Proceedings of the 2012 IEEE 12th International Conference on Bioinformatics & Bioengineering (BIBE), Larnaca, Cyprus, 11-13 November 2012

Quantitative assessment of the pupillary photomotor response dynamics to tunable, narrow band stimuli

Vasileios Kavvadias, Costas Balas Member IEEE
Department of Electronic and Computer Engineering
Technical University of Crete
Chania, 73134, Greece
vkavvadias@electronics.tuc.gr

Abstract **-** Digital pupillography presents a "window" for studying the autonomous nervous system functionality, with an uprising research interest. Multiband pupillary responses are exploited only partially up to now, due to technological limitations of the devices developed so far and to the lack of the parameterization of the measured responses. We have developed a spectral binocular pupillographic device, capable of recording papillary responses to polychromatic stimuli spanning the entire visible spectrum. The recorded direct and consensual reflexes are further processed and novel pupil mobility indices such as velocity and acceleration vs. wavelength are calculated and displayed. The wavelength dependence of these parameters is studied for the first time and it is expected to be very informative for various pathologic conditions of the autonomous nervous system. The ultimate goal of this project is to develop a new diagnostic technology for the screening and diagnosis of a wide range of neurological pathologies.

Keywords - Spectral pupillary responses, binocular pupillography

I. INTRODUCTION

Pupillary light reflex (PLR) is an automatic, involuntary motor response to light stimuli, controlled by the autonomous nervous system (ANS). It regulates retinal illumination by adjusting the pupil aperture. By increasing the light intensity the pupil constricts, allowing less light to pass through, whereas lowering light intensity causes the pupil to dilate, allowing more light to reach the retina. Pupil constriction and dilation are controlled by the ANS parasympathetic and sympathetic subsystems respectively.

The response is triggered by retinal photoreceptor neuron cells, which convert light stimuli into electric impulses. These impulses link complex neuroanatomical pathways. In brief, photoreceptors convey information to the optic nerve, via the optic disc. The optic nerve connects to the pretectal nucleus of the upper midbrain, bypassing the lateral geniculate nucleus and the primary visual cortex. From the pretectal nucleus, axons connect to neurons in the Edinger-Westphal nucleus, whose axons run along both the left and right oculomotor nerves. Oculomotor nerve axons synapse on ciliary ganglion neurons and innervate the constrictor muscle of the iris [1].

There are three groups of retinal photoreceptors, rods, cones (short - S, medium - M and long – L wavelength type) and the recently discovered intrinsically photosensitive retinal ganglion cells (ipRGCs) [2]. The first two groups are responsible for forming the representation of the visual world (sight), whereas ipRGCs contribute to non visual photical phenomena. The ipRGCs mainly regulate the suppression of the hormone melatonin and the entrainment of the body's circadian rhythms. All three groups of photoreceptors are responsible for driving pupillary reflexes and have different action spectra, although overlapping, spanning the entire visible spectrum.

Pupil examination is routinely performed by medical and paramedical personnel with the aid of simple instruments such as flashlight and pupil gauge. Through this type of examination, pupillary reflexes are only partially exploited, limited simply to the assessing of the existence of PLR in the homolateral and contralateral pupil. On top of it, it obvious that the assessment is qualitative and it is are influenced by examiner's bias. Advances in computerized pupillometry have promoted its use in clinical research on the grounds of accuracy, insusceptibility to the examiner, statistical analysis and lateralization of the reflex. Regarding the pathophysiology of the ANS, new pupillometric indices can be developed to accommodate classification of healthy and pathologic conditions.[3]. Because of the possibility of unequal direct and consensual pupil reactions, binocular pupillometers are best suited for clinical application of pupillography.

Digital pupillography presents a window for the real-time assessment of the status and functionality of the autonomous nervous system with an uprising research interest. Several clinical studies on, Alzheimer [4], sclerosis [5], heart failure [6], diabetic neuropathy [7], depression [8], schizophrenia [9], brain injury [10], as well as in the uptake kinetics of drugs and psychotropic substances which affect the ANS [11] have proven the diagnostic value of pupillometry. However, pupillometry is not yet a standardized method and is only partially exploited due to technological limitations present in the so far developed systems. Another shortcoming of current technologies is the lack of sophisticated parameterization of the reflex. We maintain that the measurement, study and modeling of the pupil motion reflex parameters as a function of the wavelength of the light stimuli will provide a new insight to our understanding of complex patho-physiological conditions of the autonomous nervous

system. We intent to fill a gap in the field since to the best of our knowledge there are no published studies reporting results from the simultaneous direct and indirect examination of the pupillary responses in narrow-band monochromatic stimuli, spanning the entire visible spectrum in a continuous manner. The wavelength dependence of series of pupil mobility indices are for the first time measured with the aid of the set-up that we have developed and it is expected to be very informative for various pathologic conditions of the autonomous nervous system.

II. MATERIALS AND METHODS

A. Expermental set up

We have developed a digital pupillography device, capable of measuring, in both eyes simultaneously, the pupillary responses to narrow band light stimuli, the centre wavelength of which can be freely tuned within the visible band of the spectrum. Two monochrome Charge Coupled Device (CCD) cameras, sensitive to the near infrared (NIR) band of the spectrum 700-1000nm (Point Grey Research, DR2-03S2M) capture automatically the pupillary reflexes of both eyes in time sequence. The temporal resolution was set to 60 Hz, spatial resolution to 640x480 and the bit sampling level at 8 bit (256 grayscale levels). NIR illumination is used throughout the entire examination and it is produced by IR LEDs. Additionally, two 800nm long-pass filters were used in front of the camera lenses, for cutting off stimuli "hot spot" reflections onto the eye surface. Each subject is aligned to the cameras by stabilizing his/her head onto a chin-rest. The pupillary spectral stimulation was performed with aid of a homemade narrow-band illuminator. The developed spectral illuminator is based on the combination of white light source, coupled with diffraction grating, the angular displacement of which has the effect of tuning the dispersed light. The intensity of the light source can be controlled in each particular wavelength, so that flat intensity profile can be achieved across its entire wavelength range. This is done for compensating for the non uniform spectral emissivity and throughput of the light source and the grating respectively. The flattening of the light stimuli is essential for insuring that changes in pupil reflexes are due to the changes of the excitation wavelength and not due to the intensity variations. The exit slit of the spectral illuminator was coupled with a liner-to-circular ended fiber optic bundle, the circular end of which was placed at an 20cm distance from the eye. The full width half max (FWHM) of the illuminator was set to 5nm and the tuning range to 380- 800 nm, being wider than the eye's sensitivity. The illuminating eye power was kept constant at 5μW across the entire wavelength range, which is much below the safety limits set by ICNIRP.

The cameras were focused at the subject's eyes, capturing mainly the front surface of the optical bulbs. The tests were held out in totally dark room and the eyes were optically isolated one from each other, so that the incident monochromatic light would stimulate directly only one eye.

Image frames recorded by the CCDs throughout the examination were transferred to a personal computer. Synchronization and control of all components of the system was performed through microcontrollers and specially designed operating software. Pupil aperture size was calculated in real time, by a contrast detection, circularity tracking,algorithm that we have developed. This algorithm was designed to be artifact insensitive and remains uninfluenced by semi-closed eyes or under-illuminated images.

B. Subjectes and measurements

The subjects were 10 healthy volunteers between 26 and 28yrs were subjected to measurement, which were performed to our labs. The measurements were conducted as follows the examination is initiated by imaging the pupil using near infrared illumination for several minutes. In these scotopic conditions, the maximum pupil diameter is obtained. During the test they were seated in a comfortable position with their heads held by a chin rest. The examiner selects through the specially designed software the stimulation wavelength and the duration of the test. The intensity of the irradiance may be pre-selected or it may be automatically adjusted to a criterion response, e.g. ½, ¾ or maximal pupillary constriction. The predefined optical stimulation will be generated, with respect to wavelength, duration and the type of visual stimulation (e.g. pulsed / continuous light). Between each stimulation, a dark vision re-adaptation must be performed. The CCD sensors record the contractions / dilations of the pupils of both eyes, before, during and after the stimulation. The software processes the captured digital images and calculates pupil mobility graphs and parameters.

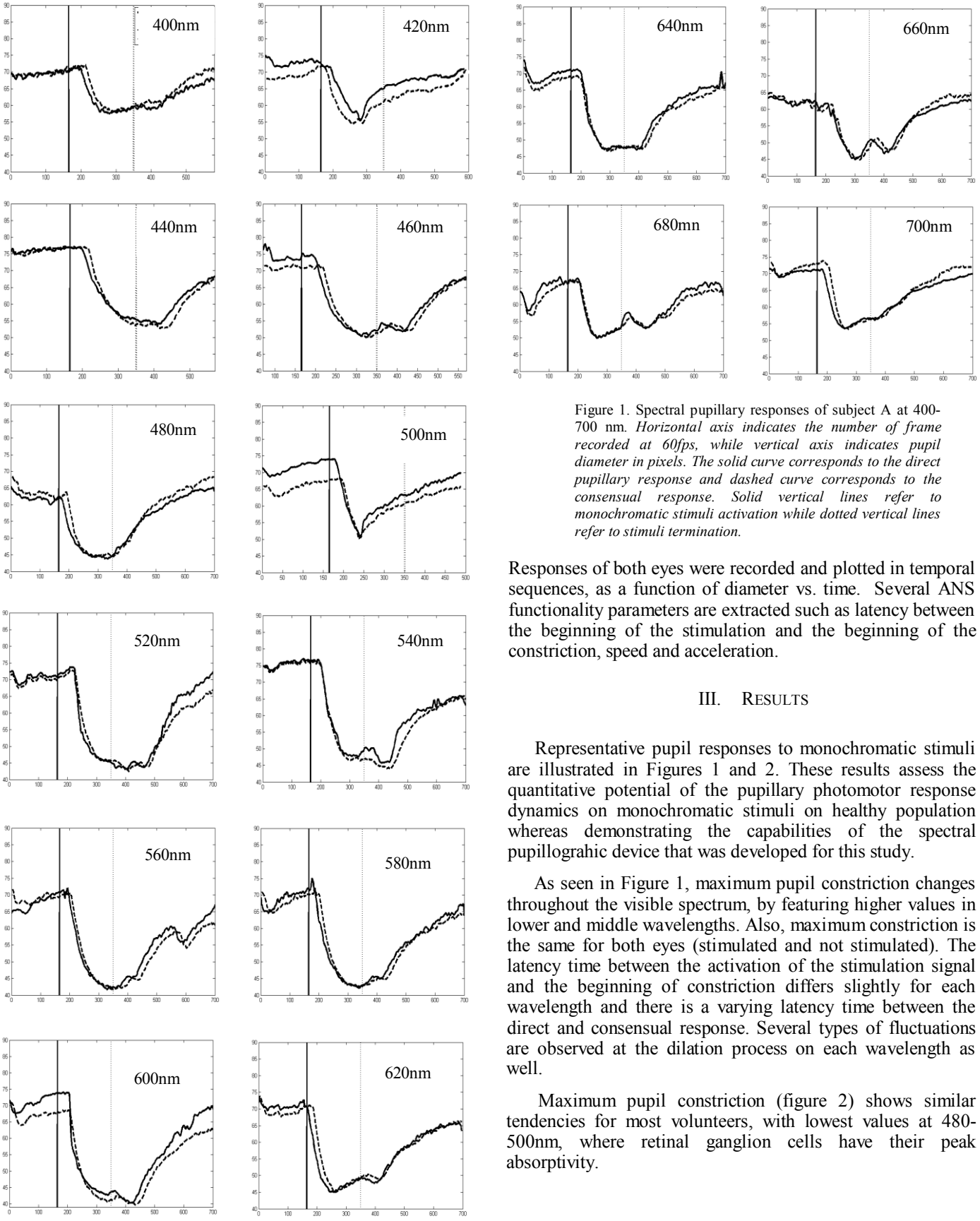

Figure 1. Spectral pupillary responses of subject A at 400-700 nm. *Horizontal axis indicates the number of frame recorded at 60fps, while vertical axis indicates pupil diameter in pixels. The solid curve corresponds to the direct pupillary response and dashed curve corresponds to the consensual response. Solid vertical lines refer to monochromatic stimuli activation while dotted vertical lines refer to stimuli termination.*

Responses of both eyes were recorded and plotted in temporal sequences, as a function of diameter vs. time. Several ANS functionality parameters are extracted such as latency between the beginning of the stimulation and the beginning of the constriction, speed and acceleration.

III. RESULTS

Representative pupil responses to monochromatic stimuli are illustrated in Figures 1 and 2. These results assess the quantitative potential of the pupillary photomotor response dynamics on monochromatic stimuli on healthy population whereas demonstrating the capabilities of the spectral pupillograhic device that was developed for this study.

As seen in Figure 1, maximum pupil constriction changes throughout the visible spectrum, by featuring higher values in lower and middle wavelengths. Also, maximum constriction is the same for both eyes (stimulated and not stimulated). The latency time between the activation of the stimulation signal and the beginning of constriction differs slightly for each wavelength and there is a varying latency time between the direct and consensual response. Several types of fluctuations are observed at the dilation process on each wavelength as well.

Maximum pupil constriction (figure 2) shows similar tendencies for most volunteers, with lowest values at 480-500nm, where retinal ganglion cells have their peak absorptivity.

IV. DISCUSSION

These results reveal many not researched areas of pupil mobility, between the direct and consensual response, where technological gaps did not allow to be researched up to now.

The device developed in this survey intends to serve as a novel diagnostic mean for extracting vital information of the ANS and brain health condition and covers a technological gap in the developed systems and the lack of parameterization of the reflex, which led to partial exploitation of pupillography up to now.

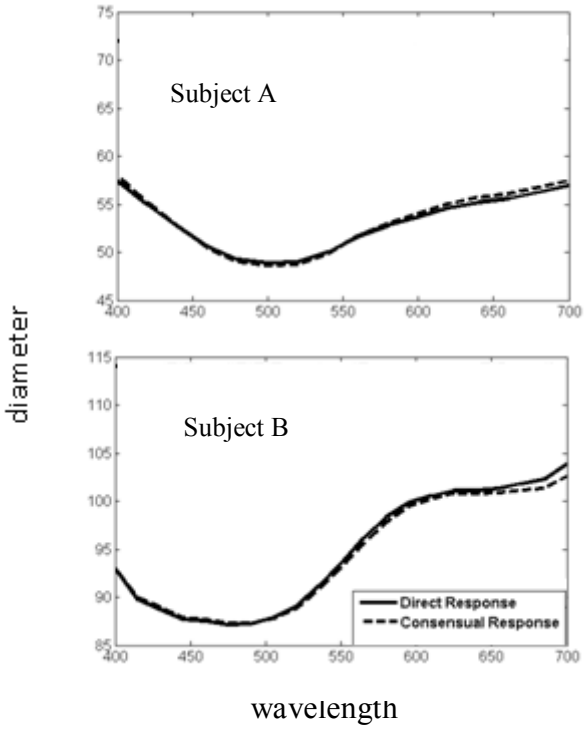

Figure 2. Maximum pupil constriction on each wavelength.

There are many cofounding influences on the subject's pupil diameter that would be incorrectly attributed to the light stimulus, such as fluctuations on the pupillary responses to light stimuli of similar intensities from day to day in the same individual, or the fact that pupillary diameter can be significantly influenced by non-photic phenomena such as changes in accommodative state, changes in state of arousal or cognitive activity [13]. Also, pupil mobility is driven by opthalmological and neurological factors respectively, which must be considered on the resulting pupillograms.

This implies that rigorous studies should be conducted on the population to establish the pupillometric indexes as meters of brain and ANS functionality.

This study is expected to establish new diagnostic pupillometric indices through the binocular study of PLR in narrow spectral bands and the quantitative lateralization of PLR. Furthermore it will provide a new, more effective approach for addressing the needs of several, neurological conditions related to disorders of the retina and the ANS. It will also provide a new insight to the pathophysiology of diseases, by selective stimulation of retinal photoreceptors, corresponding to a wide range of frequencies. This innovative approach will enable the identification of the optimum light frequencies at which the maximum diagnostic information is obtained. This is expected to maximize the signal-to-noise ratio and the reliability of the associated diagnostic test.

The device developed is currently being tested on normal population, in order to establish the healthy pupillometric indices and is about to be tested in clinical environment to establish the pathological pupillometric indices on numerous diseases.

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