

# The interaction of pupil response with the vergence system

Moritz Feil<sup>1</sup> · Barbara Moser<sup>1</sup> · Mathias Abegg<sup>1</sup>

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## Abstract

**Purpose** A gaze shift from a target at distance to a target at near leads to pupillary constriction. The regulation of this pupillary near response is ill known. We investigated the impact of accommodation, convergence, and proximity on the pupillary diameter.

**Methods** We recorded pupil size and vergence eye movements with the use of an infrared eye tracker. We determined the pupillary response in four conditions: (1) after a gaze shift from far to near without accommodation, (2) after a gaze shift from far to near with neither accommodation nor convergence, (3) after accommodation alone, and (4) after accommodation with convergence without a gaze shift to near. These responses were compared to the pupil response of a full near response and to a gaze shift from one far target to another.

**Results** We found a reliable pupillary near response. The removal of both accommodation and convergence in gaze shift from far to near abolished the pupillary near response. Accommodation alone did not induce pupillary constriction, while convergence and accommodation together induced a pupil response similar to the full near response.

**Conclusions** The main trigger for the pupillary response seems to be convergence. Neither accommodation nor proximity alone induce a significant pupillary constriction. This suggests that the miosis of the near triad is closely coupled to the vergence system rather than being independently regulated.

**Keywords** Pupil · Accommodation · Convergence · Near triad

## Introduction

A shift of gaze from a distant to a near object triggers a ‘near triad’, which consists of accommodation, convergence, and miosis [1]. These processes enable a focused image, single binocular vision, and increased depth of focus, respectively. Before the onset of the near response, the change of fixation from a distant object to a near object leads to retinal image disparity and blur, which are the two main stimuli that drive the near response. Retinal image disparity may be defined as the spatial deviation of the retinal image of an object in both eyes. Retinal disparity is a trigger for a vergence response, which serves the purpose of realigning the retinal image of an object on corresponding retinal areas [2]. Blur on the other hand is the main trigger for accommodation [3]. Accommodation and vergence are not independent processes but rather related such that accommodation alone induces vergence and vergence leads to an accommodation [4]. These processes are coupled and may be clinically measured as AC/A ratio or CA/C ratio, i.e., accommodative convergence in relation to accommodation and convergence induced accommodation in relation to convergence, respectively. Less clear is how the pupillary response is regulated.

The pupil light reflex is mediated by afferent pupillary fibers running within the optic nerve (cranial nerve II), which project to the dorsal midbrain. From there, neurons project to the pupillary motor nuclei (Edinger Westphal), which eventually enable a miosis. The motor nuclei may be activated via other inputs than retinal illumination, such as emotional state [5]. Even though the near response is a reliable activator of pupillary constriction, the underlying mechanism is not clear.

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✉ Mathias Abegg  
mathias.abegg@insel.ch

<sup>1</sup> Department of Ophthalmology, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

One might imagine a simple circuitry with a coupling of the pupil response with either convergence or accommodation or both. Indeed a coupling of accommodation with a pupillary response had been found in the past [6, 7], but could later not be reproduced [8, 9]. Based on experiments with prisms, Backer and Ogle suggested that fusional vergence alone, i.e., without accommodation, is a sufficient trigger for a pupillary response [10]. Given the paucity and heterogeneity of the results, no consensus on the triggers for pupillary near response has been reached. The aim of the current study was to investigate whether blur and image disparity, which are the triggers for accommodation and vergence, respectively, are sufficient to elicit a pupillary response. In other words, we wanted to find out whether the pupillary near response is triggered by vergence, accommodation, the combination of the two, or none altogether. For this purpose, we dissociated the near response into its accommodative component, a vergence component, a near response without accommodation, and a full near response with vergence and accommodation.

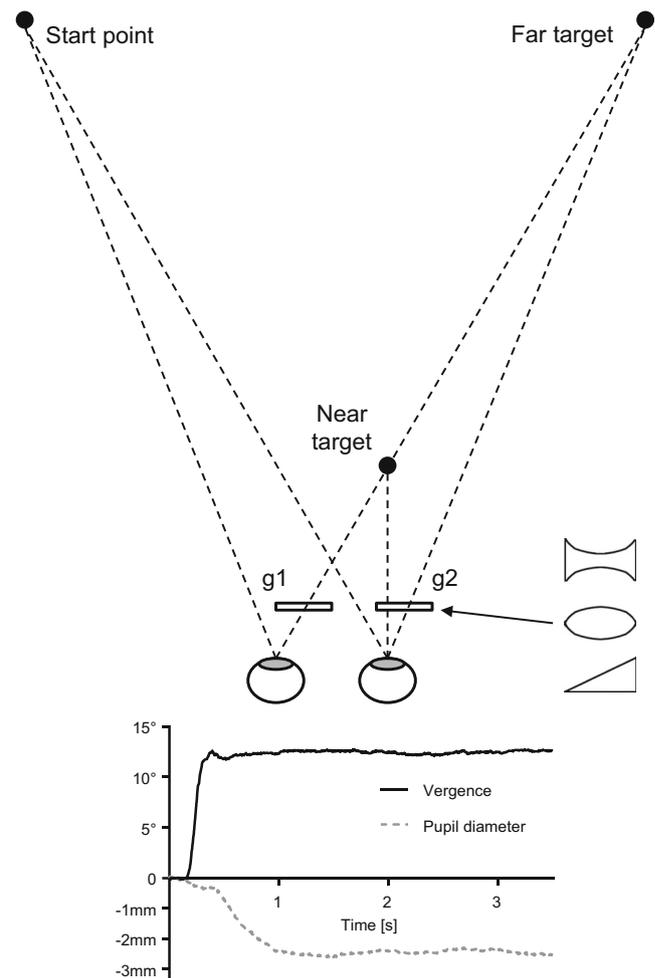
## Materials and methods

### Subjects

We have aimed at selecting healthy, non-myopic and non-presbyopic subjects. For this, we recruited 12 subjects (six female) aged between 21 and 28 years (mean, 24.5 years). In a second experiment, nine subjects participated (two female) with a mean age of 25 years with a range of 22 to 30 years. Only one subject participated in both experiments. Subjects with an uncorrected Snellen visual acuity smaller than 1.0, tested at 4 m with Landolt rings, were excluded. All subjects with a known visual disorder, in particular with a history of eye surgery and a diagnosis of strabismus in the past, were also excluded.

### Experimental setup

The experiment's design is outlined in Fig. 1. Subjects were positioned in a forehead and chin rest in front of three targets, one placed at a distance of 0.25 m from the subject's right eye and two at a distance of 4.00 m from the subject's eyes. The left target at distance functioned as the starting point, the right one was the far target. The near target was aligned with the right pupil, the far target was aligned with the near target and the left pupil. A mount for prisms or glasses was placed in front of both eyes such that the targets on the right were viewed through glasses or prisms but not the target on the left. All the targets were single Landolt rings with openings requiring a Snellen visual acuity of 1.0 to be seen. Before each change of gaze to a new target, the orientation of the gap in the Landolt ring was changed and subjects had to indicate the



**Fig. 1** Schematic representation of experimental setup is shown. In a first experiment, gaze was shifted from a fixation object at distance (starting point) to either another target at distance (far target) or to a near target. These targets were viewed by the naked eye, through prisms or glasses in order to control accommodation and vergence eye movements. The *bottom panel* shows an example of a near response. Averaged sample traces from one subject show vergence in degrees (*black line*) and change of pupil size in millimeter (*gray dotted line*) recorded after gaze shifted from a far to a near stimulus

orientation of the gap by pressing the respective arrow key on a keyboard, which was positioned outside the field of view such that subjects maintained gaze on target while pressing the key. Trials with incorrectly reported orientation of the Landolt gap were discarded.

Both experiments were conducted in room light condition, which remained constant throughout the entire experiment. Eye movements and pupil size of both eyes were recorded using the EyeLink 1000 with Experiment Builder (V 1.10.165, SR Research Ltd., Mississauga, Ontario, Canada). The infrared desktop camera was positioned at 0.6 m (0.4 m in experiment 2) from the subject's forehead, such that there was no interference with prisms or glasses. Prior to the experiment, gaze position was calibrated with a nine-point grid on a 20" display (ViewSonic G220fb) 0.65 m from the subject's

forehead. Calibration was accepted if all nine points showed an accuracy of  $1^\circ$  or less and then the calibration monitor was removed.

## Experimental procedures

*Experiment 1* consisted of five different conditions, each was tested with 20 trials. Each trial started with fixation on the starting point (see Fig. 1). After a random time interval between 1.5 and 2.5 s, after correctly reporting the orientation of the Landolt ring, an acoustic stimulus was given. This indicated that subjects were to fixate a target; 4 s later, a second acoustic stimulus was given to indicate the end of the trial and subjects fixated the starting point again.

Using prisms, glasses, and a combination of the two, we tested the following conditions:

1. *Near response*: For this, the target was positioned at near without any glasses.
2. *Accommodation alone*: The target was positioned at distance and was viewed through  $-3.75$  diopters glasses.
3. *Near response without accommodation*: The target was positioned at near and was viewed through  $+3.75$  diopters glasses (position g1 and g2 in Fig. 1).
4. *Near response without accommodation and without convergence*: The target was located at near and it was viewed through  $+3.75$  diopters glasses in front of both eyes (g1 and g2) and a 20 prism diopters prism in front of the right eye with the base on the nasal side (g2 in Fig. 1).
5. *Gaze shift from far to far*: Target at distance was viewed without any glasses installed.

Due to the crosslink between accommodation and convergence (see discussion), it is not possible to fully eradicate one while activating the other. The labels of the above conditions reflect the intended effect. “Accommodation alone” for example, indicates that only accommodation was intended, which does not exclude activation of convergence. Using eye tracking, however, we are able to measure vergence and thus monitor the amount of interference.

*Experiment 2* In experiment 2, we examined the effect of combined convergence and accommodation on the pupillary response. For this, subjects focused on a far target (at 4 m). Upon onset of an acoustic stimulus a 20 prism diopters prism with the base on the nasal side was placed in front of the left eye and glasses with  $-3.75$  diopters lenses were positioned in front of both eyes, while subjects maintained their gaze on the far target. Five seconds later, all glasses were removed, while subjects still maintained fixation. The orientation of the Landolt ring was changed after each maneuver and vision was verified. This ensured and controlled accommodation during the entire trial. For comparison, again a full near response was recorded

as follows: subjects had to focus on a far target at 4 m during 10 s and then were to focus on a target at 0.25 m during 5 s. After an acoustic stimulus, they had to look back to the far target and a new trial started. Each condition had 20 trials.

## Data analysis

For data analysis, individual pupillary responses of a duration of 3.5 s from stimulus onset were exported and analyzed offline using WinWCP (V 4.4.7, Dr. John Dempster, University of Strathclyde, Scotland). We rejected trials according to the following criteria: (1) the subject indicated the wrong or no orientation of the Landolt ring, (2) missing values due to blinks, (3) missing vergence response where vergence is expected (for example when subjects were not able to fuse the images with a prism in front of their eyes) and (4) subjects with less than two valid recordings in a given condition were also excluded from that condition. Based on this, 47% of all blocks were removed from the analysis (range 0% (subject md87) - 100% (subject mm89)). In the remaining blocks an average of 11.3 responses per subject remained for the analysis, i.e., 43% of the trials were excluded. In experiment 2, 11% of the blocks were excluded (subject CD), a mean of 14.6 trials remained per block, i.e., 27% of the remaining trials were excluded.

Vergence was obtained by subtracting the horizontal gaze position of the left eye from the horizontal gaze position of the right eye. By definition, positive values indicate convergence and negative values indicate divergence. Vergence and pupil size are expressed in prism diopters and millimeter respectively. For the latter, we converted the arbitrary units provided by the eyetracker software using to a scaling factor that we determined by a measurement series with a known pupil size (data not shown).

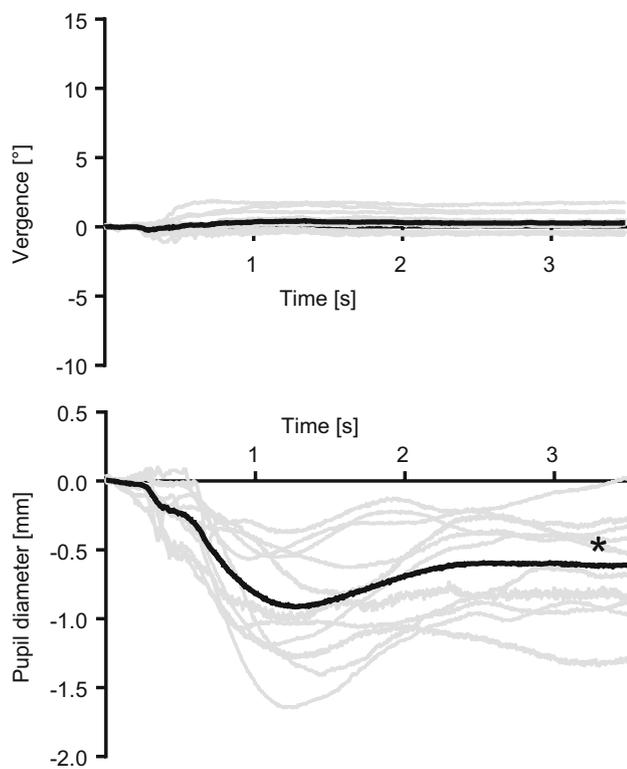
Vergence and pupil response amplitude was defined as the difference between the average of the first 100 ms and the last 500 ms of any trial. This resulted in 1 value per subject per condition. In order to measure the influence of near, accommodation, and convergence, the mean pupillary response induced by a gaze shift from far to far was subtracted from all the remaining mean pupillary responses.

To detect whether or not a significant pupillary response or vergence responses was present in a given condition, we used the one sample *t* test. To compare the pupillary responses between different conditions, we used analysis of variance (ANOVA) with pupillary response as dependent variable and condition as main effect. Direct comparisons of pupillary response between two given conditions were made with the unpaired *t* tests in SPSS (IBM SPSS Statistics 21). In experiment 2, we used a paired *t* test to compare the pupillary response between the two conditions.

## Results

In experiment 1, we first examined the control condition, i.e., the pupil response elicited when changing gaze from one far target onto another one. We found that this alone induced a significant pupillary response ( $p < 0.001$ , one-sample  $t$  test, Fig. 2). Since both targets were presented at distance and without prisms, we normalized all subsequent pupillary responses to this non-near, non-accommodative and non-convergence baseline response (Fig. 3). A gaze shift from a far object to a near object elicited both a significant vergence response and a significant pupillary response ( $p < 0.001$  for both, Figs. 1 and 3). Also the pupillary near response consisted of a sustained response which was significantly bigger than in the control condition ( $p = 0.006$ ).

Next, we compared the pupillary response between the different conditions (Fig. 4). We found that the pupil response amplitude was significantly different in the different conditions ( $p = 0.01$ , ANOVA). We then investigated the pupillary responses in each condition using  $t$  tests. We found that the pupillary response induced by accommodation alone was significantly smaller as compared to the pupillary near response



**Fig. 2** Control condition. The *upper panel* shows the vergence movement and the *lower panel* shows the pupillary response recorded after shifting gaze from one far target to another far target. *Gray lines* are the subjects' mean responses, the *black curve* is the averaged data of all subjects. While gaze shift at distance does not induce a significant vergence response, we found a consistent transient and sustained pupillary response in all subjects (*asterisk*)

**Fig. 3** Vergence responses (*left column*) and pupillary responses (*right column*) in each condition (*rows*). Each subject's mean response is represented in *gray*, the averaged response of all subjects is indicated in *black*. *Asterisks* indicate statistically significant responses

( $p = 0.033$ ) but not significantly different as compared to control ( $p = 0.954$ ). Near alone, i.e., near response without accommodation and without convergence, elicited a pupil response that was smaller compared to the near response ( $p = 0.008$ ) and was even smaller than the control response ( $p = 0.041$ ), indicating no miotic response induced by nearness alone. The pupillary near response elicited without accommodation was at an intermediate position, neither different to the full pupillary near response ( $p = 0.482$ ) nor to control ( $p = 0.178$ ).

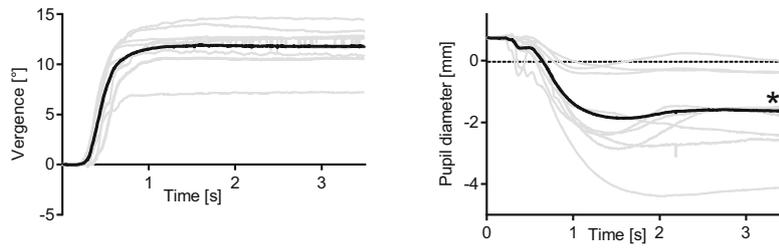
In experiment 2 we tested the influence of convergence and accommodation without a gaze shift from far to near on the pupil, and we compared the results to a full near response. Again, we found a significant near response ( $p = 0.001$ ). Convergence and accommodation alone too resulted in a significant pupillary response ( $p < 0.001$ ), which was not statistically different from the full near response ( $p = 0.265$ ).

## Discussion

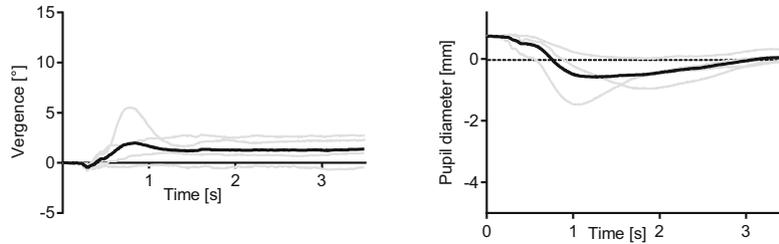
We found that a change of gaze from a distant object to an object at near reliably triggered a pupillary constriction and a convergence eye movement. Our results indicate that neither accommodation alone nor proximity, i.e., the fact that a target is located at near is a sufficient trigger for a pupillary response. Convergence on the other hand was consistently associated with a pupillary response independent of whether it was associated with a near response or whether it was induced with prisms. Taken together, our data indicate that the pupillary response is tightly coupled to convergence.

Beside these facts, we found a considerable variability of the pupillary response in all conditions. Any condition caused a transient pupillary response including the control condition that was associated with a change of gaze from one distant object to another one. There are several possible reasons for this. Since the pupil reacts to changes in psychosensory state, to mental as well as mechanical effort, the transient pupillary response may be unspecific and therefore difficult to interpret [11]. In addition to the transient pupillary response, we also found a large interindividual variability of the sustained pupillary response in all conditions: in some subjects we found only a small pupillary response despite a significant convergence. Large variability of the pupillary response has been found by others before [11]. It may be due to anatomical/physiological differences between subjects which may, for a given trigger, lead to a different pupillary response. One anatomic factor

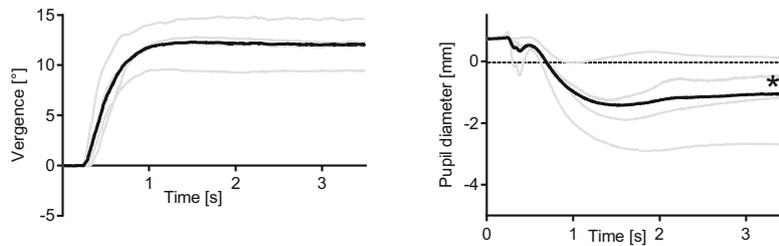
Near response Experiment 1:



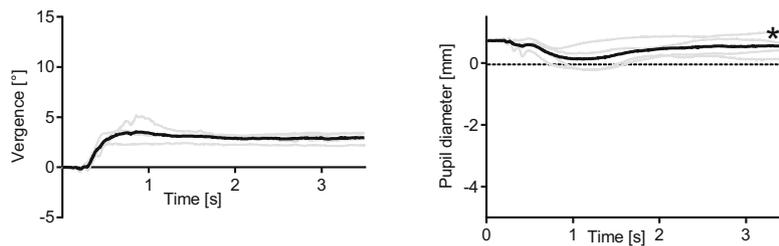
Accommodation alone:



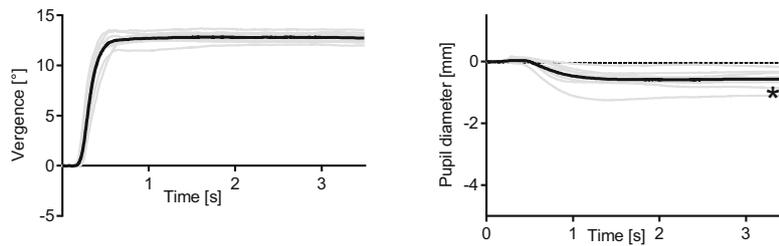
Near response without accommodation:



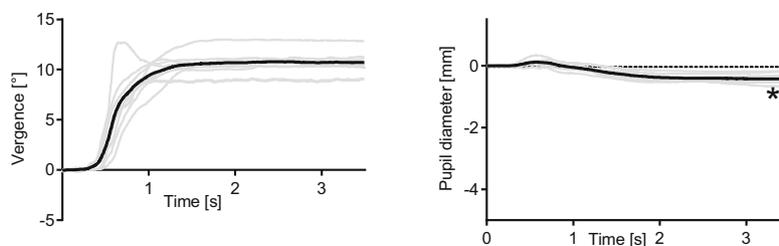
Near response without accommodation and without convergence:

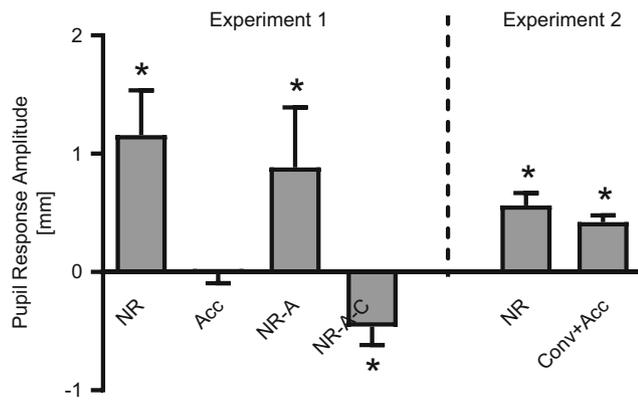


Near response Experiment 2:



Convergence and accommodation:





**Fig. 4** Summary data shows averaged pupil response amplitudes. The pupillary response elicited by a gaze shift from one far target onto another far target was subtracted from all other pupillary responses. Thus, the horizontal zero line represents the control condition. NR near response, Acc accommodation, NR-A near response without accommodation, NR-A-C near response without accommodation and without convergence, Conv + Acc convergence and accommodation. Asterisks indicate statistically significant responses

inducing some variability is the differences in interpupillary distance: We used 20 prism diopters for all subjects even though vergence in our conditions changes with interpupillary distance. This may have under-corrected convergence in the ‘near response without accommodation and without convergence’ in some subjects leading to a residual vergence and thus a residual vergence associated pupillary response in that condition (see Fig. 3). Besides that, pupillary responses have a large top-down influence reflecting all sorts of known and unknown cognitive processes. Such ongoing cognitive processes, which may have varied between subjects, may have caused different pupillary responses. Finally, the pupillary response depends on age [12]. Given the narrow range of age in our experiments, this is the least likely explanation. One theoretical consideration to explain the sustained pupil response seen after a gaze shift from one far target onto another is an artifact caused by a change in pupil geometry with respect to the eye tracking camera. This is not the case, because the pupil measured under static condition, i.e., not after a gaze shift, showed no difference of size between the two targets (data not shown). A last problem with our analysis of the pupillary response is that a large fraction of trials needed to be excluded because of insufficient data, blink artifacts, and undesired vergence.

Due to these multiple sources of noise, we tried to remain cautious with our analysis and we only analyzed our data at a group level and we compared relative changes between conditions rather than analyzing absolute response size in a given condition.

In our conditions, accommodation alone did not elicit a pupillary constriction larger than the control pupillary response. The influence of accommodation on pupillary constriction has been controversially discussed in the past

[6, 13, 14]. This is not surprising as convergence is coupled to accommodation with the AC/A ratio, thus it is difficult to entirely separate the two processes. This becomes obvious in Fig. 3, where subjects were to do accommodation alone. This led to some vergence movement in the majority of subjects; but as accommodation “alone” caused a significantly smaller pupillary response than the same accommodation associated with a corresponding convergence, our results strongly suggest that the influence of accommodation is significantly less than that of convergence. However, our data do not allow the conclusion that accommodation alone does not cause any pupillary response. Several authors [6, 13, 14] found pupil constriction associated with accommodation, while others [8, 9, 15, 16] have shown that blur-driven accommodation alone is not sufficient to induce pupil constriction. Schor et al. stated that vergence and accommodation can be induced by either spatiotopic cues (such as size, texture, and parallax) or by retinotopic cues (blur and disparity) [17]. However, in order to elicit a pupillary response, both cues are needed. Our results agree in some parts with this theory: Accommodation, induced by blur did not induce significant pupillary constriction, neither did near response without accommodation or convergence, which has only spatiotopic cues. Near response without accommodation, which has retinotopic cues due to disparity and spatiotopic cues due to physical proximity of the target, elicited a significant pupillary response. In the combined convergence and accommodation, however, we found a strong and significant pupillary response, despite the lack of spatiotopic cues, which is not in agreement with Schor et al. In all the different conditions that we tested, we found that a vergence movement is the only consistent prerequisite for a pupillary response. It is both necessary and sufficient in our conditions. Others state that the pupillary near response is regulated by a dual interaction model, driven by both accommodation and convergence [18]. Since we cannot disprove that accommodation has any influence on the pupillary near response, our results fit into this model. However, our study shows that convergence is a much stronger regulator or even a mandatory requirement for the pupillary near reflex, and that accommodation has only a minor, if any, effect. Since we intended to investigate the near response, we did not examine the effect of divergence on the pupillary response. This would be an interesting future study though.

The neuronal circuitry underlying the pupillary near response is not entirely clear. Preganglionic innervation of both the ciliary muscle and the iris sphincter originate in an area close to the dorsal part of the oculomotor nuclei. This region is usually referred to as Edinger–Westphal nucleus, even though the preganglionic neurons may, depending on species and definition, be located outside the actual Edinger–Westphal nucleus [19]. Despite colocalization, the preganglionic neurons to the ciliary ganglion seem not to be directly coupled

in the sense that accommodation does not automatically entail a pupillary response and vice versa. In contrast to that both pupillary response and accommodation are coupled to convergence. The motoneurons that control vergence too are located in the immediate vicinity to the Edinger–Westphal nucleus [20, 21]. These neurons are thought to have a connection to the nucleus of the Edinger–Westphal [18], which provides an anatomical explanation of our observation of convergence induced pupillary constriction. Possibly, pupils have a similar association to convergence as does accommodation. We presume that vergence is the supranuclear trigger that independently activates the ciliary muscle and the pupils. Due to the variability of the pupillary response, it is difficult to judge whether the pupils have a linear relationship with vergence similar to the well-known AC/A ratio. Given that we have not tested different sizes of prism induced vergence, we cannot further comment on this topic. Even though it would bear some interest as then pupil size could be used to predict the vergence tone in strabismic subjects.

A limitation of this study is that we did not objectively measure the amplitude of accommodation. Instead, accommodation was verified by testing the visual acuity in every trial with a target requiring full vision. This may have caused some variation in accommodation between different subjects. In summary, we show that the pupillary near response is tightly coupled to the associated convergent eye movement and less dependent on other factors of the near response.

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#### Compliance with ethical standards

**Funding** The Swiss National Science Foundation provided financial support to MA (Funding Number 320030-147023). The sponsor had no role in the design or conduct of this research.

**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by the local ethics committee.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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