Functional asymmetry in human primary auditory cortex: Identified from longitudinal fMRI study

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Abstract

The leftward hemispheric dominance in language processing may be associated with fundamental functional asymmetry in the primary auditory cortex (PAC). Based on repeated functional MRI (fMRI) measurements, we investigated the presence of functional asymmetry in the human PAC using binaural presentation of linguistic sounds (two-syllable nouns) and simple tonal stimulation. Eight right-handed volunteers underwent nine fMRI sessions, approximately eight weeks apart, spanning the duration of more than a year. The PAC from each hemisphere was manually segmented and the volume of activation, detected within the segmented region-of-interest, was measured across the subjects and sessions to generate functional laterality indices. Although variations existed in activation volume between sessions and subjects, we found predominant and consistent leftward functional asymmetry in PAC during both linguistic and non-linguistic sound stimulations.

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Communication by means of sophisticated spoken language is a unique human trait. Since language involves the processing of speech sounds, audition plays a pivotal role. The leftward asymmetry in language processing was hypothesized to be associated with functional asymmetry in audition, and there have been efforts to correlate anatomical volume and function, targeting auditory areas. Early findings of leftward anatomical asymmetries in primary and adjacent non-primary auditory regions were followed by the observance of cytoarchitectural leftward asymmetry in non-primary auditory areas, such as posterior regions of superior temporal gyrus (part of the classical Wernicke’s area). Later research showed conflicting observations of asymmetry in the primary auditory cortices (PAC, i.e., Heschl’s gyri) along with a significant subject-to-subject variability, which have stymied the widespread acceptance of anatomical asymmetry in PAC.

Functional magnetic resonance imaging (fMRI) has been employed to examine the functional asymmetry for auditory processing in PAC. However, fMRI data acquired at one time point (or from repeated fMRI sessions in short time intervals) may only reflect transient neural activities. Therefore, an investigation covering longer time intervals was necessary to confirm these findings and establish the range of variations in PAC activation. As of yet, the reproducibility in auditory processing and the presence of auditory asymmetry have not been thoroughly investigated.

This longitudinal neuroimaging study examined the functional asymmetry in human primary auditory areas based on the repeated fMRI examinations. Nine fMRI examinations were administered per subject over a year period, using both a binaurally presented auditory word-matching task and simple tonal stimulation. The degree of reproducibility in the
Eight healthy volunteers (one female; mean age, 35.1 ± 11.6, ranged 21–51 years) without any neurological/psychiatric abnormalities participated in the study after giving written consent. All subjects were right-handed, as assessed with the Edinburgh handedness inventory [23], to minimize any variation due to handedness [6]. English was the first language for all subjects. All experiments were performed using a 1.5T clinical MR scanner (GE Medical Systems). Each subject was scanned nine times, approximately eight weeks apart (session interval ranged 21–140 days; mean inter-session period = 56.9 ± 24.6 days), and for more than a one-year period (range, 378–536 days; mean, 454.9 ± 47.2 days).

After acquiring a T1 weighted 3-plane localizer, 24 axial Echo-planar (EP) image slices (6mm slice thickness), covering the whole brain were acquired (TE/TR = 50/2500 ms, flip angle (FA) = 90°, 64 × 64 acquisition matrix). Low-resolution anatomical images (Dual Gradient Echo sequence, TE1/TE2/TR = MIN/50/2500 ms, 128 × 64 in-plane matrix) and T1-weighted images (Spoiled Gradient Recalled (SPGR) sequence, TE/TR = MIN/30, FA = 30°, 256 × 128 in-plane matrix) were also acquired to image the same volume. Low-resolution images were additionally acquired to aid in the co-registration process of EPI images with the high-resolution T1-weighted anatomical images (3D-SPGR, sagittal orientation, TE/TR = 7/35 ms, FA = 45°, 256 × 192 in-plane matrix, slice thickness = 1.5 mm).

The task paradigm was an auditory task delivered binurally via an MR-compatible headphone (Avotec, Jensen Beach, FL). Eighty two-syllable nouns were selected from the Toronto Noun Pool [9] with common usage (frequency rating greater than 6) and randomly matched to make 40 pairs of nouns. We screened out any noun that could be associated with strong imagery content or emotion. Each noun, pronounced by a female, was recorded and stored into the computer (22kHz sampling rate, 8 bits data sample size). The pairs of nouns, lasting 2 s in duration, were then composed using sound editing software (Gold wave Inc., Canada). The timing of auditory stimulation was controlled by Presentation software (Neurobehavioral Systems, CA). The pairs of same nouns were also composed to serve as target stimulation.

Four blocks of auditory tasks, each 30 s in duration, were interleaved with five 30-s control-blocks. Each word-pair was presented in every 3 s, thus 10 word-pairs were presented during each 30 s task block. During each task block, three pairs of repeated nouns were randomly placed. Subjects were instructed to move their index finger on their right hand when they heard repeated words. During the control blocks, subjects were instructed to passively listen to ambient MR noise, which was considered constant and present throughout the scan session. Subject performance was monitored using a motion-sensitive optical device attached to the tip of the index finger. We also conducted an fMRI scan using simple-tonal stimulation to examine the presence of any differential activation in the absence of language content.

A computer-generated tone (frequency centered at 925 Hz, 500 ms long) was presented in every 1 s during this task period. Subjects were required to tap their right fingers sequentially at the same pace as the auditory stimulation. It could be argued that the differences in the type of response (type of finger movement) and stimulus duration could confound the measurement, however, we believe it was not likely since the asymmetry measures (please see ‘Laterality Index’) were generated comparing the degree of differences in activation from each task conditions separately.

In order to minimize the possible adaptation/learning of the tasks, the paradigm was practiced for 1 min prior to each functional session. A total of 114 images covering the same brain volume were obtained. The first six images in each slice series were excluded from further analysis to account for T1-equilibration. Due to its simplicity, the task is not likely to manifest any functional plasticity or learning effects. The intensity of the auditory stimulation was set at 53 ± 4 dB sound pressure level (SPL, with no weighing factor) for both words and tones as measured by a sound meter (Radioshack, Fort Worth, TX) and carefully maintained throughout the study. The level of the sound intensity exceeded the minimum threshold (>50 dB SPL) suggested by the Devlin et al. [7]. The scanner noise during functional data acquisition (EPI sequence) was reduced by the use of headphones (measured 45.7 ± 8 dB SLP), providing adequate attenuation of the scanner noise.

In order to quantify the anatomically specific functional activities, the primary auditory cortex and planum temporale were manually segmented based on the high-resolution T1-weighted anatomical images using an in-house segmentation tool. Two independent raters manually segmented the ROIs. One rater repeated the ROI segmentation one month later in order to examine session-dependent reproducibility. The segmentation was based on the recent anatomical definition presented by Devlin et al. [7] and Shapleske et al. [31]. The primary auditory cortex (PAC) was delineated from the transverse temporal gyrus (TTG), a region commencing from a point at the posterior margin of the insula next to the end of the opercular branch of the posterior central gyrus, transversing antero-laterally to the superior aspect of the temporal lobe and terminating at the lateral border of superior temporal gyrus. During the segmentation procedure, the presence of ‘duplicated HG’ [25,26] was noted. If present, the posterior branch of ‘duplicated HG’ was included in PAC. Based on the reasonable (>95%) rater reproducibility on anatomical segmentation, the segmentation results from one rater (chosen from the first segmentation session) were used to represent the anatomical segmentation. Further subdivision of the tissue class (i.e., gray or white matter) was not performed.

After the segmentation, anatomical laterality index (LI) was also calculated as to the volume of segmented ROIs from...
whereby Vol indicate the segmented volume from right (R) or left (L) hemisphere.

In the subsequent data analysis, we evaluated the hemispheric asymmetries within two pairs of ROIs by computing functional laterality indices ($LI_a$) based on the volume of activation. The reliability in segmentation was computed in terms of the volume of segmented auditory areas across eight different individuals measured twice. The inter-rater reliability, as measured by the volume of measurement for each ROI across each subject, was $96.1 \pm 3.4\%$ (right PAC) and $95.6 \pm 4.3\%$ (left PAC), suggesting reliable delineation of anatomical structures. The session-dependent reliability was $96.2 \pm 3.1\%$ (right PAC) and $95 \pm 4.2\%$ (left PAC). Table 1 shows the results of the anatomical segmentation measured from nine different sessions across eight subjects. For each individual, the range of activated volume fluctuated greatly. At the given threshold of $p < 10^{-5}$, the percent of standard deviation in the activated volume (measured with respect to the mean activation volume) ranged from 37.4 to 65.5%. It suggests that normal variations up to 60% in size of activation could be expected from the auditory cortices during fMRI examination. Paired $t$-test on activation

![Figure 1](image-url)
volume (mean value from multiple sessions) across eight individual showed a leftward asymmetry in PAC function during the processing of linguistic sound (mean ± S.E.M.: R, 218 ± 97 mm³; L, 408 ± 149 mm³; \( t_{(7)} = -3.3; p < 0.05 \)) as well as during the processing of the non-linguistic sound (mean ± S.E.M.: R, 49 ± 36 mm³; L, 101 ± 46 mm³; \( t_{(7)} = -3.2; p < 0.05 \)). We also examined the presence of any time-dependent trends in volume of activation using linear regression, but no correlation (\( p > 0.1 \)) was found from any of the ROIs. This suggests the absence of time-dependent trends such as priming or learning.

The results of session-specific functional LIs (LI) for eight different subjects are shown in Fig. 2. Although certain variations existed in several sessions, leftward asymmetry in functional activation was evident. There was no presence of any session-specific trend in LI's over time (as examined by linear regression, \( p > 0.1 \) for all subjects). LI derived from a simple non-language beep task is also shown. Although it is notable that there were few incidental sessions with slight rightward asymmetry, the averaged LI indicated the leftward asymmetry in PAC function. The LI measured from the simple sonal stimulation demonstrated that leftward functional asymmetry existed for non-linguistic sound (except for the subject 5). In the examination of the relationship between LI and LI, in terms of its directionality (whether left or right asymmetry), there was no correlation (\( p > 0.1 \)) between the two parameters, suggesting that asymmetry based on the anatomical volume cannot predict the functional asymmetry.

At more lenient threshold of \( p < 10^{-3} \), paired t-test on mean activation volume across eight individual consistently showed a leftward asymmetry with respect to the linguistic sound (mean ± S.E.M.: R, 328 ± 170 mm³; L, 656 ± 282 mm³; \( t_{(7)} = -3.1; p < 0.05 \)) as well as to the non-linguistic sound (mean ± S.E.M.: R, 153 ± 78 mm³; L, 293 ± 83 mm³; \( t_{(7)} = -3.4; p < 0.05 \)). Although the inter-subject variability in size of activation has increased for each hemisphere, the use of lenient threshold did not affect the measured LI values in either linguistic (mean ± S.E.M.: \( p < 10^{-3} \), \( t_{(7)} = -2.6; p < 0.17 \)) or the non-linguistic sound (mean ± S.E.M.: \( p < 10^{-3} \), \( t_{(7)} = 0.63 \)).

Several previous studies employing magnetoencephalography (MEG) [24,35] and fMRI [19] have shown early evidence of contralateral functional asymmetry for monaural auditory processing. However, a study on high-resolution definition of cortical function in conjunction with its anatomical parcellation to measure the hemispheric asymmetry was rare. We successfully measured the activated cortical volume responding to linguistic and non-linguistic sound stimulation, based on careful anatomical delineation of the primary auditory areas. Another important finding from this study was that the functional laterality indices were not correlated with the anatomical asymmetry. This is a rather intriguing finding since it suggests that anatomical measurement alone might not be able to unequivocally determine/predict the underlying cortical functions. The results strongly support that volumetric studies can be greatly benefited by the use of confirmatory functional information in addition to the anatomical measurement. Although the current study lacked the segmentation of gray and white matter within the ROIs, detailed parceling of these structures will lead to a deeper understanding of underlying anatomical structure and its relations to functional activation.

The strength of the current study lies in the examination of normal variation of activation using repeated measurements of BOLD-related activation. Our results indicate that there was consistent and reproducible left hemispheric asymmetry in auditory processing of sounds within the PAC. The use of different thresholding conditions did not alter our findings. The consistent leftward functional asymmetry in PAC...
Data acquisition scheme such as ‘sparse sampling’ of activation from the acquisition of multiple scan sessions. Lefward laterality was observed during the simple non-linguistic tonal stimulation, suggesting that the auditory asymmetry in the PAC was also present during non-linguistic auditory stimulation. The stronger lateralization in primary auditory processing, regardless of sound content, implies the possibility of “bottom-up” evolution of human language function and hemispheric dominance rooted in the fundamental difference in auditory function [7], as opposed to the theory that linguistic skills and associated neural processing resulted in cortical dominance. However, as also shown from the observed significant variability in activation, it is important to note that fMRI method in itself lacks the sensitivity necessary to reveal the subtle neural differences between speech and non-speech stimulation [5]. Further validation studies such as using the techniques of simultaneous measurement of electrophysiological and fMRI signals [29] would be necessary to elucidate the neural mechanism behind the auditory processing, with consideration for adjacent non-primary auditory areas.

An important technical limitation of this study is that the scanner noise was present throughout the MRI data acquisition. Periodic and densely presenting (every \(\sim 110 \text{ ms}\)) scanner noise may saturate the BOLD signal response, reducing the dynamic as well as spectral range of auditory signal detection [17]. In addition, binaural scanner noise along with the binaural presentation of the sound can potentially confound the detection of neural activation (binaural auditory presentation have shown lateralized effects with temporal processing more prominent in the left and spectral processing more prominent in the right [16]).

Data acquisition scheme such as ‘sparse sampling’ [15] in the context of monaural stimulation will be helpful to dissociate the ambient scanner noise from the main effect of monaural audition. This scheme utilizes the time leg between data acquisition (thus the scanner noise) and stimulation presentation, allowing relative ‘silent’ and ‘monaural’ presentation and measurement of the sound stimulation.

Another important limitation of this study is in the difficulties in accurate delineation of the PAC. Topological variations, such as ‘duplications’ in HG or ambiguity in the definition of lateral extent of the TTG [25,26], render the definition of PAC by macroanatomical criteria (such as from the MRI images) equivocal. Although we expect the possible errors caused by the data registration procedure is minimal, the session-by-session anatomical segmentations (including the classification of gray and white matter) and reconciliation of segmentation results between raters (for example through volume averaging), will help to reduce confounding effects of rater- or session-dependent factors.

We have established the laterality based on the volume of activation from the acquisition of multiple scan sessions. Instead of volume of activation, the mean level of BOLD signal contrast measured from the activated tissues can be gainfully employed for generating LI [8]. It was not prioritized in this study since the spatio-temporal measurement of BOLD signal contrast and its reproducibility could be significantly affected by the spatial resolution of the original data acquisition and/or the shape of chosen ROIs [36]. Although the range and magnitude of reproducibility measures were comparable to previous findings on visual tasks [20,27] and visual-motor tasks [32], there were substantial variations in the size of activation including several data-outliers. For example, as illustrated in Fig. 2, one exceptional case was observed from one male subject (subject 5) where definite laterality was not ascertained from the repeated sessions. The LI, acquired from this subject ranged from 0.7 to \(-0.7\) with rightward asymmetry shown with respect to the non-linguistic stimulation. The source of the intersession variability could be traced to numerous factors such as inconsistent task performance, changes in subject’s level of attention, image noise, or hardware instability [20,22,37].

The results of this kind suggest that a single fMRI scan session may lead to a grossly inaccurate representation of activation if a subject performs the task improperly the first time or the data itself is confounded by other confounding factors. If the acquisition of reproducible fMRI data is critically demanded, for example, in clinical situations such as brain mapping to determine the language dominance prior to the surgical intervention [8,18], the acquisition and analysis of multiple fMRI scan sessions (more than three per task) are recommended to increase the certainty of the results. Method such as taking the individual noise into account for a derivation of \(p\)-values and BOLD contrast [3] may also allow more reliable identification of activation in longitudinal studies.

In summary, we have demonstrated the predominant and consistent leftward functional asymmetry found in PAC regardless of the sound content. In addition, we have found that structural differences do not account for functional differences—at least in the PAC areas. The important limitation of the study is that the current study design could not provide detailed mechanism on causal (or mutual) relationship between language dominance and the asymmetry in PAC function. Further investigation is necessary to probe and confirm the relationship between language dominance with respect to the functional asymmetry present in adjacent secondary auditory areas such as planum temporale or planum polare. Adjunctive EEG or MEG measurement is necessary to validate these findings.

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