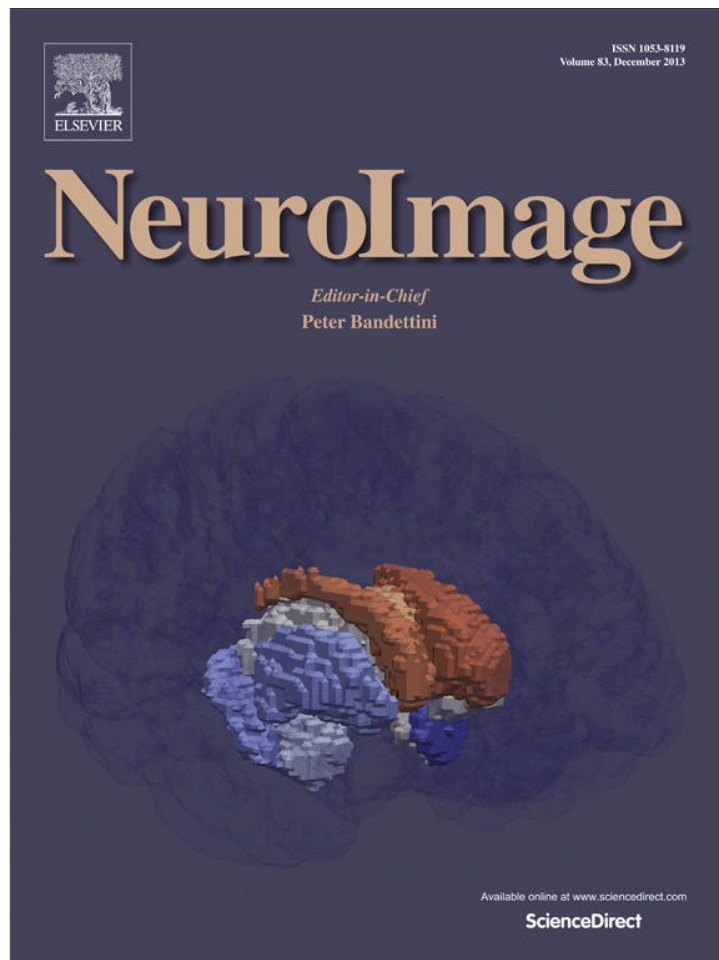


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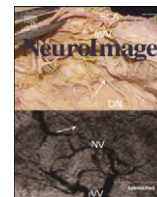
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Structural white matter asymmetries in relation to functional asymmetries during speech perception and production

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ABSTRACT

Functional hemispheric asymmetries of speech production and perception are a key feature of the human language system, but their neurophysiological basis is still poorly understood. Using a combined fMRI and tract-based spatial statistics approach, we investigated the relation of microstructural asymmetries in language-relevant white matter pathways and functional activation asymmetries during silent verb generation and passive listening to spoken words. Tract-based spatial statistics revealed several leftward asymmetric clusters in the arcuate fasciculus and uncinate fasciculus that were differentially related to activation asymmetries in the two functional tasks. Frontal and temporal activation asymmetries during silent verb generation were positively related to the strength of specific microstructural white matter asymmetries in the arcuate fasciculus. In contrast, microstructural uncinate fasciculus asymmetries were related to temporal activation asymmetries during passive listening. These findings suggest that white matter asymmetries may indeed be one of the factors underlying functional hemispheric asymmetries. Moreover, they also show that specific localized white matter asymmetries might be of greater relevance for functional activation asymmetries than microstructural features of whole pathways.

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Introduction

Functional hemispheric asymmetry is a key feature of the human language system, with about 95% of right-handers and 75% of left-handers showing left-hemispheric language dominance (Bethmann et al., 2007). This interesting phenomenon has been investigated by a multitude of studies applying different techniques ranging from lesion studies (Stowe et al., 2005) and the Wada test (Baxendale, 2009) to behavioral performance measures (Kimura, 1967; Tervaniemi and Hugdahl, 2003) and neuroimaging techniques (e.g. Badzakova-Trajkov et al., 2010; Bethmann et al., 2007; Dos Santos Sequeira et al., 2010; Ocklenburg et al., 2011a, 2012; Van der Haegen et al., 2011). Despite this multitude of methods to assess language lateralization, surprisingly little is known about its genetic background (but see: Ocklenburg et al., 2011b, 2013) and neurophysiological basis. One of the major approaches in this regard is based on the idea that functional asymmetries are a consequence of structural asymmetries in the brain (Wada, 2009). Anatomically, several left–right differences regarding macroscopic features such as size or volume of specific areas exist in the human brain

(Amunts, 2010). The idea that these structural gray matter asymmetries might be relevant for functional language lateralization started with a classic study by Geschwind and Levitsky (1968) who found that the planum temporale, a brain area located posterior to the primary auditory cortex which contains parts of Wernicke's area, is about one third larger on the left in 65% of human brains. The hypothesis that this structural asymmetry might possibly underlie functional lateralization in the language system is indirectly supported by the finding that left-handers, who have a higher prevalence of atypical right-hemispheric language dominance than right-handers (Bethmann et al., 2007), also have a less pronounced leftward structural asymmetry of the planum temporale (Steinmetz, 1996). Interestingly, in a study by Dos Santos Sequeira et al. (2006), a clear correlation between planum temporale asymmetry and functional language lateralization was only observed in right-handed male participants. In this subgroup, a greater volume of the planum temporale was related to more pronounced language lateralization as measured with the dichotic listening task. No such association was observed in female or left-handed male participants. Moreover, a voxel-based morphometry study by Jansen et al. (2010) found that a leftward asymmetry of the planum temporale can be observed in both participants with left- and right-hemispheric functional language dominance.

The difficulty to find replicable population-wide links between structural gray matter asymmetries and behavioral asymmetries lead some researchers to suggest that asymmetries in white matter pathways

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connecting brain areas relevant for a specific function may be of greater functional relevance than asymmetries in size or volume of the respective brain regions (for an overview see [Catani, 2010](#)). Interestingly, this view is strongly supported by comparative research ([Ocklenburg and Güntürkün, 2012](#)). In pigeons, a leftward functional hemispheric asymmetry in color discrimination was shown to result from an asymmetrical representation of the visual scene at forebrain level. This asymmetry, in turn, is caused by left–right differences of white matter projections at the junction between midbrain and thalamus ([Valencia-Alfonso et al., 2009](#)). In humans, the investigation of white matter connections has especially benefited from the development of diffusion-tensor imaging (DTI), a technique that is based on magnetic resonance imaging (MRI) and allows for in vivo exploration of white matter brain connectivity in the human brain ([Catani, 2010](#); [Catani et al., 2010](#); [Jones, 2010](#); [Jones and Cercignani, 2010](#); [Le Bihan et al., 1986](#)). Two types of white matter pathways relevant for language lateralization can be investigated using DTI-based approaches. Besides interhemispheric connections like the corpus callosum (e.g., [Westerhausen et al., 2006a, 2006b, 2009](#)), it has also been suggested that structural asymmetries in intrahemispheric white matter pathways connecting brain areas relevant for a specific function may be relevant for functional asymmetries (e.g., [Catani et al., 2010](#); [Huster et al., 2009](#); [Westerhausen et al., 2007](#)). At least two left-lateralized white matter structures have been shown to be functionally relevant for language tasks and thus potentially language lateralization. First, the relative fiber density of the arcuate fasciculus, a pathway initially thought to connect Broca's and Wernicke's areas, but now known to connect several areas in the frontal, temporal and parietal lobes ([Barrick et al., 2007](#); [Martino et al., 2011, 2013](#); [Nucifora et al., 2005, 2007](#)), shows a pronounced leftward asymmetry in most individuals. This leftward asymmetry has been related to verbal recall ability ([Catani et al., 2007](#)), but the findings regarding its relation with brain activation asymmetries during language tasks are mixed. While [Vernooij et al. \(2007\)](#) reported that it was positively correlated with the strength of brain activation asymmetries during a verbal fluency task in seven right-handers but not in 13 left-handers, [Powell et al. \(2006\)](#) found no correlations between arcuate fasciculus FA lateralization and activation asymmetries during a verbal fluency task in a sample of ten right-handers. However, they found significant positive correlations between arcuate fasciculus FA lateralization and frontal activation asymmetries during verb generation, as well as temporal activation asymmetries during reading comprehension. Moreover, [Propper et al. \(2010\)](#) found a relation between arcuate fasciculus volume (not FA) asymmetry and functional activation asymmetries in Wernicke's area only in seven consistent left-handers, but not in ten inconsistent left-handers or eight consistent right-handers. Since all the above studies had rather small sample sizes and, thus, low statistical power, a study investigating this structure–function relationship in a larger sample in which handedness is controlled for could help to integrate these diverging results. Another shortcoming of previous studies that needs to be addressed is the fact that they were focused only on the arcuate fasciculus. Thus, it is still unclear, whether structural asymmetries in other language-related white matter structures are relevant for language lateralization. For example, it would be interesting to relate structural asymmetries in the uncinata fasciculus, a left-lateralized pathway connecting the anterior temporal lobe with inferior frontal cortex ([Rodrigo et al., 2007](#); [Yin et al., 2013](#)) to functional activation asymmetries during language tasks. Apart from leftward asymmetries in these well-described major pathways that can be assessed using DTI tractography, it has also been suggested that more subtle structural asymmetries in smaller white matter pathways may play a role for functional asymmetries ([Barrick et al., 2007](#)). Thus a whole-brain approach, like TBSS (tract-based spatial statistics; e.g. [Takao et al., 2011](#); see [Material and methods](#) section for details), a technique that also allows for a finer grained determination of local microstructural white matter asymmetries within larger pathways, represents an ideal tool to investigate these structure–function relationships.

Another important issue to consider when investigating the structural base of functional language lateralization is the fact that partly different brain regions show activation asymmetries during speech production and perception ([Badzakova-Trajkov et al., 2010](#); [Bethman et al., 2007](#)). For example, asymmetrical brain activation induced by speech production can be assessed by using a word generation task (e.g., [Badzakova-Trajkov et al., 2010](#); [Cai et al., 2008](#); [Westerhausen et al., 2006a](#)). Using this method, [Badzakova-Trajkov et al. \(2010\)](#) found stronger left-hemispheric activations in the inferior frontal gyrus, the supplementary motor area, the precentral gyrus and the superior and inferior parietal lobules as well as in the inferior occipital gyrus. In contrast, asymmetrical brain activation induced by speech perception can be assessed by presenting words aurally or visually (e.g., [Bethman et al., 2007](#); [Josse et al., 2009](#)). Using this method, [Bethmann et al. \(2007\)](#) found greater left- than right-hemispheric activation in the inferior frontal sulcus, the inferior part of the inferior frontal gyrus, the posterior part of the superior temporal sulcus and the ascending branch of the superior temporal sulcus. Thus, it is important to differentiate between language production and perception tasks when investigating the relation of functional and structural left–right differences. Based on these considerations, the present study is aimed at investigating the relation of structural white matter asymmetries to hemispheric activation asymmetries during speech production and perception using a combined fMRI/TBSS approach.

Material and methods

Participants

Overall, 30 healthy native Norwegian speakers with no history of neurological or psychiatric diseases were tested. The data from one participant were excluded from further analysis since this participant did not complete the fMRI protocol due to discomfort in the scanner. Of the remaining 29 participants included in the analysis, 14 were male and 15 female. Participants had a mean age of 21.7 years (range: 18–27 years) and were all right-handed as determined using the Edinburgh Handedness Inventory (EHI; [Oldfield, 1971](#)). The mean lateralization quotient derived from the EHI was 84.9 (SD = 17.2; range 41.18 to 100). To assure normal hearing, all patients underwent audiometric screening. All participants gave written informed consent and were treated in accordance with the declaration of Helsinki. The study was approved by the Regional Committee for Medical Research Ethics at the University of Bergen, Norway.

Procedure

Magnetic resonance imaging was conducted on a 3 T General Electric Signa platform and consisted, besides of an initial 3D localizer, of a structural T1-weighted sequence, a DTI sequence and two functional imaging protocols. The T1 sequence was based on a Fast Spoiled Gradient (FSPGR) acquisition scheme (TR = 7.9 ms; TE = 3.1 ms; flip angle: 11°) measuring 180 sagittal slices (field of view, FOV = 256 × 256 mm; 256 × 256 scan matrix; slice thickness: 1 mm). DTI was performed using diffusion-weighted imaging with an array spatial sensitivity encoding technique (ASSET) with an acceleration factor of 1. Diffusion-sensitizing gradients were applied in 30 directions (weighting factor: $b = 1000 \text{ s/mm}^2$) and were based on a single-shot echo-planar imaging sequence (TE = 89 ms, flip angle = 90°). In addition, six reference images ($b = 0 \text{ s/mm}^2$) were acquired. The diffusion-sensitization directions followed the sampling scheme suggested by [Jones \(2004\)](#) which has been shown to allow for a robust reconstruction of the diffusion tensor and estimation of anisotropy parameters. The measurement volume consisted of 45 contiguous axial slices of 2.4 mm thickness (field of view: 220 × 220 mm; scan matrix: 128 × 128; reconstructed voxel size: 1.72 × 1.72 × 2.4 mm) which covered the entire brain.

The functional imaging protocol was the same for both paradigms (see below) and based on a sparse sampling echo-planar imaging (EPI) sequence (TE = 30 ms; flip angle: 90°). Sparse sampling was implemented using a TR of 4 s with an acquisition time of 1.5 s, leaving a scanner-noise free “silent gap” of 2.5 s between two consecutive scans. This procedure allowed for auditory stimulus presentations without direct interference of scanner noise (see passive listening task). Each paradigm consisted of 160 volume acquisitions. A volume contained 25 axial slices (inter-slice gap: 0.5 mm; field of view: 220 × 220 mm, 64 × 64 scan matrix, slice thickness: 5.0 mm, resulting in a voxel size of 3.4375 × 3.4375 × 5.0 mm) covering the entire brain and most of the cerebellum.

Functional imaging paradigms

Functional imaging consisted of two paradigms: a silent verb generation task to assess speech production and a passive listening task to assess speech perception. In order to prevent carry-over effects from the speech perception to the speech production task (e.g., participants do not generate words on their own, but remember words from the other task), all participants started with speech production task.

Silent verb generation task

This task was based on the Controlled Word Association Test (Lezak, 2004) and has previously been used in a similar form by Westerhausen et al. (2006a). Overall, the task consisted of 16 blocks of 10 scans each, with eight experimental blocks being interleaved by eight rest blocks. The length of each block was 40 s. During experimental blocks, participants were asked to think of as many Norwegian words as possible beginning with a specific letter (e.g., “B”). At the beginning of each experimental block, a different letter was given as auditory cue via headphones. The verbal command “stop” was given at the end of each word-generation block. Since vocalization-related jaw and head movements can lead to motion-artifacts in the fMRI data, participants were instructed to think of the words silently, without any lip or tongue movement. During rest blocks, participants were instructed to keep their minds blank and to focus on the sound of the fMRI scanner to avoid ongoing thinking of words.

To obtain a performance measure for the silent verb generation task, participants were asked fill out a comparable paper-and-pencil verbal fluency test outside the scanner after the end of the scanning session. The number of generated words was used as the dependent variable (Westerhausen et al., 2006a). They were instructed to write down as many words starting with a given letter in 30 s as possible. Overall, the task had two trials (S and A).

Passive listening task

This task was developed parallel to the silent verb generation task, but instead of generating verbs, participants had to passively listen to aurally presented Norwegian words starting with the same letter during task blocks (e.g., “boller” or “bukse”). In similar form, such a task has been used before by Binder et al. (2008), as well as by Specht and Reul (2003). Overall, the task consisted of 16 blocks, with eight experimental blocks being interleaved by eight rest blocks. During each experimental block, subjects listened to ten different words. During rest periods, participants were instructed to keep their minds blank and to focus on the sound of the fMRI scanner to avoid ongoing thinking of words.

Functional imaging preprocessing

The fMRI data was processed using MATLAB (MathWorks, Natick, MA, USA) and SPM8 (Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk/spm/software/spm8/; e.g., Ashburner, 2012; Frackowiak et al., 2003; Friston et al., 2007). Data from both paradigms was preprocessed in the same manner. The data was realigned to the first EPI image of each individual time-series and unwarped.

Subsequently, the images were normalized to the Montreal Neurological Institute (MNI) reference brain, resampled to a voxel size of 2 × 2 × 2 mm, and finally smoothed with a Gaussian kernel of 8 mm full width at half maximum. Following the block-design (see above), the first-level analysis was set up as hrf-convolved box-car function contrasting the respective “task” blocks against “rest”. The resulting beta-maps were then submitted to second-level analysis using a t-test against zero. Here, intensity threshold was selected to achieve family-wise error rate correction to $p = 0.05$. Additionally, following the expected voxel number per cluster as determined by SPM8, the extent threshold was set to $k = 20$ voxels per cluster. The anatomical location of each peak in every significant cluster was determined using Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002).

Afterwards, the individual degree of lateralization of activation in the functional MRI data was assessed for the frontal and temporal lobe, using the LI-Toolbox for SPM8 (<http://www.medizin.uni-tuebingen.de/kinder/en/research/neuroimaging/software/>; Wilke and Lidzba, 2007; Wilke and Schmithorst, 2006). Using the t-maps generated by the second-level analysis (see above), laterality indices (LI) were generated for activations in the temporal as well as in the frontal lobe. The midline (± 5 mm) was excluded from analysis and the intensity threshold level was set to three. LI's were generated using the formula $LI = (\text{Activation Left} - \text{Activation Right}) / (\text{Activation Left} + \text{Activation Right})$. This formula yields values between -1 (only right hemisphere activation) and $+1$ (only left hemisphere activation), with 0 denoting that no asymmetries were observed. In order to quantify both extension and strength of activation asymmetries, two LI's were calculated, one based on voxel count and the other one based on activation height (voxel value).

DTI and TBSS

DTI DICOM files were converted to NIFTI files using the dcm2nii function provided with MRICron (<http://www.mccauslandcenter.sc.edu/mricron/mricron/>). FSL 4.1.9 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) was used for further data processing (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Using the eddy_correct function of FSL, the DTI volumes were corrected for eddy current distortions, as well as for motion artifacts, by using affine registration to a reference volume. Afterwards, voxel-wise reconstruction of the diffusion tensor was conducted using the FMRIB Diffusion Toolbox (FDT). Subsequently, fractional anisotropy (FA) maps were calculated using DTIFit. The FA maps were then further analyzed using the tract-based spatial statistics toolbox (TBSS; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>) within FSL (Smith, 2002; Smith et al., 2004, 2006). After preprocessing, the FA images were normalized to MNI standard space using non-linear registration with the FMRIB58_FA standard-space image as target image (cubic voxel size of 1 × 1 × 1 mm). Then the mean FA image across all 29 participants was created and used to generate a white matter tract ‘skeleton’ mask with a threshold of FA = 0.2. This skeleton represents the centers of all tracts common to the included FA maps. In order to test for left–right asymmetries in diffusion characteristics the tbss_sym script was used and an additional symmetric FA skeleton was created. Each participants aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise statistics to identify clusters with significant leftward asymmetries ($p < 0.05$, FWE-corrected, Threshold-Free Cluster Enhancement was applied). Only clusters with a size larger than 100 voxels were considered of interest. The anatomical location of each cluster was determined using the atlas tool within fslview and the JHU ICBM-DTI-81 White-Matter Labels atlas as well as the JHU White-Matter Tractography atlas. In cases in which a white matter cluster was undefined in both white matter atlases, the Harvard–Oxford Cortical Structural Atlas was used to determine nearby gray matter structures.

Results

Silent verb generation task

The analysis of the fMRI data (see Fig. 1) resulted in three clusters showing significant activation differences compared to the control condition. All of them had peaks in the left hemisphere (see Table 1). The largest observed cluster had several peaks in the left precentral gyrus and the left inferior frontal operculum. Additionally, smaller clusters in left supplementary motor and left precentral gyrus were revealed.

The assessment of the individual degree of activation lateralization in the frontal lobe revealed that 26 out of 29 participants (89.7%) showed significant asymmetries. Of those, 23 participants showed a leftward and three participants showed a rightward asymmetry. For voxel count the mean LI was 0.49 (SD = 0.39) and for voxel value it was 0.51 (SD = 0.39), both indicating that participants on average had a leftward activation asymmetry in this task. For the temporal lobe, the results were less clear-cut. In this part of the brain, only 15 out of 29 participants (51.7%) showed significant asymmetries, whereby 13 showed a leftward and two a rightward asymmetry. For voxel count the mean LI across participants was 0.29 (SD = 0.35) and for voxel value it was 0.30 (SD = 0.36), both indicating that participants on average had a leftward activation asymmetry in this task. The analysis of the paper-and-pencil verbal fluency test outside the scanner revealed that, on average, participants generated 19.72 words (SD = 2.93), a result that is above population average (e.g. 12.5 words per minute according to Tombaugh et al., 1999).

Passive listening task

The analysis of the fMRI data (see Fig. 2) resulted in nine clusters that showed significant task-related activation; six in the left and three in the right hemisphere (see Table 2). The two largest clusters had peaks in the left and right superior and middle temporal gyrus. Other clusters in the left hemisphere had peaks in several areas in the frontal lobe, including the inferior and superior frontal gyrus, the frontal operculum, the precentral gyrus and the supplementary motor area, but also in

Table 1

Results of the silent verb generation task ($p < 0.05$, FWE correction, $k = 20$). Size gives the number of voxels in the cluster and x, y and z indicate the MNI coordinates of the peak.

Cluster	Size	Peak	x	y	z	Area
L1	1244	1	-40	2	38	Left precentral gyrus
		2	-50	10	6	Left inferior frontal operculum
		3	-52	2	48	Left precentral gyrus
L2	530	1	-4	6	62	Left supplementary motor area
		2	-6	16	50	Left supplementary motor area
L3	30	1	-34	0	68	Undefined, close to left precentral gyrus

the inferior parietal gyrus and the temporal pole. In the right hemisphere, the two additional clusters both had peaks in the inferior frontal operculum.

The assessment of the individual degree of activation lateralization in the frontal lobe revealed that 24 out of 29 participants (82.8%) showed significant asymmetries. Of those, 17 showed a leftward asymmetry and seven a rightward asymmetry. For voxel count the group mean LI was 0.19 (SD = 0.38) and for voxel value it was 0.20 (SD = 0.39), both indicating that participants on average had a leftward activation asymmetry in this task. Considering the temporal lobe, 25 out of 29 participants (86.2%) showed significant asymmetries; 12 showed a leftward, 13 a rightward asymmetry. Accordingly, the mean LI for voxel count was -0.03 (SD = 0.23) and for voxel value -0.06 (SD = 0.25). When the two groups were analyzed separately, leftward asymmetric individuals had a mean LI of 0.15 (SD = 0.14) for voxel count and a mean LI of 0.15 (SD = 0.15) for voxel value. Rightward asymmetric individuals had a mean LI of -0.22 (SD = 0.16) for voxel count and a mean LI of -0.20 (SD = 0.15) for voxel value. Since these values were considerably lower than for the silent verb generation task and LI's are a relative and highly threshold-dependent measure (Wilke and Lidzba, 2007; Wilke and Schmithorst, 2006), we also determined the absolute number of activated voxels in the left and the right hemisphere in order to get a threshold-independent measure determining whether these values do indeed indicate asymmetric activation or are more likely to reflect bilateral activations with random fluctuations around zero (e.g. due to sampling noise). For the overall group, the number of activated voxel in the

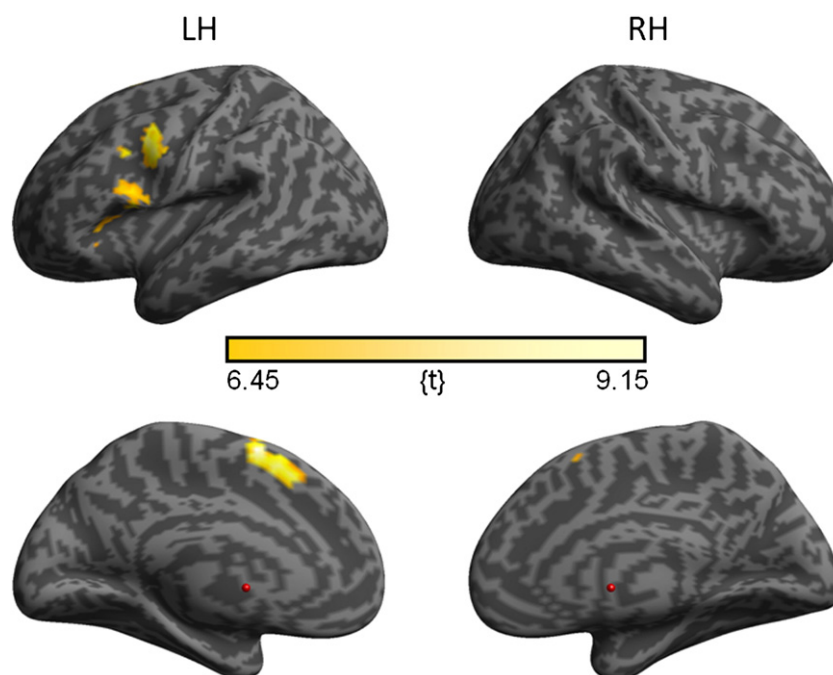


Fig. 1. Results from the fMRI analysis for the silent verb generation task for the left and the right hemisphere (LH, RH). Color-coded regions showed a significant effect of experimental vs. rest condition ($p < 0.05$, FWE-corrected, extent threshold $k = 20$ voxels). Color indicates t values, ranging from a minimum of 6.45 (orange) to a maximum of 9.15 (white). Please note that due to the flattening process and the depiction of the surface of the brain, one statistical cluster may appear as two separate colored areas on the surface of the brain in this figure.

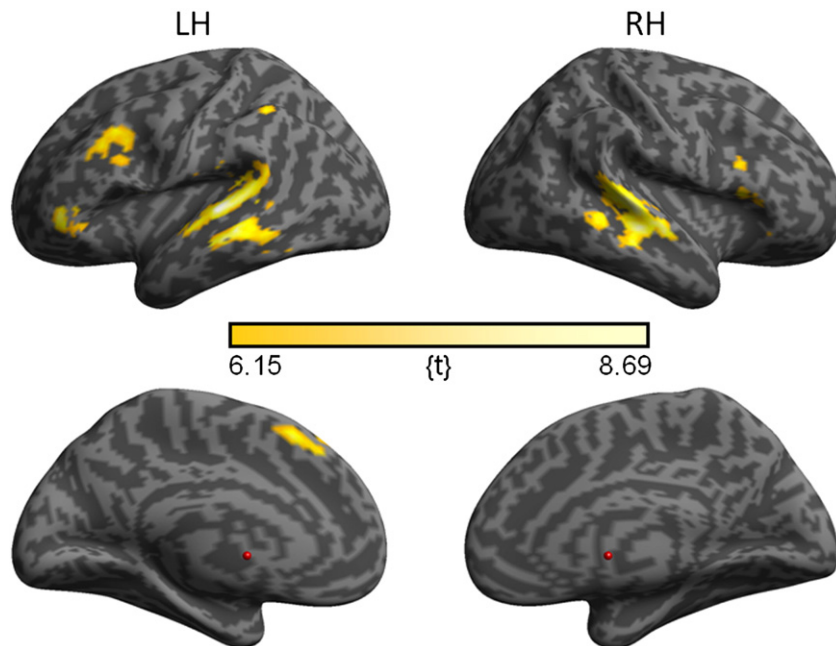


Fig. 2. Results from the fMRI analysis for the passive listening task for the left and the right hemisphere (LH, RH). Color-coded regions showed a significant effect of experimental vs. rest condition ($p < 0.05$, FWE-corrected, extent threshold $k = 20$ voxels). Color indicates t values, ranging from a minimum of 6.15 (orange) to a maximum of 8.69 (white). Please note that due to the flattening process and the depiction of the surface of the brain, one statistical cluster may appear as two separate colored areas on the surface of the brain in this figure.

left (3082.76; SD = 2523.37) and the right hemisphere (3084.76; SD = 2157.89) was almost equal. For leftward asymmetric individuals the number of activated voxel in the left hemisphere was 4466.83 (SD = 2916.25) and 3773.08 (SD = 2749.22) in the right hemisphere, while for rightward asymmetric individuals 1805.15 voxels (SD = 1168.88) were on average activated in the left and 2449.38 (SD = 1213.86) in the right hemisphere.

TBSS

The TBSS-analysis (see Fig. 3 and Table 3) revealed 18 different clusters with a voxel size larger than 100 that showed leftward structural white matter asymmetries. The largest asymmetric cluster was observed in the uncinate fasciculus (cluster 1), where also an additional smaller cluster (cluster 13) was located. Three clusters were located in the arcuate fasciculus, including the third largest cluster (cluster 3) as well as clusters 9 and 10. Additional asymmetric clusters were located

in the forceps minor, the anterior thalamic radiation, the body of the corpus callosum, the medial lemniscus, the cingulum and in several unclassified white matter regions near the superior frontal gyrus.

Relation of structural white matter asymmetries and functional activation asymmetries

The TBSS analysis revealed three clusters in the arcuate fasciculus (clusters 3, 9 and 10) as well as two clusters in the uncinate fasciculus (clusters 1 and 13) that showed significant left–right asymmetries (see Table 3) in language-relevant pathways. In order to investigate whether these white matter asymmetries are related to functional asymmetries in the fMRI tasks, we calculated Spearman correlation coefficients relating the functional LI's (voxel count and voxel value) to the magnitude of the leftward asymmetry in arcuate or uncinate fasciculus. For the silent verb generation task (see Table 4), we found positive correlations between white matter asymmetry in the arcuate fasciculus (cluster 10) and activation asymmetries in frontal regions (voxel count: $\rho = 0.47$; $p < 0.01$; voxel value: $\rho = 0.47$; $p < 0.01$), indicating that participants with more pronounced structural white matter asymmetries in this cluster had also stronger leftward activation asymmetries in this task. Moreover, we observed positive correlations between white matter asymmetry in cluster 9 in the arcuate fasciculus (voxel count: $\rho = 0.67$; $p < 0.01$; voxel value: $\rho = 0.68$; $p < 0.01$) and activation asymmetries in temporal regions. This result should however, only be interpreted cautiously, since about 50% of the participants did not show temporal activation asymmetries in this task.

For the passive listening task (Table 5), positive correlations were observed between white matter asymmetry in cluster 13 (uncinate fasciculus) and activation asymmetries in temporal regions (voxel count: $\rho = 0.43$; $p < 0.05$; voxel value: $\rho = 0.45$; $p < 0.01$), indicating that participants with more pronounced structural white matter asymmetries in this cluster had also stronger leftward activation asymmetries in this task. Moreover, we also observed negative correlations between white matter asymmetry in cluster 3 (arcuate fasciculus) and activation asymmetries in temporal regions (voxel count: $\rho = -0.34$; $p < 0.05$; voxel value: $\rho = -0.39$; $p < 0.01$). None of the correlation coefficients for frontal regions reached significance.

Table 2
Results of the passive listening task ($p < 0.05$, FWE correction, $k = 20$). Size gives the number of voxels in the cluster and x, y and z indicate the MNI coordinates of the peak.

Cluster	Size	Peak	x	y	z	Area
L1	1954	1	-62	-26	8	Left superior temporal gyrus
		2	-60	-35	10	Left middle temporal gyrus
		3	-66	-48	16	Left superior temporal gyrus
L2	481	1	-46	24	24	Left inferior frontal gyrus, triangular
		2	-48	12	36	Left precentral gyrus
		3	-38	10	26	Left inferior frontal operculum
L3	248	1	-40	40	-2	Left inferior frontal gyrus, orbital
		2	-48	34	-14	Left inferior frontal gyrus, orbital
L4	234	1	-8	18	52	Left supplementary motor area
		2	-8	30	44	Left superior frontal gyrus, medial
L5	139	1	-48	-46	46	Left inferior parietal gyrus
		2	-52	-46	54	Left inferior parietal gyrus
L6	88	1	-52	12	-6	Left superior temporal pole
R1	1445	1	62	-30	-2	Right mid temporal gyrus
		2	62	-14	-8	Right mid temporal gyrus
R2	183	1	48	18	8	Right inferior frontal operculum
		2	50	20	-2	Right inferior frontal operculum
R3	89	1	52	18	30	Right inferior frontal operculum

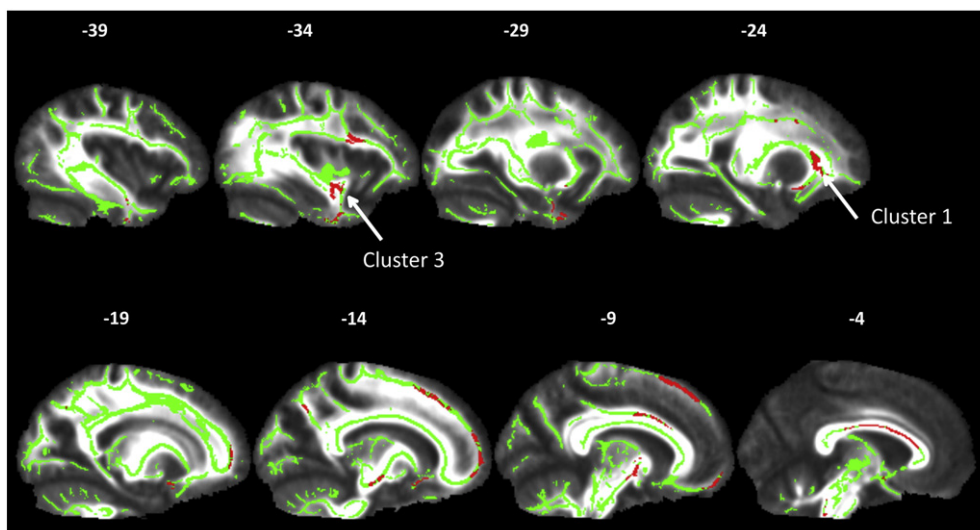


Fig. 3. TBSS Results: FA clusters that show significant left–right white matter asymmetries and have a size larger than 100 voxels are shown in red over the symmetrized skeleton (in green) that is overlaid over the mean FA image of all subjects. Sagittal slices of the left hemisphere are shown, the number over each slice gives the x coordinate in MNI space. The largest clusters in the uncinatus (cluster 1) and arcuate fasciculus (cluster 3) are indicated by white arrows.

In order to assess, whether the laterality indices obtained from the two fMRI tasks were related to each other, we also calculated correlation coefficients between the respective LI's for frontal and temporal regions. For the frontal lobe, both voxel count ($\rho = 0.40$, $p < 0.05$) and voxel value ($\rho = 0.41$, $p < 0.05$) LI's were positively correlated to each other, indicating that participants with large activation asymmetries in one task, also tend to have large activation asymmetries in the other task. In contrast, no correlation between the LI's obtained from the two tasks was observed for the temporal lobe (all p 's > 0.26).

Discussion

The present study was aimed at investigating the role of structural white matter asymmetries for functional language lateralization. To this end, we used a combined fMRI and tract-based spatial statistics approach in which we linked functional brain activation asymmetries

during speech production and speech perception to structural white matter asymmetries in language-relevant pathways. In order to assess speech production, we used a silent verb generation task. In line with earlier studies, significant activation differences between task and rest conditions were observed mainly in the left hemisphere with the largest cluster showing peaks in the left precentral gyrus and the left inferior frontal operculum. This inferior frontal activation is typical for this type of task and likely reflects language production processes (Hickok and Poeppel, 2007; Rauschecker and Scott, 2009; Van der Haegen et al., 2013). In addition, a cluster with peaks in the left supplementary motor area was observed. This area has been related to motor planning of speech. In accordance with our results, it has been reported to be activated even by language tasks without vocalization, probably reflecting an activation of speech production networks as a result of retrieving words from semantic memory (Wise et al., 1991), or speech motor program encoding (Golfinopoulos et al., 2010). In accordance with this fronto-centric activation pattern, the analysis of the LI's revealed strong leftward asymmetries (LI = 0.49 for voxel count and 0.51 for voxel value) in the frontal lobes of 23 participants, while three showed a rightward frontal asymmetry and the last three did not show any asymmetries. In contrast, almost half of the participants did not show significant temporal asymmetries. Those who did, were on average left-lateralized, but with comparably lower LI's (LI = 0.29 for voxel count and 0.30 for voxel value).

In order to assess speech perception, we used a passive listening task (Binder et al., 2008; Specht and Reul, 2003). In contrast to the silent verb generation task, participants actually heard spoken words in this task. Thus, one would expect significant activation differences between task and rest conditions bilaterally in the primary auditory cortex in the superior temporal lobe which, in accordance with earlier studies (Binder

Table 3
TBSS results: FA cluster that show significant left–right asymmetries. x, y and z denote the respective MNI coordinates of the cluster peak.

Cluster	Region	x	y	z	Voxels
1	Uncinatus fasciculus	-37	-3	-21	386
2	Forceps minor	-18	54	5	286
3	Superior part of the longitudinal fasciculus (arcuate fasciculus)	-30	6	-33	243
4	Anterior thalamic radiation	-9	-1	-3	222
5	Body of the corpus callosum	-4	8	23	209
6	Forceps minor	-9	54	-14	205
7	Unclassified white matter near the superior frontal gyrus	-11	31	47	189
8	Unclassified white matter near the superior frontal gyrus	-9	29	53	184
9	Superior part of the longitudinal fasciculus (arcuate fasciculus)	-36	5	22	165
10	Superior part of the longitudinal fasciculus (arcuate fasciculus)	-26	7	32	157
11	Body of the corpus callosum	-2	7	23	153
12	Cingulum	-12	-65	37	109
13	Uncinatus fasciculus	-24	26	6	105
14	Forceps minor	-15	58	3	103
15	Body of the corpus callosum	-6	-12	27	102
16	Medial lemniscus	-3	-38	-31	102
17	Unclassified white matter near the superior frontal gyrus	-15	37	36	101
18	Cingulum	-8	3	34	101

Table 4
Spearman rank correlation coefficients (ρ) between structural white matter asymmetries in the five clusters in the arcuate fasciculus and uncinatus fasciculus and laterality indices of frontal and temporal activation asymmetries (VC: voxel count; VV: voxel value) in the silent verb generation task. For cluster regions (C) and MNI coordinates see Table 3.

Region	Variable	C1	C3	C9	C10	C13
Frontal	VC	-0.18	0.07	0.14	0.47**	0.32
	VV	-0.21	0.07	0.15	0.47**	0.31
Temporal	VC	-0.40	0.37	0.67**	0.20	0.42
	VV	-0.34	0.38	0.68**	0.08	0.38

** $p < 0.01$.

Table 5

Spearman rank correlation coefficients (ρ) between structural white matter asymmetries in the five clusters in the arcuate fasciculus and uncinata fasciculus and laterality indices of frontal and temporal activation asymmetries (VC: voxel count; VV: voxel value) in the passive listening task. For cluster regions (C) and MNI coordinates see Table 3.

Region	Variable	C1	C3	C9	C10	C13
Frontal	VC	−0.26	−0.16	0.11	0.15	0.07
	VV	−0.27	−0.17	0.14	0.13	0.09
Temporal	VC	0.04	−0.34*	0.22	0.04	0.43*
	VV	0.09	−0.39*	0.21	0.07	0.45*

* $p < 0.05$.

et al., 2008; Specht and Reul, 2003), indeed were found. In addition, several other left-frontal clusters were detected, e.g. in the inferior and superior frontal gyrus, the frontal operculum, the precentral gyrus, and the supplementary motor area, reflecting the activation of the extended speech processing network (e.g., Friederici, 2006, 2011). Interestingly, we also observed two clusters in the right frontal operculum, an area that has been linked to paralinguistic aspects of speech processing, like speech complexity (Meyer and Jäncke, 2006) or emotional prosody (van Rijn et al., 2005). The analysis of the LI's revealed that, comparable to the silent verb generation task, participants showed a leftward frontal activation asymmetry. However, the LI's were considerably smaller ($LI = 0.19$ for voxel count and 0.20 for voxel value) and more than double as much participants showed a rightward asymmetry (seven compared to three).

The temporal LI's were also considerably different compared to the silent verb generation task, with a larger number of participants showing asymmetries on the individual level, but no clear sidedness effect on average. While the LI's indicated the existence of two subgroups, one showing left lateralization of temporal activation in this task, the other right lateralization, the LI values in both subgroups were rather low. Analysis of the average number of activated voxel in the left and right temporal lobe revealed, that in both groups activations were largely bilateral. This finding is in line with several other studies which reported bilateral, symmetrical temporal lobe activations in language tasks (Britton et al., 2009; Friederici et al., 2010; Obleser and Kotz, 2010; Price, 2010) and probably reflects the strong bilateral activation related to general auditory rather than phonological or speech processing. While the functional neuroanatomy of speech production and speech perception overlaps to some extent (Rauschecker and Scott, 2009; Scott and Wise, 2004), our fMRI results show that it is important to distinguish between speech production asymmetry and speech perception asymmetry when specifically assessing language lateralization in order to relate it to structural asymmetries. While it is well known that partly different brain regions show activation asymmetries during speech production and perception tasks (e.g., Badzakova-Trajkov et al., 2010; Bethmann et al., 2007), we directly compared the activation LI's retrieved from the two tasks within a single dataset. While we found significant positive correlations between speech production and speech perception asymmetries for both voxel count and voxel value in the frontal lobe, we did not observe any correlation between the two for the temporal lobe. This is probably due to a number of factors, including the fact that only about half of the participants showed temporal activation asymmetries in the silent verb generation task, the generally smaller temporal LI's and the right sided temporal asymmetry observed in the passive listening task. Also, the correlations we observed for frontal activation asymmetries were 0.40 and 0.41 , indicating that despite a considerable overlap between the tasks, there is also a large amount of independently asymmetric activation.

In accordance with previous TBSS studies our results showed several leftward structural white matter asymmetries with a cluster size larger than 100 voxels. For example, our findings are largely in line with a recent TBSS study in which the relation of white matter asymmetries and performance in an executive control task were investigated (Yin et al., 2013). Comparable to the present TBSS results, these authors reported

leftward asymmetries in the medial lemniscus, the forceps minor, the cingulum and the body of the corpus callosum. In regard to language lateralization, the leftward asymmetric clusters in the arcuate fasciculus and the uncinata fasciculus are likely to be most relevant.

The arcuate fasciculus is the first white matter pathway that has been identified to be relevant for the language system and was initially defined as the pathway connecting Broca's area and Wernicke's area (Friederici, 2009), but is now known to be a larger structure that connects several other areas in the frontal, temporal and parietal lobes as well (Barrick et al., 2007; Martino et al., 2011; Nucifora et al., 2005). An leftward asymmetry in white matter microstructure of the arcuate fasciculus has been reported by several studies (Catani et al., 2007; Häberling et al., 2013; Lebel and Beaulieu, 2009; Nucifora et al., 2005; Powell et al., 2006; Vernooij et al., 2007). This leftward asymmetry is functionally relevant and has been related to verbal recall ability (Catani et al., 2007). Previous results regarding the relation of structural arcuate fasciculus asymmetries and functional activation asymmetries were mixed. In a sample of ten right-handers, Powell et al. (2006) reported a significant positive correlation between the degree of mean arcuate fasciculus FA lateralization and lateralization of frontal fMRI activation during a verb generation task, but not during a verbal fluency task or a reading comprehension task. Functional lateralization of temporal lobe activation was positively related to mean arcuate fasciculus FA lateralization only for the reading comprehension task, but not the other two tasks. In contrast, Vernooij et al. (2007) who investigated the relation between functional activation asymmetries during a verbal fluency task and mean arcuate fasciculus FA did not observe a structure–function relationship in their overall sample of 13 left-handers and seven right-handers. However, when only the seven right-handers were analyzed, a strong positive correlation between FA asymmetry and whole brain activation asymmetries was observed, indicating a relevance of handedness for structure–function relationships in the language system. Correlation with regional functional activation asymmetries revealed that structural asymmetries had a strong positive correlation with functional language lateralization of parietotemporal language areas. For functional lateralization of the frontal language areas, however, the correlation did not reach significance. In contrast to Powell et al. (2006) and Vernooij et al. (2007) who found significant structure–function relationships only for right-handers, Propper et al. (2010), reported a relation between arcuate fasciculus volume (not FA) asymmetry and functional activation asymmetries in Wernicke's area only for consistent left-handers, but not for inconsistent left-handers or right-handers. Our own results, like those of Powell et al. (2006), were obtained in a right-handed sample, although with a much larger sample size. For the silent verb generation task, we found positive correlations between white matter asymmetry in cluster 10 in the arcuate fasciculus and activation asymmetries in frontal regions as well as between the arcuate fasciculus (cluster 9) and activation asymmetries in temporal regions. These findings show a specific functional role of structural white matter asymmetries in the arcuate fasciculus for functional asymmetries during language production, but not during auditory language perception. This specific effect might be explained by the fact that the arcuate fasciculus, unlike the uncinata fasciculus, has a direct connection to Brodmann Area 44 and Brodmann Area 45 that are specifically relevant for language production (Friederici, 2009). This idea is also supported by a recent study which investigated phonological functions in patients with damage to the left arcuate fasciculus, and found that almost all of these perceptive language functions were abnormal in this group (Shinoura et al., 2013).

Furthermore, our data indicate that FA asymmetry of the arcuate fasciculus as a whole as used by previous studies might not be the optimal measure to relate to functional activation asymmetries. Instead, asymmetries in specific parts of language-relevant white matter pathways might have differential impacts on activation asymmetries in frontal or temporal brain areas during speech production or perception. Thus, a finer grained determination of local microstructural white

matter asymmetries, as can be obtained by using TBSS, might be a more suitable way to investigate such structure–function relationships. In addition to these positive correlations between FA asymmetries and activation asymmetries, we also observed negative correlations between white matter asymmetry in the arcuate fasciculus (i.e. cluster 3) and activation asymmetries in temporal regions during passive listening, indicating that a larger FA asymmetry in this cluster was related to smaller functional activation asymmetries. While we can only speculate about the functional significance of this negative relationship, it might point to the existence of pathway inhibition effects as has recently been demonstrated for passive listening to dichotic consonant–vowel syllables (Della Penna et al., 2007).

In addition to the arcuate fasciculus, DTI studies have identified further dorsal and ventral white matter tracts connecting Broca's and Wernicke's area (Friederici, 2009), which had not been previously investigated in relation to functional language lateralization. For example, a dorsal pathway has been identified that runs from Broca's area via the superior longitudinal fasciculus to the posterior temporal lobe. Moreover, it has been shown that the uncinate fasciculus, together with the ventral portion of the external capsule, is part of a larger ventral language pathway (Frey et al., 2008; Friederici, 2009; Parker et al., 2005). Significantly leftward FA asymmetry has been reported for the subinsular parts of the uncinate fasciculus and it has been suggested that it might be relevant for hemispheric specialization for language (Rodrigo et al., 2007). Our results indicate for the first time that this might indeed be the case, since we observed positive correlations between white matter asymmetry in cluster 13 in the uncinate fasciculus and activation asymmetries in temporal regions during passive listening, but not during silent word generation. This dissociation may be explained by the fact that the uncinate fasciculus connects the anterior temporal lobes (Brodmann areas 20 and 38) to the lateral orbitofrontal cortex and Brodmann area 10 (Von Der Heide et al., 2013), but in contrast to the arcuate fasciculus it does not directly connect to Broca's area.

A number of methodological issues have to be taken into account when interpreting the results of the present study. One potential weakness is the use of a no-task rest condition in which the subjects were asked to listen to the scanner noise as a control condition. While rest has been used as a control condition for silent word generation or passive listening to words by a large number of previous studies (e.g., Bleich-Cohen et al., 2009; De Ciantis et al., 2008; Friedman et al., 1998; Sabbah et al., 2003; Westerhausen et al., 2006a), it has recently been suggested that an active non-linguistic control condition is needed to reliably assess activation in brain regions involved in semantic processing (Binder et al., 2008). Thus, future studies investigating the relation between structural and functional asymmetries in the language system might benefit from also including active control conditions.

Another potential issue might occur from the fact that in the silent verb generation task, hemodynamic responses to scanner noise might have interfered with task-related activations. Since subjects generated words at their individual pace during each of the 40 s long experimental blocks, hemodynamic responses to scanner noise might have overlapped with task-related activations in this task. Moreover, subjects were asked to ignore the scanner noise and pay attention to word generation during task periods, but during the control condition they were asked to pay attention to scanner noise. These attentional shifts might also create a modulation of the BOLD response. However, since the hemodynamic response to scanner noise should mainly be located in the primary auditory cortex, while a possible attentional shift should rather affect dorsal fronto-parietal areas (e.g. Li et al., 2012) this potential confound should not interfere with the fronto-temporal language production networks involved in the silent verb generation task.

Taken together, our results indicate that local microstructural asymmetries in two language relevant white matter pathways, the arcuate fasciculus and the uncinate fasciculus, are relevant for functional activation asymmetries during speech production and perception. For frontal activation asymmetries all correlations with structure

were positive, indicating that a possibly stronger and/or faster intrahemispheric connection between Broca's and Wernicke's area leads to more functional activation asymmetry. For temporal activation asymmetries, however, we also observed negative structure/function correlation indicating that pathway inhibition effects are an important factor for functional asymmetries that should be taken into account by future studies. In general, our results show that functional speech production and perception asymmetries in the frontal and temporal lobes are related to specific white matter asymmetries in differentially localized clusters, supporting the idea that further investigating task-specific local FA asymmetries instead of microstructural features of whole pathways might be a worthwhile attempt when trying to intertwine the complex relationship of white matter and functional lateralization.

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Conflict of interest

The authors declare no competing interests.

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