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Discrimination Between Healthy and Glaucomatous Subjects with TD-fNIRS.

R. Re*[1,2], D. Messenio[3], G. Marano[4], L. Spinelli[2], I. Pirovano[5], D. Contini[1], R. Colombo[3], P. Boracchi[4], E. Biganzoli[4,6], R. Cubeddu[1], and A. Torricelli[1,2]

[1]Dipartimento di Fisica, Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milan, Italy; [2]Istituto di Fotonica e Nanotecnologie, Consiglio Nazionale delle Ricerche, Piazza Leonardo da Vinci 32, 20133 Milan, Italy; [3]Eye Clinic, Department of Clinical Sciences, ASST Fatebenefratelli Sacco, University of Milan, Milan, Italy; [4]Laboratorio di Statistica Medica, Biometria ed Epidemiologia "G.A. Maccacaro", Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Via Vanzetti 5, Milan, Italy; [5]Istituto di Tecnologie Biomediche, Consiglio Nazionale delle Ricerche, via Fratelli Cervi 93, 20090, Segrate (MI), Italy; [6]Unità di Statistica Medica, Biometria e Bioinformatica, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Via Vanzetti 5, Milan, Italy.
rebecca.re@polimi.it

Abstract: In this TD-fNIRS study on 98 subjects, primary open angle glaucoma patients have an involvement of the occipital (visual) cortical region; we assess the best fNIRS parameters for discriminating between glaucoma patients and healthy subjects.

1. Introduction

Glaucoma is an optic neuropathy where the patients have a progressive loss of retinal ganglion cells, changes in optic disk morphology and visual field defects. Intraocular pressure (IOP) is a recognized risk factor for the development of this disease, but alone does not explain the glaucoma pathogenesis. Recently, clinical and experimental studies demonstrated that there is also an associated neurodegeneration up to the visual cortex [1]. In this work, we evaluate the involvement of the visual brain regions in glaucomatous patients with the employment of time domain (TD) functional near infrared spectroscopy (fNIRS). This non-invasive optical technique allows to monitor the brain hemodynamics during the presentation of visual stimuli to the subjects enhancing the signal coming from the cortex, removing the systemic confounding effects. Furthermore, the aim of this work was to find which are the best fNIRS parameters for the assessment of the differences between the healthy population and glaucomatous patients in terms of cerebral activation.

2. Material and methods

The present study was approved by the Sacco Hospital Medical Ethical Committee (n.0018034, 07/07/2015) and by the Ministry of Health (DGDMF.VI/P/I.5.m.i.2/2015/1022) and was conducted in compliance with the Declaration of Helsinki. All the enrolled subjects (98) went through a complete clinical examination and were classified according to typical papillary and perimetric changes as: healthy (NORM), and glaucoma patients (GLAUCOMA). A visual pattern reversal checkerboard (check size 1.13 cm side, reversal frequency 10 Hz, 130 cm distance screen-eye) was presented to the subjects, which were looking at the screen with one eye at a time. The protocol consists of 30 s of initial baseline and 5 repeated cycles of visual stimulation (10 s rest, 10 s visual stimulus, 10 s recovery). The TD-fNIRS medical device employed is extensively described in Re *et al*. [2]. The injection optode was placed on OZ, while the detection ones on O1 and O2 positions, according to the 10-10 EEG electrodes positioning system. The acquired photon distributions of time-of-flight were fitted with the solution of the diffusion equation for a semi-infinite homogeneous medium, after being convolved with the instrument response function. From the retrieved absorption and reduced scattering coefficients the photon pathlengths in a two-layer medium, were calculated and used to estimate the variations of the cortical O_2Hb and HHb concentration as described in Zucchelli *et al*. [3]. The O_2Hb and HHb time courses were then fitted with a canonical hemodynamic response function (HRF) [4], to determine the response amplitudes A_{O2Hb} and A_{HHb}, and latencies with respect to the stimulus onset τ_{O2Hb} and τ_{HHb}, for O_2Hb and HHb respectively.
Statistical analysis was performed to assess the ability of these parameters in assessing differences between NORM and GLAUCOMA eyes. The distributions of the values observed for the different parameters were summarized using medians and quartiles and graphically represented with boxplots. For each parameter, the relationships with the pathological classifications were assessed by logistic regression models with binary response variable (assuming the values: 1 for GLAUCOMA eyes, 0 for NORM eyes). We also employed logistic models including specific functions of the means of the parameters above: simple and absolute value for the difference ($\tau_{O2Hb} - \tau_{HHb}$) and for the ratio (A_{O2Hb}/A_{HHb}). For each of the previously mentioned models, the association of the TD-fNIRS parameters with eye pathological classification was evaluated through the estimated Odds Ratio (OR) with respective 95% confidence intervals (C.I.), and by the Wald test (Chi-square distribution), applying the proper corrections. The

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discriminating ability of TD-fNIRS parameters was assessed using the concordance index c [5]. The discriminant ability was deemed statistically significant when the confidence intervals of the concordance index did not include the value of 0.5.

3. Results

The number of subjects included in the statistical analysis (after signal and clinical evaluation) was 86, classified as: 31 NORM, 43 GLAUCOMA, and 12 "mixed subjects", where the two eyes did not have the same classification. The single eye's signal and extrapolated parameters were evaluated; after this check it was necessary to exclude some single eye's acquisition having 168 eyes and 336 hemispheres as final result. The eyes were then classified as: 73 NORM and 95 GLAUCOMA.

The baseline optical properties found for the occipital brain cortex are for the absorption coefficients: μ_a= 0.15±0.04 cm^{-1} @687 nm and μ_a=0.14±0.03 @826 nm for the NORM, and μ_a= 0.13±0.04 cm^{-1} @687 nm and μ_a=0.13±0.03 @826 nm for the GLAUCOMA subjects. Similarly, for the reduced scattering coefficients, we found: μ_s'= 10.0±1.5 cm^{-1} @687 nm and μ_s'= 8.7±1.4 @826 nm for the NORM, and μ_s'= 9.9±1.8 cm^{-1} @687 nm μ_s'= 8.7±1.6 @826 nm for the GLAUCOMA subjects.

In Fig.1 we show the distributions of A_{O2Hb} and A_{HHb} parameters as obtained from the HRF fitting. The medians of the amplitudes are closer to 0 μM for glaucomatous eyes as compared to healthy ones particularly for A_{O2Hb}. No clear patterns are visible for the latencies τ, instead.

For A_{O2Hb}, the estimated ORs, ranging from 0.32 to 0.53, indicate negative association, and this is supported by statistically significant test results in every case (p-values ranging from 0.0091 to 0.0458). For A_{HHb}, the ORs estimates range from 3.31 to 12.63, indicating an overall positive association. The association was statistically significant only for the measurements in the right hemisphere (p=0.0174). Concerning the discriminant ability, the estimates of the concordance index for both the peak amplitudes range from 0.677 to 0.707, and are significantly greater than 0.5 (no discrimination) in every case, as shown by the respective 95% C.I.s found. On the contrary, no significant association with pathological classification was found for τ_{O2Hb} and τ_{HHb}, and the estimated ORs are very close to one (from 0.89 to 1.05). The discriminant ability was not significantly higher than 0.5.

For the simple difference ($\tau_{O2Hb} - \tau_{HHb}$) no significant association with pathological classification was found, and the discriminant ability was non-significantly greater than 0.5. A significant association was found for the absolute difference $|\tau_{O2Hb} - \tau_{HHb}|$ for records at the left hemisphere (OR=1.27, p=0.0027) and for the contralateral one (OR=1.22; p=0.0049). These results suggest that the distance between τ_{O2Hb} and τ_{HHb} latencies could be tendentially higher in glaucomatous eyes as compared to healthy eyes. The association for A_{O2Hb}/A_{HHb} was weak (OR ranging from 0.99 and 1.05) and, overall, not significant.

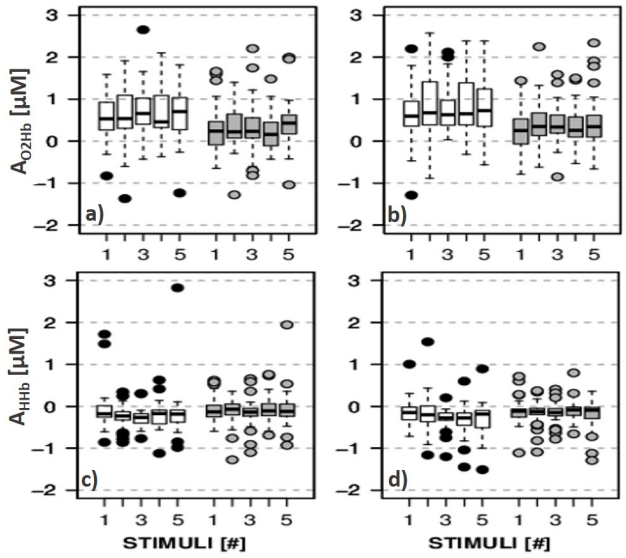

Fig. 1. Distribution of A_{O2Hb} and A_{HHb} over the 5 stimuli for the vision with the left eye. In white the NORM eyes, in grey the GLAUCOMA eyes. Panel a) and c): left hemisphere; panel b) and d): right hemisphere.

3. Conclusion

In this work, we performed TD-fNIRS acquisitions on the occipital cortex on 98 glaucomatous subjects during visual stimulations. We evaluated parameters derived from fitting of the HRF, i.e. the amplitudes and the peak latencies after the stimuli onset of O_2Hb and HHb signals. Our statistical analysis shows that the best parameters in the assessment of differences between healthy and glaucomatous patients are O_2Hb and HHb amplitudes, which are smaller in glaucomatous eyes compared to the healthy ones. To the best of our knowledge, this is the first fNIRS study with a significant large number of subjects, where it was possible to demonstrate an involvement of the occipital (visual) brain area in this pathology and the specific assessment of a marker for underlined the differences of glaucomatous patients with respect to a healthy population.

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