A Surface-based Analysis of Language Lateralization and Cortical Asymmetry

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Abstract

Among brain functions, language is one of the most lateralized. Cortical language areas are also some of the most asymmetrical in the brain. An open question is whether the asymmetry in function is linked to the asymmetry in anatomy. To address this question, we measured anatomical asymmetry in 34 participants shown with fMRI to have language dominance of the left hemisphere (LLD) and 21 participants shown to have atypical right hemisphere dominance (RLD). All participants were healthy and left-handed, and most (80%) were female. Gray matter (GM) volume asymmetry was measured using an automated surface-based technique in both ROIs and exploratory analyses. In the ROI analysis, a significant difference between LLD and RLD was found in the insula. No differences were found in planum temporale (PT), pars opercularis (POp), pars triangularis (PTr), or Heschl's gyrus (HG). The PT, POp, insula, and HG were all significantly left lateralized in both LLD and RLD participants. Both the positive and negative ROI findings replicate a previous study using manually labeled ROIs in a different cohort [Keller, S. S., Roberts, N., Garcia-Finana, M., Mohammadi, S., Ringelstein, E. B., Knecht, S., et al. Can the language-dominant hemisphere be predicted by brain anatomy? *Journal of Cognitive Neuroscience, 23*, 2013–2029, 2011]. The exploratory analysis was accomplished using a new surface-based registration that aligns cortical folding patterns across both subject and hemisphere. A small but significant cluster was found in the superior temporal gyrus that overlapped with the PT. A cluster was also found in the ventral occipitotemporal cortex corresponding to the visual word recognition area. The surface-based analysis also makes it possible to disentangle the effects of GM volume, thickness, and surface area while removing the effects of curvature. For both the ROI and exploratory analyses, the difference between LLD and RLD volume laterality was most strongly driven by differences in surface area and not cortical thickness. Overall, there were surprisingly few differences in GM volume asymmetry between LLD and RLD indicating that gross morphometric asymmetry is only subtly related to functional language laterality.

INTRODUCTION

It has long been known that speech production is lateralized in the brain, with the left side being dominant in most people. On the basis of a review of the existing clinical data, Benson and Geschwind (1985) estimated that 60% of right-handed patients with unilateral left hemisphere (LH) lesions developed aphasia, whereas only 2% of right-handed patients with right hemisphere (RH) damage did. For left-handed patients, the figures were respectively 32% and 24%. Other clinical evidence came from the Wada test (Wada & Rasmussen, 1960). In this test, sodium amytal is injected unilaterally to anesthetize a hemisphere, and the effects on speech production are monitored. The test was administered to determine speech dominance in epileptic patients before surgery. Loring et al. (1990) described the outcome of one of the best controlled studies. A total of 103 patients (91 right-handed and 12 left- or mixed-handed) were tested. Of these, 79 had exclusively LH language representation (73 right-handers) involving both production (counting) and comprehension (following simple commands). Only two patients had exclusive RH language representation (1 right-hander). The remaining 22 participants (17 righthanders) had performance decrements after injection to each hemisphere.

In the 1990s, brain imaging started to replace the Wada test. Classifications with these techniques were shown to be nearly identical to those of the Wada test (e.g., Binder et al., 1996) and made possible research on healthy individuals. Using transcranial Doppler sonography, Knecht and colleagues reported that 95% of right-handers had a larger increase in blood flow in the LH when silently generating words starting with a particular letter. For the left-handers, the percentage of left dominance was 75–90%, depending on the degree of handedness (Van der Haegen, Cai, Seurinck, & Brysbaert, 2011; Knecht et al., 2000; Loring et al., 1990).

Recently, researchers have started to investigate what consequences atypical right speech lateralization has for the lateralization of other brain functions. First, it was shown that right lateralization of Broca's area is mostly, but not always, accompanied by atypical lateralization of the occipito-temporal regions involved in word reading (Van der Haegen, Cai, & Brysbaert, 2012; Seghier & Price, 2011; Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010; Cai, Lavidor, Brysbaert, Paulignan, & Nazir, 2008). Second, it was observed that all participants with RH speech dominance were right dominant for tool use as well (Vingerhoets et al., 2013), independent of handed-ness. Good performance on this task involved the SMA (BA 6), Broca's area (BA 44/45), the dorsolateral pFC (BA 9/46), and the posterior parietal cortex (BA 40/7). Finally, Cai, Van der Haegen, and Brysbaert (2013) reported that all participants with right speech lateralization had atypical, LH lateralization of the frontoparietal network involved in visuospatial processing (the Landmark task). This network involved the inferior parietal sulcus and the superior parietal lobule (BA 39/40) together with the FEF (the intersection of BA 4/6/8) and the inferior frontal sulcus (BA 44/45) in the nondominant hemisphere. Thus, it appears that atypical speech lateralization has profound implications for functional lateralization throughout the brain.[1]

In this study, we examine how atypical speech dominance is related to the structural asymmetries of the cerebral cortex. Given the large functional implications, one might expect that atypical speech lateralization is accompanied by substantial differences in gray matter (GM). A dominant hypothesis is that the usual LH language dominance may be the result of the LH being larger in brain areas related to language processing. Indeed, both the

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[1]It was also found that participants with right hemisphere speech lateralization had an atypical left-ear advantage in a dichotic listening task (Van der Haegen et al., under revision), suggesting that the brain areas involved in spoken word recognition are atypically lateralized as well, but no fMRI data have been collected on this yet.

planum temporale (PT), involved in auditory language processing, and the opercular part of Broca's area are known to show a leftward volume asymmetry, which is larger in right-handers than in left-handers (Toga & Thompson, 2003). This discovery has lead to a number of studies in which functional laterality scores were correlated with anatomical laterality scores (e.g., Josse, Kherif, Flandin, Seghier, & Price, 2009; Josse, Mazoyer, Crivello, & Tzourio-Mazoyer, 2003; Tzourio, Nkanga-Ngila, & Mazoyer, 1998). A limitation of these studies, however, was that they usually involved small numbers of participants who were not selected for hemisphere dominance. Given the rareness of atypical right speech laterality, it is unlikely that enough participants with truly inversed speech dominance were included to draw valid conclusions (see Cai et al., 2013, for more information on the problem of drawing conclusions on the basis of samples mainly consisting of left language dominant participants).

Arguably the best study comparing left language dominant (LLD) participants with right language dominant (RLD) participants was Keller et al. (2011). The authors compared the anatomical MRI images of 15 LLD participants with those of 10 RLD participants (language dominance determined by transcranial Doppler sonography or fMRI during a silent word generation [WG]). To their surprise, Keller et al. observed no relationship between volume asymmetry of Broca's area or the PT and language dominance (the trends were even in the opposite direction, with larger leftward asymmetries for RLD participants than for LLD participants). The only region for which they found a robust relationship between volume asymmetry and language dominance was the insula, with a tendency toward rightward asymmetry for the RLD participants, making the authors conclude that the insular morphology should be given more importance in studies on the anatomical correlates of human language laterali-zation. This study performs an analysis similar to Keller et al. (2011) to see whether the surprising findings can be replicated on new groups of LLD and RLD participants and to what extent the results depend on the methodology used.

An important issue in studying the relationship between structure and function is the delineation of morphological features. Typically, cortical structures known to be involved in language are manually segmented based on landmarks to obtain measures of volume, area, length, and/or angulation. However, the cortical surface is highly folded with variable thickness, and there is a large degree of anatomical variability across participants. This variability makes it difficult to consistently and accurately define and quantify structures of interest. Manual labeling is also a tedious procedure that is not feasible in the large data sets required for testing hypotheses in human studies.

Even in the case where morphological features are well defined and quantified, they may still be somewhat arbitrary relative to the underlying function. The anatomical manifestation of a functional asymmetry may not confine itself neatly within a morphological feature chosen by an anatomist. This can cause a loss of statistical power if the entire feature is considered. In this case, exploratory methods may be more powerful because they allow the data itself to determine what the underlying morphological feature should be. Voxel-based morphometry (VBM; Ashburner & Friston, 2000) is often used in this type of application, including brain asymmetry (Luders, Gaser, Jancke, & Schlaug, 2004; Watkins et al., 2001). There has only been one study using VBM to assess structural asymmetry differences in LLD and RLD (Dorsaint-Pierre et al., 2006). This VBM study was in an epilepsy pre-surgical cohort involving a small number of patients (11 of whom were RLD), which may not reflect the general population. In addition, VBM has two other shortcomings. First, it relies on volume-based registration to align brains across participants, which is often inaccurate when attempting to align particular cortical folds (Fischl et al., 2008). Second, when differences are found with VBM, the results cannot be refined to determine whether

the underlying cause of the difference was because of differences in folding pattern, GM volume, cortical surface, or cortical thickness.

This study addresses the limitations of Keller et al. (2011) in three important ways. First, it uses a relatively large sample of healthy participants who have been verified to be strongly RLD based on fMRI *(n = 2*1 instead of 10), thereby considerably increasing the power of the study. This increase was made practical through the use of a low-cost and noninvasive screening procedure developed previously (Van der Haegen et al., 2011). Second, it uses computer-generated mesh models of the cortical surface to automatically find and accurately quantify standard morphological features, including those associated with language. Finally, it uses surface-based interparticipant and interhemispheric registration to align folding patterns so that the cortical volume, surface area, and thickness can be consistently evaluated across language dominance group, subject, and hemisphere. This registration allows for an exploratory analysis in which the data dictate the anatomical boundaries of areas that show consistent structural and functional asymmetries.

METHODS

Laterality Index

The laterality index (LI) is used to quantify the difference between left and right while removing the effects of brain size. We use the formula:

$$\mathrm{LI} = \frac{(L - R)}{(L + R)} \quad (1)$$

where L is the value from the left side and R is the value from the right side. LI has a range from −1 (completely right lateralized) to +1 (completely left lateralized). This formula can be applied to any metric including volume, area, thickness, volume of functional activation, or behavioral measure.

Participants and fMRI Analysis

Full details of subject recruitment, handedness assessment, screening procedures, fMRI analysis, and language LI calculation are provided in (Van der Haegen et al. 2011, 2012). For completeness, we summarize them here. All participants signed an informed consent form according to the guidelines of the Ethics Committee of the Ghent University Hospital. A total of 269 participants[2] were accepted to the initial screening based on the criteria that they wrote and drew with their left hand to increase the likelihood of atypical language dominance. Handedness was later assessed with the Edinburgh Handedness Inventory (Oldfield, 1971) modified to have answers in the range of −3 to −1 (degree of left-handedness) or +1 to +3 (right-handedness). Most participants underwent two visual half field (VHF) tasks (Hunter & Brysbaert, 2008) in which they were asked to name words and pictures presented to the left visual field (LVF) or to the right visual field (RVF). LIs were calculated by subtracting the mean RT to stimuli in RVF from the mean RT to stimuli in LVF.

Sixty-five participants were invited (and willing) to take part in the fMRI study. Twenty-five were expected to be LLD on the basis of their VHF scores; the remaining 40 had an LVF advantage on one of the VHF tasks and were hoped to be RLD (Van der Haegen et al., 2011; Hunter & Brysbaert, 2008).[3] The fMRI task consisted of silent WG (Hunter & Brysbaert,

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[2]We tested 19 participants more after the Van der Haegen et al. (2011) manuscript was accepted for publication. Most of these additional participants were not previously screened with the VHF tasks.
[3]As can be seen in the Results section, this turned out to be the case for about half of the participants.

2008; Knecht et al., 2000; Pujol, Deus, Losilla, & Capdevila, 1999). Participants were asked to silently think of as many words as possible, beginning with a cued letter. The control/baseline condition was silent repetition of the nonword "baba." SPMs were generated based on target letter versus nonword contrast. The functional LIs were computed in areas approximately corresponding to Broca's area (i.e., BA 44 and BA 45; AAL template; Tzourio-Mazoyer et al., 2002). These regions were chosen because they are the most active areas in the silent WG task and are known to be involved in many linguistic functions (Heim, Eickhoff, & Amunts, 2008; Amunts et al., 2004).

For statistical analysis, the 65 participants were categorized into three groups based on the functional WG LI scores: LLD if LI > 0.6, RLD if LI < −0.6, and bilateral language dominant (BLD) otherwise. This categorization was used to make a clear separation between the RLD group and the LLD group (see the Discussion for the reasoning behind this model). Figure 1 shows the distribution of the fMRI LIs of all participants. The demographics and mean LI for the three groups are shown in Table 1. The handedness scores for all groups were less than −2, indicating strong left handedness (−3 would be the most extreme for left handers). The groups did not significantly differ in handedness ($p > .55$) or age ($p > .48$). The sample was recruited from a wide range of courses at university or higher education schools. As female students seemed to be more willing to take part, they formed the majority of participants.

A second fMRI task (lexical decision task, LDT) was also collected on these participants (Van der Haegen et al., 2012). The LDT assesses the lateralization of word reading by looking at activity in the vOT. Stimuli consisted of high- and low-frequency words, consonant strings, and pixel-scrambled words. Participants were required to respond with button press as to whether the stimulus was a word or nonword. Cerebral dominance was determined on the basis of the WG task and not the LDT, in line with clinical practice (Spreer et al., 2002; Benson et al., 1999; Springer et al., 1999), which uses speech production lateralization as an index of language laterality. The brain areas involved in speech production are the most lateralized, arguably because fluent speaking requires a single control center (Kosslyn, 1987).

MRI Acquisition

Images were acquired on a 3-T Siemens Trio MRI scanner at Ghent University (Siemens Medical Systems, Erlangen, Germany) with an eight-channel radiofrequency head coil. A high-resolution anatomical image was collected using a T1-weighted 3-D MPRAGE sequence. All images were $256 \times 256 \times 176$ with voxel size = $0.9 \times 0.9 \times 0.9$ mm^3. The data were acquired with either one of two sets of pulse sequence parameters: repetition time = 1550 msec, echo time = 2.39 msec, flip angle = 9°, inversion time = 900 msec, pixel frequency = 180 Hz; or repetition time = 2530 msec, echo time = 2.58 msec, flip angle = 7°, inversion time = 1100 msec, pixel frequency = 190 Hz. Most ($n = 54$) were acquired with the first set. The proportion of each parameter set was the same (85% to 15%) in the LLD and RLD groups.

Anatomical Analysis

All participants were analyzed in FreeSurfer (www.surfer. nmr.mgh.harvard.edu, version 5.1) to provide detailed anatomical information customized for each participant (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). The FreeSurfer analysis stream includes intensity bias field removal, skull stripping, and assigning a neuro-anatomical label (e.g., hippocampus, amygdala, etc.) to each voxel (Segonne et al., 2004; Fischl et al., 2002). In addition to the volume-based analysis, FreeSurfer constructs models of the cortical surface. A surface model consists of a mesh of triangles. The location of the mesh is

controlled by adjusting the location of the vertices. A vertex is the place where the points of neighboring triangles meet (typically about 1 mm apart). The vertex positions are adjusted such that the surface follows the T1 intensity gradient between cortical white matter (WM) and cortical GM. Smoothness constraints allow the surface to cut through a voxel to model partial volume effects and provide subvoxel accuracy of the location of the surface. This highly folded surface can be "inflated" (Figure 2) to see inside the sulci. A second surface is also fit to the outside of the brain (between the GM and the pia). The first surface is called the "white" surface, and the second is called the "pial" surface (Figures 3A and 4A show pial surfaces). The LH and RH are modeled separately. All surfaces are constructed in the native anatomical space.

Cortical GM Metrics

In FreeSurfer, the distance between the white and pial surfaces at a vertex is defined to be the cortical thickness at that vertex (Fischl & Dale, 2000). The area of a vertex is defined as the average area of the triangles of which the vertex is a member. The GM volume of a vertex is defined as the area times the thickness. The surface area of a region can be computed by adding up the area of the vertices in that region, and the same can be done to compute the GM volume. The surface curvature at a vertex can be computed based on its spatial relationship to neighboring vertices. The curvature is a quantification of the folding patterns. Thus, at each point along the subject's surface, the thickness, area, volume, and curvature can be quantified, all with subvoxel accuracy.

Surface-based Intersubject Registration

The curvature is used to drive a nonlinear surface-based inter-subject registration procedure that aligns the cortical folding patterns of each subject to a standard surface space (Fischl, Sereno, Tootell, & Dale, 1999). This approach is similar to performing a volume-based registration to Talairach or Montreal Neurological Institute space but is much more accurate for cortical areas (Fischl et al., 2008). The thickness, area, and volume can be resampled into the standard space so that vertex-wise comparisons across subjects can be made in an exploratory analysis. The area and volume resampling includes a "jacobian correction" (similar to that described in Winkler et al., 2012) to account for any stretching or compression in the registration. This correction is not needed for thickness because it is measured along a vector normal to any stretching or compression.

Cross-hemisphere Symmetric Registration Template

There are two standard space surface registration templates in FreeSurfer, one for each hemisphere. Simply registering a hemisphere to a contralateral template can create biases, that is, one will get different results depending upon whether one registers both hemispheres to the LH template or to the RH template. A symmetric template is needed, which can be generated in one of two ways: (1) regenerate the template from scratch by left–right reversing the subjects used in the template and reregistering with all data (i.e., treating the reversed subjects as new, additional subjects) or (2) left–right reversing the template itself and averaging with the non reversed atlas. This second approach is easy to implement and dominants in the field (Josse et al., 2009; Eckert et al., 2008; Watkins et al., 2001). However, this approach has several drawbacks, namely a blurrier atlas is created because features are washed out, and there is no way to keep track of the amount of variance because of variability across hemispheres. For these reasons, we created a new surface template from scratch using an iterative technique described in Fischl, Sereno, Tootell, et al. (1999) modified to yield a symmetric template. The symmetric template was created using 42 participants from this study consisting of an equal number of LLD and RLD, each group represented by 3 men and 18 women. No BLD were used in the template construction. First, an initial template was created from only the LHs of these participants based on the

registration to the LH standard template. Both LHs and RHs from all participants were aligned with this initial LH template. A new template was then created from these 84 surfaces, and the surfaces were reregistered to it. This new template is a mixture of LH and RH and so less biased than the initial LH-only template. This process was repeated 35 times to remove the influence of initializing with LH. To test whether this procedure leads to a symmetrical template, the entire template creation procedure was replicated initialing with the RH. The exploratory analysis described below was performed using both the LH- and RH-initialized templates. Similarity in the results is evidence of a symmetric template.

Anatomically Defined Cortical ROIs

FreeSurfer has the ability to automatically label the cortex in a way intended to replicate the labeling of a trained anatomist (Destrieux, Fischl, Dale, & Halgren, 2010; Desikan et al., 2006; Fischl et al., 2004). This labeling goes beyond simply the mapping of an ROI atlas into the subject space because the boundaries of the labels are customized to each participant based on curvature statistics stored in the ROI atlas. Note that, whereas an anatomist uses explicit rules and landmarks to define specific areas, the automatic procedure relies only on implicit rules generated during the training process. This method has been validated using a jackknifing procedure (Fischl et al., 2004). We used the Destrieux atlas (Destrieux et al., 2010), which has 74 ROIs on each hemisphere and was derived from 12 participants not involved in this study. We selected five language-related ROIs from which to report the volume, area, and thickness (see Destrieux et al., 2010, for details on the landmarks used to define these ROIs): (1) opercular part of the inferior frontal gyrus (pars opercularis, POp), (2) triangular part of the inferior frontal gyrus (pars triangularis; PTr), (3) PT, (4) anterior transverse temporal gyrus (Heschl's gyrus, HG), (5) insula composed of superior, anterior, and inferior segments of the circular sulcus of the insula, short and long insular gyri, and the central sulcus of the insula. The PT is shown in an inflated hemisphere in Figure 5.We emphasize that the anatomical ROIs are independent of the interhemi-spheric registration. Note that the Destrieux PT definition includes both the posterior horizontal segment and the posterior ascending ramus (sometimes referred to as the planum parietale or PP). These ROIs were chosen for several reasons. POp and PTr approximate Broca's area. PT has prominent anatomic asymmetries and is an area of language function. The insula has been found to have an interaction between anatomy and language function (Keller et al., 2011). HG was chosen because of known anatomical asymmetry (Dorsaint-Pierre et al., 2006; Penhune, Cismaru, Dorsaint-Pierre, Petitto, & Zatorre, 2003; Penhune, Zatorre, MacDonald, & Evans, 1996; Rademacher, Caviness, Steinmetz, & Galaburda, 1993). Performing an anatomical ROI analysis also provides a means through which the FreeSurfer ROI results can be compared with those of other studies as well as with the exploratory analysis.

Exploratory Spatial Analysis

Both hemispheres of all 65 participants were registered to the symmetric template, and the vertex-wise cortical GM volume maps were mapped into the symmetric standard space. These were then surface-smoothed by 10 mm FWHM. For each participant, the volume LI at each vertex was computed as per Equation 1. A statistical analysis was performed at each vertex to evaluate the difference between the LLD and RLD participants using a two-group unsigned t test with 53 degrees of freedom (DOF). Clusters were defined as groups of contiguous vertices with vertex-wise $p < .01$ (the cluster forming threshold). The p value for a cluster was determined through Monte Carlo simulation in which white Gaussian noise was repeatedly synthesized on the surface, spatially smoothed, thresholded, and clustered to determine the distribution of cluster sizes under the null hypothesis (Hagler, Saygin, & Sereno, 2006). The cluster search space was constrained by two a priori regions corresponding to an anterior language area (ALA) that surrounds Broca's area and a posterior language area (PLA) that surrounds Wernicke's area, which are often mentioned as

traditional language areas (Toga & Thompson, 2003). We defined the ALA by combining four of the Destrieux ROIs: (1) POp, (2) PTr, (3) horizontal and vertical ramus of the anterior segment of the lateral sulcus, and (4) inferior part of the precentral sulcus. We defined the PLA by combining Destrieux ROIs: (1) angular gyrus, (2) supramarginal gyrus, (3) PT, (4) transverse temporal sulcus, (5) posterior ramus of the lateral sulcus, (6) lateral aspect of the superior temporal gyrus (STG; posterior half), (7) STS (posterior two thirds), and (8) sulcus inter-medius primus of Jensen. The resulting ALA and PLA are shown in yellow outline in Figure 2. Because this is an exploratory analysis, the boundaries for these areas were selected to be rather large so as to reduce the chance of missing clusters. The ALA and PLA are larger and different than the anatomical ROIs above so that the exploratory analysis might allow the data to define new ROIs that are not necessarily defined by landmarks visible to an anatomist. A cluster analysis using the whole hemisphere was also performed to search for any clusters that might be outside of traditional language areas.

RESULTS

Anatomically Defined ROIs

Figure 6 shows the average volume LI for the three groups. The PT, POp, insula, and HG where all highly significantly left-lateralized in both LLD and RLD ($p < .0001$). Post hoc analysis revealed that each ROI was significantly left lateralized in terms of surface area ($p < .0001$), but not thickness. The PTr was the only structure that was not significantly left lateralized ($p = .31$). All ROIs showed numerically greater volume LIs for LLD over RLD; however, the only structure to show a significant difference was insula ($p = .0127$, after correcting for five comparisons). The PT significance was trending toward a difference ($p = .13$, uncorrected). The numerical laterality difference was greater in PT than in insula, but the variability of insula was much smaller leading to a greater effect size. Both groups were left lateralized in insula, but LLD was more so. A post hoc analysis revealed that LLD and RLD differed significantly in insula area ($p = .0127$), but not thickness ($p = .82$), after correcting for five tests. The BLD group showed roughly the same laterality pattern across the ROIs as the LLD and RLD groups but was neither consistently greater than nor less than LLD or RLD.

Exploratory Analysis

A whole-hemisphere map of the LLD-RLD difference is shown in Figure 2. The left panel shows the results of the LH-initialized template; the right panel shows the results with the RH-initialized template. Figure 2 is a significance map thresholded a vertex-wise uncorrected two-sided threshold of $p < .01$ where red/yellow indicates LLD > RLD and blue/cyan indicates RLD > LLD. These statistics are shown on an "inflated" cortical surface of the symmetric template where the light gray indicates a gyrus and the dark gray indicates a sulcus. Within the a priori regions (yellow boundaries), there is only one cluster in STG that survives multiple comparison correction (see also Figures 3A and 5B). No significant clusters were found in the ALA. Outside these areas, there was a large cluster in the ventral occipitotemporal (vOT) cortex that survived whole hemisphere correction. See Table 2 for a list of clusters, their p values, surface areas, and coordinates. There are some other candidate clusters in Figure 2, but they did not survive correction for multiple comparisons and so are not reported further. Both the maps in Figure 2 and the cluster summaries in Table 2 indicate the results are robust to initialization hemisphere. For both the STG and vOT clusters, the coordinates of the centroids between LH and RH initialization are different by only about 1 mm (after reversing the sign of the X coordinate).

Post hoc Tests and BLD Results

Post hoc tests were performed on the STG and vOT clusters to determine whether the difference in groups was being driven by laterality differences in one or both groups and whether the underlying differences were because of volume, area, or thickness differences. Figure 3B shows a bar plot of the LIs for the STG cluster volume, area, and thickness broken down by group along with *p* values corrected for eight post hoc tests. One can see that there is a large difference in volume LI between the groups; this is expected because this cluster was selected for a volume LI difference (and why the LLD–RLD *p* value for Volume LI is not given). The LLD group has a positive volume LI, and the RLD have a negative volume LI, both of which are significantly different than 0. This indicates that both groups are asymmetric with opposite laterality. The area LI is significantly different between the groups. The LLD group has a significantly positive area LI; the RLD group has a negative area LI, but it was not significant. The LLD group shows no thickness laterality, but the RLD group has a significantly thicker right cortex than left in this cluster. There is a thickness LI difference between groups, but it does not survive correction for multiple post hoc tests. The results for the BLD group within this cluster are also shown. On each measure, the BLD group is between the LLD and RLD groups. We point out that the BLD results are completely independent of the participants used to construct the registration template and the cluster.

A close-up of the vOT cluster is shown in Figure 4A along with the post hoc tests in Figure 4B. The volume is significantly lateralized in both groups in opposite directions. There is a significant difference between groups in area lateralization but not in thickness. The RLD group is significantly rightward lateralized for both area and thickness. From this data, it appears that the difference in GM volume LI in the vOT is being driven by area and not thickness. The BLD group is between the LLD and RLD in volume and surface area.

Confirmatory Cluster Analysis

The exploratory method developed in this manuscript is novel, and so we would like to demonstrate that the STG and vOT clusters are not merely an artifact of the nonlinear registration procedure or resampling of the individual volume maps into template space. Ideally, the STG and vOT clusters would be labeled independently in each participant; these labels could then be used to compute LLD and RLD statistics to verify results from the exploratory analysis. The problem is to get clusters in each participant that are independent of the registration and resampling procedures. We cannot simply map the cluster from the template space back into the individual space because that would be dependent upon the registration. Instead, we exploit the geometrical relationship between the clusters and the labels of the Destrieux atlas. For example, the STG cluster can be approximated in the following way (see Figure 5). First, the PT is divided into three sections along its long axis (the green–brown–green labels in Figure 5A). Next, the lateral aspect of the STG (LASTG) is divided into five sections (the pink-blue-pink labels in Figure 5A). When the second section of the PT and the first section of the LASTG are combined into a single ROI (orange outline in Figure 5B), the STG cluster is covered fairly well. The same geometric operations can be performed in each individual brain to get an approximation of the STG cluster without resorting to the registration used to create the STG cluster. The results (Figure 7) have a similar pattern to that of the original cluster analysis. The volume LI for the LLD is still significantly greater than that of the RLD ($p < .02$), and the BLD is still between the LLD and RLD. The difference is that all LIs are shifted by about 0.13 to be more positive (e.g., RLD is now positive instead of negative). This shift is probably because of the fact that the approximate STG cluster does not cover the actual cluster perfectly. A similar analysis was applied to the vOT cluster with consistent findings. Although the confirmatory ROI is obviously informed by the exploratory map-based analysis, the boundaries of the

constructed ROI in each participant are completely independent of the interhemispheric registration and so confirmatory relative to this registration.

Correlations with fMRI and Behavioral Measures

In addition to the anatomical information, we also have access to various functional language lateralization measures for these participants. These include fMRI of an LDT (Van der Haegen et al., 2012) and three behavioral tasks: Dichotic Listening (DL, Van der Haegen, Westerhausen, Hugdahl, & Brysbaert, under revision), VHF task with pictures as stimuli (VHFP), and VHF task with words as stimuli (VHFW; Van der Haegen et al., 2011). We computed LIs for each of these behavioral and fMRI measures. We also have the fMRI results for the subvocal WG task; however, the correlation between the WG task LI and the cluster LIs is circular because the WG task was used to assign participants into LLD, RLD, and BLD. To gain further insight into the functional correlates of the anatomical asymmetries, we computed the correlation coefficient between all pairs of LIs. The resulting matrix is shown in Table 3. The behavioral tasks returned the expected asymmetries: a right ear advantage in the DL task for the LLD and a left ear advantage for the RLD, and RVF advantages for LLD versus LVF advantages for RLD. The only a priori defined ROI that correlated with function was the insula, which correlated with ear advantage in the DL task and fMRI laterality in the WG task. The exploratory clusters showed higher correlations with functional data: the STG cluster correlated with LDT and VHFP. The vOT cluster correlated with LDT and DL, but, surprisingly, not with the VHF tasks. The correlations in Table 3 are based on all participants; further analyses indicated that the conclusions remain the same if the bilateral participants are omitted or when the analyses are limited to those participants for whom we have data on all measures.

DISCUSSION

This study tested the surprising finding of Keller et al. (2011) that only the volume of the insula differs between healthy LLD and RLD participants (language dominance based on asymmetry in the fMRI BOLD signals during a silent WG task). We made use of the MRI scans collected by Van der Haegen et al. (2011), augmented with 19 scans collected later (footnote 2). In addition, we made use of the FreeSurfer software, which allowed us to run exploratory analyses with a greater precision.

Our results replicate Keller et al. for all regions tested by them. Only the size of the insula differed significantly between LLD and RLD participants. No significant differences were found for Broca's area or the PT, although the leftward asymmetry tended to be smaller for RLD participants than for LLD participants, which is intuitively more acceptable than the reverse trends reported by Keller et al. We also failed to replicate the rightward insular asymmetry in RLD participants, reported by Keller et al. As for the other brain regions, we found evidence for a reduced left asymmetry. In addition, we observed two new areas with reliable differences between the LLD and RLD groups (showing reversed asymmetries in the two groups). These were STG and vOT, two regions involved in language perception in the spoken and written modalities, respectively.

Our data, together with those of Keller et al. (2011), point to a divergence between the anatomical and functional asymmetries in participants with right speech dominance. Although the participants had Broca's area clearly lateralized to the right and we know that most of them also had spoken and written language perception lateralized to the RH (Van der Haegen et al., 2012, under revision), their overall volume asymmetry was leftward (Figure 6). This casts doubts on the hypothesis that the anatomical asymmetry of the human brain is the direct cause of the functional asymmetries observed. This finding also seems to put boundary conditions on the extent to which brain use can modulate GM volume. After

all, despite strong functional asymmetries in language (Van der Haegen et al., 2011, 2012), tool use (Vingerhoets et al., 2013), and visuospatial processing (Cai et al., 2013), the anatomical differences between both groups were surprisingly small in size and area.

In the remainder of the discussion, we give a more detailed description of the findings in the different ROIs and we end with some methodological observations, given that this study also introduces various new ways of brain analysis.

PT

The PT has been claimed to have a central role in spoken language processing. Geschwind and Levitsky (1968), found significant anatomical laterality in PT, and hypothesized that this was related to language laterality. Several studies to test this hypothesis followed, many of which found that PT was lateralized to the left (Keller et al., 2007, 2011; Dos Santos Sequeira et al., 2006; Eckert, Leonard, Possing, & Binder, 2006), although not all (Dorsaint-Pierre et al., 2006). Foundas, Leonard, Gilmore, Fennell, and Heilman (1994) found PT asymmetry that was reversed with RLD but only had one RLD participant. Other studies have not been able to find a PT difference between LLD and RLD (Keller et al., 2011; Dorsaint-Pierre et al., 2006), although Tzourio et al. (1998) reported that the area of left PT (rather than LI) was predictive of language laterality. We also looked for unilateral differences in PT surface area and found none. In fact, we found no unilateral LLD–RLD differences on any of our measures.

As with other studies, we found a significant left later-alization to PT in both LLD and RLD. As with Keller et al. (2011) and Dorsaint-Pierre et al. (2006), we did not find an LLD–RLD difference when analyzing the anatomically defined PT. The asymmetry in volume was driven by asymmetry in PT surface area and not in thickness. In the exploratory analysis, however, a small area that partially overlapped with both the PT and LASTG was found in which volume LI was greater for LLD than RLD. A post hoc analysis showed that the LLDs were leftward later-alized (positive LI) whereas the RLDs were rightward later-alized (negative LI). It also showed that LLD > RLD in surface area LI but not in thickness. The STG is specifically involved in processing the phonetic/phonological aspects of spoken language (Turkeltaub & Coslett, 2010; Desai, Liebenthal, Waldron, & Binder, 2008). It has also been linked to auditory STM (Richardson et al., 2011). Interestingly, this region does not seem to fit well within Hickok and Poeppel (2007) model of speech processing, according to which STG is involved in the spectrotemporal analysis of auditory input and does so bilaterally. On the other hand, the STG cluster is close to an area called SPT (sylvian parietal temporal cortex). Hickok and Poeppel (2007) speculate that area SPT is involved in translation between sensory speech codes and the motor system (though this function extends beyond speech tasks). Given that the functional asymmetry was based on asymmetric fMRI results of a WG task, it is not impossible that the STG cluster overlaps with SPT.

At first glance, the exploratory analysis appears to contradict the ROI results, which did not show a difference in PT. However, the PT ROI was trending toward significance, and the STG cluster comprised only a small part of PT. Analyzing the entire PT may wash out this effect. An advantage of the exploratory technique is that it can find clusters that do not fall into standard anatomical definitions. This finding does add some support to the Geschwind and Levitsky (1968) hypothesis.

The only other research to apply an exploratory method to the study of LLD versus RLD was Dorsaint-Pierre et al. (2006). They used VBM in a group of epilepsy patients. Dorsaint-Pierre et al. (2006) did not find any LLD–RLD differences in the PT/STG area (although they did find that simple laterality was significantly positive). This could be for several

reasons. First, they only had 11 RLD participants. Second, they used a sample of epilepsy patients who may have reorganized language areas (Brazdil, Zakopcan, Kuba, Fanfrdlova, & Rektor, 2003). Finally, it may be that VBM is less sensitive than surface-based techniques to these types of effects.

Josse et al. (2009) performed a similar VBM analysis. However, instead of classifying participants as LLD or RLD, they performed a voxel-by-voxel regression analysis between GM concentration asymmetry and fMRI activation asymmetry and found widespread correlation, including in the PT/STG region. Although this supports our results, there are several potential differences with our work. Josse et al. (2009) report having 12 RLD participants; however, by our definition of RLD (i.e., LI < -.6), they would have had only four RLD. Therefore, it is probably the case that our RLD participants are significantly more right lateralized for language. In addition, they found large correlations between GM density and functional activation across the brain even for non-language tasks. This suggests that the correlations may have been an artifact possibly caused by partial voluming, that is, if there is more GM in a voxel, then one would expect more functional activation in that voxel.

POp and PTr

The POp and PTr comprise Broca's area, which is related to speech production.[4] Studies by Keller et al. (2007, 2011) both found that POp was left lateralized but that PTr was not. Keller et al. (2011) did not find an LLD– RLD difference in either POp or PTr. Our anatomically defined ROI results are in complete agreement as are the exploratory results despite the fact that Keller et al. (2007, 2011) employed manual labeling and used only right-handed participants. We also found that the POp laterality was driven by left–right differences in surface area, not thickness. Dorsaint-Pierre et al. (2006), however, did find an LLD–RLD difference in GM concentration in Broca's area using (exploratory) VBM. The use of an epilepsy patient population may contribute to this discrepancy. Dorsaint-Pierre et al. (2006) also comment that their findings may be because of differences in curvature of the cortex that can occur in certain types of epilepsy and not because of change in GM volume. If so, then the differences may not have shown up in this surface-based because we only analyzed volume, area, and thickness.

Insula

There was a significant difference between LLD and RLD in the volume asymmetry of insula (in agreement with Keller et al., 2011). This difference was driven by area asymmetries and not thickness (again in agreement with Keller et al., 2011). The numerical difference between LIs for LLD and RLD was actually smaller for insula as compared with PT. The significance came from smaller variability, which may be because of the fact that the insula is a much larger structure and so its total volume will not be very sensitive to small changes in its boundaries or perhaps could be because of the fact that the circular sulcus and the gyri of the insula are more easily identified. In Keller et al. (2011), the variance of insula was also much less than for other structures, but they also found a large difference in laterality. In this study, both LLD and RLD had significant leftward asymmetries. Keller et al. (2011) showed a positive LI for LLD, but a negative LI for RLD. The reason for this is unclear but perhaps related to the use of left-handers in this study and right-handers in Keller et al. (2011). Interestingly, there was not a cluster in insula in the exploratory analysis. Further investigation showed a consistent but small LLD > RLD advantage across insula in the exploratory analysis. It appears that this advantage is not strong enough on a vertex-by-vertex basis to create a cluster, but it is strong enough when

[4]Modern conceptions of Broca's area are more complex than simply a "motor speech" area, for example, Carreiras, Pattamadilok, Meseguer, Barber, and Devlin (2012) have found evidence that Broca's area is involved in the understanding of syntax.

averaged over the entire insula. Keller et al. (2011) came to a similar conclusion when they explored the spatial pattern of LLD/RLD differences in insula.

Given our replication of Keller et al., we fully agree with those authors that the role of the insula in language processing needs further investigation, also given the correlations with DL performance (Table 3). The insula seems to be particularly involved in overt speech, although there is also some evidence for a role in covert speech (Price, 2012), and insular lesions are related to aphasia (Price, 2000; Donnan, Darby, & Saling, 1997). On the other hand, the insula plays a role in a wide range of intermodal functions (Flynn, Benson, & Ardila, 1999), making its involvement in language processing less pronounced than other peri-sylvian areas. Future research is needed to investigate whether the central location within the peri-sylvian network makes the insula one of the key regions to determine language asymmetry.

HG

HG, primary auditory cortex, has been studied in relation to language laterality (Dorsaint-Pierre et al., 2006). There was not a significant difference in HG anatomical asymmetry between LLD and RLD in agreement with manual labelings in Dorsaint-Pierre et al. (2006). We did find that HG was significantly lateralized to the left, in agreement with other studies (Dorsaint-Pierre et al., 2006; Penhune et al., 1996, 2003; Rademacher et al., 1993).

vOT Cortex

The only other area to be significantly different between LLD and RLD was in the vOT with LLDs being more left-lateralized and RLDs more right-lateralized in GM volume. Dorsaint-Pierre et al. (2006) did not find an LLD–RLD difference in vOT. To our knowledge, this is the first report of anatomical asymmetry differences between LLD and RLD in vOT. This area has been linked to visual word recognition (Dehaene & Cohen, 2011; Ben-Shachar, Dougherty, Deutsch, & Wandell, 2007; Cohen et al., 2000), face recognition (Kanwisher, McDermott, & Chun, 1997), and body and object recognition (Taylor & Downing, 2011). The asymmetries observed are in line with the functional lateralization of visual word recognition (Van der Haegen et al., 2012; Seghier & Price, 2011; Cai et al., 2008, 2010). Reduced GM volume in the left or bilateral vOT regions has been found to be associated with dyslexia (Raschle, Chang, & Gaab, 2011). The face recognition area (i.e., the fusiform face area) is also known to be functionally lateralized but in the opposite direction relative to the visual word recognition area. However, we do not see an area in Figure 4 where RLD > LLD inside of vOT. A possible reason for this is that all the participants in this study were left-handers and the FFA is less later-alized in left-handers than right-handers (Willems, Peelen, & Hagoort, 2010). Another reason might be that FFA and the visual word recognition area are complementary (Plaut & Behrmann, 2011; Dien, 2009) and cannot be separated anatomically.

It does not come as a surprise that asymmetry in the WG task predicts anatomical asymmetry in vOT. Evidence suggests that phonological information contributes to visual word recognition (Price & Devlin, 2011). Hemisphere dominance for word reading tends to follow that of speech production (Van der Haegen et al., 2012; Cai et al., 2008, 2010), perhaps reflecting the need for fast interactions between these areas. Also, see below for correlations between vOT and the LDT. In the history of the human species, reading is a very recent skill with no real evolutionary pressure for laterality yet. The fact that it is lateralized is arguably because of the close interactions with Broca's area.

Bilateral Participants

Eleven participants did not show strong language laterality. In the anatomically defined ROI analysis, they showed a similar laterality pattern as the LLD and RLD participants, but there was no systematic relationship. In the exploratory and confirmatory analysis of the STG cluster, the LI for volume, area, and thickness consistently fell between LLD and RLD.

Correlations between fMRI and Behavioral Measures

In line with the absence of a clear reversal of the overall anatomical asymmetry in RLD participants (Figure 1), most of the LIs in the anatomically defined ROIs were uncorrelated with functional asymmetries. This was true both for asymmetries based on fMRI BOLD signals (WG and LDT) and on behavioral data (DL, VHFP, and VHFW). Only insula showed correlations with the functional asymmetries (DL and WG). The STG cluster correlated with VHFP but, surprisingly, not with DL. The anatomical asymmetries in the vOT cluster correlated with DL and LDT, in line with the proposal that this area plays a central role in the integration of phonological and orthographic word information as mentioned above. The finding that anatomical vOT asymmetries are correlated with the ear advantage in DL is particularly noteworthy, as it is in line with the hypothesis that the orthography of a word helps the processing of spoken words in literate individuals (Ziegler & Ferrand, 1988). It is surprising vOT is not correlated with the VHF differences in word naming and picture naming.

Statistical Model Selection

The statistical analysis requires a model of the relationship between the functional LI (fLI) and structural LI (sLI). One of two models is typically used: (1) a categorical model in which participants are divided into laterality classes; differences in class means are evidence of an interaction between structure and function, or (2) a continuous model in which it is assumed that fLI and sLI are linearly related; a nonzero slope is evidence of an interaction. There are advantages and disadvantages to both methods. Categorization models the fLI–sLI relationship as piece-wise constant. Some researchers (e.g., Keller et al., 2011) use two categories (LLD and RLD), others (e.g., Dorsaint-Pierre et al., 2006) use three (LLD, RLD, and BLD). We chose three for several reasons. First, bilateral participants may represent a qualitatively different language organization than the mirror reversal hypothesized between LLD and RLD. For example, in a Wada test, bilaterality may manifest as both hemispheres being impaired or neither being impaired (Dorsaint-Pierre et al., 2006; Risse, Gates, & Fangman, 1997). Second, having three classes makes the piece-wise constant model more accurate in the case where there is continuous variation. We chose a relatively high threshold of 0.6 to assure that our results were not influenced by bilateral participants (i.e., we would rather exclude a few true LLDs or RLDs rather than risk the inclusion of BLDs).

A continuous model is attractive because language laterality is never an "all-or-nothing" trait. The continuous model only requires one regressor, saving several DOFs relative to the categorical model—a very important point when sample sizes are small. The ability to include bilateral participants also increases the DOF, but, as mentioned above, it is not clear that the bilateral participants belong with the others. The continuous model requires a parametric function relating fLI and sLI (generally linear). This is a very strong assumption given that the sLI and fLI are computed from very different data and methods. In a voxelwise structural analysis, this relationship could change from region to region.

Thus, the categorical model makes fewer assumptions than the continuous model but may have less power. The exact nature of the fLI–sLI relationship is complex and will require much more data to sort out. For completeness, we performed a follow-up test using a continuous linear model. Although the exact p values changed, there were no changes in the

conclusions made from either the ROI or the exploratory analysis (i.e., the STG and vOT clusters and insula ROI were still significant and no new areas became significant).

Methodological Considerations

This study exploited some unique methodologies. First, we had a relatively large sample ($n = 21$) of healthy RLD participants made possible by a low-cost and noninvasive screening procedure. The sample was mainly selected after screening 250 left-handers for behavioral signs of RLD. Our sample is twice as large as comparable studies ($n = 10$, Keller et al., 2011; $n = 11$, Dorsaint-Pierre et al., 2006; $n = 4$, Eckert et al., 2006). One disadvantage of the study is that the participants are only left-handers and mostly women. This prevented us from exploring the relationship of handedness and gender on the interaction between language and anatomical laterality.

We employed automated surface-based methods to compute anatomical measures. These methods include 3-D mesh models that with subvoxel accuracy; surface-based registration that aligns folding patterns across subject and hemisphere; and automated algorithms that attempt to replicate the manual labeling of an anatomist. The volumes of the anatomically defined ROIs were in the range of published manual results but consistently smaller. For example, we measured the left PT volume (including PP) in LLD to be 2204 mm^3 whereas other studies (Keller et al., 2007, 2011; Dos Santos Sequeira et al., 2006) that employed manual labelings were in the range of 3000–4000 mm^3. A possible limitation of the PT results is that the Destrieux definition of PT included the PP, which is normally excluded. This may have the effect of reducing asymmetry. Indeed, the PT LIs in this study (.09–.14) are much less than that of Dos Santos Sequeira et al. (2006). However, they are more than the PT LIs in Keller et al. (2007) (about .11) and about the same as in Keller et al. (2011) (.09–.14). The POp and PTr volumes in this study are about 66% of that found in Keller et al. (2007). Although some of this may have to do with the landmark definitions, it may also be because of partial voluming. Voxels that are partially in GM and WM will have an intensity that is darker than the typical WM voxel, and a manual rater may be inclined to label these as GM. The surface-based mesh model will cut through the middle of such voxels and thereby give a more accurate (and smaller) measure of GM volume. Despite this difference, the ratio of LH to RH PT volume in this study (1.3) is very close to that found in Dos Santos Sequeira et al. (2006) (1.4), Keller et al. (2007) (1.2), and Keller et al. (2011) (1.17). For POp, the simple volume LI was very similar for POp across the studies (0.12 for this study, 0.11 for Keller et al., 2011, and about 0.13 for Keller et al., 2007). There is a striking similarity between the ROI results presented here and those of Keller et al. (2011) despite appreciable differences in methodology. Although the ROI results are similar to previous work, we point out that the exploratory results are novel.

The surface-based registration allowed an exploratory analysis to search for areas of significant LLD/RLD difference that do not lie cleanly within the boundaries prescribed by manual labels. Such a difference was found in a cluster whose extent covered only part of the PT. The exploratory effect did not show up in the ROI approach because this cluster did not fit neatly into an anatomically defined region. The exploratory approach also allows evaluating brain regions that are outside of traditional language areas and so not targeted for tedious manual labeling procedures. Such a region was found in vOT.

The interhemispheric registration procedure was verified in two ways. First, the entire study was replicated using the RH and LH as initial targets, with very similar results. Second, an ROI covering the exploratory STG cluster was defined based on anatomical landmarks (and so independent of the registration). This ROI showed significant differences between LLD and RLD. Although this by itself does not confirm a difference between LLD and RLD, it does show that the difference found in the exploratory analysis is not a byproduct or artifact

of the registration method. The exploratory surface-based analysis is different from VBM analysis in several ways. It uses surface-based registration, which has been shown to be superior to volume-based in many instances (Tucholka, Fritsch, Poline, & Thirion, 2012; Zollei, Stevens, Huber, Kakunoori, & Fischl, 2010; Postelnicu, Zollei, & Fischl, 2009; Fischl et al., 2008). The surface-based method allows the differences in GM volume to be decomposed into effects of surface area and thickness. This is important for shedding light on the origins of asymmetry. For example, surface area and thickness are both highly heritable but genetically independent (Winkler et al., 2010; Panizzon et al., 2009). Separately measuring surface area and thickness can also be important in understanding disorders. For example, dyslexia and reading skills have been found to be related to surface area but not to thickness (Frye et al., 2010). GM volume loss in aging is related to loss of surface area not cortical thinning; however, cortical thinning accompanies Alzheimer's disease (Dickerson et al., 2009). On the other hand, VBM may be sensitive to less specific aspects of morphometry (Palaniyappan & Liddle, 2012).

Conclusion

The purpose of this study was to investigate the interaction between functional language laterality and anatomical laterality. There were several novel aspects to the study including the recruitment of a relatively large healthy sample of RLD participants made possible by a previously developed low-cost and noninvasive screening procedure. This study also used automated surface-based analysis techniques that provide several useful features: the ability to automatically delineate standard language-related anatomical ROIs such as PT, POp, and PTr; the ability to compute GM volume with subvoxel accuracy; the ability to decompose differences in GM volume into differences in surface area and thickness; and the ability to use surface-based registration to align folding patterns across hemisphere as well as participant for use in an exploratory analysis. The anatomical ROI-based results replicated those of a similar study using manual labeling in healthy right-handers (Keller et al., 2011) in that no LLD–RLD differences were found in PT, POp, and PTr, but a strong difference was found in insula GM volume. Interestingly, the exploratory analysis did reveal a small LLD > RLD cluster in STG that overlapped with PT. This capability shows the utility of exploratory analysis for finding structural differences that may cross the boundaries of anatomically defined ROIs. The exploratory analysis also indicated an LLD–RLD difference in vOT, an area associated with visual word recognition. No other differences between LLD and RLD were found in the rest of the brain, including in Broca's area. In all cases, differences in GM volume were attributable to a difference in cortical surface area and not cortical thickness. The sample used in this study was exclusively left-handed and mostly female, making it impossible to evaluate the effect of handedness and gender; however, the use of a practical language dominance screening procedure and automated surface-based analysis should make more large-scale studies of language dominance possible.

Acknowledgments

REFERENCES

Amunts K, Weiss PH, Mohlberg H, Pieperhoff P, Eickhoff S, Gurd JM, et al. Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space-the roles of Brodmann areas 44 and 45. Neuroimae. 2004; 22:42–56.

Ashburner J, Friston KJ. Voxel-based morphometry-The methods. Neuroimae. 2000; 11:805–821.

Ben-Shachar M, Dougherty RF, Deutsch GK, Wandell BA. Differential sensitivity to words and shapes in ventral occipito-temporal cortex. Cerebral Cortex. 2007; 17:1604–1611. [PubMed: 16956978]

Benson, DF.; Geschwind, N. Aphasia and related disorders: A clinical approach. In: Mesulam, MM., editor. Principles of behavioral neurology. Philadelphia: FA Davis; 1985.

Benson RR, FitzGerald DB, LeSueur LL, Kennedy DN, Kwong KK, Buchbinder BR, et al. Language dominance determined by whole brain functional MRI in patients with brain lesions. Neurology. 1999; 52:798–809. [PubMed: 10078731]

Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, et al. Determination of language dominance using functional MRI: A comparison with the Wada test. Neurology. 1996; 46:978–984. [PubMed: 8780076]

Brazdil M, Zakopcan J, Kuba R, Fanfrdlova Z, Rektor I. Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. Epilepsy & Behavior. 2003; 4:414–419. [PubMed: 12899862]

Cai Q, Lavidor M, Brysbaert M, Paulignan Y, Nazir TA. Cerebral lateralization of frontal lobe language processes and lateralization of the posterior visual word processing system. Journal of Cognitive Neuroscience. 2008; 20:672–681. [PubMed: 18052778]

Cai Q, Paulignan Y, Brysbaert M, Ibarrola D, Nazir TA. The left ventral occipito-temporal response to words depends on language lateralization but not on visual familiarity. Cerebral Cortex. 2010; 20:1153–1163. [PubMed: 19684250]

Cai Q, Van der Haegen L, Brysbaert M. Complementary hemispheric specialization for language production and visuospatial attention. Proceedings of the National Academy of Sciences, U.S.A. 2013; 110:E322–E330.

Carreiras M, Pattamadilok C, Meseguer E, Barber H, Devlin JT. Broca's area plays a causal role in morphosyntactic processing. Neuropsychologia. 2012; 50:816–820. [PubMed: 22285905]

Cohen L, Dehaene S, Naccache L, Lehericy S, Dehaene-Lambertz G, Henaff MA, et al. The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain. 2000; 123:291–307. [PubMed: 10648437]

Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis I: Segmentation and surface reconstruction. Neuroimage. 1999; 9:179–194. [PubMed: 9931268]

Dehaene S, Cohen L. The unique role of the visual word form area in reading. Trends in Cognitive Sciences. 2011; 15:254–262. [PubMed: 21592844]

Desai R, Liebenthal E, Waldron E, Binder JR. Left posterior temporal regions are sensitive to auditory categorization. Journal of Cognitive Neuroscience. 2008; 20:1174–1188. [PubMed: 18284339]

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31:968–980. [PubMed: 16530430]

Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage. 2010; 53:1–15. [PubMed: 20547229]

Dickerson BC, Feczko E, Augustinack JC, Pacheco J, Morris JC, Fischl B, et al. Differential effects of aging and Alzheimer's disease on medial temporal lobe cortical thickness and surface area. Neurobiology of Aging. 2009; 30:432–440. [PubMed: 17869384]

Dien J. A tale of two recognition systems: Implications of the fusiform face area and the visual word form area for lateralized object recognition models. Neuropsychologia. 2009; 47:1–16. [PubMed: 18805434]

Donnan GA, Darby DG, Saling MM. Identification of brain region for coordinating speech articulation. Lancet. 1997; 349:221–222. [PubMed: 9014903]

Dorsaint-Pierre R, Penhune VB, Watkins KE, Neelin P, Lerch JP, Bouffard M, et al. Asymmetries of the planum temporale and Heschl's gyrus: Relationship to language lateralization. Brain. 2006; 129:1164–1176. [PubMed: 16537567]

Dos Santos Sequeira S, Woerner W, Walter C, Kreuder F, Lueken U, Westerhausen R, et al. Handedness, dichotic-listening ear advantage, and gender effects on planum temporale asymmetry-A volumetric investigation using structural magnetic resonance imaging. Neuropsychologia. 2006; 44:622–636. [PubMed: 16098999]

Eckert MA, Leonard CM, Possing ET, Binder JR. Uncoupled leftward asymmetries for planum morphology and functional language processing. Brain and Language. 2006; 98:102–111. [PubMed: 16697453]

Eckert MA, Lombardino LJ, Walczak AR, Bonihla L, Leonard CM, Binder JR. Manual and automated measures of superior temporal gyrus asymmetry: Concordant structural predictors of verbal ability in children. Neuroimage. 2008; 41:813–822. [PubMed: 18440244]

Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proceedings of the National Academy of Sciences. 2000; 97:11044–11049.

Fischl B, Rajendran N, Busa E, Augustinack J, Hinds O, Yeo BT, et al. Cortical folding patterns and predicting cytoarchitecture. Cerebral Cortex. 2008; 18:1973–1980. [PubMed: 18079129]

Fischl B, Salat DH, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, et al. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 33:341–355. [PubMed: 11832223]

Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 1999; 9:195–207. [PubMed: 9931269]

Fischl B, Sereno MI, Tootell RBH, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. Human Brain Mapping. 1999; 8:272–284. [PubMed: 10619420]

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cerebral Cortex. 2004; 14:11–22. [PubMed: 14654453]

Flynn FG, Benson DF, Ardila A. Anatomy of the insula—Functional and clinical correlates. Aphasiology. 1999; 13:55–77.

Foundas AL, Leonard CM, Gilmore R, Fennell E, Heilman KM. Planum temporale asymmetry and language dominance. Neuropsychologia. 1994; 32:1225–1231. [PubMed: 7845562]

Frye RE, Liederman J, Malmberg B, McLean J, Strickland D, Beauchamp MS. Surface area accounts for the relation of gray matter volume to reading-related skills and history of dyslexia. Cerebral Cortex. 2010; 20:2625–2635. [PubMed: 20154011]

Geschwind N, Levitsky W. Human brain: Left-right asymmetries in temporal speech region. Science. 1968; 161:186–187. [PubMed: 5657070]

Hagler DJ Jr. Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. Neuroimage. 2006; 33:1093–1103. [PubMed: 17011792]

Heim S, Eickhoff SB, Amunts K. Specialisation in Broca's region for semantic, phonological, and syntactic fluency? Neuroimage. 2008; 40:1362–1368. [PubMed: 18296070]

Hickok G, Poeppel D. The cortical organization of speech processing. Nature Reviews Neuroscience. 2007; 8:393–402.

Hunter ZR, Brysbaert M. Visual half-field experiments are a good measure of cerebral language dominance if used properly: Evidence from fMRI. Neuropsychologia. 2008; 46:316–325. [PubMed: 17716695]

Josse G, Kherif F, Flandin G, Seghier ML, Price CJ. Predicting language lateralization from gray matter. Journal of Neuroscience. 2009; 29:13516–13523. [PubMed: 19864564]

Josse G, Mazoyer B, Crivello F, Tzourio-Mazoyer N. Left planum temporale: An anatomical marker of left hemispheric specialization for language comprehension. Brain Research, Cognitive Brain Research. 2003; 18:1–14. [PubMed: 14659492]

Kanwisher N, McDermott J, Chun MM. The fusiform face area: A module in human extrastriate cortex specialized for face perception. Journal of Neuroscience. 1997; 17:4302–4311. [PubMed: 9151747]

Keller SS, Highley JR, Garcia-Finana M, Sluming V, Rezaie R, Roberts N. Sulcal variability, stereological measurement and asymmetry of Broca's area on MR images. Journal of Anatomy. 2007; 211:534–555. [PubMed: 17727624]

Keller SS, Roberts N, Garcia-Finana M, Mohammadi S, Ringelstein EB, Knecht S, et al. Can the language-dominant hemisphere be predicted by brain anatomy? Journal of Cognitive Neuroscience. 2011; 23:2013–2029. [PubMed: 20807056]

Knecht S, Drager B, Deppe M, Bobe L, Lohmann H, Floel A, et al. Handedness and hemispheric language dominance in healthy humans. Brain. 2000; 123:2512–2518. [PubMed: 11099452]

Kosslyn SM. Seeing and imagining in the cerebral hemispheres: A computational approach. Psychological Review. 1987; 94:148–175. [PubMed: 3575583]

Loring DW, Meador KJ, Lee GP, Murro AM, Smith JR, Flanigin HF, et al. Cerebral language lateralization: Evidence from intracarotid amobarbital testing. Neuropsychologia. 1990; 28:831–838. [PubMed: 2247209]

Luders E, Gaser C, Jancke L, Schlaug G. A voxel-based approach to gray matter asymmetries. Neuroimage. 2004; 22:656–664. [PubMed: 15193594]

Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971; 9:97–113. [PubMed: 5146491]

Palaniyappan L, Liddle PF. Differential effects of surface area, gyrification and cortical thickness on voxel based morphometric deficits in schizophrenia. Neuroimage. 2012; 60:693–699. [PubMed: 22227049]

Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. Cerebral Cortex. 2009; 19:2728–2735. [PubMed: 19299253]

Penhune VB, Cismaru R, Dorsaint-Pierre R, Petitto LA, Zatorre RJ. The morphometry of auditory cortex in the congenitally deaf measured using MRI. Neuroimage. 2003; 20:1215–1225. [PubMed: 14568490]

Penhune VB, Zatorre RJ, MacDonald JD, Evans AC. Interhemispheric anatomical differences in human primary auditory cortex: Probabilistic mapping and volume measurement from magnetic resonance scans. Cerebral Cortex. 1996; 6:661–672. [PubMed: 8921202]

Plaut DC, Behrmann M. Complementary neural representations for faces and words: A computational exploration. Cognitive Neuropsychology. 2011; 28:251–275. [PubMed: 22185237]

Postelnicu G, Zollei L, Fischl B. Combined volumetric and surface registration. IEEE Transactions on Medical Imaging. 2009; 28:508–522. [PubMed: 19273000]

Price CJ. The anatomy of language: Contributions from functional neuroimaging. Journal of Anatomy. 2000; 197:335–359. [PubMed: 11117622]

Price CJ, Devlin JT. The interactive account of ventral occipitotemporal contributions to reading. Trends in Cognitive Sciences. 2011; 15:246–253. [PubMed: 21549634]

Pujol J, Deus J, Losilla JM, Capdevila A. Cerebral lateralization of language in normal left-handed people studied by functional MRI. Neurology. 1999; 52:1038–1043. [PubMed: 10102425]

Rademacher J, Caviness VS Jr. Steinmetz H, Galaburda AM. Topographical variation of the human primary cortices: Implications for neuroimaging, brain mapping, and neurobiology. Cerebral Cortex. 1993; 3:313–329. [PubMed: 8400809]

Raschle NM, Chang M, Gaab N. Structural brain alterations associated with dyslexia predate reading onset. Neuroimage. 2011; 57:742–749. [PubMed: 20884362]

Richardson FM, Ramsden S, Ellis C, Burnett S, Megnin O, Catmur C, et al. Auditory short-term memory capacity correlates with gray matter density in the left posterior STS in cognitively normal and dyslexic adults. Journal of Cognitive Neuroscience. 2011; 23:3746–3756. [PubMed: 21568634]

Risse GL, Gates JR, Fangman MC. A reconsideration of bilateral language representation based on the intracarotid amobarbital procedure. Brain and Cognition. 1997; 33:118–132. [PubMed: 9056279]

Seghier ML, Price CJ. Explaining left lateralization for words in the ventral occipitotemporal cortex. Journal of Neuroscience. 2011; 31:14745–14753. [PubMed: 21994390]

Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, et al. A hybrid approach to the skull stripping problem in MRI. Neuroimage. 2004; 22:1060–1075. [PubMed: 15219578]

Spreer J, Arnold S, Quiske A, Wohlfarth R, Ziyeh S, Altenmuller D, et al. Determination of hemisphere dominance for language: Comparison of frontal and temporal fMRI activation with intracarotid amytal testing. Neuroradiology. 2002; 44:467–474. [PubMed: 12070719]

Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PS, et al. Language dominance in neurologically normal and epilepsy subjects: A functional MRI study. Brain. 1999; 122:2033–2046. [PubMed: 10545389]

Taylor JC, Downing PE. Division of labor between lateral and ventral extrastriate representations of faces, bodies, and objects. Journal of Cognitive Neuroscience. 2011; 23:4122–4137. [PubMed: 21736460]

Toga AW, Thompson PM. Mapping brain asymmetry. Nature Reviews Neuroscience. 2003; 4:37–48.

Tucholka A, Fritsch V, Poline JB, Thirion B. An empirical comparison of surface-based and volume-based group studies in neuroimaging. Neuroimage. 2012; 63:1443–1453. [PubMed: 22732555]

Turkeltaub PE, Coslett HB. Localization of sublexical speech perception components. Brain and Language. 2010; 114:1–15. [PubMed: 20413149]

Tzourio N, Nkanga-Ngila B, Mazoyer B. Left planum temporale surface correlates with functional dominance during story listening. NeuroReport. 1998; 9:829–833. [PubMed: 9579674]

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002; 15:273–289. [PubMed: 11771995]

Van der Haegen L, Cai Q, Brysbaert M. Colateralization of Broca's area and the visual word form area in left-handers: fMRI evidence. Brain and Language. 2012; 122:171–178. [PubMed: 22196742]

Van der Haegen L, Cai Q, Seurinck R, Brysbaert M. Further fMRI validation of the visual half field technique as an indicator of language laterality: A large-group analysis. Neuropsychologia. 2011; 49:2879–2888. [PubMed: 21708178]

Van der Haegen L, Westerhausen R, Hugdahl K, Brysbaert M. Speech dominance is a better predictor of functional brain asymmetry than handedness: A combined fMRI word generation and behavioral dichotic listening study. Neuropsychologia. under revision.

Vingerhoets G, Alderweireldt AS, Vandemaele P, Cai Q, Van der Haegen L, Brysbaert M, et al. Praxis and language are linked: Evidence from co-lateralization in individuals with atypical language dominance. Cortex. 2013; 49:172–183. [PubMed: 22172977]

Wada J, Rasmussen T. Intracarotid-injection of sodium amytal for the lateralization of cerebral speech dominance, experimental and clinical observations. Journal of Neurosurgery. 1960; 17:266–282.

Watkins KE, Paus T, Lerch JP, Zijdenbos A, Collins DL, Neelin P, et al. Structural asymmetries in the human brain: A voxel-based statistical analysis of 142 MRI scans. Cerebral Cortex. 2001; 11:868–877. [PubMed: 11532891]

Willems RM, Peelen MV, Hagoort P. Cerebral lateralization of face-selective and body-selective visual areas depends on handedness. Cerebral Cortex. 2010; 20:1719–1725. [PubMed: 19889713]

Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or gray matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage. 2010; 53:1135–1146. [PubMed: 20006715]

Winkler AM, Sabuncu MR, Yeo BT, Fischl B, Greve DN, Kochunov P, et al. Measuring and comparing brain cortical surface area and other areal quantities. Neuroimage. 2012; 61:1428–1443. [PubMed: 22446492]

Ziegler J, Ferrand L. Orthography shapes the perception of speech: The consistency effect in auditory word recognition. Psychonomic Bulletin & Review. 1988; 5:683–689.

Zollei L, Stevens A, Huber K, Kakunoori S, Fischl B. Improved tractography alignment using combined volumetric and surface registration. Neuroimage. 2010; 51:206–213. [PubMed: 20153833]
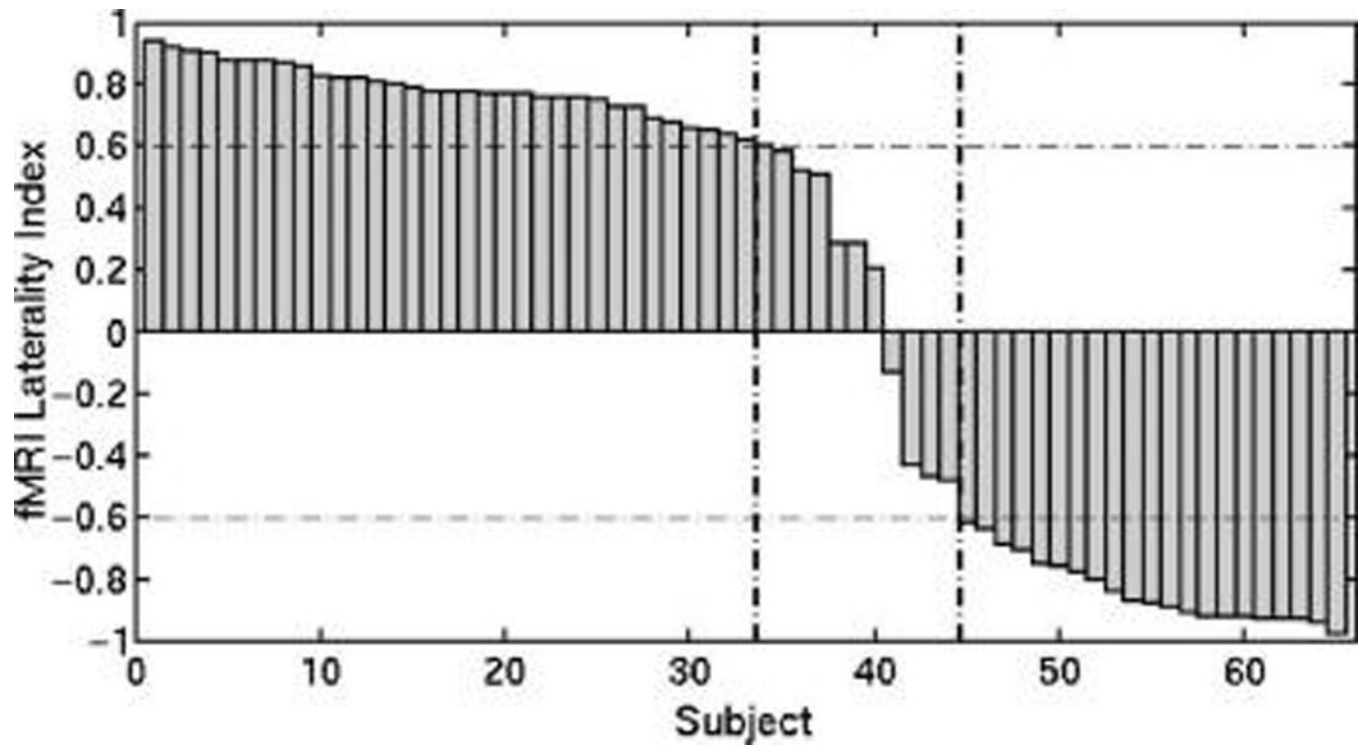
Figure 1.
Distribution of the functional LI from the WG task for all participants. The horizontal dashed lines indicate the threshold of ±0.6. The vertical dashed lines indicate the categorical boundaries of LLD, BLD, and RLD.
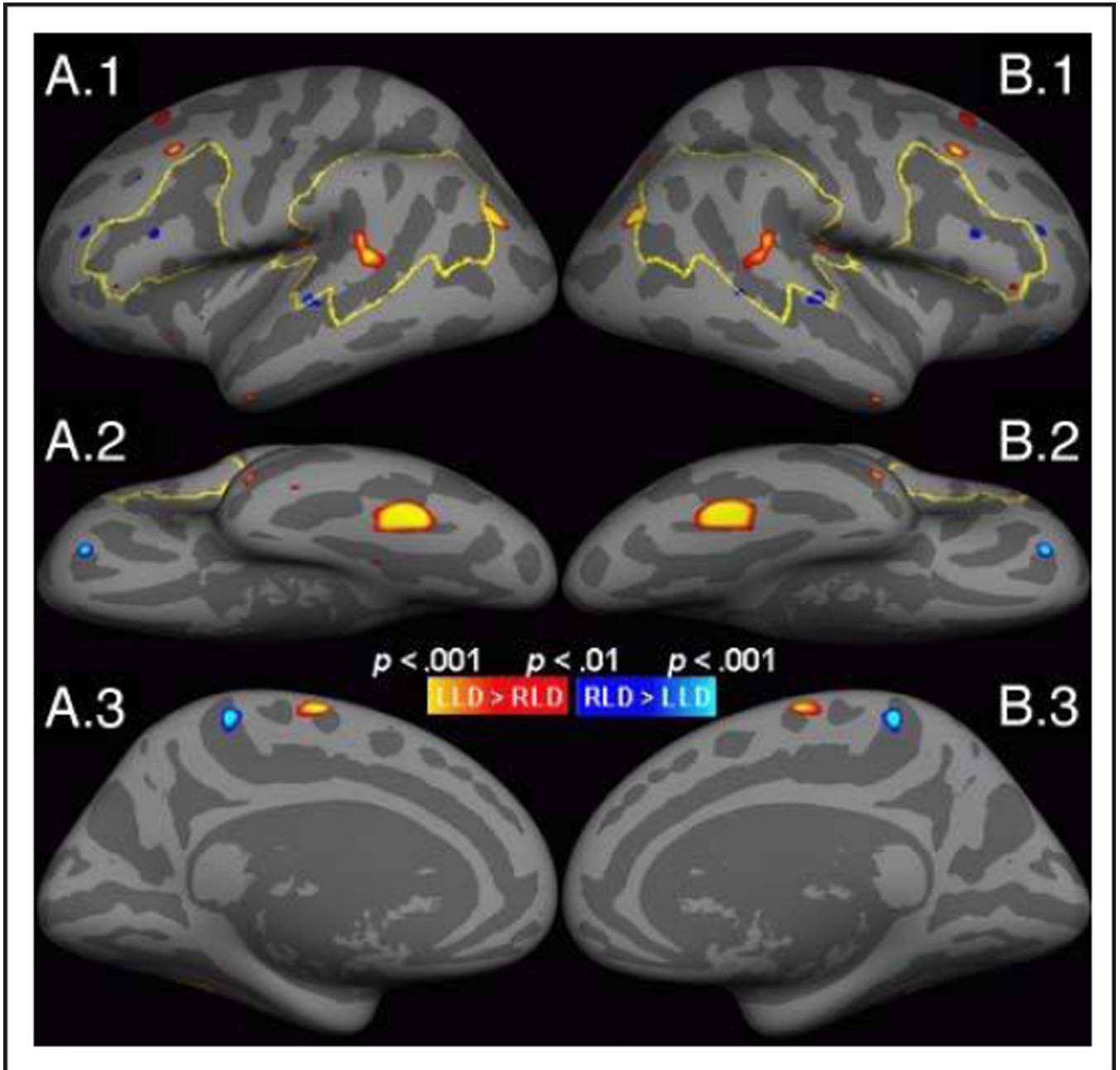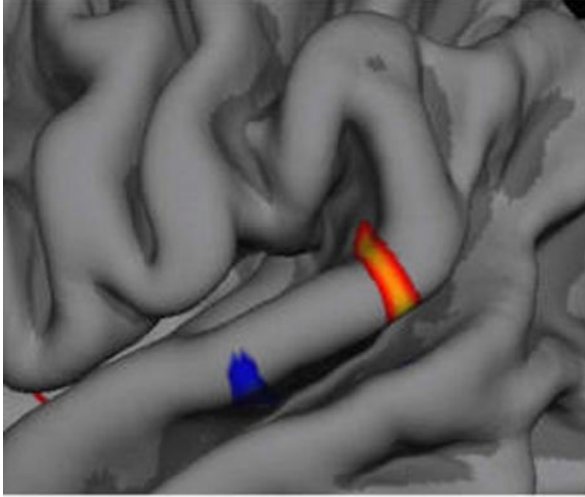
Figure 2.
Significance map of volume LI difference between LLD and RLD rendered on the inflated cortical surface of the symmetric template (uncorrected vertex-wise threshold $p < .01$). Red/yellow indicates that LLD > RLD; blue/cyan indicates that LLD < RLD. The yellow outlines indicate the boundaries of the a priori ROIs (ALA and PLA). (A) Results from the template initialized with the LH. (B) Results from the template initialized with the RH. From top to bottom: (1) lateral view, (2) inferior view, (3) medial view.
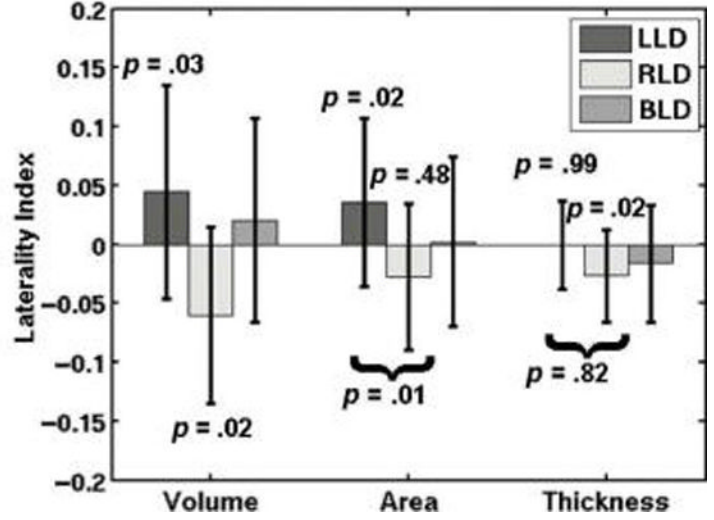
Figure 3.
(A) View of the left posterior sylvian fissure including the STG cluster on the folded symmetric template pial surface (same data as in Figure 2A1). (B) LI results broken down by subject group and volume, area, and thickness (with standard deviation bars across subject) based upon averages from within the exploratory STG cluster. The *p* values are for post hoc tests of laterality or differences in laterality between LLD and RLD. The *p* values have been corrected for the eight post hoc tests. All *p* values are based on a two-sided *t* test with 53 DOF.
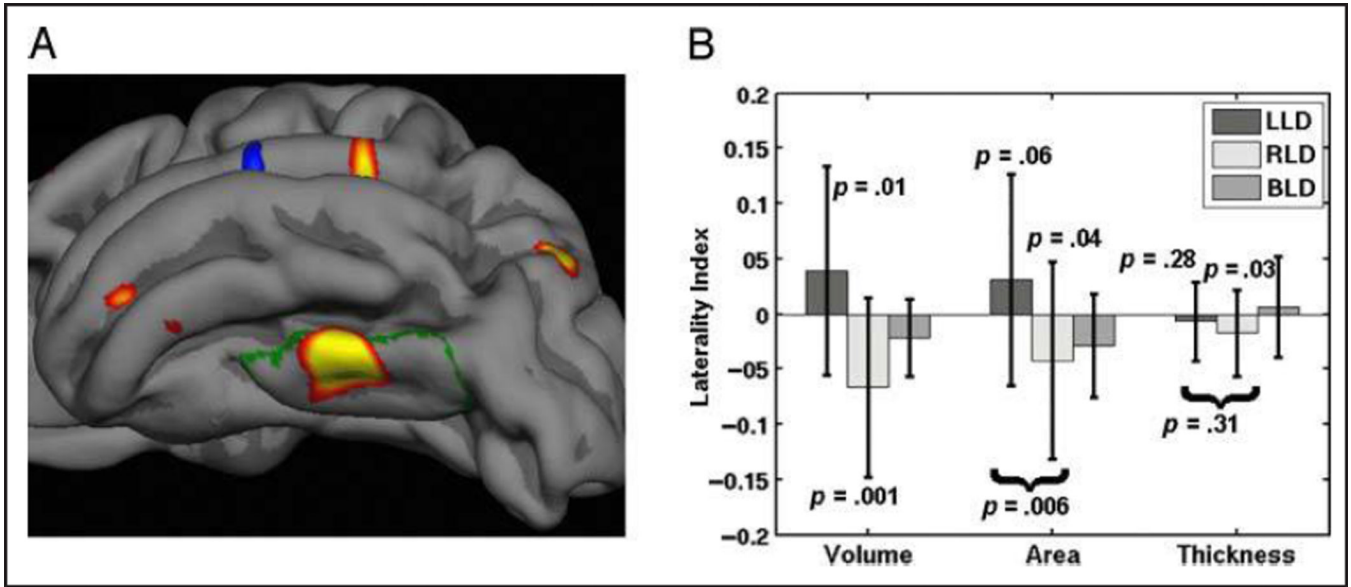
Figure 4.
(A) vOT cluster shown on the pial surface of the LH (view is inferior and slightly lateral). The green outline is the lateral occipito-temporal gyrus from the Destrieux atlas. This is the same data as in Figure 2A2. (B) LI results broken down by subject group and volume, area, and thickness (with standard deviation bars across subject) based upon averages from within the vOT cluster. The p values are for post hoc tests of laterality or differences in laterality between LLD and RLD. The p values have been corrected for the eight post hoc tests. All p values are based on a two-sided t test with 53 DOF.
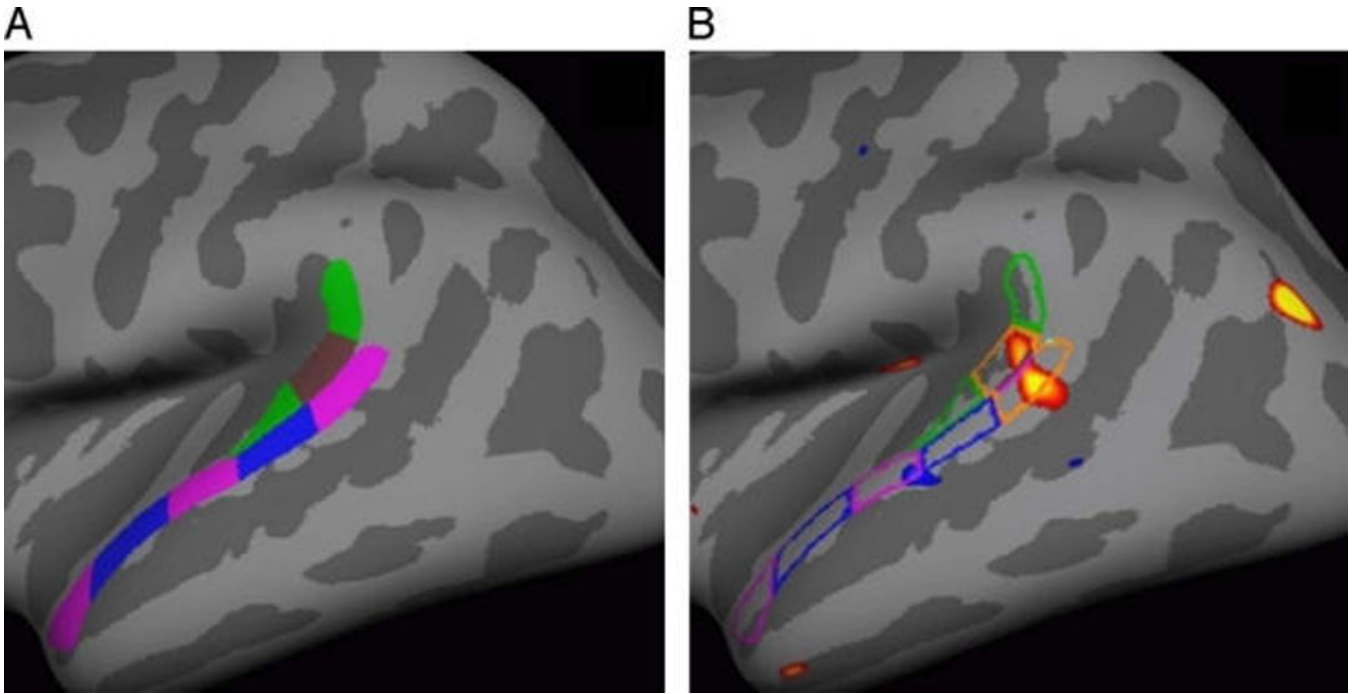
Figure 5.
Method used to geometrically construct an ROI to cover the STG cluster. (A) The PT was divided into three sections along its long axis (green–brown–green labels). The lateral aspect of the STG (LASTG) was divided into five sections (pink–blue– pink labels). (B) The second section of the PT and the first section of the LASTG are combined to cover the STG cluster fairly well (orange outline). The significance map is the same as in Figure 2A1 and Figure 3.
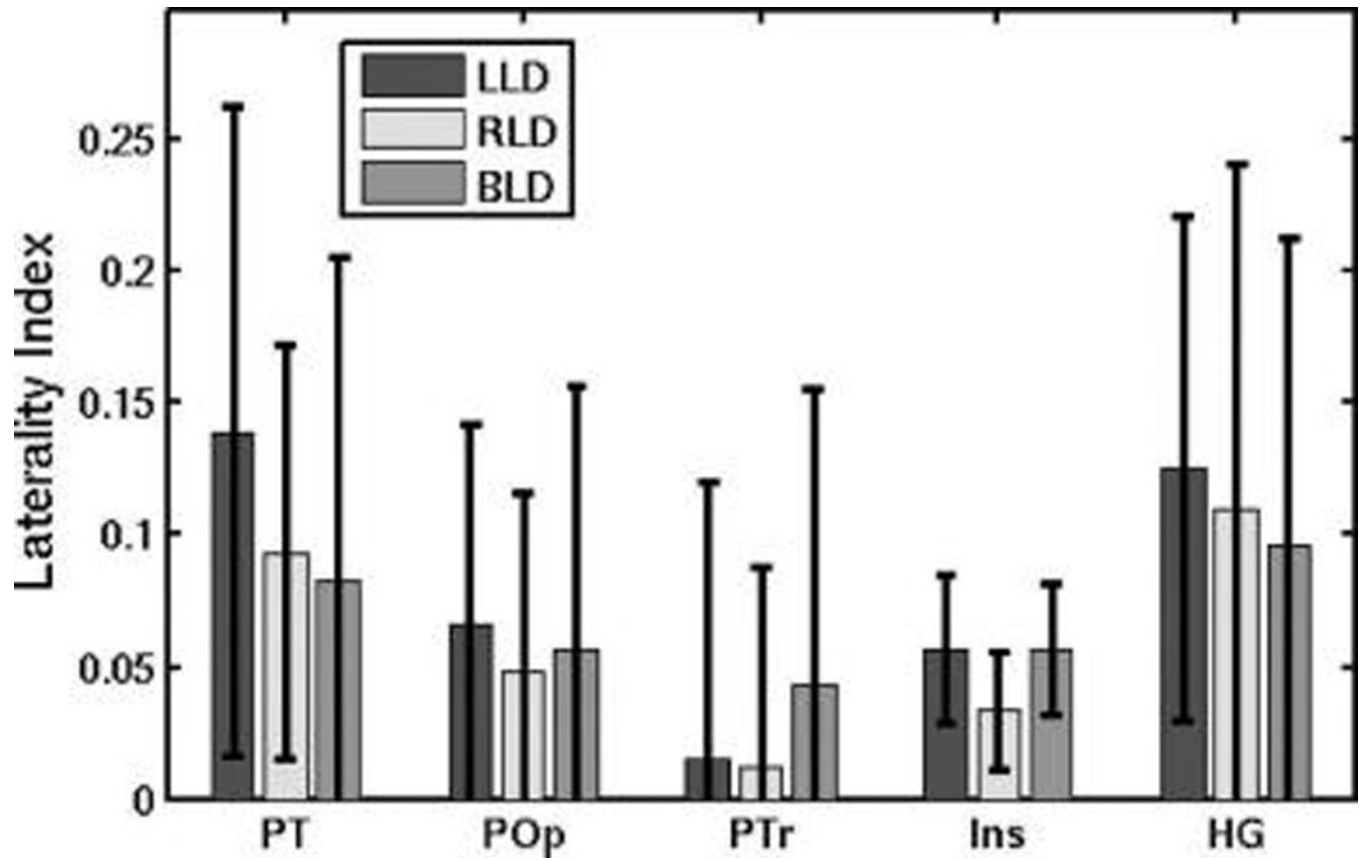
Figure 6.
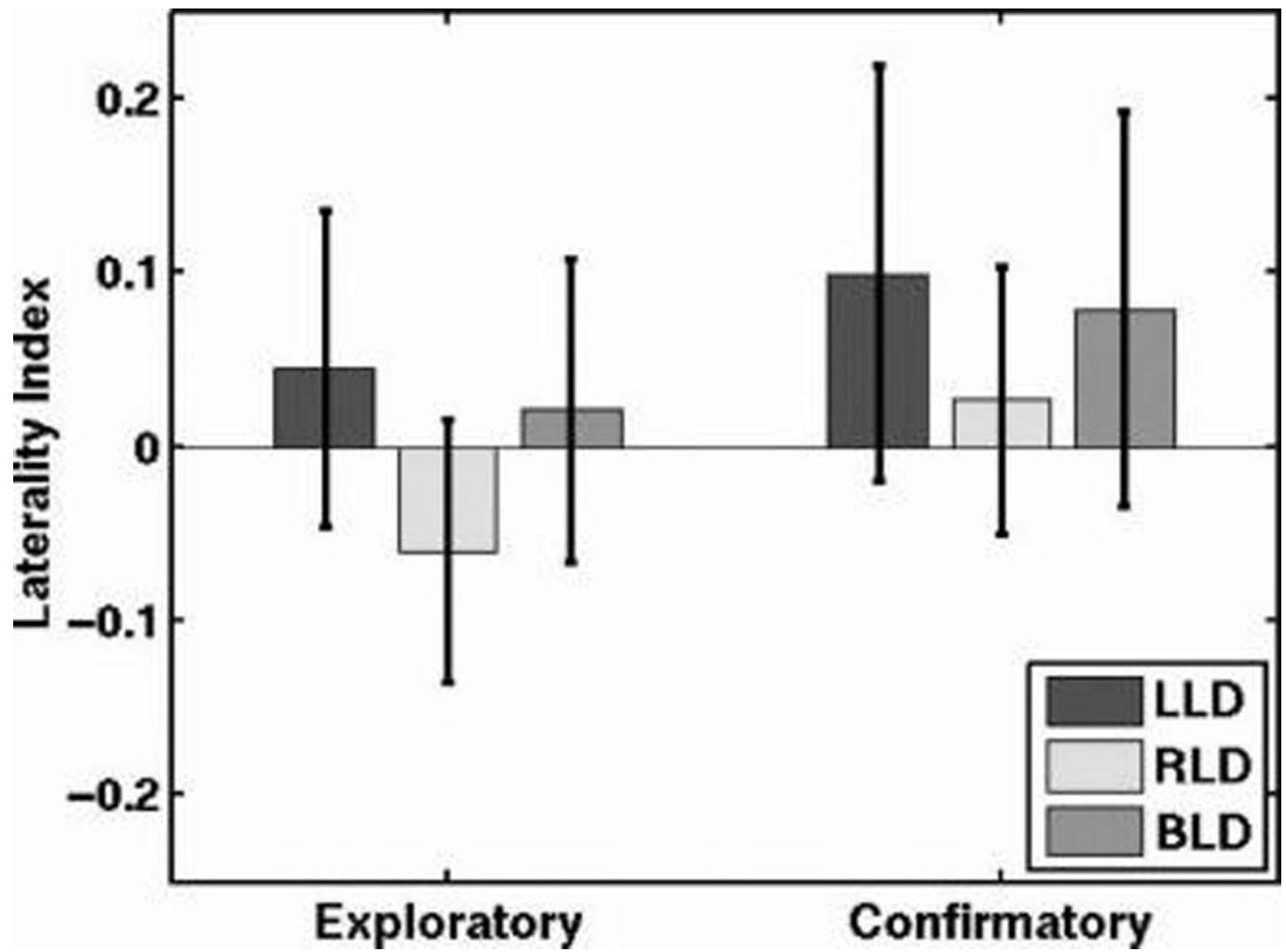Mean volume LIs for anatomically defined ROIs (with standard deviation bars). Ins: Insula.

Figure 7.
Comparison of Volume LI within the STG (exploratory) cluster and within the (confirmatory) anatomically constructed ROI (with standard deviation bars across subject). The bars for the LLD and RLD are the same as the "Volume" bars in Figure 3.

Table 1

Participant Demographics

Group	Total	Male	Female	Age (SD)	Handedness (SD)	fMRI LI (SD)	Template
LLD	34	8	26	20.4 (2.6)	−2.12 (1.06)	+0.78 (.09)	21
RLD	21	3	18	20.9 (2.8)	−2.35 (0.78)	−0.84 (.11)	21
BLD	10	4	6	21.0 (1.7)	−2.01 (1.36)	+0.14 (.43)	0

Table 2

Significant Clusters in the LLD–RLD Exploratory Analysis

Cluster	Initialization Hemisphere	Cluster p Value	Area (mm^2)		Centroid MNI305 Coordinates (XYZ)	
STG	LH	.0076	207	−58.2	−39.9	12.7
	RH	.0094	187	58.6	−39.3	13.5
vOT	LH	.0482	337	−36.9	−49.6	−17.8
	RH	.0390	343	37.8	−49.2	−17.4

Table 3

Correlation Coefficients between Anatomical Asymmetries and Functional Data (Number of Participants in the Lower Left Half)

		Anatomical Measures							fMRI			Behavioral	
	PT	POp	PTr	HG	Insula	STG	vOT	WG	LDT	DL	VHFP	VHFW
PT		−.16	−.12*	.11	−.06	.42**	.10	.17*	.05	−.05	.07	.09
POp	65		−.05	.12	.12	−.03	.11	.16	.00	.16	.01	−.03
PTr	65	65		.10	.15	−.11	−.00	−.06	−.17	.25	−.18	−.02
HG	65	65	65		−.10	.03	−.15	.08	−.17	.07	.05	.08
Insula	65	65	65	65		.15*	.27**	.38*	−.03	.38*	.16	.20
STG	65	65	65	65	65		.41^a	.46^a	.26	.20	.27*	.11
vOT	65	65	65	65	65	65		.47^a	.31*	.49**	.11	.06
WG	65	65	65	65	65	65	65		.62**	.58**	.51**	.53**
LDT	52	52	52	52	52	52	52	52		.23	.46**	.23*
DL	42	42	42	42	42	42	42	42	35		.21	.38*
VHFP	58	58	58	58	58	58	58	58	48	38		.60**
VHFW	58	58	58	58	58	58	58	58	48	38	58	

WG = LI fMRI BOLD signal in WG; LDT = LI fMRI BOLD signal in lexical decision; DL = LI accuracy dichotic listening; VHF*p* = LI naming times pictures; VHFW = LI naming times words.

*
p < .05 in this analysis or in the analysis of participants with data on all measures (*n* = 34).

**
p < .05 in both analyses.

^{a} A cell where the correlation is circular, for example, the STG and vOT clusters were defined based on fMRI activation in WG, so a high correlation is expected.