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Functional neuroimaging with MEG: Normative language profiles

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The reliability of language-specific brain activation profiles was assessed using Magnetoencephalography (MEG) in five experiments involving ninety-seven normal volunteers of both genders ranging in age from seven to eighty-four years. MEG data were analyzed with a fully automated method to eliminate subjective judgments in the process of deriving the activation profiles. Across all experiments, profiles were characterized by significant bilateral activity centered in the superior temporal gyrus, and in activity lateralized to the left middle temporal gyrus. These features were invariant across age, gender, variation in task characteristics, and mode of stimulus presentation. The absolute amount of activation, however, did decline with age in the auditory tasks. Moreover, contrary to the commonly held belief that left hemisphere dominance for language is greater in men than in women, our data revealed an opposite albeit a not consistently significant trend. © 2006 Elsevier Inc. All rights reserved.

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Introduction

In a series of studies (Breier et al., 2001, 2005; Papanicolaou et al., 2004; Simos et al., 1998, 1999; Castillo et al., 2001) we established the efficacy of Magnetoencephalography (MEG) in assessing hemispheric dominance for receptive language and in defining the borders of Wernicke's area in individual patients. In both cases we used a simple evoked response paradigm whereby single words are presented and the Evoked Magnetic Fields (EMFs) to these words are recorded and averaged. The sources of that evoked activity are then assessed with iterative application of the single dipole model (Sarvas, 1987; see also Papanicolaou, 1998). Given the nature of the referral questions in those studies, we focused attention on the left and right perisylvian regions, to the

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exclusion of other brain areas. In the experiments reported here, we explored the entire cortical surface by using a completely automated analysis procedure for deriving brain activation profiles in an extensive sample of participants of both genders who performed receptive language tasks. The establishment of such normative profiles allowed us to address additional questions, namely, whether there are recognizable variations in activation profiles in terms of degree of activation, laterality, or latency of activation of particular brain regions, contingent on variations in the language tasks used, the modality of the stimuli, or the age and gender of the participants. With respect to gender differences we were able to address the claim that the brain mechanisms supporting language are less strongly lateralized in women than in men (e.g., McGlone, 1977, 1978; Lukatela et al., 1986; Kimura, 1987, 1992; Crossman and Polich, 1988; Zaidel et al., 1995; Shaywitz et al., 1998); this claim, however, has not always been supported by data (e.g., Buckner et al., 1995; Price et al., 1996; Frost et al., 1999).

The first two experiments in this series involved adult subjects. In both experiments we examined activation profiles for receptive language during the performance of an auditory word recognition task. The experiments differed, however, in one feature of the task, namely in the ratio of target words to distractors, and in the average age of the participants. The last three experiments included child participants only. These additional experiments allowed us to determine whether further changes in the task, namely the use of pseudoword stimuli and mode of presentation (i.e. visual and aural), as well as age and gender affected the language-specific brain activation profiles.

General methods

MEG as a functional brain imaging method

In view of the fact that there are no standard MEG recording and analysis procedures, we provide here a brief, general overview of the method as we have used it in these and in our previous studies. The interested reader may find a more detailed description of the method in Papanicolaou et al. (1999). MEG measures

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neurophysiological activity in the form of magnetic flux generated by intracellular electrical currents in large neuronal aggregates. Imaging of the intracranial sources of that activity involves multiple steps: Stimuli, whether somatosensory, visual, auditory, simple or complex (e.g. linguistic), evoke brain activity soon after they impinge on sensory receptors. One basic aspect of that activity is the intracellular flow of ions, which generates electrical currents and magnetic fields. Repetitive application of a given stimulus results in repeated evocation of the same currents and fields which, when recorded on the head surface and averaged, result in eventrelated potentials (ERPs) and their magnetic counterparts, evoked magnetic fields (EMFs). The distribution of EMFs on the head surface lends itself, much more readily than the distribution of ERPs, to mathematical estimates of the location and extent of activation of the sets of brain cells that produced them.

EMFs, much like ERPs, are waveforms representing variations of brain activity over time, following the onset of an external stimulus. Early portions of the EMF waveform (i.e., up to 150 ms after stimulus onset) most likely reflect neurophysiological activity in primary sensory areas. Conversely, later portions of the EMF waveform are primarily generated by activity in association areas, namely those that are part of the brain mechanism that processes the stimuli beyond the sensory stage; that is, the mechanism of a cognitive or linguistic function, the nature of which depends on the type of stimuli and, more importantly, on task instructions.

As part of the MEG language-mapping procedures in the present studies, subjects were exposed to a series of auditory or visual word stimuli. Each word produced an EMF record, in each point of the head surface monitored by each of the 248 channels of the neuromagnetometer system. The EMF records at each point of the head surface, associated with consecutive word stimuli, were then averaged together. To identify the brain areas producing the averaged EMF's, the intracranial sources that may have accounted for their amplitude at successive points during their temporal unfolding (typically every 4 ms) were modeled as equivalent current dipoles embedded in a spherical conductor (see details below). The location estimates of each "dipolar" source were specified with reference to a Cartesian coordinate system, anchored on three fiducial points on the head (the nasion and the external meatus of each ear). The same fiducial points were marked on the participant's MRI, thus enabling precise registration of the location of each dipolar source. The estimated sources, thus projected onto the structural image of the brain, circumscribe the brain areas that generated the recorded EMFs, that is, the areas most likely responsible for processing the word stimuli, or the areas that are part of the brain mechanism of the receptive language function.

Participants

Ninety-seven participants (45 males; 52 females) ranging in age between 7 and 84 years participated in five experiments. Mean ages for each experiment are reported below. All participants were free of neurological and psychiatric disorders, and were paid for their participation. A subset of participants also volunteered for a structural MRI scan which was used for co-registering the MEGderived activity profile, as detailed below.

Tasks

The experiments involved a number of different linguistic tasks. Detailed descriptions of these tasks are given below, but several features shared by all tasks and are summarized here: All tasks involved the use of an Apple Macintosh Powerbook computer running Superlab Pro (version 1.76) for stimulus control. In tasks that required a yes or no response, participants were instructed to lift their index finger for a positive response and do nothing for a negative response. The responding hand was counterbalanced across participants within each experimental task. All auditory stimuli (Experiments 1–3) were delivered binaurally through two 5-m-long plastic tubes terminating in ear inserts at an intensity of 80 dB SPL at the participant's outer ear. Visual stimuli (Experiments 4 and 5) were projected through an LCD projector onto a white screen located about 0.5 m in front of the participant and subtending 1.0–4.0 and 0.5 degrees of horizontal and vertical visual angle, respectively.

In the auditory word recognition task (Experiments 1–3), participants heard target words before the MEG recording session began, and were instructed to remember them so as to identify them when they appeared with new, distractor words during the MEG recording session. During MEG recordings, the participants heard, one word at a time, all the target words as well distractor words mixed randomly. The ratio of target to distractor items varied across experiments (see specific methods below). The auditory word stimuli were produced by a native English speaker with a flat intonation (duration between 300 and 750 ms; mean 450 ms). Recordings of these words were then digitized with a sampling rate of 22,000 Hz and 16-bit resolution, and stored on the same Powerbook computer used for stimulus presentation.

The visual word recognition and the "pseudoword" task (Experiments 4 and 5) involved presentation of visual stimuli. The visual word recognition task (Experiment 4) was nearly identical to the aural word recognition tasks (Experiments 1–3). The pseudoword task involved reading of projected pronounceable letter strings. Procedural details for each experiment are given in the next section below (Methodological details of each experiment).

MEG data acquisition and reduction

All participants were tested with a whole-head neuromagnetometer (4D Neuroimaging, San Diego, CA.) equipped with 248 gradiometer sensors and housed in a magnetically shielded room designed to reduce environmental magnetic noise. The recording sessions required the participants to lie as still as possible, on a bed with their head inside the helmet-like device for approximately 15 min for each experimental session. The recorded signals were filtered online with a band pass between 0.1 and 20 Hz, and digitized at a rate of 254 Hz. The records were then submitted to a series of computer routines which accomplished the tasks of artifact rejection, averaging, accounting for the sources of activity, and profile construction, as follows: First, those MEG channels presenting random drift beyond the acceptable range (correlation with adjacent channels ≤ 0.6) were identified and these channels were excluded from further processing. Second, epochs were inspected, and those containing artifacts (peak-to-peak deflections ≥ 2 pT) were excluded from further analysis. Third, artifact-free epochs in each channel were averaged. The averaged data were then submitted automatically to another set of procedures which scanned the averaged digitized EMF's; identified at each point in time (every 4 ms) the presence of single dipolar distributions; estimated the channel grouping that best covered each such distribution and used the portion of

the flux distribution covered by such channel groupings to estimate the underlying dipolar source. In this paper we introduce for the first time this routine for Automatic Channel Group Selection (ACGSTM) which constitutes the core of the automated analysis program. This routine first determines (at a given latency) the appropriate channel grouping by calculating the planar gradients of the field map from the measured data for each channel using the channel and its nearest neighbors. For purposes of choosing the channel groups, the gradient could be calculated for either a single latency of the data or the average gradient over a range of latencies, which could be chosen based on the underlying characteristic of the signal being analyzed. In general, sources are located below the maxima of the planar gradients of the field. Center channels of the channel groups were selected based on the local maxima of the calculated gradient pattern. Up to five were selected at each time point, or EMF latency. Any maxima that were less that 10% of the strongest maxima were rejected.

Once a maximum in the planar field was found its width was estimated by fitting it to a Gaussian function. This was a fit of the 'hill' in the planar gradient distribution that was calculated from the fields measured. The size of the Gaussian parameter (typically labeled sigma) was a rough estimate of the width of this 'hill', or maximum. All of this estimation was done in a two-dimensional plane corresponding to a local flattening of the array around the maximum. This width of the maximum was then compared to widths of maxima calculated in the same way from field patterns generated from a single dipole forward model. Based on this comparison the extent of the channel group was inferred. This was done by a linear fit of the width versus channel group extent from the simulated data. The range between a minimal and maximal diameter was enforced simply by clipping this estimating function.

This adjustment was limited such that the radius of the resulting channel-group was always greater than 7 cm and less than 9.5 cm. From this comparison the extent of the channel-group was determined. Finally, to help reject maxima that would often occur near the edge of the array due to edge effects, the resulting channel group was inspected to make sure it extended across a zero line in the filed data. If either the number channels having positive or negative field values was less than 10% of the total number of channels, then the group was rejected.

Next, the single dipoles that accounted for surface dipolar maps were derived using the standard model (Sarvas, 1987) and the entire procedure was repeated at successive latency points until the entire EMF duration was exhausted. Finally, those dipolar sources that met our criteria of acceptability (Correlation ≥ 0.9 , Confidence volume $\leq 20 \text{ cm}^3$) were selected for constructing the activation profiles or maps through co-registration with normalized structural MRI's involving the following steps:

Dipolar sources that were automatically computed with reference to the MEG Cartesian coordinate system mentioned above were coregistered on T1-weighted, magnetic resonance (MR) images (TR 13.6 ms; TE 4.8 ms; recording matrix 256×256 pixels, 1 excitation, 240 mm field of view, and 1.4 mm slice thickness) obtained from a subset of the participants. For those participants that did not volunteer for an MRI scan we used the MRIs of others on the basis of similarity in their digitized head shape files. Transformation of the MEG

coordinate system into MRI-defined space was achieved with the aid of three lipid capsules inserted into the ear canals and attached to the nasion, which could be easily visualized on the MRIs, using the MR Overlay tool which is part of the 4-D Neuroimaging software.

To allow comparison and averaging of results across subjects, activity source locations were transformed into MNI-standard (Montreal Neurological Institute) coordinate space. After registration of the subject's MEG data with the MRI, MEG-coordinate locations were determined for three reference points: the Anterior Commissure (AC), Posterior Commissure (PC), and a point in the Falx Cerebri (F). In conjunction with brain dimensions measured along a set of axes parallel to the AC–PC line, these reference points were used to translate, rotate, and scale activity source locations into universal coordinates.

Spatially normalized activity sources were then averaged across subjects within a given experimental condition and sorted into 41 Regions of Interest (ROIs) defined within the MNI synthetic brain, with no overlap between ROIs. Regions were based on the Anatomical Automatic Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and Brodmann areas. The list of all ROIs and a description of each is included in the Appendix. Some of the regions thus defined were excluded from consideration because localization of dipoles in them was deemed either clearly inaccurate (as in regions including white matter, or the ventricles) or extremely likely inaccurate (as in the cerebellum or the basal ganglia). Consequently, the rest of the ROIs considered were only those that covered cortical areas.

It should be noted that the occasional use of head shape files of subjects who did not undergo structural MR scanning, to guide selection of similar size and shape MR scans with which to coregister their MEG activity, as well as the use of average activation maps across subjects, constructed on the basis of MNI-normalized data, places restrictions on all localization claims made in this series of studies: Specifically, localization of task-specific activation is an estimate that applies to the subject group and not to individual subjects.

Data analysis

In all experiments the sources that were deemed reliable (on the basis of the criteria detailed above) were divided into early and late



Fig. 1. A set of auditory and a set of visual EMFs from two subjects demonstrating the division of the brain response into the early and late components. Each figure contains responses recorded overall 248 MEG channels.

corresponding to the early, sensory (50–150 ms post-stimulus onset) and late, putative cognitive components of the EMFs (>150 ms post-stimulus onset). The rationale for such a division is rendered obvious in Fig. 1. Specifically, 150 ms marks the end of the first major component of both auditory and visual EMFs and there are many indications that the sources of these early components are found almost exclusively in primary auditory and primary visual cortex, respectively (Nakasato et al., 1995; Pantev et al., 1995; Papanicolaou et al., 1990; Reite et al., 1994; Seki et al., 1996).

The number of early and late activity sources that fell within each ROI provided a measure of that region's involvement in the processing of the word (and pseudoword) stimuli and provided an outline of the task-specific activation profiles. Those included some cortical areas that were consistently active, and others that showed minimally consistent or inconsistent activity (see Results below). We excluded the later and based all further analyses on data from the consistently active areas only.

Methodological details of each experiment

Experiment 1

Participants

Twenty-four volunteers, 19 male and 15 female aged 18 to 84 years (M=48.08, SD=19.97) participated in the study. All were right-handed, as determined by the Edinburgh Handedness Questionnaire (Oldfield, 1971).

Task

Participants were given the auditory word recognition task described above. The word list consisted of 165 English words, including nouns, adjectives and verbs, which were one or two syllables in length. Five words were used as targets and the remaining 160 as distractors in each list. Four blocks of 45 trials each were created with the five targets presented in random order among 40 new distractors in each block for a total of 180 trials. Seven of the 24 participants had been given a 160-trial version of the paradigm with 35 distractors and 5 targets in each block. Their data were retained in this study as there was no relation between age and version given (p > 0.7), and there was no difference in the signal-to-noise ratio between the two groups (p > 0.9).

The target stimuli were presented for study immediately prior to the MEG recording session until the participants managed to accurately repeat all five targets. Stimulus presentation parameters were identical during the actual recording and study sessions. Stimuli were presented with a variable interstimulus interval (2.5– 3.5 s). Participants were asked to lift their index finger whenever they detected a target word. The responding hand was varied randomly across participants. The experiment was repeated at a later time in order to assess replicability of the results. Data from each replication were first analyzed separately, compared, and, once replicability was ascertained, were merged for subsequent comparisons (see Results below).

Experiment 2

Participants

Fifteen healthy adults, 5 males and 10 females, participated. The mean age was 33.4 years (age range of 22-55 years), with an average of 18.2 years of education. All but two were righthanded. Each received \$50 for his or her participation.

Task

Participants were given the same recognition memory task as in the previous experiment, with the following modifications: The word list consisted of 90 abstract English nouns with scores of 3 or lower on the Paivio Concreteness Scale (Paivio et al., 1968). Word frequency ranged from very frequent (scored AA) to nine occurrences per million for some words. Thirty words from each list were used as targets and the remaining 60 as distractors. comprising six blocks of 240 trials in total. The target stimuli were repeated in every block (in a different random order each time) and were mixed with 10 new distractors. The target stimuli were presented for study once immediately prior to the MEG recording session. There was no significant difference between the concreteness of frequency means for target and distractor word lists. Stimulus presentation parameters were identical during the actual MEG recording and the study session. Stimuli were presented with a variable interstimulus interval (2.5-3.5 s).

Experiment 3

Participants

Twenty-three children volunteers, 11 males and 12 females, aged 8 to 13 years (M=10.35, SD=1.61) participated. All participants were right-handed as determined by the Edinburgh Handedness Questionnaire (Oldfield, 1971). None of the participants had a history of neurological disorder or other medical problems that might potentially affect participation in the study. All participants had an estimated IQ over 80 as determined by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

Task

Participants were given the recognition memory task for spoken words described above and EMFs were recorded to each word stimulus. Two versions of the task were used – the difference between the tasks being that the younger children had 5 target words to remember mixed with 35 distractors and three blocks were presented (120 trials). Older children had 15 targets to identify, mixed with 5 unique distractors per block and six blocks were presented (120 trials). The word lists consisted of words with scores of 3.0 or lower on the Paivio Concreteness scale (Paivio et al., 1968). Word frequency ranged from "very frequent" (AA) to 9 occurrences per million for some words. Other parameters were identical to those used in Experiment 2.

Experiment 4

Participants

Fifty-two healthy children, 27 male and 22 female, aged 7 to 13 years (M=9.98, SD=1.6) participated in the study. All were righthanded as determined by the Edinburgh Handedness Questionnaire (Oldfield, 1971) and had an estimated IQ over 80 as determined by the WASI (Wechsler, 1999).

Task

Children first viewed the target words and were instructed to remember to identify them during the MEG recording session. The stimuli presented during that session consisted of the target and

distractor items mixed randomly. Each word had a frequency of >20 per million in the corpus of second grade-level reading materials according to the norms provided by Zeno et al. (1995). Thirty-three words were used as targets and 30 as distractors. The target stimuli were presented for study for a period of one min before each scan. The method of presentation of the stimuli was the same in the recording and study sessions. MEG recordings were obtained during three blocks of trials. The target stimuli were repeated in each block in a different random order and mixed with 10 new distractors. Words were presented for one second in order to prevent potential contamination of the EMF record by visual "offset" responses. During recording the subject was asked to keep his/her eyes open, fixating on a dark dot placed on the ceiling at eye level, in order to reduce eye movements or blinks and prevent EMF contamination by rhythmic activity, which can interfere with the accurate detection of task-related brain activity.

Experiment 5

Participants

52 healthy children volunteered for the study. Forty-four of them who participated in experiment 4 were also involved in this experiment.

Task

MEG data were acquired while children performed a pseudoword task, involving reading of three-letter pronounceable non-words (e.g., *lan*). The printed stimuli were projected centrally for 1500 ms, one at a time, with a randomly varied interstimulus interval of 3–4 s. The children were instructed to read the "made-up" words as soon as they disappeared from the screen to avoid contamination of the MEG data segments by movement-related magnetic artifacts. Stimuli for each task were arranged randomly into four blocks of 25 items. EMFs were recorded between the presentation of the stimuli and the onset of the child's reading of them, in order to avoid myogenic artifacts.

Statistical analysis

The number of early and late activity sources that fell within each ROI provided a measure of that region's involvement in the processing of the word (or pseudoword) stimuli and provided an outline of the task-specific activation profiles. Those included some cortical areas which were consistently active, and others that showed minimal or inconsistent activity. In order to determine whether a region was consistently active or not, we modeled the number of dipoles from the early and later segments using a generalized estimating equation (GEE; Zeger and Liang, 1986) approach. Such a procedure was needed because the data consist of frequency counts of dipoles, which are typically quite skewed. GEE models are themselves a generalization from generalized linear models (McCullagh and Nelder, 1989). Generalized linear models are general linear models (regression, ANOVA) that are not restricted to normal distributions. As long as the distribution to be modeled follows a distribution from the exponential family (binomial, Poisson, negative binomial, etc), it can be modeled using a generalized linear model along with a link function that makes the relation between the predictors in the model and the outcome approximately linear (such as a log function for the Poisson

or negative binomial, or the logit function for the binomial distribution). The GEE model expands the generalized linear model to situations where the data are repeated or clustered. Since our data consist of the number of dipoles observed in various regions and across the two hemispheres of the brain, the GEE model is appropriate. We assumed a negative binomial distribution, which provides control for the over-dispersion of these distributions, with a log link function. Since the time frame for measurements was not equal for all subjects, we used an offset in the model to produce estimates per 100 ms. A region having significantly more than 1 dipole per 100 ms was considered to be consistently active.

Results

Replicability

Data from the two replications of Experiment 1 are juxtaposed in Fig. 2. As shown in Fig. 2, the patterns are almost identical. However, we wished to examine statistically these two replications prior to reporting the data on the remaining experiments. In order to model the data appropriately, there needs to be a sufficient number of non-zero observations. To establish this, we considered that the minimal distribution would be a Poisson with a mean of 1 dipole. Such a distribution would predict that about 37% of the time a zero count would occur. We then applied a binomial test to each region in each hemisphere for both the early and late activation. Only those regions where the number of zeros was not significantly more than 37% were then analyzed for replicability. There were seven such regions for early activation: right Frontal, left Insular, left MTG, right MTG, left Perisylvian, right Perisylvian, and right Supramarginal. A 2 (replication)×7 (ROI) generalized estimating equation verified the absence of significant differences, in that there was no main effect of the replication factor ($X^2(1)=0.22$, p=0.64), nor any interaction effects for the early activity. A second analysis was performed to determine the degree of relation between the replications. This was done separately for each region of early activity. The median Spearman correlation was 0.42 with a range from 0.13 to 0.71. Those regions with lower correlation all had fewer than 2 dipoles observed in either replication.

There were 21 regions with sufficient values for modeling late activity. The GEE model also indicated no significant differences between replications for the late activity $(X^2(1)=0.67, p=0.41)$. Correlation analyses for these regions indicated that the median Spearman correlation was 0.61 with a range from 0.17 to 0.84. Only three of 21 regions had correlations less than 0.5 and these had relatively few dipoles observed. The three regions with the largest number of dipoles (left MTG, left Perisylvian, and right Perisylvian) had correlations of 0.75, 0.84, and 0.83, respectively). Since the replications were comparable, we conducted all subsequent analyses involving Experiment 1 using the averaged data from the two replications.

Early activity

The source of the early response components, for both auditory and visual tasks, were found in the respective primary auditory and visual areas, as is almost invariably the case (Nakasato et al., 1995; Pantev et al., 1995; Papanicolaou et al.,



Fig. 2. Top: Activation profiles for late activity for the two replications of Experiment 1 (bars) and the average of the two replications (line). Bottom right: time-courses of activation (number of dipolar sources) for averaged replications of the MTG and the Perisylvian ROIs of the left and right hemispheres during Experiment 1. Bottom left: 3-D view of the MNI brain surface with the average number of dipoles in the Perisylvian and MTG ROIs projected onto it.

1990; Reite et al., 1994; Seki et al., 1996). Specifically, we found bilateral superior temporal gyrus (Perisylvian ROI) activation for auditory tasks and a bilateral Visual ROI activation for visual tasks. Additional early bilateral Perisylvian sources were found in Experiment 4, for children completing the visual word recognition task.

In order to assess hemispheric symmetry in the degree of activation of the primary sensory cortex, a series of generalized linear models using the same negative binomial distribution with a log link function were performed separately for each experiment. As expected, symmetrical, early sources were found in the Perisylvian ROI (which included Heschl's gyrus; see description of ROIs in the Appendix) for the auditory tasks used in Experiment 2 (younger adults, auditory word task; $X^2(1)=1.24$, p=0.26), and Experiment 3 (children, auditory word task; $X^2(1)=0.27$, p=0.61). However, for Experiment 1 (older adults, auditory word task) a right hemispheric dominance for the Perisylvian region was observed ($X^2(1)=4.67$, p=0.031, for the averaged tasks. All visual tasks resulted in bilateral activation of

the Visual ROI (Experiment 4 (children, visual word task), $X^2(1)=0.01$, p=0.91; Experiment 5 (children, pseudoword task), $X^2(1)=1.59$, p=0.21). The early Perisylvian response observed during the visual word recognition task for children in Experiment 4 was also symmetrically distributed ($X^2(1)=0.80$, p=0.37). No other regions besides the Perisylvian ROI for auditory tasks and the Visual ROI for visual tasks contained significant early activity.

Late activity

As previously mentioned, the common normalized brain space was divided into a number of ROIs (see Appendix). Angular gyrus and Supramarginal gyrus were considered as one ROI and labeled as Supramarginal; Heschl's gyrus and superior temporal gyrus were also considered as one region and labeled Perisylvian. Also as previously mentioned, the "Cerebellum," "Basal Ganglia," "Outside" and "Inside" ROIs were excluded from the analyses because the dipoles were deemed to be unreliable. Included were ROIs which contained, on average, significantly more than 1 dipole per 100 ms.

For all experiments involving auditory word stimuli the most active regions were the superior and middle temporal gyri (Perisylvian and Middle Temporal Gyrus ROIs, respectively). For Experiments 4 and 5 involving visual word stimuli, the most active regions in both conditions were Visual, Perisylvian, and MTG. An additional consistent activation in the Prefrontal ROI was observed in Experiment 4 (children, visual word task).

In order to assess laterality, we included in the analyses ROIs homotopic to the active ones, whether or not they showed consistent activation. For example, in all analyses we included the right MTG along with the left, although in some cases the former, unlike the latter, did not show significant activation (as defined above).

First we established the laterality of activity patterns in each experiment in a series of generalized estimating equations with hemisphere and ROI as independent factors, and the number of dipolar sources as the dependent variable. The results of these analyses are as follows.

Auditory task profiles

Experiment 1: Older adults, auditory word recognition task (2 replications)

The most active areas in Experiment 1 were Perisylvian and MTG, each with an average number of dipoles significantly greater than 1 per 100 ms. Being interested in ROIs that were most active, we continued our analysis with these ROIs only. Generalized estimating equations with hemisphere (Left, Right) and ROI (Perisylvian and MTG) as within-subject variables resulted in a main effect of ROI ($X^2(1)=13.32$, p=0.0003). Expected values showed greater activity in the Perisylvian region

compared with MTG (see Fig. 3). Analyses also revealed a significant result for the hemisphere by area interaction $(X^2(1)= 6.25, p=0.012)$. Examination of the simple main effects showed that left MTG was more active than the right (p=0.0036) whereas there was no difference between hemispheres for the Perisylvian region. This feature of laterality was found in all experiments, as shown below.

Inspection of the latencies at which activation was observed showed that the activation of both the right and left Perisylvian region peaked around 400 ms. MTG showed an activation peak around 250–350 ms in the left hemisphere and a gradual decline in activation from 350 to 800 ms. In the right hemisphere, MTG peaked around 150–250 ms and showed a faster drop in activation. Inspection of the MTG spatio-temporal profile suggests that the significant hemisphere differences were due to sustained activity that lasted 200–250 ms longer in the left hemisphere (see Fig. 2).

Experiment 2

As can be observed in Fig. 3, participants in Experiments 1 and 2 showed a similar profile of activation, characterized by bilateral Perisylvian and left lateralized MTG activation.

Generalized estimating equations with hemisphere (left, right) and region (Perisylvian and MTG) as within-subject factors again showed a significant main effect of area $(X^2(1)=24.40, p<0.0001)$. Examination of the expected values indicated that Perisylvian was significantly more active than the other regions, including MTG. Results also revealed a significant hemisphere difference $(X^2(1)=5.45; p=0.020)$ with the left hemisphere being more active than the right, but the hemisphere by region interaction was also significant $(X^2(1)=4.92, p=0.027)$. As was the case in experiment 1, only MTG showed a significantly more activation of the left hemisphere (p=0.0032). See Fig. 4.



Fig. 3. Profile of late activation in Experiment 2 (younger adults; auditory word recognition) and Experiment 1 (older adults, auditory word recognition).



Fig. 4. Top: Profile of activation of Experiment 2 (auditory word recognition, young adults). Bottom right: time-courses of activation (number of dipolar sources over time) for the MTG and Perisylvian ROIs in the left and right hemispheres. Bottom left: 3-D view of the MNI brain surface with the average number of dipoles in the Perisylvian and MTG ROIs projected onto it.

Time-courses of activation for the Perisylvian and MTG regions showed a similar pattern to the one observed for Experiment 1. See Fig. 4.

Experiment 3

Children in Experiment 3 showed similar profiles to the adults in Experiments 1 and 2. Consistent activation was observed for this group in the Perisylvian and MTG regions. See Fig. 5. A generalized estimating equation with hemisphere (left, right) and region (Perisylvian and MTG) as within-subject factors revealed a significant main effect of region (X^2 (1)=16.64, p < 0.0001). The Perisylvian ROI was significantly more active than the MTG ROI. There was also a significant nemisphere difference (X^2 (1)=4.69; p=0.030) and a significant region by hemisphere interaction (X^2 (1)=10.53; p=0.0012), explained by greater left than right MTG activation (p=0.0020). The hemisphere difference for the Perisylvian ROIs showed no significant difference (p=0.072).

The inspection of latencies in Experiment 3 (Fig. 5) revealed a similar pattern to those observed for Experiments 1 and 2. Perisylvian activity in each hemisphere showed a peak latency

between 450 and 550 ms. Left MTG showed sustained activity from 250 to 750 ms. Like the adult groups, children in Experiment 3 showed less activity in right compared with left MTG, but unlike adults, the children in Experiment 3 showed later right MTG latencies, without a clear maximum activation.

Cross-experiment comparisons for auditory word recognition

Auditory tasks were characterized by some common features, including greater bilateral Perisylvian activation compared to other regions of interest. The auditory profile was also characterized by consistent left lateralized MTG activity (see Fig. 6).

In order to assess possible differences in the pattern of commonly active areas across tasks, repeated measurements generalized estimating equations were performed with region (MTG, Perisylvian) and hemisphere (L, R) as within-subject factors, and Experiment (1, 2, 3) as between-subject factors. As observed for individual task analyses, there was a significant main effect of region, with the Perisylvian region showing a greater number of dipoles than MTG, $X^2(1)=29.91$, p=<0.0001. There was also a difference by hemi-



Fig. 5. Top: profile of activation in Experiment 3 (auditory word recognition, kids). Bottom right: time-courses of activation (number of dipolar sources over time) for the MTG and Perisylvian ROIs in the left and right hemispheres. Bottom left: 3-D view of the MNI brain surface with the average number of dipoles in the Perisylvian and MTG ROIs projected onto it.

sphere, $X^2(1)=11.64$, p=0.0006, and a hemisphere by region interaction, $X^2(1)=12.87$, p=0.0003. Across experiments, the left hemisphere was more active than the right hemisphere for the MTG region (p<0.0001). See Table 1 for MTG laterality ratios for all auditory tasks. See also Fig. 7(a).

A significant region by experiment interaction was also observed $(X^2(2)=6.40, p=0.041)$. Bonferroni-corrected post-hoc comparisons showed a smaller number of dipoles in the Perisylvian region in the Experiment 1, when compared with activation in this region in Experiment 2 (p=0.011) and a trend relative to Experiment 3 (p=0.0680). See Fig. 7(b). Given the higher mean age of participants in Experiment 1, this result suggested a possible effect of age on activity in the Perisylvian ROI. This possibility was explored further in follow-up comparisons, as detailed below.

The effect of gender on auditory language profiles

The main feature of language-specific activation that is reputed to differentiate the genders is laterality, with females purportedly having greater bilateral brain activation for language than males (McGlone, 1977, 1978; Lukatela et al., 1986; Kimura, 1987, 1992; Crossman and Polich, 1988; Zaidel et al., 1995; Shaywitz et al., 1998). In Experiments 1-3 we found consistent left lateralization of MTG activity, which was also equivalent across tasks (no significant main effects of Experiment were found). In order to assess possible differences between male and female participants, we calculated the ratio of lateralization in MTG (left MTG-Right MTG/Left+Right MTG) (Breier et al., 1999, 2001; Papanicolaou et al., 2004). Next, we inspected the MTG ratio data distribution and we observed that the data were negatively skewed. Since non-parametric tests make no assumptions about the distribution of the data, a Mann-Whitney non-parametric test was carried out to test for possible gender differences in MTG laterality ratio. No significant gender differences were found (Z=-1.380, p=0.17); however, contrary to expectation, females tended to show a greater degree of left lateralization than males (as shown in Fig. 8).

In order to assess possible gender-related differences in total number of dipoles, we also carried out generalized estimating



Fig. 6. Profile of activation for all auditory tasks (Experiments 1 to 3). The average number of dipoles over all tasks (line) shows the comparable agreement of degree of activation in each ROI, and a comparable degree of lateralization of the MTG activity across tasks.

equations with hemisphere and region as within-subject factors and gender as a between subject factor for the number of dipoles. No significant differences by gender were found.

The effect of age on auditory language profiles

Following the observation of a significant difference between Experiments 1 and 3 in the number of dipoles in the Perisylvian region, as reported above, we explored the possible influence of age on the auditory receptive language profiles. First, we combined the results from the first three experiments, which included the same auditory word recognition paradigm, for commonly active regions, the Perisylvian and MTG ROIs. We then conducted a curve estimation regression analysis for these two regions, with the total amount of activity in these regions as the dependent variable and age as the independent variable. The estimations were significant for the Perisylvian region in both the left and right hemispheres (right: p=0.000, left: p=0.010). The number of dipoles decreased with increasing age of the participants in both hemispheres. See Fig. 9.

In order to assess possible age effects on the degree of MTG lateralization further, we also performed the curve estimation regression for the MTG laterality ratio. No significant age effects on the degree of lateralization were found.

Table 1

Hemisphere laterality ratios ((L-R)/(L+R)) of the number of late dipolar sources in MTG for auditory tasks

Task	Ratio (L-R)/(L+R)	
Experiment 1 (adults)	0.38834	
Experiment 2 (adults)	0.49495	
Experiment 3 (kids)	0.70018	

(Values closer to 1.0 indicate a higher degree of left lateralization).

These follow-up regression analyses suggest that the lower number of dipoles observed in the Perisylvian region in Experiment 1 may be related to the higher mean age of the participants in that study compared with participants in Experiments 2 and 3. Participants in the first experiment had a mean age of 48.08 years (range of 18–84 years), whereas adults from experiment 2 had a mean age of 32.87 (range 22–55 years). We caution that these results are only suggestive of age effects, because the version of the auditory word recognition tasks performed by younger participants in Experiments 2 and 3 was altered slightly from the version performed by the older adults in Experiment 1. Thus, a specific task effect cannot be ruled out.

We also used a generalized estimating equation but included age as an ordered predictor in the same manner as gender in the previous analysis. Results indicated a significant age by region by experiment interaction $(X^2(2)=6.37; p=0.041)$. Examination of the parameter estimates suggested that there was a stronger inverse relation of age to the number of dipoles activated in the MTG region for those in experiment three as compared to Experiments 1 and 2 (p=0.0009). There was also an indication that age was more positively related to activation on the left side ($X^2(1)=4.78; p=0.029$, with a trend for differences between experiments, $X^2(2)=5.67; p=0.059$. The trend suggested a greater relation of age to left sided activation in Experiment 3 as compared to Experiments 1 and 2 (p=0.001). These results are possibly due in part to the confounding of age and experiment, with Experiment 3 including child participants only.

Next we investigated whether age had an effect on mean latencies in the Perisylvian and MTG regions. A curve estimation regression procedure was performed with the average latency at these regions as the dependent variable and age as the independent variable. We found that average latencies in the right hemisphere for both the Perisylvian region (p=0.002) and the MTG region (p=0.000) tended to be reduced with increasing age. See Fig. 10.



Fig. 7. (a) Mean number of dipolar sources in MTG for each task and hemisphere. (b) Mean dipolar sources in the Perisylvian ROI for each experiment.

Visual task profiles

Experiment 4

Children in Experiment 4, who performed the visual word recognition task, showed consistent activity (i.e., significantly more than 1 dipole per 100 ms in the late latency range) in four ROIs: Visual, Perisylvian, MTG, and Prefrontal. See Fig. 11. A GEE analysis with these regions and hemisphere as within-subject factors resulted in a main effect of hemisphere $(X^2(1)=8.75,$ p=0.0031), with the left hemisphere more active than the right. A significant main effect of region ($X^2(3) = 23.28$, p < 0.0001) was also found, as well as a significant hemisphere by region interaction $(X^{2}(3)=9.60, p=0.0222)$. Bonferroni-corrected post-hoc comparisons revealed that the Visual region was significantly more active than the other regions (p < 0.0001). The Perisylvian region was also more active than the combined MTG and Prefrontal regions (p=0.0054). Considering the hemisphere difference for each region (simple main effects), the MTG (p=0.0025) and Prefrontal (p=0.0185) regions tended to be more active in the left hemisphere than the right but there were no differences for the Perisylvian or Visual regions.

Inspection of spatio-temporal patterns of activation for Experiment 4 (Fig. 11) revealed continuous, bilateral activation of Visual regions that remained active up to 650–750 ms, particularly in the left hemisphere. The Perisylvian region also showed bilateral activity with two peaks, the first between 250–350 ms and the second between 550–650 ms. As observed in the auditory tasks (Experiments 1–3), there was a left lateralized response for MTG, with a peak of activation between 450 and 550 ms in the left hemisphere. MTG showed a maximum between 250 and 350 ms in the right hemisphere.



Fig. 8. Mean MTG laterality ratio for females and males in the auditory word recognition task. Higher values indicate a higher degree of left lateralization.

Experiment 5

Children performing the pseudoword task in Experiment 5 showed the most consistent activity in Visual regions, followed by the Perisylvian, MTG and Prefrontal regions. However, using the GEE analysis, only the Visual and Perisylvian regions had significantly more than 1 dipole per 100 ms. See Fig. 12. GEE analyses with hemisphere (left and right) and region (Visual and Perisylvian) as within-subject factors revealed a trend for hemisphere, with the left hemisphere more active than the right hemisphere ($X^2(1)=2.73$, p=0.099. As also observed in Experiment 4 for the word recognition task, there was a significant main effect of region for the pseudoword task in Experiment 5 ($X^2(1)=3.82$, p=0.051). Unlike Experiment 4, in this case the interaction was not significant. Examination of the expected values showed that the Visual region was significantly more active than the Perisylvian region.

The time-course of activation in Experiment 5 (Fig. 12) was characterized by a large Visual response, with peak activity occurring in the left hemisphere between 150 and 250 ms, and two peaks of activity in the right hemisphere between 150–250 and 350–450 ms. Peak activity in the Perisylvian ROI occurred between 450 and 550 ms in the left hemisphere, whereas there were two peaks of activity for that region in the right hemisphere, between 150–250 ms and again between 550–650 ms. Peak activity peaked earlier in this region in the right hemisphere, around 250–350 ms.

Cross-experiment comparisons for visual word recognition

We next compared the results of Experiments 4 and 5 to determine consistencies and differences in children's activation profiles across visual tasks. Consistent activity was observed across Experiments 4 and 5 in two ROIs: Visual and Perisylvian, whereas in Experiment 4 there was also consistent activation in the MTG and Prefrontal regions. We examined the combined data for all four regions. To test for possible differences in profiles of activation, a series of three-way repeated measures GEE analysis with region (MTG, Prefrontal, Perisylvian and Visual), experiment (4-Words, 5-Pseudowords) and hemisphere (Left, Right) as factors was performed. Significant main effects for region $(X^2(3)=36.41;$ p < 0.0001), hemisphere (X²(1)=15.20; p < 0.0001, and experiment $(X^{2}(1)=12.72; p=0.0004)$ were observed, as well as a region by side interaction ($X^2(3)=10.99$; p=0.0118). The Visual region was more active than the remaining ones ($X^2(1)=66.22$, p<0.0001) and the Perisylvian was more active than the MTG and Prefrontal



Fig. 9. Scatterplots of the average number of dipolar sources in the left and right Perisylvian regions as a function of age, with regression line superimposed.

regions (X²(1)=24.10, p < 0.0001), whereas there was no difference between the MTG and Prefrontal regions (p=0.7132). The left hemisphere was more active than the right but this depended on the region. Analysis of simple main effects (using a Bonferroni correction) indicated that the left hemisphere was more active for the MTG region (p < 0.0001), and was nearly so for the Prefrontal (p=0.0171), but the Perisylvian and Visual regions were more bilateral. Activation was also greater in Experiment 4 (words) than Experiment 5 (pseudowords).

The effect of gender on visual language profiles

We assessed possible gender effects on visual language activation profiles by conducting analyses similar to those performed for auditory task comparisons (as described above). Since no hemisphere by experiment effects were seen on the initial visual task comparisons, we averaged the results from the two experiments and calculated the MTG laterality ratio ((L-R)/(L+R)). Next, a Mann–Whitney Rank Analysis was conducted

to determine for possible male and female differences. Results showed that females tended to show a greater degree of leftward lateralization than males (Z=-2.072, p=0.038). See Fig. 13.

To assess possible gender-related differences on mean latencies, we carried analogous analyses to those performed for auditory tasks. We averaged the results from Experiments 4 and 5 and performed a repeated measures ANOVA with hemisphere (left and right) as a within-subject factor and gender as a between-subject factor on mean MTG latencies. No significant differences in MTG latencies were found.

Discussion

The purpose of the MEG experiments described here was to determine whether there are consistent features of brain activation profiles for receptive language tasks in a large sample of individuals, and whether such features vary with stimulus presentation parameters, including modality of presentation, task



Fig. 10. Scatterplots of the latency of dipolar sources in the right hemisphere for the Perisylvian and MTG ROIs as a function of age with the regression line superimposed.







Fig. 11. Top: profile of activation in Experiment 4 (visual word recognition task, children). Bottom right: number of dipolar sources over time in the Visual, Perisylvian, MTG, and Prefrontal ROIs of the left and right hemispheres. Bottom left: 3-D view of the MNI brain surface with the average number of dipoles in the Visual, Perisylvian and MTG ROIs projected onto it.

characteristics, or by the age or gender of the participant. We used a new, fully automated analysis method in order to minimize experimenter bias, and we found consistent features in the activation profile across stimulus modality, task variations, age, and gender in five experiments.

Brain activation profiles featured two components: an early and a late one corresponding to the early (sensory) and late (task-specific) components of the EMFs. The first component (>150 ms) consisted of modality-specific dipolar sources in the primary sensory cortex, as expected (e.g. Nakasato et al., 1995; Pantev et al., 1995; Papanicolaou et al., 1990; Reite et al., 1994; Seki et al., 1996). Specifically, early, bilateral sources were observed in Perisylvian cortex, including Heschl's gyrus, during the auditory tasks (Experiments 2 and 3; with the one exception of Experiment 1) and in the occipital cortex during the two visual tasks (Experiments 4 and 5).

The second, late component (>150 ms) consisted mainly of a significant concentration of sources in both the left and right Perisylvian ROI (superior temporal and Heschl's gyrus) and a significantly greater concentration of sources in the left middle

temporal gyrus. Those features remained constant across task parameters, stimulus modality, age and gender of the participants, indicating that they constitute the basic aspects of the language perception mechanism.

The validity of these activation profiles has been assessed in previous MEG investigations using slightly different methods of analysis and patient samples instead of healthy participants (e.g. Papanicolaou et al., 1999, 2004) and their dramatic difference in morphology from those arising in either expressive language or non-language tasks has also been established (see e.g. Castillo et al., 2001; Billingsley et al., 2004a, Billingsley et al., 2004b; Papanicolaou et al., 2002). In the present studies, however, we were able to discern the differences in the response of the middle as oppose to the superior temporal gyrus and verify that it is the MTG that accounts for hemispheric dominance, a phenomenon reported in other imaging studies as well (see e.g. Binder et al., 1996, Poeppel et al., 2004).

However, when we attempted to verify the widely held notion that lateralization of language mechanisms to the left hemisphere is better defined in men than in women (e.g. McGlone, 1977, 1978; Lukatela et al., 1986; Kimura, 1987, 1992; Crossman and



Fig. 12. Top: profile of activation in Experiment 5 (pseudoword reading task, children). Bottom right: number of dipolar sources by latency for the Visual, Perisylvian and MTG ROIs in the left and right hemispheres. Bottom left: 3-D view of the MNI brain surface with the average number of dipoles in the Visual, Perisylvian and MTG ROIs projected onto it.

Polich, 1988; Zaidel et al., 1995; Shaywitz et al., 1998), either by comparing all active regions in the two hemispheres or the left and right middle temporal gyri only, we found the opposite trend of stronger lateralization among women. This finding raises doubts about the validity of beliefs in gender differences in the



Fig. 13. Mean MTG laterality ratio for female and male subjects in visual tasks. Higher values indicate a higher degree of left lateralization.

degree of lateralization of brain mechanisms of receptive language.

Age also did not have any effect on the main features of the profile of auditory language perception. Children as well as old and young adults displayed generally bilaterally symmetrical activation of the superior temporal and asymmetrical activation of the middle temporal gyrus. In terms of absolute amount of activation, however, there was a significant age-related decline in the superior temporal gyrus. Yet, the functional import of such decline is not clear and it is further complicated by the fact that it is attended by an apparent improvement in the latency of the activation of the superior temporal gyrus among the older subjects.

The main profile features also remained unaffected by the mode of stimulus presentation (auditory and visual) except in a reduction in the amount of temporal lobe activation and the appearance of visual cortex activation in the latter experiments. That additional activity involved mainly anterior, inferior and lateral aspects of the secondary visual areas, which has been observed in our previous studies involving reading of words (e.g., Simos et al., 2001).

Profile changes, however, were observed when the task involved pseudowords. Besides the fact that absolute amount of activation was higher in the word tasks in the temporal and the occipital region (Experiment 4 vs. Experiment 5), the word task profile entailed a secondary feature, namely activation of the prefrontal region, whereas the pseudoword task did not.

The establishment of these profiles was greatly facilitated by the introduction of the automated procedures for signal reduction and analysis. Although it is not possible to quantify the degree of improvement in the construction of the activation maps achieved through the use of this set of automated procedures, it is clear that they are superior to the methods we have used in the past in at least two basic ways. First, they reduce substantially the amount of analysis time. Manual analysis of the data resulting in construction of an activation map usually requires several hours depending on the expertise of the technician, whereas the automated analysis procedures complete the same task in about 15 min.

Second and more importantly, the automated routines of channel selection for solving for a dipolar source guarantees consistent application of the same objective criteria in all cases and eliminates the possibility of error due to inconsistent application of the same criteria on the part of an analyst, whether inconsistency is due to fluctuations of attention or unconscious biases induced by expectations. Most likely, however, in spite of the improvements that this automated analyses introduced, the profile features thus established are but a subset of those that constitute the brain mechanism of language. Many features are likely missed by the single equivalent dipole model that we have been using, which is applied to only a small fraction of the recorded activity (that fraction that is suggestive of dipolar sources). These features could possibly be captured by alternative models such as multiple (e.g. Schwartz et al., 1999) and/or extended source models (e.g. Liu et al., 1998; Moradi et al., 2003; Moran and Tepley, 2000; Mosher et al., 1999), some of which have the desirable feature of taking into account the complex geometry of the cortical surface (e.g., Moran and Tepley, 2000; Mosher et al., 1999; Kober et al., 2003). Yet none of these alterations have been subjected to external validation of their accuracy in localizing intracranial activity sources as the single dipole model has (e.g. Papanicolaou et al., 1999; Simos et al., 1999, 2000). Nevertheless, the introduction of these automated procedures for data analyses, using the single equivalent dipole model, makes it possible to compare objectively and with relative ease the degree of concordance among the solutions provided by alternative models and to evaluate the degree of their complementarity.

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Appendix A

 Regions of Interest
 Angular_L

 Angular_L
 Angular Gyrus left (AAL: Angular_L)

 Angular_R
 Angular Gyrus right (AAL: Angular_R)

 Basal_Temporal_L
 Inferior Temporal and Fusiform Gyrus left (AAL: Temporal_Inf_L, Fusiform_L)

Basal_Temporal_R	Inferior Temporal and Fusiform Gyrus right
Broca_L	(AAL: Temporal_Inf_R, Fusitorm_R) Inferior Frontal left (Brodmann Areas 44 left, 45 left)
Broca_R	Inferior Frontal right (Prodmann Aroog 44 right, 45 right)
*Cerebellum	All AAL Cerebellum regions minus Visual_L
Cingulate_L	and Visual_R (below) Cingulate left (AAL: Cingulum_Ant_L,
Cingulate_R	Cingulum_Mid_L, Cingulum_Post_L) Cingulate right (AAL: Cingulum_Ant_R,
Frontal_L	Cingulum_Mid_R, Cingulum_Post_R) Precentral left (Brodmann Area 4 left)
Frontal_R	Precentral right (Brodmann Area 4 right) minus Perisylvian R (below)
*Ganglia_L	Basal Ganglia and Thalamus left (AAL: Caudate_L, Putamen_L, Pallidum_L,
*Ganglia_R	Thalamus_L) Basal Ganglia and Thalamus right (AAL: Caudate_R, Putamen_R, Ballidum, P., Thalamus, P.)
Heschl I	Pallidum_R, Inalamus_R) Heschl's Gyrus left (AAI : Heschl I)
Heschl R	Heschl's Gyrus right (AAL: Heschl R)
*Inside	All areas within the skull not included in
	another region
Insula_L	Insula left (AAL: Insula_L)
Insula_R	Insula right (AAL: Insula_R)
Mesial_Temporal_L	Mesial Temporal left (AAL: Hippocampus_L, Parahippocampal_L, Amygdala_L)
Mesial_Temporal_R	Mesial Temporal right (AAL: Hippocampus_R, Parahippocampal_R, Amygdala_R)
MTG_L	Middle Temporal Gyrus left (Superior, posterior
MTC D	portion of Brodmann Areas 37 left, 21 left)
MIG_K	portion of Brodmann Areas 37 right, 21 right)
*Outside_L	All areas outside the skull not included in another region left
*Outside_R	All areas outside the skull not included in another region right
Parietal_L	Parietal left (Brodmann Areas 5 left, 7 left)
Parietal_R	Parietal right (Brodmann Areas 5 right, 7 right)
Postcentral_L	Postcentral left (AAL: Postcentral_L)
Postcentral_R	Postcentral right (AAL: Postcentral_R)
Prefrontal_L	Prefrontal left (AAL: Olfactory_L; Brodmann Areas
Prefrontal_R	8 left, 9 left, 10 left, 11 left, 46 left, 47 left) Prefrontal right (AAL: Olfactory_R; Brodmann Areas 8 right, 9 right, 10 right, 11 right,
Perisylvian_L	46 right, 4/ right) Superior Temporal Gyrus left (expanded posterior portion of Brodmann
Perisylvian_R	Superior Temporal Gyrus right (expanded
Supp_Motor_Area_L	Supplementary Motor Area L)
Supp_Motor_Area_R	Supplementary Motor Area right (AAL: Supp_Motor_Area_R)
Regions of Interest	· · · · · · · · · · · · · · · · · · ·
SupraMarginal_L	Supramarginal Gyrus left
SupraMarginal_R	(Brodmann Area 40 left minus Perisylvian_L) Supramarginal Gyrus right (Brodmann Area 40 right
	minus Perisylvian_R)
Temporal_Pole_L	Temporal_Pole_left (AAL: Temporal_Pole_Mid_L, Temporal_Pole_Sup_L)

Appendix A (continued)

Temporal_Pole_R	Temporal Pole right (AAL: Temporal_Pole_Mid_R, Temporal_Pole_Sup_R)
Visual_L	Visual Cortex left (Upper Cerebellum left; AAL: Lingual L. Calcarine L. Brodmann Areas 17 left
	18 left, 19 left)
Visual_R	Visual Cortex right (Upper Cerebellum right; AAL: LinguaLR, Calcarine_R; Brodmann Areas 17 right, 18 right, 19 right)

* Indicates that the region was excluded from analysis.

References

- Billingsley, R.L., Simos, P.G., Castillo, E.M., Sarkari, S., Breier, J.I., Pataraia, E., Papanicolaou, A.C., 2004a. Spatio-temporal cortical dynamics of phonemic and semantic fluency. J. Clin. Exp. Neuropsychol. 26, 1031–1043.
- Billingsley, R.L., Simos, P.G., Sarkari, S., Fletcher, J.M., Papanicolaou, A. C., 2004b. Spatio-temporal brain activation profiles associated with line bisection judgments and double simultaneous visual stimulation. Behav. Brain Res. 152, 97–107.
- Binder, J.R., Frost, J.A., Hammeke, T.A., Rao, S.M., Cox, R.W., 1996. Function of the left planum temporale in auditory and linguistic processing. Brain 119, 1239–1247.
- Breier, J.I., Simos, P.G., Zouridakis, G., Wheless, J.W., Willmore, L.J., Constantinou, J.E., Maggio, W.W., Papanicolaou, A.C., 1999. Language dominance determined by magnetic source imaging: a comparison with the Wada procedure. Neurology 53, 938–945.
- Breier, J.I., Simos, P.G., Wheless, J.W., Constantinou, J.E., Baumgartner, J. E., Venkataraman, V., Papanicolaou, A.C., 2001. Language dominance in children as determined by magnetic source imaging and the intracarotid amobarbital procedure: a comparison. J. Child Neurol. 16, 124–130.
- Breier, J.I., Castillo, E.M., Simos, P.G., Billingsley-Marshall, R.L., Pataraia, E., Sarkari, S., Wheless, J.W., Papanicolaou, A.C., 2005. Atypical language representation in patients with chronic seizure disorder and achievement deficits using magnetoencephalography. Epilepsia 46 (4), 540–548.
- Buckner, R.L., Raichle, M.E., Petersen, S.E., 1995. Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. J. Neurophysiol. 74, 2163–2173.
- Castillo, E.M., Simos, P.G., Venkataraman, V., Breier, J.I., Wheless, J.W., Papanicolaou, A.C., 2001. Mapping of expressive language cortex using magnetic source imaging. Neurocase 7, 419–422.
- Crossman, D.L., Polich, J., 1988. Hemispheric differences for orthographic and phonological processing. Brain Lang, 35, 301–312.
- Frost, J.A., Binder, J.R., Springer, J.A., Hammeke, T.A., Bellgowan, P.S., Rao, S.M., Cox, R.W., 1999. Language processing is strongly left lateralized in both sexes: evidence from functional MRI. Brain 122, 199–208.
- Kimura, D., 1987. Are men's and women's brains really different? Can. Psychol. 28, 133–147.
- Kimura, D., 1992. Cognitive function: sex differences and hormonal influence. In: Smith, B., Adelman, G. (Eds.), Neuroscience year: Supplement 2 to the encyclopedia of neuroscience. Birkhauser, Boston, pp. 41–43.
- Liu, A.K., Belliveau, J.W., Dale, A.M., 1998. Spatiotemporal imaging of human brain activity using functional MRI constrained magnetoencephalography data: Monte Carlo simulations. Proc. Natl. Acad. Sci. U. S. A. 95, 8945–8950.
- Lukatela, G., Carello, C., Savic, M., Turvey, M.T., 1986. Hemispheric asymmetries in phonological processing. Neuropsychologia 24, 341–350.
- McCullagh, P., Nelder, J.A., 19889. Generalized Linear Models. Chaman and Hall, London.

- McGlone, J., 1977. Sex differences in the cerebral organization of verbal functions in patients with unilateral brain lesions. Brain 100, 775–793.
- McGlone, J., 1978. Sex differences in functional brain asymmetry. Cortex 14, 122–128.
- Moradi, F., Liu, L.C., Cheng, K., Waggoner, R.A., Tanaka, K., Ioannides, A.A., 2003. Consistent and precise localization of brain activity in human primary visual cortex by MEG and fMRI. NeuroImage 18, 595–609.
- Moran, J.E., Tepley, N., 2000. Two dimensional inverse imaging (2DII) of current sources in magnetoencephalography. Brain Topogr. 12, 201–217.
- Mosher, J.C., Baillet, S., Leahy, R.M., 1999. EEG source localization and imaging using multiple signal classification approaches. J. Clin. Neurophysiol. 16, 225–238.
- Nakasato, N., Fujita, S., Seki, K., Kawamura, T., Matani, A., Tamura, I., Fujiwara, S., Yoshimoto, T., 1995. Functional localization of bilateral auditory cortices using an MRI-linked whole head magnetoencephalography (MEG) system. Electroencephalogr. Clin. Neurophysiol. 94, 183–190.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia 9 (1), 97–113.
- Paivio, A., Yuille, J.C., Madigan, S.A., 1968. Concreteness, imagery, and meaningfulness values for 925 nouns. J. Exp. Neurol. 76, 1–25.
- Pantev, C., Bertrand, O., Eulitz, C., Verkindt, C., Hampson, S., Schuierer, G., Elbert, T., 1995. Specific somatotopic organizations of different areas of the human auditory cortex revealed by simultaneous magnetic and electric recordings. Electroencephalogr. Clin. Neurophysiol. 94, 26–40.
- Papanicolaou, A.C., 1998. Fundamentals of functional brain imaging: A guide to the methods and their applications to psychology and behavioral neurosciences. Swets and Zeitlinger, Netherlands.
- Papanicolaou, A.C., Baumann, S.B., Rogers, R.L., Saydjari, C., Amparo, E.G., Eisenberg, H.M., 1990. Localization of auditory response sources using MEG and MRI. Arch. Neurol. 47, 33–37.
- Papanicolaou, A.C., Simos, P.G., Breier, J.I., Zouridakis, G., Willmore, L.J., Wheless, J.W., Constantinou, J.E., Maggio, W.W., Gormley, W.B., 1999. Magnetoencephalographic mapping of the language-specific cortex. J. Neurosurg. 90, 85–93.
- Papanicolaou, A.C., Simos, P.G., Castillo, E.M., Breier, J.I., Katz, J.S., Wright, A.A., 2002. The hippocampus and memory of verbal and pictorial material. Learn. Mem. 9 (3), 99–104.
- Papanicolaou, A.C., Simos, P.G., Castillo, E.M., Breier, J.I., Sarkari, S., Pataraia, E., Billingsley, R.L., Buchanan, S., Wheless, J., Maggio, V., Maggio, W.W., 2004. Magnetocephalography: A noninvasive alternative to the Wada procedure. J. Neurosurg. 100 (5), 867–876.
- Poeppel, D., Guillemin, A., Thompson, J., Fritz, J., Bavelier, D., Braun, A. R., 2004. Auditory lexical decision, categorical perception, and FM direction discrimination differentially engage left and right auditory cortex. Neuropsychologia 42, 183–200.
- Price, C.J., Moore, C.J., Friston, K.J., 1996. Getting sex into perspective. NeuroImage 3 (3 Pt 2), S586.
- Reite, M., Adams, M., Simon, J., Teale, P., Sheeder, J., Richardson, D., Grabe, R., 1994. Auditory M100 component. 1: Relationship to Heschl's gyri. Cogn. Brain Res. 2, 13–20.
- Sarvas, J., 1987. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. Phys. Med. Biol. 32, 11–22.
- Schwartz, D.P., Badier, J.M., Bihoue, P., Bouliou, A., 1999. Evaluation of a new MEG-EEG spatio-temporal localization approach using a realistic source model. Brain Topogr. 11, 279–289.
- Seki, K., Nakasato, N., Fujita, S., Hatanaka, K., Kawamura, T., Kanno, A., Yoshimoto, T., 1996. Neuromagnetic evidence that the P100 component of the pattern reversal visual evoked response originates in the bottom of the calcarine fissure. Electroencephalogr. Clin. Neurophysiol. 100, 436–442.
- Shaywitz, S.E., Shaywitz, B.A., Pugh, K.R., Fulbright, R.K., Constable, R. T., Mencl, W.E., Shankweiler, D.P., Liberman, A.M., Skudlarski, P.,

Fletcher, J.M., Katz, L., Marchione, K.E., Lacadie, C., Gatenby, C., Gore, J.C., 1998 (Mar 3). Functional disruption in the organization of the brain for reading in dyslexia. Proc. Natl. Acad. Sci. U. S. A. 95 (5), 2636–2641.

- Simos, P.G., Breier, J.I., Zouridakis, G., Papanicolaou, A.C., 1998. Identification of language-related brain activity using magnetoencephalography. J. Clin. Exp. Neuropsychol. 20, 706–722.
- Simos, P.G., Papanicolaou, A.C., Breier, J.I., Wheless, J.W., Constantinou, J.E., Gormley, W.B., Maggio, W.W., 1999. Localization of languagespecific cortex by using magnetic source imaging and electrical stimulation mapping. J. Neurosurg. 91, 787–796.
- Simos, P.G., Breier, J.I., Wheless, J.W., Maggio, W.W., Fletcher, J.M., Castillo, E.M., Papanicolaou, A.C., 2000. Brain mechanisms for reading: the role of the superior temporal gyrus in word and pseudoword naming. NeuroReport 11 (11), 2443–2447.
- Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Mouzaki, A., Papanicolaou, A.C., 2001. Age-related changes in regional brain

activation during phonological decoding and printed word recognition. Dev. Neuropsychol. 19, 191–210.

- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in spm using a macroscopic anatomical parcellation of the MNI MRI single subject brain. NeuroImage 15, 273–289.
- Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonio, TX.
- Zaidel, E., Aboitiz, F., Clarke, J., Kaiser, D., Matteson, R., 1995. Sex differences in interhemispheric relations for language. In: Kitterle, F.L. (Ed.), Hemispheric communication: mechanisms and models. Lawrence Erlbaum, Hillsdale (NJ), pp. 85–175.
- Zeger, S.L., Liang, K.-Y., 1986. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42, 121–130.
- Zeno, S.M., Ivens, S.H., Millard, R.T., Duvvuri, R., 1995. The Educator's Word Frequency Guide. Touchstone Applied Science Associates, Brewster, NY.