Strengthening of Laterality of Verbal and Visuospatial Functions During Childhood and Adolescence

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Abstract: Cognitive functions in the child's brain develop in the context of complex adaptive processes, determined by genetic and environmental factors. Little is known about the cerebral representation of cognitive functions during development. In particular, knowledge about the development of right hemispheric (RH) functions is scarce. Considering the dynamics of brain development, localization and lateralization of cognitive functions must be expected to change with age. Twenty healthy subjects (8.6–20.5 years) were examined with fMRI and neuropsychological tests. All participants completed two fMRI tasks known to activate left hemispheric (LH) regions (language tasks) and two tasks known to involve predominantly RH areas (visual search tasks). A laterality index (LI) was computed to determine the asymmetry of activation. Group analysis revealed unilateral activation of the LH language circuitry during language tasks while visual search tasks induced a more widespread RH activation pattern in frontal, superior temporal, and occipital areas. Laterality of language increased between the ages of 8–20 in frontal ($r = 0.392$, $P = 0.049$) and temporal ($r = 0.387$, $P = 0.051$) areas. The asymmetry of visual search functions increased in frontal ($r = -0.525$, $P = 0.009$) and parietal ($r = -0.439$, $P = 0.027$) regions. A positive correlation was found between Verbal-IQ and the LI during a language task ($r = 0.585$, $P = 0.028$), while visuospatial skills correlated with LIs of visual search ($r = -0.621$, $P = 0.018$). To summarize, cognitive development is accompanied by changes in the functional representation of neuronal circuitries, with a strengthening of lateralization not only for LH but also for RH functions. Our data show that age and performance, independently, account for the increases of laterality with age. *Hum Brain Mapp* 30:473–483, 2009. © 2008 Wiley-Liss, Inc.

Key words: functional asymmetry; functional development in childhood; functional magnetic resonance imaging (fMRI); right hemispheric function; left hemispheric function

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The functional laterality of the hemispheres has been attributed to structural differences, which are influenced by genetic and environmental factors in the course of development [Geschwind and Galaburda, 1985]. Phase-like development is thought to occur in different systems at different times. Hence, skills may be established individually at different times and rates depending on structural as well as environmental factors. Postmortem studies of fetuses' brains and newborns have demonstrated that hemispheric asymmetry of the planum temporale becomes visible on a structural level as early as in the last gestational trimester [Preis et al., 1999]. Giedd et al. [1996] showed a significant difference in the hemispheric volume in children aged 4–18 years: the left hemisphere (LH) caudate volume and the overall LH volume are significantly larger than in the right hemisphere (RH). Several other brain areas have been shown to be asymmetrical not only in children, but also in adults. This indicates that structural asymmetries are not merely related to maturational changes [Good et al., 2001].

Not only structural but also functional asymmetries are present in the brain. The functional asymmetry of the brain, especially for motor and language functions, is clearly documented in the literature. fMRI studies using verb generation paradigms describe age-related increases in activity with less consolidated and more bilateral representations of language processing areas in younger compared to older children and an increasing lateralization with age [Holland et al., 2001; Szaflarski et al., 2006]. Unfortunately, it is impossible to differentiate how much of a functional shift is due to structural development and how much is due to changes in the cognitive strategy applied to solve the task. Other studies using functional magnetic resonance imaging [fMRI; Gaillard et al., 2003; Wood et al., 2004] suggest that laterality of activation does not change with age and is strongly lateralized by the age of 7 years.

The most common language paradigms used in fMRI are verbal fluency paradigms [word generation to letters, nouns, or categories; Cuenod et al., 1995; Schlaggar et al., 2002] or semantic tasks [Seghier et al., 2007]. Although unilateral LH functions (such as language) is well defined, there is neither consistent nor convincing data about unilateral functions of the RH. It is widely accepted and described by means of fMRI that visuospatial skills are located predominantly in the RH in adults [Vogel et al., 2003]. Visuospatial functions involve a wide range of cognitive processes such as spatial working memory, which relies on structures of the RH prefrontal and RH superior parietal cortex, not only in adults [Zarahn et al., 2000] but also in children [Nelson et al., 2000]. A further function known to be located predominantly in the RH is the mental rotation of objects, primarily subserved by the RH parietal cortex, such as shown in a PET study with healthy adults [Harris et al., 2000]. So far, the development of laterality of RH functions was never documented with fMRI.

The present study aims to detect developmental changes in the localization and lateralization of cognitive functions during childhood and adolescence. Functional asymmetry is thought to increase with age and a correlation between cognitive performance and the laterality of activation is hypothesized. fMRI paradigms developed to study unilateral cognitive processes in healthy children and adults [Lidzba et al., 2006; Wilke et al., 2006] will be used to assess the representation of language (LH function) and visual search (RH function) during normal brain development.

MATERIAL AND METHODS

Participants

Twenty healthy children, adolescents and young adults (11 males, 9 females), aged 8.6–20.5 years (mean 12.9) were recruited. Seven participants were siblings ($n = 3$) or peers ($n = 4$) of pediatric stroke patients participating in an fMRI study at the University Hospital Bern. Thirteen participants were friends or family members of staff from the University Hospital Bern. Ten participants visited regular school, four children attended the secondary level, and six children were in high school. All subjects met the following inclusion criteria: right-handed, native German speaking, normal hearing, normal or corrected-to-normal vision, free of neurological diseases or psychiatric disorders, not taking medication affecting the central nervous system, no history of cognitive deficits (intelligence, reading, language) in the past or at the present time, and no metal implants or other contraindications for a MRI. All subjects were naïve to the fMRI. Experiments were undertaken with the understanding and written consent of each subject according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the local ethics committees of Bern.

fMRI Paradigms

Participants performed four different paradigms in the scanner; two tasks activating predominantly LH structures [language tasks, Wilke et al., 2006] and two tasks activating predominantly RH regions [visual search tasks, Lidzba et al., 2006]. LH language paradigms consisted of the *vowel detection task* and the *synonym task* (Fig. 1), RH paradigms consisted of the *Rey search task* and the *animal search task* (Fig. 1). Response buttons allowed for a “yes” (left hand) or “no” (right hand) answer. In all tasks, the order of targets and nontargets was pseudorandomized, and overall odds were 50:50. Subjects were prepared extensively for the exam according to a preparation protocol described earlier [Wilke et al., 2003]. The preparation included the explanation and hands-on training of the tasks outside the scanner as well as the introduction of the scanner surrounding. Scanning was only begun when the scientist

Figure 1.

Activation (left) and contrast (right) condition of the two language tasks (above) and the visual search tasks (below). Original tasks were presented in color.

conducting the exam was convinced that the subject was able to execute the tasks.

Neuropsychological Protocol

Neuropsychological assessment with a focus on verbal skills, visuomotor, and visuospatial functions was performed with 16 of 20 participants. Four participants could not be recruited for a neuropsychological examination because of individual time constraints. Since no specific language tests with normative data exist within the age range of 7–20 years in German, age-appropriate subtests of Wechsler Intelligence Scale for Children [aged 6–17 years; Tewes, 1991] or Wechsler Adult Intelligence Scale [>17 years; Wechsler, 1992] were used to assess verbal skills. The following subtests contribute to the Verbal IQ: information, similarities, arithmetic's, vocabulary, comprehension, and digit span. Visuomotor and visuospatial functions were assessed using the Rey-Osterrieth Complex Figure [Rey, 1941] and the Block-tapping test [Schelling, 1997]. All raw scores of cognitive tests were transformed either to IQs or *T*-values according to the age norms of the test manual. In order to make results comparable, *z*-scores were constructed from the respective transformed test score according to $z = X - \mu/\sigma$.

Data Acquisition

MRI experiments were performed on a Sonata 1.5-T whole body scanner (Siemens Erlangen, Germany),

equipped with a 40 mT/m (200 mT/m-ms) gradient system and a CP standard head coil. The scanner was equipped with the Syngo MR 2002B (VA21B) software release. Anatomical imaging was obtained using a T1-weighted, sagittally oriented 3D-MPRAGE sequence (TR/TE/TI 2000/3.93/590 ms, matrix 256×256 , FOV 256×256 mm, flip angle 15° , slab 160 mm) with a 1 mm^3 isovoxel resolution. Whole-brain functional echoplanar images were used for the language tasks (TR = 5,000 ms with 1 s delay, TA = 5 min 30 s/66 scans, TE = 60 ms, 16 axial slices, $2 \times 2 \times 4 \text{ mm}^3$ voxel size) and for the visual search task (TR = 3,000 ms, TA = 9 min 54 s/198 scans, TE = 60 ms, 16 axial slices, $2 \times 2 \times 4 \text{ mm}^3$ voxel size). All paradigms were presented in a block design. Sparse sampling procedure allowed auditory instructions in the pause between the scans.

Data Analysis

Data were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience, University College London, UK). The images of every subject were spatially realigned to eliminate movement artifacts. To allow for intersubject comparison, data were normalized using custom templates. After smoothing with a Gaussian filter of full width at half maximum = 12 mm, the functional data were subjected to a voxel-based statistics according to the general linear model [Friston et al., 1995] to assess activation contrasts for the different tasks. First level single subject statistics were assessed by contrasting the activation

condition with the contrast condition, treating the contrast condition as a condition of no interest. For modeling, basic box-car functions were convolved with the hemodynamic response function. To account for technical or physiological noise and intersubject activation variability, the functional data were subjected to a high-pass filter of 128 s and individual activation strength was rescaled by means of global scaling. For the description of differences between activation and control conditions in single data, a height threshold of $P < 0.05$, FWE-corrected [familywise error; Nichols and Hayasaka, 2003] for multiple comparisons and an extent threshold $k > 50$ voxels were chosen. Group analyses were performed using a random effect analyses, a height threshold of $P < 0.05$, FWE-corrected for multiple comparisons, and an extended threshold $k > 50$ voxels. To investigate whether activation patterns change with age, a regression analysis was performed using age as the covariate of interest. This allows describing where activation changes significantly with age, positive (stronger activation in older children) or negative (stronger activation in younger children).

Laterality Index

A laterality index (LI) was computed to describe the laterality of activation over seven different brain anatomical delineations based on Tzourio-Mazoyer et al. [2002]. They served to describe the brain's hemispheric specialization for a given task in a regionally specific fashion. LIs were calculated for each subject and each paradigm. Voxel values from both sides of the brain [disregarding 5 mm left and right of the interhemispheric fissure, Wilke and Lidzba, 2007] were taken from the resulting statistical t -maps. One of the most commonly used approaches [Adcock et al., 2003; Holland et al., 2001] which was used in the present study is to calculate a lateralization index (LI) based on $LI = (\text{left} - \text{right}) / (\text{left} + \text{right})$. The index of this formula results in positive values for predominantly LH lateralization (+1) and negative values for RH lateralization (−1). Such as proposed by various authors describing the asymmetry of language representation [Springer et al., 1999; Wilke and Lidzba, 2007], LH dominance was assumed at $LI > 0.2$, whereas RH dominance was assumed at $LI < -0.2$. The definition of RH dominance if $LI < -0.2$ for a *visual search task* is applied in the study at hand for the first time and, hence, has to be interpreted with caution. In order to calculate LIs, a bootstrapping approach was employed as recently suggested [Wilke and Schmithorst, 2006]. This approach avoids the issue of using a fixed threshold, however defined, which has been recognized as one of the main drawbacks when assessing laterality [Wilke and Lidzba, 2007] by applying the concept of threshold-dependent laterality curves [Deblaere et al., 2004]. It employs a bootstrapping procedure which repeatedly samples, with replacement, the underlying data, yielding a robust estimator of the true underlying data distribution. Additionally, it allows deriving an overall later-

alization index based on the weighted mean values as computed during the iterative thresholding steps, which is thus based not on one but several thousand comparisons between both sides, disregarding outliers. This overall weighted LI was used in this study.

Behavioral Data

Subject responses in the scanner were recorded for all paradigms and conditions, thus allowing for performance monitoring by comparing the subjects recorded actual responses with the expected ones. The feedback system used does not allow for the detection of right or wrong answers, but uncovers only the *number* of targets (if answer is “yes”) and nontargets (if answer is “no”). Differences between conditions as well as differences between paradigms were analyzed using the nonparametrical Kruskal-Wallis H -test, which is adequate when dealing with small sample sizes.

Statistical Analysis of Behavioral Data

Paired t -tests were conducted to test for differences between the groups (gender, paradigms). To compare neuropsychological test results with the expected norm, the nonparametrical χ^2 test was used. Partial two-tailed correlations (controlling for age) were calculated to examine the relation among neuropsychological test results and LIs. The relation between LIs and age was analyzed using the nonparametrical Spearman's rank-correlation coefficient.

RESULTS

fMRI Data

All subjects performed the four paradigms, which all consistently elicited suprathreshold activations ($P < 0.05$, FWE-corrected) on the single subject level. Group analysis revealed a focal activation during the vowel detection task in the inferior frontal gyrus of the LH (pars triangularis and pars opercularis) corresponding to the functional Broca's area (Fig. 2). Further, an activation cluster in the left middle temporal lobe of the LH was detected. The synonym task elicited LH activation in the pars orbitalis of Broca's area and in the inferior temporal lobe.

During the *visual search tasks*, single subject activations occurred in bilateral areas, but with RH dominance in occipital, parietal, and frontal structures. On the group level, the animal search task elicited activation of the right occipital, right anterior temporal, and right frontal (basal central region) lobe (Fig. 2). There was further activation in left inferior and middle temporal regions. In the Rey search task, the global maximum for the group was found in the left and right occipital lobe and the right frontal cortex (basal central region). Figure 3 indicates the trend toward LH dominance for language tasks and the trend toward RH dominance for the visual search tasks. Neverthe-

Figure 2.

Group analysis of children ($n = 20$) during the two visual search tasks (left) and the two language tasks (right). Group analysis: $n = 20$, random effect analysis, $P < 0.05$, FWE-corrected, extended threshold $k > 50$ voxels. One child (animal search task) or two children (Rey search task) were excluded from analysis due to movement $> 3\text{mm}$. See text for details regarding the identified activation sites. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

less, regarding the mean LI over all brain regions, bilateral activation ($-0.2 < \text{LI} < 0.2$) were found in around a quarter to half of all participants (animal search task $n = 11$, Rey search task $n = 9$, synonym task $n = 5$, vowel detection task $n = 6$).

Behavioral Data

Neuropsychological results

Mean verbal skills were above average (z-value Verbal IQ 1.26; SD 0.99; range 0–3.9). Mean visuomotor perform-

ance (z-value Copy Rey Figure -0.21 ; SD 1.12; range -0.2 to 1.7) and mean visuospatial short-term memory (z value Corsi 0.65, SD 0.5, range 0–1.8) and long-term memory (z-value Recall Rey-Figure -0.21 ; SD 1.12; range -3 to 1.7) was within the normal range ($-1 < z < 1$). In a healthy population, up to 18% of all children are expected to have scores above or below the normal range [Sattler, 1988]. Subjects deviated from the expected norm in the domain of verbal skills (mean verbal IQ 116.6, SD 13.4), which was significantly better than expected in a normal population (χ^2 ; $P = 0.023$). There was no correlation between neuropsychological data and age at examination.

Figure 3.

Mean laterality indices (LI) over all brain regions of the four paradigms. Left lateralization was assumed at laterality index > 0.2 , right lateralization was assumed at laterality index < -0.2 .

Figure 4.

Relation between age at examination and laterality indices for the frontal and parietal region during the Rey search task ($n = 19$). * indicates significant correlation at the $P < 0.05$ level (partial 2-tailed Pearson correlation controlling for visuo-spatial performance, copy of the Rey Figure). One child with RH language is not included in the analysis.

Feedback in the scanner

Participants showed a good to very good task cooperation in the scanner. The number of expected button presses was 60 for the language tasks and 66 for the visual search tasks. Mean responses (SD, range) during the vowel detection task were 58.2 (16, 38–94), during the synonym task 56.5 (12, 39–84), during the Rey search task 68.6 (13, 42–95), and during the animal search task 66.9 (9, 44–82).

Movement parameters

Motion was significantly more pronounced in the two visual search paradigms than in the two language paradigms, likely because of the longer task duration. Since the tasks were presented on a small mirror with a fixation of the participants head, head movement due to the enhanced eye movements during the visual search task is unlikely contrib-

uting to this effect. The most extensive movement was 6.2 mm in an individual during the Rey search task. This subject was excluded from the group analyses.

Correlations

LIs of the vowel detection task and the Rey search task correlated significantly with age at examination even when controlling for neuropsychological performance (Figs. 4 and 5). During the vowel detection task, activation of frontal ($r = 0.293$, $P = 0.049$) and temporal ($r = 0.387$, $P = 0.051$) areas increased in asymmetry with age (including all participants except one with right sided language representation). When excluding the youngest participant, a trend toward an increase of laterality with age remained (frontal area: $r = 0.344$, $P = 0.081$). When excluding the youngest as well as the oldest participant from the analysis, no significant age effect remained.

Figure 5.

Relation between age at examination and laterality indices for the frontal and temporal region in the vowel detection task ($n = 19$). * indicates significant correlation at the $P < 0.05$ level (partial 2-tailed Pearson correlation controlling for Verbal-IQ). One child with RH language is not included in the analysis.

Figure 6.

Regression analyses according to age at examination. Regression: simple, $P > 0.001$, uncorrected. The regression analysis shows areas that are more active in older children compared to younger ones. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

During the Rey search task, frontal ($r = -0.525$, $P = 0.009$) and parietal areas ($r = -0.439$, $P = 0.027$) increased significantly in laterality throughout childhood and adolescence, even when excluding the youngest and the oldest subject from the analysis (frontal $r = -0.530$, $P = 0.013$; parietal $r = -0.353$, $P = 0.075$). There was no significant

relation between age and laterality found for the synonym and the animal search task in either region of interest.

Regression analyses detected age-related activation in the left-sided supramarginal gyrus, the posterior/middle frontal gyrus, and the inferior temporal lobe during language tasks. Older children had significantly more activation in these regions than did younger children. An increase of asymmetry with age was also found in a visual search task; especially the right superior middle temporal region, the right middle occipital lobe, and the right supramarginal gyrus were significantly more active in older than in younger children (Fig. 6).

The strength of laterality was not only related to age but was significantly related to neuropsychological functioning (Table I). When controlling for age, laterality during the visual search tasks correlated significantly with visuospatial and visuomotor perception (Copy Rey Figure $r = -0.621$, $P = 0.018$), while there was a relation between LIs of language tasks and Verbal-IQ (vowel detection $r = 0.585$, $P = 0.028$, synonym task $r = 0.467$, $P = 0.092$). Furthermore, a partial correlation analysis controlling for age revealed a relation between task performance in the scanner (measured by the amount of responses given) and laterality of the activation during the visual search tasks. A high amount of false positives related to less laterality in the RH in cerebellar regions (animal search task $r = -0.834$, $P = 0.039$; Rey search task $r = -0.988$, $P = 0.007$).

DISCUSSION

This study presents data about the development of lateralized cognitive functions in healthy children and adolescents. Group analysis over all participants shows a predominantly left-sided cortical network involved in language, with Broca's area, middle and inferior temporal

TABLE I. Correlation between behavioral data (neuropsychological functioning), demographic data and laterality indices

		Verbal-IQ	Copy Rey-figure	Recall Rey-Figure	Corsi
Age at exam $n = 20$	Pearson's r	0.072	0.176	-0.006	-0.076
	Two-tailed P	0.739	0.411	0.978	0.731
Gender $n = 20$	Pearson's r	-0.038	0.140	-0.276	-0.053
	Two-tailed P	0.834	0.619	0.319	0.852
LI animal search $n = 15$	Pearson's r	0.114	0.621	-0.275	0.093
	Two-tailed P	0.697	0.018*	0.342	0.752
LI Rey search $n = 15$	Pearson's r	0.405	-0.073	0.271	-0.242
	Two-tailed P	0.151	0.805	0.347	0.406
LI vowel detection $n = 15$	Pearson's r	0.585	0.139	0.484	0.369
	Two-tailed P	0.028*	0.636	0.080 ⁺	0.194
LI synonym $n = 15$	Pearson's r	0.467	-0.133	0.364	0.013
	Two-tailed P	0.092 ⁺	0.651	0.201	0.964

LI = mean laterality index over all brain regions.

*Indicate that correlation was significant at the $P < 0.05$ level. ⁺indicate a trend toward significance ($P < 0.1$). Partial correlation was performed controlling for age at examination. Four participants did not take part in the neuropsychological examination.

regions being active. The same brain regions are known to be involved in language processing in adults [Price, 2000]. Activation of the middle region of Broca's area (pars opercularis) during the vowel detection task is related to phonological processing [Demonet et al., 1992], while the most inferior part of the Broca's area (pars orbitalis) is involved in semantic-related activities [Demonet et al., 1992] needed during the synonym task. Activation clusters in the left middle temporal region likely reflect lexicosemantic retrieval [Cabeza and Nyberg, 2000]—a function needed during the vowel detection and synonym task.

While the cerebral representation of language functions is described in the literature [Gaillard et al., 2003; Holland et al., 2001], loci of activation of typical RH functions, such as visual search, are rarely specified. Our data shows activation in bilateral frontal, superior temporal, and occipital networks. These widespread activations indicate the involvement of various brain regions during a visual search task, leading to the assumption that multiple networks underlie complex visual search functions, possibly reflecting different strategies to approach the task.

In our sample, a significant increase of laterality for language and visual search functions between the ages of 8–20 is demonstrated. Since the majority of participants was between the age of 10–15 years ($n = 17$), we repeated our analyses after excluding the oldest and youngest participant. Even when excluding the outliers, the trend toward an increase of asymmetry with age is evident, in particular, for visual search functions.

For the first time we can demonstrate an age-related increase in hemispheric specialization for *visual search functions* in late childhood and adolescence. The functional asymmetry of frontal and parietal regions increases during the Rey search task. Why there is no such increase of laterality during the animal search task remains within supposition. Maybe the animal search task activates more verbal components than the Rey search task (i.e. naming of the animal, counting the claws of the bird) and hence, involves more LH regions leading to more symmetric lateralization than the fully nonverbal Rey search task. Regarding the complexity of the visual search tasks, the Rey search paradigm is more complex and thus involves a larger number of independent neural processes [Dhamala et al., 2002]. This is reflected by the more widespread activation patterns found during the Rey search than during the animal search task.

Not only the asymmetry of visual search functions, but also the asymmetry of language function, namely word production and phonological processing increases throughout childhood and adolescence. It is the left supramarginal gyrus [known to be involved in phonological processing, Prabhakaran et al., 2006] and the posterior and middle frontal gyrus which is more active in older than younger individuals, and hence seems to become functionally more specialized with age.

Our results nicely tie in with the ongoing development of the left, but not the right, arcuate fasciculus, the crucial

connecting pathway between supramarginal and frontal language areas, as seen using diffusion tensor imaging in normal children [Schmithorst et al., 2002]. A further structural explanation for the increase of both, the laterality of language as well as visual search functions, is proposed in a study by Thompson et al. [2000], presenting prolonged changes in the volume of the corpus callosum that supplies the association and language cortices. Since the corpus callosum is crucial for the exchange between the hemispheres, its developmental changes are likely to influence laterality of cognitive functions. In addition, Nagy et al. [2004] describe an increase in myelination of frontal and parietal axons during childhood. These structural developmental changes might be related to differences of activation patterns between children and adults, e.g. during a word processing task [Schlaggar et al., 2002].

Functional specialization might not only result from an enhancement of activation in some areas, but from a decrease of activation in others. Possibly the so-called pruning process [Low and Cheng, 2006] underlies such a decrease of synaptic activation in childhood. The elimination of synapses is thought to be accompanied by a strengthening of crucial neuronal connections (colloquially also known as “use it or lose it”). fMRI studies about language representation in epilepsy patients and healthy participants show varying degrees of activation in the homologous regions of the nondominant hemisphere, particularly in frontal regions [Binder et al., 1995, 1996; Gaillard et al., 2000]. The extent to which the activated areas in the nondominant hemisphere contribute directly to language processing is unclear.

Why is laterality only increasing with age in one of the two language paradigms used? Why is it phonological processing but not semantic judging that increases in asymmetry during childhood? Semantic judgment, the function underlying the synonym task, is thought to be a linguistically more complex task than the word production task. According to Just et al. [1996], the amount of neural activity that a given cognitive process engenders is dependent on the computational demand that the task imposes. Semantic judgment tasks might involve a higher degree of neural activity, relating to more widespread and less lateralized activation patterns than a word production task. The higher computational demand of the synonym task (which might be related to a bilateral cortical representation) can be a reason for the lack of a significant age-related increase of asymmetry. In contrast to this, the vowel detection task can be performed even by younger children with a high degree of accuracy [Wilke et al., 2006], arguing in favor of age, not performance, being the main determinant of the increase in lateralization. This is also in line with earlier observations in a verb generation paradigm, which is easily mastered by younger children, and despite this, it still shows an increase of hemispheric specialization with age [Holland et al., 2001].

Comparing recent pediatric functional neuroimaging studies using similar language paradigms (verb genera-

tion), some authors found a relation between lateralization of activation and age [Holland et al., 2001; Szaflarski et al., 2006], whereas others could not detect this increase [Gaillard et al., 2003; Wood et al., 2004]. Some authors use the approach of voxel counts within brain regions, which contrast with the approach to use the sum of voxel values as in a study by Holland et al. [2001] and in the present study. The use of the sum of voxel values is suspected to be more sensitive to smaller changes. It is further possible that the higher field strength used in the earlier study [Holland et al., 2001] allowed detecting effects that were not seen at 1.5 T [Wood et al., 2004]. Additionally, the mode of stimulus delivery [visual presentation: Wood et al., 2004, or auditory presentation: Holland et al., 2001] might contribute to the observed discrepancy. The present results argue in favor of the assumption that presentation alone is not a decisive factor, as our visually presented tasks induced an increase of laterality throughout childhood and adolescence in two of the four paradigms (even at 1.5 T field strength).

Beside technical details, the divergent results might also be an indication for a complexity-dependent laterality or for a function-dependent development of laterality. Our correlation analyses, showing that both age and performance independently account for increases of laterality with age, would also argue in favor of both effects playing a role.

Our data shows that better cognitive performance can be linked to a more lateralized and focal activation pattern of a certain function. Not only neuropsychological test results correlate with the strength of laterality, also performance in the scanner is correlated with the degree of asymmetry in cerebellar regions. Consequently, we conclude that there is a relation between the performance level and the lateralization of the functional representation of the task. Hence, differences in adult and pediatric activation maps may reflect different age-dependent strategies or the proceeding maturation of cognitive networks [Gaillard et al., 2000]. Whether laterality of functions increases due to the development of refined cognitive strategies [which accompany the maturation of white matter tracts sustaining connections across hemispheres; Nagy et al., 2004] remains unknown.

Our subjects show above-average intelligence as measured by the Wechsler scale, which might have implications for the interpretation of our results. The literature suggests that the more competent a subject performs a certain function (i.e., a calculation task) the less "general purpose" processes, such as working memory and executive control, are needed [Ischebeck et al., 2006]. Intelligent participants might solve our fMRI paradigm more efficiently and, thus, with less involvement of executive networks than participants with lower IQ. Executive processes are located in frontoparietal brain areas. Consequently, our sample might have less frontoparietal activations than subjects with lower IQ. For example, Wood et al. [2004] found a relation between voxel counts in frontal regions and performance level during a verb generation task, and Schmithorst and Holland [2007] suggest that an interaction of intelligence

and lateralization of language functions exists (more intelligent individuals show an increased hemispheric specialization with age). However, a correlation analysis between IQ and laterality of functions showed no significant interaction in our sample, suggesting that intelligence is not a major confound for this study. We therefore believe that the slightly above-average intelligence of the present sample does not invalidate the interpretation of our results.

Larger age groups over more distinct age ranges are needed to enhance generalizability of the present data. A very recent paper of Seghier et al. [2007] proposes that while 15–20 subjects are sufficient to reveal reliable and robust LH language activations, >30 subjects are necessary for revealing more variable and weak RH language representations. To avoid the contaminating effect of variable complexity levels, tasks should be adjusted to the individual performance level of the child. It would be of great interest to know whether developmental changes observed in children appear in a reversed manner in aging, where cognitive capacities decrease, and cognitive strategies become less specific and thus maybe less unilateral. First studies investigating the development of lateralization over the whole life span seem to suggest such an effect [Szaflarski et al., 2006].

To summarize, our data lend support to an ongoing development of functional lateralization throughout childhood and adolescence. Cognitive functions in the language domain emerge from an initially bilateral pattern toward more and more specialized unilateral networks, confirming and extending earlier studies. Additionally and for the first time, we here describe the development of laterality of predominantly RH functions, which also show a significant increase with age. It is difficult to discern from this data alone, if increasing specialization of cognitive skills lead to the strengthening of laterality, or if strengthening of laterality makes specialization of cognitive skills possible. Our data show that age and performance, independently, account for the increases of laterality with age. Likewise, the interplay between anatomical and functional increases in laterality is difficult to distinguish: is the increased myelination in the left arcuate fasciculus cause or consequence of a more leftward language network? Our data about the physiological maturational changes during childhood can contribute to the understanding of mechanisms of functional reorganization after brain lesions, in children as well as in adults.

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