Brain & Language 129 (2014) 1-6

ELSEVIER

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Short Communication

Cerebral lateralization for language in deaf children with cochlear implantation



Anna Maria Chilosi ^{a,*}, Alessandro Comparini ^a, Paola Cristofani ^a, Marco Turi ^b, Stefano Berrettini ^c, Francesca Forli ^c, Giovanni Orlandi ^d, Alberto Chiti ^d, Nicola Giannini ^d, Paola Cipriani ^a, Giovanni Cioni ^{a,d}

^a Dipartimento di Neuroscienze dell'Età Evolutiva, IRCCS Fondazione Stella Maris, Pisa, Italy

^b Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), Università di Firenze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), Università di Firenze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), Università di Firenze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), Università di Firenze, Psicologia, Area del Farmaco e

^c Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa, Via Paradisa 2, 56100 Pisa, Italy

^d Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Via Roma 67, 56100 Pisa, Italy

ARTICLE INFO

Article history: Accepted 11 December 2013

Keywords: Cerebral language lateralization Functional transcranial Doppler ultrasonography Deaf children Cochlear implantation Language outcome

ABSTRACT

Functional Transcranial Doppler ultrasonography (fTCD) was used to investigate the effects of early acoustic deprivation and subsequent reafferentation on cerebral dominance for language in deaf children provided with Cochlear Implantation (CI). Twenty children with CI (13 in right ear and 7 in left ear) and 20 controls matched for age, sex and handedness were administered a fTCD animation description task. Left hemisphere dominance for language with comparable mean Laterality Indexes (LIs) was found in children with CI and controls; right-ear implanted subjects showed cerebral activation controlateral to implanted ear more frequently than left-ear implanted ones. Linguistic proficiency of CI recipients was below age expectation in comparison to controls; language scores did not significantly differ between children with left and right LI, whereas both age and side of implantation were significantly related to language outcome. Theoretical implication and potential clinical application of fTCD in CI management are discussed.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

One of the central issues of developmental neuroscience is the understanding of how highly specialized functions, such as language, are biologically constrained and to which extent they depend on and can be modified by environmental inputs.

In the case of congenital deafness, there is evidence from animal and human studies that early auditory deprivation leads to an atypical organization of auditory nervous system (Gilley, Sharma, & Dorman, 2008; Kral & Sharma, 2012). Profound congenital deafness may also alter the pattern of cerebral asymmetry for language that has been shown to favor the left hemisphere in the first months of life in typically developing infants with normal hearing (Dehaene-Lambertz et al., 2006).

Results of earlier studies aimed at determining whether deaf children develop the same pattern of hemispheric asymmetry for language as hearing children (Kelly & Tomlinson-Keusey, 1981) revealed an inverse laterality pattern in the two groups. In fact, in a visual half-field presentation task of words or letters, deaf subjects showed a left visual field advantage (suggestive of right

* Corresponding author. Address: Dipartimento di Neuroscienze dell'Età Evolutiva, IRCCS Fondazione Stella Maris, Viale del Tirreno 331, 56128 Calambrone, Pisa, Italy. Fax: +39 050886247. hemisphere dominance for linguistic stimuli), whereas hearing subjects showed a right visual field advantage (indicative of a left hemisphere dominance). In a study by Marcotte and Morere (1990) cerebral lateralization for speech in right-handed normal hearing and deaf adolescents was assessed using a dual-task paradigm. Subjects with normal hearing at birth and deafness acquired after 3 years of age displayed left hemispheric dominance for speech production, whereas children with both congenital and early acquired deafness (onset 6-36 months) showed an atypical cerebral representation. These results support the hypothesis that exposure to adequate environmental stimulation during a critical developmental period may be needed to activate left hemispheric dominance for speech. Nevertheless, according to D'Hondt and Leybaert (2003), hemifield paradigm studies do not provide clear empirical evidence of left hemisphere advantage for written words by deaf children, because lateralization effects may vary in relation to the semantic or phonological nature of the task.

In the last twenty years with the advent of Cochlear Implant (CI), deaf children can benefit, from those critical sensory inputs that are necessary for developing a 'listening brain'. Restoring auditory input through monoaural cochlear implantation in children who are born profoundly deaf, offers a unique opportunity for investigating the role of stimulus-dependent mechanisms in the asymmetrical organization of neurofunctional circuitries

E-mail address: achilosi@inpe.unipi.it (A.M. Chilosi).

⁰⁰⁹³⁻⁹³⁴X/\$ - see front matter \circledcirc 2013 Elsevier Inc. All rights reserved. http://dx.doi.org/10.1016/j.bandl.2013.12.002

sub-serving language and on the variables that influence these processes, such as CI side, age at implantation and language experience before CI. As reported by several authors (Hugdahl, 2005; Kimura, 1967; Langers, van Dijk, & Backes, 2005; Woldorff et al., 1999), although in the normal hearing population, both auditory cortices receive sensory input from both ears, they are excited most strongly by stimulation of the contralateral ear. In the case of deaf children with unilateral auditory reafferentation, the question on the effects of right- or left-sided CI on the hemispheric dominance for language has never been clearly settled.

Direct measures of cerebral language lateralization by means of classical non-invasive methods such as the dichotic listening paradigm and functional Magnetic Resonance Imaging (fMRI) are not feasible in deaf subjects with CI: for the former, since most patients are monaurally fitted with CI, and for the latter, because high MRI magnetic fields (≥ 1.5 T) may interfere with the magnetic components of the implant. In the past decade neuroimaging with Near Infrared Spectroscopy (NIRS) has shown to be a potential complement to the above objective techniques but application in deaf subjects with CI has just started (Sevy et al., 2010). Some indirect evidence on cerebral language lateralization of implanted subjects has been recently provided by Gilley et al. (2008), who used high density EEG recordings to estimate generators of the P1 response.

In recent years, functional transcranial Doppler ultrasound (fTCD) has been proposed as a reliable alternative method for measuring cerebral lateralization during speech in both adults and children. This technique assesses cerebral lateralization by comparing changes in mean blood flow velocity in the middle cerebral arteries (MCAs) during domain-specific tasks. fTCD has been shown to be highly correlated with classic measures of hemispheric lateralization such as the Wada test (Knecht et al., 1998) and fMRI (Deppe et al., 2000; Somers et al., 2011). fTCD has good temporal resolution and provides continuous information about event-related changes in cerebral blood flow associated with functional cortical activation (Deppe et al., 2000); it is non-invasive and is particularly suitable for children (Bishop, Watt, & Papadatou-Pastou, 2009; Haag et al., 2010). Furthermore, Bishop et al. (2009) has created an fTCD animation description task designed to be particularly engaging for children. This paradigm has shown good split-half reliability in children and in adults, and a highly significant correlation with other fTCD tasks, such as word generation and picture description tasks.

From a theoretical point of view, the study on cerebral language organization in deaf children after acoustic reafferentation could provide insights into the plasticity of the auditory system and the neural substrates underlying language processing. From a clinical point of view, fTCD may prove to be a valuable technique in assessing cerebral language processing in deaf children with CI, and could help clinical teams in CI management.

The aim of this study was three-fold:

- to evaluate whether fTCD is suitable for deaf children provided with Cl;
- to investigate the effects of early severe acoustic deprivation and subsequent reafferentation on patterns of hemispheric dominance for language in comparison with healthy peers;
- to evaluate whether hemispheric dominance for language varies in relation to CI side, in terms of fTCD activation contra-or ipsilateral to the ear implanted.

In order to avoid any confounding effect related to different communication modes, only children with exclusively audioverbal training participated in the study. Cerebral lateralization was assessed by fTCD using the animation description task developed by Bishop et al. (2009). Participants were 20 deaf children fitted with CI (13 in right ear and 7 in left ear) and 20 controls matched

for chronological age, sex and handedness. For each subject a Laterality Index (LI) was computed offline, using AVERAGE software and analyzed on the basis of age at implant, ear implanted and language outcome.

2. Results

2.1. fTCD data

The number of accepted epochs did not differ between subjects with CI (M 22.9, SD 6.2; range 13–30) and controls (M 23.8, SD 6.7; range 14–30).

Fig. 1 plots mean activation values, averaged over all epochs for right and left MCAs in deaf and control subjects. No statistically significant difference was found between CI recipients and controls in the measurements taken by the right (CI M -0.82, SD 2.43; controls M -0.23, SD 3.17; t = -0.85, p = 0.45) or left probe (CI M 0.14, SD 1.77; controls M 0.30, SD 2.74; t = -2.19, p = 0.83).

Evaluation of the figure indicates that the control group's average activation for left and right MCAs was comparable to that reported by Bishop et al. (2009) using the same paradigm.

Mean laterality indexes in controls and patients with CI (see Table 1), did not differ significantly (t = 0.44, p = 0.5), although children with CI showed a slightly higher interindividual variability.

The mean LI significantly differed from 0 in both control (t = 2.01, p = 0.05) and CI subjects (t = 2.07, p = 0.05). However, if side of implantation was considered, mean LI values of right-ear implanted children differed significantly from 0 (M 3.32., SD 4.46; t = 2.68, p < 0.005), whereas left-ear implanted children showed more inconsistent results and the mean LI did not differ significantly from 0 (M 0.02, SD 4.5; t = 0.02, p = 0.99). Though age at implantation differs between children with right and left-ear CI, the effect of side on LI was statistically significant, when adjusted for age at implantation (ANCOVA, p = 0.005).

Odd–even split-half reliabilities were sufficiently high for both control and CI groups (r = 0.80 and r = 0.86 respectively, p < 0.001). Following Haag et al. (2010), we calculated the standard error of the mean (SEM) of the lateralization index of each subject and compared the mean values of CI and control subjects (Table 1). The mean SEM of the two groups did not differ significantly (t = 0.56, p = 0.43), suggesting a comparable signal quality and performance continuity in both groups.

On a categorical level, 70% of control subjects showed a positive LI, indicative of left hemisphere dominance (LH), 20% had right hemisphere dominance (RH) and 10% were uncertain; these figures were comparable to the values reported in literature for typically developing children (Bishop et al., 2009; Haag et al., 2010; Lohmann, Dragger, Muller-Ehrenberg, Deppe, & Knecht, 2005), confirming the reliability of the results obtained in this study. A similar distribution was observed in children with CI (65% left, 20% right and 15% uncertain) and did not differ significantly from controls (Chi square = 1.47, df = 3, p = 0.68). Comparison between age at implantation of deaf subjects with negative and positive LI did not reveal any statistically significant difference (Mann–Whitney U = 34, p = 0.8).

Hemispheric activation was contralateral to the side of implanted ear (LH with right ear CI, and RH with left ear CI) in 13/ 20 children, and ipsilateral (LH with left-ear CI and RH with right-ear CI) in 4/20 children; three patients failed to show statistically significant hemispheric superiority. By taking into consideration direction (positive or negative values), and not magnitude of LIs, the frequency of controlateral activation was significantly higher in right- than in left-ear implanted children (Chi square = 3.77, df = 1, p = 0.05). About 77% of right-ear implanted children presented contralateral activation in left hemisphere,



Fig. 1. Average activation across epochs for left (black) and right (gray) MCA in the control and CI groups.

Table 1 Mean laterality indexes, mean standard error of the mean and frequency of left, right and uncertain lateralization according to Knecht criteria in control and CI children.

	Lateralization Index (LI)		Standard error of the mean (SEM)		Frequency of lateralization types (number)		
	Mean (SD)	Range	Mean (SD)	Range	Left	Right	Uncertain
Controls	1.67 (0.92)	-5.6 to 9.8	0.83 (0.55)	0.3-2.2	14	4	2
Children with CI	2.15 (1.03)	-6.4 to 13	1.03 (0.44)	0.5-2.8	13	4	3

15% were uncertain and only one activated the ipsilateral right hemisphere. In the case of left-ear implantation, 43% of children activated the controlateral right hemisphere, 43% showed left hemisphere activation, ipsilateral to the implanted ear, and only one presented an uncertain activation.

Only one girl with CI and her normal control were left-handed and both showed right hemisphere dominance for language.

2.2. Linguistic data

Evaluation of language outcome revealed that CI participants with both left and right hemisphere activation performed significantly lower than controls (U = 66, p < 0.000).

The composite score of implanted children with left hemisphere activation was higher (M 7, Range 4–8) than the composite score of patients with right hemisphere activation for language (M 6, Range 4–8). The difference was not statistically significant (U = 29.5, p = 0.49), although 40% of subjects with left- but only 20% with right-hemisphere activation attained the maximum score in language outcome. When considering single language tests, no statistically significant differences were found between deaf children with left and right LI.

Language composite score varied in relation to age at implantation with a statistically significant inverse correlation between age at implantation and language outcome (Spearman's rho = -0.49, p = 0.03).

Language composite scores also varied in relation to side of implantation (right CI: M 6.7, SD 1.5; left CI: M 4.7, SD 0.9) for a significantly lower language performance in left- compared to right-ear implanted subjects (Mann–Whitney test U = 16.5, P = 0.046). The effect of side on language score was almost statistically significant, when adjusted for age at implantation (ANCOVA, p = 0.06).

Taking into consideration language performance on each single test statistically significant differences were found between children with left and right-sided CI in grammar comprehension (f 4.2, p = 0.05), and expressive vocabulary for low frequency words (f 5.5, p = 0.033) for better performances of right-compared to left-ear implanted children.

3. Discussion

The current study addresses the question of how hemispheric asymmetry for language develops in children with profound sensorineural hearing loss, who receive monoaural cochlear implantation.

Data by Bishop et al. (2009) were replicated and confirmed that the fTCD animation description task is a suitable and valid tool for assessing normally developing children's hemispheric lateralization during overt speech. This study demonstrated validity of the procedures in analyzing cerebral language lateralization also in deaf children fitted with CI, a population in which, to the best of our knowledge, this issue has never been specifically investigated.

Both normal hearing and children with CI showed a similar intra-subject performance variability and stability of signal quality, as documented by comparable SEMs and fTCD signal values across all recording epochs. Furthermore, the relatively high split-half correlation coefficients confirmed the reliability of this procedure, which also appeared to be ecologically valid and easily applicable to CI recipients.

Mean LIs of deaf patients and controls were comparable in terms of prevalent left hemisphere activation during speech that approached values reported in literature for normal-hearing children (Bishop et al., 2009; Haag et al., 2010; Lohmann et al., 2005).

This finding provides some evidence in support of child brain developmental plasticity, because it is well known from both animal and human studies, that absence of sensory input from birth affects normal growth and connectivity necessary to form a functional sensory system and may alter the organization of language-related neural circuitries (Gilley et al., 2008; Kral & Sharma, 2012; Peterson, Pisoni, & Miyamoto, 2010).

Language activation was contralateral to the side of implanted ear in 70% of our participants, in accordance with the normal hearing population, in which auditory signals from one ear reach both auditory cortices, but contralateral projections are stronger and more preponderant than ipsilateral ones (Hugdahl, 2005; Langers et al., 2005). However, the proportion of patients with prevalent activation of the contralateral pathway varied in relation to the side of implanted ear. Almost 80% of right-, but only 60% of left-ear implanted children showed normal left-hemispheric activation; thus, 40% of left-ear implanted children atypically activated the right hemisphere. These findings show that most deaf children in the group keep the inborn i.e. biologically constrained left-hemispheric language preference.

Activation of the contralateral right hemisphere in the presence of left-ear CI occurred in 3 out of 5 subjects implanted within 4 years of age, whereas the two children who received left-ear CI at a much later age (8 years) showed ipsilateral activation of the left hemisphere.

These findings suggest that unilateral reafferentation of the left ear may induce reorganization of language functions in the right hemisphere if it occurs early in life. According to this hypothesis the transfer of language functions to the right hemisphere may be the effect of cerebral plasticity analogously to what occurs in children with early left focal brain lesions (Chilosi et al., 2005; Guzzetta et al., 2008; Staudt et al., 2001).

Considering the whole sample, hemispheric dominance for language appeared to be influenced by both age and side of implantation. The age at implantation effects on LI difference between children with left and right CI were significant statistically and the effect of side was still significant when adjusted for age at implantation.

Looking at language outcome, all deaf children showed a rather satisfactory language development after CI and acquired lexical and grammar skills sufficient to carry out the fTCD narrative task. However, implanted children's linguistic proficiency was, on average, significantly lower in comparison to hearing peers, as about fifty percent of the patients performed below age expectation, under task-demanding conditions like standardized language testing.

Language scores did not significantly differ between children with left and right LI, whereas both age and side of implantation were significantly related to language outcome. Though age at implantation was significantly lower in right- compared to leftear implanted subjects, the effect of side on language proficiency was almost statistically significant, when adjusted for age at CI.

From a theoretical point of view, the results of the present study may provide arguments both in favor and against neuroplasticity. Neural language organization, after auditory deprivation and subsequent reafferentation, seems to follow a near-normal pattern of hemispheric dominance, but language proficiency may be nonoptimal in some children. Taken together, our results suggest that brain organization of language functions is the result of a complex interaction between experience-dependent mechanisms and asymmetrical neurobiological constraints (Neville et al., 1998, Sharma, Nash, & Dorman, 2009). Thus, neurodevelopmental plasticity after cochlear implantation seems to be influenced by stimulus-driven experience within a time-limited sensitive period (Kral & Sharma, 2012).

In conclusion, our data indicates that fTCD is a valid tool in evaluating cerebral language dominance in deaf children fitted with CI and shows that, despite severe auditory deprivation, normal predisposition for language processing in the left hemisphere is generally maintained.

From a clinical perspective, early age at implantation and rightear CI appear to contribute to a more favorable language outcome, thanks to the convergence of an optimal sensitive period for language learning and reafferentation of the auditory route contralateral to the left hemisphere.

The choice of which ear to implant may be more problematic when CI fitting occurs later in life, because the effects of CI reafferentation on hemispheric dominance could be influenced by previous neural organization related to the longer pre-implantation hearing experience.

Though the results of this study must be considered preliminary, they provided evidence in supporting the hypothesis that, in verbal deaf subjects, fTCD evaluation of language lateralization may represent an easy and non-invasive procedure that could be added to the standard pre-implantation assessment protocols currently in use. Further investigation on larger samples is required to confirm our data.

4. Methods

4.1. Participants

The experimental sample consisted of 40 subjects, 20 deaf children fitted with CI and 20 controls matched for chronological age (CI: M 8.5 y, SD 3.1 y, range 4–14.4 y; Controls: M 8.5 y, SD 3.0 y, range 4.5–14 y; t = -0.10, p = 0.91), sex (9 males, 11 females) and handedness (1 left, 19 right). Children with CIs were recruited from a wider sample of patients referred to the Department of Developmental Neuroscience, IRCCS Stella Maris and to the Otorhinolaryngology, Audiology and Phoniatrics Unit of Pisa University Hospital. Originally 22 CI patients were included in the study, but two did not produce enough useable epochs with fTCD because of insufficient collaboration.

Thirteen children received a right CI (at a mean age of 2.3 y, SD 1.02 y; range 1.3–5 y), whereas seven were provided with a left-ear implant (at a mean age of 4.8 y, SD 2.03 y, range 3–8 y). The age difference at implantation of the two groups was statistically significant (t = -3.5, p = 0.001). The mean length of CI use (hearing age) was 5.3 y (SD 2.4 y, range 2–9.3 y). Hearing age of right- (M 5.5 y, SD 2.4, range 2.4–9.3) and left-ear implanted children (M 4.9 y, SD 2.3, range 2–8.1 y) did not differ statistically.

At the time of fTCD and clinical evaluation the mean chronological age of right CIs was 7.9 y (SD 3.5 y, range 4–14.4 y) and 9.6 y for left ones (SD 2.4 y, range 5.5–13.5 y) and did not significantly differ (t = -1.19, p = 0.084).

The main criteria for inclusion were: profound preverbal sensory-neural hearing loss; age at diagnosis and provision of hearing aids within 18 months; no signs of either neurological or psychiatric disorders associated with deafness and normal non-verbal IQ at Leiter International Performance Scale-Revised (M 103.9, SD 9.8, range 87–114); exposition to only oral Italian language and auditory-verbal language training after implantation; the length of CI use was set at 24 months (or more) post cochlear implant activation. The presence of additional neurological and psychiatric disorders was excluded by clinical and instrumental evaluation (including cerebral MRI performed before CI implantation). Moreover, only children who showed lexical and grammar skills sufficient to carry out the fTCD narrative task participated in the study.

Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Clinical and audiological characteristics of the sample are reported in Table 2.

Parental consent and child assent were obtained in all cases. The study was approved by the Ethics Committee of the IRCCS Fondazione Stella Maris (Number 36/2010).

4.2. Apparatus

Bilateral blood flow velocity in middle cerebral arteries (MCAs) was measured simultaneously by a commercially available Doppler ultrasonography device (DWL Multidop T2: manufacturer, DWL Elektronische Systeme, Singen, Germany), using two 2-MHz transducer probes mounted on a flexible headset. For the experimental presentation and stimulus design, Presentation software (Neurobehavioral System) was used. Visual stimuli (videoclips) were presented on a standard 15' Dell laptop, which sent parallel port marker pulses to the Multidop system to signal the start of each epoch. Table 2

Characteristics of patients with Cochlear Implantation. Legend: PTA = Pure tone audiometry, mean threshold at 500, 1000, 2000 HZ, Cl = Cochlear Implant, Ll = Lateralization Index.

Subject N.	Gender	Handednesss	Age at first hearing aids fitting (months)	Age at CI (years)	Ear implanted	Age at behavioural and Doppler testing (years)	LI side	LI value
1	F	Right	5	1.7	Right	4	Left	3.34
2	М	Right	10	2.1	Right	4.7	Left	3.03
3	F	Right	8	1.5	Right	5	Uncertain	-0.84
4	F	Right	14	1.4	Right	5.5	Left	2.75
5	F	Right	6	1.7	Right	5.6	Right	-4.06
6	F	Right	12	1.6	Right	5.5	Uncertain	1.18
7	F	Right	10	1.3	Right	5.7	Left	1.35
8	Μ	Right	16	3	Right	7.5	Left	3.43
9	Μ	Right	18	2.5	Right	10	Left	11.08
10	Μ	Right	14	2.2	Right	10.6	Left	4.55
11	М	Right	14	2.2	Right	10.6	Left	2.29
12	Μ	Right	18	3.5	Right	14.4	Left	13
13	F	Right	36	5	Right	13.5	Left	2.06
14	F	Right	12	3.7	Left	5.5	Uncertain	0.49
15	F	Left	30	3.8	Left	9.6	Right	-6.48
16	М	Right	9	8	Left	9.7	Left	4.56
17	F	Right	9	3	Left	10.4	Right	-3.54
18	М	Right	9	3.2	Left	11.3	Right	-3.07
19	F	Right	9	4	Left	8.2	Left	2.52
20	М	Right	25	8	Left	13.1	Left	5.61

4.3. Data recording

Cerebral blood flow velocity (CBFV) in the MCAs was recorded bilaterally during the whole experiment. Insonation techniques including correct identification and depth adjustment have been published elsewhere (Ringelstein, Kahlscheuer, Niggemeyer, & Otis, 1990). For the identification of the beginning of each trial ("epochs"), a marker signal was generated by the animation presentation software and recorded simultaneously with the CBFV signals.

4.4. fTCD Language paradigm

Language lateralization was assessed by the animation description task (Freeze Foot Story), developed by Bishop et al. (2009), which includes 30 twelve-second silent videoclips. All the original animated .avi files were kindly provided to us by Professor Bishop and were sequenced into a single movie, run by "Presentation Program".

As described by the Authors (Bishop et al., 2009), during each videoclip the child was asked to silently observe a 12-s cartoon, and then, cued by an acoustic signal and a visual question mark, to describe for 10 s what he/she had seen; each trial ended with an 8-s silent rest period. The 12 s during which the participant watches the videoclip constitute the baseline period, whereas the 10-s description time is considered the activation period. The whole experiment had a duration of about 30 min for each subject. The Multidop system records the activation and baseline times. The mean velocity of blood flow during the activation period is then compared to that of the baseline.

In order to familiarize the participants with the experimental fTCD task, each child took part in a training session consisting of an animated movie representing a part of the complete story (5 of the original videoclips). The observation and description times were the same as in the fTCD condition, that is 12 and 10 s, respectively. Children were usually accompanied by a parent who sat behind them.

4.5. Data analysis

The fTCD data were analyzed with the Average software (Deppe, Knecht, Henningsen, & Ringelstein, 1997). CBFV data was segmented into epochs related to marker signals, and averaged. Epochs containing CBFV values outside the range of 60–140% of the mean were excluded as measurement artifacts. Transformation to relative units was performed using the following formula:

$$dv = 100 rac{V(t) - V_{
m pre.mean}}{V_{
m pre.mean}}$$

where V(t) is the CBFV over time and $V_{\text{pre.mean}}$ is the mean velocity during the 12-s precueing interval.

As a measure for the quantification of the perfusion differences between the left and right hemisphere, the fTCD Lateralization Index (LI) was calculated with the formula:

$$LI = \frac{1}{Tint} \int_{t_{min} - \frac{1}{2}Tint}^{t_{max} + \frac{1}{2}Tint} \Delta V(t) dt$$

where $\Delta V_i(t) = dV_i(t)_{left} - dV_i(t)_{right}$ is the difference between the relative velocity changes of the left and right MCAs. The time point t_{max} represents the latency of the absolute maximum of $\Delta V(t)$ within the activation intervals (4–10 s); as the integration interval, a time period of $t_{int} = 2$ s was chosen. The Li quantifies the average difference of relative CBFV changes in the activation period in comparison to baseline in percent. A positive value corresponds to greater left than right hemisphere activation indicating left hemisphere asymmetry for language, while a negative value indicates right hemisphere lateralization. The LI standard error of the mean (SEM) represents the variability between the lateralization index accounts for higher performance continuity and higher quality of the Doppler signal throughout the investigation.

Following Knecht et al. (1998) hemispheric dominance was classified as left or right when mean LI deviated more than two standard errors from 0, for lower LI deviation values lateralization was considered uncertain or bilateral.

The internal consistency of LI measures was tested by split-half and odd–even Pearson's product moment correlation coefficients.

4.6. Language evaluation

Language assessment was performed by using Italian standardized tests for both lexical and grammatical comprehension and production. Expressive vocabulary was tested with the One-Word Picture Vocabulary Test (Brizzolara, 1989), consisting of 104 black-and-white pictures which the child must name.

For the assessment of receptive vocabulary, children were administered the Italian version of the Peabody Picture Vocabulary Test PPVT-R (revised 3rd Edition Dunn & Dunn, 1997; Italian standardization Stella, Pizzoli, & Tressoldi, 2000).

Grammatical comprehension was measured by the Test of Comprehension of Grammar for Children – TCGB (Chilosi & Cipriani, 1995), a multiple choice test that assesses the child's ability to understand 6 different, orally presented, grammatical structures.

Evaluation of expressive grammar was carried out by analyzing language production elicited by the fTCD paradigm and by a sentence repetition task (Bottari, Cipriani, & Chilosi, 1998).

In order to estimate the overall level of linguistic proficiency of participants, a composite score was calculated by assigning each language test, one or two points for a z-score respectively lower or higher than -1.5; total scores ranged from 4 to 8 (8 being the maximum score).

Acknowledgments

This research was supported by the Mariani Foundation (Grant R-10-82 to AMC) and by the European union (Grant ERC STANIB to MT).

We thank Professor Dorothy Bishop for providing the Animation Description paradigm and instructions about related experimental procedures. We also thank Giulia Carignani, MD and Giada Giuntini, ST, for their help in collecting data on controls and some experimental subjects, Patrizia Fornigoni, MD for referral of two deaf participants, Vincent Corsentino for reviewing the English version manuscript, and Giuseppe Rossi for statistical advises.

References

- Bishop, D. V. M., Watt, H., & Papadatou-Pastou, M. (2009). An efficient and reliable method for measuring cerebral lateralization during speech with functional transcranial Doppler ultrasound. *Neuropsychologia*, 47, 587–590.
- Bottari, P., Cipriani, P., & Chilosi, A. M. (1998). Dissociation in the acquisition of clitic pronouns by dysphasic children: A case study from Italian. In S. M. Powers & C. Hamann (Eds.), *The acquisition of scrambling and cliticization* (pp. 237–277). Dordrecht: Kluwer Academic Publishers.
- Brizzolara, D. (1989). Test di vocabolario figurato. Technical Report of the Research Project 500.4/62.1/1134 supported by a grant from the Italian Department of Health to IRCCS Stella Maris.
- Chilosi, A. M., & Cipriani, P. (1995). TCGB, Test di Comprensione Grammaticale per Bambini. Pisa: Edizioni Del Cerro.
- Chilosi, A. M., Pecini, C., Cipriani, P., Brovedani, P., Brizzolara, D., Ferretti, et al. (2005). Atypical language lateralization and early linguistic development in children with focal brain lesions. *Developmental Medicine and Child Neurology*, 47, 725–730.
- Dehaene-Lambertz, G., Hertz-Pannier, L., Dubois, J., Mériaux, S., Roche, A., Sigman, M., et al. (2006). Functional organization of perisylvian activation during presentation of sentences in preverbal infants. *Proceedings of National Academy* of Science, 19, 14240–14245.

- Deppe, M., Knecht, S., Henningsen, H., & Ringelstein, E. B. (1997). AVERAGE: A Windows[®] program for automated analysis of event related cerebral blood flow. *Journal of Neuroscience Methods*, 75, 147–154.
- Deppe, M., Knecht, S., Papke, K., Lohmann, H., Fleischer, H., Heindel, W., et al. (2000). Assessment of hemispheric language lateralization: A comparison between fMRI and fTCD. Journal of Cerebral Blood Flow Metabolism, 20, 263–268.
- D'Hondt, M., & Leybaert, J. (2003). Lateralization effects during semantic and rhyme judgement tasks in deaf and hearing subjects. *Brain and Language*, 87, 227–240. Dunn, L, & Dunn, L. M. (1997). *Peabody picture vocabulary test e PPVT-third edition*.
- Circle Pines, MN: American Guidance Service. Gilley, P. M., Sharma, A., & Dorman, M. F. (2008). Cortical reorganization in children
- with cochlear implants. *Brain Research*, 123, 56–65. Guzzetta, A., Pecini, C., Biagi, L., Tosetti, M., Brizzolara, D., Chilosi, A. M., et al. (2008).
- Language organisation in left perinatal stroke. *Neuropediatrics*, 39, 157–163. Haag, A., Moeller, N., Knake, S., Hermsen, A., Oertel, W. O., Rosenow, F., et al. (2010). Language lateralization in children using functional transcranial Doppler
- sonography. Developmental Medicine and Child Neurology, 52, 331–336. Hugdahl, K. (2005). Symmetry and asymmetry in the human brain. European Review, 13, 119–133.
- Kelly, R. R., & Tomlinson-Keusey, C. (1981). The effect of auditory input on cerebral laterality. Brain and Language, 13, 67–77.
- Kimura, D. (1967). Functional asymmetry of the brain in dichotic listening. Cortex, 3, 163–168.
- Knecht, S., Deppe, M., Ringelstein, E. B., Wirtz, M., Lohmann, H., Dräger, B., et al. (1998). Reproducibility of functional transcranial Doppler sonography in determining hemispheric language lateralization. *Stroke*, 29, 1155–1159.
- Kral, A., & Sharma, A. (2012). Developmental neuroplasticity after cochlear implantation. Trends in Neuroscience, 35, 111–122.
- Langers, D. R., van Dijk, P., & Backes, W. H. (2005). Lateralization, connectivity and plasticity in the human central auditory system. *Neuroimage*, 28, 490–499.
- Lohmann, H., Dragger, B., Muller-Ehrenberg, S., Deppe, M., & Knecht, S. (2005). Language lateralization in young children assessed by functional transcranial Doppler sonography. *Neuroimage*, 24, 780–790.
- Marcotte, A. C., & Morere, D. A. (1990). Speech lateralization in deaf populations: Evidence for a developmental critical period. *Brain and Language*, 39, 134–152.
- Neville, H. J., Bavelier, D., Corina, D., Rauschecker, J., Karni, A., Lalwani, A., et al. (1998). Cerebral organization for language in deaf and hearing subjects: Biological constraints and effects of experience. *Proceedings of National Academy of Science*, 95, 922–929.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 24, 97–113.
- Peterson, N. R., Pisoni, D. B., & Miyamoto, R. T. (2010). Cochlear implants and spoken language processing abilities: Review and assessment of literature. *Restorative Neurology and Neuroscience*, 28, 237–250.
- Ringelstein, E. B., Kahlscheuer, B., Niggemeyer, E., & Otis, S. M. (1990). Transcranial Doppler sonography: Anatomical landmarks and normal velocity values. Ultrasound in Medicine and Biology, 16, 745–761.
- Sevy, A. B., Bortfeld, H., Huppert, T. J., Beauchamp, M. S., Tonini, R. E., & Oghalai, J. S. (2010). Neuroimaging with near-infrared spectroscopy demonstrates speechevoked activity in the auditory cortex of deaf children following cochlear implantation. *Hearing Research*, 270, 39–47.
- Sharma, A., Nash, A. A., & Dorman, M. (2009). Cortical development, plasticity and re-organization in children with cochlear implants. J Commun Disord., 42, 272–279.
- Somers, M., Neggers, S. F., Diederen, K. M., Boks, M. P., Kahn, R. S., & Sommer, I. E. (2011). The measurement of language lateralization with functional transcranial Doppler and functional MRI: A critical evaluation. *Frontiers in Human Neuroscience*, 28(5), 31.
- Staudt, M., Grodd, W., Niemann, G., Wildgruber, D., Erb, M., & Krägeloh-Mann, I. (2001). Early left periventricular brain lesions induce right hemispheric organization of speech. *Neurology*, 57, 122–125.
- Stella, G., Pizzoli, C., & Tressoldi, P. E. (2000). Peabody. Test di Vocabolario Recettivo. Torino: Omega Edizioni.
- Woldorff, M. G., Tempelmann, C., Fell, J., Tegeler, C., Gaschler-Markefski, B., Hinrichs, H., et al. (1999). Lateralized auditory spatial perception and the contralaterality of cortical processing as studied with functional magnetic resonance imaging and magnetoencephalography. *Human Brain Mapping*, 7, 49–66.