differences for caffeine consumption ($F_{1, 19} = 0.055$, $p = 0.818$), time-on-task ($F_{4, 76} = 1.704$, $p = 0.158$), habitual caffeine intake ($F_{1, 19} = 0.128$, $p = 0.725$) or any interaction (all p-values > 0.05) (Figure 12, panel A).

The variability of accommodation revealed statistical significance for caffeine consumption ($F_{1, 19} = 6.366$, $p = 0.021$, $\eta_p^2 = 0.219$) and habitual caffeine intake ($F_{1, 19} = 4.494$, $p = 0.047$, $\eta_p^2 = 0.191$), however, no effects were found for time-on-task ($F_{4, 76} = 1.259$, $p = 0.294$) or interactions (all p-values > 0.05). Subsequently, two separate repeated measures analyses of variance were carried out for the low and high caffeine consumers. We found that the low caffeine consumers did not show differences for caffeine consumption ($F_{1, 9} = 0.183$, $p = 0.679$), whereas high caffeine consumers exhibited a statistical significant effect for caffeine consumption ($F_{1, 10} = 9.677$, $p = 0.011$, $\eta_p^2 = 0.492$) (Figure 12, panel B).

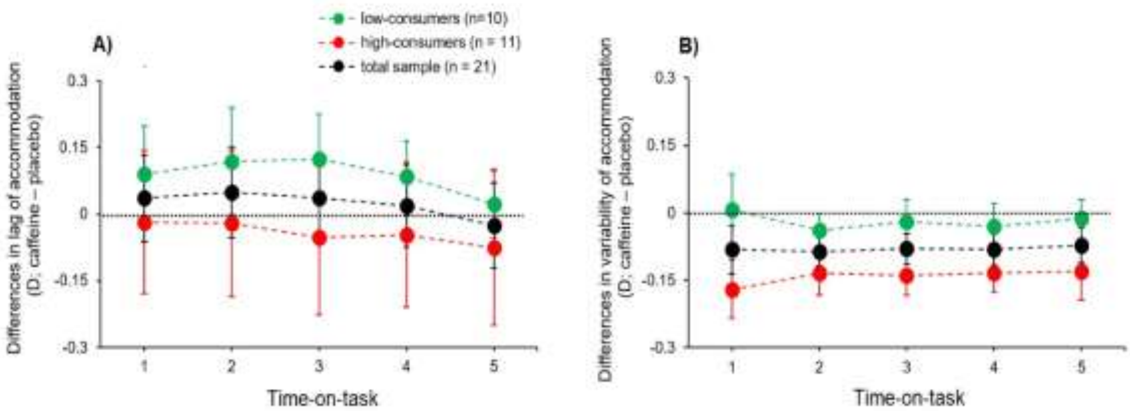

Figure 12. Effect of caffeine consumption in high and low caffeine consumers, as well as for the total experimental sample, during the execution of the sustained attention task. Panel A shows the difference between the caffeine and placebo conditions for the lag of accommodation, and Panel

B represents the difference between the caffeine and placebo conditions for the variability of accommodation. Error bars represent the standard error.

The impact of caffeine consumption on behavioural performance (reaction time) demonstrated a statistical significant effect for caffeine consumption ($F_{1, 18} = 14.946$, $p = 0.001$, $\eta_p^2 = 0.342$) and time-on-task ($F_{4, 72} = 15.279$, $p < 0.001$, $\eta_p^2 = 0.458$), whereas no differences were found for habitual caffeine intake ($F_{1, 18} = 0.208$, $p = 0.654$). For the interactions, there were only differences for caffeine consumption x habitual caffeine intake ($F_{1, 18} = 10.770$, $p = 0.004$, $\eta_p^2 = 0.246$), observing no effects for the rest of interaction (all p-values > 0.05). Additionally, we performed two separate analyses of variance for the low and high caffeine consumers, indicating that shorter reaction times for the caffeine condition in comparison to the placebo condition were observed in the group of high caffeine consumers ($F_{1, 9} = 21.914$, $p < 0.001$, $\eta_p^2 = 0.709$; mean reaction time change: - 35.90 ± 34.90 ms), whereas the group of low caffeine consumers did not exhibit differences ($F_{1, 9} = 0.205$, $p = 0.662$; mean RT change: - 2.93 ± 31.57 ms).

Perceived levels of activation reached statistical significance for caffeine consumption ($F_{1, 19} = 6.356$, $p = 0.021$, $\eta_p^2 = 0.241$) and the interaction caffeine consumption x measurement moment ($F_{2, 38} = 50259$, $p = 0.010$, $\eta_p^2 = 0.213$). However, no differences were observed for measurement moment ($F_{2, 38} = 0.304$, $p = 0.739$), habitual caffeine intake ($F_{1, 19} = 0.821$, $p = 0.376$) or the rest of other interactions (all p-values > 0.05). Post-hoc tests yielded no statistically significant differences for the comparison between both experimental conditions at each of the three measurement moments (all corrected p-values > 0.05) (Figure 13, panel A). Lastly, perceived levels of fatigue demonstrated that the factor of caffeine consumption yielded statistically significant differences ($F_{1, 19} = 6.444$, $p = 0.020$, $\eta_p^2 = 0.244$), whereas the measurement moment ($F_{2, 38} = 1.660$, $p = 0.204$), habitual caffeine intake ($F_{1, 19} = 0.242$, $p = 0.629$) or the interactions (all p-values > 0.05) showed no significant effects. Post-hoc tests evidenced that the comparisons between both experimental conditions (caffeine vs. placebo) at the three measurement moments were only significant when participants reported their perceived levels of fatigue after the Psychomotor Vigilance Task (corrected p-value = 0.036, d = 0.599) (Figure 13, panel B).

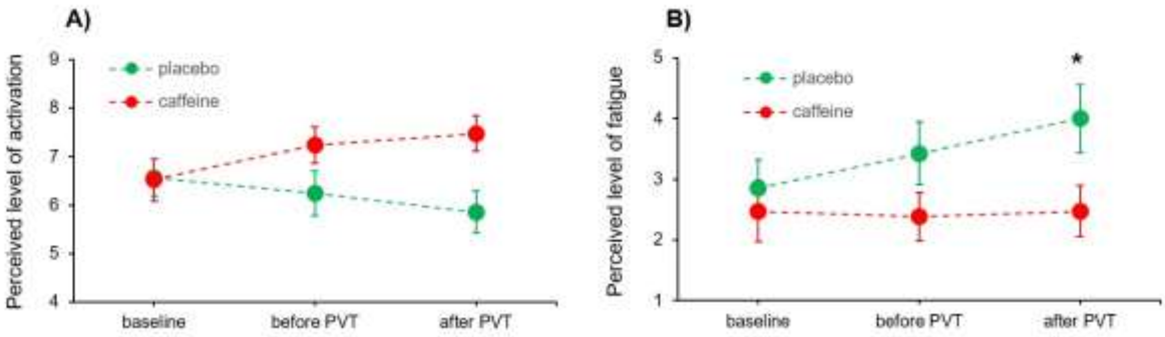

Figure 13. Effect of caffeine consumption for subjective levels of activation (Panel A) and fatigue (Panel B) at the different points of measure. * denotes statistical significance (corrected p-value < 0.05). Error bars represent the standard error.

Discussion

The main aims of this study were to examine the acute effect of caffeine intake on the ocular accommodation while performing a sustained attention task, as well as to compare the possible differences between low and high caffeine consumers. Although the lag of accommodation was slightly larger for all time points in low consumers after caffeine ingestion, we did not find any statistical difference. However, the variability of accommodation was sensitive to acute caffeine ingestion, promoting a more stable ocular accommodation after consuming caffeine in comparison to placebo. Notably, the variability of accommodation was dependent on habitual caffeine intake, with high caffeine consumers exhibiting a lower variability in comparison to low caffeine consumers. Complementarily, behavioural performance was enhanced by caffeine, being these effects also mediated by habitual caffeine intake (lower reaction time for high caffeine consumers). Our data also evidenced that subjective measures of arousal and fatigue were also modulated as a function of caffeine consumption.

The analyses of perceived levels of alertness/sleepiness (Stanford Sleepiness Scale) before each experimental session allowed us to confirm that participants attended to both experimental sessions with comparable levels of activation. Although it was beyond to the main objectives of the present study, we assessed the impact of caffeine intake on subjective levels of activation and fatigue and behavioural performance. In convergence with previous investigations, caffeine intake results in increased arousal and decreased feelings of fatigue (Childs & De Wit, 2006). Also, caffeine enhanced reaction time, as it has been widely described in the literature (McLellan, Caldwell, & Lieberman, 2016), although in our study this fact only occurred in high caffeine consumers. In this sense, there is relatively little work concerning the influence of habitual caffeine consumption on the task performance under the effects of caffeine, being this effect more susceptible under complex rather than simple tasks (Einöther & Giesbrecht, 2013). However future research might further address this question. These results are in accordance with other studies that observed that behavioural performance is related to habitual caffeine intake, suggesting that caffeine improves task performance in habitual consumers of this beverage (Attwood, Higgs, & Terry, 2007; Smit & Rogers, 2000). Although the caffeine intake had a positive impact on the subjective measures in non-low consumers, it is likely that the caffeine-related behavioural effect could have been offset by an increase in anxiety/jitteriness as a low tolerance response to ingestion in this group, resulting in no significant benefit for mental alertness (Rogers, Heatherley, Mullings, & Smith, 2013). In any case, relevant here is that these results in conjunction with the design of the study (placebo-controlled and double-blind) allows us to confirm a successful experimental manipulation.

The neurochemical mechanisms underlying the central effects of caffeine suggest that its intake can enhance a range of cognitive functions, with most pronounced effects in conditions with explicit attentional demands or under situations of reduced arousal or fatigue (Lorist & Tops, 2003). In addition, previous studies argue that the accommodative response worsen over time as a consequence of visual discomfort and fatigue (Thiagarajan & Ciuffreda, 2013; Tosha et al., 2009). In view of this, we considered of interest to test the possible effects of caffeine on visual fatigue during sustained attention in order to check whether caffeine ingestion may mitigate the ocular accommodation changes (greater lags of accommodation) associated with prolonged near viewing activities. Despite 10-min task is sensitive enough to induce a vigilant decrement and fatigue (Loh, Lamond, Dorrian, Roach, & Dawson, 2004; Luque-Casado et al., 2016), we did not find any significant change for time-on-task (fatigue effect) in the dynamics of ocular accommodation. Notably, as indicated by Tosha et al., (2009), the increased lag of accommodation caused by prolonged near work is more evident in individuals with high levels of visual discomfort. Future studies should consider incrementing the task time and including participants with visual fatigue symptomatology in order to assess this plausible effect of caffeine on visual fatigue.

We partially failed to accept our initial hypothesis, there was no effect of caffeine consumption on the lag of accommodation. To the best of our knowledge, there is only one study that has tested the acute impact of caffeine on ocular accommodation. In this investigation, Abokyi et al. (2016) observed that in non-habitual coffee consumers, the ingestion of 250 mg of caffeine increased the amplitude of accommodation. Nevertheless, we assessed the accommodative response, which reflects the accuracy of the eye to fixate one point in the space, whereas the amplitude of accommodation indicates the maximum capacity of the eye to focus a near object (Millodot, 2014). Based on this, the physiological response to caffeine of both ocular accommodation variables may be different. In addition, it should be noted that Abokyi and colleagues used a fixed amount of caffeine whereas our caffeine capsules were chosen based on participant´s weight (~ 4 mg/kg), and also, they only included non-habitual caffeine consumers whereas our experimental sample was formed by low and high caffeine consumers.

Retinal image quality is highly dependent on the accuracy and the stability of the accommodative response (López-Gil et al., 2013), with ocular accommodation typically varying within an envelope of about ± 0.5D in order to optimize overall accommodative performance and to obtain directional cues for dynamic accommodation (W. Neil Charman & Heron, 2015; Metlapally et al., 2016). Regarding the variability of accommodation, our data revealed preliminary evidence on the better stability of ocular accommodation during a sustained attention task when participants ingested a pill of caffeine in comparison to placebo. The main novelty of this study is that the benefits of caffeine intake were limited to the group of high caffeine consumers, obtaining a reduction of the variability of accommodation of approximately 0.15 D after caffeine ingestion. The mediating role of habitual caffeine intake have been previously reported for physiological (Kennedy & Haskell, 2011; Vera et al., 2019) and subjective (Attwood et al., 2007) responses, as well as cognitive and physical performance (McLellan et al., 2016). Our findings seem to be in agreement with previous researchers that have stated that high caffeine consumers are more likely to perceive broadly positive effects of caffeine (Attwood et al., 2007; Smit & Rogers, 2000), showing also an activation of the autonomic nervous system that in not associated with negative physiological changes (i.e., blood pressure or intraocular pressure rise) (Corti et al., 2002; Vera et al., 2019). We deem that the differences in the variability of accommodation between consumers and non-consumers may be induced by an increase in jitteriness/nervousness in response to caffeine for non-consumers because of a predisposition to this effect (and this is why they avoid caffeine) (Porter, 2012; Rogers, Martin, Smith, Heatherley, & Smit, 2003). Accordingly, caffeine consumption habits seem to be an important factor to consider when analysing the impact of caffeine on ocular accommodation, and specifically in the variability of the accommodative response.

Our results showed that the variability of accommodation is sensitive to caffeine intake and to its habitual consumption. However, these findings must be understood in the context of some limitations. The pharmacokinetics and pharmacodynamics of caffeine are affected by numerous factors such as age, hormonal status or sex among many others, and thus, there are considerable inter-individual differences (Nehlig, 2018). Our results need to be cautiously interpreted in this regard. The relatively small sample size used in this study could mask any effects in the accommodative response behaviour after caffeine intake. Here, our data revealed a slightly larger accommodative lag in low consumers, however, these differences did not reach statistical significance. Larger sample sizes would help to address this question. Additionally, changes induced by caffeine on body functions have showed a dose-response effect (Chen & Parrish, 2009; Quinlan et al., 2000), and here, we used a discrete amount of caffeine based on the estimations of mean daily caffeine intake for United States consumers (Barone & Roberts, 1996). Future investigations are required to test the impact of different doses of caffeine on ocular accommodation. Similarly, the effects of caffeine have been tested after 60 minutes of capsule ingestion, and peak plasma concentrations have been determined between 15 and 120 minutes following ingestion (Magkos & Kavouras, 2005), therefore, these effects should be tested after different periods from caffeine ingestion. Lastly, an increased variability of accommodation has been linked to asthenopia after extensive periods of near work (Charman & Heron, 2015; Thiagarajan & Ciuffreda, 2013). It is our hope that further investigation will test the possible influence of caffeine intake on visual fatigue associated with longer near tasks and in individuals with high levels of visual discomfort, and its relationship with the stability of ocular accommodation.

Conclusions

The present placebo-controlled, double-blind, balanced crossover design study was the first to examine the acute effects of caffeine on the dynamics of ocular accommodation in habitual and non-habitual caffeine consumers during a sustained attention task. We found that the acute intake of caffeine (4 mg/kg) enhances the stability of accommodation in high caffeine consumers but not in low caffeine consumers. Nevertheless, the lag of accommodation did not change as consequence of caffeine consumption. The current outcomes incorporate novel insights into the influence of caffeine intake on the dynamics of ocular accommodation and highlight the relevance of considering caffeine consumption habits when analysing the changes induced by caffeine on the ocular physiology and visual functioning.

STUDY IV: ASSOCIATIONS BETWEEN ACCOMMODATIVE DYNAMICS, HEART RATE VARIABILITY AND BEHAVIOURAL PERFORMANCE DURING SUSTAINED ATTENTION: A TEST-RETEST STUDY.

Introduction

It is well known that cognitive demand alters the activity of the autonomic nervous system, with these alterations being manifested in different physiological parameters such as skin conductance, respiration rate, blood pressure and heart rate variability (Haapalainen et al., 2010). Heart rate variability is a particularly sensitive index of interaction between the autonomic nervous system and the cardiovascular system, which provides indirect information about the sympathovagal balance by measuring the temporal oscillations between successive R-R interval variations of sinus origin (Malik et al., 1996; Pumprla et al., 2002). In addition to physiological variables, a number of ocular parameters, including oculomotor movements (Di Stasi et al., 2017; Grier et al., 2003), pupil size (Macatee et al., 2017), blink rate (McIntire et al., 2014), ocular aberrations (Jiménez et al., 2017), visual perception (Park et al., 2012), and intraocular pressure (Vera et al., 2017) have also been demonstrated to be sensitive to autonomic balance, exhibiting different behaviours depending on the level of arousal. Similarly, the accommodative response, which reflects the precision of the accommodative system in providing a clear image of a target of interest on the fovea (Cogan, 1937; Millodot, 2014), has been shown to be impaired with cognitively demanding tasks, which is predominantly attributable to attenuated involvement in the parasympathetic innervation (Bullimore & Gilmartin, 1988; Davies, Wolffsohn, & Gilmartin, 2005; Davies, Wolffsohn, & Gilmartin, 2009; Gilmartin, 1986). Also, ocular accommodation has been demonstrated to be sensitive to circadian variations, suggesting that the time of measurement (morning vs. night) might lead to different results (McDougal & Gamlin, 2015). Based on this, autonomic nervous system alterations seem to be partially captured by cardiovascular and ocular accommodation activity. As such, objective assessment of these physiological parameters might be used as an indicator of the state of the autonomic nervous system.

Another important parameter related to the accommodative function, which may be affected by cardiopulmonary signals or other rhythmical physiological systems, is microfluctuations of accommodation (Charman & Heron, 1988; Collins, Davis, & Wood, 1995; Jeng et al., 2014; Winn et al., 1990). This index is based on accommodative response not remaining constant throughout time when a subject is focusing on a stationary target, but instead, exhibiting small temporal variations of approximately 0.5 D, providing a mechanism to sustain the accommodative response and to acquire directional cues for the accommodative response (Metlapally et al., 2016). The microfluctuations of accommodation are a result of central neurological control (Charman & Heron, 1988; Cogan, 1937; Gilmartin, 1986; Winn & Gilmartin, 1992), and it can be used as an indicator of the negative feedback of accommodative response (Gray, Gilmartin, & Winn, 2000). Some studies have demonstrated that an increase in cognitive engagement might improve the accuracy of the accommodative response and reduce the microfluctuations of accommodation (Hynes et al., 2018; Malmstrom et al.,1980; Roberts et al 2018; Rosenfield et al., 2015).

The ability to maintain optimal cognitive engagement in humans is not constant over time, and an extended period of attentional demands on a single task leads to fluctuations and reduction in performance, i.e., a time-on-task effect or vigilance decrements (Grier et al., 2003; Lim et al., 2010). In this regard, functional magnetic resonance imaging studies of sustained attention have shown that the execution of a Psychomotor Vigilance Task modulates brain areas and networks associated with attentional processes (Asplund & Chee, 2013; Lim et al., 2010). Importantly, numerous everyday activities require to preserve the cognitive capabilities for a long period of time and, therefore, are conditioned by the time-on-task effect (e.g., driving [Larue, Rakotonirainy, & Pettitt, 2011]), performing surgery (Gawandeet al., 2003), attending academic lessons (Steinmayr et al., 2010) and handling air-traffic control (Loft et al., 2007). Therefore, investigation into underlying physiological factors linked to performance fluctuations in attention over time is highly relevant. Due to a reduced vigilance state and the mitigated predominance of parasympathetic activity linked to prolonged attentional tasks (Davies et al., 2009), it is plausible to expect that ocular accommodation might be modulated by function of time-on-task, and these effects on the accommodative response could be associated with variations in autonomic vagal control. However, to the best of our knowledge, there are no studies analysing the effect of time-on-task during sustained attention on the accommodative response and their relationship with heart rate variability since previous studies just considered short periods of cognitive demand (Davies et al., 2009; Davies et al., 2005). The previously mentioned neuropsychological signals (e.g., accommodation dynamics and heart rate variability) have demonstrated the capacity to estimate the state of the autonomic nervous system, which is linked to task performance in multiple activities such as driving (Borghini et al., 2012) or controlling air traffic (Brookings, Wilson, & Swain, 1996). Notably, the consideration of different physiological variables that may be sensitive to autonomic nervous system changes would allow to enhance the ability of predicting the state of the autonomic nervous system by objective and continuous indices.

To address the caveats found in the scientific literature, the main aims of this investigation were: (1) to assess the effect of time-on-task during a Psychomotor Vigilance Task on the lag and microfluctuations of accommodation in young adults; (2) to establish the association of behavioural performance (reaction time during The Psychomotor Vigilance Task) with accommodative function and vagal control, as measured by heart rate variability; and (3) to evaluate the inter-session repeatability of these effects, since it was well known that ocular accommodation and heart rate variability measures showed large day-to-day variations (McDougal & Gamlin, 2015) and inclusion of two identical experimental sessions on two different days in the same participants could help to reduce random sources of variability (Streiner, Norman, & Cairney, 2015). We hypothesized that increments of the time-on-task would be associated with a gradual decrement in heart rate variability and behavioural performance, along with greater values of lag and microfluctuations of accommodation (Davies et al., 2005; Jeng et al., 2014; Luque-Casado et al., 2015), with these changes being similar in two sessions performed under the same experimental conditions. In addition, these physiological indices might have an association with cognitive performance, although the lack of previous evidence did not permit us to elaborate a clear hypothesis in this regard.

Methods

Participants and ethics

Twenty-five undergraduate students (13 women and 12 men) participated in the study, ranging in age from 18 to 33 years (mean age ± standard deviation, SD = 22.4 ± 4.5 years). All participants had normal or corrected-to-normal vision (visual acuity of ≤0 logMAR in each eye). They were compensated with soft contact lenses when necessary, with all contact lens users having at least one year of experience. Refractive errors were limited to myopia < 0.50 D, hyperopia <1.00 D, and astigmatism or anisometropia < 1.00 D. All participants included had low visual discomfort (cut off value < 24), as measured by the Conlon visual discomfort survey (Conlon et al., 1999). They were also free of any systemic disease, were not under pharmacological treatment and were non-smokers. Before each experimental session, they were asked to abstain from alcohol and from caffeine drinks for 24 and 12 hours, respectively, and to sleep for at least 7 hours on the previous night. Both experimental sessions were carried out at the same time of the day (± 1 hour) in order to control for possible circadian variations. When participants arrived at the laboratory, the level of alertness/sleepiness was assessed using the Stanford Sleepiness Scale (Hoddes et al., 1973), in order to check that participants performed both sessions under similar levels of activation. The present study was conducted according to the tenets of the Declaration of Helsinki, and under the guidelines of the University Institutional Review Board (IRB approval: 546/CEIH/2018).

Psychomotor vigilance task

The visual stimulus used during the measurement of accommodation consisted of a modified version of the Psychomotor Vigilance Task used in previous research (Luque-Casado et al., 2015; Vera et al., 2019). For stimulus presentation and response collection, a 15.6″ LCD laptop personal computer and E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) were used. The personal computer keyboard was used for response collection. This task allows to measure attention or vigilance, and is based on a simple visual reaction time-task in which a target stimulus is presented at random inter-stimulus intervals for a standard administration length of 10 minutes (Basner & Dinges, 2011). This duration of the Psychomotor Vigilance Task at 10 minutes had been recommended in studies for which time constraints were not of concern, although shorter versions of 5 minutes have also been proposed as viable alternatives. Nevertheless, the 10-minute Psychomotor Vigilance Task was chosen as it was the most commonly used version, and had been demonstrated to be more sensitive to different performance metrics than shorter versions (Loh et al., 2004). The Psychomotor Vigilance Task had been extensively used in related investigations, and had been demonstrated to alter the brain areas linked to sustained attention (Asplund & Chee, 2013; Lim et al., 2010). Therefore, it allowed us to provide the proper stimuli for assessing accommodation, as well as determining whether participants were attending to the stimuli displayed on the screen. The simultaneous assessment of accommodative function and behavioural performance allowed us to establish associations.

The Psychomotor Vigilance Task commenced with the presentation of an empty high-contrast black circle, which subtended a viewing angle of 6.73° in the horizontal and vertical axes, at the centre of the screen against a white background. After it, the circle was filled all at once in black, and in a random time interval between 2000 and 10000 ms. Participants were asked to press as fast as possible the space bar on the keyboard, using their dominant hand, when the circle was filled. The filled circle was displayed for 500 ms and they had a maximum of 1500 ms to press the space bar. Reaction time was defined as the length of time (in milliseconds) between the stimulus presentation and the response of the participant by pressing the space bar. A visual feedback message of the reaction time was displayed for 300 ms after each response, except in the case of an anticipated response or if no response was made within 1000 ms after target offset, when messages ‘‘wait for the target’’ and ‘‘you did not answer’’ were displayed, respectively. Following the feedback message, the next trial began (see Fig. 14 for a schematic illustration of the Psychomotor Vigilance Task procedure). The procedure lasted 10 minutes, and participants were instructed to maintain the accommodative stimuli as clear as possible during the entire task.

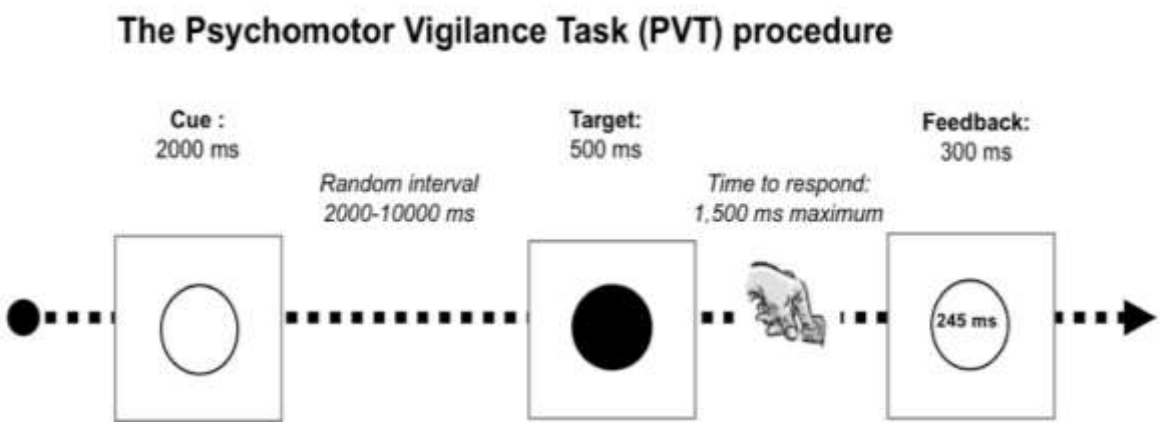

Figure 14. Timeline of the Psychomotor Vigilance Task.

Accommodative response

AR values were dynamically measured with a WAM-5500 binocular open-field autorefractor (Grand Seiko Co. Ltd., Hiroshima, Japan) in hi-speed mode (continuous recording). This apparatus had been clinically validated and was shown to acquire reliable and accurate data of accommodation at a temporal resolution of ~5 Hz (Sheppard & Davies, 2010). First, to determine the baseline refractive value, we obtained the monocular static refractive measure for both corrected eyes, while participants looked at a 5m stationary target. Then, we performed a dynamic accommodative test, recording the magnitude and microfluctuations of accommodation for 10 min, while the high-contrast visual stimulus from the Psychomotor Vigilance Task appeared on a 15.6″ LCD screen 50 cm from the observer. Participants looked at the target in binocular conditions, and the accommodative response was recorded in the dominant eye (Momeni-Moghaddam et al., 2014). They were asked to rest their forehead and chin in the corresponding supports while looking at the visual stimulus at the centre of the screen (see the *Psychomotor vigilance task* subsection above for details). The illumination in the laboratory was kept constant during the experiment (217 ± 8 lx as measured in the corneal plane). Following previous recommendations for the accommodative response data processing, we discarded data points of ± 3 SD from the average spherical refraction value, which may be caused by blinking or measurement errors (Tosha et al., 2009; Vera et al., 2016). Accommodative lag was calculated by subtracting from the target distance (2D), the mean point of focus during dynamic testing and the baseline static spherical equivalent refraction value (Poltavski et al., 2012). The microfluctuations of accommodation referred to the standard deviation of the accommodative response recording (Redondo et al., 2018).

Heart rate variability

We used a Polar RS800 CX monitor (Polar Electro, Kempele, Finland) to monitor the cardiovascular activity in both experimental sessions. The time series of heart rate variability data were obtained by identifying the occurrence of each R wave and calculating the elapsed time between two consecutive R waves (R-R interval). Thus, heart rate variability analysis consisted of a series of measurements of successive R-R intervals and determining their variation, which provided indirect information about autonomic tone (Malik et al., 1996; Pumprla et al., 2002). Cardiovascular data were collected at a temporal resolution for 1 ms (1000 Hz). A heart rate monitor was placed on the participant before each experimental session, and then they rested for five minutes in a quiet room in a supine position to record the baseline heart rate variability. Cardiovascular activity was also recorded during the 10 minutes of the Psychomotor Vigilance Task. For data analysis, we transferred all recordings to the Polar electro interface all, and then, the RR files were analyzed using the Kubios heart rate variability analysis software 2.0 (Tarvainen et al., 2009). Following the recommendations of Malik et al., (1989), the recordings were preprocessed to exclude artifacts by eliminating R-R intervals which differed more than 25% from either the previous or the subsequent values. Bioelectric signal recordings could often be contaminated by low-frequency interference that would cause baseline trending of the recorded signals. In cardiac recordings, the signals might also be contaminated by various low frequency noises such as breathing, sweating, electrode motion and even the slow activities of the muscles. These low-frequency interferences or trends could often have a significant impact on signal interpretation. Thus, we applied a method based on the smoothness prior approach to detrend heart rate variability data (Tarvainen et al., 2002; Zhang et al., 2014). This approach could be automatically implemented from the Kubios heart rate variability analysis software (Tarvainen et al., 2009). In order to analyse heart rate variability within the time domain, the root-mean-square difference of successive normal R-R intervals (RMSSD) was used as the index of vagal control. The guidelines for heart rate variability data collection and analysis in this paper follow those established by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Malik et al., 1996).

Procedure

Participants attended the laboratory on three different days. In the first session, participants were screened for the established inclusion criteria, and the experimental protocol was also explained to them. The remaining two sessions, the main experimental sessions, were identical, and were used to assess inter-session repeatability. All sessions were performed at the same time of the day (±1 hour) and under similar environmental conditions (~22 ºC and ~60% humidity). First, participants signed the consent form and filled in documentation for the Stanford Sleepiness Scale. A baseline heart rate variability was then obtained during a six minutes rest period in a supine position. No measurements were used during the first minute of this period, with the last 5 min being considered for the resting heart rate assessment (Vera et al., 2018). The participants were then sat in front of the computer in a dimly illuminated room and isolated from external noise. Prior to testing, they received instructions and practiced for one minute with the Psychomotor Vigilance Task. At this point, the 10-minute Psychomotor Vigilance Task was started, and the accommodative function and heart rate variability were monitored during the entire period. in order to assess the time-on-task effects, the psychomotor vigilance task, ocular accommodation and cardiovascular related variables were divided into five-time blocks of two minutes each.

Experimental design and statistical analysis

In this study, we used a repeated measures design to assess the time-on-task effect of sustained attention during two separate experimental sessions on ocular accommodation, vagal autonomic control and behavioural performance.

Four separate two-way analysis of variance were performed to determine the effect of time-on-task on the dynamics of the accommodative response (lag and microfluctuations) during the Psychomotor Vigilance Task, as well as its influence on the RMSSD index of heart rate variability and reaction for the Psychomotor Vigilance Task (objective 1). These statistical tests were conducted separately for each of the four dependent variables (lag of accommodation, microfluctuations of accommodation, RMSSD and reaction time), considering the time-on-task (block 1, block 2, block 3, block 4, and block 5) and the session (session 1 and session 2) as within-participants factors. The magnitude of the differences was analysed by partial eta squared (η_p^2) for multiple comparisons. Significant main effects and interactions were further explored by using pairwise comparisons with paired Student's t-tests, which were also interpreted based on the magnitude of the difference using Cohen´s d. Multiple comparisons were corrected with the Holm-Bonferroni method. We also performed linear regression analysis to explore the behaviour of the dependent variables over time.

In order to assess objective 2, multiple regression analysis was used to predict behavioural performance (reaction time during the Psychomotor Vigilance Task) from the lag of accommodation, microfluctuations of accommodation, and heart rate variability (RMSSD). In order to find the model that permits to explain the greatest amount of variance with the minimum number of predictors, we used the backward elimination procedure. For all dependent variables, the average value from both sessions was considered for this analysis.

In addition, inter-session repeatability (objective 3) of the different dependent variables (lag of accommodation, microfluctuations of accommodation, RMSSD, and reaction time) was examined by the analysis of the standard error of measurements in relative terms. For this, pairwise t-tests were conducted with the session (session 1 and session 2) as the only within-participants factor, and the differences were interpreted by the standardized mean differences (Cohen´s d), following the recommendations of Hopkins et al. (2009). Subsequently, we calculated the within-participants coefficient of variation, intra-class correlation coefficients, and their corresponding 95% confidence intervals to determine inter-session repeatability. In addition, the level of agreement between both sessions was explored by the method of Bland and Altman (1986).

The level of statistical significance was set at 0.05. The JASP statistics package (version 0.9.0.1) was used for analyses of variance and regression analysis. Repeatability analyses were performed with a custom spreadsheet developed by Hopkins (2000).

Results

Baseline differences between experimental sessions

First, the participants attending the laboratory were assessed for their baseline cardiovascular activity and perceived level of sleepiness/alertness. Similarity in the participants for these values was confirmed by analysis of baseline heart rate variability (t_{24} = 0.610, p-value = 0.550 for the RMSSD) and from subjective levels of alertness reported by participants (t_{24} = 0.296, p = 0.770 for the Stanford Sleepiness Scale) at the beginning of each experimental session.

Influence of time-on-task on the accommodative response

The analysis of the lag of accommodation did not reveal any effect for either session, time-on-task or interaction (all Fs < 1 (Fig. 15A).

The microfluctuations of accommodation exhibited a statistically significant effect for time-on-task ($F_{4, 96}$ = 10.060, p < 0.001, and η_p^2 = 0.295). The main factor of session and the interaction *time-on-task x session* were far from showing any significance (F < 1 in both cases). Post-hoc comparisons are depicted in Fig. 15B, and they showed statistically significant differences for block 1 when compared to block 3 (corrected p-value = 0.009, d = 0.659), block 4 (corrected p-value = 0.005, d = 0.707), and block 5 (corrected p-value

= 0.002, d = 0.789; (Fig. 15 B). There was a positive and linear relationship between the microfluctuations of accommodation and time (Pearson´s r = 0.97 and 0.91 for sessions 1 and 2, respectively).

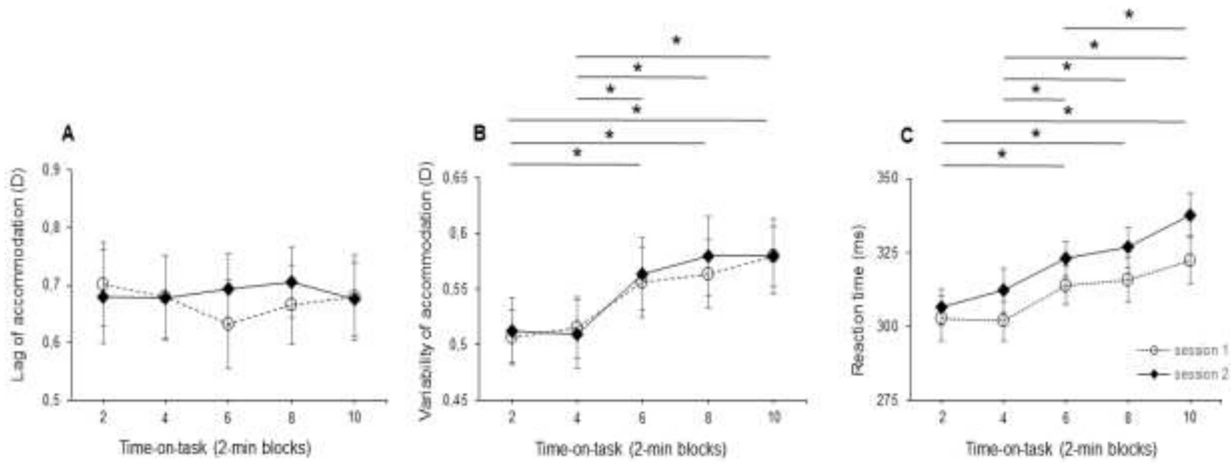

Figure 15. Effects of time-on-task in both experimental sessions on lag of accommodation (Panel A), microfluctuations of accommodation (Panel B), and reaction time (Panel C). * denotes statistically significant differences between the different time blocks (corrected p-value < 0.05). Error bars represent the standard error (SE). All values are calculated across participants (n = 25).

Influence of time-on-task on behavioural performance

Behavioural performance, as measured by reaction time, revealed a statistically significant effect on time-on-task ($F_{4, 96} = 15.853$, $p < 0.001$, $\eta_p^2 = 0.398$). The main effect of session ($F_{1, 24} = 2.913$, $p = 0.101$) and the interaction *time-on-task x session* ($F_{4, 96} < 1$) did not show statistical significance. Post-hoc comparisons revealed that the reaction time was significantly lower in block 1 compared to block 3 (corrected p-value = 0.004, d = 0.799), block 4 (corrected p-value < 0.001, d = 1.025) and block 5 (corrected p-value < 0.001, d = 1.172; (Fig. 15C). There was a positive and linear relationship between reaction time and time-on-task (Pearson´s r = 0.95 and 0.99 for sessions 1 and 2, respectively).

Influence of time-on-task on heart rate variability

The RMSSD component of heart rate variability did not reach statistical significance for either of the factors, time-on-task ($F_{4, 96} = 1.202$, $p = 0.315$), session ($F_{1, 24} = 2.455$, $p = 0.130$), or the interaction *time-on-task x session* ($F_{4, 96} < 1$).

Prediction of behavioural performance from ocular accommodation and heart rate variability

The results of the multiple regression model are displayed in Table 4, and they revealed that microfluctuations of accommodation were positively associated with reaction time ($p < 0.001$; Fig. 16). No significant association was observed for lag of accommodation and heart rate variability with behavioural performance (both p-values > 0.05).

Table 4. Multiple regression coefficients (β), and coefficients of determination (R^2) examining the association of ocular accommodation (lag and variability of accommodation) and heart rate variability (RMSSD) with behavioural performance (reaction time).

Dependent Variable	*Predictors*	*t*	*p*	*β*	R^2
Reaction time	RMSSD	-1.077	0.294	-0.164	0.065
	Lag of accommodation	-0.330	0.745	-0.051	0.033
	Variability of Accommodation	4.332	< 0.001	0.671	0.493

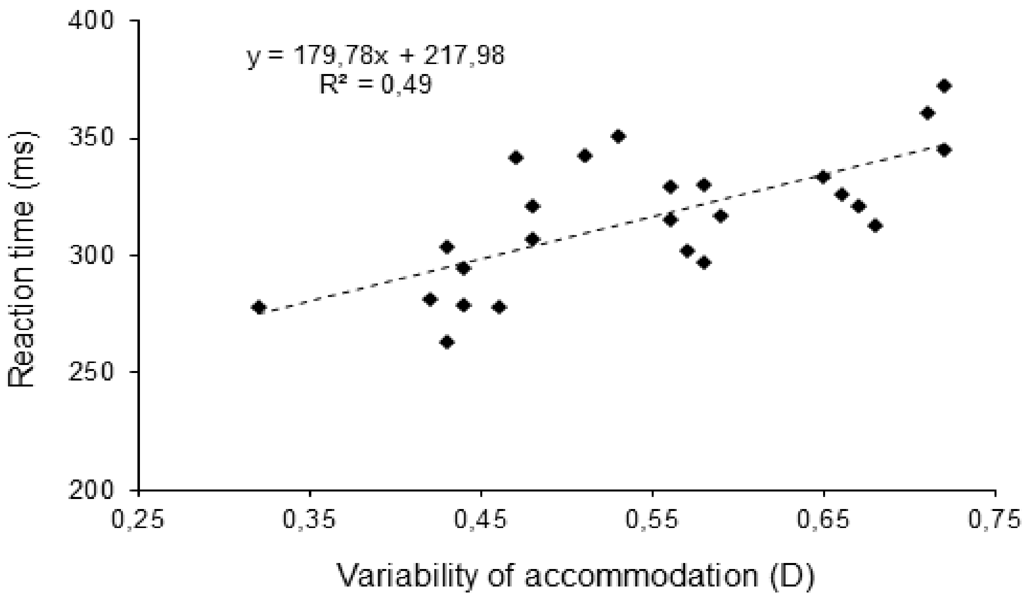

Figure 16. Relationship between the reaction time and microfluctuations of accommodation. The linear equation is displayed with the corresponding coefficient of determination (R^2). Values are calculated across the total sample size (n = 25). Both indices demonstrated a considerable level of correlation ($p < 0.001$, $r = 0.70$).

Inter-session repeatability

Table 5 displays the descriptive and inter-session repeatability values of the dependent variables for the five 2-min blocks, as well as the average values from the 10 minutes Psychomotor Vigilance Task. All dependent variables demonstrated a low to moderate inter-session repeatability, when measured on two different days under similar experimental conditions, with coefficients of variation and intraclass correlation coefficients ranges: 26.79─39.46% and 0.51─0.74 for lag of accommodation; 19.08─24.90% and 0.20─0.44 for microfluctuations of accommodation; 6.05─8.27% and 0.41─0.71 for reaction time; and 24.25─31.42% and 0.65─0.78 for heart rate variability, respectively. Bland-Altman plots revealed limits of agreement from -0.67D to 0.64D, -0.32D to 0.31D, and -66.56ms to 46.81ms for lag of accommodation, microfluctuations of accommodation, and reaction time, respectively (Fig. 17).

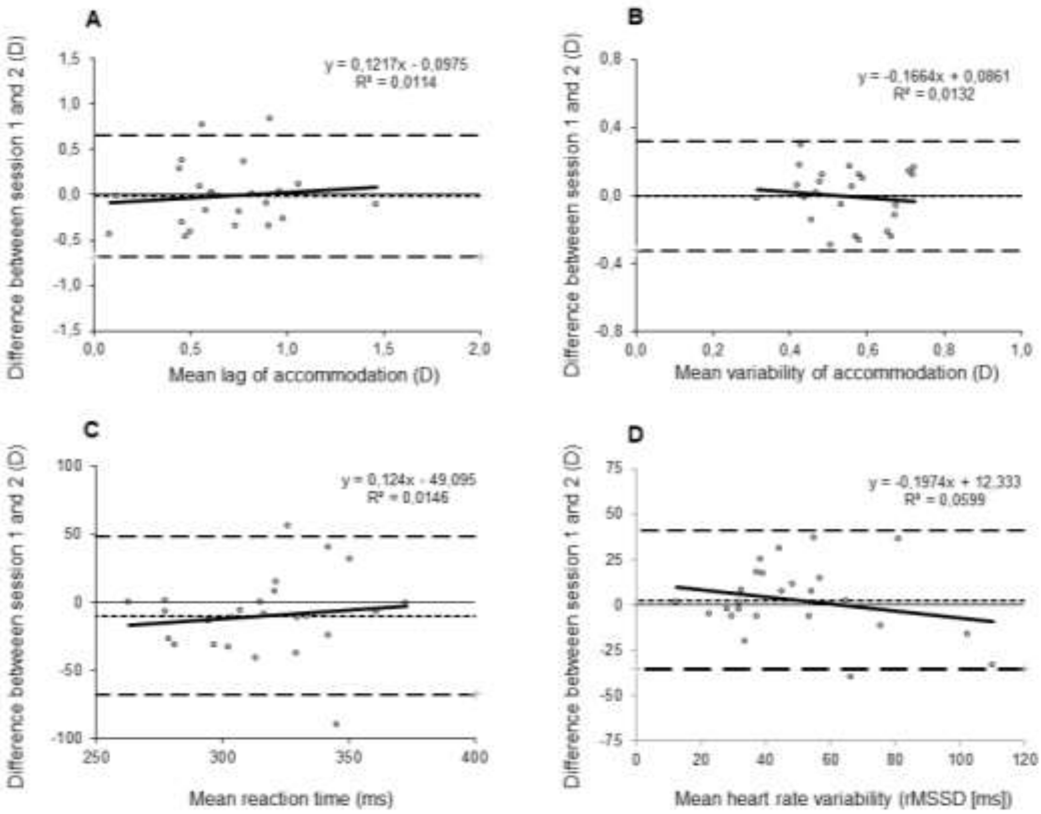

Figure 17. Bland and Altman plots illustrating the intersession repeatability of lag of accommodation (panel A), microfluctuations of accommodation (panel B), reaction time (panel C), and heart rate variability (panel D). The x-axis shows the mean value from session 1 and 2. The dotted line represents the mean bias and the dashed lines show the 95% limits of agreement. The regression line is represented by a solid black line, and the grey lines indicate the value zero.

Table 5. Inter-session repeatability of the values of accommodative lag, variability of accommodation, behavioural performance, and heart rate variability at each of the five 2-min block, as well as the average result from the 10-min psychomotor vigilance task.

		Session 1	Session 2	ES	CV (95% CI)	ICC (95% CI)
Lag of accommodation (D)	***Block 1***	0.70 ± 0.36	0.68 ± 0.41	0.05	39.46 (30.19 to 56.98)	0.52 (0.11 to 0.76)
	Block 2	0.68 ± 0.35	0.68 ± 0.37	0.00	33.22 (25.50 to 48.13)	0.62 (0.26 to 0.81)
	Block 3	0.63 ± 0.39	0.69 ± 0.31	0.17	37.86 (28.97 to 54.67)	0.51 (0.09 to 0.75)
	Block 4	0.67 ± 0.35	0.71 ± 0.31	0.12	33.65 (25.74 to 48.59)	0.52 (0.10 to 0.76)
	Block 5	0.68 ± 0.37	0.67 ± 0.32	0.01	26.79 (20.50 to 38.69)	0.74 (0.46 to 0.88)
	Mean	0.67 ± 0.35	0.69 ± 0.32	0.04	30.61 (23.42 to 44.20)	0.64 (0.29 to 0.82)
Variability of accommodation (D)	***Block 1***	0.51 ± 0.12	0.51 ± 0.14	0.05	23.75 (18.17 to 34.30)	0.20 (-0.30 to 0.56)
	Block 2	0.52 ± 0.14	0.51 ± 0.15	0.04	21.54 (16.48 to 31.11)	0.44 (-0.01 to 0.71)
	Block 3	0.56 ± 0.16	0.56 ± 0.16	0.05	23.98 (18.35 to 34.63)	0.31 (-0.17 to 0.63)
	Block 4	0.56 ± 0.15	0.58 ± 0.18	0.10	24.90 (19.05 to 35.96)	0.27 (-0.22 to 0.61)
	Block 5	0.58 ± 0.13	0.58 ± 0.17	0.00	19.94 (15.26 to 28.80)	0.43 (-0.01 to 0.71)
	Mean	0.54 ± 0.13	0.55 ± 0.14	0.04	19.08 (14.59 to 27.55)	0.43 (-0.02 to 0.71)
Reaction time (ms)	***Block 1***	302.69 ± 37.91	306.57 ± 30.31	0.11	8.06 (6.16 to 11.64)	0.50 (0.08 to 0.75)
	Block 2	301.70 ± 33.22	312.07 ± 37.13	0.29	8.27 (6.33 to 11.95)	0.50 (0.07 to 0.74)
	Block 3	313.84 ± 32.68	322.82 ± 30.58	0.28	7.75 (5.93 to 11.19)	0.41 (-0.05 to 0.69)
	Block 4	318.73 ± 38.90	326.76 ± 33.75	0.30	7.85 (6.01 to 11.34)	0.53 (0.13 to 0.77)
	Block 5	322.47 ± 40.72	337.51 ± 37.65	0.38	6.55 (5.01 to 9.46)	0.71 (0.41 to 0.86)
	Mean	311.27 ± 33.19	321.15 ± 30.07	0.31	6.05 (4.63 to 8.74)	0.65 (0.31 to 0.83)
RMSSD (ms)	***Block 1***	52.23 ± 23.00	50.39 ± 26.63	-0.07	24.25 (18.55 to 35.02)	0.76 (0.50 to 0.89)
	Block 2	50.70 ± 24.80	48.00 ± 30.21	-0.10	29.58 (22.63 to 42.71)	0.73 (0.45 to 0.87)
	Block 3	51.72 ± 25.60	48.88 ± 28.40	-0.10	32.51 (24.88 to 46.95)	0.65 (0.31 to 0.83)
	Block 4	49.31 ± 24.80	45.92 ± 27.31	-0.13	26.64 (20.38 to 38.47)	0.78 (0.53 to 0.89)
	Block 5	49.40 ± 22.50	47.24 ± 28.54	-0.08	31.42 (24.04 to 45.38)	0.67 (0.33 to 0.84)
	Mean	50.67 ± 23.30	48.09 ± 27.69	-0.10	27.43 (20.98 to 39.60)	0.73 (0.45 to 0.87)

Abbreviations: ES = effect size, CV = coefficient of variation, ICC = intra-class correlation coefficient, CI = confidence interval.

Discussion

The present study was designed to explore whether the influence of time-on-task during a vigilance task modulated the accommodative response (lag and microfluctuations), as well as exploring the capacity of ocular accommodation and heart rate variability to predict behavioural performance, as measured by reaction time. We also tested the inter-session repeatability of time-on-task effects on ocular accommodation, heart rate variability and reaction time. Our data demonstrated that the microfluctuations of accommodation were sensitive to time-on-task during sustained attention, showing greater fluctuations over time. However, the execution of a 10 min vigilance task did not induce any change in the lag of accommodation. The microfluctuations of accommodation predicted a significant amount of variance in reaction time during the vigilance task, whereas the rest of indices were not associated with reaction time. Accommodative response indices (lag and microfluctuations), reaction time, and heart rate variability revealed a poor level of inter-session repeatability. Taken together, these results indicated that microfluctuations of accommodation were modulated as a function of time-on-task and were associated with behavioural performance during sustained attention.

Our data revealed that the magnitude of the accommodative response did not change during the execution of the vigilance task (Fig. 15 A); however, previous studies have found a bidirectional relationship between attention and ocular accommodation functioning. For example, Poltavski et al., (2012) found that alteration of the accommodative-vergence system during a sustained attention task (Conner’s continuous performance test) impaired cognitive performance, as measured by a slower reaction time, whereas Redondo et al., (2018) demonstrated that children with attentional deficits had an altered accommodative response (higher lags of accommodation) in comparison to healthy controls. Based on the findings of Rosenfield & Ciufredda (1990), ocular accommodation seems to be a reliable objective index of brain activity during cognitively demanding tasks, with the dynamics of ocular accommodation being sensitive to the effects caused by mental effort on the sympathetic nervous system (Davies et al., 2005; Bullimore & Gilmartin, 1988). As previously stated, we found no effects of time-on-task during the Psychomotor Vigilance Task for lag of accommodation, in contrast to the study of Davies et al., (2005), who found a reduction of the accommodative response with increasing cognitive demand. Nevertheless, these differences might be explained by cognitive demands in the present study and those in Davies et al., (2005), not being comparable. Two different tasks were employed, Psychomotor Vigilance Task in the current study and a numerical forced-choice paradigm task in Davies et al., (2005), and recent investigations have showed that physiological responses to mental effort, such as intraocular pressure and heart rate variability, are highly dependent on task complexity. In regard to the stability of ocular accommodation, greater microfluctuations of accommodation were found in the second half of the task, in comparison to the first 2-minute block (Fig. 15B), suggesting that more than five minutes of sustained attention were needed to observe significant changes in the dynamics of ocular accommodation. Notably, higher microfluctuations of accommodation have proven to be an accurate and sensitive indicator of visual fatigue and stress (Jeng et al., 2014; Kajita et al., 2001), whereas other visual indices such as accommodation magnitude, pupil diameter, visual acuity, eye movement velocity and critical function frequency have been less valid in this regard (Chi & Lin, 1998). A recent study has demonstrated that young adults have a more stable accommodative response (lower variability) when viewing highly engaging tasks (Roberts et al., 2018). The increased microfluctuations of accommodation over time observed in the present study could be caused by cognitive fatigue, leading to reduced attention capabilities (Grier et al., 2003). In view of the current results, microfluctuations of accommodation could be considered as an objective indicator of performance impairment associated with mental workload, fatigue or drowsiness in real-world contexts, such as driving, piloting, and air traffic management. Clearly, this is an area for future studies.

Consistent with the microfluctuations of accommodation and previous reports (Luque-Casado et al., 2016), we found that sustained attention induced a decrement in behavioural performance over time, as measured by slower reaction times. This change was particularly pronounced in the second half of the 10-minute Psychomotor Vigilance Task, when compared with values obtained in the initial stages of the task (Fig. 15C). This set of results was consistent with many studies that have reported a time-on-task effect during the execution of the Psychomotor Vigilance Task, with reaction time increasing continuously due to the depletion of cognitive resources (Basner & Dinges, 2011; Lim et al., 2010).

Maintaining high levels of attention or cognitive engagement is paramount for professional duties, such as piloting an aircraft, performing a surgical task, driving and managing air traffic; therefore, monitoring the attentional state of individuals in these situations constitutes a key element in terms of safety. Self-reported measures have been commonly used to assess cognitive states, including levels of attention. However, these measures present several limitations due to their dependence on personal and motivational factors (Podsakoff et al., 2003). To overcome these constraints, numerous physiological indices, such as electroencephalographic or cardiovascular activity, ocular dynamics and intraocular pressure have attracted research interest as potential markers of levels of attention (Borghini et al., 2012; Di Stasi et al., 2013; Vera et al., 2018). Regarding ocular accommodative mechanisms, there is controversy regarding the changes that occur during mental effort and attention tasks. These variations depend on the methodology, nature of the processing task and the fixation distance (Davies et al., 2005; Gray et al., 2000; Winn & Gilmartin, 1992). Overall, it has been suggested that mental processing tasks induce greater variations on the accommodative response in open-loop stimulus dependent conditions (Edgar, 2007). The present study incorporated preliminary results on the utility of microfluctuations of accommodation as a reasonably good predictor of behavioural performance for a sustained attention task, as measured by reaction time, in closed-loop conditions.

We hypothesized a gradual decrease in the vagal component of heart rate variability (i.e., RMSSD) as a function of the time-on-task, which could presumably be associated with both the dynamics of ocular parameters and the task performance (Davies et al., 2005; Jeng et al., 2014; Luque-Casado et al., 2015). Although vagal tone has previously been linked to Psychomotor Vigilance Task performance and dynamics over time (Luque-Casado et al., 2016; Luque-Casado et al., 2015), our results were not consistent with these reports. However, the time-related dynamics of vagal tone have only been observed in the male population (Luque-Casado et al., 2016), and more importantly, it seems to depend on the level of physical fitness of the participants (Luque-Casado et al., 2013). Therefore, given that the current experiment included men and women with different levels of physical fitness, it cannot be ruled out that the study sample did not influenced the null result reported for this parameter. Future studies should consider gender and fitness level as potential contributory factors. In addition, the current study did not find a significant association between the cardiovascular and ocular accommodation functioning. In this regard, some authors have reported a relationship between the dynamics of ocular accommodation and cardiovascular activity (Davies et al., 2005; Bullimore & Gilmartin, 1988); however, the association of the frequency components of heart rate variability with ocular accommodation seems to be fairly weak (Hampson, et al., 2005).

Repeatability concerns the precision of repeated measurements by an observer when all external factors are kept constant (McAlinden, Khadka, & Pesudovs, 2011). For the current study, repeating the protocol under the same experimental conditions generally revealed a low repeatability for ocular accommodation, behavioural performance and heart rate variability (Table 5). This result suggested that variables measured at different times should be interpreted with caution in both a clinical and research setting. In previous studies, cardiac autonomic regulation, as measured by heart rate variability (Cipryan & Litschmannova, 2013), as well as reaction time (Lemay et al., 2004) have demonstrated a considerable random inter-day variability, and our results for ocular accommodation seem to be consistent with these findings. There have been no previous studies examining inter-day repeatability of ocular accommodation. We found a comparable repeatability for accommodative response with respect to that observed for cardiovascular activity and behavioural performance. Nevertheless, the results of ocular accommodation for the entire group remain stable, when measured on two different days under identical experimental conditions, as shown by the negligible effect sizes between sessions. In summary, while group behaviour was reasonably robust, inter-subject variation was quite substantial for accommodative responses. These findings should be considered when assessing ocular accommodation, both in clinical practice and the laboratory.

The functioning of ocular accommodation and attentional state are predominately mediated by the same brain structures, such as the reticular formation and cerebellum (McDougal & Gamlin, 2015); therefore, a bidirectional relationship might be expected between ocular accommodation and behavioural performance. In this regard, a recent study concluded that the superior colliculus, which is located at reticular formation, may be altered in a rodent model of attention-deficit/hyperactivity disorder (Brace et al., 2015), suggesting an association between attention capabilities and the structures involved in the control of accommodation. In the present study, we found a significant association for microfluctuations of accommodation with sustained attentional performance, whereas lag of accommodation or cardiovascular activity failed to predict behavioural performance. Future studies should explore the brain mechanisms that might explain the relationship between the stability of ocular accommodation and reaction time during a vigilance task, as well as the lack of association between the magnitude of ocular accommodation and sustained attentional performance.

This study was not exempt from limitations. Our data revealed a positive linear association between behavioural performance (reaction time) and microfluctuations of accommodation. Nevertheless, we are aware that correlation does not imply causation, and thus, our results need to be interpreted accordingly. This study was conducted in a group of university students, and the external validity of these results to the general public where there would be greater variation in age and cognitive skills was unknown. Lastly, several factors, such as circadian variations, gender, caffeine intake, fitness level and sleep deprivation (Ballard, 1996; Luque-Casado, Perales, et al., 2016; Luque-Casado et al., 2013), may alter the physiological response during prolonged attention; therefore, these factors should be tested in future investigations, particularly due to their potential relevance in applied settings. Currently, researchers are attempting to find standardized systems to measure physiological parameters related to task overload or fatigue, especially in real-world scenarios where the aim is to enhance safety (Di Stasi et al., 2013).

Conclusions

This study demonstrated that performing a sustained attention (vigilance) task induced greater levels of microfluctuations of accommodation over time, whereas lag of accommodation remained unchanged during the 10-minute attention task. There was a positive association between reaction time and microfluctuations of accommodation, suggesting that the dynamics of ocular accommodation might be considered as a potential predictor of behavioural performance. However, these results might be limited by the low levels of inter-session reliability of ocular accommodation and behavioural performance. The present findings might be of special relevance due to their possible implications in the design of assistance systems in real world situations, such as driving, piloting and other occupational settings where public safety is paramount.

CHAPTER 4: EFFECTS OF ATTENTION ON THE ACCOMMODATIVE RESPONSE

STUDY V. ACCOMMODATIVE DYNAMICS AND ATTENTION: THE INFLUENCE OF MANIPULATING THE ATTENTIONAL CAPACITY ON ACCOMMODATIVE LAG AND VARIABILITY

Introduction

Appropriate functioning of accommodation system is paramount to achieve a sharp retinal image at different distances, with the dynamics of ocular accommodation being dependent on numerous factors (e.g., image blur, retinal disparity, optical aberrations) (Fincham & Walton, 1957; Gambra & Marcos, 2009; Phillips & Stark, 1977). In addition to optical signals, different cognitive demands have been shown to alter ocular dynamics, possibly due to the overlap between the brain areas involved in processing cognitively demanding tasks and those controlling the dynamics of ocular accommodation (Davies et al., 2005; Vera et al., 2016). Recent studies have evidenced that a reduction in the level of attention/alertness promotes greater lags of accommodation (Francis et al., 2003; Vera et al., 2016), and also, a less accurate accommodative response has been found in children with attention deficits in comparison to age-matched controls (Redondo et al., 2018).

Evidence suggests that connections from the cerebellum via the Edinger–Westphal are targeted to the ciliary muscle, and thus controlling the dynamics of ocular accommodation (McDougal & Gamlin, 2015). Also, there are other brain areas that have demonstrated to play a role in driving the near triad (e.g., midbrain, frontal eye fields, extrastriate cortex or parietal cortex) (May et al., 2019; McDougal & Gamlin, 2015; Ostrin & Glasser, 2010). Similarly, some of those mentioned brain areas (i.e., cerebellum, midbrain and frontal cortex) also regulate the attentional state (Kellermann et al., 2012; Knudsen, 2011; Scolari et al., 2015). Based on the shared brain mechanisms between attention and ocular accommodation, an association between the level of attention (i.e., the ability to focus on task-relevant stimuli in order to optimize task performance) and the dynamics of the accommodative response seems plausible, as has been showed for the pupil dynamics (Hopstaken et al., 2015; Konishi et al., 2017) and eye movements (Corbetta et al., 1998; Kustov & Robinson, 1996).

Notably, greater values of lag and variability of accommodation have been linked to visual discomfort and myopia progression (Charman & Heron, 2015; Schmid & Strang, 2015; Tosha et al., 2009), suggesting that a thorough knowledge of the factors affecting accommodative response dynamics has theoretical and practical relevance. Regarding the attentional state, there are different strategies that allow to enhance the capacity to focus on task-relevant stimuli (attention facilitators), as well as to reduce the attentional capacity (attention distractors). In this sense, auditory or visual biofeedback has been commonly used to enhance attention (Schwartz & Andrasik, 2017), whereas dual-tasking leads to divide attention, limiting the attentional resources for both tasks (Wickens, 2008). Hitherto, there are no studies that have assessed the influence of manipulating the attentional capacity on the accommodative response dynamics, which may be of relevance for the prevention and management of visual discomfort and myopia progression.

Aiming to fulfil the limitations found in the scientific literature, the main objectives of the present study were: (1) to assess the short-term effects of attention distractors and facilitators on the dynamics of the accommodative response and pupil size, and (2) to test whether these changes are dependent on the level (low and high) of attention distractors and facilitators, as well as the accommodative demand (0 D, 2.5 D, 5 D). We hypothesized that the accommodative response dynamics will be sensitive to changes in the levels of attention, as it has been showed in children with attentional deficits (Redondo et al., 2018), as well as for the pupil dynamics (Hopstaken et al., 2015; Konishi et al., 2017).

Methods

Participants

Prior to data collection, we performed an a-priori power analysis with the GPower 3 software (Faul et al., 2007), assuming an effect size of 0.20, alpha of 0.05, and power between 0.80 and 0.90, for repeated measures (within factors) analysis of variance. This analysis projected a required sample size between 16 (power 0.80) and 20 (power 0.90) participants. Consequently, 20 healthy young adults (13 women and 7 men; mean age ± standard deviation = 22.8 ± 4.5 years, range age = 18 – 30 years) were recruited. All participants were screened for the following inclusion criteria: (i) be free of any ocular disease, as assessed by slit lamp and direct ophthalmoscopy examination, (ii) normal or corrected-to-normal vision at far and near distances (visual acuity of ≤ 0 logMAR in each eye), (iii) no significant uncorrected refractive error (myopia < 0.50 D, astigmatism and anisometropia < 1.00 D, and/or hyperopia of < 1.50 D) (Chase et al., 2009), (iv) amplitude of accommodation within the normal range, as calculated by the Hofstetter's formula (Hofstetter, 1950), (v) near stereoacuity of 50 seconds of arc or better as measured with the Randot stereotest (Scheiman & Wick, 2008), and (vi) be free of visual discomfort based on the scores of the Conlon survey (Conlon et al., 1999). In addition, participants were asked to avoid the performance of highly demanding physical exercise on the day of testing, and abstain from alcohol and caffeine ingestion for 24 and 12 h, respectively, prior to data collection (Redondo et al., 2019; Vera et al., 2018). The study adhered to the tenets of the Declaration of Helsinki, and was approved by the University of Granada Institutional Review Board (IRB approval: 546/CEIH/2018). Written informed consent was obtained from all participants.

Accommodative response and pupil dynamics assessment

A binocular open-field autorefractor (WAM-5500, Grand Seiko Co. Ltd., Hiroshima, Japan) was used to objectively assess the dynamics of the accommodative response and pupil size (Sheppard & Davies, 2010). This instrument allows to acquire continuous recordings (temporal resolution of ~ 5 Hz) of accommodation and pupil size in its high-speed mode, with a sensitivity of 0.01 D and 0.1 mm, respectively. Accommodative response and pupil size were recorded continuously during the 90 seconds of each trial while participants fixated on the Maltese cross. All measurements were performed under binocular conditions, and the dominant eye, as determined by the Hole-in-card method (Durand and Gould, 1910), was chosen for data acquisition (Momeni-Moghaddam et al., 2014). For data analysis, data points varying more than 3 SD from the mean value were removed, since they are considered blinks or recording errors (Tosha et al., 2009). The remaining data points were used for further analyses. For the calculation of the lag of accommodation, we subtracted the average accommodative response during the 90 seconds trial to the accommodative demand at the different target distances (500 cm = 0.2 D; 40 cm = 2.5 D; and 20 cm = 5 D). Also, aiming to control for the effects of residual refractive errors, the average accommodative response was corrected by the baseline static refractive value at far distance (Poltavski, Biberdorf, & Petros, 2012; Redondo et al., 2018). The standard deviations from the continuous recording of accommodation and pupil were considered as the variability of accommodation and pupil size, respectively. Pupil data from four participants were lost due to recording failure, and thus, data from sixteen subjects were used for the analysis of pupil dynamics.

Procedure

The experiment was conducted in a single session with 15 trials (3 target distances x 5 experimental manipulation), which were performed in a randomized manner. Each trial lasted 90 seconds, with a 3-minute break given between two successive trials. Upon arrival at the laboratory, participants signed the consent form and an experienced optometrist performed the optometric tests required to ensure the inclusion criteria were met. Participants were seated at the autorefractometer, using the corresponding chin and forehead supports. Baseline distance refractive error was obtained and used to determine the lag of accommodation in subsequent data analyses. At this point, the experimental conditions were carefully explained to the participants, and the main part of the experimental session started. In all experimental conditions, participants wore their soft contact lenses when necessary and were asked to look at a high-contrast Maltese cross (Michelson contrast = 79%, base luminance = 31 cd m^{-2}) while positioned on the chin and forehead supports of the WAM-5500. The illuminance levels of the room were kept constant during the entire experiment (~ 150 lx as measured in the corneal plane, T-10 Konica Minolta Inc., Tokyo, Japan).

The experimental manipulation was as follows:

(i) Control: participants were asked to fixate and maintain on focus the Maltese cross for 90 seconds.

(ii) Low mental load: based on Siegenthaler et al., (2014), participants were instructed to count forwards mentally, as fast and accurately as possible, in steps of two starting at a random three-digit number for 90 seconds. At the same time, they were asked to maintain on focus the Maltese cross.

(iii) High mental load: in line with the instructions given by Siegenthaler et al., (2014), and while fixating and maintaining on focus the Maltese cross, participants were asked to count mentally backwards, as fast and accurately as possible, in steps of 17 starting at a random four-digit number.

(iv) Low feedback: as auditory cues may enhance visual attention (Ho & Spence, 2005), four auditory beeps were randomly introduced during the trial while fixating on the Maltese cross, which were previously described to participants as a type of feedback for inaccurate accommodation. Thus, one auditory beep meant an out-of-focus image detected by the instrument.

(v) High feedback: eight auditory beeps were randomly introduced during the trial while participants kept in focus the Maltese cross, which were previously described to participants as a type of feedback for inaccurate accommodation.

Experimental design

A repeated measures design (3 target distance x 5 experimental manipulation) was used to explore the effects of manipulating the attentional resources on the accommodative response and pupil dynamics. The within-participants factors were the target distance (500 cm, 40 cm and 20 cm) and the experimental manipulation (control, low mental load, high mental load, low feedback, high feedback). The dependent variables were the lag and variability of ocular accommodation, and the magnitude and variability of pupil size.

Statistical analysis

The normal distribution of the data was confirmed by the Shapiro-Wilk test ($P > 0.05$). Repeated measures analyses of variance, considering the target distance (500 cm, 40 cm and 20 cm) and the attentional resources manipulation (control, low mental load, high mental load, low feedback, high feedback) as within-participants factors, were conducted for each dependent variable. Post hoc comparisons were corrected with Holm-Bonferroni procedure, and the magnitude of the changes was reported by means of Cohen´s d and partial eta squared (η^2_p) for T-tests and Fs, respectively. An alpha level of 0.05 was adopted to determine statistical significance.

Results

In this study, data from seven myopes (mean spherical equivalent > -0.50 D, maximum value -2.25 D), five hyperopes (mean spherical equivalent > +0.75 D, maximum value +1.50 D), and eight emmetropic (mean spherical equivalent between -0.50D and +0.75D).

The analysis of the lag of accommodation yielded a statistically significant effect for the target distance ($F_{2, 34} = 93.49$, $P < 0.001$, $\eta^2p = 0.85$), the experimental manipulation ($F_{4, 68} = 4.95$, $P = 0.001$, $\eta^2_p = 0.23$), and the interaction target distance × experimental manipulation ($F_{8, 136} = 5.53$, $P < 0.001$, $\eta^2_p = 0.25$). Post hoc comparisons between target distances exhibited greater lags of accommodation at 20 cm in comparison to 40 cm (corrected P-value < 0.001, d = 0.98) and 500 cm (corrected P-value < 0.001, d = 2.58), as well as greater lags at 40 cm when compared to 500 cm (corrected P-value < 0.001, d = 2.41). The comparisons between the different experimental conditions reached statistical significance for the comparison between the high-feedback and control conditions (corrected P-value = 0.009, d = 0.95), with the high-feedback condition leading to lower lags of accommodation. Also, pairwise analyses were performed for the values obtained in the low- and high-loads conditions, as well as the low- and high-feedback conditions in comparison to the control condition at each of the three target distances, and they are displayed in Figure 18 (panel A).

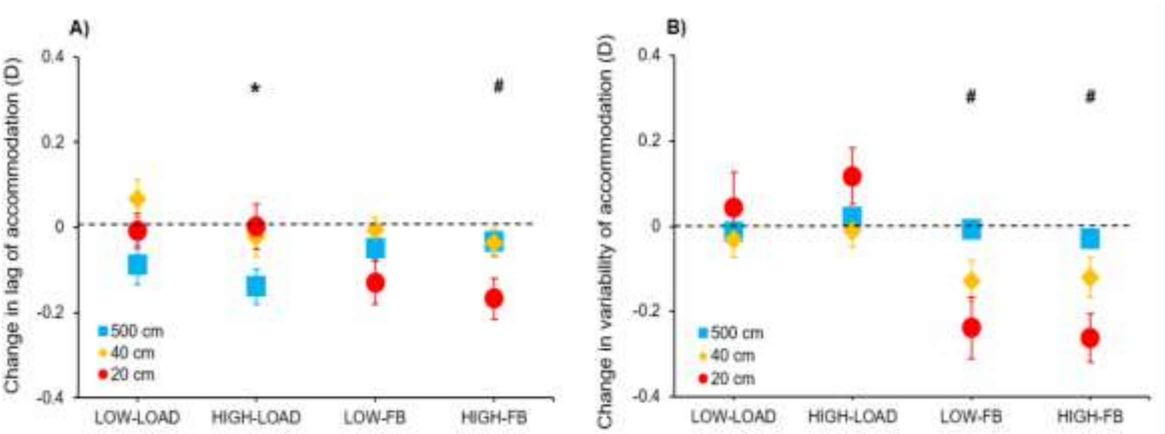

Figure 18. Effect of attentional resources manipulation on the lag (panel A) and variability (panel B) of accommodation. Values are calculated as the difference between each experimental condition and the control condition. * and # denote a statistically significant difference (corrected P-value < 0.05) in comparison to the control condition at 500 cm and 20 cm, respectively. Error bars show the standard error. All values are calculated across participants (n = 20). The low- and high-load conditions refer to the two levels of mental load, counting forward in steps of 2 and backwards in steps of 17, respectively. The low- and high- FB conditions indicate the two levels of auditory feedback, consisting in four and eight auditory beeps, respectively.

The analysis of the variability of accommodation exhibited statistically significant differences for the target distance ($F_{2, 34}$ = 78.07, P < 0.001, η^2_p = 0.82), the experimental manipulation ($F_{4, 68}$ = 12.76, P < 0.001, η^2_p = 0.43), and the interaction target distance × experimental manipulation ($F_{8, 136}$ = 5.30, P < 0.001, η^2_p = 0.24). Post-hoc comparison between the three target distances revealed a greater variability of accommodation at 20 cm in comparison to 40 cm (corrected P-value < 0.001, d =1.63) and 500 cm (corrected P-value < 0.001, d = 2.26), as well as for 40 cm when compared with 500 cm (corrected P-value < 0.001, d = 2.70). For its part, a lower variability of accommodation was found for the high-feedback condition in comparison to the control (corrected P-value < 0.001, d = 1.30), low-load (corrected P-value = 0.013, d = 0.84) and high-load (corrected P-value < 0.001, d = 1.46) conditions. Also, the low-feedback condition induced a more stable variability of accommodation in comparison to the control (corrected P-value = 0.005, d = 0.98), low-load (corrected P-value = 0.011, d = 0.87) and high-load (corrected P-value = 0.002, d = 1.09) conditions. Further pairwise comparisons at each of the three target distances are depicted in Figure 18 (panel B).

The pupil size showed statistically significant differences for the target distance ($F_{2, 30}$ = 13.62, P < 0.001, η^2_p = 0.48) and the experimental manipulation ($F_{4, 60}$ = 39.85, P < 0.001, η^2_p = 0.73), but no differences were observed for the interaction ($F_{8, 120}$ = 0.25, P = 0.980). Post hoc comparison between the different target distances demonstrated that there were lower pupil sizes at 20 cm in comparison to 500 cm (corrected P-value = 0.006, d = 0.88) and 40 cm (corrected P-value < 0.001, d = 1.43). However, no differences were reached for the comparison 500 cm vs 40 cm (corrected P-value = 0.585). For its part, the comparison between the five experimental conditions exhibited that there were greater pupil sizes in the low-load and high-load conditions in comparison to the control, low-feedback and high-feedback conditions (all corrected P-values < 0.001). Figure 19 (panel A) shows the comparisons performed for the low- and high-mental load conditions, and the low- and high-feedback conditions with the control condition at each of the three target distances.

Lastly, the variability of the pupil size was sensitive to the target distance ($F_{2, 30}$ = 5.06, P = 0.013, η^2_p = 0.25) and the experimental manipulation ($F_{4, 60}$ = 11.08, P < 0.001, η^2_p = 0.43). However, no differences were obtained for the interaction target distance × experimental manipulation ($F_{8, 120}$ = 1.01, P = 0.435). Post-hoc comparisons for the target distances revealed a greater variability at 40 cm in comparison to 20 cm (corrected P-value = 0.020, d = 0.78). Post-hoc comparisons for the experimental manipulation showed that there were lower values of pupil size variability in the high-feedback condition in comparison to the control (corrected P-value = 0.009, d = 0.98), low-load (corrected P-value = 0.002, d = 1.19) and high-load (corrected P-value < 0.001, d = 1.35) conditions, as well as in the low-feedback condition when compared with the low-load (corrected P-value = 0.013, d = 0.93) and high-load (corrected P-value < 0.001, d = 1.31) conditions.

Also, further comparisons between experimental conditions at each target distance are displayed in Figure 19 (panel B).

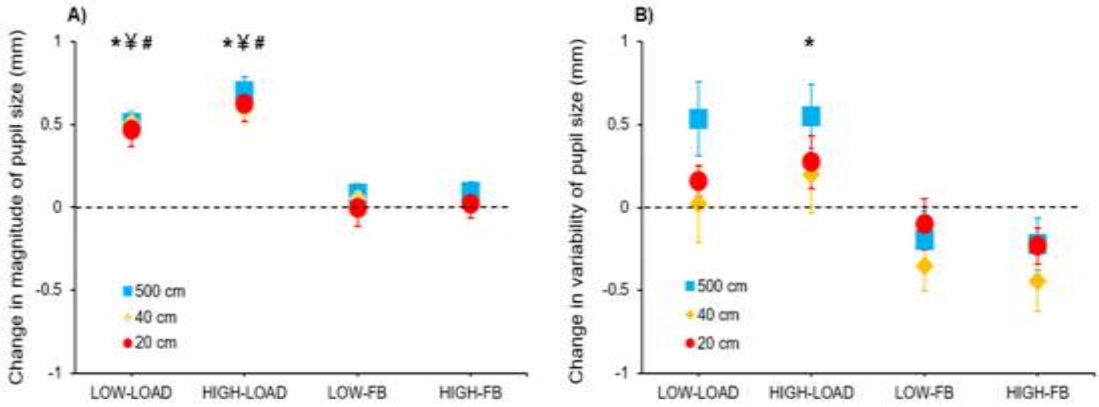

Figure 19. Effect of attentional resources manipulation on the magnitude (panel A) and variability (panel B) of pupil size. Values are calculated as the difference between each experimental condition and the control condition. *, ¥ and # denote a statistically significant difference (corrected P-value < 0.05) in comparison to the control condition at 500 cm, 40 cm and 20 cm, respectively. Error bars show the standard error. All values are calculated across participants (n = 16). The low- and high-load conditions refer to the two levels of mental load, counting forward in steps of 2 and backwards in steps of 17, respectively. The low- and high- FB conditions indicate the two levels of auditory feedback, consisting in four and eight auditory beeps, respectively.

Discussion

The present study was designed to assess the impact of manipulating the attentional state on accommodative and pupil dynamics. Our results incorporate novel insights into the short-term effects of auditory biofeedback on the lag and variability of the accommodative response. Auditory feedback improved both the lag and variability of accommodation, with these changes being significant at closer distances, while dual-tasking promoted a greater accommodative response at far distance. We also found that only dual-tasking altered the pupil dynamics, observing a greater magnitude of pupil size when performing arithmetic tasks and a higher variability of pupil size while performing the low- and high load conditions of dual-tasking. These findings open up new avenues for modulating the accommodative response dynamics, which may have important implications for the prevention and management of myopia progression and asthenopia.

Regarding the impact of attentional distractors, our data showed that the imposition of an arithmetic task while fixating on a distance visual target alters the dynamics of ocular accommodation. Specifically, a greater accommodative response was found in the more mentally demanding task in comparison to the control condition (mean difference = 0.14 ± 0.18 D). Although there are numerous studies that have assessed the accommodative response changes associated with mental effort (Bullimore & Gilmartin, 1987; Jainta et al., 2008; Kruger, 1980; Malmstrom & Randle, 1984; Rosenfield & Ciuffreda, 1990), the direction and magnitude of the changes in accommodation have been unclear, which may be mainly attributable to discrepancies in the measurement methods, viewing target and individual differences. Our results are consistent with those reported by Davies and colleagues (2005), who using an open-view infrared autorefractor, found a reduction in the lag of accommodation while performing a two-alternative forced-choice task. Also, this specific result is in line with Bullimore & Gilmartin (1988), who found that mental effort caused a heightened accommodative response at the farthest stimulus (1 D), but no changes were observed at closer distances (3 and 5 D). Based on the fact that the greater accommodative response with mental load was only evident at far distance, it cannot be attributable to sympathetic activity, since this branch is inhibitory and is only present with concurrent activity from the parasympathetic system (i.e., near-work) (Chen et al., 2003; Gilmartin et al., 2002; Mallen et al., 2005). Accordingly, there is evidence that changes in ocular accommodation seems to be associated with changes in systemic parasympathetic nervous system, with these changes being associated with cognitive effort (Davies et al., 2009). As proposed by Toates (1972), parasympathetic withdrawal is required for distance targets, and thus, the greater accommodative response observed in the high mental load condition may be due to an increased parasympathetic tone during cognitive effort (Iwasaki, 1993).

The use of auditory feedback reduced the lag and variability of accommodation at near distances, with these effects being more evident for the stability of the accommodative response (Figure 18). In agreement with Wagner et al., (2016), we found a greater reduction in the lag of accommodation with auditory feedback at the closer target distance (5.00 D, 20 cm), observing a lower accommodative lag of 0.17 ± 0.21 D at the 20 cm target distance for the high-feedback condition in comparison to the control condition. Likewise, the most relevant outcomes of this study are probably those achieved in relation to the behaviour of accommodative variability with auditory feedback, since to the best of our knowledge, this is the first study assessing the impact of auditory feedback on stability of the accommodative response. Indeed, a significant improvement in the stability of accommodation was observed with both levels of auditory feedback at closer distances, with these changes ranging from ~ 0.10 D at 40 cm to ~ 0.25 D at 50 cm. In this sense, a better performance in visual tasks has been observed when adding auditory cues, supporting the capacity of the auditory system to capture visual attention (see Koelewijn, Bronkhorst, & Theeuwes, 2010 for a review). This study seems to confirm this idea and shows that auditory cues allow to enhance the accuracy of the accommodative response dynamics.

Complementarily, we assessed the impact of manipulating the attentional state on the pupil dynamics. The imposition of an arithmetic task while focusing on the visual target induced a substantial increment of the pupil size (~ 0.50 and ~ 0.65 mm for the low and high mental load conditions, respectively), showing a similar pupil dilation for the three target distances (Figure 19). Notably, there is extensive evidence that pupil dilation is a surrogate measure of cognitive effort (Kahneman & Beatty, 1966; van der Wel & van Steenbergen, 2018), and it may be used as an objective indicator of attentional lapses (Van Den Brink et al., 2016). Our findings fully agree with the fact that mental load induces pupil dilation. Based on the fact that cognitive effort was associated with pupil dilation regardless of target distance, but the changes in ocular accommodation caused by the mental load conditions were dependent on target distance, it is reasonable to state that changes in pupil appear to have little effect on ocular accommodation in this study. In fact, there is scientific evidence that the accommodative response is only affected by changes in pupil size when the pupil diameter is lower than 3 mm (Ward & Charman, 1985). Our participants exhibited a pupil size ranging between 3.37 and 7.87 mm across experimental conditions and target distances, and thus, the accommodative changes induced by mental load or auditory feedback seem to be independent of variations in pupil diameter.

Attention is a selective process, which is related to limited cognitive and brain resources to process information imposed by the fixed amount of overall energy available to the brain (Carrasco, 2011). In view of the observed results, the inclusion of attentional distractors (dual-tasking) may provoke that the accommodative stimulus location become less relevant, whereas the preservation of all the attentional resources on the accommodative stimuli (auditory feedback condition) seems to optimize visual performance. As previously stated, the ocular dynamics is linked to brain areas controlling attention, and neural alterations in attention-related mechanisms may lead to changes in the accommodative response dynamics (McDougal & Gamlin, 2015; Ostrin & Glasser, 2010; Steinmetz & Moore, 2014). Our findings indicate that the dynamics of the accommodative response are affected by the experimental manipulation of non-optical factors (i.e., attentional state). From a clinical perspective, an altered functioning of ocular accommodation may be an important risk factor in the progression of myopia, with greater lag and variability of accommodation being associated with myopia progression (Allen & O´Leary, 2006; Charman & Heron, 2015; Langaas et al., 2008; Millodot, 2015; Schmid & Strang, 2015). Based on the link between attention and accommodative response, it would be of interest to explore the influence of the attentional state (e.g., children with attention-deficit/hyperactivity disorder) on the development and progression of myopia, as well as the potential utility of using auditory feedback training to prevent and reduce the onset and progression of myopia in subjects with an impaired accommodative response. Also, deficits in the magnitude and stability of the accommodative response (Charman & Heron, 2015; Iwasaki & Kurimoto, 1987; Tosha et al., 2009) seem to be associated with visual discomfort, and thus, the attentional state should be considered for the prevention and management of this condition.

The present study incorporates novel insights into the association between the attentional state and accommodative dynamics, suggesting that increasing the level of attention on the visual target with auditory feedback may optimize accommodation accuracy. Nevertheless, this investigation is not exempt of limitations, and they must be acknowledged. First, we have speculated that there are common brain areas in the control of attention and ocular dynamics, and therefore, they may play a role on the changes in the dynamics of the accommodative response when manipulating the attentional state. However, future brain-imagining studies should consider determining the specific brain areas and mechanisms involved in this association. Second, our experimental sample was formed by healthy young adults, and it is our hope that future studies will include clinical populations (e.g., individuals with attentional or accommodative deficits) and children in order to ascertain the external validity of the current findings. Third, there are controversial results about the mediating role of refractive error in accommodative dynamics (Anderson et al., 2010; Charman & Heron, 2015; Millodot, 2015). The inclusion of larger sample sizes would allow to divide the experimental sample according to the refractive error and ascertain the association between the attentional state and the accommodative response in different refractive error groups. Forth, physiological reactivity and perceived mental load are subject to individual differences (Hancock & Desmond, 2000), and thus, the two levels of mental complexity used in this study are unlikely to be equally difficult for all participants. Lastly, we have investigated the short-term effects of manipulating the capacity to focus on task-relevant stimuli on the accommodative dynamics, however, future studies would be required to explore the long-term effects in clinical settings.

Conclusions

Our data indicate that the accommodative response dynamics is sensitive to changes in the capacity to focus on task-relevant stimuli. The imposition of an arithmetic task while fixating on a distant target induced a greater accommodative response, whereas the use of auditory feedback to capture attention led to a reduction in accommodative lag. For the accommodative variability, there was a substantial stabilization of the accommodative response at near distances with auditory feedback. These findings highlight the impact of the attentional state on the ocular dynamics and may help in the development of strategies for the prevention and management of myopia progression and visual discomfort in subjects with accommodative deficits.

STUDY VI. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CHILDREN EXHIBIT AN IMPAIRED ACCOMMODATIVE RESPONSE

Introduction

Attention-deficit/hyperactivity disorder is a common neuropsychiatric disorder with onset in childhood and persistence into adulthood (Barkley, 2014). It is characterized by symptoms of inattention, hyperactivity, and impulsiveness (American Psychiatric Association., 2013) with a prevalence of 5.29% in those younger than 18 years old (Polanczyk et al., 2007). Children with attention-deficit/hyperactivity disorder have a disproportionately high incidence of behavioural problems and learning disabilities (Tannock & Brown, 2000), and they show a greater prevalence to repeat grades or to be placed in special-education classes in comparison to children without attention-deficit/hyperactivity disorder (Loe & Feldman, 2007). The incorporation of brain-imaging studies to this area of research have revealed a brain maturation delay in attention-deficit/hyperactivity disorder with a reduced striatal volume, and differences in accumbens, hippocampal, and amygdala volumes between cases and control, possibly contributing to deficits in emotional regulation, motivation, and memory in patients with attention-deficit/hyperactivity disorder (Hoogman et al., 2017).

The eyes are considered a prolongation of the central nervous system (Di Stasi et al., 2012), and therefore the ocular system permits the detection of the nervous system's state of activation or neurological alterations (Vera, et al., 2017). Several ocular indices have proved sensitive to central nervous system alterations. In particular, eye-movement deficits and binocular alterations have been shown in children with attention-deficit/hyperactivity disorder (Puig, Zapata, Puigcerver, & Iglesias, 2015), and related studies have found an association between convergence insufficiency and attention-deficit/hyperactivity disorder (Granet et al., 2005; Rouse et al., 2009). Poltavski et al. (2012) suggested a bidirectional relationship between the mechanisms of attention and accommodation, showing that induced accommodative stress raises the lag of accommodation and impairs sustained attention to visual stimuli. Importantly, certain factors may alter the visual function such as age (Jiménez, Gonzalez, Pérez, & García, 2003) and pharmacological treatment (Molina-Carballo, Checa-ros, & Muñoz-Hoyos, 2016), which is quite frequent in attention-deficit/hyperactivity disorder management.

Thus, the available literature makes it advisable to investigate the potential influence of attentional disorders on the accommodative function by controlling the above-mentioned confounding factors.

The accommodative response reflects the accuracy of the ocular accommodation mechanism to focus objects clearly at different distances (Millodot, 2014), and an inaccurate accommodative response has been shown to be caused by neurological abnormalities or imperfections in the neural system that controls accommodation (Mcclelland, Parkes, Hill, Jackson, & Saunders, 2017). Testing accommodation with clinical procedures (e.g., push-up test, monocular estimation method) might not be sensitive to an accommodative dysfunction, especially in the paediatric population (Chase et al., 2009). However, the recent incorporation in clinical and research settings of binocular open-field autorefractors, which dynamically test accommodation, has led to more consistent and accurate measures of accommodation (Sheppard & Davies, 2010). Despite that the accommodative response magnitude is one of the most widely used parameters to test the accommodative function, in recent studies, the accommodative response fluctuations over time (variability of accommodation) have been incorporated due to the fundamental role of this parameter on asthenopia and myopia progression (Charman & Heron, 2015; Tosha et al., 2009; Wallman & Winawer, 2004). In addition, the execution of sustained attentional tasks (e.g., reading) has been demonstrated to alter the variability of accommodation (Harb et al., 2006). Tosha et al. (2009) showed an impaired accommodative response in individuals with high levels of ocular discomfort when compared with a control group while viewing at near distances during a 90-second target fixation task. No works available have objectively evaluated the accommodative response in attention-deficit/hyperactivity disorder children. Here, we measured the magnitude and variability of the dynamic accommodative response at different viewing distances, to static stimuli during a 90-second task, in a group of non-medicated attention-deficit/hyperactivity disorder children and an age-matched control group. The aim of the present study was to explore any difference in the magnitude and variability of accommodation between groups (attention-deficit/hyperactivity disorder vs. control) in order to analyse the change over time in the magnitude and variability of accommodation as a consequence of prolonged static viewing in this population. Based on previous research (Borsting, Rouse, & Chu, 2005; Chase et al., 2009; Tosha et al., 2009), we hypothesised that higher lags and variability of accommodation would be found in the attention-deficit/hyperactivity disorder group, and those differences will be higher at closer viewing distances over time.

Methods

Subjects

Eighteen children diagnosed with attention-deficit/hyperactivity disorder (5 girls), aged between 6 and 14 years old (mean age ± standard deviation [SD]: 8.94 ± 2.39) and 18 healthy children (8 girls) within the same age range (mean age ± SD: 9.27 ± 2.63) participated in this study. attention-deficit/hyperactivity disorder children were recruited from the health area of Granada (Spain) where they received a suspected diagnosis of attention-deficit/hyperactivity disorder from their primary care paediatrician and they were referred to the Neuropsychology and Early Intervention Unit of San Cecilio University Hospital (Granada) for subsequent monitoring and evaluation by the neuropaediatric services. Control children, recruited from three different schools, were all screened by a medical doctor and psychologist, confirming the absence of any systemic or mental disorder. The medical doctor and psychologist provided a list of possible control children to the only person who knew the diagnosis of the subjects (control or attention-deficit/hyperactivity disorder), who contacted the control children with the same age range from this list. For the diagnosis of attention-deficit/hyperactivity disorder and possible comorbidities, a complete and identical protocol was followed by all patients. Firstly, a physical examination was made, and a medical record consulted, including interviews with the patient and parents as well as seeking information provided from the teachers. Additionally, a complete neuropsychological evaluation was made following standard procedures. The concluding diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders 5th edition (American Psychiatric Association, 2013). None of the children had been administered methylphenidate or submitted to any other treatment for attention-deficit/hyperactivity disorder and they did not present any metabolic, endocrinal or neurological disease. Regarding ocular health and function, we considered the following inclusion criteria for both groups: 1) Similar age range, ≥ 6 years old and ≤ 14 years old, 2) corrected visual acuity of 0.10 logMAR (Snellen 6/7.5) in each eye, 3) no strabismus and/or amblyopia, 4) uncorrected spherical equivalent refractive error < ± 1D, 5) near stereoacuity of 50 seconds of arc or better with the Randot Stereotest (Stereo Optical Company, Chicago, IL, USA) and 6) no ocular disease. Before participating in the study, parents or guardians received detailed instructions and signed an informed agreement. The protocol was approved by the local Ethical Committee of Biomedical Research of Granada (Spain). All procedures were carried out in accordance with the Declaration of Helsinki.

Procedure

In the present study, the optometric measures were performed by two optometrists (BR and RM) who were blinded regarding the group to which participants belonged, in order to avoid potential bias. First, clinical information about the children and family members was collected by clinical psychologists and paediatricians. Parents, with their children's help, completed the Conlon Visual Discomfort Survey (Conlon et al., 1999), to assess the level of visual symptomatology. The survey consisted of 23 items with scores ranging from 0 to 69. Participants who scored from 0 to 24 were defined as a visually low-discomfort group, those who scored from 25 to 48 as a moderate-discomfort group, and those who scored above 48 as a severe-discomfort group. Each participant underwent an optometric examination which included monocular and binocular visual acuity measurement using a computerized monitor with the logarithmic letter-chart test employing the Bailey-Lovie design (POLA VistaVision, DMD Med Tech SRL, Torino, Italy) at a distance of 5 m, objective ocular refraction by using the Grand Seiko WAM-5500 auto-refractor static mode (Grand Seiko Co. Ltd., Hiroshima, Japan), followed by a subsequent monocular and binocular non-cycloplegic subjective refraction or over-refraction techniques, using an endpoint criterion of maximum plus consistent with best vision. The participants were compensated when necessary by considering the exact ocular refraction, except for astigmatisms less than 0.75 D using the appropriate spherical equivalent. The trial frame was adjusted for their interpupillary distance and pupil heights to avoid prismatic effects. After 5 minutes of wearing the optical correction, visual acuity was again evaluated, and we ensured that subjects felt comfortable with their new compensation. Notably, six attention-deficit/hyperactivity disorder and four control children already had optical correction and four attention-deficit/hyperactivity disorder, and five control children needed a new refraction using additional lenses from a trial frame. In addition, we examined the presence of any ocular pathology by a direct ophthalmoscopy examination.

We performed a monocular static refractive measure in both corrected eyes in order to determine the baseline refractive value to be used for the data analysis (see below). Next, we measured the dynamic accommodative response in binocular conditions, thus not eliminating convergent accommodation, from the dominant eye as recommended by Momeni-Moghaddam et al., (2014), which was determined by the hole-in-the card method. We used the clinically validated (Sheppard & Davies, 2010) Grand Seiko WAM-5500 binocular open-field autorefractor in hi-speed (continuous recording mode), which allows refractive data collection at a temporal resolution of 5 Hz. The dynamic accommodative response was measured at 3 distances (500 cm, 40 cm and 20 cm) for 90 sec for each recording, with a three-min break between measures in order to avoid tonic accommodation (Lin, Lin, & Chen, 2016). Viewing angles for the three distances tested were 0.23º, 2.86º, and 5.73º, respectively. We asked the participant to keep focused on a high-contrast Maltese cross positioned in the participant's midline in all cases. This target consisted of a 2cm high-contrast (Michelson = 79%) five-point black-star target presented on a white background card, and it contained a wide range of orientations with a suitable cue for central fixation. The base luminance of the target was 31 cd m^{-2}, and the experimental room illuminance condition, as measured at the corneal plane, was ~ 150lx (Illuminance meter, T-10, Konica Minolta Inc., Tokyo, Japan).

For data analysis, we identified and removed data points of ± 3 standard deviations from the mean spherical refraction value, which could be related to blinking or to recording errors (Tosha et al., 2009; Vera et al., 2016). The accommodative response was determined by subtracting the mean point of focus from the accommodative demand distance (500cm = 0.2D; 40cm = 2.5D; and 20cm = 5D) during dynamic testing after the children had been compensated with their exact refraction (Poltavski et al., 2012). When ophthalmic lenses were necessary (Jiménez et al., 2011), we calculated the ocular accommodation demand referring to the corneal vertex, following the equation of Atchison et al. (2017) for an assumed vertex distance of 12mm. To assess the possible effect of time-on-task, each viewing distance was divided into nine consecutive 10-sec blocks. The standard deviation from the entire dynamic accommodative response measure (90 sec) and each 10-sec block were used to define the variability of accommodation.

Experimental design and statistical analysis

The present study followed a mixed design. The target distance (500 cm, 40 cm and 20 cm) and the time blocks (9 ten-second intervals) were the within-participants factor while the group (attention-deficit/hyperactivity disorder and control) was the between-participants factor. The accommodative response and its variability were used as the dependent variables.

First, to analyse the possible differences in age and visual symptomatology (Conlon survey), we performed separated t-tests for independent samples with the group (attention-deficit/hyperactivity disorder and control) as the between-participants factor. Then, a mixed analysis of variance, considering the target distance (500 cm, 40 cm, and 20 cm) as the within-participants factor and the group (attention-deficit/hyperactivity disorder and control) as the between-participants factor, while the accommodative response magnitude and variability were used as the dependent variables.

Additionally, to test the possible effects of time-on-task, the time blocks (9 intervals of 10 sec) was incorporated to our analyses. Therefore, the accommodative magnitude and variability were submitted to a mixed analysis of variance with the target distance (500 cm, 40 cm, and 20 cm) and the time blocks (9 ten-second intervals) as the within-participants factors while the group (attention-deficit/hyperactivity disorder and control) was the between-participants factor.

The level of significance was set at 0.05, and the Holm-Bonferroni correction for multiple comparison was used. Standardised effect size was reported by means of the partial η^2 for *F*s and the Cohen's *d* for *t* tests.

Results

No significant age differences were found between the two groups ($t_{34} = -0.067$, $p = 0.947$, $d = -0.02$), whereas there was a significant difference for the visual symptomatology, the attention-deficit/hyperactivity disorder group showing higher scores on the Conlon survey ($t_{34} = 3.56$, $p = 0.001$, $d = 1.19$). See Table 6.

Table 6. Sample characteristics and optometric clinical measures for the attention-deficit/hyperactivity disorder and control group.

	ADHD (*n*=18) Mean (SD)	Control (*n*=18) Mean (SD)	p	Cohen's *d*
Age (years)	8.94 (2.39)	9.27 (2.63)	0.95	-0.02
Gender (% female)	27.7%	44.4%	-	-
Corrected VA (logMAR)	-0.05 (0.05)	-0.12 (0.06)	0.002*	1.12
Corrected VA (Snellen)	6/5.5 (0.13)	6/4.5(0.15)	<0.0001*	-1.25
Ocular Refraction (SE; D)	0.88 (1.62)	0.36 (0.36)	0.12	0.54
Conlon survey	15.17 (13.14)	3.71 (4.64)	0.001*	1.19

Note: ADHD = Attention-deficit/hyperactivity disorder; SD= Standard deviation; VA= Visual acuity; MAR= minimum angle of resolution; SE= Spherical equivalent; D= Dioptres. * denotes significant differences between groups (p<0.05).

Both attention-deficit/hyperactivity disorder and control groups showed accommodative lag or under-accommodation to the accommodative demand distance, with higher lags of accommodation in the attention-deficit/hyperactivity disorder group in comparison to controls at 500 cm (0.27 ± 0.32 vs. 0.18 ± 0.25), 40 cm (1.12 ± 0.56 vs. 0.84 ± 0.33), and 20 cm (1.41 ± 0.87 vs. 0.98 ± 0.46). A 3 (*target distance*) x 2 (*group*) analysis of variance with the lag of accommodation as the dependent variable demonstrated significant effects for *target distance* ($F_{2,68}$ = 43.48, p < 0.0001, η_p^2 = 0.56) and *group* ($F_{1,34}$ = 5.61, p = 0.024, η_p^2 = 0.14), whereas no effect was detected for interaction *target distance x group* ($F_{2,68}$ = 1.18, p = 0.32) (Figure 20). The variability of accommodation showed a statistical significance for the *target distance* ($F_{2,68}$ = 152.63, p < 0.0001, η_p^2 = 0.82), and a marginally significant difference was found for the effect of *group* ($F_{1,34}$ = 3.605, p = 0.066, η_p^2 = 0.1). No significance resulted for the interactive effect *target distance x group* ($F_{2,68}$ = 2.155, p = 0.147) (Figure 20). As expected, the Bonferroni-Holm correction for multiple comparisons revealed significant differences between the three distances tested for the magnitude and variability of accommodation (corrected p-value < 0.0001 in all cases).

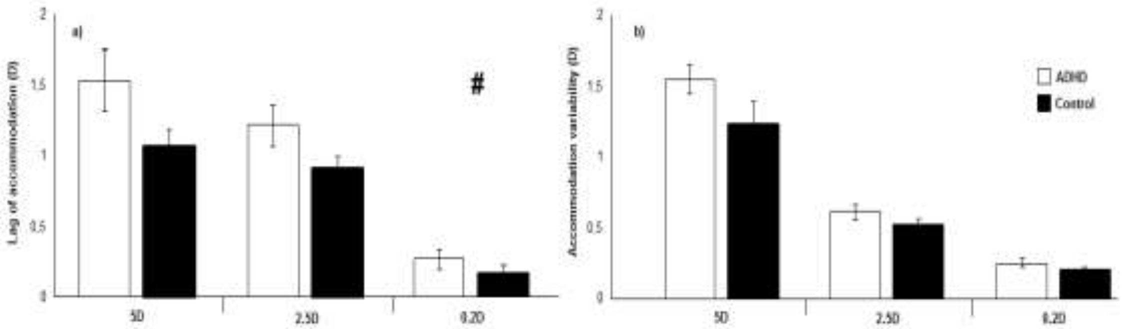

Figure 20. Accommodative response for attention-deficit/hyperactivity disorder and control groups with different accommodative demands (5D, 2.5D and 0.2D). The panel a) displays the lag of accommodation, and the panel b) the variability of accommodation. # indicates significant main effect of group (p < 0.05). Error bars show the standard error (SE).

Complementarily, the *time-on-task* was also included as a within-participants factor. In this case, a 3 (*target distance*) x 9 (*time blocks*) x 2 (*group*) analysis of variance, with the lag of accommodation as the dependent variable, showed significant effects for the *target distance* ($F_{2,68} = 85.40$, $p < 0.0001$, $\eta_p^2 = 0.58$), for the *time-on-task* ($F_{8,272} = 3.154$, $p = 0.002$, $\eta_p^2 = 0.08$), and for the *group* ($F_{1,34} = 5.37$, $p = 0.027$, $\eta_p^2 = 0.14$), whereas no significance was reached for any interactive effects ($p > 0.05$) (Figure 21). The same analysis but considering the variability of accommodation as the dependent variable gave significant differences only for the *target distance* ($F_{2,68} = 232.\ 55$, $p < 0.0001$, $\eta_p^2 = 0.87$). The *time-on-task* and the *group* did not yield statistical significance ($F_{8,272} = 1.60$, $p = 0.124$; and $F_{1,34} = 1.44$, $p = 0.239$, respectively) (Figure 22). The *post hoc* correction for multiple comparisons showed differences for the three distances tested (corrected p-value < 0.0001 in all cases), but no differences appeared between the 9 ten-second intervals (corrected p-value > 0.05 in all cases).

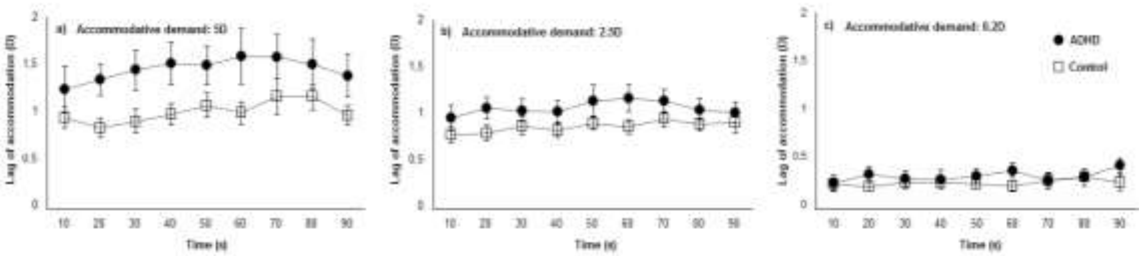

Figure 21. Changes in accommodative response magnitude (lag of accommodation) for attention-deficit/hyperactivity disorder (ADHD) and control groups over time (90 seconds) at different accommodative demand distances (a) 5D, b) 2.5D and c) 0.2D). Error bars show the standard error (SE).

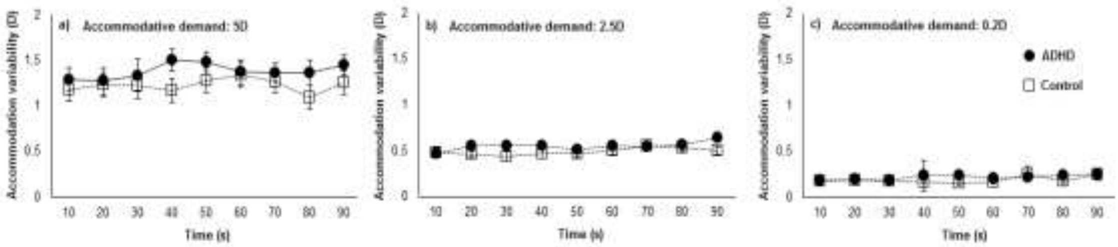

Figure 22. Changes in accommodative variability for Attention-deficit/hyperactivity disorder (ADHD) and control groups over time (90 seconds) at different accommodative demand distances (a) 5D, b) 2.5D and c) 0.2D). Error bars show the standard error (SE).

Discussion

The ocular dynamics have been linked to brain areas controlling attention (Steinmetz & Moore, 2014), and also have been proved sensitive to changes in the attentional state (Poltavski et al., 2012). Here, we examined the accommodative response (magnitude and variability) in a group of attention-deficit/hyperactivity disorder children at three different distances during a 90-second target fixation task in comparison to a control group. Our results revealed higher lags of accommodation for the attention-deficit/hyperactivity disorder children than for the age-matched control group, showing a tendency to increase as the viewing distance decreased (higher accommodative demand). These results support the idea that attention-deficit/hyperactivity disorder children have a less accommodative accuracy that becomes more accentuated with a higher accommodative demand. Notably, attention-deficit/hyperactivity disorder group exhibited a significantly marginal increase of accommodation variability in comparison to the control group. Although the analysis over time yielded differences between groups for the accommodation lag, both groups exhibited a similar behaviour for the accommodation lag and variability for 90 sec at the three distances tested. Our findings may have relevance on the management of visual function in attention-deficit/hyperactivity disorder since higher accommodation lags at closer distances may create asthenopia and decrease the efficiency of the task performance (Tosha et al., 2009), this being consistent with the symptoms and signs observed in this population. Taken together, the association between attention resources and the visual system could be plausible. However, our results do not permit to stablish the direction of this causal relationship, thus, further study are needed in this regard.

The insufficient or inaccurate magnitude of accommodative function has been related to a wide variety of negative outcomes such as asthenopia (Iribarren, Fornaciari, & Hung, 2002), reduced attentional resources (Poltavski et al., 2012), and myopia progression (Wallman & Winawer, 2004). Accommodative disorders are closely related to near-work-related asthenopia (Iribarren et al., 2002), characterized by unpleasant somatic symptoms and perceptual distortion. Additionally, recent studies have demonstrated that short periods of intense near work can induce blurred vision due to slowed accommodation dynamics (Chase et al., 2009; Tosha et al., 2009). Although it was beyond the aim of this study, the results from the Conlon questionnaire demonstrated a higher incidence of visual discomfort in attention-deficit/hyperactivity disorder children in comparison to controls (see Table 6). However, it should be noted that the range of visual discomfort was below the cut-off value of 23 in both groups, which is considered to determine moderate visual discomfort (Conlon et al., 1999). This finding concurs with Tosha et al., (2009), who demonstrated that high visual discomfort was associated with high accommodative lag during a period of 90 sec, which increased at closer distances. However, in contrast to that study, ours found that attention-deficit/hyperactivity disorder children did not experience a greater accommodative lag over time, perhaps due to a relatively short time-on-task or test characteristics (Loh et al., 2004). Attention assessment is conducted by tests which require longer time and imply sustained and selective attention (e.g., 14 min Continuous Performance Test (Epstein et al., 2003). Future studies should assess the accommodative response during these types of attentional tasks.

Regarding attentional resources, accommodative-vergence mismatches could have adverse consequences on attentional and cognitive performance. In these cases, the effort to maintain accommodation and convergence within the clear zone could require a greater recruitment of attentional resources (Poltavski et al., 2012). Several studies have stated that ocular dynamics can be associated with attention, probably due to the extensive overlap between the system that controls attention and the system that controls ocular dynamics (Siegenthaler et al., 2014; Steinmetz & Moore, 2014). Thus, attention-deficit/hyperactivity disorder symptomatology could be heightened by visual dysfunctions, or even by near work under stressful conditions that activate the central nervous system. If a person can decrease the amount of attention needed for the task, then more attention should be available for a current task such as reading (Schneider, 1977). Based on the related background, if attention-deficit/hyperactivity disorder children present an accommodative deficit, they should be able to use part of their attentional resources to compensate for it, leaving less attention in reserve to attend or maintain the attentional state. This appears to be supported by the fact that the greater possibility of presenting attention-deficit/hyperactivity disorder or a more severe degree of attention-deficit/hyperactivity disorder occurs in those subjects with moderate vision problems (Borsting et al., 2005). On the other hand, an alternative explanation for this association is also quite possible in the opposite direction, since a lack of engagement and interest due to the inherent nature of attention-deficit/hyperactivity disorder may cause poorer accommodation.

The accommodative response when focusing on a stationary target is not constant over time as it exhibits small temporal variations in order to maintain the accommodative response and gather directional cues for the dynamic accommodative response (Charman & Heron, 2015). Here, we failed to find significant differences between groups, although attention-deficit/hyperactivity disorder children tended to show higher values of accommodation variability. This would need further study, as no solid conclusion can be drawn from this investigation. As stated above, the time spent on task and cognitive requirements of the test or type of stimulus may influence these results (Loh et al., 2004). Accommodation variability is a result of central neurological control (Winn & Gilmartin, 1992), and thus neural alterations in eye-related brain areas could precipitate changes in accommodation. Furthermore, abnormal accommodative responses in attention-deficit/hyperactivity disorder, where the neural control is altered, could be expected due to the fact that the neural controllers of attention and ocular dynamics are shared. If the small differences found in this study are corroborated in future research or even greater differences are detected with different attentional tasks, these results may be of interest in several areas.

A recent study has provided physiological evidence that the superior colliculus might be dysfunctional in a rodent model of attention-deficit/hyperactivity disorder (Brace et al., 2015). Superior colliculus is involved in the control of near response as well as in the association of accommodation, convergence and visual fixation (Suzuki, 2007), and it is a structure linked to distractibility and it constitutes the main subcortical area involved in ocular control (Hafed, Goffart, & Krauzlis, 2009; Overton, 2008). To date, there is a large body of scientific evidence demonstrating the existence of abnormal eye movements, particularly inhibiting saccades and pro-saccades in this neuropsychiatric disorder (Muñoz, Armstrong, Hampton, & Moore, 2003). However, no available studies have analysed the possible association between superior colliculus and a less accurate ocular accommodation in attention-deficit/hyperactivity disorder. Previous studies, influenced by studies on the oculomotor dynamics (Di Stasi et al., 2012), have stated that the accommodative response may arise at the level of the excitatory connection from hypothetical arousal neurons to the superior colliculus, and through the Edinger-Westphal nucleus to alter accommodation (Vera et al., 2016). Therefore, these brain structures, which are sensitive to the levels of attention (Siegenthaler et al., 2014), may be responsible of the impaired accommodative function in attention-deficit/hyperactivity disorder children, as occurs with oculomotor movements.

The bidirectional relationship between attention and ocular function has been addressed from both perspectives. On the one hand, Poltavski et al., (2012) indicated that an improvement in the visual system could have direct benefits on the cognitive aspects of attention, and Braddick et al., (2011) stated that effective visual behaviour depends on cognitive control processes, specifically the control of attention. Similarly, Hoffman et al., (2008) with unnatural accommodative-vergence conflicts created by three-dimensional (3D) displays, showed that the reduction of these conflicts may enhance visual performance and diminish visual fatigue, and it may be extrapolated to real-life contexts, as in attention-deficit/hyperactivity disorder children, who present a hindered accommodative-binocular function. Borsting et al. (2012) reported that convergence insufficiency treatment in school-age children reduced the frequency of adverse academic behaviour and parental concern associated with reading and schoolwork. Previous studies have demonstrated a higher prevalence of convergence insufficiency in children diagnosed of attention-deficit/hyperactivity disorder (Borsting et al., 2005; Granet et al., 2005), and therefore by dealing with visual impairments such as convergence insufficiency or accommodative-vergence mismatch, attention-deficit/hyperactivity disorder academic behaviour associated with reading and school work could be enhanced. However, future studies are needed to verify this possibility. In any case, it could be beneficial for children with vision problems to be examined for signs and symptoms of attention-deficit/hyperactivity disorder and vice versa, so that this possible dual impairment of vision and attention could be best addressed. Moreover, some research strongly supports the contention that some children with vision problems are incorrectly identified as attention-deficit/hyperactivity disorder, compounded by their inability to see something and not keep their attention focused on their work (DeCarlo, Swanson, McGwin, Visscher, & Owsley, 2016). Many visual skills are indispensable for schoolwork, which may be affected by poor accommodation, and it may play a role on their general and intellectual development. A visual assessment of all children with attention-deficit/hyperactivity disorder, including an objective measure of their accommodative response should be thoroughly studied in order to determine whether it may be included in the standard clinical protocol. From that point on, depending on the visual impairments, specific recommendations may be suggested, such as increasing the working distance to diminish visual discomfort and learning disabilities, or referring to a visual therapy program in order to improve visual function and symptomatology, among others. Nevertheless, our data cannot definitively determine the causal directionality between attention-deficit/hyperactivity disorder and accommodative function. Thus, it would be useful to explore the relative contribution of each casual direction in future treatments, which may help to manage attentional or visual anomalies.

The present study provides evidence of a worse accommodative response in the attention-deficit/hyperactivity disorder children in comparison to the age-matched control group. However, some factors may be considered a limitation to our findings. We found no time effect on the lag and variability of accommodation, which may be explained by the insufficient time-on-task used in this work or a reduced cognitive demand task. Previous studies have indicated that shorter tasks are less sensitive to performance decline in vigilance tasks when comparing 10-min tasks against a 5- and 2-min tasks (Loh et al., 2004). In view of this, future studies should consider incrementing the task time beyond 90 sec during completion of a sustained attention task. In addition, the task selection could influence the accommodative response, and therefore it could be of interest to analyse the effect of different types of tasks on accommodation, such as cognitive demanding ones (e.g., Continuous Performance Test, which has been shown to differentiate attention-deficit/hyperactivity disorder and control children (Epstein et al., 2003)), or more engaging tasks (e.g., movie cartoons [Anderson et al., 2010]). Most of the latest advances on attention-deficit/hyperactivity disorder focus on attentional deficits, so that it would be helpful for further studies to divide the attention-deficit/hyperactivity disorder group according to their classification into inattentive, hyperactive-impulsive or the combined type, and thereby assess the accuracy of accommodative response and its differences between the various subgroups of attention-deficit/hyperactivity disorder. Consequently, a higher group size of participants would be needed. Finally, attention-deficit/hyperactivity disorder children exhibited a larger variance of refractive error than the control group (see Table 6), and this may be acknowledged as a possible limitation to our findings, since accommodative response depends on refractive error (Millodot, 2015). Future studies could divide their experimental sample according to refractive error, which would permit an assessment concerning whether the refractive error mediates in the association between attention-deficit/hyperactivity disorder and accommodative function. It is our hope that future studies will explore the long-term effects of attention-deficit/hyperactivity disorder pharmacological and/or behavioural treatment on the ocular dynamics, as well as the possible benefits of visual therapy on attention-deficit/hyperactivity disorder symptomatology.

Conclusions

This study reveals that the attention-deficit/hyperactivity disorder children showed a decreased accommodative response (significantly greater lag of accommodation) in relation to the control group, these differences being more accentuated at closer distances. This association between accommodative response and attention-deficit/hyperactivity disorder may be explained by the extensive overlap between the neural system controlling the ocular dynamics and attention. More studies are needed to elucidate the neural mechanism involved in this bidirectional relationship. We hope that this study helps to demonstrate the importance of a multidisciplinary approach from different health care areas for a more accurate diagnosis and appropriate management of these patients, which may have a direct impact on the academic, cognitive, and visual development of attention-deficit/hyperactivity disorder children.

STUDY VII. ACCOMMODATIVE RESPONSE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: THE INFLUENCE OF STIMULUS TYPE AND STIMULANT MEDICATION.

Introduction

Optometric examination requires patient´s continuous cooperation (Scheiman & Wick, 2008). When the test is boring and lasts for a long time, the children's response may become less accurate or even wrong. Therefore, maintaining children's attention is crucial to ensure a correct diagnosis of visual impairment, especially when, an altered behavioural functioning is present (Börger, & van der Meere, 2000, Coulter, & Shallo-Hoffmann, 2000, Ishikawa, Yoshimura, Sato, & Itakura, 2019, Piast et al., 2003, Yeshurun, & Carrasco 1998).

Attention-deficit/hyperactivity disorder is one of the most common psychological disorder diagnosed in childhood (worldwide prevalence of 5.29%) (Polanczyk et al., 2007), which is characterized by inattentive, impulsive and hyperactive symptoms (American Psychiatric Association, 2013). There is an estimated prevalence rate of 16 % of vision problems associated with this disorder (Akmatov, Ermakova & Bätzing, 2019), with deficits in eye saccadic movements (Rommelse, Stigchel & Sergeant, 2008), ocular vergences (Puig et al., 2015, Varela Casal et al., 2018), visual processing (Lenz et al., 2010), and colour vision (Kim, Banaschewski & Tannock, 2014) being often observed in this population.

The accommodative response has also been accomplished, using objective techniques (open- field autorefractometer), in children with attention-deficit/hyperactivity disorder, observing a decreased accommodative response in comparison to age-matched controls (Redondo et al., 2018). However, the causal relationship between the altered accommodative functioning and attention-deficit/hyperactivity disorder remains unknown, since the visual attention (Lawson, Crewther, Junghans, Crewther, & Kiely, 2005) and cognitive effort required during visual testing (Davies, Wolffsohn & Gilmartin 2005, Roberts et al., 2018, Rosenfield & Ciuffreda, 1990) have been demonstrated to influence the magnitude of the accommodative response. In this regard, it is possible that an altered accommodative functioning is inherent to this disorder, as it has been previously observed in other neurological disorders such as Down syndrome (Woodhouse et al., 2000), autism (Anketell et al., 2018), and dyslexia (Evans, Drasdo & Richards, 1995). Nevertheless, it is also plausible to hypothesize that the lack of engagement, interest or motivation for the task could cause a less accurate accommodative response. Several researchers have included engaging stimulus (e.g., cartoon videos or games) in order to achieve children's attention and co-operation (Anderson et al., 2010, Aslam, Rahman, Henson, 2011, Gaggi & Ciman, 2016, Wang et al., 2017). Therefore, the manipulation of the levels of attentions may help to elucidate the mechanisms underlying the deficits in ocular accommodation found in children with attention-deficit/hyperactivity disorder.

Scientific evidence suggests that pharmacological treatment of attention-deficit/hyperactivity disorder with psychostimulants (e.g., methylphenidate and amphetamines) has a beneficial effect on the symptoms of hyperactivity, impulsivity and inattention (Greenhill 2001), which seems to be mediated by increasing activation in dopamine and norepinephrine fronto-striatal circuitry (Arnsten, 2006, Molina-Carballo, Checa-ros & Muñoz-Hoyos, 2016). A few studies have assessed the effects of medication on the ocular function in attention-deficit/hyperactivity disorder. In some cases, methylphenidate has shown to improve ocular motility (Fried et al., 2014, Klein, Raschke & Brandenbusch, 2003), as well as visual acuity and visual field (Martin et al., 2008), whereas other studies did not find any changes in the refractive error (Larrañaga-Fragoso et al., 2015) or visual acuity (Whitman, Lindsay, & Cruz, 1997) after using methylphenidate. Of note, Grönlund et al., (2007) found a high frequency of visual dysfunctions in children with attention-deficit/hyperactivity disorder that did not significantly improve with pharmacological treatment. However, they observed that children with attention-deficit/hyperactivity disorder concentrated and cooperated better with the use of stimulants. To date, there are no studies that have assessed the impact of attention-deficit/hyperactivity disorder treatment on the accommodative response.

In order to address the limitations found in the scientific literature, the present study aimed to evaluate the influence of the levels of attentional engagement on the accommodative response in a population of medicated and non-medicated children with attention-deficit/hyperactivity disorder, which would allow to ascertain whether the previously detected deficits in the accommodative function is a primary accommodative problem or is a consequence of the underlying attentional problem. For this purpose, we objectively recorded the accommodative and pupil dynamics (magnitude and variability) by a binocular open-field autorefractor in medicated and non-medicated children with attention-deficit/hyperactivity disorder and an age-matched control group while viewing three different stimuli at 25 cm. In counterbalanced order, participants were asked to focus for 180 seconds on a high-contrast Maltese cross, a picture (a frame extracted from the cartoon movie), and a cartoon movie chosen from a range of ten available options. We hypothesised that if there is a primary deficit in accommodation, the differences in accommodative response will be independent of the stimulus type whereas if the accommodative deficit is a consequence of the attention disorder, the magnitude of the accommodative deficit will be reduced when the child is more engaged (Gaggi & Ciman, 2016, Horwood & Riddell, 2010). However, the mixed results given by previous studies about the effects of attention-deficit/hyperactivity disorder medication on the visual function (Fried et al., 2014, Grönlund et al., 2007, Klein, Raschke & Brandenbusch, 2003, Larrañaga-Fragoso et al., 2015, Whitman, Lindsay, & Cruz, 1997) does not allow us to establish an hypothesis in this regard.

Methods

Participants

23 non-medicated (mean age 10.05 ± 2.38 years) and 21 medicated (methylphenidate hydrochloride) children with attention-deficit/hyperactivity disorder (mean age 10.97 ± 3.78 years), as well as 23 healthy controls (mean age 10.55 ± 1.92 years) took part in this study. Children with attention-deficit/hyperactivity disorder were diagnosed by the Neuropsychology and Early Intervention Unit of San Cecilio University Hospital (Granada), using the Diagnostic and Statistical Manual of Mental Disorders 5th edition (American Psychiatric Association, 2013). Children with an intelligence quotient lower than 85 were excluded (Wechsler, 1974). Participants were screened according to the following inclusion criteria: (1) visual acuity of 0.10 logMAR or better in each eye, (2) no history of strabismus and/or amblyopia, (3) minimal un-corrected refractive error as determined by objective and subjective refraction (myopia of ≤ 0.50, astigmatism and anisometropia of <1.00 D, and hyperopia ≤1.00 D) (Kulp et al., 2017), and (4) be free of any history of ocular disease. After it, 4 participants (1 non-medicated attention-deficit/hyperactivity disorder, 2 medicated attention-deficit/hyperactivity disorder and 2

control) were excluded due to non-compliance of inclusion criteria, and thus, twenty-two non-medicated children with attention-deficit/hyperactivity disorder , nineteen medicated children with attention-deficit/hyperactivity disorder and twenty-two controls were considered for further analyses. All parents or guardians received detailed instructions and signed an informed consent. The protocol followed the tenets of the Declaration of Helsinki and the study was approved by the University of Granada Institutional Review Board (546/CEIH/2018).

Manipulation of visual target engagement

Participants were asked to maintain on focus three different visual stimuli for three minutes each. The first one consisted of an engaging cartoon movie, which participants chose their favourite cartoon movie from a range of ten available options selected according to children's actual preferences to increase engagement (Heidy, SpongeBob, Dragon Ball, Adventure Time, Pepa Pig, Geronimo Stilton, Futurama, Robot Trains, Doraemon and Paw Patrol). The second stimulus was a picture took from the carton movie they chose with similar contrast and colour characteristics compared to the cartoon movie. Finally, the third stimulus consisted of a Maltese cross, which is a 2 cm high-contrast (Michelson = 79%) five-point black-star target presented on a white background card, which contains a wide range of orientations with a suitable cue for central fixation. All tasks were displayed on a smartphone (iPhone 4, Apple Inc., Cupertino, CA) in randomised order (screen resolution 640 x 960 pixels, 3.5-inches). Figure 23 shows an example for each of the three stimuli types used in this study.

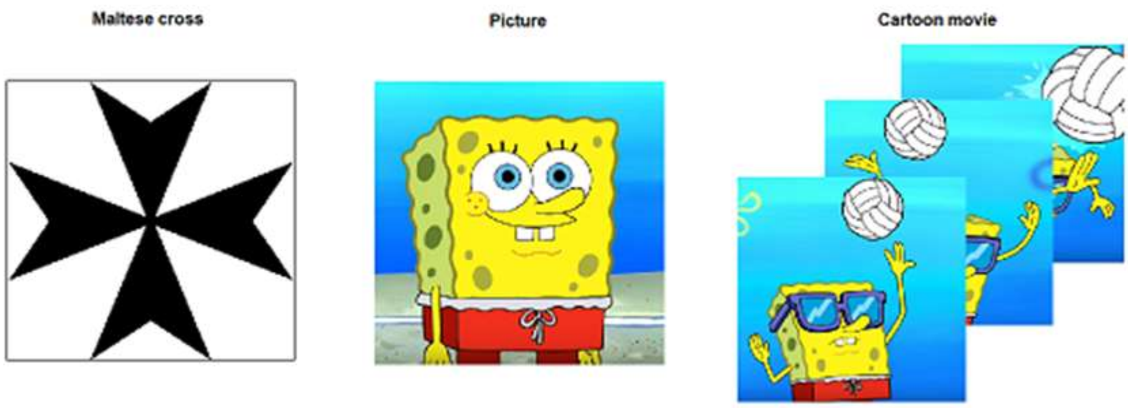

Figure 23. A graphical illustration of the three stimuli types used in this study for the SpongeBob choice. From left to right: the Maltese cross condition, the picture condition (a frame extracted from the cartoon movie), and the cartoon movie condition.

Grand Seiko WAM-5500 Autorefractor

The accommodative and pupil responses were measured with the open-field Grand Seiko Auto Refractometer WAM-5500 (Grand Seiko, Hiroshima, Japan), which is known to be capable of acquiring reliable and valid measures (Sheppard & Davies, 2010). Data recording was performed in the hi-speed mode (continuous recording mode) of the WAM-5500 at a temporal resolution of ~5 Hz while the visual stimulus was displayed on the centre of the smartphone screen at a distance of 25cm from the observer at his/her gaze height (Wang et al., 2013). All measures were performed in binocular conditions, thus not eliminating convergent accommodation, and accommodation and pupil response data were taken from the dominant eye (determined by the hole-in-the card method) as recommended by Momeni-Moghaddam et al., (2014).

For the analysis of the accommodative response, we identified and removed data points of ± 3 standard deviations from the mean spherical refraction value, which could be due to blinking or recording errors (Tosha et al., 2009). After it, the remaining data (average percentage: 88%, range: 82 to 93%) were used for further analyses. The lag of accommodation was determined for each subject and experimental condition by subtracting the accommodative response to the accommodative demand (4 D at 25 cm), with the accommodative response being adjusted for the baseline static refraction value (Poltavski, Biberdorf & Petros, 2012). The standard deviation was used to define the variability of accommodation.

Procedure

First, clinical information about the children and family members was collected, and the presence of any ocular pathology was checked by slit lamp and direct ophthalmoscopy examination. Participants underwent an optometric examination that included distance and near monocular and binocular visual acuities, and non-cycloplegic objective refraction and over-refraction techniques, using an endpoint criterion of maximum plus consistent with best vision. When necessary the children were compensated and an objective monocular static refraction was performed in both eyes with the WAM-500 in order to determine the baseline refractive value, which was used for the subsequent data analysis. Subsequently, accommodation and pupil data were continuously recorded while viewing the corresponding stimulus for 3 minutes. A three-min break was given between conditions in order to avoid the influence of tonic accommodation. To assess the effect of time-on-task, all the dependent variables were divided into three consecutive 60-s blocks. The base luminance of the smartphone screen was 38 cd/m2 (PR-745 SpectraScan Spectroradiometer, Photo Research Inc., Chatsworth, CA). All measurements were obtained under the same illumination conditions (~150 lux as measured in the corneal plane; Illuminance meter T-10, Konica Minolta, Inc., Japan).

Experimental design and statistical analyses

The study followed a 3 × 3 × 3 mixed factorial design. We considered the Group (non-medicated attention-deficit/hyperactivity disorder, medicated attention-deficit/hyperactivity disorder, and control) as the between-participants factor, and the visual task (Maltese cross, picture, and cartoon movie) and the time-on-task (block1, block 2, and block 3) as the within-participants factors. The dependent variables were lag of accommodation, variability of accommodation, pupil size and variability of pupil size.

Before any statistical analysis, the normal distribution of the data (Shapiro-Wilk test) and the homogeneity of variances (Levene's test) were confirmed ($p > 0.05$). To explore the possible differences in age between the experimental groups, we performed an unifactorial analysis of variance with the Group (non-medicated attention-deficit/hyperactivity disorder, medicated attention-deficit/hyperactivity disorder, and control) as the only between-participants factor. Then, separate mixed analyses of variance, considering the Group (non-medicated attention-deficit/hyperactivity disorder, medicated attention-deficit/hyperactivity disorder, and control) as the between-participants factor, and the visual task (Maltese cross, picture, and cartoon) and the time-on-task (block1, block 2, and block 3) as the within-participants factors, were carried out for each dependent variable (lag of accommodation, variability of accommodation, pupil size, and variability of pupil size). We reported partial eta squared (η^2) and Cohen's d (d) as effect size indices for Fs and t-tests, respectively. Statistical significance was set at an alpha level of 0.05, and post hoc tests were corrected with Holm-Bonferroni procedure.

Results

Descriptive values (mean and standard deviation) for the accommodation and pupil response in the three experimental groups at each experimental condition are reported in Table 7.

An unifactorial analysis of variance to test for possible age-differences between groups revealed that no statistically significant age-differences were found between the three experimental groups (F_{57} = 0.79, p = 0.492, η^2 = 0.025).

Table 7. Descriptive values (mean ± standard deviation) of visual variables for the non-medicated attention-deficit/hyperactivity disorder, medicated attention-deficit/hyperactivity disorder and control groups and different tasks.

		Non-medicated ADHD	Medicated ADHD	Control
Lag of accommodation (D)	Malta cross	1.19 ± 0.57	1.04 ± 0.41	0.71 ± 0.61
	Picture	1.06 ± 0.52	1.05 ± 0.42	0.66 ± 0.56
	Cartoon movie	1.05 ± 0.50	0.93 ± 0.43	0.78 ± 0.52
Variability of accommodation (D)	Malta cross	1.14 ± 0.28	1.16 ± 0.31	1.21 ± 0.39
	Picture	1.30 ± 0.27	1.25 ± 0.35	1.27 ± 0.41
	Cartoon movie	1.13 ± 0.32	1.13 ± 0.35	1.12 ± 0.31
Pupil size (mm)	Malta cross	4.68 ± 0.89	4.43 ± 0.87	4.29 ± 0.44
	Picture	4.35 ± 0.91	4.41 ± 0.99	4.34 ± 0.45
	Cartoon movie	4.47 ± 0.93	4.60 ± 1.07	4.30 ± 0.59
Variability of pupil size (mm)	Malta cross	1.96 ± 0.50	1.74 ± 0.54	1.70 ± 0.44
	Picture	2.04 ± 0.48	1.83 ± 0.59	1.79 ± 0.30
	Cartoon movie	1.92 ± 0.52	1.91 ± 0.65	1.58 ± 0.45

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, D = diopters, mm = millimeters

The analysis of the lag of accommodation exhibited significant effects for the group ($F_{2, 60}$ = 4.073, p = 0.022, η^2 = 0.120), and the interaction time-on-task × group ($F_{4, 120}$ = 0.717, p = 0.006, η^2 = 0.112). No statistically significant differences were observed for the visual task ($F_{4, 120}$ = 0.715, p = 0.491, η^2 = 0.012) and any other main or interactive factor (p-values > 0.05 in all cases). Post-hoc analysis revealed greater lags of accommodation for the non-medicated children with attention-deficit/hyperactivity disorder in comparison to controls (corrected p-value = 0.023, d = 0.347), however no statistically significant accommodative lag differences were observed for the comparison between medicated children with attention-deficit/hyperactivity disorder and controls (corrected p-value =

0.104, d = 0.250) or between medicated and non-medicated children with attention-deficit/hyperactivity disorder (corrected p-value = 0.504, d = 0.085) (Figure 24).

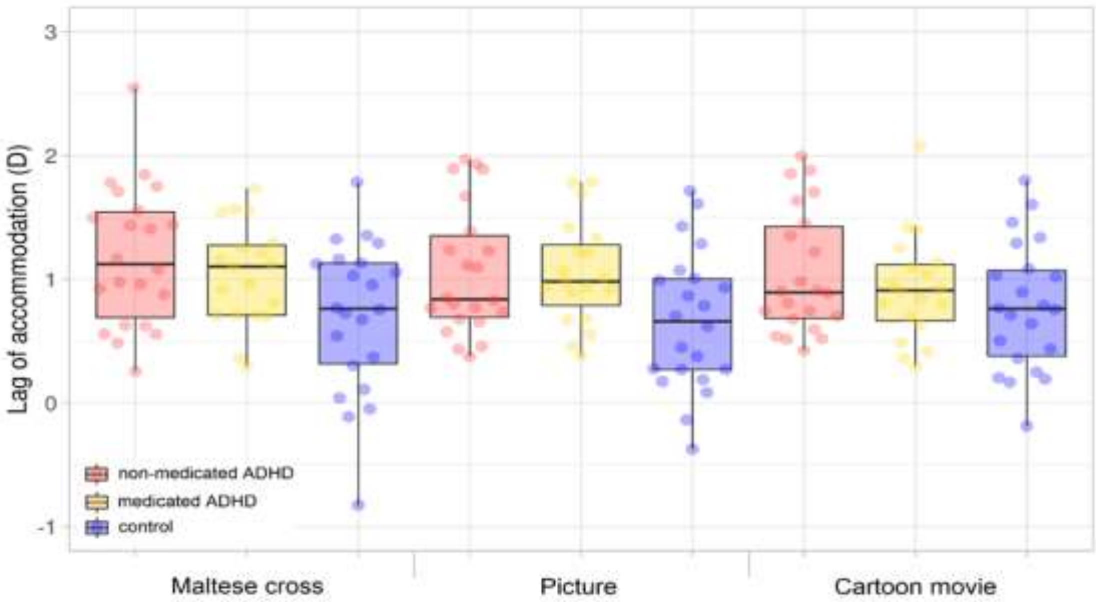

Figure 24. Lag of accommodation for the non-medicated attention-deficit/hyperactivity disorder (ADHD), medicated ADHD, and control groups while viewing the three types of stimuli. The box plots represent 75th and 25th centiles, and individual data are displayed as jittered dots. The horizontal line into the box indicates the median value. The whiskers show the range of values within the 1.5 × interquartile range.

The variability of accommodation yielded statistically significant differences for the visual task ($F_{2,\ 120} = 8.433$, $p < 0.001$, $\eta^2 = 0.123$), and time-on-task ($F_{2,\ 120} = 3.723$, $p = 0.027$, $\eta^2 = 0.058$), whereas no differences were obtained for the main factor of group ($F_{2,\ 60} = 0.067$, $p = 0.935$, $\eta^2 = 0.002$) or any other interaction (p-value > 0.05). Post-hoc analysis exhibited a higher variability of accommodation for the picture condition in comparison to the Maltese cross (corrected p-value = 0.006, d = 0.389), and the cartoon movie conditions (corrected p-value < 0.001, d = 0.499). However, there were no difference when the Maltese cross was compared with the cartoon movie condition (corrected p-value = 0.355, d = 0.117) (Figure 25). In addition, post-hoc analyses for the comparison between the three 60-sec blocks did not show statistically significant differences, although there was a trend toward higher variability over time (block 3 vs block 1: corrected p-value = 0.056; and block 3 vs. block 2: corrected p-value = 0.056).

The pupil size did not exhibit statistically significant differences for the main factors of visual task, time-on-task or group, as well as any interaction (p-value > 0.05 in all cases). Lastly, the analysis of the variability of pupil size showed a statistically significant effect for the interaction visual task × group ($F_{4, 114} = 2.660$, $p = 0.036$, $\eta^2 = 0.029$), and time-on-task × group ($F_{4, 114} = 2.754$, $p = 0.031$, $\eta^2 = 0.087$), but not for other main or interactive effects (p-value > 0.05 in all cases).

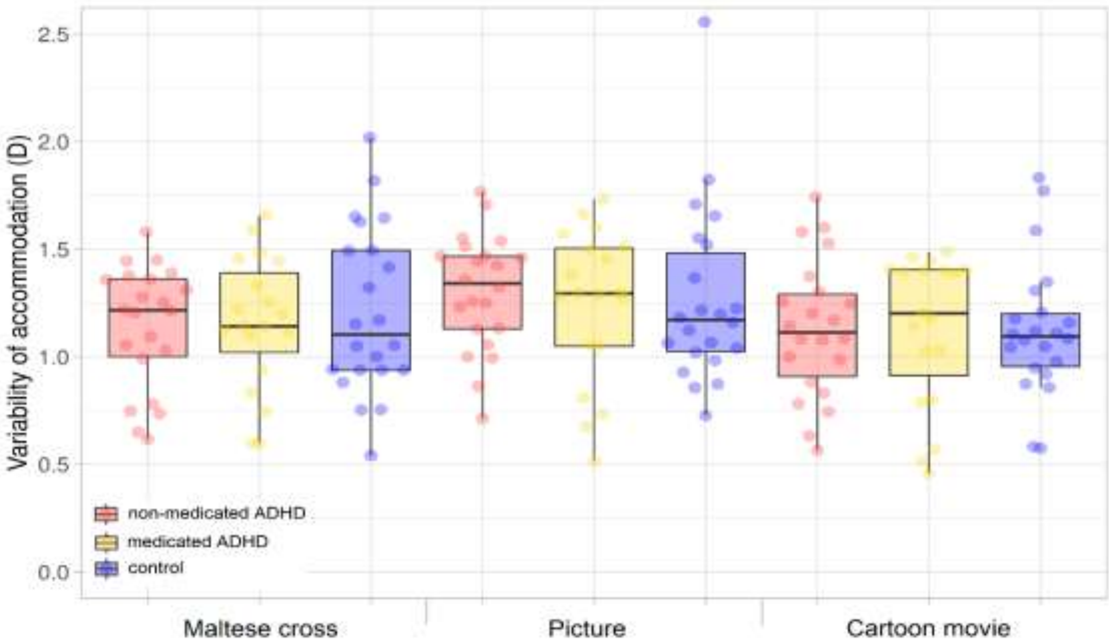

Figure 25. Variability of accommodation for the non-medicated attention-deficit/hyperactivity disorder (ADHD), medicated ADHD, and control groups while viewing the three types of stimuli. The box plots represent 75th and 25th centiles, and individual data are displayed as jittered dots. The horizontal line into the box indicates the median value. The whiskers show the range of values within the 1.5 × interquartile range.

Discussion

The present study was aimed at determining the nature of the relationship between an impaired accommodative response and the presence of attention-deficit/hyperactivity disorder, as well as the possible influence of stimulant medication on these effects. Our data revealed that the lag of accommodation was significantly higher for the group of non-medicated children with attention-deficit/hyperactivity disorder in comparison to the control group, however, no differences were obtained between medicated children with attention-deficit/hyperactivity disorder and healthy controls. interestingly, the lag of accommodation was not influenced by the manipulation of the stimulus, observing that children with attention-deficit/hyperactivity disorder have a greater lag of accommodation while viewing passive (Maltese cross and picture) and active (cartoon movie) visual stimuli which they chose. For its part, the variability of accommodation was dependent on the visual task, yielding a less stable accommodation for the picture condition, but there were not between-groups differences. The current findings indicate that children with attention-deficit/hyperactivity disorder have a reduced accommodative response, which is independent of the attentional engagement with the visual target, and thus, the accommodative lag may not be due to the attentional deficit, suggesting a primary deficit of accommodation. Regarding stimulant medication, it seems to partially attenuate the accommodation deficit in the group of medicated children with attention-deficit/hyperactivity disorder.

We found that children with attention-deficit/hyperactivity disorder had a mean lag of around 0.5 D greater than the control group when fixating on the Maltese cross at 25cm. Our results agree with a previous study that found a higher lag of accommodation in a population of non-medicated children with attention-deficit/hyperactivity disorder in comparison to a healthy age-matched control group (approximately 0.5D greater in the attention-deficit/hyperactivity disorder group at 20 cm) (Redondo et al., 2018), confirming an impaired accommodative response in children with this disorder. High lags of accommodation have shown to create asthenopia and impair behavioural performance (Sterner, Gellerstedt & Sjöström, 2006), which could partly explain the greater near symptomatology (i.e., converge insufficiency) reported by children with attention-deficit/hyperactivity disorder (Borsting, Rouse & Chu, 2005, Granet et al., 2005). In regard to the clinical relevance of the present findings, normative data indicate that an accommodative lag, as measured by MEM retinoscopy at 40 cm, of approximately 0.50 ± 0.40 D may be expected on 10 years-old children (Jiménez et al., 2003). We found a mean accommodative lag, using an open-field autorefractor, of 1.19 ± 0.57 D at 25 cm in children with attention-deficit/hyperactivity disorder, and thus, these results may be considered of clinical significance. Also, the difference found between the attention-deficit/hyperactivity disorder and control groups (~0.50 D) is quite large. For example, the accommodative lag obtained with the WAM-5500 at 25 cm is around 0.30 D higher in individuals with visual discomfort in comparison to asymptomatic subjects (Tosha et al., 2009).

Notably, a link between accommodation and attention has been previously discussed, suggesting that attentional factors may mediate the ability to accommodate (Edgar, 2007). In this study, we hypothesized that the inherent difficulty of attention-deficit/hyperactivity disorder to focus attention could be the principal cause of the accommodative deficit found during the optometric evaluation. Since children's attention during eye testing can potentially be improved with attractive stimuli and the behavioural performance of children with attention-deficit/hyperactivity disorder can be enhanced by increasing task stimulation and engagement (Lee, Zentall & Lee, 2002), we manipulated the interest elicited by the visual task using different types of stimuli. Surprisingly, our results showed that children with attention-deficit/hyperactivity disorder present a worsened accommodative response regardless the interest and motivation toward the task, as the differences in accommodative response between children with attention-deficit/hyperactivity disorder and healthy controls was similar under engaging (cartoon movie) or less engaging (Maltese cross). This suggests that the relationship between accommodation and attention-deficit/hyperactivity disorder is inherent to this disorder rather than caused by the lack of interest while performing the accommodative test.

The accommodative response is not stable when focusing on a stationary target and typically fluctuates (~ 0.5D) around the mean response (Charman & Heron, 2015). The variability of accommodation is influenced by a variety of optical (e.g., depth of field [Day et al., 2009]) and non-optical (e.g., cognitive effort [Hynes et al., 2018]) factors. In regard to cognitive processing, Roberts et al., (2018) observed that the variability of accommodation was lower while performing an active sustained task of 10 minutes in comparison to a passive and non-engaging task in children. Similarly, our results showed that the variability of the accommodative response is dependent on the visual task, namely all children exhibited a higher variability for the picture condition in comparison to the cartoon movie. Therefore, when the optical characteristics (i.e., colour, contrast) were similar (cartoon movie vs. picture), there was a more stable accommodative response on the more engaging task. However, we did not find any group difference of the variability of accommodation, which is in concordance with Redondo et al., (2018), who also only found differences between the attention-deficit/hyperactivity disorder and a control group in the lag of accommodation, but not the variability of accommodation.

Regarding time-on-task effects, there was a trend toward to higher variability of accommodation over time, with these effects being evident in the last minute of the 3-minute viewing task. Previous studies have reported a stable behaviour of the accommodative response in an attention-deficit/hyperactivity disorder and control population (Redondo et al., 2018, Tosha et al., 2009), which may seem contradictory to our findings since we found that the variability of accommodation was significantly less stable after 120-sec of viewing. Nevertheless, both studies recorded ocular accommodation during a 90-sec period. Indeed, a recent study has showed that more than 4 minutes is necessary to observe a reduction in the stability of ocular accommodation while performing a psychomotor vigilance task in healthy young adults (Redondo et al., 2019), although, it should be noted the age differences in the experimental samples of these studies. Taken together, this set of results suggests that the variability of accommodation remains unaltered in children with attention-deficit/hyperactivity disorder in comparison to controls. in addition, the stability of accommodation is sensitive to the stimulus attractiveness and accumulated time-on-task in the attention-deficit/hyperactivity disorder and control groups.

It is well known that changes in pupil size and accommodation are strongly correlated but not necessarily causally related (Miller 1985). The pupillary response provides valid information about the sympathetic and parasympathetic branches of the autonomic nervous system and has shown to be sensitive to changes in the attentional state (Donaghue et al., 1995, Unsworth & Robison, 2016). In agreement with Kara et al., (2013), we did not find significant differences between the attention-deficit/hyperactivity disorder and control groups (main effect of group) for the magnitude or variability of pupil size, suggesting that these variables are not sensitive enough to be used as physiological markers for diagnosis of Attention-deficit/hyperactivity disorder. Here, the analysis of the pupil dynamics was carried out in order to explore whether the changes in the accommodative response may be explained by variations in the pupil behaviour. However, we did not find an association between the changes in the accommodative and pupil dynamics, since all the dependent variables exhibited a different responsiveness to our experimental manipulation.

The chronic use of methylphenidate has demonstrated to induce changes in the brain neurochemistry, modifying the cognitive and neural functioning (Gray et al., 2007).

However, its effects on the visual function are not well-established due to the mixed results reported in the scientific literature (Fried et al., 2014, Klein, Raschke & Brandenbusch, 2003, Martin et al., 2008, Larrañaga-Fragoso et al., 2015, Whitman, Lindsay & Cruz, 1997, Grönlund et al., 2007). In our study, the medicated attention-deficit/hyperactivity disorder group exhibited slightly lower values of accommodative lag than the non-medicated attention-deficit/hyperactivity disorder group (see Table 7), although these differences were far from yielding statistical significance (corrected p-value = 0.504). This finding agrees with studies that did not observe any benefits associated with stimulant medication for attention-deficit/hyperactivity disorder treatment on the visual function (Grönlund et al., 2007, Whitman, Lindsay, & Cruz, 1997). It is plausible to speculate that the brain areas (e.g., superior colliculus) controlling the near response (Suzuki 2007) are unaffected by the stimulant medication. Other studies observed improvements in blink and microsaccade rates and visual fields when children with attention-deficit/hyperactivity disorder were treated with stimulant (Fried et al., 2014, Martin et al., 2008). However, it should be noted that these visual functions are controlled by different physiological mechanisms than those responsible for driving the dynamics of the accommodative response (Skalicky 2016). Based on the results of this study the use of stimulants (i.e., methylphenidate) in treatment of attention-deficit/hyperactivity disorder medication does not eliminate the accommodative deficits found in children with this neuropsychological disorder.

This study shows that children with attention-deficit/hyperactivity disorder present a worsened accommodative response regardless of stimulus type and treatment with stimulants. Our study is not exempt of limitations and they should be acknowledged. First, the screen luminance and colour conditions were not matched between the Maltese cross and picture and cartoon movie conditions, and it may lead to some differences in the accommodative response behaviour (Ward 1985). Second, although we found an inherent accommodative deficit on this population, we cannot stablish the physiological cause of this fact, since there are multiple brain mechanisms shared by attentional processing and the control of ocular dynamics (Di Stasi et al., 2013, Hafed, Goffart & Krauzlis, 2009, McDougal & Gamlin, 2015, Nadel & Barnes, 2019). It is our hope that future studies could determine the brain mechanisms responsible for the impaired accommodative function in children with attention-deficit/hyperactivity disorder. Third, the pharmacological treatment does not seem to improve the accommodative function in the attention-deficit/hyperactivity disorder population, and thus, the effectiveness of alternative treatment strategies such as visual therapy should be investigated since some researchers have found that visual therapy in children with attention-deficit/hyperactivity disorder improves the visual function and the symptomatology of attention-deficit/hyperactivity disorder (Hagen et al., 2008, Lee, Moon & Cho, 2014). Lastly, there is evidence that some comorbidities or attention-deficit/hyperactivity disorder symptoms cannot be exclusively addressed by the stimulant medication, supporting that the development of new drugs is necessary to manage the symptoms and signs associated with attention-deficit/hyperactivity disorder (Molina-Carballo, Checa-Ros, & Muñoz-Hoyos, 2016). Therefore, the impact of different pharmacological interventions on the accommodative function should be explored in future investigations.

Conclusions

This study provides further evidence for an impaired accommodative response in children with attention-deficit/hyperactivity disorder. we found that children with attention-deficit/hyperactivity disorder present a higher lag of accommodation than age-matched controls, with this effect being independent of the stimuli even when these are designed to increase engagement. Methylphenidate treatment induced a marginal improvement in the accommodative lag, although these changes were far from reaching normal values. The variability of accommodation was sensitive to the visual task, showing a more stable accommodative response while viewing the more engaging task (cartoon movie). However, children with attention-deficit/hyperactivity disorder and healthy controls exhibited a similar stability of accommodation. taken together, the present outcomes incorporate novel insights into the inherent accommodative deficit of children with attention-deficit/hyperactivity disorder, since our results suggest that this effect is not due to the lack of engagement in the visual task. Future studies are needed to determine the effects of using visual therapy for treating the accommodative deficit of children with attention-deficit/hyperactivity disorder on their academic, cognitive, and visual development.

STUDY VIII. ACCOMMODATION AND PUPIL DYNAMICS AS OBJECTIVE PREDICTORS OF BEHAVIOURAL PERFORMANCE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Introduction

Attention-deficit/hyperactivity disorder is a clinically heterogeneous psychiatric disorder, which is estimated to have a worldwide prevalence of about 3 to 5% in children and adolescents (American Psychiatric Association, 2013). Children with attention-deficit/hyperactivity disorder have demonstrated to suffer emotional and neuropsychological deficits (e.g., executive function, working memory, inhibition, sustained attention, delay aversion, motor activity and timing response) (Sjöwall, Roth, Lindqvist, & Thorell, 2013), and they have been linked to abnormal functional connectivity, as well as structural and functional brain deficits (Castellanos & Aoki, 2016; Hoogman et al., 2017).

Psychological problems have been previously related with visual impairments (Pinquart & Pfeiffer, 2014). There is scientific evidence that children with attention-deficit/hyperactivity disorder are more frequently diagnosed with different visual abnormalities, including refractive errors (hyperopia and astigmatism), strabismus (Reimelt et al., 2018), atypical oculomotor behaviour (Mahone, 2012), amblyopia (Su, Tsai, Tsai, & Tsai, 2019), visual processing deficits (Lenz et al., 2010), colour perception alterations (Kim, Banaschewski, & Tannock, 2014), or convergence insufficiency (Granet et al., 2005) in comparison to healthy controls. Also, the accommodative response, which refers to changes in the refraction of the ocular lens to provide a sharp retinal image (Millodot, 2014), has demonstrated to be deteriorated in a population of non-medicated children with attention-deficit/hyperactivity disorder in comparison to an age-matched control group, with children with attention-deficit/hyperactivity disorder exhibiting an under-accommodation while viewing an stationary high-contrast stimulus at near distances (Redondo et al., 2018). The accommodative response is controlled by the action of the ciliary muscle which is innervated by the autonomic nervous system (McDougal & Gamlin, 2015). Accommodation is determined by a complex integration of factors, namely it is primarily stimulated by alterations in the retinal image (e.g. blur), but also by task demands with a behavioural component caused by changes in the autonomic balance of the subject (Bullimore & Gilmartin, 1988; Rosenfield & Ciuffreda, 1990).

An effective visual performance depends on control processes, and especially the brain areas controlling attention seem to play a fundamental role on the functioning of the visual system (Braddick & Atkinson, 2011). In particular, the accommodative response seems to be influenced by attention, with these changes being caused by variations of the autonomic nervous system activity (Davies et al., 2005; Roberts et al., 2018; Vera et al., 2016). Previous studies have suggested a bidirectional relationship between attention and accommodative response (Braddick & Atkinson, 2011; Poltavski et al., 2012), however, the causal relationship has not yet been elucidated. Regarding attentional deficits, accommodative fatigue has revealed to exacerbate the severity of attentional problems, as measured by a computerized test of sustained attention used in the diagnosis of attention-deficit/hyperactivity disorder (Poltavski et al., 2012), while a reduced accommodative response has been also found in children with attentional deficits (Redondo et al., 2018).

Some studies have found that attention-demanding tasks leads to changes in the pupil behaviour (Granholm, et al. 1996; Morad, Lemberg, Yofe, & Dagan, 2003; Steinhauer, Siegle, Condray, & Pless, 2004; Unsworth & Robison, 2016). Due to this fact, the pupil dynamics has been proposed as an objective index to track attentional lapses in healthy subjects (Unsworth, Robison, & Miller, 2018) and attention-deficit/hyperactivity disorder patients (Wainstein et al., 2017). Taken together, if accommodative response and pupil size are mediated by the attentional state, it is plausible to expect that these objective visual indices may be used to predict attentional deficits during the execution sustained attention tasks, and that the monitoring of both ocular indices would allow to improve the current models used to determine attentional performance in attention-deficit/hyperactivity disorder.

To address the limitations found in the scientific literature, the main objectives of this study were (1) to compare the accommodative response and pupil dynamics (magnitude and variability) during the execution of the Continuous Performance Task between a population of non-medicated children with attention-deficit/hyperactivity disorder and an age-matched control group, (2) to determine the effect of time-on task on these variables, and (3) to establish the association between Continuous Performance Task performance and accommodative response and pupil size. Based on previous studies, we hypothesized that children with attention-deficit/hyperactivity disorder will show a worsened accommodative response in comparison to controls (Redondo et al., 2018), and the accommodation and pupil dynamics will change over time due to the variations in the attentional state (Poltavski et al., 2012; Wainstein et al., 2017). In regard to the predictive capacity of behavioural performance by ocular accommodation and pupil size, we expect that the combination of both ocular indices will permit to obtain more robust models for attentional performance prediction that those studies only using pupillary responses (Wainstein et al., 2017).

Methods

Participants

An a priori power analysis to determine the sample size, assuming an effect size of 0.20, alpha of 0.05, and power of 0.80, predicted a required sample size of 42 participants (21 per group) using a linear multiple regression analysis. Twenty-seven children diagnosed with attention-deficit/hyperactivity disorder, which were evaluated by performing interviews with the patient, parents and teachers as well as by completing a neuropsychological evaluation following standard procedures and by using the Diagnostic and Statistical Manual of Mental Disorders 5th edition (American Psychiatric Association, 2013), and thirty-two healthy (no systemic diseases or mental disorders) controls took part in this study. Within the group of children with attention-deficit/hyperactivity disorder, 15 were diagnosed as combined subtype (inattentive/hyperactive), 11 as being inattentive and 1 as predominantly hyperactive/impulsive. All control children were recruited from local schools, and they underwent the annual physical, psychological and psychiatric examination provided by the National Health System. All participants were free of any metabolic, endocrinal or orthopaedic disease. Children with attention-deficit/hyperactivity disorder were diagnosed at the Neuropsychology and Early Intervention Unit of San Cecilio University Hospital, and none of them had been administered methylphenidate or submitted to any other treatment for attention-deficit/hyperactivity disorder before participating in this investigation.

Participants were tested in order to check the following inclusion criteria: (1) age range, ≥ 6 years old and ≤ 14 years old, (2) uncorrected or, when necessary, corrected visual acuity of 0.10 logMAR or better in each eye, (3) no strabismus and/or amblyopia, (4) refractive error, or residual refractive error, as determined by subjective refraction (spherical equivalent refractive error lower than ± 1D), (5) no ocular disease or surgery, (6) intelligence quotient less than 85, according to the Wechsler Intelligence Scale for Children 4th edition, and (7) medication-naïve status. After it, 5 participants (4 attention-deficit/hyperactivity disorder and 1 control) were excluded due to non-compliance of inclusion criteria, and thus, twenty-three children with attention-deficit/hyperactivity disorder and thirty-one controls were considered for further analyses (see Table 8 for a description of the experimental sample). All parents signed an informed consent form, and this study conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (546/CEIH/2018).

Measurements

Assessment of behavioural performance

A continuous Performance Task programmed in E-prime 2.0 (Schneider, Eschman, & Zuccolotto, 2012) was used for the assessment of behavioural performance. The Continuous Performance Task is a validated neuropsychological valuable tool that measures subprocesses of attention (focused attention, impulsivity–hyperactivity, sustained attention, vigilance, and change in control), which is commonly used to differentiate between attention-deficit/hyperactivity disorder and healthy children in the diagnostic process (Berger, Slobodin, & Cassuto, 2017), mainly when teacher and parent ratings are inconclusive (Tallberg, Råstam, Wenhov, Eliasson, & Gustafsson, 2019). The test lasted for approximately 14 min, and it was performed on a 17 inches LCD screen. In each trial, high-contrast black letters constant in size and distance appeared on the screen in a white background, subtending a viewing angle of 3.6° in the horizontal and vertical axes. Children were instructed to press with their dominant hand the space bar of a keyboard when any letter (“target”) except X appears on the screen, while refraining from pressing the space bar when the letter X (“non-target”) is presented. The letters were presented in three blocked inter-stimulus intervals of 1000, 2000 or 4000 ms. The sequence of these blocks was randomized for each participant The measures included mean hit reaction time (measure of speed of processing), variability in reaction time, hit (accurate responses), commission errors (impulsivity, response to X), omission errors (inattention, absence of response to others letters than X), d'(detectability, reflects how well a subject discriminates between targets and non-targets, higher values indicating a higher attentiveness), and perseverations (reaction time less than 100 ms). In order to match the samples in time intervals of equal duration, we considered the first 800 seconds of each task.

Assessment of ocular accommodation and pupil dynamics

The accommodative response and pupil size were dynamically measured with an open-field Grand Seiko Auto Refractometer WAM-5500 (Grand Seiko, Hiroshima, Japan), which has demonstrated to acquire reliable and valid data (Sheppard & Davies, 2010; Win-Hall, Houser, & Glasser, 2010). Accommodative response (lag and variability of accommodation) and pupil size (magnitude and variability) measurements were continuously obtained at a temporal resolution of ~5 Hz in high-speed mode and in binocular conditions. Data were recorded from the dominant eye, which was determined by the hole-in-the card method (Momeni-Moghaddam et al., 2014). Recording was conducted while the visual stimulus from the Continuous Performance Task appeared on the centre of the screen, which was situated at 40 cm from the participants' head and at their eye level.

Following previous studies, data points of ± 3 standard deviations from the mean spherical refraction value were removed, as they were considered as blinking or recording errors (Tosha et al., 2009). The lag of accommodation, which refers to the dioptric value in which the accommodative demand exceeds the accommodative response, was calculated by subtracting the mean value from the dynamic measures and the baseline static refractive value obtained in far distance to the accommodative demand at 40cm (2.5D). Additionally, when ophthalmic lenses were necessary, we followed the equation of Atchison & Varnas (2017) for obtaining the ocular accommodation demand referring to the corneal plane. The standard deviation of dynamic accommodative response and pupil size measurements was considered for the variability of both ocular indices.

Procedure

First, parents read and signed the informed consent. Each participant underwent an optometric examination performed by two experienced optometrists to assess if they met the inclusion criteria. The following optometric measures were taken: distance and near monocular and binocular visual acuity, non-cycloplegic subjective refraction using an endpoint criterion of maximum plus consistent with best vision, cover test at distance and near. Also, slit lamp and direct ophthalmoscopy examinations were performed. The participants were compensated when necessary by considering the exact ocular refraction. Then, we performed a monocular static refractive measure with the WAM-5500 in order to determine the exact baseline refractive value, which was used for the lag of accommodation calculation (see above). All the measurements were taken in a dimly illuminated room (~ 150 lx, as measured at the corneal plane [Illuminance meter, T-10, Konica Minolta Inc., Tokyo, Japan]) isolated from external noise, and with the participants placing their chin and forehead in the corresponding supports of the WAM-5500 autorefractometer. For the Continuous Performance Task, all participants received verbal and written instructions, and they had a familiarization period with the test. After it, the Continuous Performance Task started, while accommodative response and pupil size were continuously recorded during the entire task, and divided in eight blocks of 100 seconds to test the time-on-task effects.

Statistical analysis

First, the normal distribution of the data (Shapiro-Wilk test) and the homogeneity of variances (Levene's test) were confirmed ($p > 0.05$). To test the possible differences in age between groups and to verify the attention-deficit/hyperactivity disorder diagnosis, we performed separate t-tests for independent samples for the participants´ age and the different indices of behavioural performance (reaction time, variability in reaction time, hits, commission errors, omission errors, d', and perseverations), and considering the group (attention-deficit/hyperactivity disorder and control) as the only between-participants factor.

Separate mixed repeated measures analyses of variance, considering the group (attention-deficit/hyperactivity disorder and control) as the between-participants factor, and the time-on-task (eight blocks of 100-s) as the within-participants factor, were carried out for the magnitude and variability of ocular accommodation and pupil size. We calculated the

Pearson correlation coefficients (Pearson r) to explore the possible associations between the ocular indices and behavioural performance parameters. After it, a multiple regression analysis was used to predict behavioural performance from the different ocular variables. These analyses were performed considering the entire experimental sample (attention-deficit/hyperactivity disorder and control groups), as well as for each group separately. We implemented the backward elimination procedure to obtain the model capable of explaining the greatest amount of variance with the minimum number of predictors. Statistical significance was set at an alpha level of 0.05 and post hoc tests were corrected with Holm-Bonferroni procedure. Standardised effect sizes were reported by means of the partial η^2 for Fs and the Cohen's d for t tests.

Results

Manipulation check

Our analysis revealed no statistically significant age-differences between both groups ($t_{52} = 0.787$, $p = 0.435$, $d = 0.217$). We found a statistically significant poorer performance on the Continuous Performance Task commission errors, omission errors, reaction time, perseverations and d' (all p-values < 0.05) for children with Attention-Deficit/Hyperactivity Disorder in comparison to controls. However, no group-differences were obtained for the variability of reaction time ($t_{52} = 1.709$, $p = 0.093$) and hits ($t_{52} = 0.963$, $p = 0.340$) (Table 8).

Lag of accommodative response

The analysis of the lag of accommodation showed a statistically significant effect of the time-on-task ($F_{7, 364} = 3.745$, $p < 0.001$, $\eta^2 = 0.066$), and the group ($F_{1, 52} = 4.527$, $p = 0.038$, $\eta^2 = 0.080$), with the attention-deficit/hyperactivity disorder group showing higher lags of accommodation. No statistically significant differences were observed for the interaction time-on-task × group ($F_{7, 364} = 1.254$, $p = 0.273$). Post-hoc analysis did not reveal any significant difference for the comparisons between the eight 100-s blocks (corrected p-value > 0.05) (Figure 26, panel A).

Table 8. Participant's characteristics, and Continuous Performance Task performance indices for the attention-deficit/hyperactivity disorder and control groups.

	ADHD (n = 23) Mean (SD)	Control (n = 31) Mean (SD)	t	p-value	Cohen´s d
Descriptive characteristics					
Age (years)	10.1 (2.6)	10.6 (2.4)	0.787	0.435	0.217
Gender (female %)	39.1	41.9	--	--	--
Spherical equivalent (D)	0.1 (0.4)	0.2 (0.3)	0.730	0.411	0.228
CPT indices					
Reaction time (ms)	461.3 (72.8)	404.3 (73.9)	-2.818	0.007**	-0.775
Variability in reaction time (ms)	161.8 (43.3)	186.4 (57.8)	1.709	0.093	0.470
Hits (%)	83.2 (14.0)	86.2 (8.0)	0.963	0.340	0.265
Commission errors (%)	52.4 (32.5)	23.6 (30.5)	-3.334	0.002**	-0.918
Omission errors (%)	14.2 (13.6)	6.4 (8.1)	-2.607	0.012*	-0.717
d'	1.1 (0.9)	2.2 (0.9)	4.331	<0.001***	1.192
Perseverations (%)	11.4 (9.3)	5.4 (5.6)	-2.953	0.005**	-0.813

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CPT = Continuous Performance Task, SD = standard deviation, D = diopters, ms = milliseconds, *,** and *** indicate statistical significant difference between groups (p < 0.05, <0.01 and <0.001, respectively).

Variability of accommodation

The variability of accommodation yielded statistically significant differences for the time-on-task ($F_{7, 364} = 4.398$, $p < 0.001$, $\eta^2 = 0.076$), whereas no effects were obtained for the group ($F_{1, 52} = 1.113$, $p = 0.296$) and the interaction time-on-task × group ($F_{7, 364} = 1.373$, $p = 0.216$). Post-hoc analysis exhibited significant difference for first block when compared with third (corrected p-value = 0.011, d = -0.510), fourth (corrected p-value = 0.008, d = -0.527), fifth (corrected p-value = 0.003, d = -0.565), sixth (corrected p-value = 0.014, d = -0.495), seventh (corrected p-value = 0.005, d = -0.550), and eighth (corrected p-value = 0.014, d = -0.498) (Figure 26, panel B).

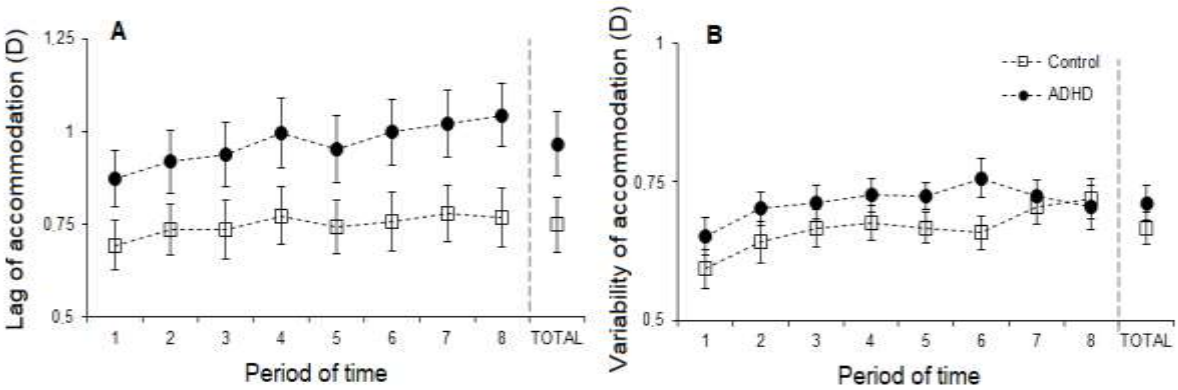

Figure 26. Lag of accommodation (A) and variability of accommodation (B) for attention-deficit/hyperactivity disorder (ADHD) and control groups over time (100-s intervals each block). Error bars show the standard error (SE).

Magnitude of pupil size

The pupil size exhibited statistically significant differences for the time-on-task ($F_{7, 364}$ = 10.036 $p < 0.001$, $\eta^2 = 0.161$), however no effects were obtained for the group ($F_{1, 52}$ = 0.884, p = 0.352) and the interaction time-on-task × group ($F_{7, 364}$ = 1.232, p = 0.284). Post-hoc analyses showed significant differences for the first block when compared with second (corrected p-value = 0.002, d = 0.595), third (corrected p-value < 0.001, d = 0.664), fourth (corrected p-value < 0.001, d = 0.638), fifth (corrected p-value < 0.001, d = 0.730), sixth (corrected p-value < 0.001, d = 0.684), seventh (corrected p-value < 0.001, d = 0.816), and eighth (corrected p-value = 0.034, d = 0.457), as well as between the seventh and eighth blocks (corrected p-value =0.007, d = 0. -0.530) (Figure 27, panel A).

Variability of pupil size

Pupil oscillations showed statistically significant differences for the time-on-task ($F_{7, 364}$ = 3.262, p = 0.002, η^2=0.059), however no effects were obtained for the group ($F_{1, 52}$ = 0.976, p = 0.328) and the interaction time-on-task × group ($F_{7, 364}$ = 0.863, p = 0.536). Post-hoc analyses showed significant difference for the first when compared with eighth block (corrected p-value = 0.023, d = -0.487) (Figure 27, panel B).

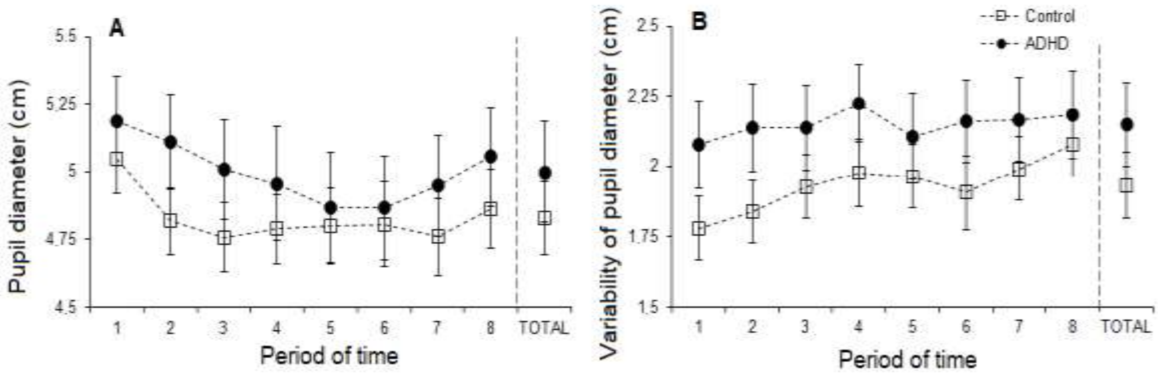

Figure 27. Pupil diameter (A) and variability of pupil diameter (B) for attention-deficit/hyperactivity disorder (ADHD) and control groups over time (100-s intervals each block). Error bars show the standard error (SE).

Prediction of behavioural performance from ocular accommodation and pupil size

Regarding Continuous Performance Task performance, five (reaction time, d', commission error, omission error and perseverations) and two (hits and omission error) parameters showed a statistically significant level of correlation with ocular parameters for the total and attention-deficit/hyperactivity disorder groups, respectively. However, no bivariate correlations were found for the control group. The results showed that the accommodative lag was not a good predictor for any of the performance indices on Continuous Performance Task. On the other hand, pupil size and variability of accommodation and pupil seem to be better predictors. The results of the multiple regression model for each group (total participants and attention-deficit/hyperactivity disorder) are displayed in Table 9.

Table 9. Multiple regression analysis summary for the association between the objective visual indices and parameters of Continuous Performance Task.

Dependent variable	Predictors	t	p-value	β	Adjusted R^2 (p-value)
Total sample					
Reaction time (ms)	Pupil size (mm)	1.490	0.142	0.255	0.123 (0.012)
	Variability of pupil size (mm)	1.015	0.315	0.174	
Omission errors (%)	Variability of accommodation (D)	2.963	0.005*	0.377	0.213 (0.001)
	Pupil size (mm)	2.394	0.020*	0.393	
	Variability of pupil size (mm)	-0.598	0.553	-0.103	
D’	Pupil size (mm)	-1.164	0.250	-0.203	0.085 (0.035)
	Variability of pupil size (mm)	-0.990	0.327	-0.173	
ADHD group					
Hits (%)	Variability of accommodation (D)	-2.526	0.020*	-0.444	0.343 (0.006)
	Pupil size (mm)	-2.169	0.042*	-0.381	
Omission errors (%)	Variability of accommodation (D)	1.890	0.073	0.320	0.389 (0.003)
	Pupil size (mm)	3.126	0.005*	0.530	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, β = Standardized multiple regression coefficients, Adjusted R^2 = Adjusted coefficients of determination, D` = detectability, ms = milliseconds, mm = millimetres, D = dioptres.

Discussion

The results of this study demonstrated that the accommodative response is altered in children with attention-deficit/hyperactivity disorder (greater lags of accommodation) in comparison to healthy controls, however, no group-differences were observed for other ocular indices. we found that the dynamics of ocular accommodation and the pupil size exhibited changes in both experimental groups (attention-deficit/hyperactivity disorder and control) as a function of time-on-task. Also, our data revealed an association between the ocular dynamics during the execution of the Continuous Performance Task and different parameters of behavioural performance. The variability of accommodation and the dynamics of pupil size (magnitude and variability) during the continuous performance task predicted a significant amount of variance in different parameters of behavioural performance, mainly when only considering the attention-deficit/hyperactivity disorder group. complementarily, we tested the differences in continuous performance task Between attention-deficit/hyperactivity disorder and control children, and as expected, children with attention-deficit/hyperactivity disorder exhibited a worse behavioural performance in the continuous performance task in comparison to healthy controls.

Behavioural performance

Although it was beyond the main aims of this study, our results from the Continuous Performance Task are in line with previous studies (Epstein et al., 2003; Huang-Pollock, Karalunas, Tam, & Moore, 2012), showing a slower and more inaccurate behavioural performance for the attention-deficit/hyperactivity disorder group in comparison to an age-matched control group (see Table 8). A reduced capacity of attention is present in children with attention-deficit/hyperactivity disorder as a consequence of an impaired self-regulation or executive control (Barkley, 1997), and therefore, the longer reaction times, reduced d’, higher perseverations and more commission and omission errors found for children with attention-deficit/hyperactivity disorder in comparison to controls supported the diagnosis of attention-deficit/hyperactivity disorder based on the DSM-5. However, we failed to find any difference for hits and variability of reaction time, which has demonstrated to be higher in attention-deficit/hyperactivity disorder in comparison to controls (Kofler et al, 2013).

Accommodation dynamics

The accommodative response seems to be particularly sensitive to neurological alterations since it has demonstrated to be reduced in a variety of mental disorders such as Down syndrome (Woodhouse et al., 2000), autism (Anketell, Saunders, Gallagher, & Bailey, 2018), cerebral palsy (Mcclelland et al., 2017) and dyslexia (Evans, Drasdo, & Richards, 1995). Ours results incorporate the attention-deficit/hyperactivity disorder into this list of neurological disorders, after observing that the lag of accommodation was significantly higher in the attention-deficit/hyperactivity disorder group in comparison to an age-matched control group, corroborating the results of our earlier study (Redondo et al., 2018). The accommodative response to a stimulus is usually smaller than the stimulus itself. The normative value of lag of accommodation at 40 cm is about 0.50 D and 0.75 D or higher when measured with autorefractor (Abbott, Schmid, & Strang, 1988; Jiménez, González, Pérez, & Garcia, 2003; Manny, 2009), while greater values of accommodative lag have been associated with asthenopia (Allen, Hussain, Usherwood, & Wilkins, 2010; Birnbaum, 1993; Chase et al., 2009; Tosha et al., 2009). here, we found that children with attention-deficit/hyperactivity disorder had a mean lag of around 0.25D greater than the control group which may be related to visual discomfort. Additionally, accommodative insufficiency, which is related to multiple clinical signs including a high lag of accommodation (Cacho, García, Lara, & Seguí, 2002), has been described as the main source of convergence insufficiency symptomatology in children (Marran, De Land, & Nguyen, 2006), with convergence insufficiency being one of the most prevalent binocular anomalies in children with attention-deficit/hyperactivity disorder (Granet et al., 2005; Mitchell, 2009; Rouse et al., 2009). As indicated by Borsting, Rouse, & Chu, (2005), a poorer control of the accommodative or vergence mechanisms is present in children with symptomatic accommodative dysfunction or convergence insufficiency, and it could lead to greater difficulties in processing information using the visual attention system.

For its part, the variability of accommodation is a result of the combination of neurological control and physiological rhythmic variations (Barry Winn & Gilmartin, 1992), with this ocular index fluctuating approximately 0.50 D in amplitude around the mean response (Charman & Heron, 1988). A number of factors such as age (Anderson et al., 2010), refractive error (Day et al., 2009), pupil diameter (Gray & Winn, 1993) and accommodative distance (Jiménez et al., 2019) have demonstrated to influence the variability of the accommodation. Additionally, the variability of accommodation decreases during tasks that require cognitive effort or are attractive to subjects (Hynes et al., 2018; Roberts et al., 2018), and thus, cognitive processing seems to be also of relevance in this regard. However, we did not find any significant difference between groups for the variability of accommodation, suggesting that the neural mechanisms that controls the variability of accommodation may be preserved in children with attention-deficit/hyperactivity disorder or that the task used in our study may not be appropriate in terms of cognitive requirements to capture possible differences associated with attentional deficits. Future studies are needed to verify this issue.

Pupil dynamics

The assessment of the pupil provides an important metric of the autonomic nervous system (Donaghue et al., 1995), which is generally assumed to be impaired in attention-deficit/hyperactivity disorder as a result of a prefrontal cortex hypofunction and noradrenaline dysregulation (Cortese, 2012; Musser et al., 2011). Here, we did not find any differences between groups for the magnitude and variability of pupil size, and thus, we cannot confirm that these variables allow to differentiate between children with attention-deficit/hyperactivity disorder and healthy controls. Similarly, Kara et al., (2013) found no statistically significant differences on photopic and mesopic pupil diameters between a group of attention-deficit/hyperactivity disorder and control children.

Time-on-task effects on accommodation and pupil dynamics

Regarding the time-on-task effects of sustained attention on the ocular variables, we found that all of them showed changes during the execution of Continuous Performance Task (see Figures 26 and 27) in both experimental groups. In particular, the accommodative response experienced a decrease in magnitude (higher lags of accommodation), and the variability of accommodation was less stable (greater variability) over time. The pupil size was modified following a U-shape function and the variability of pupil was positively associated with time-on-task. These results could be explained by arousal changes experienced during sustained attention, which alters attention capabilities, and it may induce changes in the ocular dynamics as a consequence of accumulated visual or mental fatigue (Edgar, 2007; Vera et al., 2016). In this regard, accommodative fatigue has been described as a worsened performance of the accommodative response dynamics due to visual discomfort or prolonged effort (Hasebe et al., 2001), with visual fatigue being characterised by an increase in the lag of accommodation (Tosha et al., 2009) and/or instability in the variability of accommodation (Iwasaki & Kurimoto, 1987; Jeng et al., 2014).

Also, there is evidence that the pupil dynamics is sensitive to changes in arousal, attention and mental effort (Morad et al., 2003; Reimer et al., 2016; Steinhauder & Harekem, 1992). Here, the pupil size behaviour over time, instead of approaching to a straight line (control group: $R^2 = 0.236$, attention-deficit/hyperactivity disorder group: $R^2 = 0.364$), it is significantly better adjusted to a second-degree polynomial equation (control group: $R^2 = 0.810$, attention-deficit/hyperactivity disorder group: $R^2 = 0.904$), showing a U-shape. Based on the arousal theory (Dodson, 1908), this decline in pupil diameter until the fifth time block (see Figure 27) is due to the greater engagement on the task (Nieuwenhuis & Jepma, 2011), in which intermediate arousal levels lead to optimal engagement whereas low and high levels of arousal are linked to disengagement, and therefore, pupil diameter increases. In this case, the high activation at the beginning of the task and the fatigue and boredom at the end may be the responsible of the increased pupil diameters. These results are in line with the available literature, since a similar pupil behaviour has been found in previous studies (Hopstaken, van der Linden, Bakker, & Kompier, 2015; Nieuwenhuis & Jepma, 2011). However, other studies have reported contradictory results, with smaller pupil diameters being associated with a reduced task engagement (Hopstaken et al., 2015; Kristjansson, Stern, Brown, & Rohrbaugh, 2009; Van Orden et al., 2000). A possible explanation of this discrepancy may be due to the wide variety of tasks used, as well as the fact that the assessment of these associations are based on categorical approaches (Van Den Brink et al., 2016). From the results of this study, we can state that both experimental groups showed a similar influence of accumulated effort on the accommodation and pupil dynamics.

Association between accommodation and pupil dynamics and behavioural performance

Based on the association between mental states and the ocular dynamics (Unsworth et al., 2018; Vera et al., 2016; Wainstein et al., 2017), we aimed to explore the utility of ocular accommodation and pupil dynamics as predictors of Continuous Performance Task performance in a population of children with attention-deficit/hyperactivity disorder and healthy controls. When considering the accommodative indices, the behavioural performance was only associated with the variability of accommodation. For the total experimental sample, the variability of accommodation was positively and negatively associated with the and hits, respectively, and in conjunction with the pupil dynamics (see Table 9), it was also associated with the omissions. The analysis of the attention-deficit/hyperactivity disorder group revealed that the variability of accommodation was included in multiple regression models predicting the hits and omissions (see Table 9). To the best of our knowledge, only Redondo et al., (2019) have recently explored the utility of the variability of accommodation as a physiological marker of behavioural performance in healthy young adults. They observed that this objective index predicted a significant amount of variance in reaction time during the execution of a psychomotor vigilance task. Lastly, it should be noted the lag of accommodation was independent of task performance, and thus an increased lag of accommodation in the attention-deficit/hyperactivity disorder group may be inherent in this disorder, but it do not explain their attention-deficit/hyperactivity disorder symptoms on Continuous Performance Task tests (Redondo et al., 2018). It may be plausible that the brain structures involved in the control of accommodation are also damaged in the attention-deficit/hyperactivity disorder population. Remarkably, previous studies have proved that the superior colliculus plays an important role in the control of lens accommodation (Sawa & Ohtsuka, 1994). This brain structure has been linked with distractibility and it was found to be dysfunctional in a rodent model of attention-deficit/hyperactivity disorder (Brace et al., 2015). Therefore, it is possible that these brain structures may be responsible of the impaired accommodative function in children with attention-deficit/hyperactivity disorder. However, future studies should explore the brain mechanisms that may explain this outcome or whether information about the accommodative response behaviour could enhance our understanding in the neural basis of attention deficits in humans.

Regarding pupil dynamics, it has been correlated with brain states, neural responsiveness and behavioural performance (McGinleyet al., 2015; Wainstein et al., 2017). Our data showed that for the entire experimental sample (attention-deficit/hyperactivity disorder and controls), both magnitude and variability of pupil size are good predictors of some indices (reaction time, d´, and omissions) related to Continuous Performance Task performance. for the attention-deficit/hyperactivity disorder group, the magnitude of the pupil size was positively associated with reaction time, and was included as a significant predictor of hits and omissions (see Table 9). In accordance with our study, Wainstein et al., (2017) observed that non-medicated attention-deficit/hyperactivity disorder showed a decreased pupil size response in a visuo-spatial working memory task in comparison to controls, which correlated with subjects' performance, measured as response accuracy and reaction time variability. This association between pupil and behavioural performance may be explained by the mediation role of the neuromodulatory locus coeruleus–norepinephrine system, which is one of the most important attentional systems and has demonstrated to play an important role in pupil diameter (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Nieuwenhuis & Jepma, 2011).

This set of findings may be of special relevance in the enhancement of diagnostic procedures and medication management for children with attention-deficit/hyperactivity disorder, since the combination of objective measures to the Continuous Performance Task has been recommended for improving the robustness of the clinical diagnosis (Hall et al., 2016). For example, the QbTest system (QbTech Ltd) is a commercially available neuropsychological test that combines the Continuous Performance Task with the assessment of the motor activity during the test, and it allows to better differentiate between attention-deficit/hyperactivity disorder and non-attention-deficit/hyperactivity disorder patients (Hult, Kadesjö, Kadesjö, Gillberg, & Billstedt, 2018; Vogt & Shameli, 2011). Moreover, the ocular dynamics may be also considered as a potential alternative for enhancing the clinical tools used for attention-deficit/hyperactivity disorder diagnosis and management, however future studies are needed to test this possibility.

Limitations and Future Research

This study showed that the children with attention-deficit/hyperactivity disorder have an impaired accommodative response since higher lags of accommodation were present in this population in comparison with an age-matched control group. Additionally, our results suggest that the variability of accommodation, as well as the magnitude and variability of pupil size could be used as objective physiological markers of behavioural performance on a sustained attention task, which may be of utility in the diagnosis of attention-deficit/hyperactivity disorder. however, this study is not exempt of limitations, and they should be mentioned. first, despite the fact that subject's cooperation is required during the task, it could be possible that children's engagement was different between groups, which could be associated with the greater lags of accommodation observed in children with attention-deficit/hyperactivity disorder. We recommend future studies to assess the accommodative function with more engaging stimulus (e.g., cartoon movies) in order to elucidate whether these differences are partially explained by the lack of attention to the visual target (Anderson et al., 2010). Second, the relatively small sample size may reduce the likelihood of finding significant associations between objective ocular indices and behavioural performance, mainly when both experimental groups (attention-deficit/hyperactivity disorder and controls) were considered independently. Third, future studies are needed to determine the aetiology of the visual impairment found in children with attention-deficit/hyperactivity disorder, as well as to assess the effects of attention-deficit/hyperactivity disorder medication, and the possible differences between attention-deficit/hyperactivity disorder subtypes (i.e., inattentive, hyperactive-impulsive type). Fourth, children with attention-deficit/hyperactivity disorder are often diagnoses with at least one comorbid condition. Here, we excluded children with intellectual disability, however other comorbidities such as conduct disorder may influence the present findings. Further research including several comorbidities of attention-deficit/hyperactivity disorder is needed to clarify their role on the ar. lastly, the potential utility of combining ocular objective measures and neuropsychological tests for enhancing attention-deficit/hyperactivity disorder diagnosis requires further investigation.

Conclusions

The present study supports that children with attention-deficit/hyperactivity disorder exhibit a worsened accommodative response, with children with attention-deficit/hyperactivity disorder showing higher lags of accommodation in comparison to an age-matched control group. However, the variability of accommodation and the pupil dynamics did not differ between children with attention-deficit/hyperactivity disorder and healthy controls. The magnitude and variability of the accommodative response and pupil size were modulated as a function of time-on-task in both experimental groups. Our results evidenced that the variability of accommodation, as well as the magnitude and variability of the pupil size, predicted a significant amount of behavioural performance for some Continuous Performance Task parameters. The outcomes of this study incorporate novel insights into the impaired accommodative function in children with attention-deficit/hyperactivity disorder and suggest the potential utility of ocular accommodation and pupil dynamics as objective measures of attentional performance, allowing to improve attention-deficit/hyperactivity disorder diagnosis strategies.

CHAPTER 5: DISCUSSION

DISCUSSION

SUMMARY OF THE MAIN FINDINGS

In normal visual environments, the accommodative response is determined by a complex integration of many factors. The main aim of this Doctoral Thesis was to determine the impact of different psychological factors, namely arousal and attention, on the dynamics of the accommodative response. Most of the experimental work has been conducted in laboratory settings, using different strategies to modulate the arousal and attentional states. Significant changes in the accommodative response have been observed as a consequence of these experimental manipulations.

First, the results of the study support that the level of arousal modulates the accommodative response. This change in the level of arousal was achieved by physical effort through two high-intensity interval protocols differing in exercise intensity. The low-intensity protocol consisted in 8 sprints with 60 s of rest between two consecutive sprints whereas participants were asked to perform 8 sprints with 30 s of rest between two consecutive sprints for the high-intensity condition, and both exercise conditions were compared with a control condition in which participants were instructed to walk. We found that the cardiovascular system is sensitive to high-intensity interval training, exhibiting higher values of heart rate and lower values of heart rate variability as exercise intensity increases. It allowed us to assess the autonomic changes induced by physical effort. Regarding accommodative response, we observed a higher accommodative lag after the high-intensity protocol in comparison to the low-intensity protocol and control condition. Although heart rate variability was sensitive to the physical effort, we did not find any correlation between the accommodative response and the cardiovascular system, which may be probably due to the complexity of the autonomic nervous system.

Similarly, studies II and III investigated the effects of the most consumed psychoactive drug worldwide (i.e., caffeine) on the lag and variability of accommodation. Since caffeine is a stimulant of the central nervous system that promotes physiological variations, we hypothesised that the accommodative function may be altered after its consumption. In study II, we performed 2-minutes recordings of the lag and variability of accommodation at six viewing distances after 30 minutes of ingesting a capsule of caffeine in comparison to a capsule of placebo. We found that the variability of accommodation was lower in the caffeine condition, however no differences were observed for the lag of accommodation. Due to the fact that the variability of accommodation is linked to visual fatigue and caffeine effects have proved to be stronger under fatigue conditions (Lorist & Tops, 2003), in our next study (study III) we incorporated a sustained attention task in order to test the possible influence of caffeine on visual fatigue. Additionally, we explored the mediating role of habitual caffeine intake, since some physiological changes induced by caffeine have shown to be sensitive to caffeine consumption habits. In the same line, we did not find any changes for the lag of accommodation, whereas the variability of accommodation was reduced for the caffeine condition. In addition, the changes in the variability of accommodation were dependent on the caffeine consumption habits, with high caffeine consumers exhibiting a more stable accommodative response than low caffeine consumers. However, we found that caffeine intake did not modulate the time-on-task effects of sustained attention on the variability of accommodation.

Aiming to further explore the time-on-task effects during sustained attention on the accommodative function, as well as to clarify the link between ocular accommodation, cardiovascular system and behavioural performance, we designed the study IV. For this purpose, the accommodative response and hear rate variability were recorded during a 10 minutes Psychomotor Vigilance Task. Our results evidenced that the variability of accommodation is sensitive to time-on-task effects during sustained attention and demonstrated that ocular accommodation may be considered as potential objective predictors of behavioural performance, with lower stability of accommodation being associated with a worse behavioural performance.

Study V aimed to deepen our knowledge about the attentional processes that influence the accommodative response. In particular, we investigated the effects of two different intensities (low and high) of attention facilitators (auditory feedback) and distractors (arithmetic task) on the lag and variability of accommodation. Our findings show that auditory biofeedback improves both the accommodative lag and variability, being these results, more pronounced for the high intensities conditions. Dual-tasking (arithmetic task) promoted an increase in the magnitude of accommodation but only at far distance. These outcomes seem to support the importance of the attentional state on the ocular dynamics.

The last three studies examined the accommodative response in a clinical population of children with attention-deficit/hyperactivity disorder. Study VI compared the accommodative response in a group of children diagnosed with attention-deficit/hyperactivity disorder and an age-matched control group. Our results showed that the group of non-medicated children with attention-deficit/hyperactivity disorder present a higher lag of accommodation than the control group, with these effects being more evident at closer distances. We did not find a decline of the accommodation accuracy over time, probably due to an insufficient time-on-task (90 seconds). These findings suggest a link between the accommodative function and attention-deficit/hyperactivity disorder, however, it is possible that the difficulty to focus attention of this disorder is the main cause of the worsened accommodative response. In order to clarify whether the previously mentioned deficit in the accommodative function is due to an accommodative or attentional problem, we performed the study VII. In this study, we measured the lag and variability of the accommodative response while fixating on different visual stimuli in a population of medicated and non-medicated attention-deficit/hyperactivity disorder, and a healthy control group. Our results proved an altered accommodative response in children with attention-deficit/hyperactivity disorder, which is independent on the visual stimulus even when these stimuli where designed to increase engagement during the task. We also assessed the role of methylphenidate treatment on the accommodative function, observing that the use of stimulant medication leads to a marginal improvement of the accommodative lag, although the accommodative response values of the medicated children with attention-deficit/hyperactivity disorder were not restored to normal values. Lastly, in study VIII, we investigated the behaviour of the accommodative response during the execution of a 14 minutes Continuous Performance Task, and explored the relationship between the dynamics of ocular accommodation and behavioural performance. In line with our previous results, children diagnosed with attention-deficit/hyperactivity disorder exhibited higher lags of accommodation than the control group, but there were no group differences for the variability of accommodation. Interestingly, the variability of accommodation, but not the lag of accommodation, predicted a significant amount of variance in several indicators of behavioural performance.

DISCUSSION OF THE MAIN FINDINGS WITH PREVIOUS LITERATURE

From the results of this International Doctoral Thesis, it is evident that the influence of psychological factors on the accommodative response is complex. We focused on the effects of physical activity, psychostimulants, sustained attention at near, attention distractors, auditory feedback and an inherent attention disorder on the dynamics of the accommodative response. The experimental manipulation of the arousal and attentional states was checked by measuring the cardiovascular responsiveness (heart rate variability), subjective levels of perceived arousal, pupil size and cognitive performance.

Previous studies have reported conflicting results when assessing the effects of non-optical factors on the magnitude of the accommodative response (Bullimore & Gilmartin, 1987; Davies et al., 2005; Jaschinski-Kruza & Toenies, 1988; Kruger, 1980; Malmstrom 1984; Malmstrom et al., 1980; Post et al., 1984; Rosenfield & Ciuffreda, 1990; Winn et al., 1991), whereas there are scarce available data on the changes in variability of accommodation caused by non-optical factors. The findings of the different studies revealed that the magnitude of accommodative response was affected by the acute effects of high exercise intensity, attention distractors and facilitators, and was deteriorated in attention-deficit/hyperactivity disorder, showing in all cases, except for attention distractors and facilitators, a greater lag of accommodation. On the other hand, the variability of accommodation was sensitive to caffeine consumption, time-on-task during sustained attention, attention facilitators, attentional engagement, and it has shown to be a good predictor of behavioural performance in two attentional tasks. Namely, the variability of accommodation was reduced after caffeine consumption, attention facilitators and attractive stimuli, while it increased over time during sustained attention and non-engaging tasks.

Influence of arousal on the accommodative response

The effects of physical exercise on the accommodative response has been previously investigated by Ritter and Huhn-Beck (1993), with their findings being opposite to ours. Specifically, they observed an increase in the accommodative magnitude after running 400 m in trained individuals whereas we found a reduction in the accommodative response after performing a very physically demanding high-intensity interval-training protocol. These differences may be due to the intensity of the physical protocol used, being the physical effort in our study much more intense than in the study of Ritter and Huhn-Beck (1993). Both results could be explained by the arousal-theory, which asserts that performance depends on the level of activation, where an optimal level of arousal is described for optimal performance, with both under-arousal and over-arousal being detrimental (Diamond et al., 2007). Here, moderate intensity exercise promotes a rise in the levels of arousal, and therefore an optimal accommodative performance is expected, while very demanding physical exercise is associated with over-arousal or overload (active fatigue), and it may have an unfavourable effect on accommodative performance (McMorris & Hale, 2012).

The effects of passive fatigue or underload, induced by monotonous or boring activities (Saxby, Matthews, Hitchcock, & Warm, 2007), on the accommodative response has been addressed in previous investigations. Some studies have found a decline in the magnitude of accommodation as consequence of prolonged near-work (Becker et al., 1979; Berens & Sells, 1950; Hasebe et al., 2001; Ostberg, 1980; Owens & Wolf-Kelly, 1987; Takeda et al., 1988), whereas other investigations found non-significant time-on-task effects on the magnitude of the accommodative response while performing a visual task at near distances (Miller et al., 1983; Vilupuru et al., 2005; Wolffsohn et al., 2011). Our results indicate that performing near-work during a moderate amount of time do not alter the magnitude of the accommodative response. Regarding the variability of accommodation, we found that it is modulated as a function of time-on-task, yielding greater fluctuations after the first five minutes of an attentional task at near distance. This outcome agrees with Harb et al., 2006, who observed that the variability of accommodation increases over time during the execution of a reading task. Additionally, we found that a lower stability of accommodation was closely linked to reduced behavioural performance (higher reaction time). The predictive capacity observed for the variability but not for the magnitude of accommodation could be explained by the fact that the accommodative variability provides feedback to the mechanisms controlling accommodation in order to maintain an optimal accommodative response, as indicated by Charman & Heron, (2015). Abnormal sensory information reached during a vigilant task could lead a reduced quality of the signal, inducing higher variability in the accommodative response to ensure the appropriate accommodative magnitude (Simmers, Gray, & Wilkins, 2001).

Caffeine ingestion also allows to alter the levels of arousal without manipulating the task requirements (Barry et al., 2008). Caffeine's increase in cortical arousal is compatible with an antagonist action on adenosine receptors in the brain, reducing inhibition of neuronal excitability (Ferré, 2008). The effects of caffeine on the eye are mixed due to high variability between subjects in physiological response to caffeine, difficulty estimating dietary exposure, and poorly characterisation of neuro-ophthalmic processes (Yoon & Danesh-Meyer, 2018). Here, we found that caffeine consumption induces significant changes in the variability, but not in the lag of accommodation, with the effects on the variability of accommodation being dependent on the habitual caffeine consumption. Caffeine effects on arousal seem to optimise the accommodative behaviour, as we observed a better stability of accommodation after caffeine ingestion.

Taken together, our results seem to corroborate that the accommodative response is sensitive to changes in arousal, namely a better accuracy of accommodation (lower variability) is reached under caffeine-induced arousal. Whereas a higher instability and an increased lag are observed when arousal was in favour of the underload (passive fatigue) and overload (intense exercise) hypotheses, respectively.

Influence of attention on the accommodative response

Most studies analysing the effects of attention on the accommodative response suggest that attention improves the overall accommodative behaviour dynamics of accommodation (Edgar, 1997, 2007; Francis, Jiang, Owens, & Tyrrell, 2003; Horwood & Riddell, 2010; Owens, Andre, & Owens, 2000; Roberts et al., 2018; Wagner et al., 2016). Our results of study V corroborate this statement. since we observed an improvement in both the lag and variability of accommodation when participants´ attention was enhanced with auditory feedback. However, when the ability to maintain attention was reduced with cognitive distractors, we found a reduction in accommodative lag at far distance. Attention is considered as a limited source of processing capacity, and it can be allocated in varying amounts to different tasks or to different locations in the visual field (Eriksen, & James, 1986). The lag and variability of accommodation decreased when participants were aware of the accommodative process and maintained all their attentional resources on the accommodative stimulus and the perception of blur. On the contrary, when including cognitive distractors, the accommodative stimulus location and its sharpness become less relevant, and thus the concomitant cognitive processing (i.e., arithmetic task) to the visual task may induce alterations in the balance of autonomic innervation on the ciliary smooth muscle that result in an increased accommodative magnitude, but only at far distance. This outcome agrees with Bullimore and Gilmartin (1988), who suggested that task distance may influence the accommodative response under cognitive efforts, exhibiting greater values of accommodative response at far distance. Likely, due the higher interaction between cognitive and proximal factors during near viewing in comparison with distance tasks, the balance autonomic innervation of ciliary smooth muscle is not sufficiently modified to affect the accommodative response, and therefore, it demonstrates that the complexity of the non-optical contributions to the accommodative response should be considered (Winn et al., 1991).

In addition, our results of study VI evidenced that the accommodative response is altered in a clinical population of children with attentional problems. Children diagnosed with attention-deficit/hyperactivity disorder exhibited an accommodative deficit, namely greater lags of accommodation, in comparison to an age-matched control group regardless of the visual stimuli, even when the stimuli were chosen by themselves from a range of ten popular cartoon movies (study VII). This finding reveals that the relationship between accommodation and attention is inherent in children with attention-deficit/hyperactivity disorder rather than caused by the lack of interest or motivation while performing the task. Although other ocular variables such as eye movements (Rommelse, Van Der Stigchel, & Sergeant, 2008) or vergences (Puig et al., 2015) have demonstrated to be altered in this population, this is the first time that the accommodative function has proven to be deteriorated in children with attention-deficit/hyperactivity disorder. This deficit in accommodation may create asthenopia and impair behavioural performance, which could partly explain the symptoms frequently reported in persons suffering this disorder while performing near tasks (i.e., loss of concentration during reading) (Sterner, Gellerstedt, & Sjöström, 2006; Willcutt & Pennington, 2000).

Although the variability of accommodation did not differ between children with attention-deficit/hyperactivity disorder and healthy controls, our results from study VIII showed that this variable is a reasonably good predictor of attentional performance. This finding suggests that the variability of accommodation could be used as a physiological marker of attention, aiming to facilitate the diagnosis of attention-deficit/hyperactivity disorder. We should be aware that the diagnosis and management of this condition is complex due to the habitual presence of additional comorbid conditions (Gillberg et al., 2004; Spencer, 2006), and thus, the inclusion of the variability of accommodation along with other previously used markers could improve the robustness of the diagnostic procedure in this disorder.

Link between the accommodative system and cardiovascular and brain function

It is well known that the accommodative response is principally innervated by the parasympathetic nervous system and supplemented by the sympathetic nervous system (McDougal & Gamlin, 2015). A few studies have simultaneously included measures of autonomic activity while assessing the accommodative response in order to better understand the link between ocular dynamics and the autonomic nervous system (Davies et al., 2009; Davies et al., 2005). However, the contradictory findings reported in these studies did not permit to draw robust conclusions in this regard. Here, in conjunction with the assessment of the accommodative function, we recorded the heart rate variability, which permits to assess the sympathetic and parasympathetic influences on the cardiovascular system, while manipulating the behavioural state. However, we did not observe any significant correlation between the accommodative response and heart rate variability after performing two different protocols of high-intensity interval training (study I) and when executing a psychomotor vigilance task (study VIII). This result is in line with Jainta et al. (2008), who did not observed a robust link between mental demand and accommodative behaviour. On the contrary, Davies et al., (2005) found a reduction in accommodation with cognitive effort, which seems to be explained by a concurrent reduction in the relative power of the parasympathetic branch. Nevertheless, these discrepancies may be influenced by a variety of factors such as environmental or situational aspects, mental task demands and subject characteristics among others (Ballard, 1996; Hautala et al., 2009; Luque-Casado et al., 2013). Notably, further imaging studies of those brain areas that play a role in controlling ocular accommodation may help to elucidate the possible mechanisms underlying the influence of central nervous system alterations on ocular accommodation.

Lastly, the study of patients with traumatic brain injury that affects to the cerebellum has proved static and dynamic accommodative abnormalities (Kawasaki, Kiyosawa, Fujino, & Tokoro, 1993). Also, other brain injuries affecting the superior temporal and posterior parietal lobes and superior colliculus can potentially induce an accommodative disfunction (Green et al., 2010). There is evidence of dynamic and reciprocal functional connectivity between accommodation and attention in certain brain structures (e.g., frontal area, parietal area, occipital area and superior colliculus) (Petersen & Posner, 2012; Richter, Lee, & Pardo, 2000; Somers et al, 1999), and therefore, psychological differences in attention may result in physiological changes in the ocular dynamics at the level of both the brain and the eye (Steinmetz & Moore, 2014). In this regard, attention-deficit/hyperactivity disorder has been associated with widespread structural brain abnormalities, including smaller overall cerebral volumes, reductions in total grey matter volumes, and delays in cortical maturation (Friedman & Rapoport, 2015). In addition, there is widespread evidence about electroencephalographic power differences between individuals with attention-deficit/hyperactivity disorder and healthy control (Başar & Güntekin, 2013). Therefore, it is plausible that these brain abnormalities may be responsible of the inherent accommodative dysfunction observed in this population. Future studies are needed to clarify the specific brain areas that are responsible for the mentioned outcomes.

LIMITATIONS AND STRENGTHS

LIMITATIONS

The studies comprising the present International Doctoral Thesis are not exempt of limitations and they must be acknowledged. The specific limitations of the eight studies have been previously described in detail for each study. Here, we are summarising the most relevant limitations. In studies I and IV, we failed to find an association between ocular accommodation and cardiovascular functioning. Participants' characteristics (i.e., age, gender or fitness level), circadian variations, exercise type, physiological variables assessed, or the time points of measure chosen may also influence the results, and therefore, the control of this factors may allow to achieve further insights in this regard. Studies II and III evaluated the effects of caffeine on the accommodative response, observing a reduction in the variability of accommodation, but not in the lag of accommodation. The relatively small sample size, the dose of caffeine chosen (4 mg/kg), and the time spent after caffeine intake for the evaluation of the accommodative response could play an important role in the results, and therefore the conclusions found in these studies must be cautiously interpreted.

Study V investigated the short-term influence of attention on the accommodative response, however, to fully understand the impact of attention on visual discomfort or myopia progression, further studies should explore the long-term effects in clinical settings. Studies VI, VII and VIII included a clinical population of children with attention-deficit/hyperactivity disorder, which is a neurological disorder that commonly present different comorbidities, including language and learning disorders, mood disorders, disruptive behaviour disorders, autism spectrum disorders and tic disorders (Efron, Bryson, Lycett, & Sciberras, 2016). The complex and heterogeneous nature of this disorder must lead us to be cautious when interpreting the accommodative deficits found in children with attention-deficit/hyperactivity disorder. For example, accommodative dysfunction has been previously reported in individuals with autism disorders (Anketell et al., 2018), and therefore, presenting this comorbidity could interact with the attention-deficit/hyperactivity disorder and exacerbate the accommodative deficit. Additionally, the attention-deficit/hyperactivity disorder subtype classification (inattentive, hyperactive-impulsive, or combined) and severity could also influence the results.

STRENGTHS

The main strength of this International Doctoral Thesis is the inclusion of several physiological and psychological variables that allows to better understand the complex interaction between changes in the arousal and attentional sates and the behaviour of the accommodative response from a multidisciplinary perspective. Our results permit to contextualise the accommodative function in real-world conditions, which include optical and non-optical factors capable of inducing changes in the accommodative function. This has been possible due to the cooperation of experts in the areas of psychology, neuropediatric, ophthalmology, optometry and sports science. Additionally, the collaborative research work conducted with the University of Bradford during my research stay has allowed us to constitute an international team with leading researchers in this field.

FUTURE DIRECTIONS

The results obtained in the eight studies included in this thesis have opened new lines of research that still require additional work in order to clarify the link between the accommodative function and the whole-body physiological state, as well as to determine the potential utility of the dynamics of ocular accommodation as objective predictors of behavioural performance. It may be of potential interest for the diagnosis of attentional deficits and enhance operator´s safety in applied situations (e.g., drivers or surgeons). Based on the obtained results, we suggest the following future directions:

- To explore the impact of different environmental, situational and motivational factors, subject characteristics, exercise type, gender, fitness level among others inter-individual factors on the accommodative response (Ballard, 1996; Hautala et al., 2009). To do so, higher sample size and an appropriate isolation of each factor would be desirable.
- To investigate whether the ingestion of caffeine improves the accommodative function in those patients with high levels of visual discomfort (Chase et al., 2009) as determined by the Conlon Visual Discomfort Survey (Borsting, Chase, & Ridder, 2007).
- To clarify the effect of caffeine on the ocular physiology by the balance of the sympathetic–parasympathetic branches in order to determine the physiological mechanisms that explain the observed decrease in the variability of accommodation but not in the lag of accommodation. The recent developments in ocular imagining techniques (e.g., anterior segment optical coherence tomography) would help to elucidate the effects of caffeine on the ocular physiology.
- To implement and standardise the lag and variability of accommodation as physiological markers related to task overload or fatigue, which may help to develop fit-for-duty tests in real-world situations (e.g., drivers, surgeons, air traffic controllers).
- To explore the brain areas involved in controlling the accommodative response, aiming to clarify the mechanisms underlying the effects of changes in arousal and attention on ocular accommodation.

- To separate the children with attention-deficit/hyperactivity disorder according to their classification into inattentive, hyperactive-impulsive, or the combined type, symptoms severity, and comorbidities in order to characterise the accommodative function according to these subdivisions.
- To assess the benefits of non-pharmacological strategies such is visual therapy for treatment of attention-deficit/hyperactivity disorder, aiming to achieve an appropriate functioning of the accommodative system, as well as to improve the visual and/or behavioural symptomatology associated with this disorder.
- To study the possibility of incorporating the accommodative response in conjunction with other visual and neuropsychological indices for enhancing the diagnosis of attention-deficit/hyperactivity disorder.

CHAPTER 6:
CONCLUSIONS/CONCLUSIONES

CONCLUSIONS

The specific conclusions of the present International Doctoral Thesis based on the obtained results are:

1. The acute effects of exercise on ocular accommodation are dependent on exercise intensity, with highly demanding physical effort inducing a greater lag of accommodation.
2. Caffeine-induced arousal reduces the variability of accommodative response after 30 minutes of caffeine intake. However, we did not observe any effect of caffeine consumption on the lag of accommodation.
3. Caffeine improves the stability of the accommodative response in high caffeine consumers, but not in low caffeine consumers. Nevertheless, the lag of accommodation did not change after caffeine consumption.
4. The variability of accommodation is sensitive to time-on-task effects during sustained attention, with a lower stability of accommodation over time. In addition, the variability of accommodation was a reasonably good predictor of behavioural performance.
5. The use of auditory biofeedback as attention facilitators induces a reduction on the lag and variability of the accommodative response, with these changes being more evident at closer distances, while attention distractors (dual-tasking) promote a heightened accommodative response at far distance.
6. Children with attention-deficit/hyperactivity disorder exhibit higher lags of accommodation in comparison to age-matched controls, with these differences being more evident at closer viewing distances.
7. The higher lags of accommodation observed in children with attention-deficit/hyperactivity disorder are not dependent on the visual stimuli. The use of methylphenidate for the treatment of this disorder does not permit to restore the accommodative lag to normal values.
8. The variability of accommodation, but not the lag of accommodation, predicts a significant amount of variance in several indicators of behavioural performance in a population of children with attention-deficit/hyperactivity disorder and healthy controls.

CONCLUSIONES

Los objetivos específicos de la presente tesis doctoral internacional basados en los resultados obtenidos son:

1. Los efectos agudos del ejercicio sobre la acomodación ocular dependen de la intensidad del ejercicio, mostrando que el ejercicio físico de alta intensidad induce un incremento en el retraso acomodativo.
2. La actividad inducida por la cafeína reduce la variabilidad de la acomodación, pero no afecta el retraso de acomodación.
3. La cafeína mejora la estabilidad de la respuesta acomodativa para los consumidores altos de cafeína, pero no para los consumidores bajos. Sin embargo, el retraso de acomodación no cambió a consecuencia del consumo de cafeína.
4. La variabilidad de acomodación mostró ser sensible al tiempo acumulado durante una tarea de atención sostenida, con una reducción de la estabilidad acomodativa asociada a un peor rendimiento conductual. Además, la variabilidad de acomodación fue un predictor del rendimiento conductual razonadamente bueno.
5. Los efectos de facilitadores atencionales indujeron una reducción en el retraso acomodativo y la variabilidad de acomodación, siendo estos cambios más evidentes para distancias cercanas, mientras que los distractores atencionales promovieron un aumento de la respuesta acomodativa para distancias lejanas.
6. Niños con trastorno por déficit de atención e hiperactividad mostraron mayores retrasos de acomodación en comparación con un grupo de niños control de edad equivalente, siendo estas diferencias mayores en distancias próximas.
7. Los altos retrasos de acomodación encontrados en niños con trastorno por déficit de atención e hiperactividad no dependen de la tarea visual, sino que parecen ser inherentes a este trastorno. El tratamiento con metilfenidato no fue suficiente para restablecer el retraso acomodativo a valores normales.
8. La variabilidad de acomodación, pero no el retraso de acomodación, predijo una gran cantidad de cambios en numerosos marcadores del rendimiento atencional en una población de niños con trastorno por déficit de atención e hiperactividad y controles sanos.

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LIST OF TABLES

LIST OF FIGURES

Figure 18. Effect of attentional resources manipulation on the lag (panel A) and variability (panel B) of accommodation. Values are calculated as the difference between each experimental condition and the control condition. * and # denote a statistically significant difference (corrected P-value < 0.05) in comparison to the control condition at 500 cm and 20 cm, respectively. Error bars show the standard error. All values are calculated across participants (n = 20). The low- and high-load conditions refer to the two levels of mental load, counting forward in steps of 2 and backwards in steps of 17, respectively. The low- and high- FB conditions indicate the two levels of auditory feedback, consisting in four and eight auditory beeps, respectively.

Figure 19. Effect of attentional resources manipulation on the magnitude (panel A) and variability (panel B) of pupil size. Values are calculated as the difference between each experimental condition and the control condition. *, ¥ and # denote a statistically significant difference (corrected P-value < 0.05) in comparison to the control condition at 500 cm, 40 cm and 20 cm, respectively. Error bars show the standard error. All values are calculated across participants (n = 16). The low- and high-load conditions refer to the two levels of mental load, counting forward in steps of 2 and backwards in steps of 17, respectively. The low- and high- FB conditions indicate the two levels of auditory feedback, consisting in four and eight auditory beeps, respectively.

Figure 20. Accommodative response for Attention-deficit/hyperactivity disorder (ADHD) and control groups with different accommodative demands (5D, 2.5D and 0.2D). The panel a) displays the lag of accommodation, and the panel b) the variability of accommodation. # indicates significant main effect of group (p < 0.05). Error bars show the standard error (SE).

Figure 21. Changes in accommodative response magnitude (lag of accommodation) for attention-deficit/hyperactivity disorder (ADHD) and control groups over time (90 seconds) at different accommodative demand distances (a) 5D, b) 2.5D and c) 0.2D). Error bars show the standard error (SE).

Figure 22. Changes in accommodative variability for Attention-deficit/hyperactivity disorder (ADHD) and control groups over time (90 seconds) at different accommodative demand distances (a) 5D, b) 2.5D and c) 0.2D). Error bars show the standard error (SE).

Figure 23. A graphical illustration of the three stimuli types used in this study for the SpongeBob choice. From left to right: the Maltese cross condition, the picture condition (a frame extracted from the cartoon movie), and the cartoon movie condition

Figure 24. Lag of accommodation for the non-medicated attention-deficit/hyperactivity disorder (ADHD), medicated ADHD, and control groups while viewing the three types of stimuli. The box plots represent 75th and 25^{th} centiles, and individual data are displayed as jittered dots. The horizontal line into the box indicates the median value. The whiskers show the range of values within the 1.5 × interquartile range.

Figure 25. Variability of for the non-medicated attention-deficit/hyperactivity disorder (ADHD), medicated ADHD, and control groups while viewing the three types of stimuli. The box plots represent 75th and 25^{th} centiles, and individual data are displayed as jittered dots. The horizontal line into the box indicates the median value. The whiskers show the range of values within the 1.5 × interquartile range.

Figure 26. Lag of accommodation (A) and variability of accommodation (B) for attention-deficit/hyperactivity disorder (ADHD) and control groups over time (100-s intervals each block). Error bars show the standard error (SE).

Figure 27. Pupil diameter (A) and variability of pupil diameter (B) for attention-deficit/hyperactivity disorder (ADHD) and control groups over time (100-s intervals each block). Error bars show the standard error (SE).

SHORT CURRICULUM VITAE

BEATRIZ REDONDO CABRERA

Date of Birth 21/12/1994

Country: Spain

E-mail beatrizrc@ugr.es

ACADEMIC TRAINING

Graduate degree in Optics y Optometry (2012-2016). Universidad de Granada, Granada Spain.

Master's degree in Clinical Optometry and Advanced Optics (2016-2017). Universidad de Granada, Granada Spain.

Expert Course in Paediatric Optometry and Visual Therapy (2016-2018). Universidad Europea de Madrid, Madrid, Spain

RESEARCH STAY

University of Bradford. Faculty of Life Sciences, School of Optometry & Vision Sciences. Bradford, United Kingdom. Duration: 3 months.

PUBLICATIONS

Beatriz Redondo Cabrera has already published 24 scientific articles in Journals indexed in the JCR (Journal Citation Reports), has presented 17 abstracts in scientific congresses and has reviewed scientific articles for 3 JCR Journals. These publications have received 53 citation from 2017 and the h index of the doctoral student is 4 (based on Google scholar).

Scientific publications included in the present International Doctoral Thesis

1. Vera, J., Luque-Casado, A., Redondo, B., Cárdenas, D., Jiménez, R., & García-Ramos, A. (2019). Ocular accommodative response is modulated as a function of physical exercise intensity. Current Eye Research, 44(4), 442-450. doi: 10.1080/02713683.2018.1557210

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