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Functional Transcranial Doppler (fTCD) investigation of brain lateralization following visual stimuli*

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***Abstract*—This preliminary investigation of the local cerebral perfusion evaluated by Transcranial Doppler (TCD) monitoring of the Posterior Cerebral Arteries shows that selective stimulation of visual hemifields evokes significantly different vascular responses. TCD can therefore allow for functional evaluation of lateralized enhancements in cerebral metabolism.**

***Clinical Relevance*—The cerebral lateralization evaluated with the functional TCD can be a useful and low-cost approach to evaluate the effectiveness of the rehabilitation therapy in post stroke subjects experiencing hemianopia or to assess cerebral reorganization after cerebrovascular accidents.**

I. Introduction

The cerebral blood flow (CBF) is regulated by the vasodilation and vasoconstriction of the cerebral arteries, that determines an increase or decrease in blood perfusion in the cerebral area they supply. The cerebral activity can be estimated by measuring the cerebral flow velocity (CBFV) of the main cerebral arteries, which is closely linked to cerebral metabolism and cerebral function. Accordingly, the functional Transcranial Doppler (fTCD) can be used to analyzes brain activity. The proportionality between changes in CBFV and in CBF holds as long as there is no change in arterial diameter at the point of insonation [1].

Many studies have used fTCD to estimate brain activation and lateralization. Various tasks were used such as tactile [2], visuo-spatial [3]-[4], cognitive [5], word generation and language [6]-[7], search and visual memory [8].

Regarding visual stimulation, lateralization of responses has been little investigated. Aaslid in [9] reported the correlation between the visual stimulation (white light) and the hemodynamic response of the posterior cerebral artery (PCA). In fact, the visual cortex is an excellent brain area to this purpose as it occupies a large and well-defined part in the brain and is supplied by the PCA which is easily insonated with the TCD. For the clinical use, the PCA can be divided into four segments (P1-P4). In particular, P1 is the shortest and most proximal segment and P2 begins at the anastomosis with the posterior communicating artery and is the longest segment.

Other studies have combined the fTCD and the visual stimulation. Wiedensohler et al. [10] evaluated the correlation between the mean flow response and the pulsatilly index of the P2 segment of PCA using an altering chessboard and complex stimuli; Gomez et al. [11] investigated what frequency in photonic stimulation produces the largest response and Leacy et al. [12] used a strobe light stimulus in P2 to evaluate the age and sex contribution to the hemodynamic response.

To our knowledge, cerebral lateralization of the hemodynamic response to hemifield visual stimulation has never been evaluated using the fTCD.

This study aims at investing the lateralization of the visually evoked flow response (VEFR) to selective stimulation of the right and left hemifields vs. full field stimulation, and its relation to ocular dominance. To this purpose, we used the inversion of the checkerboard pattern as standardized visual stimulus and bilateral monitoring of the left and right PCAs.

II. Material and Methods

A. Participant and Setting

The study has ethics approval from the ethics committee of the University of Torino (n. 219859, April 2021). Twelve healthy subjects (20-54 years old range; three women, nine men) participated in the study after giving informed consent, however only data from nine subjects were used to determine lateralization, due to unsuccessful bilateral monitoring in three subjects. The volunteers had no history of cerebral vascular disease or visual impairment. The experiment was made in a dark and quiet room with the subject seated in a comfortable chair, with the chest against the table to avoid trunk movement, in front of the screen (63x35 cm^2) placed at 50 cm.

The inversion of the black-and-white checkerboard pattern (20x10 checks in full field stimulation) at a frequency of 10Hz was adopted as visual stimulus and delivered in three modes: bilateral, left hemifield only and right hemifield only, obtained by extending the checkerboard over the full screen or limiting it to left or right half-screen, respectively. Stimulation, in each of the three modes, was delivered 5 times to each subject, alternating 30 s of rest (black screen) and 30 s of visual stimulation. Subjects were asked to close their eyes in the rest phase and to keep their attention on the red dot in the center of the screen during the activation phase.

The subject's ocular dominance was determined with the Point-Test. In case of doubt the dominance was tested also with the Miles, Hole-in-Cord and Brock-String test.

An acoustic cue (100 Hz tone of 500 ms duration) was given to indicate beginning and end of visual stimulation.

Data acquisition was started after a period of relaxation of one minute in order to stabilize the blood flow velocity of the two arteries. The sequence of the three stimulation modes was randomized for each participant.

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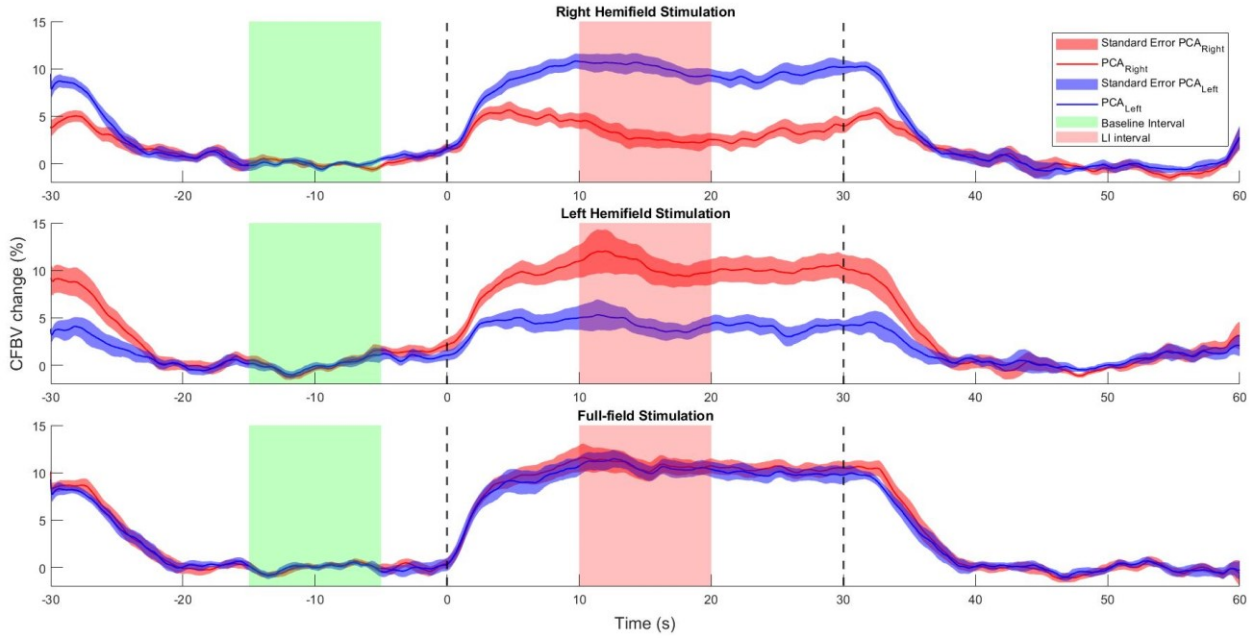

Figure 1. Mean curve of all subjects of the Right-blood flow velocity of PCA (in red) and Left- blood flow velocity of PCA (in blue) in the different trials. Note that the last 30s are the rest-phase (in eyes closed) before the next trial.

B. Recording

Cerebral blood flow velocity (CBFV) from the two posterior cerebral arteries (PCA, segment P1) was measured using a helmet with two 2 MHz motorized probes (Dolphin/XF Robot - Viasonix) connected to the TCD instrument (TCD module; Dolphin/IQ – Viasonix).

To find the PCA signal, the middle cerebral artery (MCA) and the ACA/MCA bifurcation were first identified. Then the transducers were aimed posteriorly and inferiorly and the depth was increased to 60-70 mm. The numerical values of the mean velocity, lower than the MCA, and the direction of the flow allowed to identify the P1 segment of the PCA. Ipsilateral carotid compression was applied [13].

Bilateral PCA insonation was achieved in all subjects, except for the left PCA in two subjects and for the right PCA in one subject. The outline of the spectral envelope (maximum frequency) of the Doppler signals was recorded with a sample rate of 100 Hz and stored for off-line data analysis and post-processing.

C. Analysis

Data analysis and post-processing were carried out by using Matlab software (MathWorks, Natick, MA, USA).

Firstly, the data were smoothed with a moving average filter and the high frequency noise was filtered out by a low-pass filter with a cutoff frequency of 20Hz. Subsequently, individual cardiac cycles were identified in CBFV signals to calculate instantaneous heart rate and to calculate average CBFV on a cycle-by-cycle basis [14]-[15] so that the cardiac pulsatility was removed and average CBFV trend remained.

The data was segmented into epochs synchronized with the stimuli, each epoch starting 30 s before the acoustic cue (the stat of the visual stimulus, t = 0 s) and terminating 60 s after. In each epoch, a 10 s baseline interval [-15, -5] s is defined in the resting phase, before the visual stimulus, and a 10 s interval, [10, 20] s after the beginning of the stimulus, was defined to quantify the effect during visual stimulation (this interval was chosen because it is the time-period in which there is a greater VEFR in all three modes). Accordingly, the averages of CBFV over these two intervals were computed to represent baseline (V_B) and stimulation (V_S).

The VEFR was then quantified as % change from baseline:

$$\Delta V\%\,(t) = \frac{V_S(t) - V_B}{V_B} \cdot 100. \qquad (1)$$

Also, for graphical presentation of the time courses, the CBFV tracings in each epoch were normalized to (V_B), to remove the dependence of the measurement angle and diameter of artery and to permit the comparison between the different subjects. Then (V_B) was subtracted from the normalized tracing and multiplied by 100, so that each point in the tracing expressed the percentage change from the baseline [16].

For each subject the epochs corresponding to the 5 responses to the repetition of the same stimulus were averaged, thus obtaining the average CBFV response of the right and left PCA to that stimulus (ΔVr% and ΔVl%, respectively).

A lateralization index (LI), described by equations (1) and (2), was estimated to quantify the difference between right and left PCA responses to a given stimulus.

$$LI = \Delta Vr\% - \Delta Vl\%. \qquad (2)$$

The lateralization index expresses how much CBFV right is larger than CBFV left in terms of % of baseline.

It was calculated when both eyes are simultaneously exposed to the same stimulation mode (full field (FF), right hemifield (RH), left hemifield (LH)). In addition, it was also calculated when the hemispheres are concerned by the same stimulus: contralateral (CL), ipsilateral (IL) or bilateral (BL) stimulation. For example, LI_{CL}, is calculated from the right

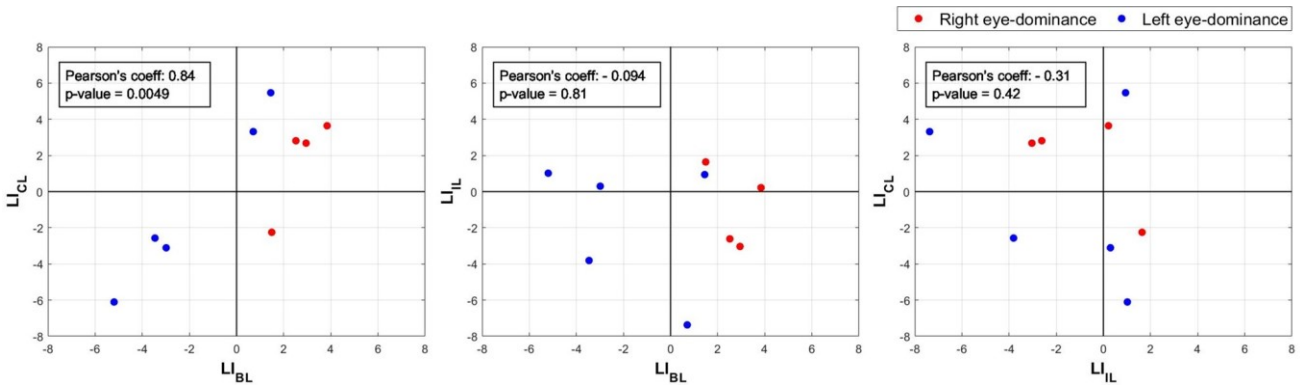

Figure 2. Correlations of lateralization index calculated for the different modalities: bilateral, contralateral, or ipsilateral. The Pearson's value and the p-value are reported in each plot. Individuals presented right (red) or left (blue) ocular dominance.

PCA response to left hemifield stimulation and the left PCA response to right hemifield stimulation (obviously recorded at different times), see Appendix. LI_{BL} coincides with LI_{FF}.

D. Statistics

Statistical analysis was performed on the lateralization index of all subjects in which both right and left CBFV were measured (n = 9). In each stimulation mode, a one-sample t-test was applied to determine whether LI was significantly different from zero. This statistical test was used after verifying the normality of the data.

III. Results

For each stimulation mode, the mean CBFV responses from the left and right PCAs were obtained averaging over all the subjects (Figure 1).

Bilateral visual stimulation (Full-Field stimulation) causes a similar CBF increase in the two hemispheres. On the contrary, a larger increase in the contralateral vs. ipsilateral CBFV was observed in response to both right and left hemifield stimulations (the maximal lateralization indexes and its standard error in the chosen interval are LI_{RH}=7.98±1.21, LI_{LH}=6.99±1.22, LI_{FF}=0.831±0.633).

Statistical analysis was used to determine whether the increased difference between the arteries of the two hemispheres was significantly different from zero. A p-value less than 0.05 was considered as statistically significance level. LI is significantly different from zero, i.e. the two arteries significantly differ from each other, for trials where a single visual hemifield is stimulated ($p\text{-value}_{RH}= 1.38\cdot10^{-5}$, $p\text{-value}_{LH}=3.73\cdot10^{-4}$), and not in the case of full field stimulation ($p\text{-value}_{FF}= 0.894$).

Although on average the LI to bilateral (full field) stimulation was not significantly different from 0, there was some individual variability. It is interesting to observe that the individual LI to bilateral stimulation is well correlated with LI to contralateral (Figure 2, left) but not ipsilateral stimulation (Figure 2, middle). Accordingly, LI in contralateral and ipsilateral stimulation also appear uncorrelated (Figure 2, right). Moreover, the distribution of LI appears to be dependent on ocular dominance: the 4 subjects with right ocular dominance present the highest LI_{BL}values (Cohen's Kappa = 0.571)

IV. Discussion and Conclusion

According to what expected from the functional splitting of visual pathways through the optic chiasm, which makes stimuli from the right visual field to be projected to the left occipital cortex and vice versa, the present results indicate a greater CBFV increase in the contralateral than in the ipsilateral PCA in response to single hemifield stimulation, and a similar response of the two arteries to bilateral stimulation.

The observed magnitude of increase is around 10%, for both bilateral and contralateral stimulation. Some studies reported responses about twice as large [10]-[11]. This difference can be justified by the fact that in our study we insonated the P1 rather than the P2 segment of the PCA. In general, the P2 branches have a most pronounced CBFV increase to visual stimuli compared to the P1 segment [17]. However, responses of lower magnitude were also reported in the P2 segment (8-13%), which might be attributed to the fact that subjects were stimulated with a lower stimulus frequency (1 Hz) [18]. The greatest responsiveness is obtained with a frequency of 10-20Hz [11].

The results showed that individuals may exhibit some lateralization of the hemodynamic response to bilateral stimulation (LI_{BL}). Given that most of the excitation of the visual cortex comes from the contralateral hemifield, the good correlation between LI_{BL} and LI_{CL} indicates that the result is consistent. It seems also that this lateralization may be affected by ocular dominance, as the 4 subjects with right ocular dominance all had positive LI_{BL} and actually scored the 4 highest LI_{BL} values (Figure 2, left). However, this preliminary observation needs to be confirmed over a sample of larger size.

As expected, the hyperaemia induced by ipsilateral stimulation is of lower magnitude than by contralateral.

The hyperaemia on the ipsilateral side of the single hemifield stimulation could be related to the ipsilateral activation of the extrastriate visual cortex of healthy subjects as demonstrated with the study of Nelles et Al. [19]-[20] conducted with functional magnetic resonance imaging (fMRI). They found a bilateral activation of the extrastriate visual cortices and an activation of the primary cortex contralateral to the stimulated side (in healthy subjects). Interestingly, the hyperaemic response of the ipsilateral side appears to lack a dependency on ocular dominance and does

not seem to add to the contralateral during full field stimulation, i.e. the response to full field stimulation is lower than the sum of contra- and ipsilateral hemifield stimulation. Further investigations are necessary to understand the ensuing implications.

Functional TCD, although with a much lower spatial resolution than fMRI, could be a less expensive (< 20,000 €) and easily movable alternative allowing robust methods to evaluate the activations of brain areas. In fact, some studies addressed this issue by combining different methods such as fTCD and electroencephalogram (EEG) [21]-[23].

The assessment of cerebral lateralization evaluated with the fTCD can be an additional feature in supporting and monitoring rehabilitation in post stroke subjects [24]-[25] or to understand cerebral reorganization after the cerebrovascular accident, especially for patient which experienced hemianopia, which accounts for the majority of visual deficits following infarction of the PCA, in alternative to MRI [19].

APPENDIX

The different expression of Lateralization Index described in Methods and used for the Figure 2.

$$LI_{CL} = \Delta Vr\%_{LH} - \Delta Vl\%_{RH}$$

$$LI_{IL} = \Delta Vr\%_{RH} - \Delta Vl\%_{LH}$$

$$LI_{BL} = LI_{FF}$$

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