Brain and Behavior

Does cerebral lateralization develop? A study using functional transcranial Doppler ultrasound assessing lateralization for language production and visuospatial memory

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Abstract

In the majority of people, language production is lateralized to the left cerebral hemisphere and visuospatial skills to the right. However, questions remain as to when, how, and why humans arrive at this division of labor. In this study, we assessed cerebral lateralization for language production and for visuospatial memory using functional transcranial Doppler ultrasound in a group of 60 typically developing children between the ages of six and 16 years. The typical pattern of left-lateralized activation for language production and right-lateralized activation for visuospatial memory was found in the majority of the children (58%). No age-related change in direction or strength of lateralization was found for language production. In contrast, the strength of lateralization (independent of direction) for visuospatial memory function continued to increase with age. In addition, boys showed a trend for stronger right-hemisphere lateralization for visuospatial memory than girls, but there was no gender effect on language laterality. We tested whether having language and visuospatial functions in the same hemisphere was associated with poor cognitive performance and found no evidence for this "functional crowding" hypothesis. We did, however, find that children with left-lateralized language production had higher vocabulary and nonword reading age-adjusted standard scores than other children, regardless of the laterality of visuospatial memory. Thus, a link between language function and left-hemisphere lateralization exists, and cannot be explained in terms of maturational change.

Introduction

Cerebral lateralization refers to the functional specialization of the two cerebral hemispheres. Whereas the left hemisphere of most adults is more active than the right during language production, the reverse pattern has been observed during tasks involving visuospatial abilities (Springer and Deutsch 1993). Although these findings are among the most replicated in neuropsychology, many questions remain about when, how, and why humans arrive at this pattern. Studying devel-

opment of cerebral lateralization of function can add to our understanding of these issues. Within this setting, the current paper focuses on two main points. First, we assess lateralization for language production and visuospatial memory across age in a large cross-sectional sample of typically developing children. Second, the relationship between lateralization of these functions and cognitive performance is investigated in this group.

Structural asymmetries between the hemispheres have been reported even in fetuses (Chi et al. 1977; Kasprian

et al. 2011) and infants (Dubois et al. 2009). However, how such structural differences relate to language development is unclear. In recent years, several neuroimaging studies have looked at the development of lateralization for language function. Activation of left perisylvian structures by speech has been found in infants as young as three months of age (Dehaene-Lambertz et al. 2006), whereas progressively more lateralized responses to speech have been reported to occur later during the first year of life (e.g., Arimitsu et al. 2011; Minagawa-Kawai et al. 2011). With regard to language production, most functional magnetic resonance (fMRI) studies in older children find an increase in the strength of left lateralization with age (Gaillard et al. 2000, 2003; Holland et al. 2001, 2007; Wood et al. 2004; Szaflarski et al. 2006a, b; Everts et al. 2009; Lidzba et al. 2011). This reflects more bilateral activation in younger children (Gaillard et al. 2000), with increasing involvement of left inferior and medial frontal and left medial temporal areas in older children and adolescents (Szaflarski et al. 2006b). Two studies failed to find an association between the strength of cerebral lateralization on a language task and age (Gaillard et al. 2003; Wood et al. 2004), even though the experimental task used was highly similar to the one used in studies that did find such an association. Possible explanations for this discrepancy include differences in the method of calculation of the laterality index (LI; global vs. regional and voxel counts vs. *t*-statistic peaks), the modality of the task (visual vs. auditory), and the field strength at which the images were acquired (1.5 T vs. 3 T). Overall, then, the imaging literature suggests that left-sided lateralization for language is evident in infancy, but with age, it becomes more pronounced, and language representation within the left hemisphere becomes more focal.

There is far less literature on lateralization of visuospatial functioning, and it is often assumed that this is complementary to language lateralization, resulting in a division of labor between hemispheres that ensures cognitive efficiency. Studies examining the development of visuospatial memory function using fMRI typically report activation of an extensive network of frontal and parietal brain areas (Nelson et al. 2000; Klingberg 2006). Although many of these studies report activation of areas in the right hemisphere, only two studies have looked specifically at changes in the strength of lateralization of activation associated with visuospatial function with age (Thomason et al. 2009). Everts et al. found an increase in the strength of right lateralization with increasing age when examining participants aged eight to 21 years with a visuospatial search task. In contrast, Thomason et al. (2009) reported lateralization to the right hemisphere in children aged seven to 12 years using a visuospatial memory task, but reported no association between cerebral lateralization and age. The more limited age range of the participants in the latter study might be an explanation for the null finding.

The pattern of left-sided language and right-sided visuospatial cerebral processing is characteristic of the population as a whole, but there are numerous exceptions. Early analyses based on consequences of focal pathology estimated that 4% of right-handed and 15% of left-handed people had right-hemisphere language (Rasmussen and Milner 1977; Satz 1979). More recent studies in healthy adults report slightly higher percentages with right-hemisphere language in around 7.5% of right-handed and 25% of left-handed people (Knecht et al. 2000; Whitehouse and Bishop 2009; Lust et al. 2011b). Bilateral representation of language functions is also not uncommon, with estimates ranging from 10% based on studies with healthy adults (Whitehouse and Bishop 2009; Lust et al. 2011b) to 15% in patient studies (Rasmussen and Milner 1977). There has been considerable interest in the question of whether atypical cerebral lateralization is related to cognitive function. Developmental data are important here, as they allow us to consider whether departures from the normal pattern of cerebral laterality might be an indication of neurodevelopmental immaturity.

A very different theory argues that cerebral lateralization is a genetically influenced trait associated with cognitive performance. The best-known version of such a theory is Annett's Right Shift Theory (Annett 1985, 2002), which maintains that left-hemisphere language evolved to enable language function in humans. According to this theory, individuals who lack a genetic bias to left-hemisphere language will have poor phonological skills (Annett and Turner 1974; Annett and Manning 1990; Annett 1996; Smythe and Annett 2006). However, to date the theory has relied largely on indirect data on relative hand skill to categorize individuals, and results have been inconsistent from study to study, and dependent on specific measures or methods of categorizing individuals. As such several large-scale studies failed to find support for its predictions with regard to associations between cognitive and language ability and handedness (e.g., Resch et al. 1997; Natsopoulos et al. 2002).

In the few studies that have used more direct measures of cerebral lateralization, results have also been mixed. While some studies have found that increased lateralization was associated with higher performance on a task, others failed to replicate these results (Lohmann et al. 2005; Lust et al. 2011a, b; Stroobant et al. 2011). Furthermore, healthy adults with atypical (right-hemisphere) lateralization for language do not tend to show any deficit in terms of intelligence, mastery of foreign languages, or artistic abilities (Knecht et al. 2001; Jansen et al. 2005).

A possible explanation for this inconsistent set of results might be that lateralization in itself is not associated with performance, but that a specific constellation of lateralized brain functions is advantageous for cognitive performance, as suggested in the "functional crowding hypothesis" (Lansdell 1969; Levy 1969; Teuber 1974). The idea

originates from neurological studies with patients with early left-hemisphere lesions, in whom atypical (right-hemisphere) language laterality was accompanied by a greater impairment in nonverbal than verbal skills (Lansdell 1969; Levy 1969; Teuber 1974). It is thought that competition for neural resources would result in a functional deficit if multiple functions rely on the same hemisphere. It has also been referred to as the "cognitive laterality profile" hypothesis (Illingworth and Bishop 2009), "load imbalance" (Yeo et al. 1997), or the "parallel processing" account (Rogers 2000; Hirnstein et al. 2008). Indeed, a recent fTCD study in adults supports the functional crowding hypothesis. People with language and spatial processing lateralized to different hemispheres performed better than people showing bilateral representation for one or either function or both functions lateralized to the same hemisphere when carrying out a language and a spatial task simultaneously (Lust et al. 2011a). Nevertheless, several fTCD studies have found that all patterns of lateralization occur in healthy adults without any obvious disadvantages as judged from their education level (Flöel et al. 2001, 2005; Whitehouse and Bishop 2009; Rosch et al. in press).

A better understanding of the relationship between cognitive performance and lateralization is presently hampered by at least three factors. First, for a long time, functional lateralization has been assessed using behavioral measures such as hand preference, visual half-field techniques, or dichotic listening. These techniques show weak to moderate correlations with cerebral lateralization as determined by the "gold-standard" of the Wada test (Bishop 1990; Pelletier et al. 2007). Second, to date, the majority of studies have investigated lateralization of a single function, such as language (Hertz-Pannier et al. 1997; Gaillard et al. 2000, 2003; Holland et al. 2001, 2007; Knecht et al. 2001; Wood et al. 2004; Lohmann et al. 2005; Szaflarski et al. 2006a, b; Haag et al. 2010; Stroobant et al. 2011), but only few studies have examined lateralization of multiple functions (e.g., Gur et al. 2000; Badzakova-Trajkov et al. 2010). Considering the pattern of lateralization for multiple functions is critical to test the functional crowding hypothesis. Finally, cognitive performance has been assessed by either looking at highly specific measures of performance at the task used to assess lateralization or at very general indications of ability such as IQ, education level, mastery of foreign languages, or artistic activities.

One reason why there are few studies of development of cerebral lateralization using direct brain measures is because fMRI studies of young children present a number of challenges. First, the method is expensive, making large samples uneconomical (Pelletier et al. 2007). This problem is compounded by high drop-out rates at young ages (Holland et al. 2001; Byars et al. 2002), though studies by Holland et al. (2007) and Szaflarski et al. (2006a) form notable exceptions. Further, due to movement restrictions, tasks are typically

covert and often involve considerable meta-cognitive skill, which are challenging for young children to perform and add extra assumptions when interpreting results. This makes it hard to establish to what extent it is the ability to comply with complex task instructions rather than the process of interest itself that drives developmental changes in cerebral lateralization. A viable alternative method has presented itself in recent years in the form of functional transcranial Doppler ultrasonography (fTCD). This noninvasive and relatively inexpensive technique has been shown to be a reliable method for determining cerebral lateralization of function (Deppe et al. 2004). Because fTCD is quick to set up and can be carried out in a quiet and comfortable environment, it has great potential for assessing cerebral lateralization in children. Furthermore, fTCD is relatively insensitive to movement which makes it possible for participants to speak while lateralization of function is assessed, making complex task instructions unnecessary. To date studies using fTCD with children have mainly focused on documenting feasibility, validity, and reliability of child-friendly tasks (Lohmann et al. 2005; Bishop et al. 2009; Haag et al. 2010; Groen et al. 2011; Stroobant et al. 2011). Studies of lateralization of language function in children using fTCD report left-lateralized activation in the majority of children (Lohmann et al. 2005; Bishop et al. 2009; Haag et al. 2010; Stroobant et al. 2011), even in toddlers (Lohmann et al. 2005; Bishop et al. 2009). Studies that did include children of different ages did not report changes in the direction lateralization with age (Lohmann et al. 2005; Haag et al. 2010; Stroobant et al. 2011).

The first aim of the present study was therefore to assess the direction and strength of lateralization across age for language production and for visuospatial memory in a large group of typically developing children. Additionally, we considered the effect of gender on functional lateralization as the idea of gender differences in brain anatomy and function remains popular (Wallentin 2009), typically suggesting more bilateral activation on language tasks in women, but little evidence has been reported to support these claims (Sommer et al. 2004, 2008; Wallentin 2009).

The second aim of the current study was to consider whether individual differences in cerebral lateralization were related to cognitive function. In particular, we aimed to test the functional crowding hypothesis by reliably assessing lateralization of multiple functions and cognitive abilities in the same individuals.

To achieve these aims we used fTCD to assess simultaneously the cerebral blood flow velocity to the left and right hemisphere during a language production and a visuospatial memory task in a large group of school-aged children. Additionally, we used a battery of psychometric tests to assess several aspects of language ability, emphasizing phonological skills, which are deemed to rely on the left hemisphere (e.g., Vigneau et al. 2006, 2011) in these same children. With

regard to our first aim, we tested the hypothesis that there is an increase in lateralization with age. This could be both in terms of direction (left-lateralized vs. right-lateralized) or in terms of strength, by which we mean the amount of lateralization irrespective of direction of lateralization. With regard to our second aim, the functional crowding hypothesis clearly predicts that children with functions lateralized to different hemispheres (i.e., left-lateralized for language and right-lateralized for visuospatial memory or vice versa) should outperform children with both functions lateralized to the same hemispheres (either the left or the right hemisphere) on psychometric tests.

Methods

Participants

Participants were 60 typically developing children (34 girls, 26 boys) across three age bands 6–8 ($M = 6.94$ years, $SD = 0.40$ years), 10–11 ($M = 10.79$ years, $SD = 0.43$ years), and 13–16 years of age ($M = 14.33$ years, $SD = 0.94$ years) recruited from schools around Oxfordshire, UK. Two additional children (one 8-year-old and one 10-year-old) were dropped from the study because of noisy fTCD recordings for both tasks. Data on the language production task were obtained for 58 children, and on the visuospatial memory task for 57 children. In 55 children, data were obtained on both tasks. Results on the visuospatial memory task from 20 six- to eight-year-olds have previously been reported on in a paper describing the development of that task (Groen et al. 2011). Participants were without any history of neurological disorder and with normal or corrected-to-normal vision. Parents of the participants confirmed that no child had a diagnosis of a neurodevelopmental disorder, such as autism, specific language impairment, or dyslexia, and that English was the main language spoken at home. Hand preference was assessed with the Edinburgh Handedness Inventory1 (Oldfield 1971), with scores of 40 or above denoting right-handedness, 40 or below denoting left-handedness, and scores in between denoting mixed-handedness. The sample included 47 right-handed (28 girls), four left-handed (three girls) and eight mixed-handed (three girls) children. No hand preference data were available for one boy.

Parental consent and child assent were obtained for all participants. The project was approved by the Central University Research Ethics Committee of the University of Oxford and is in accordance with the WMA Declaration of Helsinki for experiments involving humans.

Cognitive and language tests

Nonverbal cognitive ability

Two subtests (Sequential Order and Repeated Patterns) of the nonverbal IQ test, Leiter International Performance Scale-Revised (Roid and Miller 1997), were used to derive a "Fluid Reasoning IQ" score ($M = 100$, $SD = 15$).

Vocabulary

Receptive vocabulary was assessed using the British picture vocabulary scale, 2nd ed. (BPVS-2; Dunn et al. 1997), in which the child was asked to identify, from four choices, the illustration that best depicted the meaning of a word presented orally by the experimenter. Reported scores are standard scores ($M = 100$, $SD = 15$).

Reading

Word recognition and decoding ability were assessed at the single-word level using the two subtests of the Test of Word Reading Efficiency (TOWRE; Torgesen et al. 1999): the "Sight Word Efficiency" and the "Phonemic Decoding Efficiency" subtest, respectively. Participants are presented with a list of words (Sight Word Efficiency) or nonwords (Phonemic Decoding Efficiency) of increasing difficulty, and asked to read as many items as possible in 45 sec. Reported scores are standard scores ($M = 100$, $SD = 15$).

Phonological short-term memory

The Repetition of Nonsense Words subtest of the NEPSY (Korkman et al. 1998) was used to measure phonological short-term memory. In this assessment, the child listens to recorded nonsense words increasing in length and complexity and repeats each word after it is presented. Scores reported are raw scores, reflecting the number of syllables pronounced correctly, as standard scores were not available for all ages. The maximum score a child could achieve was 46.

Apparatus

Blood flow velocity through the right and left middle cerebral arteries (MCA) was measured with a Doppler ultrasonography device (DWL Multidop T2: manufacturer, DWL Elektronische Systeme, Singen, Germany). Participants were fitted with a flexible headset, which held in place a 2-MHz transducer probe over each temporal skull window. The experimental paradigms were controlled by Presentation Software (Neurobehavioral Systems, Albany, CA, USA) on a Dell laptop computer, which sent markers to the fTCD to denote the start of each epoch. Responses during the visuospatial memory paradigm were given via a Microtouch touch screen (3M Touch Systems, Bracknell, UK).

Experimental paradigms

In the *Language Production* (animation description) paradigm, participants watched clips from a children's

cartoon (Bishop et al. 2010). The cartoon included sounds but no speech. Each trial started with the 12 sec cartoon clip, which the participant was asked to watch silently. Then a response cue indicated the start of a 10 sec animation description period during which the participant described what had been seen in the previous clip. This was followed by an 8 sec silent rest period. A maximum of 30 clips were used. Note that during the prespeaking baseline period participants watched the animation. We had previously established in pilot studies that there was no evidence of lateralized activation while participants passively watched these animations. The Language Production paradigm has previously been show to have good validity and reliability (Bishop et al. 2009).

In the *Visuospatial Memory* paradigm (Groen et al. 2011), each trial started with a cueing tone and a "clear mind" message was displayed on the screen for an initial 5-sec interval. Then a number of black circles "the holes" appeared on a green background. The holes were distributed approximately evenly across the screen, but were not aligned in rows or columns. A few of the holes had a cartoon picture of a white rabbit in the centre. Participants were instructed to memorize which holes had a rabbit in them. The holes and rabbits remained on the screen for 4 sec, and were then replaced by a blank screen for 6 sec. Following another cueing tone, the holes reappeared and the participant was asked to indicate which holes had had a rabbit in them in the previous screen by touching those holes on a touch screen. The trial ended after the participant had touched the correct number of holes. This was followed by a 25 sec rest period. The numbers of holes and rabbits was varied to create five levels of difficulty. The easiest level showed seven holes, two of which had a rabbit in them, the most difficult level showed 20 holes, six of which had a rabbit in them. Intermediate levels had 10, 13, or 17 holes, three, four, or five of which had a rabbit in them, respectively. Participants completed a practice run prior to the experimental blocks in which two trials were presented at each difficulty level. For the experimental blocks the child was presented with the highest difficulty level at which he or she located all rabbits correctly on at least one of the two trials during the practice run. The locations of the holes were the same on all trials, while the locations of the rabbits varied across trials. The same random locations were used for each participant. Participants completed two blocks of 10 trials responding with their left hand in one block and their right hand in the other block. Block order and response hand were counterbalanced across participants. Groen et al. (2011) previously reported reasonable reliability for the Visuospatial Memory paradigm in children (odd–even split-half reliability, $r = .53$). Test–retest reliability of LIs using a highly similar paradigm was excellent in adults ($r = .84$; Whitehouse et al. 2009).

Procedure

Participants were tested in a quiet laboratory, a separate room in their school, a testing van, or at home. All participants completed the cognitive and language tests in the first testing session and both experimental paradigms in the second session. The order in which the experimental paradigms were completed was counterbalanced across participants.

Functional transcranial Doppler analysis

Data from each fTCD paradigm were analyzed using do-pOSCCI (Badcock et al. 2012), which is a MATLAB script (Mathworks Inc., Sherborn, MA, USA) written by one of the authors (NAB). The following steps were carried out: (1) the blood flow envelope from each probe was downsampled to 25 Hz, (2) heart beat activity was removed by determining local peaks in the signal from the left probe and using the heart cycle integration described by Deppe et al. (1997), (3) in order to control for global differences in recorded velocity, unrelated to the task, between the left and the right probe, blood flow velocity was normalized to a mean of 100% on a trial-by-trial basis. Time-locked epochs were then averaged, after rejecting epochs with unusually high or low levels of activity (±40% of the average blood flow velocity). The mean difference curve for left and right channels was corrected to give a mean value of zero over a baseline period of 10 sec prior to the presentation of the stimulus.

An LI was calculated as the mean blood flow velocity difference in a 2 sec window centered on the peak difference value during the period of interest. The period of interest was based on previous work (Bishop et al. 2009; Groen et al. 2011) and occurred during the speaking phase for the language production paradigm (4–14 sec after onset of the cue to speak) and the remembering phase for the visuospatial memory paradigm (20–35 sec after the start of the trial). A positive LI indicated greater left than right hemisphere activation, with a negative index signifying the reverse. For both paradigms, trials during which the participant was not "on task" (e.g., not paying attention, talking during the baseline) were excluded from the analysis. For the visuospatial memory paradigm trials used to calculate the LI were balanced in terms of response hand (i.e., the same number of trials responded to with each hand were included). Only children who had at least 12 accepted epochs on a paradigm were included in the analysis. For children with data on both paradigms, the number of accepted epochs for the language production paradigm ($M = 18.29$, $SD = 2.83$) and the visuospatial memory paradigm ($M = 17.42$, $SD = 2.30$) did not differ significantly ($t(54) = 1.92$, $p = .060$, $r = .25$). The number of trials included for a paradigm was not associated with age (language production: $r(58) = .01$, $p = .957$, visuospatial memory: $r(57) = .07$, $p = .599$).
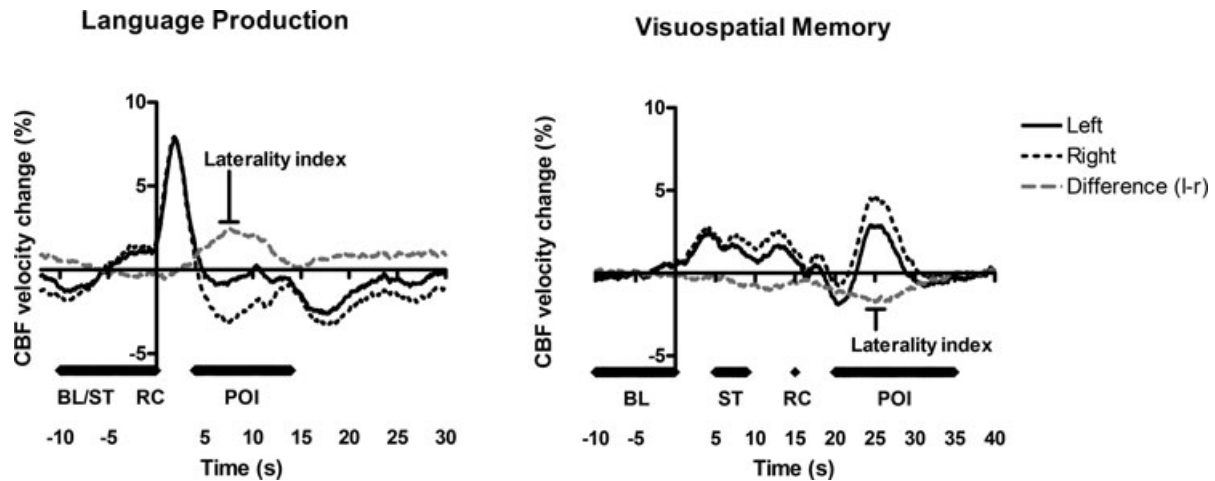
Language Production

Visuospatial Memory

Figure 1. Average baseline-corrected cerebral blood flow velocity for the left (black continuous line) and right (black dotted line) channels, and the difference between the two (gray broken line) over time for the language production (left panel) and the visuospatial memory (right panel) task. The time-course of the task is indicated at the bottom of each graph. BL = baseline, ST = stimulus, RC = response cue, POI = period of interest for the computation of the LI.

Results

Mean activation plots for the two paradigms for the participant sample as a whole are shown in Figure 1. Children showed the expected pattern of cerebral lateralization for the two tasks. The LI for the language production paradigm was positive ($M = 2.09$, $SD = 3.24$, range = 6.31–7.77) and significantly different from zero, $t(57) = 4.91$, $p < .001$, $r = .55$, indicating lateralization to the left hemisphere at the group level. Conversely, for the visuospatial memory paradigm, the LI was negative ($M = -1.68$, $SD = 3.01$, range = 7.96–5.54) and significantly different from zero, $t(56) = -4.22$, $p < .001$, $r = .49$, indicating lateralization to the right hemisphere at the group level.

Effects of age and gender on cerebral lateralization

Next we explored the extent to which lateralization for language production and visuospatial memory was influenced by age and gender. To this end we carried out regression analyses with age as a predictor variable. Gender was entered into the regression model at a second step to see if any additional variance was explained. Because previous fMRI studies led us to hypothesize that the strength rather than the direction of lateralization might change with age, we repeated the analyses with the absolute LIs. Results of the regression analyses are summarized in Table 1. None of the regression models reported was unduly influenced by individual cases as indicated by Cook's distance, which was below 0.21 for all cases.

Age did not significantly predict lateralization for the language production task, either in terms of direction (LI) or strength (absolute LI), and neither did gender.

With regard to the visuospatial memory task, age did not significantly predict the direction of lateralization, but there was a significant effect of gender, with greater right-lateralized activation in boys (LI: $M = -2.76$, $SD = 2.38$) compared to girls (LI: $M = -0.89$, $SD = 3.19$). We considered whether boys performed the task better than girls, but they did not. The difficulty level at which a child completed the visuospatial memory task was determined during a practice run, and did not differ for boys and girls (boys: $M = 4.75$, $SD = 0.79$; girls: $M = 4.82$, $SD = 0.89$; $t(55) = 0.30$, $p = .765$, $r = .04$). Furthermore, the percentage of correct responses did not vary with gender (boys: $M = 87.38$, $SD = 8.91$; girls: $M = 87.24$, $SD = 7.36$; $t(55) = -0.07$, $p = .948$, $r = .01$). Turning to the measure of strength of lateralization (regardless of direction), it was found that older children had bigger absolute LIs than younger children, with age explaining a modest but significant portion (7%) of the variance of the visuospatial memory task. Here too we considered whether this effect might be due to task performance. On average, older children completed the task at a higher difficulty level, which was characterized by a higher number of possible locations and a higher number of targets whose locations should be remembered (see Methods for details). Overall, difficulty level at which the task was administered was significantly correlated with age ($r(57) = .77$, $p < .001$). However, when the regression was re-run, substituting difficulty level for age, the prediction of the absolute LI was no longer significant

Table 1. Results of the regression analyses.

Paradigm	Lateralization	Model	Predictor	B	SE B	β	R^2	df	F
Language production	Direction	1	Constant	2.25	1.59				
			Age	−0.02	0.14	−.01	.00	1,56	0.01
		2	Constant	1.35	1.64				
			Age	0.07	0.14	.01			
			Gender	1.48	0.85	.23	.23	2,55	1.51
	Degree	1	Constant	2.46	0.77				
			Age	0.09	0.07	.18	.03	1,56	1.85
		2	Constant	2.40	0.83				
			Age	0.10	0.07	.18			
			Gender	0.10	0.43	.03	.03	2,55	0.94
Visuospatial memory	Direction	1	Constant	−2.02	1.45				
			Age	0.03	0.13	.03	.01	1,55	0.06
		2	Constant	−0.86	1.48				
			Age	−0.01	0.13	−.01			
			Gender	−1.88	0.79	−.31*	.10	2,54	2.89^
	Degree	1	Constant	1.71	0.71				
			Age	0.13	0.07	.26*	.07	1,55	4.01*
		2	Constant	1.43	0.75				
			Age	0.14	0.07	.28*			
			Gender	0.45	0.40	.15	.09	2,54	2.65^

^$p \leq .10$; *$p \leq .05$.

($R^2 = .01$, $F(1,55) = 0.54$, $p = .465$; $\beta = .10$, $t(55) = 0.74$, $p = .465$).

Associations between cerebral lateralization and performance on cognitive and language tests

As well as computing an LI, it is possible to categorize a participant as being left- or right-lateralized or showing bilateral activation, using the standard error of the LI across epochs to determine if the 95% confidence interval of that individual's LI overlaps with zero. Figure 2 summarizes the data considered in this manner. The majority of participants ($n = 32$; 58%) showed the expected pattern of left-lateralized activity for language production and right-lateralized activity for visuospatial memory (Fig. 2, bottom left quadrant). Three children (5%) showed the reversed pattern, right-lateralized activity for language production and left-lateralized activity for visuospatial memory (Fig. 2, top right quadrant). In a considerable number of children, activity for both tasks lateralized to the same hemisphere (left hemisphere: $n = 12$, 22%, Fig. 2 top left quadrant; right hemisphere: $n = 5$, 9%, bottom right quadrant). The remaining children showed bilateral activity for one task (language production, $n = 2$, 4%; visuospatial memory, $n = 1$, 2%) and right-lateralized activity for the other task.

The functional crowding hypothesis predicts poorer performance on cognitive and language tasks for children with both language production and visuospatial memory lateral-
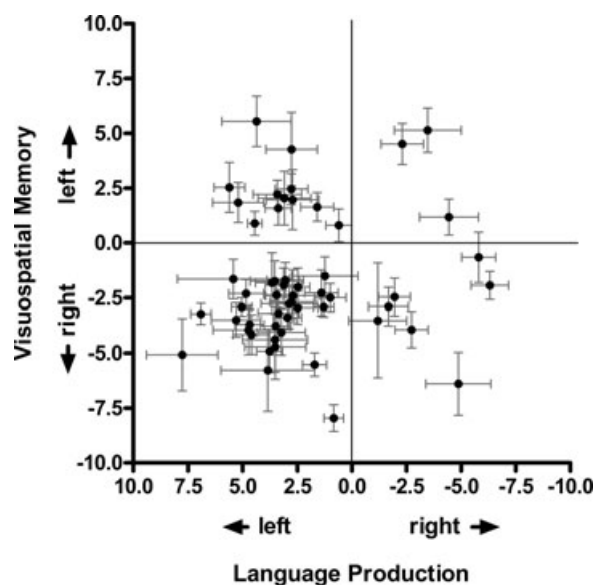

Figure 2. Scatterplot of laterality indices (LIs) for the language production and the visuospatial memory paradigm. Error bars indicate 95% confidence intervals. Children for whom error bars overlap with zero are considered to show bilateral activation.

ized to the same hemisphere compared to children in whom these functions are lateralized to different hemispheres. We therefore compared the performance of children with the functions lateralized to different hemispheres, either showing the typical pattern of lateralization (left for language,

Table 2. Means (standard deviations), independent *t*-tests, and effect sizes for performance on cognitive and language tests for children with language production and visuospatial memory lateralized to different hemispheres (Different) or the same hemisphere (Same). The latter group included children with bilateral activation for one of the tasks.

	Different	Same	t	p	r
N	35	20			
Age	10.66	10.65	−0.01	.993	.00
	(2.93)	(3.22)			
Nonverbal cognitive ability	102.74	101.20	−0.38	.706	.05
	(13.44)	(16.24)			
Vocabulary	110.43	104.95	−1.77	.082	.24
	(11.87)	(9.37)			
Reading					
Words	103.31	105.05	0.50	.617	.07
	(12.83)	(11.34)			
Nonwords	106.57	108.30	0.46	.649	.06
	(14.12)	(12.24)			
Phonological short-term memory	34.62[1]	33.05	−0.91	.365	.13
	(4.69)	(7.94)			

[1]*N* = 34.

right for visuospatial memory) or the mirror image pattern of lateralization (right for language, left for visuospatial memory) with that of children with both functions lateralized to the same hemisphere (both functions to the left or both to the right hemisphere or a bilateral representation for one of the functions) on tests of nonverbal cognitive ability, vocabulary, reading, and phonological short-term memory. Means, standard deviations, *t*-tests, and effect sizes are summarized in Table 2. No significant differences were observed, although a nonsignificant trend for higher vocabulary scores in the

group of children with functions lateralized to different hemispheres was found.

To clarify the relationship between lateralization pattern and vocabulary knowledge, these variables are plotted in Figure 3 (left panel). It appears that instead of lateralization to the same versus different hemispheres, it is lateralization for language production that seems crucial in predicting vocabulary skill. We therefore compared performance of children with language production lateralized to the left (Language Left), either showing the typical
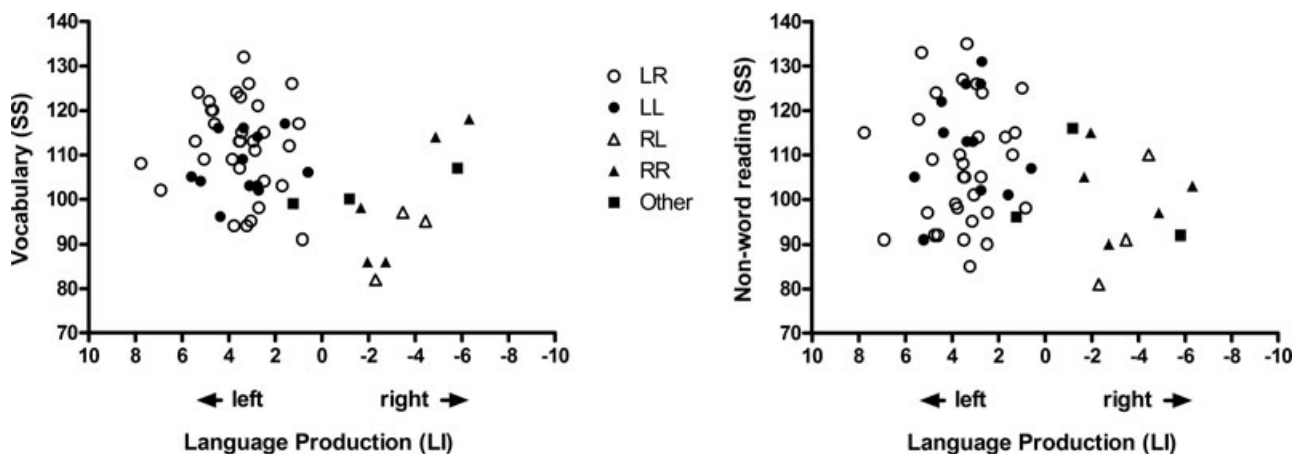

Figure 3. Scatterplots showing associations between cerebral lateralization and vocabulary knowledge (left panel) and non-word reading (right panel). Open symbols indicate children with language production (LP) and visuospatial memory (VSM) lateralized to different hemispheres; closed symbols indicate children with both functions lateralized to the same hemisphere or with bilateral activation for one of the functions. Error bars indicate 95% confidence intervals for Language Production laterality index (LI). Children for whom error bars overlap with zero are considered to show bilateral activation. LR = Left-lateralised activation for LP, Right-lateralised activation for VSM; LL = left for LP and VSM; RL = right for LP, Left for VSM; RR = right for LP and VSM; Other = bilateral activation for LP or VSM.

Table 3. Means (standard deviations), independent *t*-tests, and effect sizes for performance on cognitive and language tests for children with language production lateralized to the left hemisphere (Language Left) or not (Language Other).

	Language Left	Language Other	*t*	*p*	*r*
N	44	11			
Age	10.55	11.07	0.51	.615	.07
	(2.91)	(3.50)			
Nonverbal cognitive ability	101.73	104.00	0.47	.644	.06
	(13.11)	(19.34)			
Vocabulary	110.95	98.36	−3.69	.001	.45
	(9.82)	(11.38)			
Reading					
Words	105.41	98.09	−1.81	.076	.24
	(12.20)	(11.00)			
Nonwords	109.09	99.64	−2.17	.035	.29
	(13.32)	(11.16)			
Phonological short-term memory	34.51[1]	32.18	−1.14	.426	.16
	(5.11)	(9.09)			

[1]*N* = 43.

pattern of lateralization (left for language, right for visuospatial memory) or both functions lateralized to the left, with that of children with language lateralized to the right hemisphere or a bilateral representation for language production (Language Other). Lateralization for visuospatial memory in the latter group was to the right, the left, or exhibiting a bilateral representation. Means, standard deviations, *t*-tests, and effect sizes are summarized in Table 3. Children with language lateralized to the left hemisphere showed significantly better vocabulary and nonword reading skills than children for whom language was not lateralized to the left hemisphere. However, phonological short-term memory was unrelated to language lateralization (see Table 3). It has been proposed that the development of absolute skill might drive lateralization (Holland et al. 2007; Yamada et al. 2010). In the case of vocabulary, this would mean that the number of words you know is crucial, regardless of age. This was not the case. When we repeated the analyses with raw scores for vocabulary (Language Left: $M = 109.34$, $SD = 18.39$; Language Other: $M = 99.91$, $SD = 22.43$) and nonword reading (Language Left: $M = 37.93$, $SD = 15.17$; Language Other: $M = 32.18$, $SD = 14.20$), we did not find significant differences between groups (vocabulary: $t(53) = −1.19$, $p = .239$, $r = .16$; nonword reading: $t(53) = −1.14$, $p = .260$, $r = .15$). This suggests that children who had language lateralized to the left hemisphere had better vocabulary and nonword reading skills *for their age* compared with other children.

Discussion

In this study, we assessed cerebral lateralization for language production and visuospatial memory in a group of 60 typi-

cally developing children between the ages of six and 16 years. As has been found in fTCD studies in adults (Flöel et al. 2001; Whitehouse and Bishop 2009; Lust et al. 2011a, b; Rosch et al. in press), the majority of children showed left-lateralized activation on the language production task and right-lateralized activation on the visuospatial memory task.

Our first aim was to assess whether lateralization changed with age. For the language production task, we did not find any association between the direction or the strength of lateralization and age. This is in agreement with other fTCD studies (Lohmann et al. 2005; Haag et al. 2010; Stroobant et al. 2011), but does not tally with the fMRI work (Gaillard et al. 2000; Holland et al. 2001, 2007; Szaflarski et al. 2006a, b). One possible explanation for this result could be that developmental changes are area-specific (Holland et al. 2007) and fTCD does not have the spatial sensitivity necessary to detect such changes. Another factor that likely contributes to the lack of association is that our language activation task likely involved language skills that mature early. Holland et al. (2007) found that the largest age-related changes in lateralization occurred for language skills that show the most protracted period of development, such as verb generation or syntactic processing. For early acquired skills such as word-picture matching, age-related changes in lateralization were minimal. Our language production task required the description of simple animations which is achievable for four-year-olds (Bishop et al. 2009). As such the skills involved are probably early-acquired, and accordingly little age-related changes in lateralization were found. Differences between early- and late-acquired skills as proposed by Holland et al. (2007) probably implicate qualitative differences between tasks in terms of underlying language processes as well as quantitative differences in task difficulty. In this context a recent study

comparing functional lateralization for different language tasks is relevant (Badcock et al. 2011). They found that language lateralization derived from different tasks varies, but this variation could not be explained by task difficulty (Badcock et al. 2011). As such it is unlikely that our lack of finding an association between language lateralization and age is due to differences in task difficulty.

For the visuospatial memory task, the strength but not the direction of lateralization was predicted by age, with older children showing a more lateralized response. This replicates work by , and corresponds with the hypothesis proposed by Holland et al. (2007) that most change in lateralization with age is seen in late-acquired skills. Children in the studied age range significantly improved their performance on the visuospatial memory task with age. Whereas younger children performed the task at level 3 or 4, progressively older children completed levels 5 or 6. The visuospatial memory task therefore appears to probe late-acquired skills that are still developing between six and 16 years of age. Nevertheless, it was striking that individual differences in task performance, as indicated by the level at which the experimental task was carried out, were not predictive of cerebral lateralization on this task. Though, a similar lack of association between behavioral responses and functional lateralization has been reported in other studies assessing visuospatial attention (Rosch et al. in press) and visuospatial memory (Groen et al. 2011).

A limitation of our study with regard to assessing developmental changes in functional lateralization is its cross-sectional design. Repeatedly assessing functional lateralization in the same children at different ages would allow for stronger conclusions.

Our failure to find an association between lateralization for language production and gender is in accordance with other fTCD studies in adults (Knecht et al. 2000) and children (Haag et al. 2010; Stroobant et al. 2011), and tallies with recent reviews suggesting that claims of gender differences for language lateralization lack empirical support (Sommer et al. 2004, 2008; Wallentin 2009). However, we did find a trend for gender to predict the direction of lateralization for visuospatial memory, indicating greater right-lateralized activation for visuospatial processing in boys compared to girls. This is in agreement with findings for lateralization of spatial processing (Voyer and Bryden 1990; Ernest 1998; Johnson et al. 2002; Vogel et al. 2003) and spatial memory (Frings et al. 2006) in adults, but was not found in a previous adult fTCD study (Whitehouse and Bishop 2009). Given that the finding refers to a statistical trend, replication in a larger sample would be necessary to draw strong conclusions.

Our second aim was to consider how individual differences in patterns of lateralization relate to cognitive and language ability. The functional crowding hypothesis predicts poorer performance on cognitive and language tasks

for children with both language production and visuospatial memory lateralized to the same hemisphere compared to children in whom these functions are lateralized to different hemispheres. We did not find support for this hypothesis as no significant differences on cognitive and language tasks existed between the two groups. This is in contrast to the finding of a recent fTCD study in adults that people in whom functions lateralized to different hemispheres performed better on a dual-task than people with both functions lateralized to the same hemisphere (Lust et al. 2011a). One possible explanation for this discrepancy is that cognitive performance as measured by means of dual-task interference is quite different from our cognitive and language ability measures. A second possibility is that the group in whom functions were lateralized to different hemispheres in the study by Lust et al. (2011a) included people with language lateralized to the left, and spatial processing lateralized to the right hemisphere, but no individuals with the mirror image pattern (right-hemisphere lateralization for language, left-hemisphere for spatial processing). This latter group presents a crucial test case for the functional crowding hypothesis and children with this mirror image pattern were present in the current sample.

In contrast to the predictions of the functional crowding hypothesis, we found that children with language lateralized to the left hemisphere showed significantly higher scores on vocabulary and nonword reading, but not on nonverbal cognitive ability, compared to children in whom language was not lateralized to the left. This was the case irrespective of the status of lateralization for visuospatial memory. In fact, in about a quarter (27%) of children with language lateralized to the left hemisphere, visuospatial memory was also lateralized to the left. Together, these results suggest that lateralization of language function to the left hemisphere is advantageous to the individual and this advantage is independent of lateralization of visuospatial memory. This result is not in agreement with earlier fTCD studies in adults that suggested no disadvantage in terms of education level (Flöel et al. 2001, 2005; Whitehouse and Bishop 2009; Rosch et al. in press), intelligence, mastery of foreign languages, or artistic abilities (Knecht et al. 2001; Jansen et al. 2005) in individuals with atypical (right-hemisphere) lateralization for language. Our use of more specific tests of language ability and the inclusion of children from across the normal range of ability (instead of well-educated university students) are possible explanations for this discrepancy. The finding of a link between nonword reading and cerebral lateralization is consistent with a study by Illingworth and Bishop (2009) that used fTCD to demonstrate reduced cerebral lateralization for language in dyslexic adults.

Previously, where links have been found between language level and cerebral laterality, it has been noted that weak lateralization could be the consequence rather than the cause of language limitations. With regard to reading, a recent

neuroimaging study lends support to the "consequence rather than cause" idea. Reading development in typically developing five-year-olds was associated with a shift from bilateral to left-lateralized activation in the temporoparietal region with age whereas no such shift was observed in a group of children at-risk of reading difficulties (Yamada et al. 2010). This relation to absolute skill development does not bear out in our data as the associations found in the current study were with age-scaled scores; age, which is strongly associated with raw vocabulary level, was not a significant predictor of language lateralization and raw vocabulary and nonword reading scores did not differ between lateralization groups. Although cause cannot be distinguished from consequence within the current dataset, the results suggest that skill level within an age band rather than absolute skill level was associated with lateralization for language production.

As postulated by the Right Shift Theory, we found language advantages for those with left-hemisphere language. Our findings differ from predictions of that theory in some details; in particular, the largest effect was seen for a vocabulary measure, whereas phonological skills have been emphasized by Annett and colleagues (Annett and Turner 1974; Annett and Manning 1990; Annett 1996; Smythe and Annett 2006). Nevertheless, our findings suggest that individual differences in cerebral lateralization may influence language ability, and that such associations are worth investigating further with direct measures of brain function, rather than handedness, which is a weak and indirect indicator of language laterality.

Interestingly, our findings are also consistent with several brain imaging studies with typically developing children in the literature. For instance, reports on lateralization of the arcuate fasciculus, a major white matter tract connecting frontal and temporal language areas or their right-hemisphere homologues, show a similar association with language and literacy abilities (Lebel and Beaulieu 2009; Yeatman et al. 2011). Specifically, more leftward lateralization of the arcuate fasciculus was associated with better vocabulary and phonological awareness skills (Lebel and Beaulieu 2009) and phonological memory and reading skills (Yeatman et al. 2011) in children.

It remains to be seen whether structural differences between the hemispheres, including the larger cells, wider microcolumns, and larger spacing of macrocolumns in the left hemisphere (Seldon 1981; Hayes and Lewis 1993; Galuske et al. 2000; Hutsler and Galuske 2003), and differences in its connectivity (Penhune et al. 1996; Stephan et al. 2007; Duffau 2008; Lebel and Beaulieu 2009) are related to individual differences in cerebral lateralization. Combined structural and functional longitudinal neuroimaging studies would be necessary to assess this.

In summary, no age-related change in direction or strength of lateralization was found for language production in our sample of school-age children. In contrast, the strength of lat-

eralization (independent of direction) for visuospatial memory function, continued to increase with age. In addition, boys showed a trend for stronger right-hemisphere lateralization for visuospatial memory than girls, but there was no gender effect on language laterality. Having both language and visuospatial functions in the same hemisphere was not associated with poor cognitive performance and we therefore found no evidence for the functional crowding hypothesis. We did, however, find that children with left-lateralized language production had higher vocabulary and nonword reading age-adjusted standard scores than other children, regardless of the laterality of visuospatial memory. Thus, a link between language function and left-hemisphere lateralization exists, and cannot be explained in terms of maturational change.

Acknowledgments

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