



Research report

Sex differences in language asymmetry are age-dependent and small: A large-scale, consonant–vowel dichotic listening study with behavioral and fMRI data

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ABSTRACT

Men are often believed to have a functionally more asymmetrical brain organization than women, but the empirical evidence for sex differences in lateralization is unclear to date. Over the years we have collected data from a vast number of participants using the same consonant–vowel dichotic listening task, a reliable marker for language lateralization. One dataset comprised behavioral data from 1782 participants (885 females, 125 non-right-handers), who were divided in four age groups (children <10 yrs, adolescents = 10–15 yrs, younger adults = 16–49 yrs, and older adults >50 yrs). In addition, we had behavioral and functional imaging (fMRI) data from another 104 younger adults (49 females, aged 18–45 yrs), who completed the same dichotic listening task in a 3T scanner. This database allowed us to comprehensively test whether there is a sex difference in functional language lateralization. Across all participants and in both datasets a right ear advantage (REA) emerged, reflecting left-hemispheric language lateralization. Accordingly, the fMRI data revealed a leftward asymmetry in superior temporal lobe language processing areas. In the $N = 1782$ dataset no main effect of sex but a significant sex by age interaction emerged: the REA increased with age in both sexes but as a result of an earlier onset in females the REA was stronger in female than male adolescents. In turn, male younger adults showed greater asymmetry than female younger adults (accounting for <1% of variance). There were no sex differences in children and older adults. The males in the fMRI dataset ($N = 104$) also had a greater REA than females (accounting for 4% of variance), but no sex difference emerged in the neuroimaging data. Handedness did not affect these findings. Taken together, our findings suggest that sex differences in language lateralization as assessed with dichotic listening exist, but they are (a) not necessarily reflected in fMRI data, (b) age-dependent and (c) relatively small.

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1. Introduction

“Women use their whole brain, men just half of it” (Anitei, 2007). Statements like this can be found in several publications as the idea of a sex difference in brain lateralization has become part of our folklore. Its origin probably lies in a study by Lansdell (1961). He found that lesions of the left temporal lobe disrupted performance on a verbal test only in men, and suggested that women might be less affected by unilateral lesions because they have a more bilateral language organization. Sex differences in lateralization thus do not only have anecdotal value, but might have important practical clinical implications. Moreover, sex differences in lateralization have been suggested to be the reason why, on average, men and women differ on certain cognitive tasks. For example, the female advantage in verbal tasks, such as verbal fluency or verbal memory (Kimura, 2000), is said to be based upon a more bilateral representation of language in women (Levy, 1971). In turn, the male advantage in spatial abilities, such as mental rotation (Voyer et al., 1995), is considered to rely on a more asymmetrical brain organization in men (Levy, 1971).

The actual empirical evidence for a more asymmetrical, male brain, however, is far less convincing than popular beliefs suggest. A vast number of studies, review articles (e.g., McGlone, 1980), or books (e.g., Kimura, 2000) have addressed sex differences in lateralization. The first meta-analyses on this topic reported that the proportion of studies that found a more asymmetrical pattern in females than males was between 6.4% and 14.9% in the auditory (Hiscock et al., 1994), between 7.8% and 12.3% in the visual (Hiscock et al., 1995), and between 5.5% and 13.8% in the tactile modality (Hiscock et al., 1999a). Voyer (1996) was the first to systematically quantify the magnitude of sex difference in functional laterality. Indeed, a significantly stronger functional asymmetry emerged in males in the visual, auditory and tactile modality; however, the sex effect was very small accounting for approximately .1% of variance. A recent update that focused on sex differences in dichotic listening (DL) corroborated Voyer’s earlier findings: a significant but small bias favoring males with Cohen’s $d = .054$ (Voyer, 2011, i.e., well below .1% explained variance). The studies described so far relied mostly or solely on behavioral data. However, the two meta-analyses of Sommer et al. focused on studies that used neuroimaging techniques to investigate sex differences in language lateralization [structural and functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography, and transcranial Doppler Sonography]. The structural and functional imaging data did not reveal any significant sex effects (Sommer et al., 2004, 2008). However, some of the studies also collected behavioral data alongside neuroimaging data. Here, a small bias favoring men emerged (Hedge’s $g = .30$, i.e., about $d = .30$ and 2% explained variance), but only when consonant–vowel DL tasks were employed (Sommer et al., 2008). Taken together, meta-analyses for functional asymmetries in general, and functional verbal asymmetries in particular, point to a very small but reliable sex effect with a more asymmetrical brain organization in males.

The advantage of meta-analyses is that they provide sufficient statistical power to detect smaller population effects.

However, their results might be subject to publication bias, i.e., findings are more likely to be published when they find sex differences as compared to null results. In fact, Sommer et al. (2008) argued that the small, behavioral male advantage in DL they found is the result of a publication bias. In order to reliably test for sex differences in lateralization in a single study large numbers of participants are required since – from the results of the meta-analysis – small population effects can be expected. Over the years, we have collected data from a consonant–vowel DL task, which although collected by different researchers and different laboratories (cf. Hugdahl, 1995), were acquired with the same stimulus material and instructions. The Bergen DL task is a well-documented, reliable procedure to assess speech lateralization, which has been validated through comparisons with amobarbital sodium (Amytal) injections (Hugdahl et al., 1997). The task typically reveals a right ear advantage (REA) for verbal material reflecting a left-hemispheric speech lateralization (for review see e.g., Bryden, 1988). The Bergen DL database comprises purely behavioral data from $N = 1783$ participants – more than three times larger than the largest sample size reported by Voyer’s (2011) meta-analysis on DL ($N = 477$, from Hiscock and MacKay, 1985). Furthermore, the Bergen DL database comprises behavioral and fMRI data of the same Bergen DL task from an additional 104 right-handed participants. Together, the two datasets combine the strength of a meta-analysis (large statistical power) with the strength of a single study (no publication bias). In addition, the datasets enable us not only to investigate behavioral effects but also their underlying neuronal activity in the same paradigm.

The large sample size also allows for the investigation of inter-individual differences. For example, sex differences in language lateralization as measured with DL have been shown to depend upon age. For instance, adult men yielded an increasing while adult women yielded a decreasing REA with age (Cowell and Hugdahl, 2000). This finding is of particular relevance for the claim that women’s more bilateral representation of language might protect them against verbal impairments after unilateral lesions. Since unilateral lesions affect older rather than younger adults, one would expect that a sex difference in lateralization should be particularly pronounced in older adults. The results of Cowell and Hugdahl (2000) are in alignment with this hypothesis. In children, an early review came to the conclusion that a REA in DL exists from birth, with boys and girls being similarly lateralized (Hahn, 1987). This is supported by more recent empirical findings (e.g., Westerhausen et al., 2010a). In general, studies interested in age effects tend to be either restricted to children (e.g., Hahn, 1987) or compare children with younger adults (Hugdahl and Andersson, 1986), or compare younger adults with older adults (e.g., Cowell and Hugdahl, 2000; Bracco et al., 2011). The large, purely behavioral sample of the Bergen DL database comprises participants from 5 yrs up to 89 yrs, allowing us to investigate sex differences in verbal asymmetry across an almost complete age range.

In non-right-handers language is more often represented bilaterally or in the right hemisphere than in right-handers (e.g., Knecht et al., 2000). Since the large, purely behavioral

sample comprised 125 non-right-handers, we also investigated whether the putative sex difference in language lateralization is modulated by handedness.

In sum, the behavioral and functional imaging data from the Bergen DL database enables us to provide a comprehensive test of whether sex differences in verbal asymmetry as measured with DL exist and whether they are dependent upon age and handedness. Based on meta-analyses, a small advantage favoring a more asymmetrical brain in males was expected. A REA, reflecting left-hemispheric language lateralization, should be present in all age groups, and functionally stronger lateralization in men should appear first in younger adults and then increase in older adults. Moreover, non-right-handers were expected to show a smaller REA than right-handers.

2. Methods

2.1. Participants

The Bergen DL database comprises a sample with purely behavioral DL data from a total of 1783 healthy participants (henceforth termed ‘main sample’). The data have been accumulated from several different experiments and laboratories that all employed the same DL paradigm and standardized instructions (see below). The individual studies were conducted during the last 15 yrs and the included participants were native Norwegian-, English-, Finnish-, German-, Slovak-, Spanish-, and Swedish-speaking individuals. We removed one participant from the dataset, whose handedness was unknown. Of the remaining 1782 participants 897 were male and 885 female. Information on the exact age in years was only available for 936 of the 1782 participants, but all participants had been assigned to four age groups: children (<10 yrs), adolescents (10–15 yrs), younger adults (16–49 yrs), and older adults (>50 yrs). These pre-defined groups were used to investigate age effects. The proportion of right-handers was 93%. The characteristics of the sample are presented in Table 1.

Another sample of the Bergen DL database comprises behavioral and fMRI data from 104 healthy, right-handed participants (henceforth referred to as ‘neuroimaging sample’). The participants were younger adults between 18 and 45 yrs (mean $M = 28.5$, $SD = 7.2$ yrs) of whom 49 were female and 55 male [no significant age difference between sexes; $t(102) = 1.07$, $p = .29$]. All participants thus fell within the age

range of the ‘younger adults’ group in the main sample and age effects were consequently not examined. The fMRI data for all participants was acquired between 2005 and 2010 at the University of Bergen using the same fMRI protocol, experimental design, and MRI sequences (see also Kompus et al., 2012). Furthermore, all participants were native Norwegian speakers. For the current analysis, the individual fMRI datasets were re-processed and re-analyzed to test for hemispheric differences in brain activation and have not been analyzed or presented in this form before.

In both samples, hand preference was determined either with the Raczkowski (Raczkowski et al., 1974) or Edinburgh handedness inventory (Oldfield, 1971). If participants preferred to use their right hand to carry out the majority of activities in these questionnaires they were classified as right-handed. Participants preferring to use their left hand or showing no hand preference at all were classified as non-right-handers. Exclusion criteria were a history of psychiatric or neurologic diagnosis, as well as hearing deficits. In addition, hearing thresholds for both ears were determined in the majority of participants. All these participants could detect frequencies of up to 3000 Hz at an intensity of 20 dB and had an interaural acuity difference of no more than 10 dB.

2.2. Stimulus material

The DL test is based on the six consonant–vowel syllables /ba/, /da/, /ga/, /pa/, /ta/, and /ka/. The six syllables are paired (e.g., /ba–da/, /pa–ta/) to obtain all possible 36 combinations, including the six homonymic pairs (e.g., /ba–ba/). The two syllables of each pair are temporally aligned to achieve simultaneous onset of the initial energy release of the consonant segment, whereby one syllable is presented to the left ear and the other to the right ear channel (Hugdahl and Andersson, 1986; Hugdahl et al., 2009). In all language versions of the paradigm the syllables are spoken by a male voice with constant intensity and intonation and have a mean stimulus duration between 350 and 450 msec (depending on the voice onset time differences between unvoiced vs voiced consonant–vowel syllables and on the language).

2.3. The behavioral paradigm

The 36 stimulus pairs were presented in a pseudo-randomized order with an inter-stimulus interval of 4000 msec. The syllable pairs were presented with the instruction to report

Table 1 – Number of right- and non-right-handed male and female participants across the different age groups in the main sample [$N = 1782$].

Sex	Handedness	Age group				Σ
		<10 yrs	10–15 yrs	16–49 yrs	>50 yrs	
Male	Right-handed	100	293	348	88	829
	Non-right-handed	9	24	31	4	68
	Σ	109	317	379	92	897
Female	Right-handed	99	208	420	101	828
	Non-right-handed	3	9	40	5	57
	Σ	102	217	460	106	885
Total		211	534	839	198	1782

the syllable that was heard best, with the responses given after each trial. The stimuli were presented via headphones by either using CD versions or computerized versions of the paradigm (using EPrime software; Psychology Software Tools Inc., Pittsburgh, PA), with a sound intensity of about 70 dB SPL. The response was given orally, and was recorded by the experimenter either manually (using a score sheet) or by using a computer keyboard. The data analysis was based on the 30 dichotic pairs for which the correct report of left (LE) and right ear stimuli (RE) was determined for each participant. Finally, the laterality index (LI) was calculated as the percentage difference between correct left and right ear reports relative to the overall number of correct reports according to the formula: $LI = (RE - LE) / (RE + LE) \times 100$. This is a common procedure to control for differences in overall performance in laterality studies which are likely to occur across such a wide age range (cf. Birkett, 1977; Bryden and Sprott, 1981). LI values range between -100 and $+100\%$, with negative LIs indicating a left ear and positive LIs a REA. To examine whether men are generally more strongly lateralized regardless of direction of lateralization, the absolute LI (LI_{abs}) was additionally computed. The six homonymic pairs serve as a control measure to ensure that the participants were able to correctly identify the syllables.

2.4. Functional imaging paradigm

The 30 dichotic syllable pairs from the behavioral paradigm were presented in blocks of ten syllable pairs following an fMRI block design (see below). The full experiment included nine task and nine rest blocks, of which the first three blocks were presented with the standard instruction to report on each trial the syllable that was heard the best. The other six task blocks were presented with a different instruction and were for this reason not included in the present analysis (for details see van Wagensingen et al., 2009; Kompus et al., 2012). Before entering the MR scanner, a general instruction was given and all participants conducted five practice trials in order to familiarize themselves with the procedure. Inside the MR scanner, instructions were presented through head-coil mounted goggles (Nordic Neuro Lab, Bergen, Norway). More specifically, before each block an instruction screen was presented containing a brief statement about what to do in the following block, which was after 2500 msec replaced by a fixation cross on which the participants were instructed to focus their eyes. The fixation cross was also presented during the rest blocks which were preceded by the instruction to relax. Stimulus administration and synchronization with the MR image acquisition was controlled by EPrime software and the auditory stimuli were presented using MR-compatible headphones (Nordic Neuro Lab, Bergen, Norway). The participants' responses were given orally and recorded with an mp3-recorder connected to an MR-compatible microphone. After the experiment, individual recordings were analyzed and coded by the experimenter. In accordance with the behavioral data (see above), the percentage of correctly reported syllables from the left and right ear was recorded and the LI was calculated for each participant.

2.5. MRI

All participants underwent MR imaging on the same 3.0 T GE Signa scanner. The imaging protocol included structural T1-weighted images as well as functional imaging. The T1-weighted images were acquired using a Fast Spoiled Gradient Recall sequence (FSPGR, echo time = 14 msec, repetition time = 400 msec, inversion time = 500 msec) with 188 consecutive sagittal slices (1 mm thick, no gap, scan matrix: 256×256 ; field of view $256 \times 256 \text{ mm}^2$). The functional images were measured with a sparse-sampling echo-planar imaging (EPI) sequence, that is, EPI images were sampled with a repetition time of 5500 msec, an acquisition time of 1500 msec, and leaving a silent gap of 4000 msec. The stimulus presentation and the verbal response took place in this silent period (van den Noort et al., 2008). Functional imaging was performed in a single session during which 180 BOLD sensitive EPI volumes were acquired. Each volume consisted of 25 axial slices of 5 mm slice thickness (.5 mm inter-slice gap) and having a field of view of $220 \times 220 \text{ mm}^2$ (scan matrix 64×64 ; echo time of 30 msec), covering most of the cerebrum. The experimental stimulation followed a block design with nine task and nine rest blocks. Each of the task blocks entailed ten volume acquisitions with one stimulus pair presented per silent gap and lasted for 55 sec.

2.6. Pre-processing of the fMRI data

Pre-processing and statistical analysis of the fMRI data was performed using Statistical Parametric Mapping routines (SPM8, Wellcome Department of Cognitive Neurology, London, UK). For each participant, EPI images were realigned to the first image in each time series and unwarping was performed to correct for movement-related distortions. Then, the realigned images were normalized to a symmetrical template (using a 12-parameter affine registration followed by a nonlinear deformation step, using the mean functional image generated during the realignment process). The symmetrical template was based on the MNI EPI template provided with SPM8 and obtained by calculating the mean of the original template and the template flipped across its midline. During normalization step the images were re-sampled to a voxel size of $2 \times 2 \times 2 \text{ mm}^3$. Finally, spatial smoothing was applied using a 3D Gaussian kernel of 8 mm FWHM.

The first-level (individual) analysis of the fMRI data, a statistical model containing a predictor for the experimental manipulation conditions was created (see above), whereby the predictors were additionally convolved with the canonical hemodynamic response function and high pass filtered. After estimation of the model, the beta maps were used to perform a functional voxel-based relative asymmetry analysis (fVBRA; Kompus et al., 2011; Friston, 2003). For this purpose, the beta maps were flipped across the midline and subtracted from the original beta map. The resulting images represent the individual's relative functional asymmetry during the task, with the left "hemisphere" of the images coding asymmetry in favor of the left hemisphere, and the right coding asymmetry in favor of the right hemisphere. These asymmetry maps were used for second-level statistical analysis (as described below).

2.7. Statistical analysis

The data of the main sample was analyzed using two-factorial ANOVAs with the factors sex and age group (four levels; <10 yrs, 10–15 yrs, 16–49 yrs, >50 yrs) and the dependent variables LI and LI_{abs} . Possible handedness effects were investigated in a subsequent analysis since (as can be seen in Table 1) some cells contained very few non-right-handers and there were large differences in sample size between right- and non-right-handed participants (i.e., more than ten times as many right-handers as non-right-handers). There were 68 male and 57 female non-right-handers in total [$\chi^2(1) = .97$, $p = .325$]. A subsample of right-handers was selected, so that it matched non-right-handers in terms of sex and age. That is, if the exact age of a non-right-hander was known, either the only right-hander with exactly the same age (and of the same sex) or a randomly selected right-hander with the same age (and with the same sex) was chosen. If the exact age was not known, then a right-hander from the same age group (and of the same sex) was randomly picked. The two samples were then compared using three factorial ANOVAs with the factors sex, age group (10–15 yrs, 16–49 yrs), and handedness. Children and older adults were not considered because there were fewer than five non-right-handed participants in some of the cells (see Table 1). In all ANOVAs post-hoc comparisons were performed using Fisher's LSD procedure.

The data of the neuroimaging sample was performed as fVBRA analysis using the GLM as implemented in SPM8 to test for overall asymmetry, as well as for differences between male and female participants. Family-wise error (FWE) correction was applied to achieve a corrected significance threshold of $\alpha = .05$, and an extended threshold of $k = 20$ voxels was used. Further, the behavioral data collected during the scanning was analyzed using a t-test to compare the LI (and LI_{abs}) of male and female participants. Since the behavioral data was collected during MR scanning, that is, an unusual and maybe distracting situation for the participants, we decided not to pool the data of the neuroimaging sample with the larger behavioral sample.

For all analyses effect sizes are expressed as partial η^2 (percentage explained variance) and Cohen's d (standardized mean difference) whereby positive and negative d values indicate stronger asymmetry in males and females, respectively.

3. Results

3.1. Main sample [N = 1782]

Across all participants the analysis of the signed LI (preserving the direction of the laterality) revealed the typical REA as indicated by a significant intercept [$F(1,1774) = 619.49$, $p < .0001$, $\eta^2 = .26$] and an overall positive LI ($M = 16.3$, $SE = .7\%$). A significant main effect of age group [$F(3,1774) = 11.35$, $p < .0001$, $\eta^2 = .02$] suggested that the REA was weakest in children ($M = 11.4$, $SE = 1.6\%$) and steadily increased with age (adolescents: $M = 13.7 \pm SE = 1.0\%$; younger adults: $M = 18.6$, $SE = .8\%$; older adults: $M = 21.4$, $SE = 1.7\%$). Only the difference between children and adolescents as well

as the difference between younger and older adults did not reach significance [$t \leq 1.51$, ns; all other $t \geq 3.23$, $p \leq .001$]. There was no significant main effect of sex [$F(1,1774) = .27$, $p = .61$, $\eta^2 < .001$, $d = .02$]. However, the interaction between sex and age group reached significance [$F(3,1774) = 3.60$, $p = .013$, $\eta^2 = .01$]. Post-hoc comparisons revealed that in adolescents (10–15 yrs) girls displayed a more asymmetrical pattern than boys [$t(532) = 2.64$, $p = .009$, $d = -.23$], while there was no sex difference in children [$t(209) = 1.14$, $p = .26$, $d = .16$] and older adults [$t(196) = .47$, $p = .64$, $d = .07$], and a trend toward stronger asymmetry in male, younger adults [$t(837) = 1.91$, $p = .056$, $d = .13$]. The steady rise in REA across age thus depended upon sex: only females [$t(248.51) = 2.63$, $p = .009$] but not males [$t(424) = .73$, $p = .47$] yielded a significant increase in REA between childhood and adolescence. In turn, only males [$t(694) = 5.35$, $p < .001$] but not females [$t(675) = .49$, $p = .63$] yielded a significant rise in REA between adolescence and younger adulthood. No significant rise in REA was observed between young and old adulthood in either sex [both $t \leq .91$, $p \geq .367$]. LI distributions across males and females of every age group as well as mean sex differences in LIs can be seen in Figs. 1 and 2, respectively.

The results for the absolute laterality indices (LI_{abs}) are almost identical with the directional LI findings. No main effect of sex emerged [$F(1,1774) = 2.07$, $p = .15$, $\eta^2 = .001$, $d = -.07$], but the main effect of age group [$F(3,1774) = 29.41$, $p < .001$, $\eta^2 = .05$] as well as the interaction between sex and age group [$F(3,1774) = 4.93$, $p = .002$, $\eta^2 = .008$] was significant. As with directional laterality indices, only adolescents yielded a significant sex difference with females ($M = 22.5$, $SE = 1.2\%$) showing greater asymmetry than males [$M = 17.2$, $SE = .9\%$, $t(532) = 3.28$, $p = .001$, $d = -.31$, all other $t \leq 1.72$, $p \geq .087$]. Moreover, again females [$t(266.5) = 3.56$, $p < .001$] but not males [$t(424) = .32$, $p = .75$] yielded a significant increase in REA between childhood and adolescence, whereas males [$t(683.2) = 5.22$, $p < .001$] but not females [$t(675) = .33$, $p = .74$] yielded a significant increase in REA between adolescence and young adulthood.

The comparison of non-right-handers with the age-matched, randomly selected subsample of right-handers did not reveal any significant main or interaction effects for directional laterality indices [all $F \leq 2.41$, $p \geq .122$]. For absolute laterality indices a trend emerged indicating females and right-handers had a greater REA than males and left-handers, respectively [main effect sex: $F(1,200) = 3.66$, $p = .057$, $d = -.27$; main effect handedness: $F(1,200) = 2.78$, $p = .097$]. All other main effects and interactions were not significant [all $F \leq .94$, $p \geq .332$, $d = .05$]. Both directional and absolute laterality indices, however, yielded significant intercepts, reflecting an overall REA [both $F \geq 102.89$, $p < .001$, $\eta^2 \geq .34$].

3.2. Neuroimaging sample [N = 104]

The results of the fVBRA analysis are presented in Fig. 3. A significant asymmetrical activation during the performance of the DL task was revealed in several brain regions (see also Table 2). More specifically, a leftward asymmetry was found in the posterior superior temporal gyrus (pSTG) extending into the ventral pre- and postcentral gyrus (PCG), in the supplementary motor areas (SMA), as well as in the inferior parietal

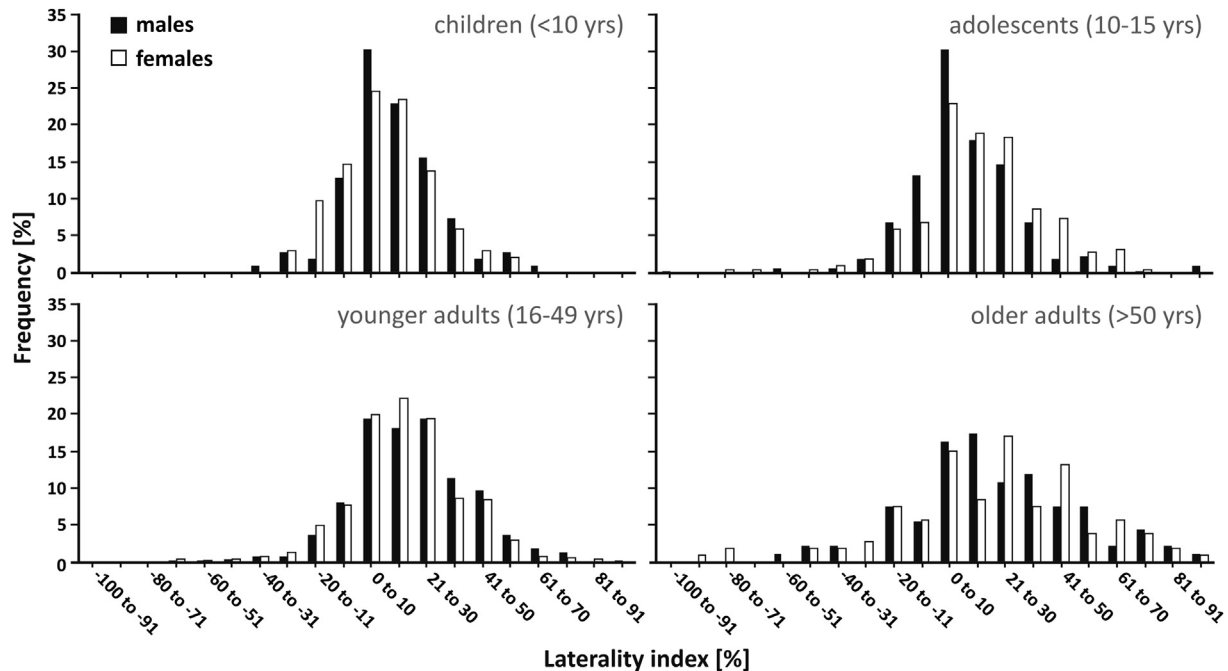


Fig. 1 – Frequency of males and females (across the four age groups) with respect to their LI in the large behavioral sample [N = 1782]. Note the large overlap between the sexes and the rightward shift of the normal distribution reflecting the REA.

lobe. Rightward asymmetry was revealed in the middle frontal gyrus (MFG) as well as in the middle temporal gyrus (MTG). However, the fVBRA did not reveal any regions showing a significant sex difference in hemispheric asymmetry. Fig. 3 illustrates the hemispheric asymmetry calculated separately for male and female participants. Clusters showing significant asymmetries were detected in the same anatomical regions for men and women, namely pSTG, PCG, SMA, and MTG.

The behavioral data analysis revealed a significant sex effect [$t(102) = 2.12, p = .036, \eta^2 = .04, d = .42$] with men ($M = 24.1, SE = 3.7\%$) showing a larger asymmetry than women ($M = 13.5, SE = 3.4\%$). The overall mean LI was $19.1 \pm 2.5\%$ and thus slightly higher than in the main sample. The stronger male bias also emerged in absolute laterality indices [males: $M = 30.3, SE = 2.7\%$; females: $M = 21.2, SE = 2.4\%$; $t(102) = 2.51, p = .013, d = .49$].

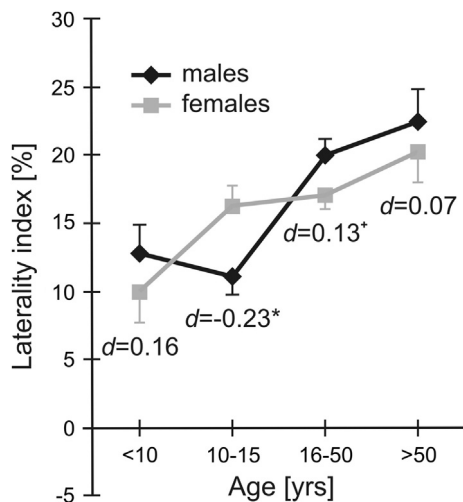


Fig. 2 – Mean laterality indices ($\pm SE$) across different age groups in the large behavioral sample [N = 1782]. A positive LI corresponds to a REA/left-hemispheric language lateralization. Cohen's d denotes the effect size of the sex difference. * $p < .05$, + $p < .10$.

4. Discussion

Using a large pool of participants that had all been tested on the same paradigm, the aim of the present study was to provide a comprehensive test of whether there is a sex difference in language lateralization as determined with DL and whether this sex difference is dependent upon age or handedness.

4.1. Findings from the main sample

4.1.1. Sex differences in DL are age-dependent

There is no evidence for an overall sex difference in DL. However, as indicated by the significant interaction of age and sex, language lateralization appears to be sometimes larger in males and sometimes larger in females – depending on the developmental stage. In children, younger adults, and older adults there was a small bias toward greater asymmetry in males with effect sizes accounting for less than .6% variance in LI (all $d < .16$). This is neatly within the range that was previously reported by Voyer (2011; $d = .05, < .1\%$) and Sommer et al. (2008; $d = .30, 2\%$) for DL. Yet, this bias toward a stronger

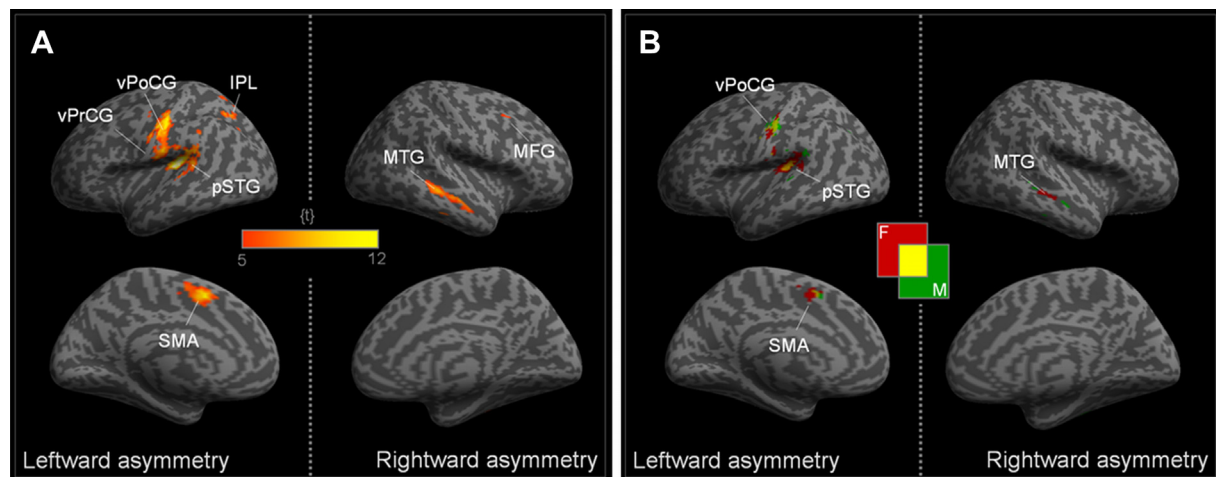


Fig. 3 – Results of the fVBRA analysis of DL in the neuroimaging sample [N = 104]. (A) Color-coded statistical probability map coding hemispheric asymmetry overlaid on an inflated mesh brain template as provided by SPM8 (FWE correction, to $p < .05$); (B) Showing regions of significant hemispheric asymmetries in female (F, red) and male (M, green) participants (threshold with FEW correction to $p < .05$). Overlap of female and male asymmetry maps is colored yellow. Abbreviations: vPrCG/vPoCG = ventral pre- and postcentral gyrus; IPL = inferior parietal lobe.

asymmetry in males was small and it failed to reach statistical significance in all age groups except younger adults, where a statistical trend was revealed. Female adolescents, on the other hand, showed a significantly stronger REA than their male counterparts, although the effect was small ($d = -.23$) accounting for only 1% of variance. As a result of the small asymmetry bias toward females in adolescence and the small bias toward males in children, younger adults and older adults, there is no significant overall sex difference ($d = .02$). Given the present sample size ($N = 1782$) the present analysis was sufficiently sensitive to reliably detect population effects as small as $d = .13$ (with a test power of $>.80$, two-tailed). Hence, a population effect larger than $d = .13$ can be excluded. The magnitude of the overall sex effect is

remarkably close to the $d = .05$ reported in the meta-analysis by Voyer (2011). Interestingly, Voyer (2011, 1996) also included children and adolescents as he reported that 23.7% of participants were younger than 18 yrs (Voyer, 2011). It would be interesting to see whether the adolescents in these meta-analyses also showed a female bias and thus reduced the overall sex difference.

In general, the REA increased across all age groups (Fig. 2). This is not in line with the HAROLD model (hemispheric asymmetry reduction in older adults) according to which older (rather than younger) adults employ additional resources from the subdominant hemisphere resulting in a functionally more symmetrical brain organization (Cabeza, 2002). However, a stronger ear asymmetry in older compared to younger adults is a well-established finding (Roup et al., 2006; Jerger et al., 1994; Clark and Knowles, 1973). According to Jerger et al. (1994) it is the result of a left ear reduction that mainly emerges as the consequence of structural changes with respect to interhemispheric transfer. According to the structural model of DL, information from the left ear is projected primarily to the right hemisphere and then needs to cross the corpus callosum to reach the language dominant left hemisphere (Kimura, 1967). Accordingly, a body of evidence exists showing a positive correlation between callosal thickness and the number of correctly reported consonant-vowel syllables from the left ear in adults (for review Westerhausen and Hugdahl, 2008). Thus, it has been speculated that as interhemispheric transfer via the corpus callosum is becoming less efficient with age (e.g., Fling et al., 2011; Sullivan et al., 2002), the number of reported syllables from the left ear might drop, resulting in a larger REA (Gootjes et al., 2004; Jerger et al., 1994; Goldstein and Braun, 1974).

The present study additionally demonstrates that the REA also increases from childhood via adolescence to adulthood. This time period has often been overlooked in DL research (Moncrieff and Wilson, 2009), but there is empirical evidence

Table 2 – Overview of regions showing a significant activation asymmetry in the fVBRA analysis.

Cluster location	MNI coordinates ^a			k	t ^c
	x ^b	y	z		
<i>Leftward asymmetry</i>					
pSTG, vPrCG, vPoCG	−36	−34	12	2094	12.03
SMA	−9	6	50	399	8.55
IPL/IPS	−28	−64	42	239	6.75
<i>Rightward asymmetry</i>					
MTG	48	−22	−16	512	7.59
MFG	40	12	56	43	5.90

Notes:

a MNI coordinates of peak activation are based on symmetrical template (see Method section for details), i.e., they will deviate from coordinates derived from a standard “asymmetrical” analysis.

b The sign of the x-coordinate indicates the direction of the asymmetry, i.e., negative sign indicated leftward asymmetry, a positive sign rightward asymmetry.

c t-value of cluster peak; Abbreviation: k = cluster size.

for developmental changes. For instance, when participants were asked to report dichotically presented digits from both ears, left ear performance steadily improved from 10 to 28 yrs (Moncrieff and Wilson, 2009). The authors attributed these improvements to brain maturation, in particular to maturation of interhemispheric connections.

The REA increased with age in both males and females. Yet, the onset of this rise is earlier in females than in males (Fig. 2). The most parsimonious explanation for this finding is that the refinement process of the corpus callosum that might underlie the REA increase begins earlier in females. Females enter puberty earlier than males and during puberty sex specific changes in white matter tracts have been reported (Lenroot and Giedd, 2010). Since the adolescent group marks the early and middle stages of puberty it may well be that the male adolescents were too young to show the rise in REA. However, males catch up after the age of 15 and their slightly stronger REA that already existed in childhood returns.

Thus, it appears tempting to suggest that the general increase in ear advantage across all age groups, as well as the interaction of sex and age found in the present study, is at least partly the result of developmental changes of the corpus callosum. However, one has to bear in mind that age-related changes in the callosal architecture might only be secondary to changes in the organization of the cerebral cortex. For example, the degeneration of callosal axons in older age (e.g., Sullivan et al., 2002) will likely reflect neuronal loss in the originating and/or projection regions of the cortex. Likewise, developmental callosal changes during early childhood will follow the cortical maturation; learning to speak, read, or write will shape the entire language processing brain network (e.g., Sakei, 2005) and callosal changes will only reflect the needs of the developing system for interhemispheric interaction. Thus, the development of cortex and corpus callosum are not separable, and it remains to be determined whether callosal changes alone suffice to explain the developmental changes in the DL ear advantage.

4.1.2. No significant handedness effects

The proportion of non-right-handers (7%) was slightly below the typical 10%, and in accordance with the literature (e.g., Sommer et al., 2008) we had a small (nonsignificant) excess of male versus female non-right-handers. Thus, the present sample appears to be representative in terms of handedness. Both right- and non-right-handers showed a significant REA. This is well in line with previous findings according to which the majority of both right- and non-right-handers have language primarily represented in the left hemisphere (e.g., Knecht et al., 2000; Rasmussen and Milner, 1977). Based on the literature we also expected non-right-handers to show a reduced REA, because the rate of right-hemispheric language representation is higher as compared with right-handers (e.g., Westerhausen et al., 2006a, 2006b; Knecht et al., 2000). However, we only found a trend toward stronger asymmetry in right-handers when direction of asymmetry was ignored and the absolute LI served as dependent variable. Crucially, handedness neither affected the age-dependent sex differences outlined above nor overall sex and age effects. It should be noted, however, that only adolescents and younger adults were examined

due to the low number of non-right-handers in the children and older age groups.

4.2. Neuroimaging sample: sex difference in behavior but not neuronal activity

Behaviorally, males in the neuroimaging sample showed a significantly stronger REA than females suggesting stronger language lateralization. The effect size ($d = .42$) lies slightly above the range for sex differences in DL ($d = .05-.30$) reported by previous meta-analyses (Voyer, 2011; Sommer et al., 2008), but is still considered small and accounts for only 4% of variance in LI. It may surprise that a significant sex difference emerged in the neuroimaging and not the main sample given that the sample size in the neuroimaging sample was much lower than in the main sample. Since participants were tested in the scanner, it is possible that the scanning environment might have somehow augmented the sex difference in DL. We also cannot fully rule out that a sampling bias increased the sex difference in the neuroimaging sample. It should be pointed out, however, that in the neuroimaging sample only younger adults were tested and that the effect is close to $d = .30$ reported by Sommer et al. (2008), who also investigated only adults. Together with the data from the main sample, these findings corroborate that at least for younger adults there is a small but reliable sex difference favoring greater asymmetry in males.

Interestingly, the behavioral sex difference is not reflected in sex differences in neuronal activity. Although the fVBR revealed clusters of significant activation differences between the hemispheres, no significant sex differences in asymmetry were detected. As can be seen in Fig. 3, men and women showed a comparable asymmetry pattern with considerable regional overlap. The present study is, to our knowledge, the first to investigate sex differences in DL in a large sample. Yet, other functional imaging studies with sample sizes of around and above $N = 100$ that investigated all kinds of language aspects, from language comprehension (Springer et al., 1999) to word production (Knecht et al., 2000), also did not find any sex differences in language lateralization. This is in alignment with meta-analyses by Sommer et al. (2004, 2008). As we have argued above, large sample sizes are required to reliably detect small population differences between males and females in specific age groups and even more so between males and females across all ages. The present study with $N = 104$ and even the largest sample size in a functional imaging study we could find ($N = 326$, Knecht et al., 2000) may still lack the required test power. Nevertheless, this observation further supports the conclusion that sex differences in the underlying neuronal activity – if they exist – are likely to be small. Studies with relatively small sample sizes, on the other hand, may have a higher chance of obtaining significant results due to chance. For example, when the claim is made that women have a more bilateral representation of language than men an fMRI study by Shaywitz et al. (1995) is often cited. Frost et al. (1999) used a similar paradigm as Shaywitz et al., but had a much larger sample size ($N = 100$ vs $N = 38$), and did not find any significant sex difference. Frost et al. (1999) might have lacked test power, while Shaywitz et al. (1995) were simply lucky to find a significant sex difference. Finally, the

neuroimaging sample shows that even if a significant sex difference emerges on a behavioral level this may not necessarily be reflected in neuronal activity. This discrepancy might be explained by ceiling effects in the BOLD response or an insufficient spatial resolution.

Nonetheless, the asymmetric pattern found in the neuroimaging data is in accordance with the auditory-verbal nature of the DL paradigm, which can be seen as further support that DL is a valid indicator of language lateralization (Hugdahl et al., 1997; Hund-Georgiadis et al., 2002). The largest cluster of leftward activation asymmetry encompassed the pSTG and the ventral precentral gyrus. Interestingly, both regions have been previously implicated to be part of a left-hemispheric dorsal auditory-motor integration network (Hickok and Poeppel, 2007; Specht and Reul, 2003), which is thought to support the discrimination of auditory stimuli as well as the articulation of verbal utterances (e.g., Dos Santos Sequeira et al., 2010; Vigneau et al., 2006). This neatly reflects the fact that in the present task the participants not only had to discriminate the two dichotically presented stimuli but also to articulate their response. Along these lines, another cluster of leftward asymmetry found in the medial SMAs might also be related to the planning of the verbal response as reported in Seghier et al. (2004). In addition, the dorsal inferior parietal lobe showed a cluster of leftward lateralization. This region has been found to be activated when a selection between competing stimuli is required, i.e., when attentional resources are deployed to separate the competing stimuli (Vandenberghe and Gillebert, 2009; Corbetta and Shulman, 2002). Thus, the observed inferior parietal activation could be the neuronal substrate of a late-selection process in which participants use attentional and cognitive control processes to separate left and right ear stimulus in preparation of their response (Hiscock et al., 1999b). Further, one might speculate that the leftward asymmetry observed in this region reflects an additional attentional enhancement of the more salient right ear stimulus in the DL situation, initiated to facilitate the selection process (Westerhausen et al., 2010b; Falkenberg et al., 2011). In line with this interpretation, lesions of this region result in a stronger interference by ipsilateral distractors in a selective attention task (e.g., Molenberghs et al., 2008).

Two further regions, the MFG as well as the MTG, showed a rightward activation asymmetry. The MFG has been considered part of a ventral fronto-parietal attention control system, especially involved in stimulus-driven attentional reorientation (Corbetta and Shulman, 2002). In accordance with the present asymmetry, this control system has been found to be lateralized to the right hemisphere (Corbetta and Shulman, 2002; Falkenberg et al., 2011). Regarding the MTG asymmetry, a previous study by Rimol et al. (2005) revealed a right- but not left-hemispheric activation when contrasting consonant–vowel syllables with noise in a functional imaging study, indicating that especially the right-hemispheric MTG might be involved in the identification of verbal stimuli.

4.3. Possible explanations for behavioral sex difference

Together with data from meta-analyses the present study suggests that there are small, age-dependent sex differences

in language lateralization with stronger lateralization in female adolescents and stronger lateralization in at least young adult males. The question thus arises as to what the underlying neuronal mechanisms are. The functional imaging data did not reveal new insights with this respect. In the literature, sex differences in the anatomy of the corpus callosum are often discussed as possible explanations for sex differences in functional lateralization (e.g., Voyer, 1996). Given the close links between interhemispheric transfer and DL outlined above, this is a particularly promising lead for the results of the present study. There is much controversy regarding a sexual dimorphism in the corpus callosum, but on the basis of the two latest reviews and meta-analyses it appears that due to their larger body size adult males have a larger corpus callosum in absolute terms (Bishop and Wahlsten, 1997) and adult females have a relatively larger corpus callosum (Smith, 2005). Following the structural model of DL outlined above (Kimura, 1967), a relatively larger corpus callosum in adult females might enable better inter-hemispheric interaction leading to a reduced DL asymmetry as observed here.

A more general theoretical framework that comprises the corpus callosum and may aid explaining sex differences in hemispheric asymmetry was provided by Ringo et al. (1994). The authors argued that hemispheric asymmetry prevents transfer time loss that arises when information needs to be sent back and forth between the two hemispheres via thinly myelinated, slow conducting fibers. This transfer time loss would be greater in larger brains since a greater distance between hemispheres needs to be covered. In support of this notion a few studies showed that larger brains are associated with smaller corpora callosa, irrespective of sex (Jäncke et al., 1997; Leonard et al., 2008). Since adult males have on average larger brains than adult females, they should also display greater asymmetry to maximize intrahemispheric transfer and to reduce the transfer time loss. One might speculate that a similar mechanism underlies the stronger asymmetry of female adolescents: the rapid growth on body and brain size during puberty might demand a more functionally asymmetric brain organization, which arises earlier in females because of the earlier onset of puberty.

Alternative to explanations comprising the corpus callosum, sex differences in functional lateralization are also often accounted for by sex hormones such as testosterone, estrogen, and progesterone (e.g., Geschwind and Galaburda, 1987). There are even studies reporting that sex hormones affect functional lateralization by affecting interhemispheric transfer (Hausmann and Güntürkün, 2000; Bayer et al., 2008). Thus, sex hormonal and corpus callosum explanations are not mutually exclusive. However, the sex hormone literature is often contradictory. In DL, for example, there are reports of a higher REA during the midluteal phase when estrogen and progesterone levels are elevated as compared with menses (e.g., Wadnerkar et al., 2008). A more recent study, on the other hand did not find a cycle phase effect (Hjelmervik et al., *in press*).

Taken together, there are a few promising leads but the underlying neuronal mechanisms of sex differences in DL lateralization – and sex differences in functional lateralization in general – remain elusive. A practical problem for

investigations is the fact that the effects are so small, and thus hard to study with “normal” sample sizes. As the present study demonstrates large numbers of participants are necessary to reveal significant sex differences in DL, while especially in neuroimaging as well as sex hormone studies it is difficult to test many participants.

4.4. Limitations

The purely behavioral sample comprised individuals from a variety of different countries and languages. Their data was pooled to investigate sex differences across a wide age range and with high test power. It cannot be fully ruled out, however, that language somehow affected our findings. Possible language differences in the perception of the syllables were prevented by utilizing recordings from native speakers. Furthermore, the REA appears to be a universal phenomenon, i.e., it is well-documented in numerous languages including those of the present study (e.g., Hirnstein, 2011; Gadea et al., 1997; Westerhausen et al., 2006a, 2006b; Della Penna et al., 2007).

We assessed language lateralization with consonant–vowel DL. Thus other measures of language lateralization or other aspects of language might lead to different results. However, since other large-scale neuroimaging studies that investigated language comprehension (Springer et al., 1999) or word production (Knecht et al., 2000) also failed to find sex differences, it seems that our findings are not limited to DL.

4.5. Conclusions and implications beyond DL

In summary, the present study suggests that sex differences in DL exist but they are generally small and dependent on age. In both sexes, the REA, reflecting left-hemispheric language lateralization, increases with age. This increase begins earlier in females, presumably due to an earlier onset of puberty, and as a result female adolescents yield a stronger lateralization than male adolescents. When young adulthood is reached, males have caught up and in fact display greater asymmetry than women. This small male advantage might persist until older adulthood and appears to be already present in children, but the present study – even with a sample size of 1782 – does not reveal a significant sex difference for these age groups. Likewise, despite $n = 104$ in the neuroimaging sample, the present study was not able to detect a sex difference in functional language lateralization in younger adults, although the DL task led to activations of typical language areas in the brain.

Naturally, it is difficult to generalize our findings on DL to other functional and structural hemispheric asymmetries. On the other hand, our findings are very much in alignment with meta-analyses on other visual, tactile or auditory functional asymmetries (Hiscock et al., 1994, 1995, 1999a; Sommer et al., 2004, 2008; Voyer, 1996, 2011) and these meta-analyses reveal surprisingly consistent findings. It thus seems justified to make a few general remarks. First, there is the idea that females are less susceptible to speech impediments after unilateral brain lesions. Here, we refer to Sommer et al. (2004) who briefly reviewed the empirical evidence and dismissed this notion concluding: “Thus, a sex difference after left-

hemispheric lesions has not been consistently reported and differences in aphasia after right-hemisphere lesions have never been demonstrated” (p. 1849). The second recurring idea is that females have superior verbal and males superior spatial skills because females are less lateralized than males (Levy, 1971). Sex differences in mental rotation, for example, show effect sizes of up to one standard deviation (Voyer et al., 1995) and sometimes even higher (e.g., Ocklenburg et al., 2011; Hirnstein et al., 2009). We find it difficult to believe that a sex difference in lateralization that seems to be around one twentieth ($d = .05$) to one fifth ($d = .2$) can account for such large cognitive sex differences (cf. Voyer, 2011). On the other hand, effect sizes in other sex-sensitive domains like spatial perception, verbal fluency, verbal memory, and perceptual speed are small to medium sized (Kimura, 2000) and even with mental rotation it cannot be fully ruled out that a (very) small sex difference in lateralization forms the basis of a larger sex effect in cognition. Thus the case is far from being closed.

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