Original article

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Near-infrared spectroscopy as an alternative to the Wada test for language mapping in children, adults and special populations

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ABSTRACT – The intracarotid amobarbital test (IAT) is the most widely used procedure for pre-surgical evaluation of language lateralization in epileptic patients. However, apart from being invasive, this technique is not applicable in young children or patients who present mental retardation and/or language deficits. Functional magnetic resonance imaging (fMRI) is increasingly employed as a non-invasive alternative. Again, this method is more difficult to use with young children, especially hyperactive ones, since they have to remain motionless during data acquisition. The aim of this study was to determine whether near-infrared spectroscopy (NIRS) can be used as an alternative technique to investigate language lateralization in children and special populations. Unlike Wada test, NIRS is non-invasive, and it is more tolerant to movement artefacts than fMRI. In the present study, NIRS data were acquired in four epileptic children, a 12-year-old boy with pervasive developmental disorder and a 3-year-old, healthy child, as well as three healthy and two epileptic adults, while they performed a verbal fluency task and a control task. When applicable, the results were compared to the subjects' fMRI and/or IAT findings. Clear laterality of speech was obtained in all participants, including the two non-epileptic children, and NIRS results matched fMRI and IAT findings. These results, if replicable in larger samples, are encouraging and suggest that NIRS has the potential to become a viable, non-invasive alternative to IAT and fMRI in the determination of speech lateralization in children and clinical populations that cannot be submitted to more invasive techniques.

Key words: language, near-infrared spectroscopy, Wada, fMRI, children, presurgical evaluation, epilepsy surgery

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Until recently, the intracarotid amobarbital test (IAT or Wada test) (Wada and Rasmussen 1960, Rutten *et al.* 2002) has been the main and most widely used procedure for the exploration of language lateralization in epileptic patients destined for surgery. This procedure consists of separate sodium amytal injections into each of the carotid arteries through a transfemoral catheter (Loring *et al.* 1994, Smith 2001). The injection produces a temporary dysfunction in the ipsilateral cerebral hemisphere, lasting five to 12 minutes during which it is possible to assess language and memory functions of the contralateral hemisphere. Each hemisphere is tested separately. The results of language tests, administered during the procedure, provide a relatively reliable indication of language lateralization (Milner *et al.* 1962, Trenerry and Loring 1995, Rouleau *et al.* 1997).

However, the procedure has several limitations. Besides being very uncomfortable for the patient, the test does not provide precise information about language localization (Gaillard *et al.* 1997). Furthermore, it is time-constrained by the variability of the sodium amytal action (Binner *et al.* 1992), and its validity cannot be verified by means of test-retest studies (Boas 1999). In addition, the patients' altered level of consciousness and their behavioural and emotional reactions can obscure the results of this technique (Trenerry and Loring 1995). The procedure is particularly difficult to apply in young children (Williams and Rausch 1992) and patients with mental retardation, language and/or behaviour problems. This is an important limitation because early surgical intervention is crucial in many cases. Clinical evidence suggests that the younger the child, the more effective is the surgery (Engel 1987).

Since the advent and refinement of imaging techniques, functional magnetic resonance imaging (fMRI) (Gaillard 2000, Gaillard *et al.* 2004), magnetoencephalography (Papanicolaou *et al.* 2004) and positron emission tomography (Hunter *et al.* 1999, Kaplan *et al.* 1999) are increasingly used as non-invasive, or minimally invasive alternatives to IAT in many epilepsy centres. Again, these techniques are not easily applied in young children or patients with serious cognitive and/or behaviour problems, since the patients have to lie motionless in the scanner for relatively long periods. Furthermore, although some studies have successfully used overt verbal responses in the scanner (e.g., Palmer *et al.* 2001, Schlaggar *et al.* 2002), most experimental designs have employed silent paradigms to avoid movement artefacts. This requires not only that the child refrains from verbalization during data acquisition, it also renders it difficult to ensure that s/he is actually performing the mental task as instructed or at least is trying to do so.

Several studies suggest that near-infrared spectroscopy (NIRS) may be used to explore language lateralization (Watanabe *et al.* 1998, Kennan *et al.* 2002, Noguchi *et al.* 2002, Watson *et al.* 2004). NIRS is a relatively new technique, which allows the measurement of haemodynamic changes associated with neural activity (Villringer *et al.* 1993). The different light absorption spectra of oxy-haemoglobin (HbO_2) and deoxy-haemoglobin (HbR) within the near-infrared spectrum, allow for the measurement changes in the concentration of these substances in living tissues (Boas *et al.* 2001). Near-infrared light of a wavelength between 680 and 1000 nm is directed through optical fibres to the head of the patient. The amount of detected light reflects the amount of absorption of the two wavelengths in targeted cerebral areas (for review see Villringer and Chance 1997).

This technique has several advantages over other imaging methods (Gratton and Fabiani 2001a and 2001b, Villringer and Chance 1997). First, it allows measurement of independent concentration changes of HbO_2 and HbR. Second, the equipment is portable (Hintz *et al.* 2001, Liebert *et al.* 2005) and less costly than fMRI or PET. Finally, and most importantly, there are no major restrictions on movements or verbalization during recording, which renders the technique suitable for studies in mentally-challenged people as well as young children, and even infants (Wilcox *et al.* 2005). During data acquisition, the child is seated comfortably in a chair or on his/her mother's lap.

A potential disadvantage of this technique is the shallow penetration of the photons (between 3 and 5 cm), which renders it difficult or impossible to collect reliable data from subcortical structures and from individuals with a dense skull and/or thick, dark hair. Nonetheless, a spatial resolution below 1 cm can be obtained in most patients. Furthermore, the limited penetration should not have a major impact on studies investigating cortical areas, especially in children, who usually have a thinner skull than adults.

Although NIRS has already been successfully used to assess language laterality in healthy (Kennan *et al.* 2002, Noguchi *et al.* 2002) and epileptic adults (Watanabe *et al.* 1998, Watson *et al.* 2004), to our knowledge no study has employed this technique to determine language lateralization in epileptic children and clinical populations that cannot be evaluated with other techniques. The aim of the present study was to investigate the applicability of NIRS for the exploration of speech lateralization in a paediatric population that cannot be subjected to comprehensive language testing with the Wada test or fMRI. We used a very simple, verbal fluency task of the kind that has been employed in Intelligence Scales for young children (*i.e.* McCarthy, 1972). According to the norms of these scales, children as young as three years are able to generate a limited number of words belonging to food, clothes and/or animal categories. We chose this task since paradigms involving a semantic decision, which are frequently used in adult patients (*i.e.* Binder *et al.* 1996), were deemed too difficult for our younger children and/or mentally challenged patients. A non-linguistic task (syllable repetition) served as control task. The latter task was chosen to quantify artefacts arising from the movement of the vocal apparatus during overt speech. The targeted regions were primarily Broca's area and secondarily, Wernicke's area and homologous cortical regions in the contralateral, right hemisphere.

To validate our technique, we first studied a small sample of healthy and epileptic adults who had previously undergone fMRI and/or IAT testing. We then collected NIRS data from four epileptic children and compared the results to their IAT findings. Finally, we employed NIRS to study speech lateralization in a child with pervasive development disorder and a healthy 3-year-old to explore whether this technique can be adapted to very young children and developmentally-challenged individuals who, because of their age or mental limitations, would not be able to undergo the IAT or imaging procedure.

Material and methods

Participants

The sample was composed of eleven participants (five adults, six children). Demographical data of the participants are presented in *table 1*. The handedness of all participants was assessed using the Edinburgh Inventory (Oldfield 1971). Except for the healthy controls, all participants were submitted to neuropsychological testing to determine their cognitive status. The test batteries included an intelligence scale and standardized tests assessing perceptual abilities, different aspects of attention and memory as well as expressive and receptive language skills. Informed consent was obtained from all participants or their parents in the case of children under the legal age. In addition, the project was approved by the Ethics Committees of the Sainte-Justine and Notre-Dame Hospitals.

Table 1. Demographic data of the participants.

Participants	Gender	Age	Handedness	Neurological condition	Age (yrs) at seizure onset	Cognitive status [a]	Method of language lateralization
Healthy adults							
1	M	28	R	Normal	-	Normal	fMRI
2	M	25	R	Normal	-	Normal	fMRI
3	F	26	L	Normal	-	Normal	fMRI
Epileptic adults							
4	M	18	R	Right temporal lobe epilepsy	11	Mild frontal dysfunction	IAT, fMRI
5	M	29	L	Lennox-Gastaut Syndrome, callosotomy	2	Borderline mental abilities, callosal disconnection syndrome	fMRI
Epileptic children							
6	M	13	R	Left temporal lobe epilepsy	1	Language and executive deficits	IAT
7	M	9	R	Left temporal lobe epilepsy	5	ADHD, expressive dysphasia, memory and executive deficits	IAT
8	F	15	R	Left fronto-temporal epilepsy	8	Mild mental retardation, language deficit, executive problems, memory deficits, generalized anxiety disorder	IAT-left hemisphere, intercranial grid
9	M	14	B	Left fronto-temporal epilepsy	9	Receptive and expressive language deficiencies, slowing of information processing	IAT
'Special' populations							
10	M	12	R	Pervasive developmental disorder, prenatal subcortical lesion	-	Mild to moderate mental retardation, severe dysphasia	None
11	F	3	R	Normal	-	Normal	None

M = male; L = left; R = right; IAT = intracarotid amobarbital test (Wada test).
[a] See methods for cognitive measures used.

Healthy adults

Three neurologically-intact volunteers, two right-handed men, aged 28 and 25 years (participants 1 and 2), and a left-handed woman, aged 26 years (participant 3) took part in the study.

Epileptic adults

The epileptic adults were one right- and one left-handed male, aged 18 and 29 years (participants 4 and 5).
All the adult participants had previously undergone fMRI or IAT or both at Notre-Dame Hospital to determine language lateralization (see *table 1*).

Epileptic children

Four, young, epileptic patients, three right-handed children (participants 6, 7, 8) and one left-handed child (participant 9), aged nine to 15 years (mean age = 12.75 yrs) were selected from the patient population of the Sainte-Justine Hospital Center in Montreal. All participants underwent IAT as part of their presurgical work-up. However, two of the children (participants 6 and 8) had a panic reaction during the procedure, which prevented the collection of reliable data. In participant 8, only the left hemisphere could be tested before the procedure was aborted. The results suggested left hemisphere dominance for speech. An intracranial grid was subsequently installed over the left hemisphere to ascertain the IAT finding. For participant 6, the procedure (and subsequent surgery) had to be postponed until the patient was older and more mature.

"Special" populations

The participants were a 12-year-old, right-handed boy (participant 10) with pervasive developmental disorder, moderate mental retardation and severe dysphasia which would preclude IAT or fMRI investigation, and a healthy 3-year-old right-handed girl (participant 11) who would be too young to undergo fMRI or IAT.

Language tasks

All participants performed two tasks: 1) a verbal fluency by category task (language task) and 2) a nonsense syllable repetition task (non-linguistic, motor control task) during optical imaging. Ten blocks with 10 different category words and 10 different pairs of nonsense syllables were presented. Within each block, one trial of the language task was followed by one trial of the control task. The same protocol was administered to all participants.
Each block had a duration of 2 minutes and 15 seconds. This time was divided as follows: a 30-sec baseline period (T1), followed by 30 seconds of testing with the verbal fluency task (T2), a 30-sec resting period (T3), 30 seconds of testing with the nonsense syllable repetition task (T4) and a final 15-sec resting period (T5: see *figure 1*). During both tasks, the participants' responses were tape recorded. All participants underwent a practice session prior to optical imaging recording.
Testing took place in a dimly-lit, sound-attenuated room. During the baseline and the resting periods, participants were instructed to relax while they were viewing a dark computer screen located at a distance of 84 cm from their head. During the verbal fluency task, the printed name of a familiar category (e.g., first names, toys, clothes) appeared on the computer screen and remained there for 30 seconds. The same name was also read out aloud by the experimenter who remained in the testing chamber during the entire experiment to ensure that the participant was actually performing the task or at least attempting to do so. Participants were instructed to name as many items as possible belonging to the specified category and to continue as long as the category name remained on the screen. If they stopped before the word disappeared from the screen, the experimenter encouraged them by a gesture to continue.
In the nonsense syllable repetition task, two pronounceable syllables (e.g. be ra) appeared on the screen for 30 seconds and were read by the experimenter. Participants were asked to repeat the syllables as long as they remained on the screen.

Near-infrared spectroscopy recording

NIRS was performed using a multi-channel Imagent Tissue Oxymeter (ISS Inc., Champaign, Ill, USA) with 32 sources operating at 690 nm, 32 sources operating at 830 nm (sources are laser diodes with a power of ≈1 mW, connected to the head by 0.4 mm fibres) and 8 detectors, (photomultiplier tubes connected to the head by 3 mm fibre bundles). The Oxymeter used a frequency-domain, time-resolved method that implies that light sources vary in intensity over time at 110 MHz, thus providing a more precise quantification of HbO_2 and HbR concentrations. Activity was recorded in four regions of interest: Broca's area, Wernicke's area and their mirror image counterparts in the right hemisphere. The optical fibres were placed on the surface of the head, using a light and comfortable, but rigid, helmet, which could be adapted to all head sizes without restricting head movements.
An individual montage was created for each participant, using the program *Brainsight™ Frameless 39* (Rogue research, Montreal, Qc, Canada). This is a stereotaxic system which enables the transfer of the regions of interest, determined by MRI, onto the helmet, thus allowing for a 3D brain reconstruction using the MRI and *Brainsight F39*. The four regions of interest (left Broca and Wernicke areas, and right counterparts) and four anatomical points of reference (nasion, left pre-auricular, right pre-auricular and tip of the nose) can then be marked on the magnetic resonance images and the reconstructed brain.
For this purpose, all participants, except the 3-year-old, healthy girl (participant 11), had an anatomical MRI prior

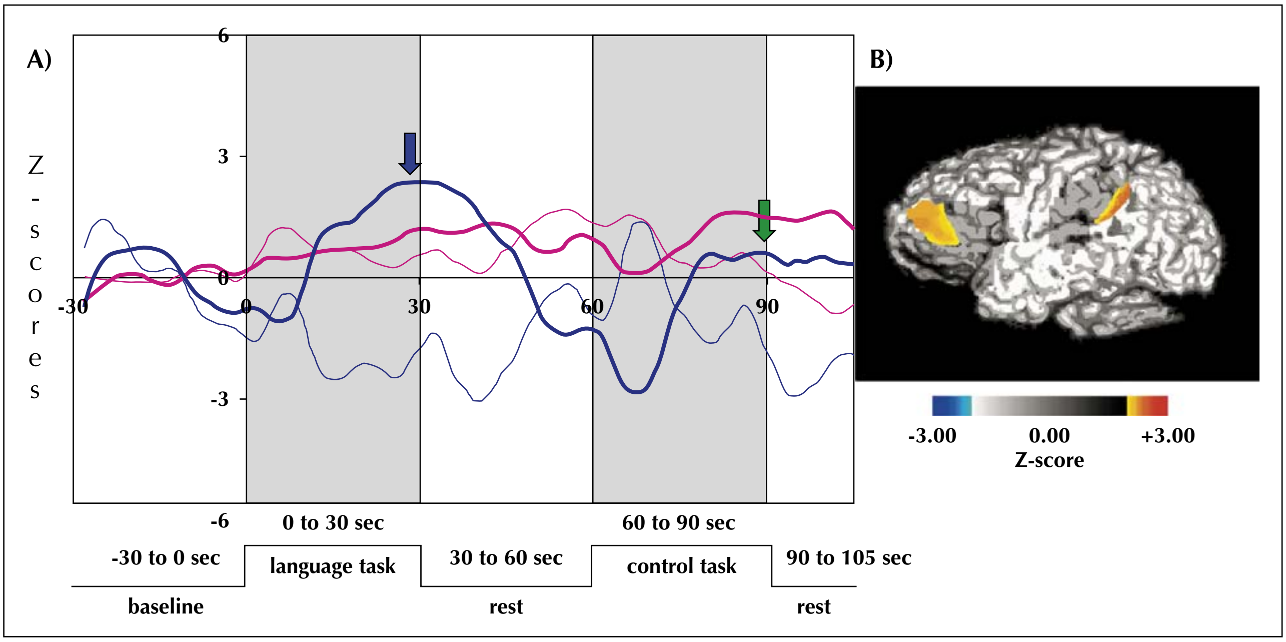

Figure 1. One-block time course including baseline, language task, resting period, control task and resting period. These data were gathered from the healthy 3-year-old girl (participant 11). In *figure 1A*, left hemisphere activations (Talairach coordinates of this channel: x = surface, y = 49, z = 17) are illustrated in blue, and right hemisphere activations in red. HbO_2 concentrations are indicated as solid lines whereas HbR levels correspond to the dotted lines. A clear left hemisphere activation is shown by an increase in HbO_2 concentration and a decrease in HbR concentration during the language task (zero to 30 seconds) as compared to the right hemisphere, in which no clear increase in HbO_2 concentration and decrease in HbR concentration are observed during either task. The blue arrow indicates maximal increase of HbO_2 during the language task (z = 2.5) and the green arrow indicates HbO_2 concentration at the end of the control task (z = 0.5), which was the maximal activation time point observed during this task. The sum of these two values (in this case, a z-score of 3.00) was used to determine the plot range when visualizing the data on the template *(figure 1B)*.

to the experimental session. For participant 11, an earlier MRI, which proved to be normal, was available.

During a first visit, a co-registration of the 3D brain reconstruction and the participant's head was performed with the stereotaxic system using a pointer. This enabled the experimenter to visualize on the 3D reconstruction image, the position of the pointer in relation to the participant's head and to draw the four regions of interest on his/her helmet. The procedure served to obtain the best possible montage in terms of source-detector numbers, locations and distances of the four targeted regions of each participant by taking into account their individual anatomical differences.

Optical intensity (DC), modulation amplitude (AC) and phase data were sampled at 39.0625 Hz and acquired in a block design paradigm. The montages comprised 128 channels (8 detectors and 16 multiplexed channels-source-detector combinations). The source-detector distance was held constant between 2 and 5 cm. The number of usable channels for each subject is displayed in *table 2*. The location of each source, each detector, and the four fiducial points (nasion, and left and right pre-auricular and tip of the nose), was digitized and recorded by means of the same *Brainsight™ Frameless* system to allow for precise alignment between the optical and the anatomical data. During the installation of the optical fibres, which took approximately 20 minutes, the participant was quietly watching a movie. To increase the signal-to-noise

Table 2. Number of usable NIRS channels (2 to 5 cm) for each participant.

Participants	Number of usable channels
Healthy adults	
1	88
2	76
3	98
Epileptic adults	
4	96
5	86
Epileptic children	
6	96
7	88
8	90
9	78
"Special" populations	
10	98
11	92

ratio, hair was moved out from under the detectors. The total duration of the NIRS session was approximately one hour.

Optical data analysis

Optical intensity (DC), modulation amplitude (AC) and phase data were first normalized by dividing each value by the mean value across time points for each block, and channel and pulse corrected (Gratton and Corballis 1995, Gratton and Fabiani 2006). The DC and AC data were then transformed to quantify concentration changes of HbO_2 and HbR for each channel. The MRI images of each participant permitted co-registration of the digitized optical channels and individual brain anatomy after Talairach transformation, using software *AFNI*^{TM}. The data were combined and visualized across channels by means of *OPT-3D* software (Gratton, 2000), which uses the digitized locations of the fibres. This software allows for the selection of channels based on the standard error of phase variations across trials which eliminates "noisy" channels, whose source-detector distance is too large to detect higher levels of illumination. The *OPT-3D* also permits the calculation of z-scores in a region of interest across time computed across the 10 blocks. The data were then orthogonally projected onto a standard, adult brain template in Talairach space.

Unlike in fMRI and other imaging techniques, in NIRS, individual features such as color and thickness of hair and skull may determine changes in signal strength between participants. Dense and dark hair absorbs more light, thus affecting the signal quality. To account for this variability, we established the activation level for each participant by using the most central channel in Broca's area, as determined on the subject's MRI. This level was obtained by using the following formula:

$$L = P_l + P_c$$

where L is the activation level (absolute value) in the central Broca channel, P_l is the maximum increase in HbO_2 concentration in this channel during the language task and P_c is the absolute maximum HbO_2 concentration at the end of the control task for the same channel. The latter point corresponds to the maximal activation during performance of the syllable repetition task for each participant. The L value (+ for activation and – for deactivation levels) was then used to determine the plot range for the visualization of the data in Talairach space.

Intracarotid amobarbital test

The Wada test was performed at the Notre-Dame Hospital (participant 4) or the Sainte-Justine Hospital Center (participants 6, 7, 8, 9) in Montreal. The amobabital doses used for the adult patients and the children were 150 mg and 120 mg, respectively. The language tasks, administered during the procedure, were object naming, reading of words and sentences, as well as word and sentence repetition. Since the procedure is uncomfortable and can be traumatic, especially for children (they are occasionally found to be aggressive, confused or panicky after the injection), a three-hour simulation was enacted the day before to prepare them adequately and minimize anxiety. The right and left hemisphere were tested on two consecutive days and the results were compared to determine hemispheric language representation. Oral comprehension deficits and phonemic paraphasias during the reading, repetition and naming tasks, as well as word-finding difficulties and prolonged speech arrest in the absence of vigilance alteration, were taken as indications of language representation in the injected hemisphere.

Functional magnetic resonance imaging

The five adult participants underwent functional magnetic resonance imaging at Notre-Dame Hospital in Montreal using a Siemens Vision 1.5T scanner. Anatomical images (3D T1 high resolution images – TR = 9.7 ms, TE = 4 ms, flip angle = 12, FOV = 250 mm, matrix 256 x 256) as well as echoplanar T2* functional images were collected (TR = 3000 ms, TE = 54 ms, voxel size = 3 X 3 X 5 mm, flip angle = 90, FOV = 215 mm, matrix 64 x 64). Twenty-eight, equally-spaced, oblique axial slices (5 mm thickness) were acquired every three seconds. The slices were then aligned in an AC-PC axis.

During image acquisition, a verbal fluency task was performed by the participants. The stimuli consisted of the letters P, F and L (phonological condition) and the categories: animals, furniture and fruits (semantic condition). The stimuli were presented visually using goggles with an LCD screen (Resonance Technology, CA, USA). The participants were instructed to lie still and to think of as many words as possible starting with the presented letter or words belonging to the specified category. A dot fixation task was administered as a non-linguistic control task. Six 30-second blocks of the verbal fluency task and six 15-second blocks of the control tasks were administered alternatively. A total of 60 activation volumes (3D images of 28 slices) and 30 control volumes were acquired.

The analyses were performed by means of SPM 99 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). Raw data conversion to SPM99 format, first volume suppression, co-registration, realignment and movement correction, spatial smoothing, segmentation and 3D images was subsequently performed. Finally, a laterality index (LI) was calculated on Broca's area (Talairach coordinates: -56, 4, 20) using a p = 0.01 statistical threshold. The LI ranged from -1 to 1, where a negative value (-1 to -0.26) indicated right language lateralization and a positive value (0.26 to 1) indicated left language dominance. Finally, a value between -0.25 and 0.25 inclusively was considered to reflect bilateral language lateralization.

Results

General considerations

Preliminary analyses were conducted for both HbO_2 and HbR concentration changes. For this purpose, a visual inspection of HbO_2 and HbR concentration data was performed for every subject during the baseline period, the two tasks and the resting periods. However, subsequent analyses were limited to HbO_2 concentration changes because the signal-to-noise ratio proved to be higher for HbO_2 than HbR (Siegel *et al.* 2003). Only the channels showing a good signal-to-noise ratio and in which an HbO_2 concentration change was accompanied by an opposite change in HbR were taken into account. For instance, a channel which showed an increase in HbO_2 concentration and a decrease in HbR concentration was considered a good channel, because this combination reflects a clear cerebral activation. By contrast, a channel that showed an increase of HbO_2 concentration without any change in HbR concentration, was not retained as a relevant channel. Across all participants, an average of 40 channels out of 128 showed a good signal-to-noise ratio and allowed for the recording of opposite changes in HbO_2 and HbR. These channels were used for the analysis. Most of these "good" channels were recorded from the adult participants since the signal-to-noise ratio depended on task performance and the ability of the patient to remain motionless. The children were less able than the adults to perform at optimal levels and to refrain from moving, which resulted in a greater number of rejected channels for these participants.

As mentioned earlier (*c.f.* Methods), the individual activation level of each participant was used to determine the plot range for the visualization of the data in Talairach space. For instance, the activation level for the data illustrated in *figure 1A* is 2.50 (blue arrow) and 0.50 (green arrow) equalling 3. Thus, the plot range used in the template (*figure 1B*) varied from -3.00 to +3.00. For greater clarity, the template results for all participants were taken from the time point at which maximal activation was seen during the language task.

NIRS results

The NIRS procedure was well tolerated. Furthermore, all participants were motivated and able to perform the tasks, albeit at different levels of competence. The epileptic patients and some of the younger participants required more practice than the healthy controls.

The results of the verbal fluency task are presented in *table 3*. Inspection of the data reveals that, on average, the healthy adults outperformed the epileptic adults, the epileptic children and the special populations, the latter being least efficient at the tasks. This, however, did not preclude the collection of clear results in these participants. In fact, conclusive data were obtained from all but one healthy adult (participant 2), whose data were too noisy to be included. The noisy signal in this participant was most probably attributable to his dense skull and thick, dark hair. The NIRS results of the remaining participants are presented in *table 4*.

Table 3. Results obtained for the verbal fluency task.

Participants	Number of words per 30 seconds
Healthy adults	
1	11
2	excluded
3	16.3
(Mean)	(13.65)
Epileptic adults	
4	8.3
5	7.6
(Mean)	(7.95)
Epileptic children	
6	11.3
7	6.1
8	7.2
9	13.6
(Mean)	(9.5)
"Special" populations	
10	5.4
11	5.4
(Mean)	(5.4)

Healthy adults

The NIRS results of the healthy controls (participant 1 and 3) are presented in *figures 2, 3*. As can be seen, participant 1 showed a strong initial activation in Broca's area during the language task (T2), which was followed by a weaker activation in the corresponding area of the right hemisphere *(figure 2)*, suggesting left hemisphere dominance for speech. The first rest period (T3) was characterized by a gradual return to baseline, with left hemisphere activation fading more slowly than right hemisphere activation. Smaller bilateral activations were found in the superior temporal gyrus, corresponding to Wernicke's area. No activation was seen at baseline (T1), during performance of the nonsense syllable repetition task (T4) and during the last rest period (T5). The left hemisphere language dominance obtained by NIRS *(figure 3A)* confirmed fMRI findings (LI = 1, $p \leq 0.01$).

The left-handed participant 3 also showed left hemisphere activation in Broca's area (*figure 3B*), which was consistent with her fMRI (LI = 0.71 $p \leq 0.01$). As in participant 1, a secondary activation could be visualized in the homologous cortex of the right hemisphere.

Table 4. Comparisons between IAT, fMRI and NIRS results.

Participants	IAT	fMRI	NIRS
Healthy adults			
1	-	LI = 1, $p \leq 0.01$; L	L
2	-	LI = 0.54, $p \leq 0.01$; L	excluded
3	-	LI = 0.71, $p \leq 0.01$; L	L
Epileptic adults			
4	L	LI = 1, $p \leq 0.01$; L	L
5	-	LI = 0.79, $p \leq 0.01$; L	L
Epileptic children			
6	L	-	L
7	B	-	B
8	L	-	L
9	L	-	L
'Special' populations			
10	-	-	L
11	-	-	L

LI = Laterality index; L = Left; B = Bilateral.

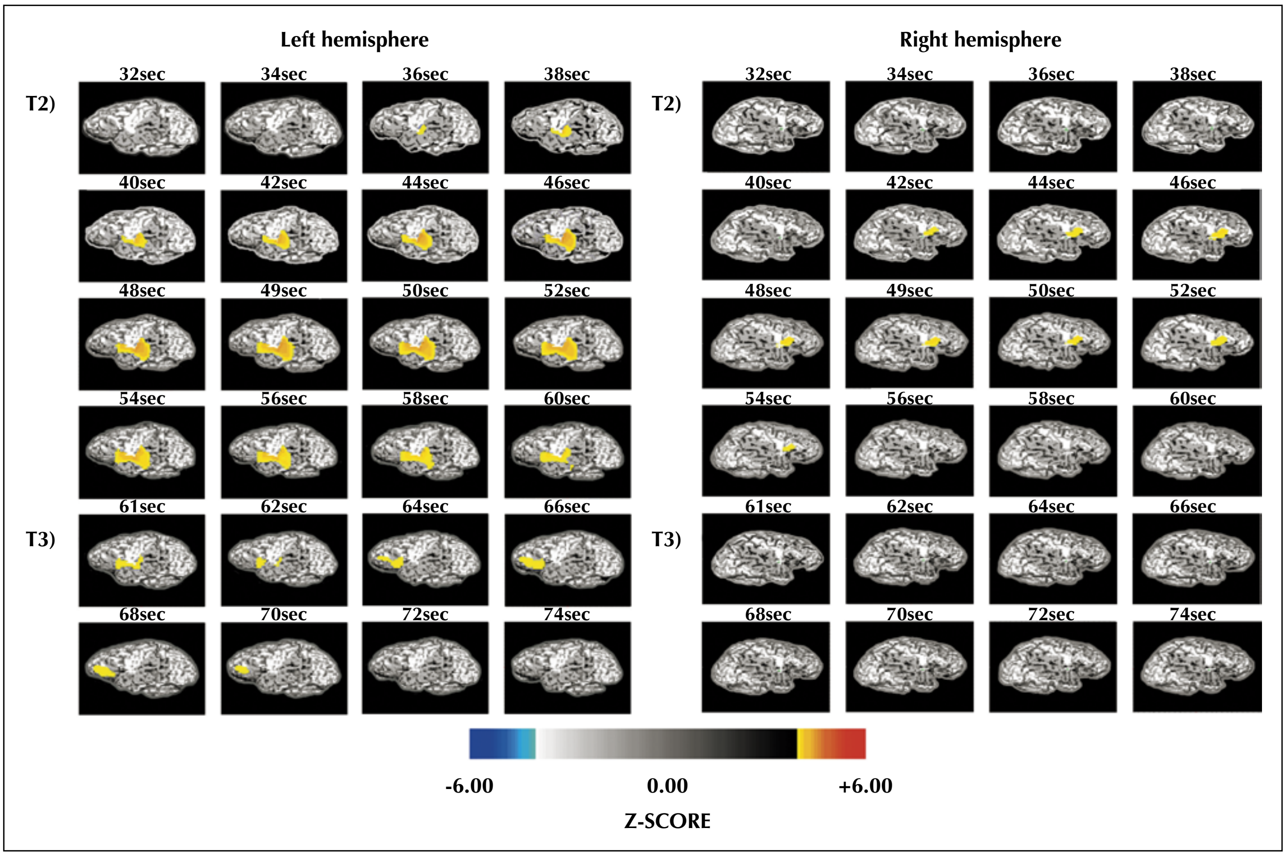

Figure 2. Left and right NIRS activations during the verbal fluency task (T2: 30 sec) and the rest period (T3: 30 sec) of **participant 1**. Since no activation was seen during the baseline (T1: 30 sec), the last 15 seconds of the rest period (T3), the control task (T4: 30 sec) or the last rest period (T5: 15 seconds), only the T2 and T3 time courses are shown. Note that activation in Broca's area starts earlier and lasts longer than activation in the corresponding area in the right hemisphere (see text for details).

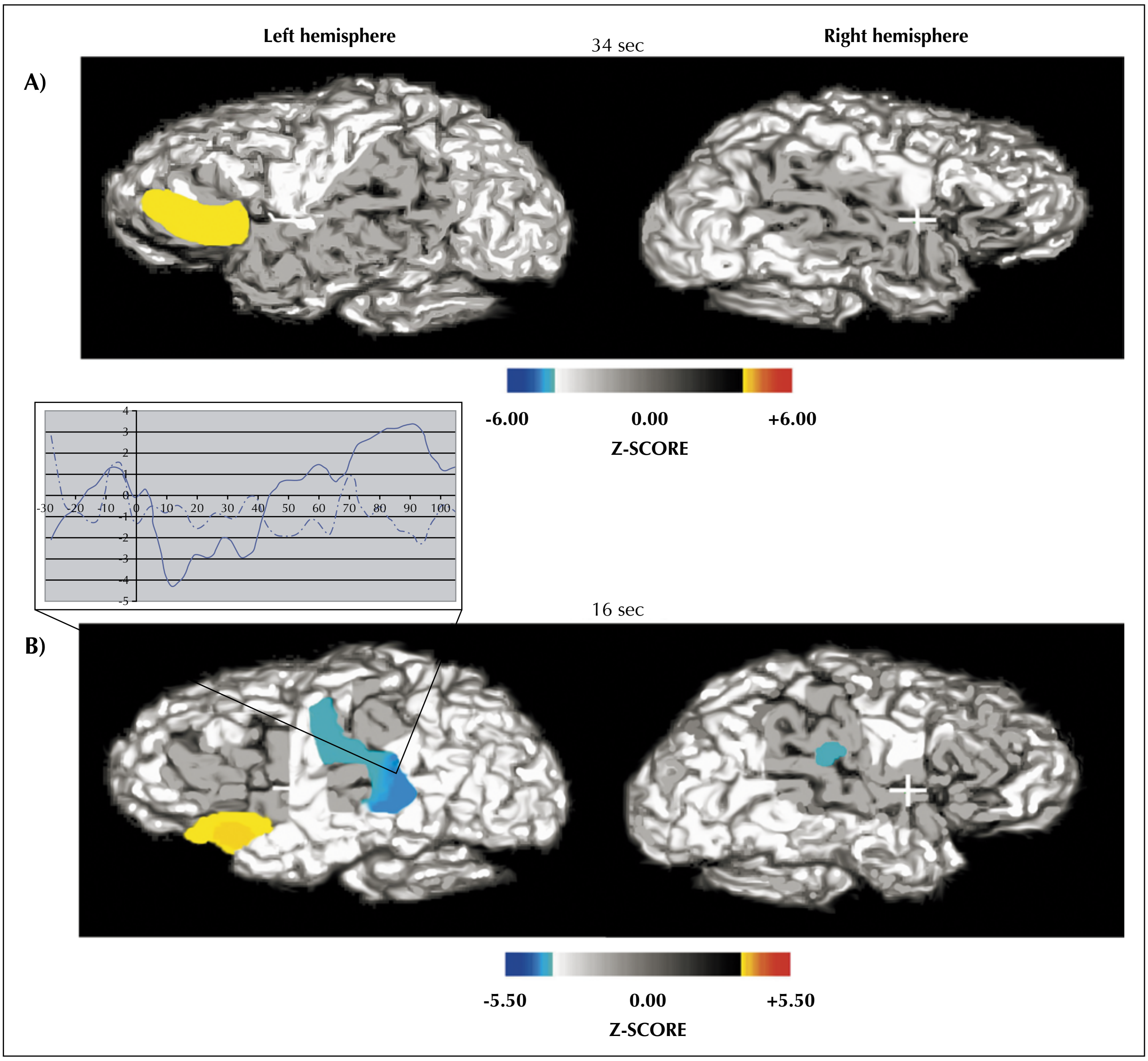

Figure 3. NIRS results for the two healthy adults (**participants 1 and 3**).
The plot range for participant 1 (A) was 6.00 and the value for participant 3 (B) was 5.50. Both participants demonstrate a clear activation in Broca's area. Note that, in contrast to participant 1, participant 3 also shows a deactivation in the equivalent area of Wernicke's area in the right hemisphere during the language task. As shown in the upper right of *figure 3B* (left hemisphere), the deactivation in the left hemisphere (blue area) in this subject is not characterized by an increase in HbR, but rather by a decrease in HbO_2 concentration during the verbal task. Thus, this deactivation is not considered to be relevant and must be reflecting noisy signals.

Furthermore, a deactivation in the angular and supramarginal gyri of the left hemisphere was observed in T2. However, as can be seen in *figure 3B* (upper right of the left image), this deactivation (blue area) did not coincide with an increase in HbR, but only a decrease in HbO_2 concentration during the language task. The deactivation must therefore reflect a noisy or atypical signal. By contrast, these same regions were activated during the non-linguistic control task (T4) in both hemispheres.

Epileptic adults

As for the healthy adults, the epileptic adults (participants 4 and 5) showed the typical left-hemisphere activation in Broca's area during the language task *(figures 4A,B)*. Again, their NIRS findings replicated the results of both IAT and fMRI (LI = 1, $p \leq 0.01$ and LI = 0.79, $p \leq 0.01$, respectively). In addition, participant 5 showed an activation in Wernicke's area.

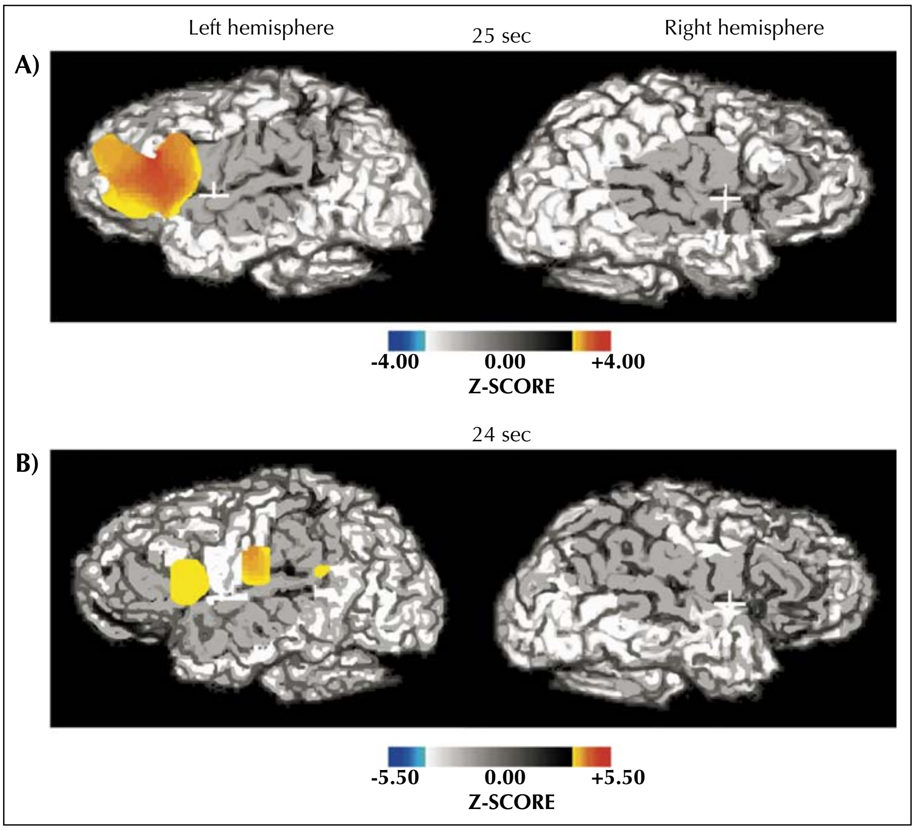

Figure 4. NIRS results for the epileptic adults (**participants 4 and 5**). The plot range for participant 4 (A) was 4.00 and the value for participant 5 (B) was 5.50. Both participants show a clear activation in Broca's area. Participant 5 also shows an activation in Wernicke's area.

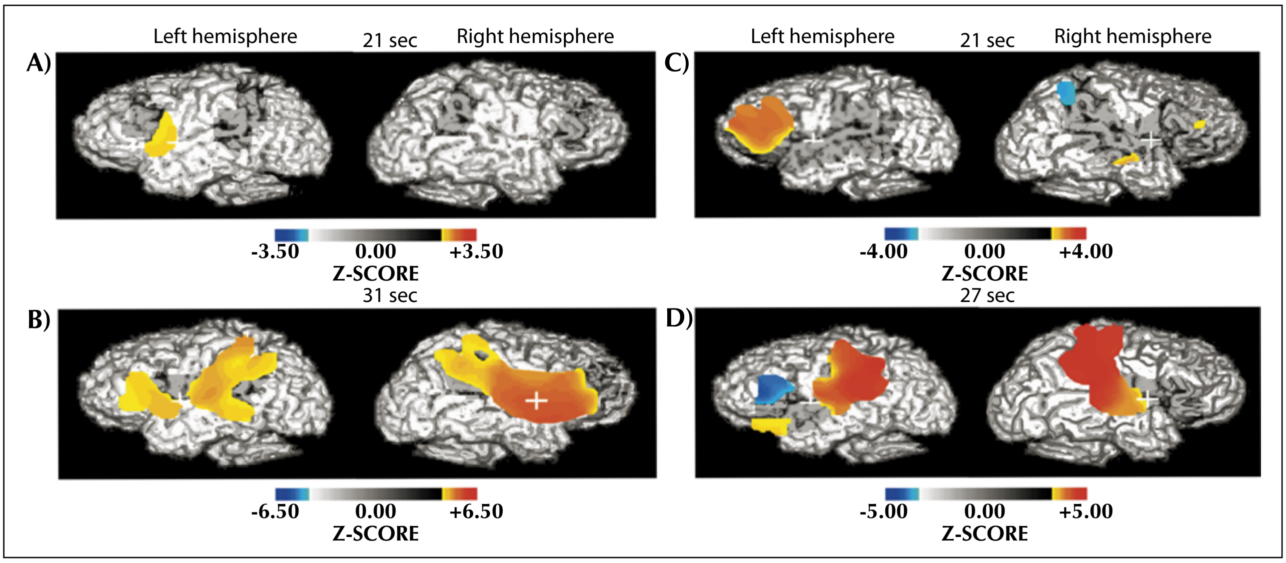

Figure 5. NIRS results of the epileptic children: (A) **participant 6** (plot range: 3.5), (B) **participant 7** (plot range: 6.5), (C) **participant 8** (plot range: 4.0) and (D) **participant 9** plot range: 5.0). Participants 6 and 8 show a clear left-hemisphere activation similar to that observed in the adults. Participant 7, the 9-year-old epileptic child who developed epilepsy at age 5, exhibits bi-hemispheric activations in Broca's and Wernicke's areas. Participant 9 shows an activation in Broca's area (most anterior yellow zone), a simultaneous bilateral activation in a posterior region corresponding to Wernicke's area and surrounding regions, as well as a deactivation in a region adjacent to Broca's area.

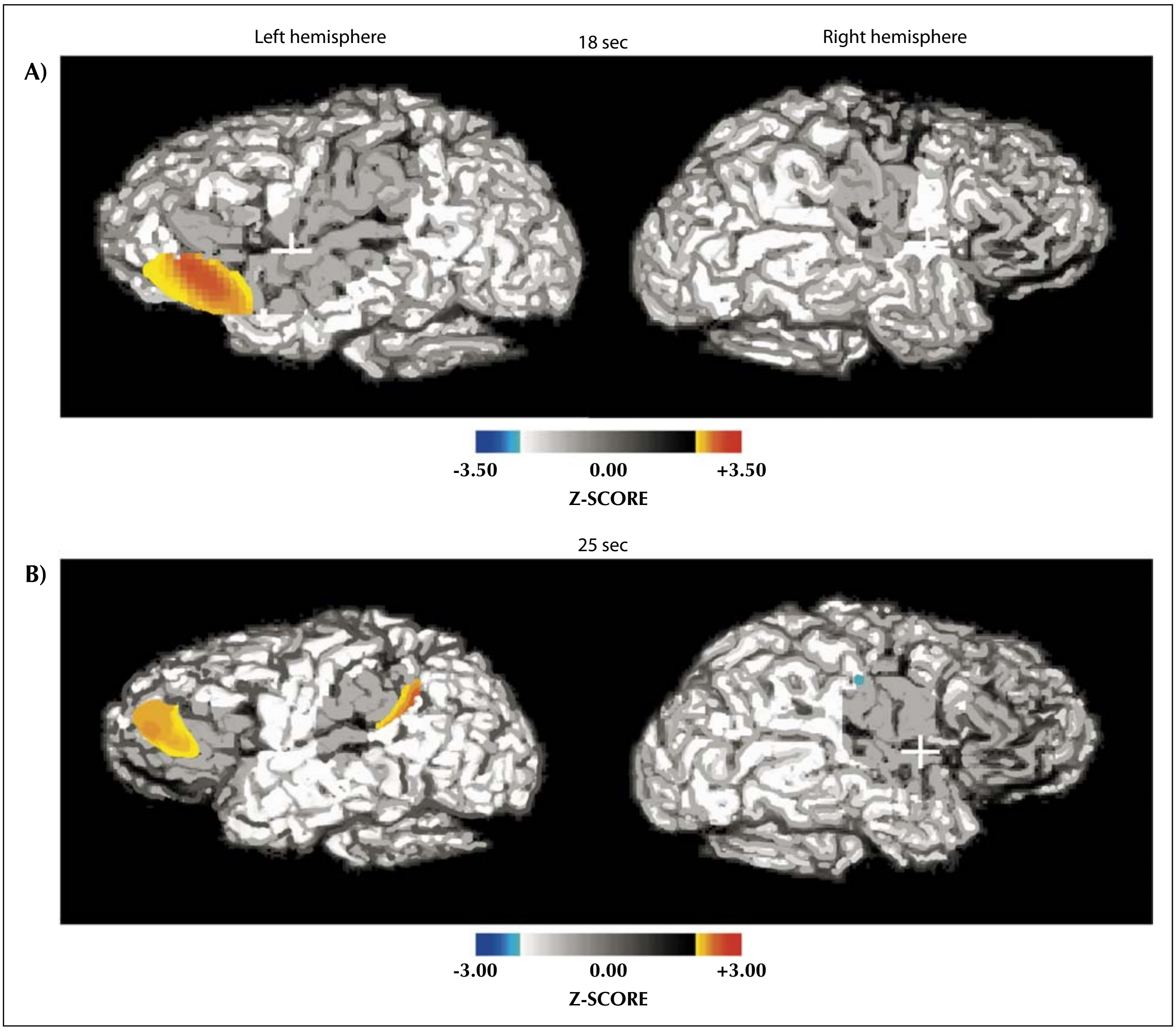

Figure 6. NIRS results for the "special" populations (**A**) **participant 10** (plot range: 3.5) and (**B**) **participant 11** (plot range: 3.0). Both subjects show the typical left hemisphere activation in Broca's area during the language task.

Epileptic children

The results for the epileptic patients are illustrated in *figure 5*. Participant 6, the 13-year-old boy who underwent IAT twice because of an anxiety reaction during the first procedure, had no adverse reaction to NIRS. In keeping with his IAT findings, his NIRS data revealed left-hemispheric representation of speech in terms of a clear activation in Broca's area *(figure 5A)*. No other areas were activated.

Participant 7 showed bilateral activation in regions corresponding to Broca's and Wernicke's areas in both hemispheres *(figure 5B)*, which replicated his IAT findings.

Clear NIRS results were also obtained from participant 8 *(figure 5C)*, even though the patient moved a great deal during recording. The activation, seen in Broca's area, was consistent with left hemisphere dominance for speech established earlier by means of IAT and presurgical intracranial mapping. In addition, a deactivation in terms of a decrease in HbO_2 concentration and an increase in HbR concentration, was simultaneously observed in the right angular and supramarginal gyri during the language task.

Left-hemispheric language representation was also demonstrated in participant 9, who is ambidextrous. Again, the optical imaging data matched the IAT results *(figure 5D)* by showing a clear activation in Broca's area. This activation was accompanied by a simultaneous deactivation in adjacent areas as well as a bilateral activation in superior temporal, angular and supramarginal gyri.

"Special" populations

Finally, conclusive NIRS results were obtained from the 13-year-old, mentally-challenged boy with pervasive developmental disorder (participant 10: *figure 6A*) and the 3-year-old healthy girl (participant 11: *figure 6B*) who could not be submitted to IAT and imaging techniques. Although the children generated fewer words and were moving throughout the procedure, a clear activation in Broca's area could be observed, indicating left hemisphere representation of speech. No significant activation was observed in Wernicke's area during the language task in either child.

Discussion

The aim of the present study was to assess whether NIRS can be used as an alternative to IAT or fMRI in the presurgical investigation of language lateralization in children and mentally-challenged individuals who cannot be submitted to IAT or imaging techniques because of their young age or cognitive and/or behavioural limitations.

As a first step, we verified the validity of this technique in an adult population by comparing the NIRS results of healthy and epileptic adults with their fMRI and IAT findings. We then proceeded to assess the applicability of NIRS in four epileptic children, a very young child and a mentally and behaviourally-challenged patient.

The results revealed that the simple verbal fluency task, used in this experiment, was sufficient to elicit a clear activation in the speech areas in all participants. Furthermore, the NIRS findings were congruent with the lateralization indices obtained with IAT (5/5 participants: one epileptic adult and four epileptic children) and fMRI (4/4 participants: two healthy and two epileptic adults). Although our small sample size limits generalization of the findings, the strong concordance of NIRS with well-established techniques tends to confirm previous findings in adults (Kennan *et al.* 2002, Noguchi *et al.* 2002, Watanabe *et al.* 1998, Watson *et al.* 2004), which have shown that NIRS can be a useful, non-invasive tool for the exploration of hemispheric language lateralization. Our results extend these earlier findings to children and to special clinical populations. A major advantage of NIRS, especially when working with children or mentally-challenged individuals, is that the procedure is less intimidating for the patient than IAT. In fact, the two epileptic children (participants 6 and 8), who had previously experienced heightened anxiety during the amobarbital test, seemed to be perfectly comfortable in the NIRS testing situation.

Another advantage of NIRS is that the procedure imposes fewer restrictions than fMRI. Apart from requiring only minimal cooperation from the participants, the technique proved to be relatively tolerant to movement artefacts, since conclusive data were obtained from participants who were restless during the procedure. This was particularly true for our "special" populations (participants 10 and 11). Both children had difficulty remaining still during data acquisition. Furthermore, their verbal output during the language task was limited. Yet, a clear lateralization in Broca's area was obtained in both participants.

Gaillard *et al.* (2000) demonstrated that the activation pattern of healthy, school-aged children resembles that of adults. Consistent with this finding, all the epileptic children in our study activated the same language areas as the healthy adults (*i.e.*, Broca's area, superior temporal gyrus as well as the angular and supramarginal gyri) during the speech production task. However, they varied with regard to the pattern of activation. In four patients (participants 4, 6, 8 and 9), the activation was limited to Broca's area, whereas in two young epileptic participants (participants 8 and 9), activation in Broca's region was accompanied by a deactivation of either the contralateral or ipsilateral surrounding areas.

A similar deactivation has been observed in other studies using optical imaging (Franceschini *et al.* 2003) or fMRI (Raichle 1998). The cause underlying this deactivation is not well understood. Enager *et al.* (2004) argued that the deactivation may be caused by a decrease in the activity of a large neural population. Chen *et al.* (2005), on the other hand, suggested that it could be the result of inhibitory connections to another cortical area. In both cases, the decrease in cerebral blood flow may be related to neural activity. Other authors (e.g., Shmuel *et al.* 2002) have proposed that decreases in cerebral blood flow may be unrelated to neural activity. According to this hypothesis, a deactivation could be generated by an increase in cerebral blood flow in some cortical regions, resulting in a redistribution of the blood supply and a decrement of cerebral blood flow in neighbouring regions. This phenomenon has been termed "blood steal".

Another explanation could be that vasoreactivity is altered in the presence of a lesion. This would account for individual differences in activation patterns observed in our epileptic participants. Although the small sample size does not permit definite conclusions to be drawn, one might speculate that the patterns seen in some of the patients could reflect cerebral reorganization, especially in the younger and the more impaired patients. For instance, in the 14-year-old, ambidextrous patient (participant 9), activation in Broca's area was accompanied by a significant activation in Wernicke's area and corresponding cortex in the contralateral, right hemisphere. This bilateral pattern of activation could suggest bi-hemispheric language organization. The fronto-temporal focus in this participant may have forced reorganization by extending the speech region in the left hemisphere to include "Wernicke's" areas in both hemispheres. Another pattern was seen in participant 5, the adult patient with Lennox-Gastaut syndrome, whose first seizures occurred at the age of two years. In this patient, the activation in Broca's area was accompanied by a simultaneous activation in the ipsilateral Wernicke area. Again, it could be argued that the early onset of the epilepsy may have resulted in atypical language representation. Finally, one patient with a seizure history of secondary generalization (participant 7), exhibited clear bilateral activation in Broca's and Wernicke's areas, which could suggest simultaneous recruitment of these language areas during speech production as part of cerebral reorganization.

The latter result is also important in that it suggests that NIRS is sensitive to bilateral speech representation. While fMRI has been found to correctly lateralize language functions in either hemisphere in most cases, this technique appears to be less efficient in detecting bi-hemispheric organization of speech (Benke *et al.* 2006).

On the other hand, NIRS has limitations related to individual variations in the signal-to-noise ratio. We found that the signal-to-noise ratio depended essentially on three factors: the participant's ability to perform the task as instructed, the amount of head movement that occurred during recording, and the density of the skull and the thickness and colour of the hair. The healthy adults, who performed the tasks well and remained motionless during data acquisition, as well as participants with lighter and thinner hair, had the highest signal-to-noise ratios. In contrast, the epileptic patients, the very young child and the boy with pervasive developmental disorder who produced fewer words and who tended to move during the procedure, obtained smaller signal-to-noise ratios, which however, did not prevent the collection of reliable data in these participants.

Conclusion

The results of the present study are encouraging in that they suggest that NIRS has the potential to determine language lateralization in patients destined for epilepsy surgery. More importantly, our findings, if replicable in larger samples, show that the procedure can be successfully employed in very young children and patients who have very little speech or who cannot remain motionless during the procedure. In these cases, IAT or fMRI cannot be performed. As a consequence, surgery may have to be postponed, which could limit its efficacy.

Although the procedure is more resistant to motion artefacts than fMRI, one limitation of NIRS is that excessive movement of the head risks reducing the signal-to noise ratio. Another disadvantage of the technique is the shallow penetration of the photons, which may prevent collection of conclusive data from individuals with a thick skull and/or dense, dark hair. However, this limitation can easily be overcome by shaving the areas targeted for fibre placement in surgical candidates with this problem.

The advantages of this technique greatly outweigh its limitations. For instance, apart from being non-invasive, NIRS can also provide important information about cortical activation during language processing, which cannot be obtained by the traditional Wada technique because an entire hemisphere is temporarily inactive during this procedure. Furthermore, NIRS allows us to follow the temporal course of cerebral activation, which is not easily achieved with other procedures. Finally, unlike IAT, NIRS provides information regarding the topography of the activation, both intra- and inter-hemispherically. In this respect, it allows not only for the determination of language lateralization, but also for the identification of individual patterns of activation and cerebral reorganization. These findings highlight the importance of analyzing cerebral activity in all language areas rather than limiting the investigation to a narrowly defined area of interest.

In the future, it would be interesting to extend the set-up so as to cover the whole brain in order to gain a better understanding of individual differences in language processing in the brain. This could be done easily by increasing the number of optical fibres used during data acquisition. Furthermore, NIRS could be employed to investigate receptive language. To evaluate both aspects of language is important since evidence suggests that expressive and receptive language abilities may reorganize independently in the epileptic brain (Kurthen 1992). Finally, NIRS may possibly find an application in the exploration of memory in surgical candidates. Our team is presently working on adapting the procedure to include these functions.

Obviously, more studies in larger patient populations, using paradigms that generate consistent results across centers, are needed before NIRS can be considered a viable alternative to the Wada technique in the presurgical exploration of language and memory functions. Until such time, the technique may find application in combination with other non-invasive techniques, such as neuropsychology and Doppler sonography (Knecht *et al.* 1996, 1998). □

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