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Non-invasive assessment of hemispheric language dominance by optical topography during a brief passive listening test: A pilot study

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: The Wada test is usually used for pre-surgical assessment of language lateralization. Considering its invasiveness and risk of complications, alternative methods have been proposed but they are not always applicable to non-cooperative patients. In this study we explored the possibility of using optical topography (OT) – a multichannel near-infrared system – for non-invasive assessment of hemispheric language dominance during passive listening.

Material/Methods: Cortical activity was monitored in a sample of healthy, adult Italian native speakers, all right-handed. We assessed changes in oxy-haemoglobin concentration in temporal, parietal and posterior frontal lobes during a passive listening of bi-syllabic words and vowel-consonant-vowel syllables lasting less then 3 minutes. Activated channels were identified by *t* tests.

Results: Left hemisphere showed significant activity only during the passive listening of bi-syllabic words. Specifically, the superior temporal gyrus, the supramarginal gyrus and the posterior inferior parietal lobe were activated.

Conclusions: During passive listening of bi-syllabic words, right handed healthy adults showed a significant activation in areas already known to be involved in speech comprehension. Although more research is needed, OT proved to be a promising alternative to the Wada test for non-invasive assessment of hemispheric language lateralization, even if using a particularly brief trial, which has been designed for future applications with non-cooperative subjects.

key words: language lateralization • optical topography • non-invasive assessment

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BACKGROUND

The Wada test [1] has been used since the early 1960s for pre-surgical assessment of language lateralization. It consists of an injection of amobarbital into the left or right carotid artery of the patient to temporarily deactivate cerebral activity in the ipsilateral perfused hemisphere. This procedure is followed by a neuropsychological test to identify the actual language lateralization, which is recognized in the anaesthetized hemisphere if the patient fails the test. Despite its validity and reliability, this technique is considered invasive, with a complication rate of up to 10% [2] and not applicable with less cooperative patients such as young children or patients with cognitive deficits, mental retardation or behavioural disorders [3].

Different techniques have been studied and proposed as possible alternatives to the Wada test in order to determine language lateralization with less invasiveness [4]. The first studies on repetitive transcranial magnetic stimulation date back to the 1990s [5], but this technique was poorly tolerated by patients [6]. Other less-invasive methods such as positron emission tomography [7], or non-invasive methods such as functional magnetic resonance imaging or fMRI [8–10] have been used as alternatives to the Wada test. However, neither technique is easily applied to young children or patients with cognitive or behavioural problems [3], as subjects must stay motionless in the scanner. Additional non-invasive alternatives are magnetoencephalography [11,12], functional transcranial Doppler [13], and high-density electroencephalography recordings [14], although such techniques need to be further validated for clinical applications [6].

Near-infrared spectroscopy (NIRS) has also been proposed as a non-invasive alternative to the Wada test, showing its feasibility to assess language dominance [15,16] also when applied to non-cooperative patients [3], even if in the latter case the task lasted more then 20 minutes. NIRS provides functional brain imaging by monitoring cerebral oxygenation and hemodynamics induced by brain activity a few centimetres below the scalp. Optical imaging of the human brain is possible because there is a window of transparency of biological tissue to light in the near-infrared spectrum [17]. Light in the 650–1000 nm wavelength range is absorbed by haemoglobin, so that absorption spectroscopy can be used to measure oxy-haemoglobin (HbO_2) and deoxy-haemoglobin (Hbb) concentration changes in the brain, reflecting cortical activation. Total haemoglobin (HbTot) concentration changes can be indirectly derived by summing HbO_2 and Hbb. HbO_2 variations are considered an estimate of cerebral blood flow (CBF), and HbTot variations an estimate of cerebral blood volume (CBV) [18]. NIRS is relatively resistant to movement artefacts [19,20] and does not require strict motion restriction during measurements [21]. Additionally, the technique has proved to be safe [22] and is easily portable. The main disadvantage of this method is that detection is limited to the cortical surface [23]. NIRS utilizes 1 or more pairs of optical fibres (or optodes) emitting and detecting near-infrared light to assess cerebral activity, and the area between each pair of emitter and detector is called channel. Optical topography (OT), a multichannel NIRS system, has markedly improved spatial resolution while maintaining its very high temporal resolution [24].

Table 1. The passive listening task.

1. W 25 SEMPRE (*ALWAYS*)
2. W 15 PIENO (*FULL*)
3. V 25 AFA
4. W 15 TUTTI (*ALL, plural*)
5. V 15 AVA
6. V 25 AGA
7. W 25 DIETRO (*BEHIND*)
8. V 15 ARA

The sequence of verbal stimuli constituting the passive listening stimulation (W – bi-syllabic word; V – vowel-consonant-vowel syllable). Numbers indicate the inter-stimulus interval, in seconds, following each stimulus.

In this study we tested the possibility of using OT as a non-invasive method to assess and map language lateralization during a test that reduced both procedure duration and participant's involvement in the test. Our aim was to assess the feasibility of this simplified approach as a first step prior to considering possible applications in non-cooperative populations who could present difficulties in longer and more involving procedures. To this end we studied bilateral cortical activations in healthy adults associated with passive listening for less than 3 minutes.

MATERIAL AND METHODS

Participants

A total of 12 healthy adults (9 females, 3 males), aged between 25 and 48 years (mean: 31.5±5.9), were enrolled in the study. They were Italian native speakers and right-handed since infancy, as assessed by the Edinburgh Questionnaire (score range: 43–95) [25]. Possible auditory disorders were excluded by audiological assessment before study enrolment. Data were collected between September and October 2009. Written informed consent was obtained from each participant after full procedural and technical explanation of the experiment. The ethics committee of the "Burlo Garofolo" Hospital in Trieste (Italy), where all the testing was conducted, granted permission.

Verbal stimulation

The stimuli used in the experiment were randomly extracted from the Italian version of the Speech Audiometry Test [26]. We selected 2 complexity levels of verbal stimulus: Italian bi-syllabic words and vowel-consonant-vowel syllables. We randomly extracted 4 stimuli for each verbal category from 200 possible bi-syllabic words and 240 possible vowel-consonant-vowel syllables. A randomized list of 8 verbal stimuli was then created and read by a male voice without dialect inflexions. Each stimulus category could not be repeated in sequence more than twice. Every stimulus followed the previous one after a period of silence of 15 or 25 seconds (inter-stimulus interval). The silent periods had varying durations to avoid synchronization between stimuli occurrences and periodic variations in the autonomic regulation of CBF [27] and were randomly assigned during the stimuli sequence. We avoided the repetition of an inter-stimulus interval of the same duration more than twice. The resulting list (Table 1) was used for the passive listening

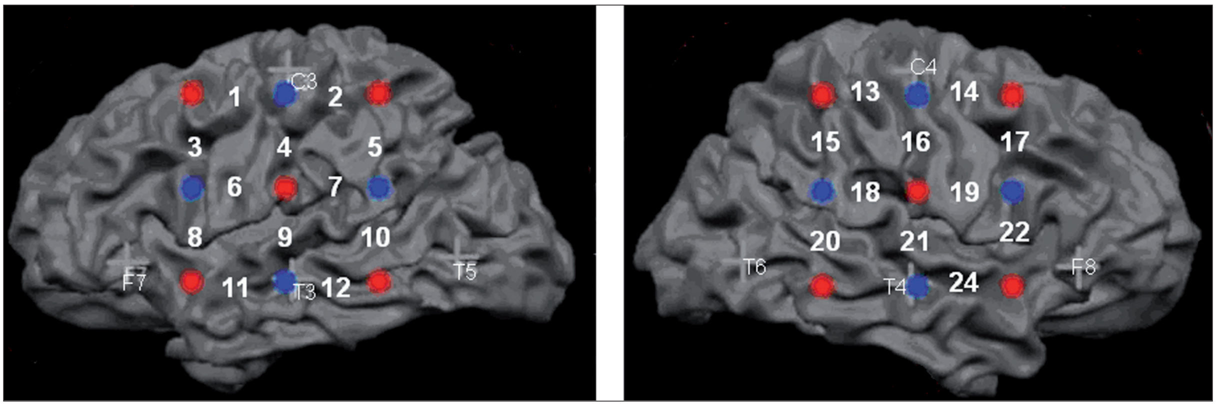

Figure 1. Probe placement on the left and right hemisphere. Red dots: near-infrared light emitters; blue dots: near-infrared light detectors; numbers 1–24 indicates channels and their localization on the cortex.

test and presented through a computer as a continuous sequence of MP3 files, managed by MEL Professional software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Its total duration was 160 seconds.

Optical topography recording

Cortical activity associated with verbal stimulation was detected non-invasively using the Hitachi ETG-100 OT device (Hitachi Medical Corporation, Tokyo, Japan). It records simultaneously from 24 channels on the cortex, which mostly measure vascular changes from its cortical surface, about 2 cm below the scalp [15,23]. The ETG-100 emits near-infrared light at 2 wavelengths, 780 and 830 nm, and their intensity is modulated at different frequencies ranging from 1 to 6.5 kHz. The reflected light is sampled once every 100 ms and is separated into 2 modulated signals, 1 for each wavelength, by a number of corresponding lock-in amplifiers. After analog-to-digital conversion, the signals are transferred to a computer. These measures allow estimation of changes in the concentration of HbO_2, Hbb and HbTot in response to stimulation. Changes are reported as mM·mm, that is the product of the haemoglobin concentration changes expressed in millimolar and the optical path length expressed in millimetres.

We used 2 plastic holders to keep optical fibres in place, each containing 9 optodes of 1 mm in diameter. Of the optodes in each holder, 5 were emitters and 4 were detectors, arranged in a 3 x 3 pattern, providing 12 channels per hemisphere. The distance between adjacent emitters and detectors was 3 cm. Since the regions of interest (ROI) of this study were the cortical areas associated with language, 1 holder was placed over the left hemisphere, covering the temporal, parietal and posterior frontal lobes and another holder was placed over the same areas of the right hemisphere. This arrangement allowed us to include most parts of the cortex involved in language processing [28–30]. In order to have a reliable cranio-cerebral structural correlation, fibre holders were placed using the international 10-20 EEG system of electrode placement [31]. The central optode of the inferior channel row of each holder was placed over T3 on the left side and over T4 on the right side (Figure 1), maintaining in both cases the central channel column of holders on the virtual line joining T3 with C3 (left) and T4 with C4 (right). When the holders were positioned, it was ensured that the fibres touched the subject's scalp. The OT device automatically detected whether the contact was adequate to measure emerging photons.

Procedure

NIRS data were acquired during passive listening of the verbal stimuli list described above. Subjects were tested in a dark and sound-proof room and were seated in front of a computer (Vectra VL, Hewlett Packard Company, Palo Alto, CA, USA) connected to 2 loudspeakers (Arena™–530, Labtec®, Inc., Vancouver, WA, USA), with 1 located on either side of the computer and both positioned centrally with respect to the participants. Verbal stimuli were presented at the acoustic intensity of 60 Sensation Level (SL) dB. Participants stayed at a distance of 90 cm. from the loudspeakers, and were blindfolded, to limit, as much as possible, stimulations other than auditory. The instructions given to the subjects were: "*listen in silence to what will be said to you*". After having correctly positioned the blindfold and the fibre holders and checked signal adequacy, the test began and ended 170 seconds later (including total duration of the passive listening test plus 10 seconds of silence that preceded the presentation of the first stimulus). The entire experimental procedure lasted no more than 10 minutes for each participant.

Data analysis

Our analyses focused on the variation of HbO_2, which estimates CBF changes in activated brain areas [18]. Possible components of the HbO_2 signal related to slow CBF fluctuations and heartbeat noise were removed by bandpass filtering between 0.02 and 1 Hz. In order to prevent movement artefacts, a filter was used to remove detections with rapid changes in HbO_2 concentration (signal variations >0.1 mM·mm over 2 consecutive samples). We also visually inspected the signals recorded in each channel of all the subjects in order to detect low signal-to-noise ratios due to bad transmission of near-infrared light (e.g., due to hair interference). All trials in all channels were used for statistical processing because signal condition was good.

An event-related design was used, and significantly activated channels during passive listening were identified by means of Student *t* tests. In accordance to data analysis proposed in

Table 2. Channels surviving the FDR threshold (q=0.05) in association to bi-syllabic word stimulation.

Channels	Mean	SD	t(11)	p value
Channel 5				
Baseline	0.003	0.004	−2.833	0.008
Stimulation	0.012	0.014		
Channel 7				
Baseline	0.004	0.005	−3.075	0.0055
Stimulation	0.014	0.014		
Channel 9				
Baseline	0.004	0.009	−3.035	0.0055
Stimulation	0.011	0.004		
Channel 11				
Baseline	0.002	0.002	−3.787	0.0015
Stimulation	0.006	0.004		

Mean column reports the average HbO_2 variation during baseline and bi-syllabic word stimulation, expressed in mM·mm, and SD the respective standard deviation.

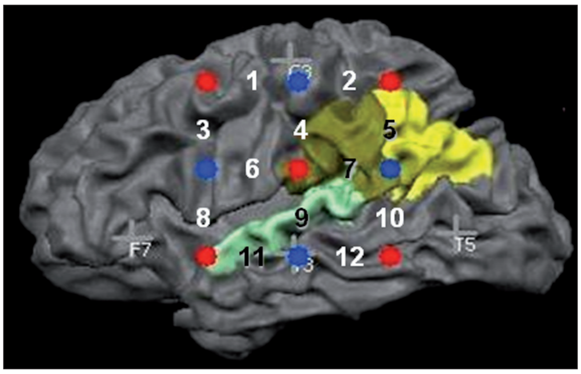

Figure 2. Cortical localization of channels significantly activated by passive listening of bi-syllabic words (P<FDR 0.05). Red dots: near-infrared light emitters; blue dots: near-infrared light detectors; numbers 1–12 indicate channels and their localization on the left hemisphere (channels found significantly activated are indicated in black). The superior temporal gyrus is showed in green, the supramarginal gyrus in brown and the inferior parietal lobe in yellow.

Homae et al. [32], for every channel in each 1 of the 2 conditions (bi-syllabic words and vowel-consonant-vowel syllables), an arbitrary baseline was calculated as the mean of relative HbO_2 changes in the 5 seconds before stimulus onset and in the 3 seconds between the 12th and the 15th second after its onset. The hemodynamic response was calculated as the mean change in HbO_2 concentration over the 12 seconds after onset of the stimuli. To identify the activated channels, we performed one-tailed paired t tests comparing the baseline and the hemodynamic response for every channel in each of the 2 conditions. In order to control Type I error in multiple testing situations, we used a false discovery rate (FDR) approach [33] that controls the proportion of false positives among the channels that are significantly detected. We selected a q value of 0.05, so that there were no more than 5% false positives (on average) in the number of channels showing significant contrasts.

To visualize the cortical areas covered by each channel, we used a software developed in our laboratory to localize on a brain template the regions of the cortex where fibres were positioned. We obtained the brain template from the program BrainVoyager Brain Tutor (website: *http://www.brainvoyager.com/bvtutor/setup_braintutor_v20.exe*) and adapted its size to the mean head size of our sample, based on a median bitragal distance of 33 cm, a median nasion-inion distance of 31 cm, and a median cranial circumference of 54 cm.

Results

All channels passing the FDR threshold (q=0.05) were: 1) located in the left hemisphere, and 2) associated with bi-syllabic word stimulation (Table 2). A significant activation was detected for channel 5 (p=0.008), located on the posterior inferior parietal lobe; channel 7 (p=0.0065), located on the supramarginal gyrus; and channel 9 (p=0.0065) and channel 11 (p=0.0015), both located on the superior temporal gyrus (Figure 2). Figure 3 shows the graphic representation of HbO_2 and Hbb values in the channels that were activated during passive listening to bi-syllabic words. There was no statistically significant difference during passive listening to vowel-consonant-vowel syllables.

Discussion

The results obtained in this study show that OT can identify a significant cortical activation in the left hemisphere, when adult, healthy and right-handed subjects listen to bi-syllabic words. Moreover, within the left hemisphere, there was a specific activation of several areas during passive listening to bi-syllabic words. Specifically, these areas were the superior temporal gyrus and the supramarginal gyrus, both already known to be involved in speech comprehension [28,29,34], and the posterior inferior parietal lobe, which may be part of the semantic memory system [35].

We found no significant cortical activation in association with vowel-consonant-vowel syllables. This may be due to failure of the NIRS technique to detect cortical activity during a very short stimulus. A verbal stimulation lasting 0.1 to 0.2 sec may be insufficient to elicit a vascular cerebral change

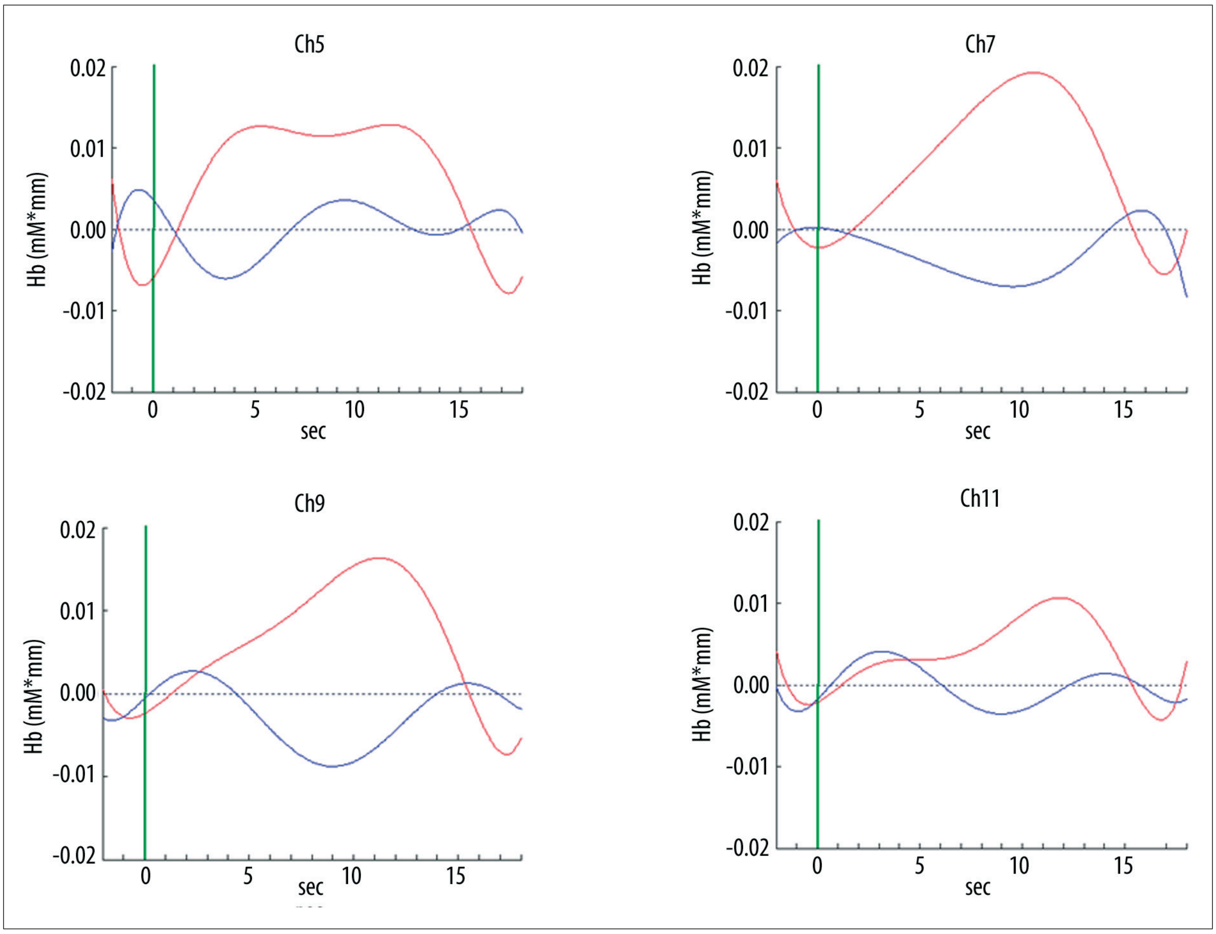

Figure 3. Graphic trends of HbO_2 (red line) and Hbb (blue line) during the passive listening of bi-syllabic words. The green vertical line indicates the onset of the stimuli. Time reported in seconds is on the x-axis and haemoglobin variations, reported in millimolar per millimeter of the optical path length, is on the y-axis.

identifiable by NIRS. Even if the bi-syllabic word stimulation did not last longer than 0.7 sec (the word was "sempre"), we speculate that such specific cues might have activated the semantic neural network that extracts meaning from verbal sound [35]. Then, the propagation of the cortical signal might have triggered hemodynamic changes of sufficient magnitude to be detected by the device. Cortical activity associated with passive listening to very brief verbal stimuli, such as single syllables, may be more appropriately assessed by neurophysiologic methods that can detect the bioelectrical activity in the brain (e.g., electroencephalography or event-related potentials).

It has already been determined that multichannel NIRS may be a feasible method for language dominance assessment in adults [15,36]. When applied to children or less cooperative persons, it has confirmed its potential of non-invasiveness and viability as well [3], although in that study the entire verbal task lasted more than 20 minutes and the installation of the optical fibres took approximately another 20 minutes. The hemispheric language dominance assessed by a NIRS system has also shown agreement with other techniques, such as the Wada test [15] and fMRI [37,38]. In our study we observed that OT can assess language lateralization with a simple and very brief passive listening test of bi-syllabic words, designed for future applications in children or non-cooperative persons due to its reduced invasiveness, duration and patient's involvement. Our listening test lasted less then 3 minutes and the entire assessment procedure (including test explanation to participants, fibres placement on head and the check of signal adequacy) took about 10 minutes. Our data analysis allowed us to map the cortical areas functionally associated with passive listening, namely the superior temporal gyrus, which includes Wernicke's area, the supramarginal gyrus and the posterior inferior parietal lobe.

Our study has some limitations. First, our findings need to be replicated in different populations, such as young children and persons unable to comply with more invasive (Wada test) or difficult (fMRI) procedures. Second, a validation of OT results by other non-invasive methods determining language lateralization with a passive listening test such ours is necessary. Third, OT may not be used in every patient, as individual differences in hair thickness may interfere with the test and significantly prolong the duration of the procedure.

Conclusions

The aim of this research was to explore the feasibility of OT to detect the hemispheric dominance for language using a simple and brief passive listening test designed for possible applications with non-cooperative patients. Although more studies are needed on this topic, OT has been shown to be a non-invasive, safe, quick, and promising method to detect language lateralization.

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