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A Surgical Planning Method for Functional MRI Assessment of Language Dominance: Influences from Threshold, Region-of-Interest, and Stimulus Mode

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Abstract Presurgical determination of language laterality is an important step for assessing potential risk of dysfunction resulting from brain resection within or near suspected language areas. Image-based functional MRI (fMRI) methods seek to address limitations to the clinical gold-standard technique by offering a safer, less costly, and non-invasive alternative. In this study we outline a set of protocols for objective determination of langue-specific asymmetry from fMRI activation maps. We studied 13 healthy, right-handed volunteers using a vocalized antonym-generation task. Initially, using the standard threshold-dependent laterality index (LI) procedure, we demonstrated an undesirably high degree of intra-subject variability and indeterminacy in LI value. We addressed this issue by implementing a novel threshold-independent method, resulting in a single, unambiguous LI for each subject. These LIs were then averaged across the group and used to compare functional laterality within the whole hemispheric volumes and six intra-hemispheric regions-of-interest (ROIs). We noted that as a result of increased bilateral activation from vocalizations, laterality assessment calculated from the whole hemisphere resulted in insignificant asymmetry. However, by focusing the LI exclusively on the inferior frontal (IFG) and supramarginal gyri (SMG), robust leftward asymmetries were observed. We also examined the influence of stimulus mode on the group mean ROI LI, and observed an increase in IFG asymmetry using visual mode, and in SMG using the auditory mode. Based on these findings, we make recommendations for optimized presurgical protocols.

Keywords Laterality index (LI) · Language dominance · fMRI threshold · Vocalized language · Region-of-interest · Presurgical mapping

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Introduction

Mapping language function has important clinical applications in patients undergoing neurosurgical interventions near critical language areas of the brain. It is well established that language processing in the normal brain is predominately located in the left cerebral hemisphere (Binder et al. 1997; Bryden et al. 1983; Springer et al. 1999; Vikingstad et al. 2000; Levy 1974). However, in patients with longstanding brain lesions, there is a higher likelihood of atypical lateralization following long-term reorganization of language function (Angrilli et al. 2003; Pataraia et al. 2004; Janszky et al. 2003). Therefore, conclusively identifying the dominant hemisphere in patients prior to surgery is generally important for surgical planning, and for counseling patients regarding post-operative risk of language dysfunction.

The preoperative clinical standard for determination of cerebral language dominance is the intracarotid amytal test (IAT), also known as the Wada test. IAT consists of injections of an anesthetic administered selectively into the right and left carotid arteries to test for induced speech errors or arrest (Wada and Rasmussen 1960). While IAT is generally reliable, there are significant disadvantages to the technique: IAT is invasive, costly, time-consuming, and carries a small but significant risk of stroke (Ammerman et al. 2005). Due to the short acting effect of the anesthetic, the number of neuro-behavioral tasks that can be performed during the procedure is restricted. There may also be cerebral vascular perfusion effects, such as cross filling, that cannot be controlled for and may obscure the IAT results. Moreover, because the anesthetic acts on an entire hemisphere, it is not possible to examine how individual cerebral lobes, or the cortical structures within them, are affected; therefore, no inference can be made about the level of participation by specific brain structures within a cerebral hemisphere. This is particularly problematic in patients who may have lesion-induced cerebral reorganization leading to mixed dominance (Boatman et al. 1999; Goldmann and Golby 2005; Hertz-Pannier et al. 2002; Rasmussen and Milner 1977). It would therefore be beneficial for presurgical planning to accurately assess language laterality with a higher spatial resolution than is possible by IAT.

Validating language functional mapping by non-invasive neuroimaging requires comparison against clinical gold-standards. Given this, it is interesting to note that non-invasive studies have recently demonstrated advantages in using overt rather than covert language tasks for functional MRI (fMRI) mapping (Borowsky et al. 2005; Huang et al. 2002; Palmer et al. 2001; Shuster and Lemieux 2005). To explain this discordance, researchers theorize a utilization of different neural substrates depending on whether the language task is performed silently or overtly (vocalized) (Borowsky et al. 2005; Shuster and Lemieux 2005). In a recent comparative study between electrocortical stimulation (ECS) and fMRI, researchers reported a repositioning of inferior frontal lobe fMRI activation—more posteriorly towards the precentral gyrus—during a vocalized task as compared to during a silent task, and was more closely correlated with ECS testing results (Petrovich et al. 2005). In addition, researchers often report relative increases of fMRI signal strength and robustness whenever vocalized language tasks are used (Palmer et al. 2001; Petrovich et al. 2005). These findings provide evidence supporting the implementation of vocalized tasks when using non-invasive language mapping techniques for clinical purposes.

Currently the most common method used to determine cerebral dominance from fMRI involves calculation of a laterality index (LI) that is based on counting activated voxels above an arbitrary activation threshold setting. A significant drawback to this approach, however, is that resulting laterality indices may differ depending on the threshold used. Typically, when setting an activation threshold, researchers recommend a statistical threshold set at $P<0.001$ or at $P<0.05$ equivalently for all subjects and for all tasks used (Binder et al. 1996; Frost et al. 1999; Lehericy et al. 2000; Springer et al. 1999; Szaflarski et al. 2002; Yetkin et al. 1998). It is not clear, however, that the optimal fMRI threshold for every individual should be the same, nor is it clear that within subjects, all tasks should have the same threshold setting. As the choice of threshold setting invariably impacts the degree, and often the direction, of asymmetry measured in an fMRI mapping, the use of threshold-dependent techniques may in some cases lead to unstable or ambiguous asymmetry outcomes. To avoid this, in the present study we apply a threshold-independent methodology that is based on whole voxel distributions without the need for arbitrary thresholds (Branco et al. 2006).

Whether the goal of a specific presurgical fMRI mapping is localization or lateralization, the choice of stimulus mode used (i.e., visual or auditory presentation) is a matter of interest since the mode used may have an impact on the resulting fMRI activation patterns. Observations made in lesion studies for example have prompted the hypothesis of a mode-dependent input lexicon that is impaired differently depending on the stimulus mode used (Hillis and Caramazza 1991). This postulate is supported by investigators reporting increased regional blood flow to the left temporal lobe when an identical language task is presented in the auditory mode compared to the visual mode; this effect has been confirmed using positron emission tomography (PET; Howard et al. 1992), and fMRI (Chee et al. 1999). These examples present evidence supporting stimulus-mode-dependent activation patterns elicited during non-invasive testing that can be of importance for laterality assessment.

In this study, we tested healthy, right-handed subjects as an initial test population. This control group has previously shown to demonstrate a robust tendency for left-dominant language function, and is often used as preliminary validation for novel functional imaging methods that seek to assess language laterality (Binder et al. 1997; Springer et al. 1999; Simos et al. 1998; Szymanski et al. 1999; Breier et al. 1999). Therefore, it is reasonable to expect our control group to similarly demonstrate left-dominant language patterns, and use this trend for the comparison of our experimentally determined LIs.

We initially plot threshold-dependent LI values vs threshold, for language-specific regions-of-interest (ROIs), non-language-specific ROIs, and hemispheric brain volumes to illustrate an undesirable level of intra-subject variability in the respective LI outcomes. We subsequently implement our original methodology that effectively eliminates intra-subject variability and yields a single LI for each subject without need for arbitrary threshold cutoffs. Using analogous visually and aurally presented language tasks, we examine the influence of stimulus mode on ROI language laterality. And finally, based on our findings in healthy right-handers, we present recommendations for optimized presurgical fMRI acquisition and analysis protocols for the lateralization of language in distinct putative language regions of interest, tailored according to the location of the planned resection.

Materials and methods

Subjects

We enrolled 13 healthy, native English speakers with no speech, hearing, or vision deficits (mean (M) age = 30.4 years, standard deviation (SD) age = 6.1 years), five were female. All volunteers were strongly right-handed as determined by the Edinburgh Handiness Inventory (Oldfield 1971), and had no history of neurological or cognitive disorders. This study was approved by the Partners' Institutional Review Board and written informed consent was obtained from all participants.

Behavioral paradigm

Subjects performed an antonym-generation task with vocalized responses. This behavioral task was selected in an effort to activate all the major aspects of language: receptive decoding, expressive encoding, and vocalization. Data acquisition sessions consisted of two separate runs lasting approximately 7.5 min each: one visually presented and one aurally presented. During each trial, subjects were presented with a visual or auditory cue word and asked to generate its antonym aloud. The antonym-generation task consisted of a rapid-presentation, event-related fMRI paradigm with a jittered inter-stimulus-interval [M = 8.3 s, SD = 5.1 s]. A baseline period of fixation was presented for 10 s at the beginning and ending of each run. Each visually presented stimulus word was shown for 2.0 s; the mean acoustic duration of aurally presented cue words was 612 ms (SD=245 ms). During any time period while visual stimuli were not presented, a "+" crosshair fixation point was shown in the center of the screen (i.e., periods between visually presented cue words, or during the entire duration of aurally presented runs). A total of 50 stimuli words were delivered during each run. The order and exact timing for delivery of stimuli words was based on a stochastic design intended to maximize the statistical significance of the fMRI paradigm, diminish subject habituation, and minimize expectation effects. Stimuli event scheduling was performed using the Optseq2 software package (NMR Center, Massachusetts General Hospital, MA, USA, <http://surfer.nmr.mgh.harvard.edu/optseq>). The total functional scan time was approximately 15 min for both runs.

Auditory stimuli were presented through headphones (Avotec Inc., Stuart, FL, USA), with the volume level adjusted for each subject to enable hearing of cue words clearly over scanner noise. Visual stimuli were presented through MRI-compatible video goggles (Resonance Technology, Los Angeles, CA, USA). Stimulus paradigms were presented on a laptop computer (Dell Inc., Round Rock, TX, USA) running the Presentation software package, version 9.70 (Neurobehavioral Systems Inc., Davis, CA, USA). Subject vocalizations were transmitted by an intercom system (Avotec Inc., Stuart, FL, USA) to an investigator in the MRI scanner control room who counted the number of incorrect or omitted responses in order to verify satisfactory task performance.

Subjects were asked to respond to each stimulus word by first taking into consideration its meaning, then saying a word having the opposite meaning. Volunteers were instructed to verbalize responses without moving their head, jaw, or lips (they were asked to "speak like a ventriloquist"). To further minimize head movement, foam padding was placed around the head, along with strips of tape spanning the video goggles and lightly adhered to the patient table.

The antonym cue/response word pairs used were chosen based upon our previous behavioral pilot study results that tested 20 English speakers (11 women and 9 men, average age of 28 years), recording their verbal responses and reaction times for each trial during the performance of antonym-generation. The initial pool of potential antonym pairs was reduced to only those word pairs that generally elicited quick and accurate responses, based on the averages from the pilot group. Antonym pairs such as UP–DOWN, LEFT–RIGHT, OFF–ON, OPEN–CLOSE, PUSH–PULL, or NORTH–SOUTH were generally observed to yield fast, accurate, and consistent responses.

Image acquisition

MR images were acquired at 3T using a GE Signa system (General Electric, Milwaukee, WI, USA) equipped with a standard birdcage head coil. Blood-oxygen-dependent (BOLD) functional imaging was performed using echo-planar imaging (EPI) in contiguous axial slices (5 mm thick with no gaps between slices). In-plane spatial resolution was 3.75×3.75 mm^2; TR=1,000 ms; TE=29 ms; 68° flip angle; 24 cm field of view; 64×64 matrix acquisition. A volumetric T1 weighted MPRAGE (Magnetization Prepared RApid Gradient Echo) acquisition was acquired to provide a high-resolution anatomic reference frame (matrix=256×256) for subsequent overlay of functional activations.

Data analysis

Following functional image reconstruction, motion correction was performed using the SPM2 (Statistical Parametric Mapping) software package (Wellcome Department of Imaging Neuroscience, London, U.K., <http://www.fil.ion.ucl.ac.uk/spm>). The realignment procedure performed a rigid co-registration of individual fMRI volumes (430 total volumes) aligning each to the first volume acquired in that run; motion realignment parameters were recorded. The maximal right-left (Δx), anterior-posterior (Δy), and superior-inferior (Δz), realignment displacements determined by SPM2 software were recorded for each subject and used to assess gross head motion, which was quantified as the maximum net displacement vector calculated from these Δx, Δy, and Δz components. From these data, an average maximum displacement vector was calculated for the subject group and used to quantify maximal head motion during each data acquisition run.

Structural and functional images were normalized to Montreal Neurological Institute (MNI) space in order to facilitate ROI analysis. Functional images were smoothed using an 8 mm Gaussian kernel. Stimulus onset vectors were automatically generated by the Presentation software. Run-specific responses were modeled in an event-related design (Friston et al. 1998) by convolving a series of Dirac's delta function, each representing a stimulus event onset, with the canonical hemodynamic response function (HRF) including time derivatives and linear summation effects. Using SPM2, statistical parametric maps based on the *T*-score correlation between HRF and voxel-by-voxel BOLD signal response were generated for each run and overlaid on individual subject anatomic images. Using the Talairach Daemon (Talairach and Tournoux 1988), Human Atlas ROI volumes were identified in MNI normalized anatomies and mask volumes generated using WFU PickAtlas software (Department of Radiologic Sciences, Wake Forest University, Winston-Salem, NC, USA, <http://www.ansir.wfubmc.edu/download.htm>). Coordinate transformations and corrections were done by the WFU PickAtlas software using the methods outlined by Maldjian et al. 2003, 2004; Lancaster et al. 1997, 2000.

ROI selection

Selecting ROIs for LI analysis was performed identically for all subjects and all tasks on the basis of standard Human Atlas segmentations by focusing on the anatomical regions generally activated by the experimental paradigm. Large gyri, such as the superior temporal and precentral, were further subdivided to include only the portion overlapped by functionally relevant divisions as defined by standard Brodmann areas. Using this procedure we identified 6 experimental ROIs for laterality assessment:

1. inferior frontal gyrus (BA44, 45, and 47)—designated *IFG*
2. supramarginal gyrus (BA40)—designated *SMG*
3. temporoparietal gyrus (BA22 and 39)—designated *TPG*
4. precentral gyrus (superior portions of BA4 and 6)—designated *PCG*
5. middle occipital gyrus (BA17 and 18)—designated *MOG*
6. transverse temporal gyrus (BA38, 41, and 42)—designated *TTG*

These ROIs can be divided into three main groups: three putative language ROIs (IFG, SMG, and TPG); a motor-specific ROI (PCG); and two sensory-specific ROIs (MOG and TTG). In order to assess the influence of ROI on LI, laterality calculations were performed on each of these experimental ROIs as well as using whole hemisphere volumes.

Threshold-dependent LI calculation

Threshold-dependent LIs were evaluated using the standard formula:

$$\mathrm{LI} = \frac{\mathrm{LH} - \mathrm{RH}}{\mathrm{LH} + \mathrm{RH}} \tag{1}$$

where LI denotes the laterality index, and LH and RH denote the number of voxels above threshold in the left and right cerebral hemispheres, respectively. Equation 1 determines LI based on a given threshold setting by comparing the numbers of supra-threshold voxels in the left vs right hemispheres and renders positive LI values as left-dominant and negative values as right-dominant. To observe the influence of threshold on LI, for each subject, we plotted LI as a function of threshold in the entire range of positive *T*-scores (in our paradigm for degrees of freedom (df)=430, the *T*-score ranged approximately 0–35). Plots of resulting LI vs threshold were made for each of the putative language ROI and for the hemispheric volume. In order to illustrate laterality ambiguity with regards to activation asymmetry using the standard threshold-dependent method, we assess the occurrence of left/right alternating LI outcomes as dependent on the specific threshold value used (e.g., LI values that alternated in sign as a function of threshold). When occurring within the statistically significant range of $P<0.001$ or better, we classify this undesirable behavior in the LI vs *T*-score curves as demonstrating "reversing asymmetry determination." Furthermore, we generally define asymmetric activation distributions as having an absolute LI value greater than 0.1, whereas LIs close to zero (i.e., $-0.1 \leq \mathrm{LI} \leq 0.1$) are denoted as bilateral activation.

Threshold-independent LI calculation

Threshold-independent LIs were determined by comparing the integrated *T*-score weighted distributions of all positively correlated voxels between the left and right hemispheres (Branco et al. 2006). Initially, a histogram was generated that tabulated the total number of voxels having positive *T*-scores within the full range of possible values

(T-score range=0–35, bin increment=0.25) for each ROI in the left and right hemispheres. Distributions were then multiplied by a weighting function defined as:

$$\text{weighting} = (T - \text{score})^2 \tag{2}$$

After applying this weighting function to each bin, a numerical integration of the areas under the entire weighted distributions was done (Fig. 1). Lastly, integrated areas were compared across left and right cerebral hemispheres to generate a unique LI value for each subject, using the formula:

$$\text{LI} = \frac{\text{LHA} - \text{RHA}}{\text{LHA} + \text{RHA}} \tag{3}$$

where LHA denotes the integrated weighted distribution for the left hemisphere, and RHA for the right hemisphere. This formula yields positive LI values for left-dominance and negative values for right-dominance. We define an asymmetric activation pattern as having an absolute LI value greater than 0.1, and denote absolute LI values equal to or less than 0.1 as representing a bilateral activation distribution.

Results

FMRI activation patterns

All of the subjects tested demonstrated strong activation of the inferior frontal lobe (IFG), and to a lesser extent, activation of gyri near the posterior portion of the Sylvian fissure (TPG and SMG); these are patterns consistent with Broca's and Wernicke's areas, respectively. The highest T-score activation in IFG was found in the left hemisphere in 12 of 13 subjects using visual mode, and in all subjects using auditory mode; highest T-score activation in SMG was found in the left hemisphere in 10 of 13 subjects using visual mode, and in 12 of 13 subjects using auditory mode; highest T-score activation in TPG was found in the left hemisphere for 6 of 13 subjects using visual mode, and in 6 of 13 subjects using auditory mode.

Auditory stimuli evoked bilateral activation of regions near Heschel's gyrus (TTG) that was absent using visual stimuli; visual stimuli showed bilateral activation in the middle occipital gyrus (MOG) that was absent in auditory mode. All of the subjects demonstrated robust activations bilaterally in the superior portions of the precentral gyrus (PCG), accompanied by less robust but also bilateral activation of the midline supplementary motor cortex. Group-level activation maps using both stimulus modes are shown in Fig. 2.

We assessed stimulus mode dependent activation patterns by comparing the mean number of activated voxels in each of the ROIs (threshold at $P<0.0001$, uncorrected, T-score=3.75, df=430). There was no significant difference in the number of activated voxels between auditory and visual stimulus mode observed in IFG [$t(24)=0.73$, $P=0.50$]. However, when using auditory compared to visual mode, mean activation was significantly increased in TPG [$t(24)=4.56$, $P<0.001$] and in SMG [$t(24)=2.66$, $P<0.01$]. Mean activation in MOG was significantly increased when visual mode was used [$t(24)=3.63$, $P<0.0001$], while activation in TTG was significantly increased when auditory mode was used [$t(24)=4.51$, $P<0.0001$]. Mean activation in PCG did not differ significantly between auditory and visual stimulus modes [$t(24)=0.81$, $P<0.43$].

Gross head motion indicators

The net displacement parameters obtained in post-processing realignment of fMRI volumes demonstrated an acceptable level of gross head motion in all the volunteers tested. The group mean maximal net displacement for aurally presented stimuli was 1.0 mm (SD=0.6 mm), and for visually presented stimuli was 1.1 mm (SD=0.7 mm).

Threshold-dependent laterality

For the purpose of assessing the degree of threshold-dependency on LI, we generated plots of each subject's LI as a function of threshold setting for each of the ROIs and for the hemispheric volume. Figure 3 illustrates hemispheric LI vs threshold for each subject. An arrow on these graphs denotes the threshold value at $P<0.001$ confidence level (corresponding to a T-score=3.11 at df=430, uncorrected). Figure 4 illustrates similar graphs for the putative language ROIs. At thresholds of $P<0.001$ and above, all the ROIs we tested demonstrated a high degree of intra-subject variability in LI values. This finding was confirmed for both stimulus modes. Moreover, there was no clear indication of a threshold setting that would distinctively indicate a unique value for LI for any of the subjects, nor in any of the ROIs. This observation is illustrated in Figs. 3 and 4, where in most cases LI alternated between left- and right-dominance (i.e., a zero-crossing in the LI curves) depending on the specific threshold chosen.

Non-language ROIs

Over the full range of positive threshold settings, the resulting LI value as a function of threshold in non-language ROIs demonstrated a high degree of variability within and across subjects. Generally, the group showed no obvious tendency towards either positive or negative LI values in either the auditory or visual sensory-specific ROIs—TTG and MOG, respectively—indicating no con-

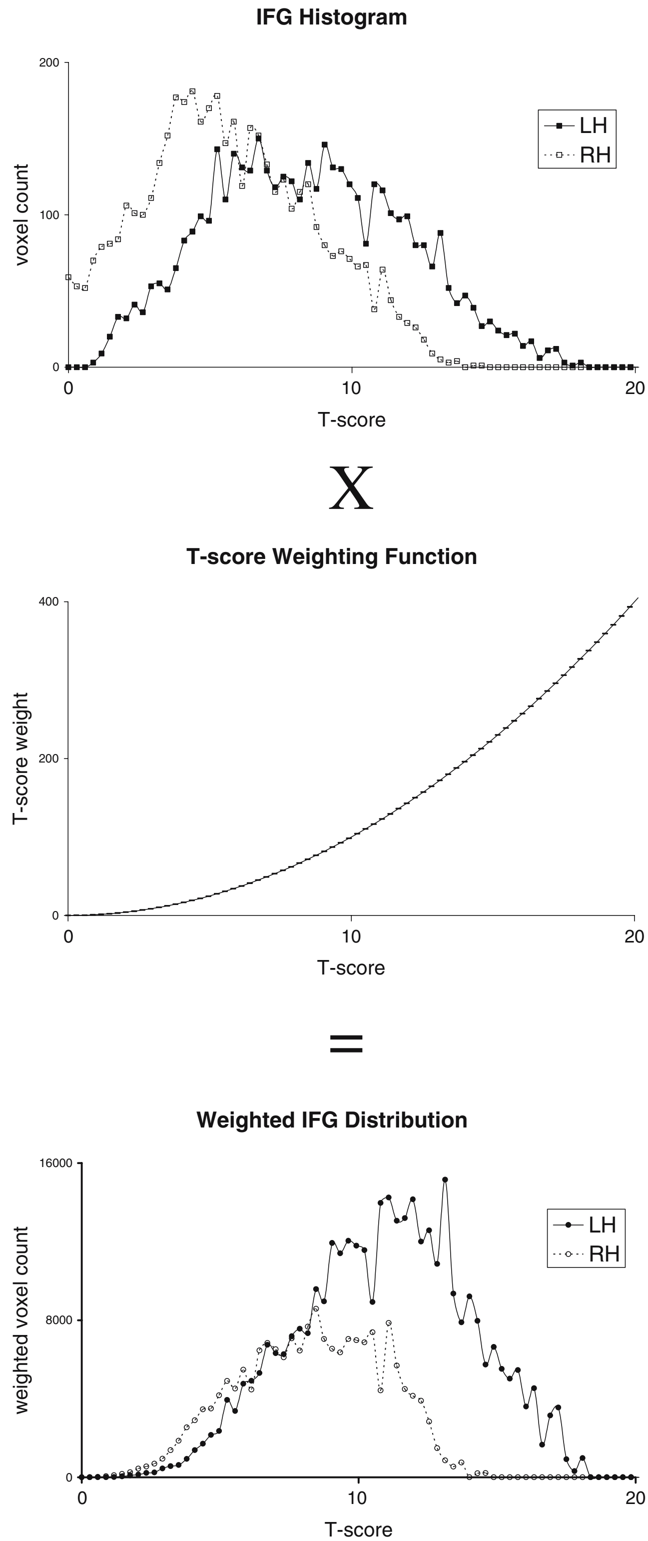

Fig. 1 Graphical illustration of the threshold-independent method used for laterality index calculation in the IFG region of a representative subject. The *left panel* illustrates the unweighted distributions represented by histograms of voxel frequency at each *T*-score bin; the *middle panel* illustrates the weighting function applied to the histograms (i.e., multiplication of bin frequency by the square of that bin's *T*-score); and the *right panel* shows the resulting weighted distributions. *LH* indicates the left hemisphere and *RH* indicates the right hemisphere. LIs are calculated by comparing the integrated areas underneath the weighed distribution curves using a standard LI quotient. This subject was determined to have an asymmetry favoring the left cerebral hemisphere in IFG

sistent asymmetry in these areas. This outcome differs from what was seen in PCG, where for the subject group, a relatively higher incidence of positive (leftward) LIs was seen in the motor-specific ROI.

Hemispheric

Hemispheric LI as a function of threshold demonstrated a high degree of variability within and across subjects at all thresh-

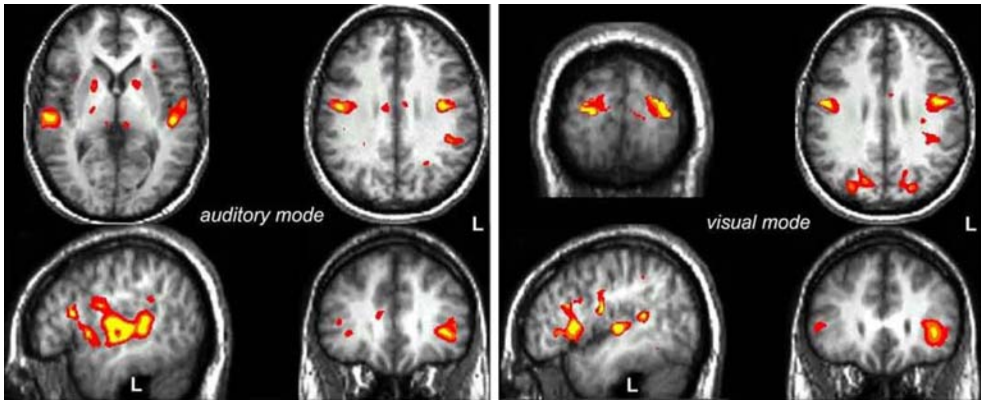

Fig. 2 Group-level fMRI activation maps from all subjects (n=13) performing vocalized antonym-generation in visual mode (*left panel*) and in auditory mode (*right panel*). Consistent activation, independent of stimulus mode, was observed bilaterally in the precentral gyrus (*PCG*), and favoring the left hemisphere in the inferior frontal gyrus (*IFG*) and the posterior portion of the superior temporal gyrus (*TPG*). Visual mode activation was observed bilaterally in the middle occipital gyrus (*MOG*); auditory mode was associated with bilateral activation in the middle portion of the superior temporal gyrus (*TTG*). Image threshold at $P<10^{-6}$, uncorrected

olds (Fig. 3). In the range of thresholds having $P<0.001$ or better, using visual stimulus presentation, 5 of 13 subjects demonstrated asymmetries of activation that flipped sides; over this range of thresholds, subjects no. 2, 6, 8, 9, and 12 demonstrated such reversing asymmetry determinations. Similarly, using auditory presentation of stimulus, 6 of 13 subjects also demonstrated reversing asymmetry determinations (subjects no. 1, 2, 6, 10, 12, and 13).

Language-specific ROIs

Over the full range of statistical thresholds, LI value as a function of threshold in putative language areas demonstrated decreased across-subject variability compared to that of non-language or hemispheric ROIs. In the putative language regions, LI values at the more stringent thresholds more generally demonstrated leftward asymmetry, particularly in IFG and SMG, but to a lesser degree in TPG (Fig. 4). Of the three putative language regions, TPG showed the highest degree of across-subject variability in LI and demonstrated no consistent asymmetry pattern within the group favoring neither the left nor right cerebral hemispheres. In TPG, using visual stimulus mode, subjects no. 3, 4, 6, and 10 illustrated reversing asymmetry determinations and when using auditory stimulus mode, all but one of the subjects tested (no. 7) illustrated reversing asymmetry determinations. SMG demonstrated less LI group variability than TPG, with a greater group tendency towards leftward asymmetry (Fig. 4). In SMG, when using visual mode, 3 of 13 subjects demonstrated reversing asymmetry determinations (subjects no. 6, 7, and 12) and using auditory mode, one subject (no. 12) demonstrated

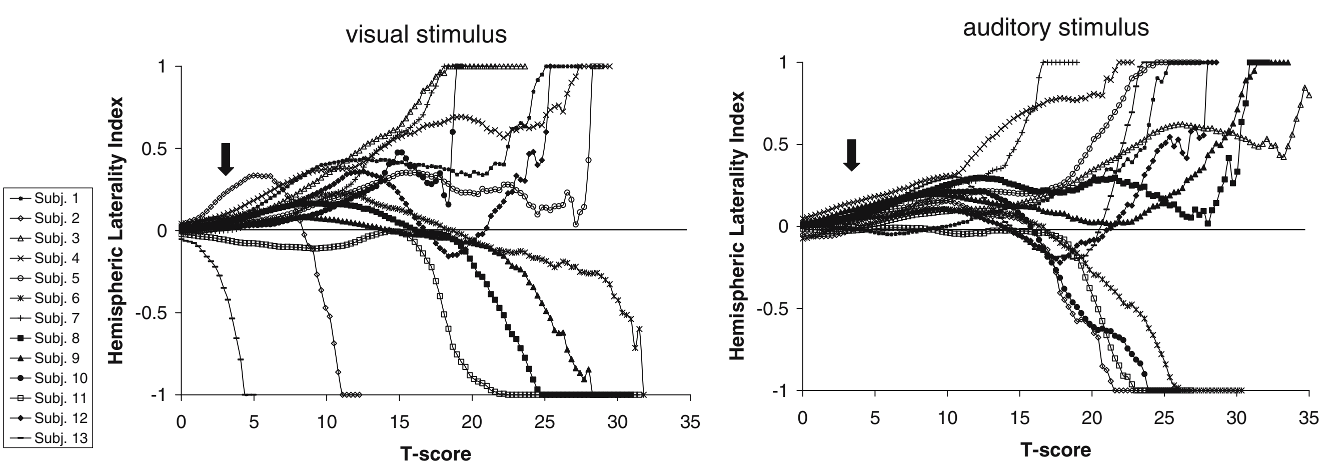

Fig. 3 Hemispheric LI as a function of fMRI threshold for 13 subjects. The *left panel* shows visual mode results and the *right panel* shows auditory mode results. Each curve represents the LI calculated at each threshold setting for a specific subject. These graphs illustrate the intra-subject variability seen in laterality values depending on the threshold used. Positive LI values indicate left-dominance and negative values indicate right-dominance; curves that alternate between positive and negative values (i.e., crossing the zero axis as a function of threshold) are examples of reversing asymmetry indications, thus yielding ambiguous laterality for that subject. The *arrows* displayed on the graphs indicate the $P<0.001$ threshold value

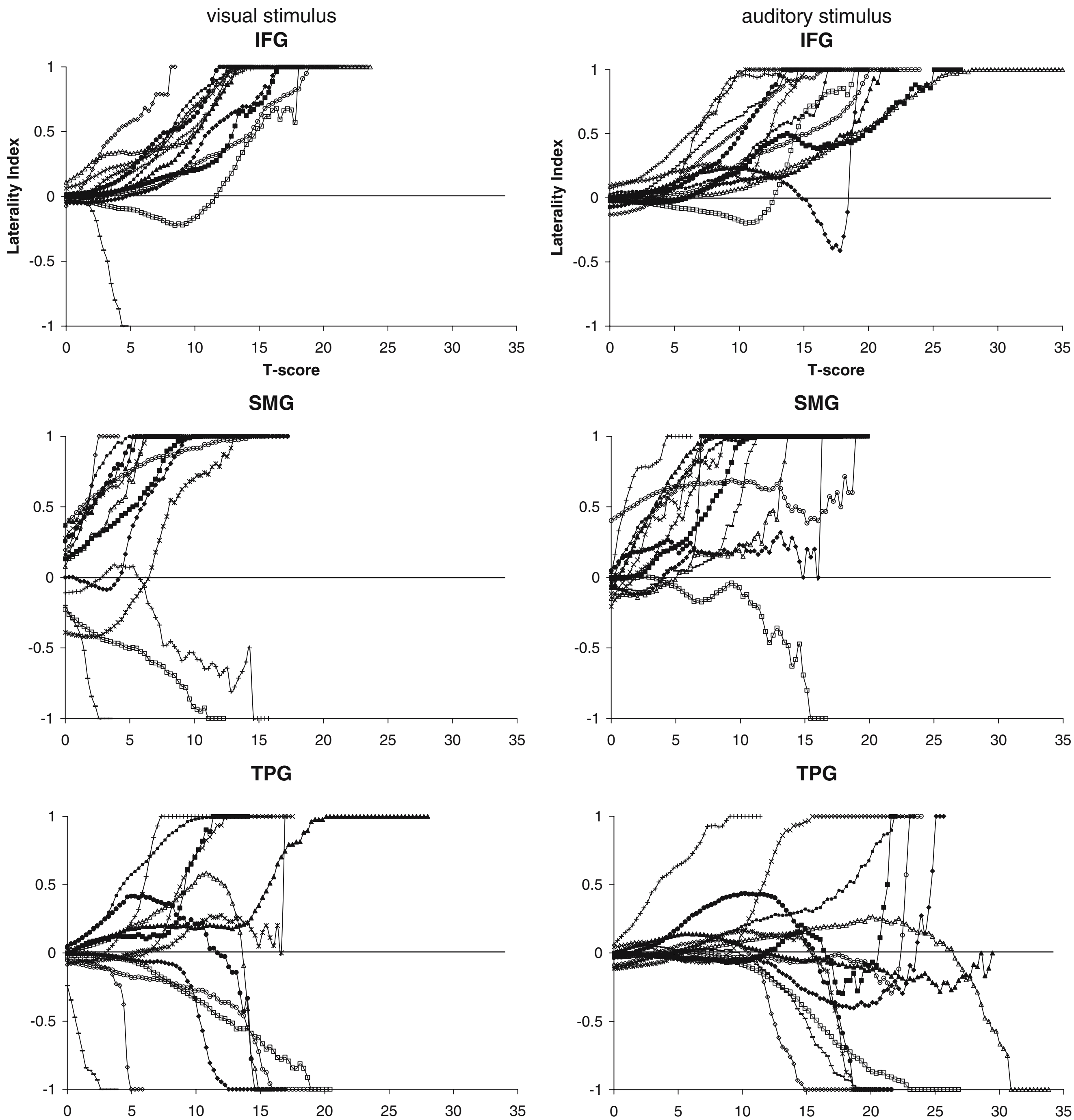

Fig. 4 For 13 subjects, the laterality indices vs fMRI threshold in the putative language ROIs: IFG, SMG, and TPG for visual (*left panels*) and auditory (*right panels*) presentation mode. Each curve represents the region-specific LI calculated at each threshold setting for an individual subject. These graphs illustrate the variability and indeterminacy seen in putative language laterality values depending on the threshold used. Positive LI values indicate leftward asymmetry and negative values indicate rightward asymmetry; curves that alternate between positive and negative values, by crossing the zero axis, are examples of reversing asymmetry indications that result in ambiguous asymmetry determination

reversing asymmetry determination. The least amount of across-subject variability was observed in IFG (Fig. 4). In IFG at a threshold range of T-score=12.5 and above, 12 of the 13 subjects tested using visual mode showed consistent leftward asymmetry across this entire range of T values, while one subject (no. 11) demonstrated a reversing asymmetry determination. Using auditory mode, all 13 subjects reached a maximum LI value of +1 in IFG, though, two subjects demonstrated reversing asymmetry determinations (subjects no. 11 and 12).

Threshold-independent laterality

In order to avoid ambiguity in LI determination resulting from threshold dependency, we used the threshold-independent method to calculate a unique LI for each ROI, and for the global hemispheric volume in each of our subjects; in this way, generating subject-specific LIs for each of the ROIs tested, that were then averaged to generate group means for comparison across ROIs. A summary of the LIs obtained for each subject is shown in Table 1.

Non-language ROIs

Group mean LIs in PCG demonstrated no asymmetry in either visual (M=0.102, SD=0.134) or auditory mode (M=0.075, SD=0.156). Mean LIs in MOG confirmed no asymmetry in either visual (M=−0.002, SD=0.181) or auditory (M=0.062, SD=0.390) mode. Group mean LIs in TTG confirmed no asymmetry in either visual (M=−0.037, SD=0.313) or auditory mode (M=0.016, SD=0.139; see Table 1).

Hemispheric

As is shown in Table 1, group mean hemispheric LIs indicated no significant asymmetry in the activation patterns measured using visual (M=0.067, SD=0.111) or auditory modes (M=0.087, SD=0.076).

Language-specific ROIs

The group mean LIs in SMG generally demonstrated laterality favoring the left hemisphere in visual (M=0.356, SD=0.487) and auditory (M=0.385, SD=0.281) modes, however, there was a relatively high degree of variability observed across subjects—SMG LIs indicated rightward asymmetry in three subjects using visual mode (subjects no. 7, 11, and 13), and in one subject (no. 11) using auditory mode, see Table 1. Group mean LI in IFG favored the left hemisphere using visual (M=0.292, SD=0.131) and auditory (M=0.234, SD=0.120) modes. One subject (no. 11) showed rightward asymmetry in IFG; this was confirmed using both stimulus modes. Mean LIs in TPG using visual mode (M=0.047, SD=0.357) and auditory mode (M=0.060, SD=0.210) both demonstrated no asymmetry.

Statistical comparisons of LIs

Figure 5 depicts a graphical comparison of the group mean LI in each of the ROI volumes tested: hemispheric, IFG, SMG, TPG, PCG, MOG, and TTG. In both stimulus mode used, ANOVA analysis revealed that mean LIs differed significantly across all the ROIs tested: [$F(5,77)=3.67$, $P<0.005$] in auditory, and [$F(5,77)=8.11$, $P<0.0001$] in visual stimulus mode.

In visual mode, hemispheric LI did not differ significantly from LI in TPG, PCG, TTG, or MOG [$t(77)=0.21$, $P=0.83$], [$t(77)=0.30$, $P=0.76$], [$t(77)=1.07$, $P=0.28$], and

Table 1 Summary of threshold-independent laterality indices using hemispheric and region-of-interest volumes

Subj.	Hemispheric		IFG		SMG		TPG		PCG		MOG	TTG
	V	A	V	A	V	A	V	A	V	A	V	A
1	**0.02**	**0.01**	0.34	0.15	0.84	0.72	0.65	0.19	0.10	−0.29	−0.02	−0.13
2	**0.02**	**0.04**	0.37	0.33	0.55	0.72	−0.11	−0.05	−0.16	−0.11	0.00	−0.17
3	**0.18**	**0.14**	0.47	0.25	0.57	0.10	0.28	0.11	0.30	0.24	0.21	0.08
4	**0.26**	**0.24**	0.38	0.21	0.67	0.34	0.24	0.23	0.17	0.16	0.22	0.31
5	**0.14**	**0.01**	0.21	0.21	0.83	0.63	−0.27	−0.03	0.04	0.01	0.06	0.11
6	**0.11**	**0.02**	0.42	0.35	0.01	0.28	0.06	0.05	0.11	0.21	0.05	0.17
7	**0.10**	**0.11**	0.33	0.41	−0.15	0.70	0.21	0.56	0.01	−0.09	0.08	0.00
8	**0.09**	**0.16**	0.25	0.15	0.61	0.45	0.17	−0.02	0.18	0.20	−0.20	0.01
9	**0.04**	**0.14**	0.29	0.19	0.68	0.67	0.27	0.01	−0.11	0.08	0.18	−0.03
10	**0.06**	**0.11**	0.28	0.19	0.62	0.23	0.28	0.25	0.19	0.09	0.10	0.08
11	**−0.10**	**−0.03**	−0.08	−0.05	−0.54	−0.10	−0.25	−0.25	0.22	0.19	−0.29	−0.12
12	**0.14**	**0.05**	0.28	0.25	0.46	0.08	−0.12	−0.12	0.23	0.15	−0.33	−0.14
13	**−0.15**	**0.13**	0.27	0.39	−0.52	0.20	−0.79	−0.14	0.05	0.16	−0.08	0.03
Mean	0.07	0.09	0.29	0.23	0.36	0.38	0.05	0.06	0.10	0.08	0.00	0.02
SD	0.11	0.08	0.13	0.12	0.49	0.28	0.36	0.21	0.13	0.16	0.18	0.14

The first column (*in bold*) indicates hemispheric LIs. Positive LI values indicate leftward asymmetry and negative values indicate rightward asymmetry.

IFG Inferior frontal gyrus, *SMG* supramarginal gyrus, *TPG* temporoparietal gyrus, *PCG* precentral gyrus, *MOG* middle occipital gyrus, *TTG* transverse temporal gyrus, *V* visual stimulus mode, *A* auditory mode

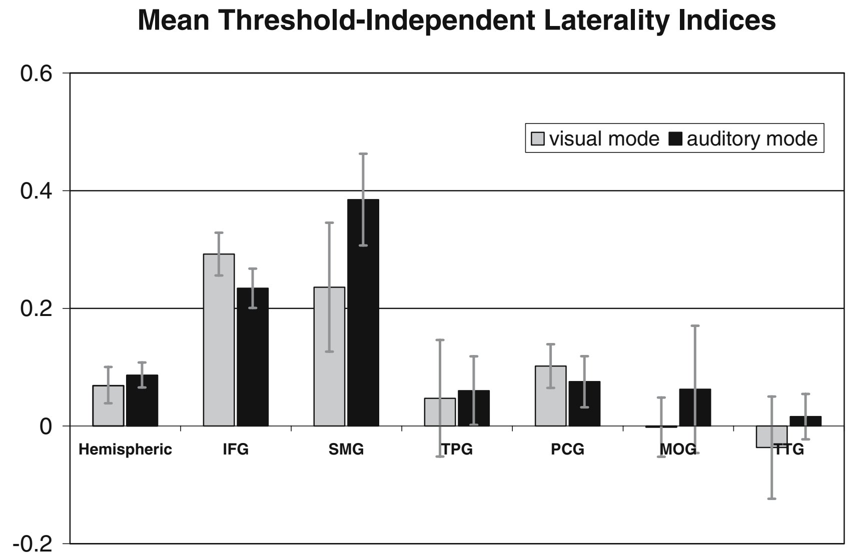

Fig. 5 Group average threshold-independent LIs (n=13) for vocalized antonym-generation using visual (*gray bars*) and auditory (*black bars*) stimulus mode. Positive LI values indicate left-dominance; negative values indicate right-dominance. Error bars represent the standard error of the mean. The average LIs are plotted for distinct region-of-interest tested shown, and for the full hemispheric volume (*dotted bars*)

[t(77)=0.67, P=0.51], respectively. However, mean LI was significantly more leftward lateralized in IFG and SMG compared to hemispheric: [t(77)=2.08, P<0.04], and [t(77)=2.68, P<0.009].

In auditory mode, as in visual mode, hemispheric LI did not differ significantly from LI in TPG, PCG, TTG, or MOG [t(77)=0.38, P=0.70], [t(77)=0.17, P=0.87], [t(77)=1.02, P=0.31], [t(77)=0.25, P=0.80], respectively. However, mean LI in IFG and SMG was significantly more leftward than hemispheric LI: [t(77)=2.12, P<0.03], and [t(77)=4.30, P<0.0001].

To assess the effect of stimulus mode on group mean LI in the putative language ROIs we compared LIs using auditory and visual stimulus mode in IFG, SMG and TPG. We found no significant differences across stimulus mode: [t(24)=1.18, P=0.25], [t(24)=0.18, P=0.81], and [t(24)=0.11, P=0.91]. However, we found that for auditory mode, LI in SMG was significantly higher than in IFG [t(24)=1.78, P<0.04]. This result contrasts with what was observed for visual mode, for which LI in SMG was not significantly different than in IFG [t(24)=1.07, P=0.29].

Discussion

Non-invasive localization and lateralization of language processing is important for presurgical planning in regions adjacent to or within critical language areas. The ideal presurgical fMRI scan should therefore be able to determine the patient's language dominance and localize critical language centers (preferably from a short duration acquisition). Our intention was to design an fMRI acquisition paradigm that would be useful for both the assessment of asymmetry, and the localization of language function. With these presurgical goals in mind, in this study we assessed language lateralization by implementing a vocalized antonym-generation paradigm that is acquired in less than 8 min.

Initially, for illustrative purposes we performed threshold-dependent laterality determination and confirmed a strong dependency between threshold setting and resulting LI, yielding an undesirable degree of within-subject variability, making the LI outcome indistinct. We addressed this issue by applying a threshold-independent method for LI determination that yields a discrete LI for each subject.

In order to assess region-specific activation asymmetry, we applied our threshold-independent methodology to six different intra-hemispheric ROIs and compared their resulting group average LIs against that derived from the whole hemispheric volume. Non-language ROIs demonstrated no asymmetric activation patterns, as was expected. However, a less expected observation was made on mean LIs from the whole hemispheric volume, which similarly indicated a lack of activation asymmetry—an outcome that is likely caused by the robust, bilateral activations resulting from motor and sensory activation. This is contrasted with the results obtained in the IFG and SMG ROIs which demonstrated significant leftward asymmetry. Thus, ROI analysis may be particularly applicable in overt language tasks.

We additionally examined the influence of stimulus presentation mode on region-specific laterality, and noted that the highest asymmetry was observed in IFG using visual mode, and in SMG using the auditory mode.

Threshold-independence in LI assessment

When using the standard threshold-dependent approach, our results have demonstrated a high degree of indeterminacy of within-subject LI values. In assessing functional asymmetry, this approach exclusively evaluates activated voxels, as defined by a cutoff threshold (Binder et al. 1996; Frost et al. 1999; Lehericy et al. 2000; Springer et al. 1999; Szaflarski et al. 2002; Yetkin et al. 1998). However, beyond picking a threshold within the statistically significant range, the method for non-subjectively choosing a cutoff setting is not clear. In Fig. 3, we highlighted the *T*-score threshold for $P<0.001$, which denotes a *T*-score of robust statistical significance; hence, any *T*-score above this would represent *P* values of increasing robustness. It is clear, however, that for all 13 of our subjects the resulting LI values did not remain constant within that range, which creates the ambiguity of where to choose a cutoff threshold for LI calculation. It is also clear that in our event-related experiment, the LI values in the $P<0.001$ range were generally of low magnitude (indicative of bi-laterality), while at more stringent *T*-scores strong asymmetries were increasingly demonstrated, making a cutoff threshold difficult to determine. Given the temporally stochastic nature inherent to event-related designs, it is reasonable to use more stringent image thresholds than would be used with more temporally ordered paradigms such as blocked designs. Therefore, if an optimal cutoff threshold exists for a given task it likely will depend strongly upon the fMRI stimulus presentation scheme used during the data acquisition—again, making the threshold choice ambiguous. Moreover, the numbers of activated voxels, at any given threshold, that ultimately characterize the LI quotient have been shown to be strikingly unstable across subjects, acquisition trials, and MR scanners (Cohen and Dubois 1999).

Alternatively, there have been a number of studies that have proposed threshold-independent approaches to voxel selection (Adcock et al. 2003; Baciu et al. 2005; Benson et al. 1999; Nagata et al. 2001; Wilke and Schmithorst 2006). Among the earlier efforts to use large distributions of voxels in LI determination was one put forward by Nagata et al. (2001), in which voxel histograms are fitted to an empirically derived reference function for comparison across the left/right cerebral hemispheres. However, given the particular histogram design used, the lowest *Z*-scores tended to dominate these distributions. Acknowledging the effect, Nagata et al. limited the distribution to a minimum *Z*-score of approximately 0.8. As such, the procedure still requires a minimally significant *Z*-score cutoff which must be subjectively selected. Additionally, in order to make the procedure more universally applicable, the reference function chosen would need to be independently validated for specific clinical cases, different ROIs, and alternative paradigms. Nevertheless, this approach established the feasibility and appeal of using larger distributions of voxels than is achievable by the standard threshold-dependent method.

As an alternative, original studies investigating laterality have instead explored specific characteristics of the fMRI signal itself as determining criteria for functional asymmetry. These methodologies sought to calculate LI without direct reference to supra-threshold activation, by instead focusing on hemispherical asymmetries in task-induced mean signal changes (Adcock et al. 2003; Benson et al. 1999), or mean signal intensities (Baciu et al. 2005). As such, these approaches require the design of objective voxel sampling schemes for the procedure of calculating mean quantities. Addressing this concern, Benson et al. equally sample all the voxels in the left and right cerebral hemispheres, selecting for laterality assessment only those having positively correlated task-induced fluctuations above a given noise threshold. This approach therefore requires an empirically defined noise level threshold, and has inherent potential of assigning equal dominance significance to voxels that may only weakly participate in the language-specific aspects of the task. Adcock et al. addressed this issue by sampling only the signal fluctuations from voxels initially deemed significantly activated and having achieved a given cluster significance, again relying on somewhat arbitrary thresholds. Similarly, Baciu et al. calculated mean signal intensities based exclusively on those voxels achieving a statistically significant activation of $P<0.05$.

Using our approach of including all positively correlated voxels in the LI calculation introduces the question of how to weight the statistical distribution. Wilke and Schmithorst (2006) addressed this matter by weighting the LI value itself by the respective threshold cutoff used to calculate it, and by this method conferred added weight to LIs calculated at higher statistical thresholds, and less to those calculated at lower thresholds. This weighting scheme assigns significance distinctly to the outcome of the LI calculation; and in doing so, weighs all supra-threshold voxels entered into the index equation equally, although individually, these voxels will invariably have higher activation values than the cutoff. We argue that it is not clear that an LI outcome should necessarily be weighted by the threshold used to determine it. What is immediately clear, however, is that distinct voxels having higher activation values should have individually greater impact within the LI calculation. For this reason, we adopted the approach of weighting voxels discretely based on their relevant *T*-score (Eq. 2), in contrast to weighting the LI outcome itself based on threshold cutoff. To this end, we redefined the quantities entered into a standard LI equation, from a direct count of supra-threshold voxels (Eq. 1) to integral sums of entire weighted distributions (Eq. 3).

In a previous work, we validated our experimental LI procedure in the assessment of presurgical laterality of memory-specific function in the hippocampus (Branco et al. 2006). For laterality analysis in hippocampal volumes, we applied voxel weighting proportionally to the respective

T-score. However, in the present study of language-specific activation in which much bigger volumes are involved, there is a higher likelihood of inadvertently including large numbers of poorly activated voxels in the ROI distribution. Therefore, in order to maximize the impact of the higher T-scored voxels, in the current study we used voxel weighting equal to the square of the respective T-score (Fig. 1). This weighting scheme gives increasingly more weight to highly activated voxels, while de-emphasizing the inclusion of greater numbers of poorly activated voxels.

Our current laterality weighting scheme is designed to reduce the contribution to LI from voxels having weak correlation values—as in for example voxels with T-scores less than 1.0, indicative of $P<0.2$—while more heavily emphasizing the contributions of voxels strongly correlated. We recognize however that other, perhaps more complex, weighting functions can be explored. While using weighted voxel distributions as determinants for LI effectively eliminates the arbitrariness of threshold setting and LI ambiguity, it nonetheless introduces a degree of arbitrariness with regards to the selection of the weighting function. Nevertheless, any weighting scheme should seek to continuously assign lower weight to insufficiently activated voxels and greater weight to robustly activated voxels.

Focused ROIs for language-specific laterality

In comparison to any of the other ROIs, or the whole hemispheric volume, our threshold-independent laterality results demonstrated leftward asymmetries only in IFG and SMG. This observation illustrates that vocalized language lateralization is measurable most effectively in the inferior frontal lobe region and the supramarginal gyrus, a finding that is supported by many years of lesion studies that place expressive language in the inferior portion of the left frontal lobe, and receptive language in the left temporoparietal regions (Baldo et al. 2006; Barbizet et al. 1975; Broca 1861; Wernicke 1874). A more unexpected result was observed in TPG, which demonstrated inconsistent laterality across subjects, although this region is widely believed to be an important receptive language center (Baldo et al. 2006; Kamada et al. 2006; Ross 1980; Wernicke 1874). While somewhat unexpected, this observation is supported by many reports documenting inconsistent laterality in the posterior temporal lobe derived by fMRI (Bahn et al. 1997; Deblaere et al. 2004; Lehericy et al. 2000; Spreer et al. 2002). However, other functional modalities such as positron emission tomography (PET) and magnetoencephalography (MEG) typically report strong leftward asymmetry of activation in this region, consistent with typically lateralized language processing (Kober et al. 2001; Muller et al. 1997; Papanicolaou et al. 1999; Shapiro et al. 2005; Simos et al. 1998; Szymanski et al. 1999). The disparity seen in temporal lobe language lateralization using fMRI compared to other functional modalities necessitates further investigation. However, our results imply that for evaluating lateralized language processing using fMRI, focusing the analysis on SMG might hold advantages over the posterior temporal lobe for detecting asymmetric activation patterns.

Stimulus delivery mode

In our assessment of stimulus mode dependency of LI we found that in comparing IFG to SMG, the use of auditory stimulus mode resulted in a significantly higher mean SMG LI compared to IFG, while the same was not true for visual stimulus mode. We also noted that SMG demonstrated less variability when auditory mode was used compared to visual (Fig. 5). This suggests that laterality measurements in SMG may be made more robust and reliable by using the auditory stimulus mode instead of the visual mode. These results are consistent with fMRI reports of increased left-sided activation in regions near the middle superior temporal sulcus, and the perisylvian areas which appear to play a role in phonemic perception (Liebenthal et al. 2005; Meyer et al. 2005; Specht and Reul 2003); the results are also supported by reports which observed specialized activation of these regions predominant in the left hemisphere that were present during auditory presentation of language stimuli, but were less robust or absent when similar language stimuli was presented visually (Booth et al. 2001, 2003, 2006; Chee et al. 1999).

Vocalized language responses

In this study, we were motivated to use an overt language task, rather than a covert one, as several studies previously demonstrated that vocalized tasks are superior to silent tasks with regards to localization precision, robustness of activation, and degree of volumetric involvement by associated functional cortex (Bookheimer et al. 1995; Huang et al. 2002; Petrovich et al. 2005; Zelkowicz et al. 1998). However, our observations in healthy, right-handed volunteers show that increased non-language activations elicited by vocalization necessitated the use of focused ROIs for the assessment of laterality.

Subject motion is often thought to be a limiting aspect of overt language studies and is the topic of several fMRI studies, some of which advocate elaborate methodologies to remove or avoid motion-related artifact in image data (Abrahams et al. 2003; Birn et al. 2004; Bullmore et al. 1999; Kemeny et al. 2005; Nelles et al. 2003). Event-related paradigms, for example, have shown significant advantages over block designs and have therefore been recommended as a method for minimizing motion-induced artifact in overt language studies (Birn et al. 1999; Haller et al. 2005; Huang et al. 2002; Palmer et al. 2001; Preibisch et al. 2003; de Zubicaray et al. 2001). In our work, we have found that carefully coaching subjects on how to generate overt responses in a way that minimizes gross head movement (by speaking with minimal tongue or jaw movement), combined with the use of event-related paradigms, is an effective method of minimizing vocalization-induced head motion and associated image artifact. An additional advantage of vocalized responses is the ability to monitor subject compliance for task performance.

Limitations

The methodologies presented in this study have not been validated by the clinical gold-standards and are presented here as an introductory investigation. It is not yet clear if these methods translate well to patient populations. The abnormal brain can present unique challenges to the procedures outlined that may pose limits to their applicability. For example, it is not yet clear if our threshold-independent approach can delineate atypical language lateralization seen in some diseased brains; BOLD responses in the vicinity of a lesion may be unpredictably affected. As such, further validations of our techniques with IAT and/or ECS are required.

Additionally, not all patients are suitable for overt language tasks: patients suffering from severe speech or neurocognitive deficits, or those having difficulty holding their head still while vocalizing, should not be considered suitable candidates.

In applying standard Human Atlas ROIs for focused LI analysis, caution must be exercised in cases of space-occupying lesions, as such abnormalities can potentially distort the anatomy such that accurate anatomical normalization becomes difficult to accomplish. In such cases, we recommend manual segmentation by a trained radiologist for precise definition of the target ROIs within the image volume. Alternatively, approaches incorporating individualized automated parcellation strategies may be particularly useful (Fischl et al. 2002; Makris et al. 2006).

Concluding recommendations

This study offers a preliminary validation based on a healthy, right-handed control group illustrating the viability of our novel approaches for objective, intra-hemispheric assessment of language-specific laterality. Based on literature demonstrating that vocalized responses offer more precise fMRI language localization, we successfully used a vocalized paradigm with our control group while avoiding excessive motion. Additionally, our results show that the non-language-specific, bilateral activations resulting from overt responses can be avoided by ROI analysis during the LI calculation.

In determining language laterality indices from fMRI activation maps, we recommend use of the objective threshold-independent method outlined in this study. Additionally, based on our lateralization findings we recommend analyzing laterality from vocalized language by focusing the LI calculation exclusively on the putative language regions as this effectively eliminates bilateral activation that result from motor-specific activation involved in vocalization. For presurgical laterality assessment in frontal lobe resection candidates, the ROI should be focused on IFG (BA44, 46, and 47); either the visual or auditory stimulus modes can be used. For temporoparietal resection candidates, the language task should be presented in auditory mode with an additional LI calculation focused on SMG (BA40).

We recommend that patient candidates be neurocognitively screened prior to vocalized language tasks in order to confirm adequate language and speech proficiency. We additionally suggest that patient overt responses from vocalized tasks be monitored during scanning to confirm satisfactory task performance.

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References

Abrahams, S., Goldstein, L. H., Simmons, A., Brammer, M. J., Williams, S. C., Giampietro, V. P., et al. (2003). Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Human Brain Mapping*, *20*(1), 29–40 (Sep).

Adcock, J. E., Wise, R. G., Oxbury, J. M., Oxbury, S. M., & Matthews, P. M. (2003). Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. *Neuroimage*, *18*(2), 423–38 (Feb).

Ammerman, J. M., Caputy, A. J., & Potolicchio, S. J. (2005). Endovascular ablation of a temporal lobe epileptogenic focus-a complication of Wada testing. *Acta Neurologica Scandinavica*, *112*(3), 189–91 (Sep).

Angrilli, A., Elbert, T., Cusumano, S., Stegagno, L., & Rockstroh, B. (2003). Temporal dynamics of linguistic processes are reorganized in aphasics" cortex: An EEG mapping study. *Neuroimage*, *20*(2), 657–66 (Oct).

Baciu, M. V., Watson, J. M., Maccotta, L., McDermott, K. B., Buckner, R. L., Gilliam, F. G., et al. (2005). Evaluating functional MRI procedures for assessing hemispheric language dominance in neurosurgical patients. *Neuroradiology*, *47*(11), 835–44 (Nov).

Bahn, M. M., Lin, W., Silbergeld, D. L., Miller, J. W., Kuppusamy, K., Cook, R. J., et al. (1997). Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. *American Journal of Roentgenology*, *169* (2), 575–579 (Aug).

Baldo, J. V., Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society*, *12*(6), 896–900 (Nov).

Barbizet, J., Duizabo, P., & Flavigny, R. (1975). [Role of the frontal lobes in language. (A neuropsychological and experimental study)]. *Revista de Neurología* (Paris), *131*(8), 525–544 (Aug).

Benson, R. R., FitzGerald, D. B., LeSueur, L. L., Kennedy, D. N., Kwong, K. K., Buchbinder, B. R., et al. (1999). Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology*, *1052*(4), 798–809 (Mar).

Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M., & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *Journal of Neuroscience*, *17*(1), 353–62 (Jan 1).

Binder, J. R., Swanson, S. J., Hammeke, T. A., Morris, G. L., Mueller, W. M., Fischer, M., et al. (1996). Determination of language dominance using functional MRI: A comparison with the Wada test. *Neurology*, *46*(4), 978–84 (Apr).

Birn, R. M., Bandettini, P. A., Cox, R. W., & Shaker, R. (1999). Event-related fMRI of tasks involving brief motion. *Human Brain Mapping*, *7*(2), 106–114.

Birn, R. M., Cox, R. W., & Bandettini, P. A. (2004). Experimental designs and processing strategies for fMRI studies involving overt verbal responses. *Neuroimage*, *23*(3), 1046–58 (Nov).

Boatman, D., Freeman, J., Vining, E., Pulsifer, M., Miglioretti, D., Minahan, R., et al. (1999). Language recovery after left hemispherectomy in children with late-onset seizures. *Annals of Neurology*, *46*(4), 579–86 (Oct).

Bookheimer, S. Y., Zeffiro, T. A., Blaxton, T., Gaillard, W., & Theodore, W. (1995). Regional cerebral blood flow during object naming and word reading. *Human Brain Mapping*, *3*, 93–106.

Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Choy, J., Gitelman, D. R., et al. (2003). Modality-specific and -independent developmental differences in the neural substrate for lexical processing. *Journal of Neurolinguistics*, *16*(4–5), 383–405.

Booth, J. R., Burman, D. D., Van Santen, F. W., Harasaki, Y., Gitelman, D. R., Parrish, T. B., et al. (2001). The development of specialized brain systems in reading and oral-language. *Child Neuropsychology*, *7*(3), 119–41 (Sep).

Booth, J. R., Lu, D., Burman, D. D., Chou, T. L., Jin, Z., Peng, D. L., et al. (2006). Specialization of phonological and semantic processing in Chinese word reading. *Brain Research*, *1071*(1), 197–207 (Feb 3).

Borowsky, R., Owen, W. J., Wile, T. L., Friesen, C. K., Martin, J. L., & Sarty, G. E. (2005). Neuroimaging of language processes: fMRI of silent and overt lexical processing and the promise of multiple process imaging in single brain studies. *Canadian Association of Radiologists Journal*, *56*(4), 204–13 (Oct).

Branco, D. M., Suarez, R. O., Whalen, S., O'Shea, J. P., Nelson, A. P., da Costa, J. C., et al. (2006). Functional MRI of memory in the hippocampus: Laterality indices may be more meaningful if calculated from whole voxel distributions. *Neuroimage*, *1532*(2), 592–602 (Aug).

Breier, J. I., Simos, P. G., Zouridakis, G., Wheless, J. W., Willmore, L. J., Constatinou, J. E., et al. (1999). Language dominance determined by magnetic source imaging: a comparison with the Wada procedure. *Neurology*, *53*(5), 938–945 (Sep 22).

Broca, P. P. (1861). Perte de la parole ramolissement chronique et destruction partielle du lobe antérieur gauche de cerveau. *Bulletins de la Société d'anthropologie de Paris*, *2*, 235–238.

Bryden, M. P., Hecaen, H., & DeAgostini, M. (1983). Pattern of cerebral organization. *Brain and Language*, 20, 249–262.

Bullmore, E. T., Brammer, M. J., Rabe-Hesketh, S., Curtis, V. A., Morris, R. G., Williams, S. C., et al. (1999). Methods for diagnosis and treatment of stimulus-correlated motion in generic brain activation studies using fMRI. *Human Brain Mapping*, *7* (1), 38–48.

Chee, M. W., O'Craven, K. M., Bergida, R., Rosen, B. R., & Savoy, R. L. (1999). Auditory and visual word processing studied with fMRI. *Human Brain Mapping*, *7*(1), 15–28.

Cohen, M. S., & DuBois, R. M. (1999). Stability, repeatability, and the expression of signal magnitude in functional magnetic resonance imaging. *Journal of Magnetic Resonance Imaging*, *10*(1), 33–40 (Jul).

de Zubicaray, G. I., Wilson, S. J., McMahon, K. L., & Muthiah, S. (2001). The semantic interference effect in the picture-word paradigm: An event-related fMRI study employing overt responses. *Human Brain Mapping*, *14*(4), 218–27 (Dec).

Deblaere, K., Boon, P. A., Vandemaele, P., Tieleman, A., Vonck, K., Vingerhoets, G., et al. (2004). MRI language dominance assessment in epilepsy patients at 1.0 T: Region of interest analysis and comparison with intracarotid amytal testing. *Neuroradiology*, *46*(6), 413–20 (Jun).

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., et al. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–55 (Jan 31).

Friston, K., Fletcher, P., Josephs, O., Holmes, A., Rugg, M., & Turner, R. (1998). Event-related fMRI: Characterizing differential responses. *Neuroimage*, *7*, 30–40.

Frost, J. A., Binder, J. R., Springer, J. A., Hammeke, T. A., Bellgowan, P. S., Rao, S. M., et al. (1999). Language processing is strongly left lateralized in both sexes. Evidence from functional MRI. *Brain*, *122*(Pt 2), 199–208 (Feb).

Goldmann, R. E., & Golby, A. J. (2005). Atypical language representation in epilepsy: Implications for injury-induced reorganization of brain function. *Epilepsy & Behavior*, *6*(4), 473–487 (Review, Jun).

Haller, S., Radue, E. W., Erb, M., Grodd, W., & Kircher, T. (2005). Overt sentence production in event-related fMRI. *Neuropsychologia*, *43* (5), 807–814.

Hertz-Pannier, L., Chiron, C., Jambaque, I., Renaux-Kieffer, V., Van de Moortele, P. F., Delalande, O., et al. (2002). Late plasticity for language in a child's non-dominant hemisphere: A pre- and post-surgery fMRI study. *Brain*, *125*(Pt 2), 361–372 (Feb).

Hillis, A. E., & Caramazza, A. (1991). Category-specific naming and comprehension impairment: A double dissociation. *Brain*, *114*(Pt 5), 2081–2094 (Oct).

Howard, D., Patterson, K., Wise, R., Brown, W. D., Friston, K., Weiller, C., et al. (1992). The cortical localization of the lexicons. Positron emission tomography evidence. *Brain*, *115*(Pt 6), 1769–1782 (Dec).

Huang, J., Carr, T. H., & Cao, Y. (2002). Comparing cortical activations for silent and overt speech using event-related fMRI. *Human Brain Mapping*, *15*(1), 39–53 (Jan).

Janszky, J., Jokeit, H., Heinemann, D., Schulz, R., Woermann, F. G., & Ebner, A. (2003). Epileptic activity influences the speech organization in medial temporal lobe epilepsy. *Brain*, *126*(Pt 9), 2043–2051 (Sep).

Kamada, K., Takeuchi, F., Kuriki, S., Todo, T., Morita, A., & Sawamura, Y. (2006). Dissociated expressive and receptive language functions on magnetoencephalography, functional magnetic resonance imaging, and amobarbital studies. Case report and review of the literature. *Journal of Neurosurgery*, *104*(4), 598–607 (Apr).

Kemeny, S., Ye, F. Q., Birn, R., & Braun, A. R. (2005). Comparison of continuous overt speech fMRI using BOLD and arterial spin labeling. *Human Brain Mapping*, *24*(3), 173–183 (Mar).

Kober, H., Moller, M., Nimsky, C., Vieth, J., Fahlbusch, R., & Ganslandt, O. (2001). New approach to localize speech relevant brain areas and hemispheric dominance using spatially filtered magnetoencephalography. *Human Brain Mapping*, *14*(4), 236–250 (Dec).

Lancaster, J. L., Summerln, J. L., Rainey, L., Freitas, C. S., & Fox, P. T. (1997). The Talairach Daemon, a database server for Talairach atlas labels. *Neuroimage*, *5*, S633.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, *10*(3), 120–131 (Jul).

Lehericy, S., Cohen, L., Bazin, B., Samson, S., Giacomini, E., Rougetet, R., et al. (2000). Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology*, *54*, 1625–1633.

Levy, J. (1974). Psychobiological implications of bilateral asymmetry. In *Hemisphere function in the human brain*. New York: Wiley.

Liebenthal, E., Binder, J. R., Spitzer, S. M., Possing, E. T., & Medler, D. A. (2005). Neural substrates of phonemic perception. *Cerebral Cortex*, *15*(10), 1621–1631 (Oct).

Makris, N., Kaiser, J., Haselgrove, C., Seidman, L. J., Biederman, J., Boriel, D., et al. (2006). Human cerebral cortex: A system for the integration of volume- and surface-based representations. *Neuroimage*, *33*(1), 139–153 (Oct 15).

Maldjian, J. A., Laurienti, P. J., & Burdette, J. H. (2004). Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage*, *21*(1), 450–455 (Jan).

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*, *19*(3), 1233–1239 (Jul).

Meyer, M., Zysset, S., von Cramon, D. Y., & Alter, K. (2005). Distinct fMRI responses to laughter, speech, and sounds along the human peri-sylvian cortex. *Brain Research Cognitive Brain Research*, *24*(2), 291–306 (Jul).

Muller, R. A., Rothermel, R. D., Behen, M. E., Muzik, O., Mangner, T. J., & Chugani, H. T. (1997). Receptive and expressive language activations for sentences: A PET study. *Neuroreport*, *18*(17), 3767–3770 (Dec).

Nagata, S. I., Uchimura, K., Hirakawa, W., & Kuratsu, J. I. (2001). Method for quantitatively evaluating the lateralization of linguistic function using functional MR imaging. *AJNR American Journal of Neuroradiology*, *22*(5), 985–991 (May).

Nelles, J. L., Lugar, H. M., Coalson, R. S., Miezin, F. M., Petersen, S. E., & Schlaggar, B. L. (2003). Automated method for extracting response latencies of subject vocalizations in event-related fMRI experiments. *Neuroimage*, *20*(3), 1865–1871 (Nov).

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113 (Mar).

Palmer, E. D., Rosen, H. J., Ojemann, J. G., Buckner, R. L., Kelley, W. M., & Petersen, S. E. (2001). An event-related fMRI study of overt and covert word stem completion. *Neuroimage*, *14*(1 Pt 1), 182–193 (Jul).

Papanicolaou, A. C., Simos, P. G., Breier, J. I., Zouridakis, G., Willmore, L. J., Wheless, J. W., et al. (1999). Magnetoencephalographic mapping of the language-specific cortex. *Journal of Neurosurgery*, *90*(1), 85–93 (Jan).

Pataraia, E., Simos, P. G., Castillo, E. M., Billingsley-Marshall, R. L., McGregor, A. L., Breier, J. I., et al. (2004). Reorganization of language-specific cortex in patients with lesions or mesial temporal epilepsy. *Neurology*, *2363*(10), 1825–1832 (Nov).

Petrovich, N., Holodny, A. I., Tabar, V., Correa, D. D., Hirsch, J., Gutin, P. H., et al. (2005). Discordance between functional magnetic resonance imaging during silent speech tasks and intraoperative speech arrest. *Journal of Neurosurgery*, *103*(2), 267–274 (Aug).

Preibisch, C., Raab, P., Neumann, K., Euler, H. A., von Gudenberg, A. W., Gall, V., et al. (2003). Event-related fMRI for the suppression of speech-associated artifacts in stuttering. *Neuroimage*, *19*(3), 1076–1084 (Jul).

Rasmussen, T., & Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences*, *30299*, 355–369 (Sep).

Ross, E. D. (1980). Left medial parietal lobe and receptive language functions: Mixed transcortical aphasia after left anterior cerebral artery infarction. *Neurology*, *30*(2), 144–151 (Feb).

Shapiro, K. A., Mottaghy, F. M., Schiller, N. O., Poeppel, T. D., Fluss, M. O., Muller, H. W., et al. (2005). Dissociating neural correlates for nouns and verbs. *Neuroimage*, *1524*(4), 1058–1067 (Feb).

Shuster, L. I., & Lemieux, S. K. (2005). An fMRI investigation of covertly and overtly produced mono- and multisyllabic words. *Brain and Language*, *93*(1), 20–31 (Apr).

Simos, P. G., Breier, J. I., Zouridakis, G., & Papanicolaou, A. C. (1998). Assessment of functional cerebral laterality for language using magnetoencephalography. *Journal of Clinical Neurophysiology*, *15*(4), 364–372 (Jul).

Specht, K., & Reul, J. (2003). Functional segregation of the temporal lobes into highly differentiated subsystems for auditory perception: An auditory rapid event-related fMRI-task. *Neuroimage*, *20* (4), 1944–1954 (Dec).

Spreer, J., Arnold, S., Quiske, A., Wohlfarth, R., Ziyeh, S., Altenmuller, D., et al. (2002). Determination of hemisphere dominance for language: Comparison of frontal and temporal fMRI activation with intracarotid amytal testing. *Neuroradiology*, *44*(6), 467–474 (Jun).

Springer, J. A., Binder, J. R., Hammeke, T. A., Swanson, S. J., Frost, J. A., Bellgowan, P. S., et al. (1999). Language dominance in neurologically normal and epilepsy subjects: A functional MRI study. *Brain*, *122*(Pt 11), 2033–2046 (Nov).

Szaflarski, J. P., Binder, J. R., Possing, E. T., McKiernan, K. A., Ward, B. D., & Hammeke, T. A. (2002). Language lateralization in left-handed and ambidextrous people: fMRI data. *Neurology*, *2359* (2), 238–244 (Jul).

Szymanski, M. D., Rowley, H. A., & Roberts, T. P. (1999). A hemispherically asymmetrical MEG response to vowels. *Neuroreport*, *2010*(12), 2481–2486 (Aug).

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotactic atlas of the human brain*. Stuttgart: Thieme.

Vikingstad, E. M., George, K. P., Johnson, A. F., & Cao, Y. (2000). Cortical language lateralization in right handed normal subjects using functional magnetic resonance imaging. *Journal of the Neurological Sciences*, *175*(1), 17–27 (Apr 1).

Wada, J., & Rasmussen, T. (1960). Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. *Journal of Neurosurgery*, *17*, 266–282.

Wernicke, K. (1874). Der aphasische Symptomencomplex. Eine psychologische Studie auf anatomischer Basis. Breslau: M. Crohn und Weigert.

Wilke, M., & Schmithorst, V. J. (2006). A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. *Neuroimage*, *133*(2), 522–530 (Nov).

Yetkin, F. Z., Swanson, S., Fischer, M., Akansel, G., Morris, G., Mueller, W., et al. (1998). Functional MR of frontal lobe activation: Comparison with Wada language results. *AJNR American Journal of Neuroradiology*, *19*(6), 1095–1098 (Jun–Jul).

Zelkowicz, B. J., Herbster, A. N., Nebes, R. D., Mintun, M. A., & Becker, J. T. (1998). An examination of regional cerebral blood flow during object naming tasks. *Journal of the International Neuropsychological Society*, *4*(2), 160–166 (Mar).