NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 24 (2005) 780–790

Language lateralization in young children assessed by functional transcranial Doppler sonography

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Received 24 May 2004; revised 6 August 2004; accepted 23 August 2004
Available online 13 November 2004

Compared to adults, children show superior recovery of language function after damage to the dominant brain hemisphere. Possible explanations are that children have different patterns of language representation or display different patterns of reorganization. Information about language lateralization in children could provide insights into the repair mechanisms of the young brain. While functional magnetic resonance imaging (fMRI) is usually difficult to perform in children younger than 5 years, functional transcranial Doppler sonography (fTCD) is nonfrightening and readily applicable in young and very young children. However, for serial examinations, sufficient validity and reliability are required. To this end, we designed a picture-description language task (PDLT) for fTCD examinations in children, compared the outcome to established protocols and determined the 1 month retest-reliability of the measurement in 16 children aged 2–9 years. The dependent variable was the task-related hemispheric perfusion difference based on averaged relative cerebral blood flow velocity (CBFV) increases in the middle cerebral arteries. This picture-description language lateralization index was compared to language lateralization by a phonetic word generation task (PWGT) in adults revealing good intermethod validity ($r = 0.70$; $P \leq 0.05$). The 1 month retest-reliability of the PDLT in the children was $r = 0.87$ ($P \leq 0.05$). With this degree of reliability, fTCD seems a promising tool for the assessment of changes in hemispheric involvement in language in young and very young children.
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Keywords: Language lateralization; Functional transcranial Doppler sonography (fTCD); Reproducibility; Retest-reliability; Cerebral lateralization; Children; Language development; Pediatric neuroimaging; Plasticity

Introduction

There is a long-standing debate whether in children language lateralization is innate or develops during language acquisition. Morphological left–right asymmetries of the planum temporale or auditory association cortex in the fetal brain suggest that it may be present at birth (Chi et al., 1977; Wada et al., 1975). Conversely, other studies suggest that healthy children have a more diffuse, less consolidated distribution of language processing networks that progressively lateralize during adolescence (Gaillard et al., 2000; Hertz-Pannier et al., 1997; Holland et al., 2001). Moreover, children recover better from brain damage and, in particular, show a superior capacity to transhemispherically compensate for impaired language functions compared to older children and adults (Boatman et al., 1999; Vargha-Khadem et al., 1994).

Functional imaging will eventually determine whether language in children is processed in an adult-like lateralized fashion or slowly develops into an adult-like lateralized pattern. This information may also inform us about the mechanisms of functional restitution in the young brain. However, at present, many techniques used in adults are difficult to apply in young children. For example, magnetic resonance scanners usually frighten children and will thus may result in poor cooperation (e.g., Holland et al., 2001). The age of the subjects seems to be a limiting factor: A review of the previous pediatric fMRI studies on language functions in nonsedated children reveals a minimum age for participation of at least 7 years (Ahmad et al., 2003; Balsamo et al., 2002; Gaillard et al., 2000, 2001a,b; Liegeois et al., 2002, 2004; Sachs and Gaillard, 2003; Schlaggar et al., 2002). fMRI studies in which actively participating subjects aged less than 7 years have been successfully included are rare (e.g., Gaillard et al., 2003a). Near-infrared spectroscopy (NIRS) and fTCD can be readily performed in subjects with less than perfect cooperation (e.g., Kennan and Behar, 2002; Kennan and Constable, 2001; Knake et al., 2003; Watanabe et al., 1998). Although these techniques are limited in spatial resolution, they can provide valuable data on task-related cerebral perfusion increases, and, in the case of fTCD, reliable and highly reproducible information on language lateralization in adults (Knecht et al., 1998b). Therefore, fTCD would seem well suited for the measurement of changes in language lateralization during normal development in the infant or during recovery after brain damage. However, such work would require validity and reliability of the measurement.

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doi:10.1016/j.neuroimage.2004.08.053

To this end, we developed a word generation task that is based on picture descriptions and suited for fTCD examinations in children. Lateralization indices based on this task were compared to lateralization indices obtained from phonetic word generation, a task validated by comparisons of fTCD with fMRI (Knecht et al., 1999), the Wada test (Knecht et al., 1998a; Rihs et al., 1999), and virtual lesions by transcranial magnetic stimulation (Epstein, 1998). The 1 month retest-reliability of the lateralization indices was assessed in children aged 2–9 years.

Methods

Subjects

We examined 16 native German speaking children (10 female, 6 male) with a mean (arithmetic mean AM) age of 5.8 years (range: 2.3–9.8 years). Fourteen subjects were right-handed, one child was ambidextrous, and one child showed left-handedness according to a manual preference test (Grooved Pegboard Test, reference: www.parinc.com; Bornstein, 1986). Handedness indices are listed in Table 1 (for details of the handedness assessment, see “Neuropsychological evaluation” section). All participants were recruited from local kindergarten. There was no reimbursement. All subjects and their parents were fully informed of the procedure. Children were included after they agreed to cooperate and after their parents gave written consent.

Only children without pathological findings in their neurological, neuropsychological or neuropsychiatric history participated in the study. Subjects were included if they had a normal cognitive and language development as assessed by the Illinois Test of Psycholinguistic Abilities (ITPA; Angermaier, 1999). Normal range in the ITPA was defined as the age-related mean in a composite score ±1 standard deviation (age-related language proficiency score-LP_{AR}; see also “Neuropsychological evaluation” section for details). LP_{AR} scores of the subjects are listed in Table 1. Due to dyslexia, the data of one 6-year-old girl was excluded from further statistical evaluation. All subjects were examined twice within 1 month with the identical experimental fTCD protocol. Additionally, for the evaluation of practice effects or habituation, one 9-year-old girl was examined 10 times within 5 months with variable inter-session intervals. The neuropsychological evaluation was administered once in each child within 3 weeks after the first fTCD examination.

The picture-description language task (PDLT) was validated with a phonetic word generation task (PWGT), an established language lateralization task validated in previous fTCD and fMRI studies (Deppe et al., 2000; Knecht et al., 1999; Paulesu et al., 1997). For this purpose, nine healthy adults (seven female, two male; mean age: 29 years) and three literate subject of our sample (subjects AW, MB, MR) completed both tasks, i.e., the PDLT and the PWGT in a fTCD examination.

Experimental set-up and stimuli

Technical devices

The assessment of the hemispheric dominance for language was performed using a computer-based version of the PDLT on a conventional personal computer including a 17-in. computer screen for stimuli presentation. Sequencing of the stimuli was run by a presentation software (“Showview”) from our laboratory. Blood flow velocity recording was accomplished by a commercially available dual transcranial Doppler ultasonography device (*DWL MultiDop T2*, Singen, Germany; DWL, 2003). For bilateral cerebral blood flow velocity (CBFV) detection at the temporal skull windows, two 2-MHz transducer probes were used mounted on a flexible headset. The fTCD procedure was based on previous studies of language lateralization in adults from our laboratory and was then adopted for the examination of children (see below; Knecht et al., 1998a,b, 1999).

Fig. 1 depicts the experimental set-up. Children were usually accompanied by one of their parents, sitting beside them on a different chair. In some cases, especially when very young children were examined, the child was sitting on their mother’s or father’s

Table 1
Sample statistics: sex, age, linguistic proficiency, handedness, and lateralization indices including accuracy coefficients and inferential statistics

No.	Subject	Sex	Age	LP_{AR}	LP_{RD}	HI	LI_1	SE_{LI_1}	CV_{LI_1}	LI_2	SE_{LI_2}	CV_{LI_2}	*P* value
1	OK	f	2.3	53	43	11	4.40	1.30	0.30	5.59	2.36	0.42	0.24 n.s.
2	MS	m	3.0	70	83	04	−3.73	1.59	0.43	−2.20	0.81	0.37	0.12 n.s.
3	IK	f	3.2	76	103	06	4.28	0.81	0.19	4.01	0.96	0.24	0.99 n.s.
4	AL	f	3.8	57	80	12	−2.45	1.22	0.50	−2.03	0.65	0.32	0.96 n.s.
5	MM	m	4.4	75	89	17	4.95	0.92	0.19	3.37	0.62	0.18	0.56 n.s.
6	KW	f	4.9	61	126	10	0.94	0.85	0.90	3.26	1.45	0.44	0.21 n.s.
7	OG	m	4.9	52	95	05	2.99	2.14	0.72	3.17	0.92	0.29	0.42 n.s.
8	AM	f	5.2	50	110	03	2.85	1.23	0.43	3.30	1.05	0.32	0.54 n.s.
9	HF	m	5.3	56	101	06	5.56	0.72	0.13	1.68	1.21	0.72	0.02*
10	JB	f	5.8	50	144	00	6.86	0.70	0.10	6.08	0.69	0.11	0.48 n.s
11	AW	f	6.8	68	189	02	−3.29	0.84	0.26	−4.46	1.28	0.29	0.11 n.s.
12	KB	m	7.1	61	151	19	4.70	0.96	0.20	4.69	0.48	0.10	0.84 n.s.
13	NB	f	8.7	62	181	10	3.51	0.53	0.15	3.63	0.68	0.19	0.35 n.s.
14	MR	m	9.3	58	178	03	6.52	0.59	0.09	4.57	0.58	0.13	0.18 n.s.
15	HM	f	9.3	55	279	20	2.86	0.93	0.33	3.20	0.46	0.14	0.77 n.s.
16	MB	f	9.8	52	202	−05	4.03	1.61	0.40	1.26	0.67	0.53	0.23 n.s.

Note. f = female, m = male; LP_{AR} = age-related linguistic proficiency level normalized in *T* scores (AM = 50, SD = 10) as measured by the ITPA; LP_{RD} = language proficiency level expressed by the composite score of the ITPA (raw data); HI = handedness index assessed by the Grooved Pegboard Test; LI_1, LI_2 = fTCD lateralization index–first and second examination, resp.; SE_{LI_1}, SE_{LI_2} = standard error first examination and second examination, resp.; CV_{LI_1}, CV_{LI_2} = coefficient of variability of the first and second examination, resp.; *P* value, Wilcoxon test, two-tailed; n.s. = (statistically) not significant; * = statistically significant ($P \leq 0.05$).

Fig. 1. Experimental set-up.

lap. Prior to each examination, much effort was spent to reduce any excitement or anxiety of the children and to create an atmosphere that stimulated the participation of the children. This was accomplished by demonstrating the ultrasonic device in a playful manner to the children. Children were encouraged to "explore" the headset and the transducer probes and to "play" with them. They were also shown pictures of other children in the experimental set-up who already had taken part in the study. At least two probe trials of the picture-description language task without blood flow recording were performed to ensure cooperation.

Fig. 2 displays the stimulation design of the PDLT. Each trial began with a resting period of 30 s in which the children were requested to hold their eyes closed and to imagine they were dreaming underneath a night sky. After 30 s, a cueing tone was given. The children were then requested to open their eyes and to attend to the computer screen. After additional 5 s, a picture of a well-known item of everyday living or a well-known animal was presented on the computer screen for 5 s. Starting with the presentation of the picture, the children were to describe the given picture aloud. They were instructed to tell what the picture was about, to name the characteristics of the item in detail, to tell what one can do with it. If the child seemed not to proceed with the task, after 10 s, standardized encouraging comments were given by the experimenter like "That's fine, please go on!" or "Fine, what else do you know about it?". A second cueing tone following 30 s after the first signaled the end of trial. The order of the trails was pseudo-randomized among subjects.

Stimuli

In total, 30 different stimuli (pictures) for all children were used. The pictures were realistic paintings of well-known items of daily living like a bicycle or an animal selected from a children's book. In Fig. 2, one of the items (elephant) is depicted. The full list of the stimuli is listed in Appendix A. For each examination, the

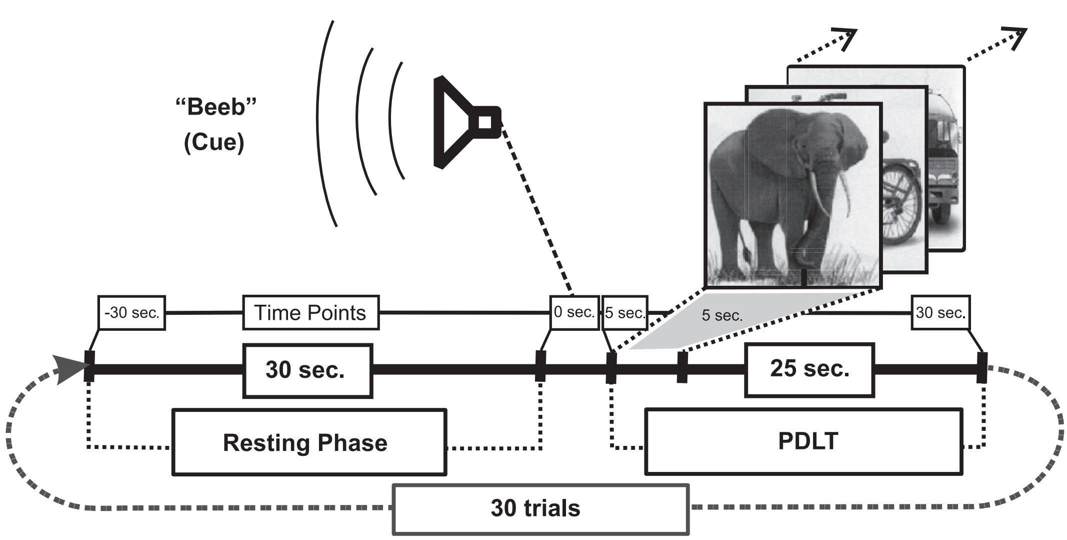

Fig. 2. Stimulation design of the picture-description language task (PDLT).

order of presentation was randomized. Each examination ended after 30 trials, thus resulting in a net examination time of 30 min.

Functional TCD (fTCD)

Functional TCD (fTCD) including off-line CBFV processing ("Averaging") was conducted in a manner previously described in detail (Deppe et al., 1997, 2004). fTCD records CBFV in two basal arteries (here the MCAs) during resting phase and task performance. A fTCD lateralization index (LI_{fTCD}) can be calculated by the average event-related CBFV changes in the two insonated arteries during task performance relative to a resting phase. Comparable to lateralization indices used in fMRI, the LI_{fTCD} indicates differences in cerebral activation in the vascular territories of the insonated arteries during task performance on the basis of CBFV changes (Deppe et al., 2000).

Data recording

CBFV was recorded bilaterally in the MCAs at a depth of 46–50 mm simultaneously to the whole experiment. Insonation techniques including the correct identification and depth adjustment have been published elsewhere (Ringelstein et al., 1990). The insonation of the MCAs provided the CBFV spectrum at the given depth of the MCA segment. The spectral envelope curves of the Doppler signal, which represented the maximum CBFV in the center of the two insonated vessels, was then stored at a sampling rate of 28 points per second. For the identification of the beginning of each trial ("epochs"), a marker signal was generated by the picture presentation software and stored simultaneously with the CBFV signals.

Data analysis

Data analysis was performed by AVERAGE, a WINDOWS® program for automated analysis of event-related cerebral blood flow data published elsewhere (Deppe et al., 1997). The program allows several processing steps like blood flow normalization, heart beat detection, noise reduction, artifact elimination, and filtering of the signal.

The CBFV data were first normalized to relative units (i.e., mean 100%) to eliminate velocity differences due to different insonation angles of the transducer probes. Heart cycle integration of the data was then performed to reduce modulation of the CBFV due to the myocardial pulsatility. CBFV data was segmented into epochs related to the cueing tone (marker signal), and finally averaged. The segmented interval was set from 20 s before and 40 s after the marker signal. Epochs containing CBFV values outside the range of 40–160% of the mean were excluded from further data processing. Transformation to relative units was performed by the following formula

$$dV = 100\,\frac{V(t) - V_{\mathrm{pre.mean}}}{V_{\mathrm{pre.mean}}} \quad (1)$$

where $V(t)$ is the CBFV over time and $V_{\mathrm{pre.mean}}$ is the mean velocity in the precueing interval −17 to −5 s. Formula (1) transformed the CBFV data into relative units (relative CBFV changes) with a mean velocity $v = 0$ over the averaged epoch. This way, signal deviations from zero reflect any event-related modulation of the CBFV over time.

fTCD lateralization index (LI_{fTCD}): For the picture-description language task, a fTCD hemispheric lateralization index was calculated. The LI_{fTCD} was calculated by the arithmetic mean

$$LI_{fTCD} = \frac{1}{N}\sum_{i=1}^{N} LI^{(i)} \quad (2)$$

of N lateralization indices LI_{fTCD} of each single trial ("epochs"). The sum index $i = 1, \ldots, n$ ($n = 30$) defines the number of each epoch. The lateralization index $LI^{(i)}$ of each epoch is calculated by the formula

$$LI^{(i)} = \frac{1}{T_{\mathrm{int}}}\int_{t_{\max} - \frac{1}{2}T_{\mathrm{int}}}^{t_{\max} + \frac{1}{2}T_{\mathrm{int}}} \Delta V_i(t)\,dt. \quad (3)$$

where

$$\Delta V_i(t) = dV_{i,\ \mathrm{left}}(t) - dV_{i,\ \mathrm{right}}(t) \quad (4)$$

was the difference between the relative perfusion changes in the left and right MCA in each epoch. The time point $t_{\max}$ represented the latency of the absolute maximum of $\Delta V_{(i)}(t)$ within the interval (13–30 s). An integration interval of 2 s at time period $t_{\max}$ was chosen to suppress nonphysiological fluctuations in the CBFV signal. The integral (Formula (3)) corresponded to the average difference of relative CBFV changes between the left and right MCA within the interval $t_{\max} \pm 2$ s.

The LI_{fTCD} quantifies the average difference of relative CBFV changes in a preset period during the PDLT in comparison to baseline in percent. By way of calculation, a positive LI_{fTCD} indicates a relative increase of the CBFV in the left MCA during the PDLT phase in comparison to the right MCA, vice versa. Thus, a positive LI_{fTCD} indicates left hemispheric language dominance. All LI_{fTCD}'s were statistically evaluated by the Wilcoxon test.

Accuracy

By calculation, each examination LI_{fTCD} of the subjects provides a stochastic sample of n LI_{fTCD} (=$LI^{(i)}$, see formula (2) above) on the basis of a maximum of 30 trials ("epochs"). Therefore, the standard error SE_{LI} defines a measure of accuracy and can be derived by the formula

$$SE_{LI} = \frac{\sigma_{LI}}{\sqrt{N}}, \quad (5)$$

where

$$\sigma_{LI} = \sqrt{\frac{\sum_{i=1}^{N}\left(LI_{fTCD} - LI^{(i)}\right)^2}{N-1}} \quad (6)$$

is the corresponding estimator for the standard deviation of each LI_{fTCD}. Normal distribution of each $LI^{(i)}$ was tested on the basis of the 10 times repetition of the activation procedure in subject HM by which a total number of 274 $LI^{(i)}$'s were obtained. Twenty-six epochs were discarded due to the nonphysiological CBFV values according to the standard preprocessing of the blood flow analysis program AVERAGE (Deppe et al., 1997). Frequency distribution of the remaining $LI^{(i)}$'s was Gaussian-shaped. Normal distribution was confirmed (Shapiro–Wilk W test, $P = 0.52$; Lilliefors probabilities $P \geq 0.20$). Therefore, SE_{LI} (Formula (5)) represents a statistical parameter for the estimation of the confidence region of each LI_{fTCD}, i.e., the accuracy of the assessment of language lateralization by fTCD. A signal-to-noise ratio of each LI_{fTCD} by a coefficient of variability CV was defined by the formula

$$CV = \frac{SE_{LI}}{|LI_{fTCD}|}. \quad (7)$$

Neuropsychological evaluation

All children were evaluated with respect to their linguistic proficiency level and degree of handedness. To test linguistic proficiency, the short version of the Illinois Test of Psycholinguistic Abilities (ITPA), revised edition, was administered. The short version of the ITPA consists of six subtests measuring (1) auditory sequential memory, (2) sound blending, (3) grammatic closure, (4) manual expression, (5) verbal expression, and (6) visual association. On the basis of the above-mentioned subtests, a composite score (=linguistic proficiency level-raw data: LP_{RD}) was calculated to estimate the global level of linguistic proficiency (Angermaier, 1999). Additionally, LP_{RD} scores of each subject were normalized into age-related *T*-scores (AM = 50, SD = 10) to assess the individual language proficiency level (=age-related linguistic proficiency level: LP_{AR}). Handedness was assessed using a manual dexterity test (grooved pegboard: www.parinc.com). Handedness index (HI) was calculated by measuring the manual speed of each hand to accomplish the pegboard task. Each hand was examined twice (sequence as follows: right–left–left–right). The arithmetic mean speed in seconds was calculated for each hand. The handedness index (HI) was defined by the formula

$$HI = \frac{t_L - t_R}{t_L + t_R} \quad (8)$$

where t_L and t_R is the mean speed in seconds of the left resp. right hand in the pegboard task.

Statistical evaluation

All statistics were computed with the software SPSS 11.0 (SPSS, 2003).

Validity

Intermethod validity was tested by the Pearson's product moment correlation coefficient r_{tc} (PDLT vs. PWGT) in the style of formula (9) (see below). Differences in activation between the two procedures were analyzed with a two-way ANOVA (factor 1 "activation procedure" [PDLT vs. PWGT]; factor 2 "group" [children vs. adults]; interaction "activation procedure" × "group"). Homogeneity of variances of the $LI^{(i)}$ assessed by the two activation procedures was confirmed (Levine test; $P = 0.11$).

Reliability

To test retest-reliability of the LI_{fTCD}'s, different linear regression analysis measures were used. For the group analysis, the Pearson's retest product moment correlation coefficient r_{tt} of the LI_{fTCD}'s on the basis of the two examinations was computed by the formula

$$r_{tt} = \frac{\sum_{k=1}^{K}(LI_k^1 - \overline{LI}^1)(LI_k^2 - \overline{LI}^2)}{\sqrt{\sum_{k=1}^{K}(LI_k^1 - \overline{LI}^1)^2 \sum_{k=1}^{K}(LI_k^2 - \overline{LI}^2)^2}} \quad (9)$$

where defines the LI_{fTCD} of subject *k* in the first ($e = 1$) and second examination ($e = 2$), respectively.

$$\overline{LI}^e = \frac{1}{16}\sum_{k=1}^{16} LI_k^1 \quad (10)$$

is the corresponding average LI_{fTCD} of the sample ($n = 16$) calculated from the first ($e = 1$) and second ($e = 2$) examination. The consistency of each examination was tested by the split-half (r_{sh}) and odd–even Pearson's product moment correlation coefficients (r_{oe}) based on formula (9), corrected by the Spearman–Brown formula (Lienert and Raatz, 1998, Chap. 10)

$$r_{sh,oe} = \frac{2\, r_{tt}}{1 + r_{tt}}. \quad (11)$$

Within each subject, a Wilcoxon test was administered to investigate any statistical difference between intraindividual LI_{fTCD}'s. The influence of the subjects' age or linguistic proficiency level on the reliability was assessed by a linear regression analysis. Therefore, the difference between the first and second LI_{fTCD} (absolute values) of each subject defined a measure of reliability (criterion score: $\Delta LI = |LI_1 - LI_2|$) as a function of age or linguistic proficiency (= predictor variables). A Friedman test (nonparametric equivalent of repeated-measures ANOVA; factor = "examination number") was computed to analyze the reliability in a single subject (HM). Practice and habituation effects over time were subsequently tested by a linear regression analysis.

Results

In Fig. 3, the average CBFV changes in the left and right MCA and the difference between the two insonated arteries ($CBFV_{left\ MCA} - CBFV_{right\ MCA}$) during resting phase and PDLT are plotted (subject AM, second examination). Differences in perfusion changes between the left and right MCA (bold black plot) during task performance are characterized by an initial relative increase in the right MCA (interval of 5–12 s), which reverses into a statistically stable left-sided perfusion increase.

Validity

The Pearson's correlation coefficient r_{tc} between the PDLT and PWGT in the sample was moderately high ($r_{tc} = 0.73$; $P \leq 0.05$; two-tailed). On a categorical level (left vs. right hemispheric dominance), the side of hemispheric dominance was confirmed in all but one subject. A two-way ANOVA revealed no significant differences in the factor 1 ("activation procedure" [PDLT vs. PWGT]; *df* 1, 18; $F = 1.92$; $P = 0.49$), factor 2 ("group" [children vs. adults]; $df = 1, 18$; $F = 0.49$; $P = 0.49$) or an interaction ("activation procedure" × "group"; $df = 1, 18$; $F = 0.08$; $P = 0.77$). The mean LI in the group with left-hemispheric lateralization was 3.91 (SD = 1.4; median = 3.81). Homogeneity of variances of the $LI^{(i)}$'s assessed by the two activation procedures was confirmed (Levine test; $P = 0.11$). Subjects with right-hemispheric lateralization ($n = 3$) were not included in the ANOVA due to the small sample.

Reliability

Test–retest reliability of the LI_{fTCD}'s in the sample was high ($r_{tt} = 0.87$; $P \leq 0.01$ two-tailed; see Fig. 4; range of the LI_{fTCD}'s:

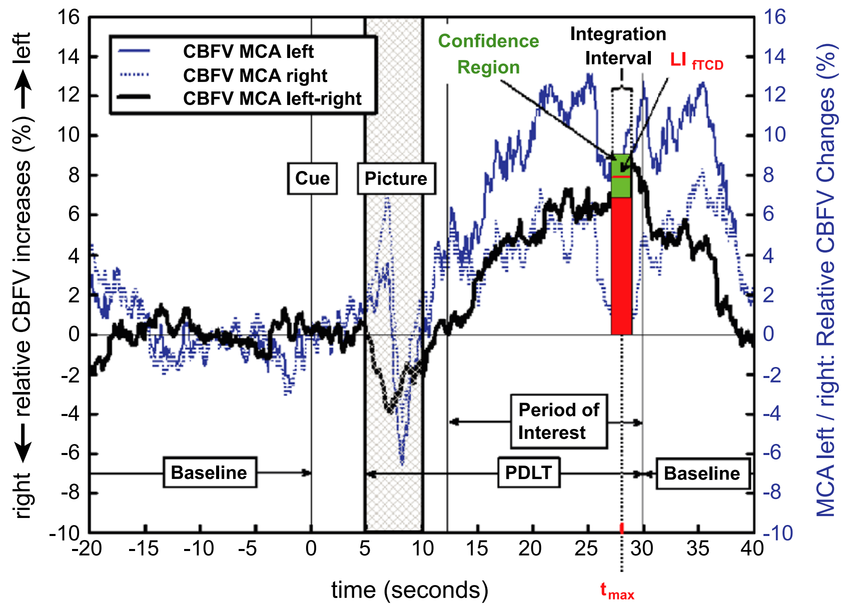

Fig. 3. Plot of the average perfusion changes in the insonated left and right MCAs during baseline and PDLT (right *y*-axis, blue plots), relative CBFV differences between the left and right MCA (left *y*-axis, black plot) including the indication of the LI_{fTCD} of one examination (red column with confidence regions in green; subject AM, second examination): differences in perfusion changes between the left and right MCA are characterized by an initial right-sided relative increase, which reverses into a statistically stable left-sided perfusion increase during the PDLT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

−4.46–6.86; AM = 2.63, SD = 3.1 [entire sample]) when reassessed within 1 month.

On a categorical level (left vs. right hemispheric dominance), the side of hemispheric dominance was reproduced in every single case. The consistency of both examinations as indicated by the odd–even and split-half reliability coefficients was also reasonable good with the exception of the odd–even reliability of the first examination (see Table 2).

On an intraindividual level, there were no differences in LI_{fTCD}'s in all but one subject (HF) when retested within 1 month (Wilcoxon test, see Table 1). Linear regression analysis revealed that the reliability of the LI_{fTCD}'s was not related to age or linguistic proficiency of the subjects (linear regression equations: $\Delta LI = 0.07$ age $+ 0.99$, $P = 0.786$, n.s.; $\Delta LI = -0.06\ LP_{RD} + 1.35$, $P = 0.813$, n.s.). Coefficients of variability ($CV_{LI1,\ LI2}$) showed a weak negative correlation (n.s.) with

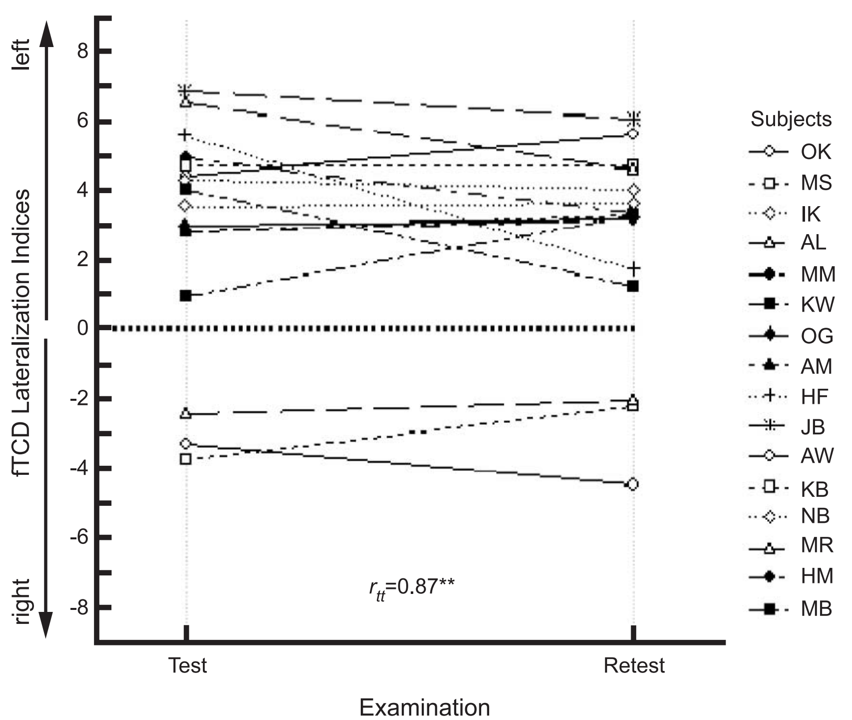

Fig. 4. One month retest-reliability assessed in 16 subjects (** = highly significant correlation; $P \leq 0.01$, two-tailed).

Table 2
Consistency measures of reliability within each examination

Consistency measures		
Examination	Split-half reproducibility	Odd–even reproducibility
1	0.53*	0.88**
2	0.87**	0.89**

* Significant correlation, $P \leq 0.05$.
** Highly significant correlation; $P \leq 0.01$, two-tailed.

linguistic proficiency (LP_{RD}) and age, i.e., the signal-to-noise ratio improves slightly (n.s.) with increasing linguistic proficiency (first examination: $r = -0.33$; $P = 0.21$; second examination: $r = -0.2$; $P = 0.48$) and age, respectively (first examination: $r = -0.25$; $P = 0.34$; second examination: $r = -0.24$; $P = 0.36$). Ten times task repetition in a single subject showed no trend indicating any practice or habituation effects (linear regression function: LI_{fTCD} = 0.01 exam. no. + 3.5; see Fig. 5). There were also no changes in accuracy (SE_{LI}) or in signal-to-noise ratio (CV) over time (linear regression equations: $SE_{LI} = -0.06$ exam. no. + 0.68, $P = 0.87$, n.s.; CV = −0.06 exam. no. + 0.27, $P = 0.37$, n.s.). The Friedman Test (factor = "examination number") showed a significant influence of the factor "examination no." (F = 9,162; $P \leq 0.01$), i.e., the fourth examination statistically differed from the other nine examination. The recalculation of the Friedman test with exclusion of examination no. 4 showed no significant differences between the examinations (F = 8, 160; $P = 0.13$).

Accuracy

Accuracy SE_{LI} in all test–retest examinations with inclusion of the 10 times repetition of the examination in subject HM ranged between 0.38 and 2.36 (see Table 1). The mean accuracy $\overline{SE}$ was 0.91 (SE 0.06). The 95% percentile of all accuracy values was 1.61, i.e., 5% of all examination displayed a lower accuracy.

Additional results

There was no consistent correlation between age and language lateralization (first examination: $r = 0.07$; $P = 0.80$; second examination: $r = -0.31$; $P = 0.31$) or linguistic proficiency and language lateralization (first examination: $r = -0.08$; $P = 0.80$; second examination: $r = -0.23$; $P = 0.45$).

Discussion

This study introduces fTCD as a noninvasive method for assessment of language lateralization in young children. Validity of the fTCD using a picture-description language task was confirmed by good intermethod correlation compared to an established phonetic word generation task. One month reliability in a group of 16 children aged 2–9 years was high. Ten repeated fTCD assessments in a single subject revealed no trend indicative of habituation or practice effects. No correlation between language lateralization and age or language proficiency was found.

Validity

In pediatric fMRI, the majority of studies on language lateralization utilized variations of semantic or phonological word generation tasks (Gaillard et al., 2000, 2003b; Hertz-Pannier et al., 1997; Holland et al., 2001; Lee et al., 1999; Schlaggar et al., 2002). These tasks reliably activate left inferior frontal gyrus, dorsolateral prefrontal cortex, and midfrontal cortex. Patterns of activation have been similar to those in adults (Schlaggar et al., 2002). However, children seem to exhibit a greater extent of activation and more bilateral frontal activation (Gaillard et al., 2000; Hertz-Pannier et al., 1997).

In modification to established semantic fluency tasks, we used a picture-description language task (PDLT) that requires to verbally

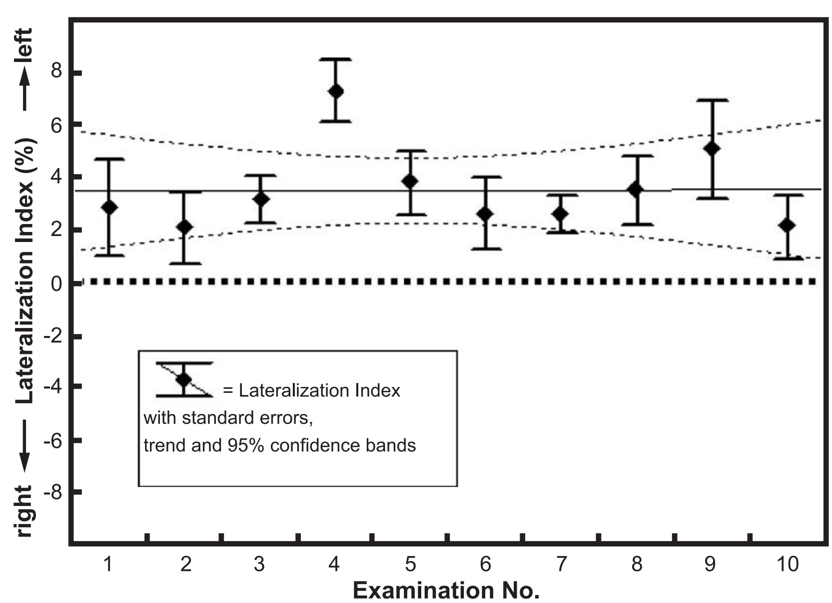

Fig. 5. Intraindividual series of 10 examinations of the LI_{fTCD} with standard error (subject HM): There is no trend in lateralization, accuracy, and signal-to-noise ratio over time. However, the Friedman test reveals one outlier (examination no. 4) with respect to differences in lateralization.

retrieve items from a given semantic context (i.e., the given stimulus in each trial) in a narrative way. This way, we enabled the participation of even young children who would not comply with the standard administration of a semantic fluency task (i.e., verbally enumerate semantic items to a given stimulus). The PDLT showed concordant results compared with an established activation procedure, i.e., phonetic word generation task (Deppe et al., 2000; Knecht et al., 1998a). We found an average language lateralization of 3.91% (average LI_{fTCD} in the group with left hemispheric lateralization), which was comparable to the lateralization indices obtained by a word generation task in healthy adult right-handers (3–4%; see Knecht et al., 2000).

Reliability

In our study, an important focus was to obtain parameters on reliability of a language lateralization index in children as assessed by fTCD. Reliability as such is a core quality criterion of any testing procedures (Anastasi and Urbina, 1997). This way, fTCD must demonstrate to be reproducible over time, and to be independent of random variability, learning, or habituation. Obtaining statistical parameters of reliability (i.e., retest reliability coefficients, consistency, signal-to-noise coefficients) is crucial when monitoring possible shifts in hemispheric functioning. However, only a few fTCD studies on brain activation explicitly deal with this issue. Stroobant and Vingerhoets (2001) tested the reliability of a number of verbal tasks (word fluency, verbal similarities, syntactic judgments) in a group of healthy adults and found a moderately high reliability (Pearson's r ranging from 0.53 to 0.68). In contrast, Knecht et al. (1998b) found an excellent correlation coefficient in a word fluency task.

There are different sources in pediatric fTCD that can produce "noise" in terms of error variance, which in turn may act on the reliability of activation tasks. These sources concern the *fTCD procedure*, the *ultrasonography technique*, and ongoing *autonomic processes.*

fTCD procedure

Appropriate external testing conditions that stimulate the participation of subjects subserve the validity and reliability of testing results (Anastasi and Urbina, 1997). Compared to other noninvasive neuroimaging tools, the fTCD procedure exhibits characteristics that make it ideal for follow-up examinations in even very young children. fTCD is nonfrightening and can be easily performed under quiet conditions in an appropriate testing room. Anxious children may be attended by their parents and the technique is fairly robust against movements of the subjects (Knecht et al., 1998a). Particularly, the latter is an important feature that prevents the occurrence of signal artifacts (Deppe et al., 2004). In our study, all candidates who fulfilled the inclusion criteria successfully participated in the fTCD examination. One child at the age of 2.3 years was successfully included. Almost half of the subjects (seven subjects) were aged less than 5 years. In contrast, pediatric fMRI, apart from studies in sedated or passively stimulated subjects (e.g., Dehaene-Lambertz et al., 2002; Souweidane et al., 1999), bears a considerable risk of study drop-outs due to anxiety or lack in task compliance (e.g., Holland et al., 2001).

Ultrasonography technique

In fTCD examinations, the insonation angle is unknown and unlike transcranial color-coded duplex sonography cannot be corrected (Bartels and Flugel, 1994). In normal anatomical conditions, the insonation angle varies between 0° and 30° when the MCA is insonated transtemporally. This leads to a negative deviation of the observed velocity up to 15% depending on the cosine function of the insonation angle (Aaslid, 1986). Compared to adults, children exhibit a larger temporal bow window which allows a more variable positioning of the ultrasonic probes (Deeg et al., 1997). This in turn increases the likelihood of variable velocities observed when multiple fTCD examinations in one subject are performed. Blood flow velocities (BFVs) assessed in the basal cerebral arteries of children increase with age. They reach their maximum about the age of 6 and then slowly converge to lower adult level (Schoning et al., 1993). However, the statistical analysis in our study is based on normalized CBFV values, i.e., only relative changes in perfusion between the left and right MCA are analyzed. This way, the influence of variable CBFV due to variable insonation angles or age-dependent differences in CBFV are eliminated (Deppe et al., 1997).

Autonomic processes

During task and resting conditions, the BFVs in the basal cerebral arteries exhibit a spectrum of different spontaneous periodic modulations that can be differentiated in frequency bands (Diehl and Berlit, 1996). The largest amount of modulations in CBFV is due to heart beat pulsatility and respiration (P and R waves), followed by low-frequency modulations with minor impact on CBFV (Mayer and B waves, resp.; Diehl et al., 1991). These modulation clearly exceed the changes in CBVF evoked by a language task itself and may lead to increases in the CBFV up 50% above the mean signal (Knecht et al., 1998a). CBVF in children reveals a similar pattern of spontaneous periodic modulation with slight shifts in frequency bands given the accelerations in heart beat and respiration in children compared to adults (Zernikow et al., 1994).

Autonomic processes that act on CBFV may fluctuate over time and thus add variability to the fTCD data. Autonomic parameters like respiration and heart beat change when cognitive tasks are repeated and are most marked for task-related arousal and attention (Frey and Siervogel, 1983; Näätänen, 1992; Rombouts, 1982). However, the influence of changes in autonomic parameters on the CBFV is global since they always affect the entire cardiovascular system. Thus, fTCD lateralization indices based on relative difference in perfusion increases between the left and right artery are not affected as recently demonstrated in a longitudinal single-subject study on the effect of task repetition using fTCD and fMRI (Lohmann et al., 2004). The influence of these non-task-related modulations can be reduced effectively by heart cycle integration, averaging and by using a lateralization measure that is based on relative differences in perfusion increases in the insonated arteries (Deppe et al., 2004). Our study demonstrated an accuracy of the language lateralization indices of 1.61% (95% percentile). This means in 95% of our sample lateralization in CBFV can be detected if the relative increase CBFV exceeds 1.61%. This accuracy is in good agreement to parameters found in adults performing silent word generation measured by fTCD (accuracy of 1% of the mean CBVF; Deppe et al., 1997; Knecht et al., 1998a).

Developmental considerations

We found no consistent evidence for an age-related change in language lateralization. Two cross-sectional fMRI studies found a slight shift in activation towards a greater left-sided language lateralization across age as measured in healthy children performing a silent verb generation task (Holland et al., 2001; Wilke et al., 2003).

Because fTCD has a low spatial resolution, there could, theoretically, have been age-related regional increases next to regional decreases of perfusion within the territory of the insonated arteries, resulting in an unchanged net blood flow velocity within the supplying middle cerebral artery. The possibility of such effects could only be ruled out by fMRI.

The absence of a shift in language lateralization with age in the present study cannot be explained by a lack of sensitivity of fTCD. In agreement with a number of fMRI and positron emission tomography (PET) studies (Blinkenberg et al., 1996; Sadato et al., 1997; Turner et al., 1998), fTCD is well capable of detecting relative blood flow increases in parallel to the increasing speed during finger tapping (Dräger and Knecht, 2002).

Crucial within the context of hemispheric specialization of language function is the large intersubject variability of language lateralization in children as well as in adults (Knecht et al., 2000; Pujol et al., 1999; Wilke et al., 2003). Therefore, it is not sufficient to approach the question of age-related changes in language lateralization by means of a between-subject design (cross-sectional study). Given the small sample size and without repeated interindividual determination of language lateralization during language development (longitudinal study), the issue of an increasing language lateralization must be postponed at this stage of investigation.

One could speculate that age, or the linguistic proficiency of the subjects could be an important factor for reliability since advanced cognitive and language proficiency is likely to facilitate complying with a cognitive task. In our study, this was not the case. Age and linguistic proficiency showed only a weak correlation (n.s.) with the accuracy of the lateralization indices with slight age-related increases in signal-to-noise ratios of the LI_{fTCD}'s. These results might be explained by a selection bias in our sample with respect to the age-related linguistic proficiency level (LP_{AR}). There was no subject with an LP_{AR} below the normal range of the general population ($LP_{AR} = 50 \pm 1$ SD). Six of the subjects (~ 43%) revealed an LP_{AR} above normal range ($LP_{AR} = 60$). This might have resulted in a homogenous sample capable to easily comply with the task.

Conclusion

Pediatric fTCD constitutes a promising tool for the investigation of language lateralization in very young children. It therefore represents an important complementary tool in pediatric neuroimaging given its applicability in early infancy where the vast part of developmental changes is likely to happen. This way, it is predestinated for follow-up investigations of hemispheric involvement in language function during childhood. This could tell us about the development of higher cortical functions and to give implications about recovery of dysfunctions and plasticity of the human brain.

Acknowledgments

We would like to thank Sabine Bruchmann and Anne Jule Geburek for their helpful comments on the manuscript. This work was supported by Nordrhein-Westfalen (Nachwuchsgruppe: Hemispheric specialization), the Innovative Medizinische Forschung (Kn-1-1-II/96-34), the Deutsche Forschungsgemeinschaft (Kn 285/4-1 and Kn 285/6-1), and the Neuromedical Foundation (Stiftung Neuromedizin), Münster.

Appendix A. PDLT—List of fTCD stimuli (in alphabetical order)

- Apple
- Backpack
- Bicycle
- Bird
- Car
- Elephant
- Flower
- Giraffe
- Goose
- House
- Ice Cream
- Cow
- Lion
- Motorbike
- Parrot (Parakeet)
- Pencils
- Pie
- Pig
- Pipe
- Refrigerator
- Sail Boat
- Slide
- Sneakers
- Socks
- Tiger
- Truck
- Umbrella
- Vacuum cleaner
- Washing machine
- Watch

Pictures of the stimuli can be accessed via: http://neurologie.uni-muenster.de/ger/mitarbeiter/lohmann/projekte.html.

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