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A human-computer interface based on the "voluntary" pupil accomodative response.

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DECLARATION OF INTEREST

SR, CdS, LM and FP have submitted a patent application covering this topic.

ABSTRACT

Objectives: Changes in pupil size are governed by the autonomic nervous system but may be systematically driven by voluntary shifting the gaze in depth. Thus, the pupil accommodative response (PAR) that accompanies voluntary gaze shifts from a far to a near target might be exploited as a simple human-computer interface (HCI), bypassing the somato-motor system. Here we aim to characterize PAR in quasi-natural conditions with low-cost equipment and test the possibility to use PAR as a binary communication tool.

Methods: Nineteen healthy subjects were instructed to voluntary switch the focus from a far to a near target upon presentation of an auditory cue. Three protocols addressed the effects of monocular/binocular vision, eye illuminance, duration of near vision, target texture and target brightness on PAR features. In a fourth protocol PAR was used to establish binary communication at different bit rates.

Results: PAR amplitude slightly decreased with increasing eye illuminance and was only little affected by monocular/binocular vision, duration of near vision or target texture. PAR amplitude was larger with a bright near target and a dark far target than *vice-versa*. PAR-based communication performance achieved an accuracy of 100% at 10 bits/min and 96% at 15 bits/min.

Significance: Voluntary PAR is a robust signal, little affected by environmental and experimental variables, and can achieve a high communication speed when used as an HCI. This study provides a proof of concept for a PAR-based HCI, potentially useful to communicate with locked-in patients with preserved visual and autonomic functions.

Keywords: Pupil accommodative response; human-computer interface; vegetative reflex; locked-in syndrome.

1 INTRODUCTION

In recent years, there has been a proliferation of studies that have investigated eye tracking as practical, non-invasive interface to support the communication of patients with neurodegenerative diseases such as Amyotrophic lateral sclerosis (ALS) (Caligari et al., 2013; Linse et al., 2017; Pasqualotto et al., 2015) and dedicated devices have been developed. However, when the paralysis eventually affects extraocular muscles, the patient enters the so-called complete locked-in state (CLIS) in which communication from the patients to the external world is precluded (Chaudhary et al., 2016a). Different non-invasive approaches have been followed to develop brain-computer interfaces (BCI) attempting to read the patient's will (Chaudhary et al., 2016b; Marchetti and Priftis, 2014; Wolpaw et al., 2002), most of them being based on extracting different features from EEG signals. Although information transfer rates as high as 25 bit/s have been reported, EEG-based BCIs are affected by several limitations. Some of the techniques, e.g., P300-based BCIs (Mak et al., 2011), still depend on control of eye gaze; others, e.g., those based on voluntary modulation of mu and beta rhythms from the sensory-motor cortex or of slow cortical potentials, require extensive training by the subject which may represent a major limitation, as instrumental learning is likely to be impaired in CLIS patients (Chaudhary et al., 2016b; Kubler and Birbaumer, 2008). Moreover, EEG signals are generally characterized by low signal-to noise ratio, are exposed to different types of artifacts, and require specialized operator for setting the electrode cap and checking and maintaining good quality recordings throughout the experimental session. For all these reasons, such techniques are not yet adequate to be autonomously used by the patients, their family and caregivers. Monitoring hemodynamic signals associated with binary yes/no answers was recently shown to be a successful approach for re-establishing communication in CLIS patients, although sharing part of the limitations outlined for EEG, while also requiring costly instrumentation (Johansson et al., 2017).

Only very few studies have addressed the possibility to establish a communication channel based on the activity of the autonomic nervous system (ANS) (Binda et al., 2014; Ekman et al., 2008b; Naber et al., 2013; Stoll et al., 2013; Wilhelm et al., 2006), a possibility that can be pursued when an activation of the ANS accompanies a voluntary act. The importance of this approach is related to the fact that, although neural impairment in ALS is not restricted to the motor systems (Baltadzhieva et al., 2005; Isaacs et al., 2007; Lule et al., 2010), ANS is largely spared and could thus constitute a possible output pathway for communication in CLIS. Pupil autonomic control, in particular, does not seem to be affected in ALS (Baltadzhieva et al., 2005), thus offering interesting possibilities for easy and non-invasive detection of voluntarily-controlled parasympathetic and sympathetic activation. The idea to use voluntary modulation of the pupil size as a possible communication tool appears to have been first introduced by Ekman et al (2008b) who ran a preliminary investigation about its feasibility in seven healthy subjects. Different operative modalities to achieve pupil size changes were compared, namely: physical activity, self-induced pain, positive emotions, point of focus, negative emotions, cognitive tasks and concentration. The authors where mostly interested in the possibility to "provide a communication channel for expression of emotional activity", which however, was later shown to be difficult to achieve (Ekman et al., 2008a) and was abandoned. More recently, the possibility was reconsidered and a communication protocol was successfully tested with ALS patients (not yet in CLIS, though) (Stoll et al., 2013) based on detecting the pupil dilation that occurs when the subject is engaged in a demanding cognitive task (mental calculations, associated with sympathetic activation). However, this procedure gives a quite variable pupillary response and may be fatiguing and difficult to sustain in elderly patients. The pupil size was also shown to change when covertly deploying visuospatial attention in the frontal plane to light or dark targets (Binda et al., 2014) or to targets blinking at different frequencies (Naber et al., 2013), or during mental imagery (Laeng and Sulutvedt, 2014), although these strategies have not been tested on patients, yet.

A pupil feature that gives systematic and stereotyped responses, but that appears to be so far unexplored as a communication tool, is the pupil near reflex: one component of the triadic accommodative response – which, in addition to pupillary constriction, includes lens curvature changes and vergence eye movements (Von Noorden, 1996). Based on this reflex, whenever we shift visuo-spatial attention (and focus) between objects placed at different depth planes, the pupil changes accordingly, namely, it constricts in response to a far-to-near shift and dilates in response to a near-to-far shift. Importantly, the shift can be purely voluntary and does not necessarily require an eye movement, provided that it is monocularly performed between two targets aligned with the eye's gaze line. We will refer to this response as to the pupillary accommodative response (PAR), a term that we prefer to the common *pupil near reflex* because we want to emphasize that here the autonomic (co-)activation accompanies a voluntary act (top-down control), rather than reflexively responding to an external (visual) stimulus.

On this basis, we hypothesized that the PAR could constitute an effective communication tool, not requiring recruitment of skeletal muscles and possibly overcoming some of the limitations outlined above for BCIs, i.e., requiring little need of training and low-cost instrumentation and presenting a relatively simple monitoring and robust detection of responses. Aim of the study was thus to provide a proof of concept for PAR as a possible communication tool. To this aim, we were interested in identifying the conditions that maximize PAR in a normal living environment for a patient (i.e., his home or a health institute for long-term care). Given the paucity of ecological studies on the PAR, a series of experiments were designed to specifically address the following questions.

1) How do eye illuminance and monocular/binocular viewing conditions affect PAR? A non-linear dependence on ambient illumination was described over the full range of pupil size (Semmlow et al., 1975), and the response may be reduced under monocular viewing condition (Bharadwaj et al., 2011; Chirre et al., 2015), but the relation between these two variables is unknown. This issue is important as the target patients, such as advanced ALS patients, may have one eye less functional than the other and thus use monocular viewing, and this might in turn impact more strongly under certain ambient illumination (e.g., at home some rooms may be darker than others). 2) Is PAR affected by the characteristics of the target? Brightness of the visual targets is likely to affect PAR, due to involvement of the light reflex pathways. In addition, it is possible that enhanced texture of the visual target may guide and facilitate the accommodative process, as compared to a target with homogeneous appearance, and thus also affect the PAR. These issues have never been previously investigated. 3) What is the optimal duration of the near vision? Although latency and time constant of the near reflex have been reported (Chirre et al., 2015; Kasthurirangan and Glasser, 2005, 2006) the question is here oriented to the implementation of communication protocols, e.g., is pupil constrictions still clearly detectable if the focus on the near target is maintained for as little as 2 s? 4) Finally, at what pace can the PAR provide a reliable signal suitable to establish efficient binary communication, at least in healthy subjects?

Thus, three experimental series are first carried out to address the first three issues and identify the experimental conditions that may help to optimize PAR in a normal, everyday environment. A further test is then implemented to address the fourth issue by measuring the accuracy of PAR-based communication at different transmission rates.

2 METHODS

2.1 Sample

The study is divided in two parts. Nineteen subjects (7 females and 12 males, aged between 22 and 77 years) participated to three experimental protocols, named A, B and C, while eight subjects volunteered for protocol D. All subjects had a normal or corrected-to-normal visual acuity, measured with Snellen chart.

The research was performed with the understanding and written consent of the subjects and followed the tenets of the Declaration of Helsinki, under the approval of the Ethics Committee of University of Turin (prot. 256076).

2.2 Apparatus

Recordings were taken from the dominant eye, determined through the Porta test. The non-dominant eye was maintained closed with the help of a piece of tape, except when binocular vision was tested (protocol B, see below). Pupil monitoring was performed either through a web cam (Logitech - HD WEBCAM C615) in Protocols A, B and C, or through an eye tracker (EyeTribe) in protocol D. The web cam was mounted at 10 cm from the dominant eye. Image resolution was 1184x656. The achieved frame rate was 8 fps, due to the on-line processing needed to display pupil size in real time. The eye tracker was positioned at about 40 cm from the eyes and was set to provide pupil size with a sampling frequency of 30 Hz.

Eye illuminance was measured by a luxmeter (Testotermo 0500, Dott. Ing. S. Ciano, Italy, Torino) and regulated at predefined levels of 300-600-1000 lux by displacing and adjusting the orientation of a light source.

A custom Matlab program was used to handle the acquisition of the video clips (50-s duration) from the web cam (protocols A, B and C) or of the relevant data from the eye-tracker (protocol D), as well as for carrying-on all the subsequent image and signal processing (see below). The program was also used to generate audio cues (sustained “beeps”) during the recordings, synchronized with the data acquisition (see below).

2.3 Procedure

2.3.1 Experimental protocols A, B and C

Subjects sat on a comfortable chair, in front of two targets positioned at 25 cm (near target) and at 4 m (far target), both aligned with the dominant eye (Fig. 1A). To prevent movements of the dominant eye, the subject was instructed to change the focal plane (i.e., to accommodate) from the far to the near target and vice-versa, without shifting the gaze (i.e., without making saccades) as shown in Fig 1B. Head position was kept stable by means of a chin rest.

The three experimental protocols were run in a single session in randomized order. Sequences of three audio cues (a “beep” at 400 Hz) separated by 10-s intervals were provided, the duration of the cue depending on the protocol. Each sequence was separated from the next by at least 1 minute. The subjects were asked to focus on the near target at the very moment and for the entire duration of the audio cue, and to focus on the far target otherwise.

Prior to the beginning of the experiment, subjects were given a familiarization session.

Protocol A: Each sequence contained three 5-s lasting audio cues. Sequences were performed both in monocular and binocular vision and with three different levels of eye illuminance (about 300, 600, 1000 lux) in randomized order. A poster reproducing a man portrait by Michelangelo was used as far target while a 3x3cm cartoon displaying a black grid (step 2 mm) on white background was used as near target (Fig. 1 and 2A). These were the *detailed targets* containing visual cues that facilitate the focusing process.

Protocol B: Each sequence contained 3 audio cues: lasting 2, 4, 8 s (order was not randomized). The near target (N) could be either homogeneous (H, plain grey) or detailed (D, grid as in protocol A). Similarly, the far target (F) could be either H (plain gray) or D (Michelangelo's drawing). The sequence was then repeated 4 times for the 4 combinations, ND-FD, ND-FH, NH-FD, NH-FH, as outlined in Fig. 2 B, in randomized order. Eye illuminance was set to 600 lux.

Protocol C: A sequence of three 5-s lasting audio cues was repeated twice in randomized order for two opposite conditions of target brightness: near target black and far target white (NB-FW) and near target white and far target black (NW-FB) (Fig. 2C). The black and white targets were simply obtained from black and white cartoons. Eye illuminance was 600 lux.

2.3.2 Experimental Protocol D

This protocol was aimed at testing PAR as a communication tool. In a dim lit environment (eye luminance < 500 lux), the subject was sitting on a comfortable chair and could monocularly switch the visual focus between the far target (Michelangelo's drawing, positioned at 4 m) and a semi-transparent near target positioned at about 40 cm. The near target was constituted by a transparent glass presenting a thin white grid (step = 1 cm) on its surface. With this arrangement the far target could be seen through the near target (Fig. 2D). Again, the eye position can remain almost immobile when switching focus between the two targets. The subjects were presented with auditory cues at two different pitches: high-frequency cue (2000Hz); low-frequency cue (250Hz). Observers were asked to shift the focus on the near target only at the high-frequency cues and to maintain the focus on the far target otherwise (during silent intervals as well as at low-frequency cues). Three randomized sequences of 10 audio cues (5 at low and 5 at high frequency) were presented at different rates of 7.5, 10 and 15 cues/min. In the first sequence cue duration was 3 s and inter-cue interval 5 s; in the second sequence cue duration was 2 s and inter-cue interval was 4 s; in the third sequence cue duration was 2 s and inter-cue interval 2 s. The sequences were presented in random order, separated by a 2-min resting interval. A jitter of ±0.25 s was randomly added to the inter-cue interval to prevent premature responses, possibly triggered by expectation. The sequence of audio cues was randomized.

2.4 Data analysis

2.4.1 Pupil diameter and center

RGB images, acquired via a USB webcam, were the input of our custom Matlab program, implementing the following steps: i) a pre-processing, devoted to reduce the amount of noise within the image, ii) a segmentation algorithm, oriented to identify pixels belonging to the pupil and iii) a post-processing step to compute pupil diameter and pupil center coordinates from the segmented region. The developed framework was provided with real-time plotting to observe the correct execution of the subject's task. The pre-processing started with a manual cropping of the region corresponding to the eye, with the twofold aim of reducing the amount of data to be processed and to reduce the variability in terms of pixel intensities. Such manual crop was performed thanks to a graphical user interface, provided within Matlab image processing toolbox. The cropped RGB image was then converted to grayscale via a linear combination of the three RGB channels values. As denoising technique we applied a median filter with a kernel size of 3x3 pixels, followed by a local adaptive histogram equalization (Pizer et al., 1987). The denoised grayscale image was the input of the segmentation phase, which consisted in two different techniques applied in parallel to localize and segment the pupil from the background. The first strategy was a simple global thresholding (Otsu, 1979) followed by a morphological erosion operation (Soille, 2004). At this stage, the binary segmentation mask was containing different connected regions, including the pupil. To identify it, some geometrical properties (namely eccentricity, circularity and area) of all regions were computed and used as selection criteria. As a secondary solution, in case of a bad signal-to-noise ratio, we implemented a strategy based on the Hough transform (Duda and Hart, 1972).

Once the pupil was segmented, the following geometrical features were extracted: pupil diameter, computed as the squared root of $4A/\pi$, where A is the estimated area of the pupil in pixels; the coordinates of the pupil centroid, computed as the centre of mass of the segmented region, in pixels. A coin of known dimension was stuck above the subjects' dominant eye and used to calibrate the camera and to obtain the pupil diameter in millimeters. Traces were offline resampled at 20 Hz and both the pupil size and center signals were cleaned from blink-related artifacts.

2.4.2 Eye movements

In addition to pupil diameter, we measured eye movements. To convert the recorded pupil centroid coordinates into degrees of visual angle, the following calibration procedure was performed before the experimental procedure. The pupil center was monitored while the subject was asked to sequentially gaze at a series of 9 dark targets drawn on a white cardboard placed at 57 cm. The points were organized in a matrix of 3 rows and 3 columns with a fixed spacing of 5 cm among them (corresponding to a visual angle of 5 deg). This information was used to convert in degrees the displacements in pixels exhibited by the pupil center during the recordings. To this aim, two-dimensional interpolation was used. Although this procedure to measure eye movements is relatively crude as compared to modern eye tracking systems, it is adequate to provide a rough assessment, thus fitting the need of this study.

2.4.3 PAR amplitude

PAR amplitude was computed as the difference in pupil diameter between the basal (far-focus) condition (average between 6.5 and 0.5 s before the audio cue) and the near-focus condition (average between 1.5 s after the beginning and 0.5 s after the end of the audio cue) and is expressed in absolute terms (mm) or relative to baseline (%).

2.4.4 Pupil stability, drift and fall time

The following parameters were evaluated for the 8-s lasting PAR of protocol B. Drift of pupil size during near vision was assessed as the slope of the linear interpolation of pupil size over time, computed in the 5-s interval starting 3 s after the beginning of the audio cue. Stability of pupil size was defined as the unaccounted variance of the linear interpolation of pupil size over time, during the same time interval. Fall time was computed as the time to complete from 10 to 90 % of the constrictory response.

2.4.5 PAR detection in Protocol D

The pupil size signal recorded by the eye-tracker was first cleaned from blink-related artifacts; then missing data points were replaced by linearly interpolating between the two samples delimiting the gap. The acquired data was then filtered using a 90^{th} order FIR low-pass filter with a cutoff frequency of 5Hz.

A simple adaptive threshold method was used to detect PAR occurrence in association to audio cues. The threshold was set to 90% of basal pupil size (average size over the last third of the inter-cue interval, preceding the incoming cue). A PAR was detected upon threshold crossing (below

90%) within the duration of the audio cue extended by 0.5 s, and not returning above threshold for at least 0.5 s, otherwise a “no-PAR” label was assigned to that audio cue.

The sequence of PARs automatically detected in this way were compared to the audio cue sequence: a positive score was given whenever a high-frequency cue matched a PAR or a low-frequency cue matched a no-PAR; a negative score was given otherwise. Success rate was then computed as the percentage of correctly decoded answers (positive scores / total scores) and the information transfer rate in bits/min was computed as $V^*(\log_2(N) + P \log_2(P) + (1-P) \log_2((1-P)/N-1))$ where N=2 for binary communication; P is the success rate (accuracy); and V is the rate at which audio cues were presented (Wolpaw et al., 2002).

The latency of the pupillary constriction from the beginning of the audio cue was also assessed. The onset of the constrictory response was computed as the intersection between the linear interpolations of the trace in the 1-s interval preceding the audio cue and the 0.5-s interval following the threshold crossing.

2.5 Statistical analysis

In protocol A, the effects on basal pupil size, PAR amplitude, relative PAR amplitude and PAR fall time were analysed by a 3-way ANOVA for repeated measures with the within-subject factors illumination level (3 levels: 300, 600, 1000 lux), vision (2 levels: monocular, binocular) and repetition (1st, 2nd, 3rd). In protocol B, the effects on PAR amplitude and relative PAR amplitude were analysed by a 3-way ANOVA for repeated measures, with the within-subject factors duration (3 levels: 2, 4 and 8 s), near target type (2 levels: homogeneous H and detailed D) and far target type (2 levels: H and D). The analysis of pupil stability and drift, which was limited to the longer stimulus duration (8 s), was based on a 2-way ANOVA, with the within-subject factors near target type (2 levels: H and D) and far target type (2 levels: H and D). We did not consider the second-order interaction of 3-way ANOVAs, as it is often open to multiple interpretations. Throughout the text we report only statistically significant results. Post-hoc pairwise comparisons were performed in case of significant main effects (Tukey’s Honestly Significant Difference test, using the error term for the current within-subject effect). In protocol C, the effect on PAR amplitude of target brightness (i.e., near bright – far dark vs. the near dark – far bright target combination, henceforth NW-FB and NB-FW, respectively) was assessed by a 2-way ANOVA for repeated measures with the within-subject factors target (2 levels: NW-FB and NB-FW) and repetition (1st, 2nd, 3rd).

Alpha level was set to 0.05. The statistical analyses were carried out using STATISTICA, version 10. Values are reported as means ± standard deviation in the text. Error bars in bar diagrams represent within-subject confidence interval (Morey, 2008)

3 RESULTS

3.1 Protocol A, effects of eye illuminance and monocular/binocular vision

A representative example of PAR voluntarily performed in response to three subsequent audio cues is shown in Figure 3. PARs are clearly visible as stereotyped pupil constrictions occurring when focusing on the near target, during the audio cue. Dilation (release of constriction) then slowly follows when focusing back on the far target.

Basal pupil size (when focus is on the far target) was affected by eye illuminance (main effect $F(2,28)=22.82$, $p<0.001$, $\eta_p^2=0.62$; Fig. 4A) and by mono/binocular vision (main effect $F(1,14)= 7.46$, $p=0.016$, $\eta_p^2=0.35$), with a significant interaction between these two factors ($F(2,28)=5.71$, $p=0.008$, $\eta_p^2=0.29$).

Regarding PAR amplitude, the only significant effect was eye illuminance (Figure 4B), which slightly decreased pupil constriction (main effect of illuminance: $F(2,28)=36,06$, $p<0.001$, $\eta_p^2=0.72$). The apparent tendency for monocular vision to produce a smaller PAR, as well as the apparent decrease of this effect with increasing illumination, both visible in the figure, were not statistically significant. Also when PAR was measured in relative terms (i.e., as a percentage of baseline pupil size), illuminance turned out to be the only factor significantly affecting pupil constriction (main effect of illuminance, $F(2,28)=10.74$, $p<0.001$, $\eta_p^2=0.43$), data not shown). On average over all factors, PAR amplitude was 21.53 ± 7.76 % of baseline pupil size. PAR amplitude (at 600 lux, averaging over vision and repetition) was not significantly correlated with participants' age ($r=-0.072$, $p=0.80$).

We also assessed the PAR fall time, for which we found a main effect of viewing condition ($F(1,14)=4.76$, $p=0.047$, $\eta_p^2=0.25$) and a significant interaction vision x illuminance ($F(2,28)=4.95$, $p=0.014$, $\eta_p^2= 0.26$). On average, fall time was larger in monocular (0.95 ± 0.27 s) than in binocular vision (0.77 ± 0.31 s), the difference being larger at low illuminance.

In sum, PAR was clearly visible in all trials, and the general visual conditions (i.e., eye illuminance and monocular/binocular vision) only slightly affected pupil behaviour.

3.2 Protocol B, effects of target duration and salience

PAR amplitude was dependent on both the salience of the far target (main effect of far target type, $F(1,18)=9.837$, $p<0.01$, $\eta_p^2=0.35$) and the duration of the constriction (main effect of duration,

$F(2,36)=21.91$, $p<0.001$, $\eta_p^2=0.55$), with significant interactions between duration and the salience of near ($F(1,18)=4.08$, $p<0.05$, $\eta_p^2=0.18$) and far target ($F(1,18)=7.90$, $p<0.01$, $\eta_p^2=0.30$), as shown in Figure 5A. Post-hoc tests indicated that PAR amplitude at 4-s duration was significantly larger than at 2 and 8 s, for both detailed and homogeneous far target (Fig. 5A).

Similarly, PAR in relative terms was dependent on both the salience of the far target, $F(1,18)=7.39$, $p=0.014$, $\eta_p^2=0.29$ and the duration of the constriction, $F(2,36)=22.09$, $p<0.001$, $\eta_p^2=0.55$.

After averaging over all conditions, the extent of pupillary constriction during the accommodative task was on average 0.87 ± 0.47 mm, equivalent to 18.37 ± 8.14 % of the baseline value.

In addition, we analysed pupil behaviour in terms of a) tendency to systematically drift (slope of linear regression of pupil size over time) and b) residual fluctuations of pupil size after discounting for drift (unaccounted variance) during the 8-s lasting PAR. Drift was dependent on near, $F(1,18)=6.26$, $p=0.022$, $\eta_p^2=0.258$, and on far target salience, $F(1,18)=4.97$, $p=0.039$, $\eta_p^2=0.21$, exhibiting the lowest value with detailed far and near targets (0.004 ± 0.031 mm/s) and the highest value with homogeneous targets (0.037 ± 0.043 mm/s). This is apparent from the average traces of Fig. 5B, and mean values are reported in Fig 5C. A similar pattern was observed for pupil size fluctuations, which on average tended to be smaller with the detailed than with the homogeneous targets (Fig 5D), although the differences did not reach statistical significance.

In sum, PAR was well developed and clearly detectable at all durations, reaching a maximum at the 4-s duration. Textured targets may slightly increase the magnitude of the PAR and help to maintain a sustained accommodative state.

3.3 Protocol C, effect of target brightness

Inverting the brightness of the targets (i.e., near target black and far target white, NB-FW, vs. near target white and far target black, NW-FB) affected PAR amplitude, which in the NW-FB condition was larger than in the NB-FW (main effect of target type, $F(1,18)=17.79$, $p<0.001$, $\eta_p^2=0.50$; Fig. 6). Conceivably, this reflected the synergic effect of the pupil light reflex, which tends to constrict the pupil when the near target is brighter.

3.4 Gaze direction when switching between far and near targets

Changes of gaze direction recorded from the dominant, seeing eye when switching from far to near targets were on average rather small (1.17 ± 0.82 deg), indicating a good alignment of the targets with the visual axis. The scatter plot in Fig. 7 reports data from all protocols and all participants. PAR was not significantly correlated with the change of gaze direction at the time of the PAR ($r=0.089$, $p=0.061$).

3.5 Protocol D. Using PAR for HCI

Fig. 8 reports an example of pupil size recording during a communication sequence (10 trials) at a rate of 7.5 cues/min. Note the easy identification of PARs in association with the high-frequency cues. At the slower transmission rates, that is, 7.5 and 10 cues/min, responses were correctly classified in all subjects (hit rate= 100%; information transfer rate = 7.5 and 10 bits/min, respectively). At the highest transmission rate tested (15 cues/min), hit rate was 100% in 5 subjects and 90% in three subjects (1 PAR not detected), resulting in an average hit rate of 96%, and information transfer rate of 11.3 bits/min. No-PARs were always correctly classified, that is, there were no false positives. The latency of the pupillary response from the audio cue was on average 0.61±0.09 s.

4 DISCUSSION

We have investigated the Pupil Accommodation Response – PAR – as a correlate of a voluntary act, triggered by an audio cue. PAR was characterized with respect to several variables and tested as a possible communication tool for completely paralysed patients. In summary, the experimental series showed that PAR is easily performed by the subjects with no need of extensive training, it is only slightly affected by eye illuminance, mono/binocular vision, brightness and texture of the visual targets, and duration of the near vision. The response is thus robust, it can be easily monitored and detected with low-cost equipment and was shown to achieve a good performance in terms of accuracy and transmission rate when used as a communication tool.

4.1 Effect of the different factors on pupil behaviour

4.1.1 Eye illuminance

In a study based on 2 subjects, Semmlow et al. (1975) first described an inverted-U dependence of PAR with initial pupil size, controlled by changes in eye illuminance. They showed that the near response was maximal at basal pupil size of about 5 mm and significantly decreased at both smaller and larger size. In the present study we did not explore small pupil diameters that are common in bright environments (<= 5mm), but the results confirm that PAR decreases with eye illuminance, and that the effect remains significant even if PAR is assessed in relative terms with respect to basal pupil size.

4.1.2 Monocular vs binocular vision

In the few studies that investigated the pupillary near response in monocular versus binocular vision, the latter condition was reported to produce a slightly larger response (about 10% larger in the binocular vs monocular condition, (Bharadwaj et al., 2011; Chirre et al., 2015), which was interpreted as the consequence of increased sensory input producing increased reflex response. Retinal disparity, which is missing in monocular viewing, is known to be an important stimulus in the near reflex, with a reinforcing action (Chirre et al., 2015; McDougal and Gamlin, 2015). In agreement with Chirre et al. (2015) we also observed increased fall time in monocular vision. However, we did not detect a clear difference in the magnitude of PAR in the two conditions. It must however be observed that we obtained monocular vision by completely closing one eye rather then simply interposing a blocker at a certain distance from the eye, to hide the visual target (Chirre et al., 2015). The ensuing mismatch in visual information occurring in the latter case could be responsible for the weakening of the near response in monocular vision previously reported (Chirre et al., 2015). In addition, the tendency to have larger basal pupil size in the monocular condition could have contributed to produce larger (absolute) PAR in the present study, according to Semmlow et al. (1975). These factors may have contributed to reduce the differences between monocular and binocular viewing, including the possible sensitivity to illumination conditions. A larger sample size might be able to detect such small differences, if present.

4.1.3 Detail of visual targets

Pupillary escape is known as the slow dilation that follows the pupillary constriction in response to a step increase in the intensity of light stimulus (Sun et al., 1983). A similar phenomenon has been observed following the pupillary constriction in the near response (Bharadwaj et al., 2011; Kasthurirangan and Glasser, 2005). Several hypotheses have been made about the possible underlying reasons, including peripheral mechanical factors (Sun et al., 1983), changes in retinal illuminance or interaction between phasic and tonic components of the accommodative system (Kasthurirangan and Glasser, 2005). The escape phenomenon was here observed in protocol B, during the longest lasting accommodative task, 8-s duration, and quantified as the slope of the pupil size in that time interval. Interestingly, we here observed that the slope is significantly reduced by increased detail of the near and of the far target. This suggests that the escape in PAR could be related to the difficulty in maintaining the focus or attention on a homogeneous near target, and could be prevented or counteracted by “anchoring” attention to the near focal plane with a detailed visual stimulus as target. It is possible that the “anchoring” effect could also reduce spontaneous fluctuations in pupil size, although this did not reach statistical significance in the present study. Interestingly, salience of the far target also slightly increased PAR magnitude (Fig. 5A). This suggests that a textured rather than a homogenous background is to be preferred to better elicit PAR (e.g., decorated rather than white walls in domestic rooms or assistance facilities environments).

4.1.4 Brightness of visual targets

Results from Protocol C showed that PAR is increased with bright near target and dark far target, as compared to the opposite configuration. This result was expected since pupil constriction during PAR would be reinforced by a concomitant synergic light reflex. Moreover, it has recently been shown that increased pupil constrictory response could be elicited by shifting covert attention to bright rather than to dark targets (Binda et al., 2014; Mathot et al., 2013), as well as by merely imagining a bright target (Laeng and Sulutvedt, 2014). Thus, a darkened background (e.g., a dark curtain before a wall) coupled with a bright target may sensibly increase the PAR.

4.1.5 Duration of the accommodative task

Protocol B provided the important information that changing the duration of the task, in the range 2 to 8 s, produces only minor changes in PAR amplitude. A finding that was *prima facie* surprising, was the slightly larger response to the intermediate 4-s duration. This phenomenon can however be possibly related to the fact that in the 2-s task the response is very close but not yet at the maximum constriction, and in the 8-s task the response might be attenuated by the above-mentioned escape effect. What is important, however, is that a 2-s duration already yields an almost full effect. To implement a HCI based on the PAR this information is relevant as it indicates that long permanence of the focus on the near target is not necessary to obtain a large pupil response. Choosing a short-duration PAR has obvious advantages in terms of shortening the overall testing time, reducing pupillary fatigue and increasing the information transfer rate.

4.2 Voluntary vs. reflex activation

The pupillary near response has often been investigated as a reflex response to visual stimuli, e.g. far and near targets that were alternatively made visible to the subject (Kasthurirangan and Glasser, 2005; Roth, 1969; Semmlow et al., 1975; Stakenburg, 1991). In the present and few other studies, the PAR is instead voluntarily performed following a verbal indication or an auditory cue (Chirre et al., 2015; Schaeffel et al., 1993). The pupillary responses are qualitatively similar in the two cases, but one peculiar difference is the latency of the response. The latency of the pupil in response to a visual stimulus was reported to be about 300-400 ms (Kasthurirangan and Glasser, 2005, 2006). To our knowledge, the latency of the voluntary response to the audio cue has not been previously measured. We here observed a mean latency of 0.61 s, which is larger than that of the near reflex. A likely reason for this difference is that the communication protocol did not just imply a reflex response, but required subjects to discriminate the acoustic cue (high-frequency vs. low-frequency tone) and to take the decision as to shifting or not shifting the focus to the near target. In the present context it is a relevant feature for optimal detection of the response.

4. 3 PAR dependence on vergence

In this study the targets were aligned with one eye, and not in cyclopean position, since this condition mimics CLIS patient testing: in that case, in fact, the lack or poor control of vergence eye movements makes targets and eye alignment mandatory, for otherwise targets would remain in the periphoveal or even peripheral visual field. Eye movement monitoring demonstrated that in most tasks the subject managed to switch the focus between far and near target with minimal movement of the eye. Of course, this did not prevent vergence movements by the fellow eye, even in monocular vision, when it was covered by a patch.

The extent of dependence of miosis on the other components of the near response, vergence and accommodation, has been investigated for several decades (Feil et al., 2017; Marg and Morgan, 1949; Stakenburg, 1991) and has not been completely elucidated yet. There is evidence that vergence movements are required for PAR to fully develop (Feil et al., 2017; Stakenburg, 1991). In this case a PAR-based HCI would be difficult to implement in completely paralyzed subjects, in whom vergence eye movements would also be impaired. On the other hand, an alternative view recently emerged suggesting that miosis is a separate output of the neural pathways that drive accommodation and vergence, based on the integration of stimuli such as blur and retinal disparity (McDougal and Gamlin, 2015). On this basis, the control of the pupil would not exclusively depend on the control of accommodation or vergence (McDougal and Gamlin, 2015). Because PAR has been observed in preliminary assessments in advanced ALS patients in whom eye movements were largely impaired (unpublished observations), we suggest that vergence and accommodation are indeed under at least partly independent neural control.

4.4 PAR as a human-computer interface

In the context of eye-based interactions, pupil detection has been rarely considered as a possible input communication channel in the “active” use of gaze, i.e. for “selection and look to shoot” (Duchowski, 2018), while gaining more interest in reading emotional and cognitive states (Majaranta and Bulling, 2014). The early and very preliminary study by Ekman et al (2008b) proposed different ways to voluntary change pupil size, namely: physical and mental efforts, self induced pain, change in point of focus (equivalent to PAR), positive and negative emotions and concentration. The results of a subsequent study were disappointing to the authors (Ekman et al., 2008a), with no further follow-up, and thus this issue remained mostly unknown to the biomedical community. The extensive development of eye-tracking devices has been to a large extent limited to video-based applications in which the depth of focus never changes, the visual targets being displayed on flat screens, thus in fact opposing any possible manifestation of the PAR.

The present results from Protocols A-C allowed us to identify some suitable working conditions to obtain a robust PAR: moderate eye luminance, bright near and dark far targets, short response duration. Importantly, we also showed that monocular viewing condition is not an impeding factor, and this facilitates using PAR with an eye patched, which may prevent the possible mismatch of retinal disparity in ALS patients.

These features were adopted for Protocol D in which PAR was tested as a binary communication tool. Rather than answering Yes/No to obvious questions, we asked the subject to discriminate between low- and high-frequency cues, which allowed us to implement high transmission rates. The results showed optimum performance at the fastest rate: 96% accuracy at 15 binary cues/min, equivalent to 11.3 bits/min. This performance appears to be considerably high, compared to other pupil-based communication systems. In a study by Stoll et al. (2013) the pupil dilatory response to mental effort (Laeng et al., 2012) was exploited, achieving 90% accuracy at 3.6 binary selections/min. More recently Mathot et al. (2013) implemented a HCI based on detecting the oscillatory components of the pupil in subjects covertly attending to blinking visual targets. In this study a 90% accuracy and a selection rate of 2.1 symbols/min among 8 different symbols was achieved, which is equivalent to binary selection rate of 6.3 binary selections/min (Mathot et al., 2013). The performance achieved in the present study appears to be good also compared to EEG-based BCIs, achieving information transfer rates of abut: 8-10 bits/min with sensory-motor rhythms (McFarland et al., 2003) and 13.7 bits/min in P300-based BCI (McCane et al., 2015).

In addition to high communication rate, another relevant feature of the present approach is that it does not require to learn a new procedure or skill as required by other brain-computer interfaces based, e.g., on P300. In fact, it has been suggested that the extinction of goal-directed thinking (Kubler and Birbaumer, 2008) may impair instrumental learning in CLIS patients, therefore explaining the failure of many attempts with these patients in the past (Chaudhary et al., 2016a). Attending objects at different depths is a simple and natural task that can be probably undertaken also by patients with limited cognitive capacity. As mentioned above, promising results have been collected from advanced ALS patients, although effectiveness of PAR communication remains to be verified in CLIS patients, who, incidentally, may also suffer of impaired vision due to drying of the cornea. However, training with this communication method patients in the transition from LIS to CLIS may help to preserve its functionality.

A relevant issue that remains to be investigated is the possible occurrence of fatigue and attention deficits in long-lasting working sessions, which could decrease performance and limit usability.

4.5 Considerations on design and usability

Although the experiments were not aimed to address usability and the subjects' impressions were not collected in a systematic way, we propose some considerations in light of future implementations.

1) Enhanced texture of visual targets is recommended. Homogeneous targets not only weaken the PAR but are also difficult to deal with: several subjects reported difficulty in focusing in the absence of visual cues and some also experienced fading of images and colours. In a few cases they even reported dizziness. In patients, fading may become an important issue, especially in advanced ALS patients, who face progressive limitation of eye movements, possibly including miniature eye movements (microsaccades, drift and tremor), which normally refresh the retinal image preventing adaptation (Duchowski, 2018; Martinez-Conde and Macknik, 2015). These patients may undergo important fading phenomena due to completely or almost completely immobile eyes. Implementation of texture- or colour-changing targets is likely to improve PAR magnitude. More generally, for these patients it might be important to recommend frequent exposure to moving images, regardless of whether or not they use a PAR-based communication device. This issue deserves further investigation.

2) Need for corrected visual acuity. In consideration of the importance to effectively focus on the (textured) target, blurred vision of the near and/or far target is likely to deteriorate PAR. Adjustment of targets' position and/or adoption of appropriate glasses seem to be appropriate interventions, although their actual efficacy was not here investigated. Fortunately, however, pupil constriction seems to survive troubles of accommodation (Schaeffel et al., 1993).

3) PAR can also be considered as an additional/complementary method for eyes-only video-based applications: in fact, it could be exploited as an "eye gesture" (Majaranta and Bulling, 2014; Ohno, 1998) for the selection of a particular target, e.g. the one that was just pointed at or that is currently highlighted on the screen. Such possibility is currently under investigation in patients.

5 CONCLUSIONS

A characterization of the PAR in quasi-natural condition has been performed, providing useful experimental indications for optimizing pupil response in clinical applications. More importantly, a proof of concept in healthy subjects has been provided for a PAR-based human-computer interface. This technique exhibits unprecedented performance in terms of accuracy and transmission rate. Data from the literature and preliminary observations in ALS patients suggest that it may be successfully applied to support communication with patients in LIS and CLIS.

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LEGENDS

Fig. 1 Experimental set-up.

The far target (poster) and the near target (small cartoon) are aligned with the subject's gaze from the dominant eye (A). Subject's view when focusing on the far (left) or on the near target (right) (B). Virtually no eye movement is required when switching the focus between the two targets if the gaze remains tangent to the border of the near target, as indicted by the white dashed circle.

Fig. 2 Target combinations used in the different protocols.

A schematic representation of the near and far targets used in the different protocols is provided: A) in protocol A targets with enhanced graphical texture (detailed targets) were used, i.e., a grid for the near target and a drawing for the far target; B) in protocol B the four possible combinations of detailed/homogeneous (plain grey) far/near targets were tested. C) In protocol C the two combinations of completely black or white targets were used. D) In protocol D a single set of target was used: at difference from protocol A, the near target was a white grid drawn on a transparent plexiglass. This feature allows see the far target through the grid, thus further reducing the need for vergence movements by the dominant eye. The subject's view when focussing on the far (left) or on the near target (right) is shown (D).

Fig. 3 Protocol A, representative pupil size recording.

An example of single-trial recording of the pupil size showing three voluntary accomodative responses prompted by audio cues (horizontal bars) is shown. The recording was taken with a webcam under monocular vision with an eye illuminance of 600 lux

Fig. 4 Protocol A, effect of eye illuminance and mono/binocular condition.

Basal pupil size (A) and PAR amplitude (B) at different levels of eye illuminance in mono- and binocular condition. Error bars represent 95% confidence intervals.

Fig. 5 Protocol B, effect of target salience.

A) PAR amplitude observed for different durations of the near vision and different salience of the far target. B) average time course of pupil size during the 8-s lasting PAR for the different saliencies (detailed, D, or homogeneous, H) of near (N) and far (F) targets; traces are normalized to basal pupil size; C) drift of pupil size during the 8-s lasting PAR; D) unaccounted variance of pupil size during the 8-s lasting PAR. For graphical clarity, data have been averaged across the levels of the near target. Error bars represent 95% confidence intervals.

Fig. 6 Protocol C, effect of target brightness.

PAR amplitude vs. target brightness NW-FB: near white and far black; NB-FW: near black and far white. Error bars represent 95% confidence intervals.

Fig. 7 PAR Amplitude vs. eye movement

Amplitude of PAR collected from protocols A, B and C in all subjects plotted against the change of gaze direction during the far-to-near transition (dominant eye, aligned with the targets). Inset: example of combined recording of pupil size and eye movements.

Fig. 8 Protocol D, discrimination of sound pitch.

Original traces of pupil size from a representative subject during simulation of communication: The subject was instructed to perform a PAR whenever a high-frequency audio cue, indicated by "*", was presented and to remain with the gaze focused to the far target in response to low-frequency audio cues (indicated by "°"). Duration of audio cues = 3 s, duration of resting intervals = 5 s (bit rate =7.5 bit/min). The algorithm detects a PAR whenever the pupil size crosses the threshold level, indicated by the 3.5-s segments; "#" indicates successful PAR detection. Each pair of vertical lines indicates the start and end of a low-frequency (dashed) or high-frequency (continuous) audio cue