FULL-LENGTH ORIGINAL RESEARCH

Distributed source modeling of language with magnetoencephalography: Application to patients with intractable epilepsy

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SUMMARY

Purpose: To examine distributed patterns of language processing in healthy controls and patients with epilepsy using magnetoencephalography (MEG), and to evaluate the concordance between laterality of distributed MEG sources and language laterality as determined by the intracarotid amobarbital procedure (IAP).

Methods: MEG was performed in 10 healthy controls using an anatomically constrained, noise-normalized distributed source solution (dynamic statistical parametric map, dSPM). Distributed source modeling of language was then applied to eight patients with intractable epilepsy. Average source strengths within temporoparietal and frontal lobe regions of interest (ROIs) were calculated, and the laterality of activity within ROIs during discrete time windows was compared to results from the IAP.

Results: In healthy controls, dSPM revealed activity in visual cortex bilaterally from ~80 to 120 ms in response to novel words and sensory control stimuli (i.e., false fonts). Activity then spread to fusiform cortex ~160–200 ms, and was dominated by left hemisphere activity in response to novel words. From ~240 to 450 ms, novel words produced activity that was left-lateralized in frontal and temporal lobe regions, including anterior and inferior temporal, temporal pole, and pars opercularis, as well as bilaterally in posterior superior temporal cortex. Analysis of patient data with dSPM demonstrated that from 350 to 450 ms, laterality of temporoparietal sources agreed with the IAP 75% of the time, whereas laterality of frontal MEG sources agreed with the IAP in all eight patients.

Discussion: Our results reveal that dSPM can unveil the timing and spatial extent of language processes in patients with epilepsy and may enhance knowledge of language lateralization and localization for use in preoperative planning.

KEY WORDS: MEG, Language, Dynamic statistical parametric mapping, Epilepsy.

Magnetoencephalography (MEG), when combined with high-resolution magnetic resonance imaging (MRI), is gaining widespread acceptance as a presurgical language mapping tool in the evaluation of patients with epilepsy (Papanicolaou et al., 1999, 2004; Bowyer et al., 2005a; Breier et al., 2005; Lee et al., 2006; Billingsley-Marshall et al., 2007). To date, most studies have focused on late activity (>200 ms) in response to auditory or visual word stimuli that are presumed to reflect sustained N400 effects elicited during lexical-semantic processing (Halgren et al., 2002; Salmelin, 2007). The vast majority of these studies have used an equivalent current dipole (ECD) or other focal source solutions to lateralize N400 effects, and have demonstrated a strong concordance

between MEG language lateralization and the intracarotid amobarbital procedure (IAP) (Papanicolaou et al., 1999; Breier et al., 2000; Maestu et al., 2002; Hirata et al., 2004; Papanicolaou et al., 2004; Bowyer et al., 2005b; Billingsley-Marshall et al., 2007). When focal source solutions are employed, N400 effects are reliably localized within left or right perisylvian cortex, centered on the superior and middle temporal gyri (Billingsley-Marshall et al., 2007), supramarginal gyrus, or within the superior temporal sulcus (Lee et al., 2006). Although each region is undoubtedly critical to language, it is well known that language processing is distributed in nature, simultaneously and sequentially recruiting multiple areas within temporal, frontal, and parietal cortex (Geschwind, 1970; Marinkovic, 2004). Therefore, ECD models, which assume that the magnetic field is generated by a focal source, will underestimate the regions involved in complex cognitive functions such as language.

To overcome limitations of focal source models, several distributed source solutions have been proposed (Hamalainen & Ilmoniemi, 1994; Dale et al., 2000; Bowyer et al., 2005a). In particular, Dale et al. (2000) have developed a distributed source solution that produces noise-normalized dynamic statistical parametric maps (dSPMs) of cortical activity similar to those generated for functional MRI (fMRI) or positron emission tomography (PET), and may offer an advantage for studying localization of language processes. This noise-normalized dSPM method has been successfully used to unveil the cortical dynamics of language processing in healthy controls by comparing event-related fields (ERFs) evoked by novel versus repeating word stimuli (Dale et al., 2000; Dhond et al., 2001; Halgren et al., 2002; Dhond et al., 2003; Marinkovic et al., 2003). Despite its appeal, dSPM of language has yet to be applied to patients with epilepsy and compared to results obtained from the IAP.

In this study, we examine spatiotemporal patterns of language processing in healthy controls and patients with epilepsy using dSPM and a novel word-reading task designed to isolate language-specific processes. In patients with epilepsy, we compare language laterality results obtained from dSPM sources within temporoparietal and frontal lobe ROIs to language laterality results obtained from the IAP. We hypothesized that language-related activity would spread along a posterior to anterior gradient, becoming increasingly left-lateralized in healthy controls within temporoparietal and frontal lobe ROIs. We further hypothesized that laterality would be greatest from ~350 to 450 ms (i.e., capturing peak N400 responses), and that laterality of N400 responses in these regions would show strong concordance with the IAP. If this method of source modeling shows the hypothesized pattern, it could enhance preoperative planning by increasing knowledge of language lateralization and localization in patients with epilepsy.

Materials and Methods

Participants

Participants in this investigation were 10 right-handed, healthy controls and eight patients with intractable epilepsy (seven right-handed; one left-handed) between the ages of 21 and 54. The study was approved by the institutional review boards at the University of California, San Diego (UCSD) and New York University (NYU), and each subject's consent was obtained in accordance with the ethical standards promulgated in the Declaration of Helsinki. The control group consisted of seven males and three females with no known history of neurologic disorder, loss of consciousness, or serious medical or psychiatric condition. All control data were collected at UCSD. The patients included four females and four males who were recruited from the UCSD and NYU Epilepsy Clinics and who were undergoing presurgical evaluation at the time of enrollment in the study. IAP results were available for all eight patients and indicated left hemisphere language dominance in six patients, right language dominance in one, and bilateral language dominance in one patient. Patient characteristics, neuropsychological data, and IAP results are presented for all patients in Table 1.

Semantic judgment task

All participants completed the same semantic judgment task in which they were instructed to respond by lifting their finger in response to low-frequency target items (i.e., animals; see supplemental Fig. S1). Task stimuli were presented visually as white letters on a black background in 12-point, Arial font. Stimuli consisted of 400 novel words that were presented only once, 400 "old" words (20 repetitions of 10 words), 400 consonant letter strings, 400 false font stimuli, and 40 target words. All real word stimuli were 4–8 letter nouns, with a written lexical frequency of 3–80 per 10 million (Francis & Kucera, 1982). The false font stimuli comprised alphabet-like characters that were matched in size and number of strokes to a real letter in the English alphabet; however, they did not resemble actual letters. In addition, false fonts were each matched to a novel word in the number of characters to visually control for the length of the stimulus. Therefore, they were designed to control for visual stimulus features, but not lexical, syntactic, or semantic content. The experimental task was organized into two separate lists, each consisting of 20 blocks, with approximately 42 stimuli per block. Each of the repeating words was presented once per block in approximately the same order, resulting in 20–30 s (~42 intervening stimuli) between presentations of a given repeated word. Novel words, letter strings, and false fonts were presented in random order, with approximately 10 of each per block. Data were collected using a rapid stimulus onset asynchrony (SOA; 600 ms) and a very large number of trials per condition in order to obtain

Table 1. Demographic and neuropsychological performances in patients with epilepsy								
	NY45	NY50	NY61	NY68	NY70	UC1	UC2	UC3
Gender	Male	Male	Female	Male	Female	Male	Female	Female
Age	33	28	41	26	53	39	25	27
Handedness	Right	Right	Right	Right	Right	Right	Right	Left
Education (years)	13	16	13	16	12	16	15	14
Seizure focus	Non-localizing	Right OL/TL	Right TLE	Left TLE	Left TLE	Left TLE	Left TLE	Left TLE
IAP laterality	Bilateral	Left	Left	Left	Left	Left	Left	Right
Age of seizure onset (years)	9	7	30	15	32	8	18	<1
Duration of seizures (years)	24	21	11	11	21	31	7	27
Seizure frequency (# per month)	5–7 CPS	4–24 CPS	2–14 GTC	1–3 CPS	1–3 CPS	15 CPS	7 CPS	1 CPS
Wechsler test of adult reading (standard score)	109	114	84	N/A	117	92	89	81
Boston naming test (T-score)	41	N/A	14	N/A	48	30	22	10
Verbal fluency (scaled score)	5	N/A	5	5	12	8	4	10
Category fluency (scaled score)	6	N/A	4	9	9	13	8	9

IAP, intracarotid amobarbital procedure; CPS, complex partial seizures; TLE, temporal lobe epilepsy; OL, occipital lobe; GTC, generalized tonic–clonic.

MEG data with a high signal-to-noise ratio (SNR) in a short time frame (~20 min), thereby maximizing the clinical utility of the task. Although this presentation rate is much faster than is customary, it is still much slower than typical word reading speed. The sequence of stimulus conditions was balanced to ensure that each condition was preceded by every other condition with equal likelihood. The task was programmed using Presentation software (Neurobehavioral Systems, Inc, Albany, CA, U.S.A.).

MEG recording

Prior to the MEG session, subjects were screened for MEG artifacts resulting from dental work or excessive eye-blinking. Magnetic fields at UCSD were recorded by an Elekta-Neuromag whole-head MEG system (Electa, Inc., Helsinki, Finland) with 204 planar dc-SQUID gradiometers and 102 magnetometers in a magnetically-shielded room (IMEDCO-AG, Hägendorf, Switzerland) at the UCSD Radiology Imaging Laboratory. Magnetic fields at NYU were recorded by a whole-head Magnes 3600 WH MEG system with 248 radial magnetometers (4D Neuroimaging, San Diego, CA, U.S.A.) in a magnetically-shielded room. At both centers, pairs of electrooculograph (EOG) electrodes were used to detect eye blinks and movements. The translation between the MEG coordinate systems and each participant's structural MRI was made using three head position coils placed on the scalp and fiducial landmarks (Hamalainen et al., 1993). Signals were recorded continuously with a 1,000 Hz sampling rate and minimal on-line filtering (0.1–200 Hz). Data were then low-pass filtered off-line at 20 Hz (transition band = 4 Hz) and downsampled by a factor of four before separate averages were created for each subject. Single trials were rejected based on amplitude criteria supplemented by visual inspection or any cases where responses were contaminated with eye blinks (>280 microvolts in the EOG electrode). All off-line averaging at NYU and UCSD was performed using the same filtering, downsampling, and artifact rejection criteria.

Procedure

MRI scanning and image processing

All imaging for UCSD participants was performed at the UCSD Radiology Imaging Laboratory on a General Electric 1.5T EXCITE HD scanner with an 8-channel phased-array head coil (General Electric Healthcare, Waukesha, WI, U.S.A.). Image acquisitions included a conventional 3-plane localizer, GE calibration scan, and two T_1-weighted volume acquisition pulse sequences (TE = 3.8 ms, TR = 10.7 ms, TI = 1,000 ms, flip angle = 8 deg, FOV = 25.6 cm, matrix = 256 × 192, slice thickness = 1.0 mm). MRI data for all NYU participants was acquired using a 3T Siemens Allegra head-only MRI scanner (TE = 3.25, TR = 2,530, TI = 1,100 ms, flip angle = 7 deg, FOV = 25.6 cm, matrix = 256 × 256, slice thickness = 1.3 mm). Acquisition parameters on both scanners were optimized for increased gray/white matter image contrast. The image files in DICOM format were transferred to a Linux workstation for morphometric analysis. The two T_1-weighted images were rigid body registered to each other and reoriented into a common space, roughly similar to alignment based on the AC-PC line. Images were corrected for nonlinear warping caused by nonuniform fields created by the gradient coils. Image intensities were normalized and made uniform with the FREESURFER (3.0.5) software package (http://surfer.nmr.mgh.harvard.edu).

Cortical surface reconstruction

Geometric representations of the cortical surface were constructed from the T_1-weighted structural volumetric images using procedures described previously (Dale et al., 1999; Fischl et al., 1999a, 2002). First, segmentation of

cortical white matter was performed and the estimated border between gray and white matter was tessellated, providing a topographically correct representation of the surface. This representation of the folded cortical surface was used to derive the locations and orientations of the dipoles used in the analysis of the MEG data. Next, the folded surface tessellation was "inflated" in order to unfold cortical activation patterns. For intersubject averaging, the reconstructed surface for each subject was morphed into an average spherical representation, optimally aligning sulcal and gyral features across subjects while minimizing metric distortion (Fischl et al., 1999b). This surface-based registration procedure results in a substantial reduction in anatomic and functional variability across subjects relative to the Talairach normalization approach (Fischl et al., 1999b).

Inverse solution: spatiotemporal analysis

To estimate the time courses of cortical activity using a distributed source solution, a noise-normalized, anatomically constrained linear estimation approach was applied to gradiometer data at UCSD and magnetometer data at NYU (Dale et al., 2000). This method is based on the observation that the main cortical generators of MEG and electroencephalography (EEG) signals are localized in the gray matter. Once the exact shape of the cortical surface is known, this information can be used to reduce the MEG solution space. Furthermore, normalization procedures are used that take into account the noise sensitivity at each spatial location, allowing for statistical parametric maps. First, the cortical surface was subsampled to about 2,500 dipole locations per hemisphere (Dale et al., 2000). Second, the forward solution at each location was calculated using a boundary element model. Third, dipole power was estimated at each cortical location every 4 ms and divided by the predicted noise power obtained from a weighted average of all conditions for each individual. The square roots of these values were then averaged on the cortical surface across individuals after aligning their sulcal–gyral patterns (Dale et al., 2000; Dhond et al., 2001). Using this procedure, spatiotemporal activity estimates were computed from 0 to 1,000 ms following stimulus presentation. This method generates statistical maps that are *F*-distributed and represent the mean activity for the entire group of participants throughout the time course. Fig. 1 demonstrates estimated cortical activity produced by novel words, false fonts, and the comparison of these conditions (i.e., novel words vs. false fonts) at selected time intervals for the healthy controls. The comparison condition was designed to provide the best estimate of language processing because it minimizes the contribution of activity associated with non–language-related functions (e.g., sensory and attentional processing) that would presumably also be evoked by false fonts.

Selected time intervals are those that were of theoretical interest based on previous MEG (Dhond et al., 2001; Marinkovic et al., 2003) and intracranial (Halgren et al., 1994b, 2006) studies of language processing.

Laterality index

To compare language lateralization results from the dSPM approach to those obtained from the IAP, activity sources associated with novel words versus false fonts were modeled, and average spatiotemporal activity estimates of the difference waveform were calculated across the cortical surface for each of the epilepsy patients. Laterality indices were then derived within temporoparietal and frontal lobe ROIs for two different time windows (240–280 ms and 350–450 ms) according to the following formula: $[(\text{left} - \text{right})/(\text{left} + \text{right})] \times 100$. These time-windows were selected based on evidence that initial lexical access and early semantic processing emerge within posterior language cortex ∼240–280 ms, whereas N400 responses within posterior and anterior language regions peak between 350 and 450 ms following exposure to a verbal stimulus (Bowyer et al., 2005b; Fujimaki et al., 2009). In each case, values >10 were arbitrarily used as a cut-off to indicate left language dominance, values <−10 were used to indicate right language dominance, and values between −10 and 10 to indicate bilateral language representation.

RESULTS

Healthy control data

In response to both novel words and false fonts, the earliest activity is seen bilaterally in occipital cortex ∼80–120 ms, representing early visual processing (see Fig. 1). By ∼160 ms, activity to novel words peaked in the ventral occipital–temporal area and was strongly left lateralized. By ∼240 ms, activity had spread to more anterior regions including the left superior, middle, and inferior temporal lobe, in addition to left prefrontal cortex, and was noticeably stronger in response to novel words relative to false fonts. Activity was also seen within the right temporal lobe by ∼240 ms in both conditions. By ∼350 ms, activity to novel words remained left lateralized in temporal cortex, but appears more prominent in multiple frontal regions as well. After ∼80–120 ms, activity to false fonts was much less robust than novel words and was not strongly lateralized. Fig. 1 (bottom panel) shows the comparison of novel words versus false fonts, demonstrating the absolute power differences in the mean waveforms. As can be seen, there is limited activity in this subtraction condition from ∼80 to 120 ms, suggesting that the novel words and false fonts were well-matched in their visual attributes. This initial response was followed by a strong left-lateralized pattern of activity after ∼240 ms that was sustained and more distributed at later latencies.
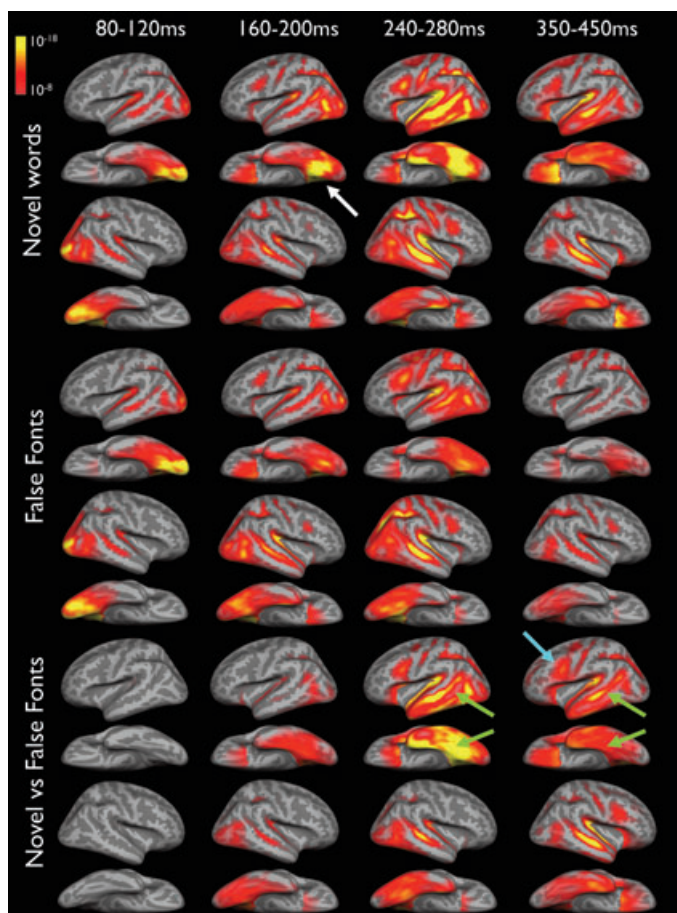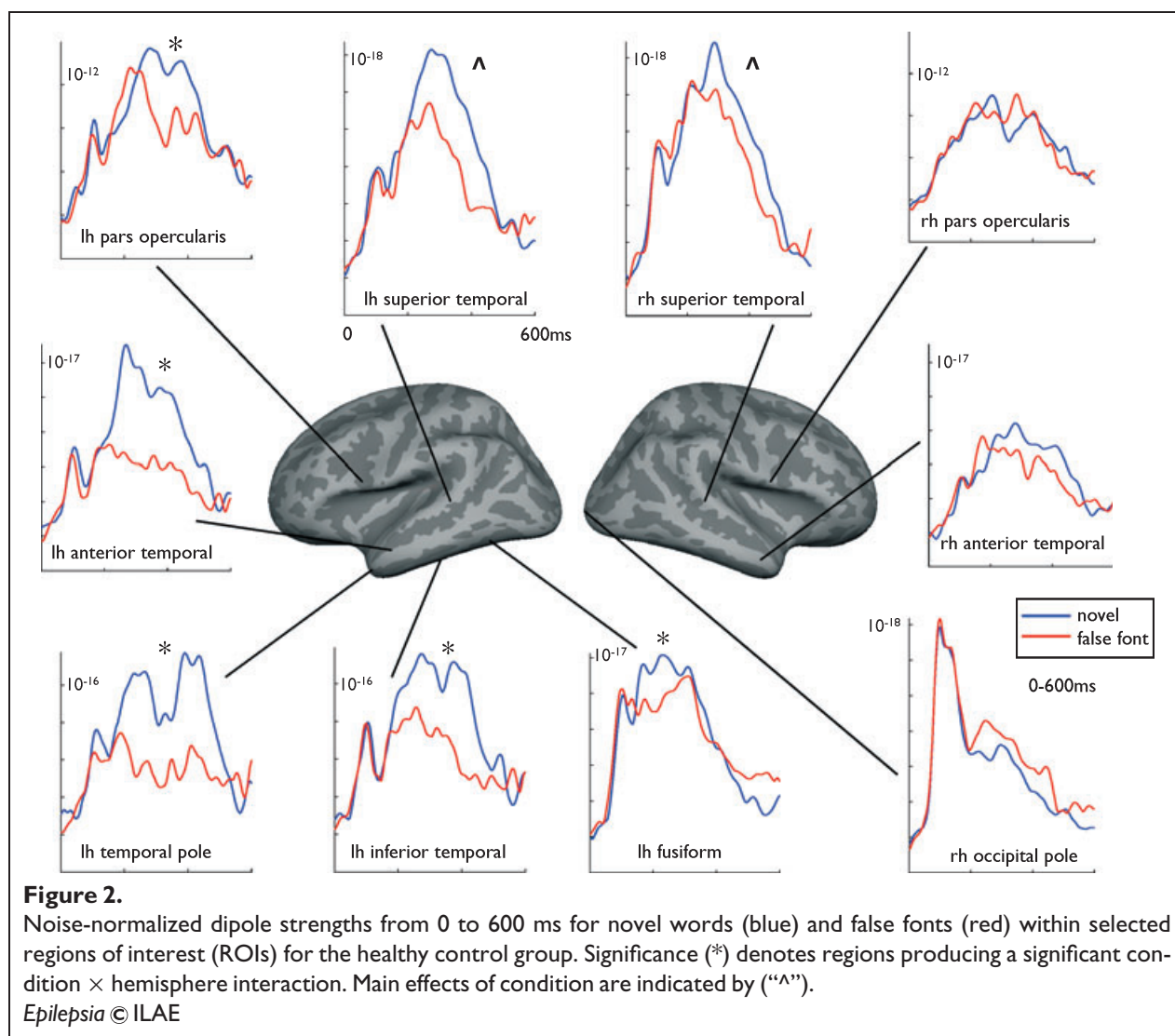
Figure 1.
Average dynamic statistical parametric maps (dSPMs) of cortical responses to novel words (top), false fonts (middle), and the novel words versus false fonts (bottom) for 10 healthy controls. Activity is seen bilaterally in occipital cortex ~80–120 ms. By ~160 ms, activity to novel words peaks in the left ventral occipitotemporal area (white arrow). By ~240 ms, activity is observed within the left superior, middle, and inferior temporal lobe, in addition to left prefrontal cortex, and is greater for novel words relative to false fonts. Activity is also seen within the right temporal lobe by ~240 ms in both conditions. By ~350 ms, activity to novel words remains left lateralized in temporal cortex, but is bilateral in multiple frontal regions. The bottom panel demonstrates the absolute power differences in the mean waveforms. As can be seen, there is minimal activity in the subtraction condition from ~80 to 120 ms. This initial response was followed by a left-lateralized pattern of activity after ~240 ms in left temporal (green arrows) and prefrontal (blue arrow) areas believed to reflect lexical, syntactic, and semantic processing. In each condition, significance thresholds are set at a minimum of $p < 10^{-8}$ (full red), with $p < 10^{-18}$ indicating peak activity (full yellow). These values represent significance levels associated with the noise-normalized dipole strength and can be conceptualized as estimates of the signal-to-noise at each vertex.
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To explore statistical differences between novel words and false fonts at the group level, condition by hemisphere repeated measures analysis of variance (RM ANOVAs) was performed on the average activity for each time window within regions of interest (ROIs). ROIs were determined a priori based on previous research from MEG (Dhond et al., 2001; Marinkovic et al., 2003) and intracranial (Halgren et al., 2006) studies of language processing. Fig. 2 portrays the estimated time courses extracted from selected ROIs for the left and right hemispheres for the group. As expected, no significant difference emerged between novel words and false fonts within the occipital pole from 80 to 120 ms [$F(1,9) = 1.2$, $p > 0.05$]. RM ANOVA revealed a significant condition by hemisphere interaction in the 160–200 ms time frame within the ventral occipitotemporal cortex, demonstrating greater responses to novel words relative to false fonts in the left hemisphere only

Figure 2.
Noise-normalized dipole strengths from 0 to 600 ms for novel words (blue) and false fonts (red) within selected regions of interest (ROIs) for the healthy control group. Significance (*) denotes regions producing a significant condition × hemisphere interaction. Main effects of condition are indicated by ("^").
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$[F(1,9) = 7.8$, $p < 0.05]$. Within the 350–450 ms time-window, condition by hemisphere interactions revealed novel > false font effects in the left, but not right, hemisphere within several temporal lobe regions, including the inferior (ventral) temporal cortex $[F(1,9) = 7.8$, $p < 0.05]$, anterior temporal cortex $[F(1,9) = 8.0$, $p < 0.05]$, and temporal pole $[F(1,9) = 7.4$, $p < 0.05]$. Within the frontal lobe, condition by hemisphere interactions revealed novel > false font effects in left pars opercularis $[F(1,9) = 9.2$, $p < 0.05]$ and left orbitofrontal cortex $[F(1,9) = 6.2$, $p < 0.05]$. Main effects of condition were seen in posterior superior temporal cortex, revealing novel > false font responses regardless of hemisphere $[F(1,9) = 5.4$, $p < 0.05]$.

Patient data

Fig. 3 shows the average noise-normalized dipole strength and laterality indices for the patient group for the 240–280 ms and 350–450 ms time windows. During the 240–280 ms time window, sources within the inferior parietal lobule, superior temporal sulcus, and fusiform gyrus showed the strongest laterality effect. Within the 350–450 ms time window, laterality was strongest in pars opercularis relative to the other ROIs. However, most temporal and frontal lobe regions showed stronger average source strength and laterality effects during this later time window when compared to their laterality estimates from 240 to 280 ms (see Fig. 3; bottom panel). Consistent with our control data, average source strength and laterality during the 350–450 ms time window appeared to capture the peak N400 effect within both posterior and anterior language regions. Therefore, this time window was selected as optimal for comparing our individual patient MEG data to results from the IAP.

Fig. 4 portrays dSPMs of novel words versus false fonts averaged across 350–450 ms for each patient, as
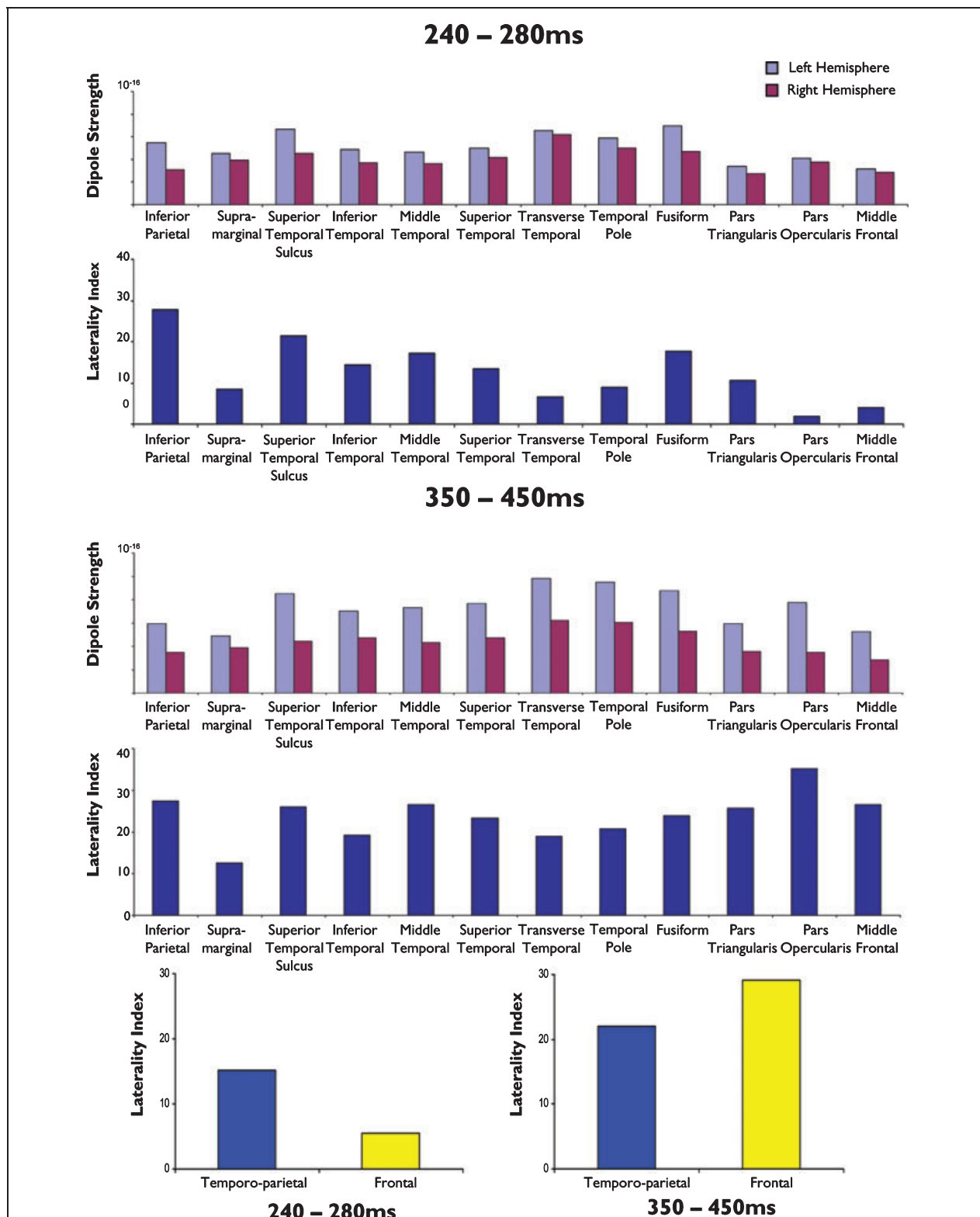
Figure 3.
Noise-normalized dipole strengths and laterality indices for each temporal, parietal, and frontal lobe subregion averaged across the patients for the 240–280 ms and 350–450 ms time windows. Positive values for the laterality indices reflect left > right activity.
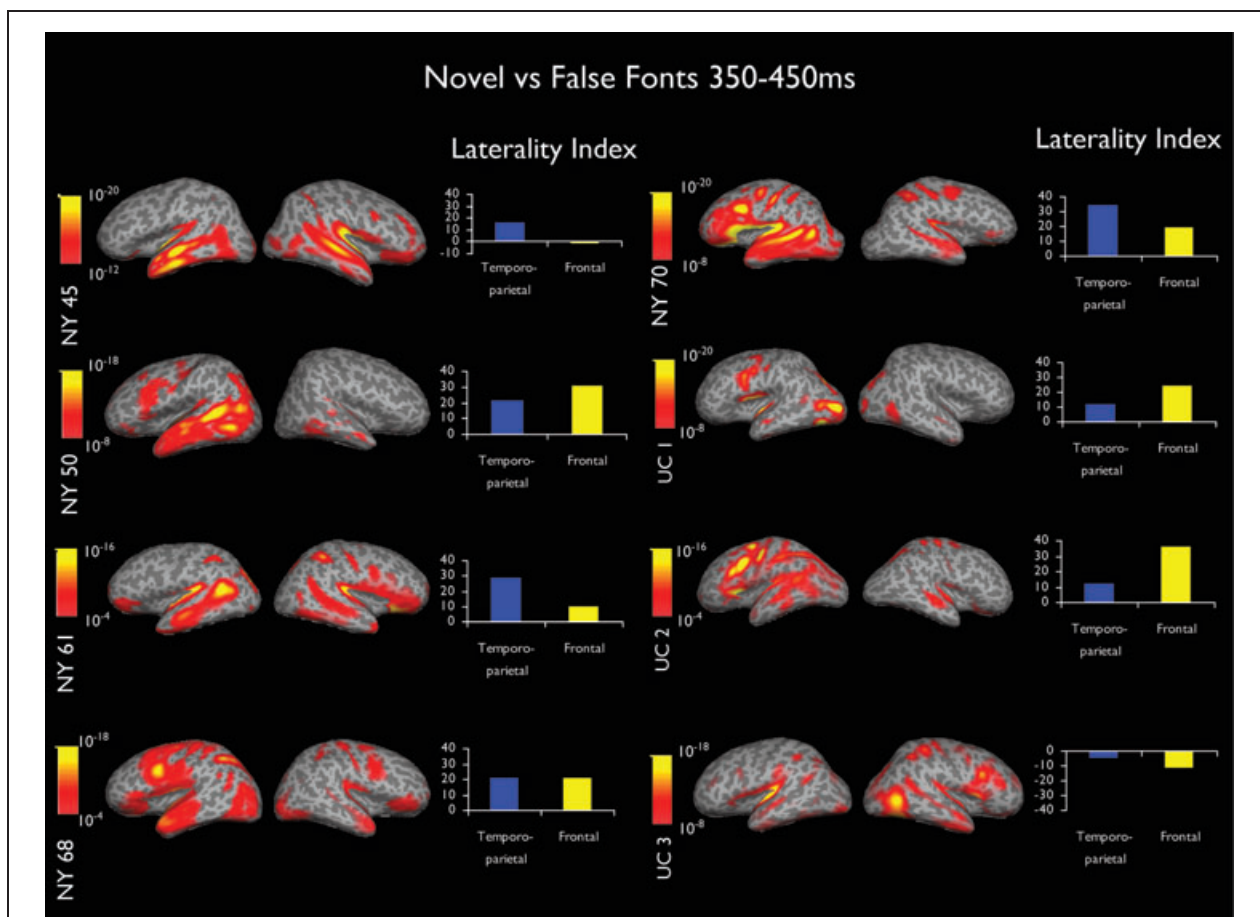*Epilepsia* © ILAE

Figure 4.
Dynamic statistical parametric maps (dSPMs) and laterality indices calculated from 350 to 450 ms for each of the eight patients. Activity is displayed on the inflated surface of each hemisphere. Sulci and gyri are shown in dark and light gray, respectively. Color bars range from moderate (orange) to high (yellow) activity and are relative to each patient's baseline. Values on the color bars represent significance values associated with the noise-normalized dipole strength at each vertex on the cortical surface. Laterality indices represent the difference between the hemispheres, where positive values reflect greater left hemisphere activity and negative values greater right hemisphere activity.
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well as the laterality index for temporoparietal and frontal lobe ROIs. As can be seen, activity appears lateralized in most patients and widely distributed among temporal, parietal, and frontal lobe regions implicated in lexical-semantic processing. Six of eight patients showed evidence of left language dominance on the IAP and across temporoparietal and frontal lobe ROIs (see supplemental Table S1). In all six of these patients (NY50, NY61, NY68, NY70, UC1, and UC2), the IAP and MEG agreed. In addition, NY68 and NY70 completed the same semantic judgment task during intracranial recordings. Clear focal N400 responses were recorded with subdural electrodes placed on the left cortex in or near Wernicke's and Broca's areas in both patients, providing further validation of the MEG sources. In the patient for whom

the IAP suggested right language dominance (UC3), frontal lobe MEG sources agreed, whereas temporoparietal sources suggested bilateral language. In the one patient for whom the IAP suggested bilateral language (NY45), frontal MEG sources agreed, but temporoparietal sources suggested left language representation. In no case did the IAP and MEG produce completely discordant results.

DISCUSSION

The goals of this study were to (1) demonstrate the spatiotemporal pattern of language processing using distributed source modeling (i.e., dSPM) and a task designed to isolate language, and (2) evaluate the concordance between the laterality of temporoparietal and frontal lobe

MEG sources and language lateralization as determined by the IAP in patients with epilepsy. In support of our initial hypothesis, dSPM revealed a left-lateralized, distributed pattern of cortical activity that evolved over time, peaking ∼350–450 ms within multiple perisylvian regions. In healthy controls, bilateral responses emerged in occipital cortex ∼100 ms, which is consistent with early visual processing in retinotopic areas (Hagler et al., 2008). This activity proceeds anteriorly along the ventral visual stream, becoming left-lateralized ∼160 ms in occipitotemporal cortex in response to novel words—a finding that is consistent with studies implicating this region in processing orthographic information or visual word forms (Allison et al., 1999). Activity then became distributed and bilateral ∼240 ms, but remained left-lateralized for novel words in most temporal and frontal lobe regions, including anterior and inferior temporal, temporal pole, and pars opercularis. All of these regions have previously been implicated in lexical-semantic processing and described as intracranial generators of the N400 (Halgren et al., 1994a, 1994b). Surprisingly, posterior superior temporal cortex (i.e., Wernicke's area) was not among the most lateralized regions in healthy controls, but rather produced strong source amplitudes within both hemispheres from ∼240 to 450 ms (see Fig. 2). The strength of the sources within these regions is reflected by the fact that most language-related ECDs are localized within superior temporal cortex (Salmelin et al., 1996; Halgren et al., 2002; Papanicolaou et al., 2004). As a result, simultaneously active, but weaker sources generated from other essential language cortex can be overshadowed when focal source solutions are employed. This may be especially important for left anterior and ventral temporal areas that are described as strong local intracranial generators of the N400 associated with word recognition (Halgren et al., 2006). These regions are not only obscured by MEG when focal source solutions are applied, but they are frequently undetected by fMRI due to susceptibility artifacts (Devlin et al., 2000).

dSPM was then applied to eight patients with longstanding refractory epilepsy who are representative of the surgical cases seen in our clinics. Consistent with our second hypothesis, laterality effects in patients were strongest from 350 to 450 ms—the time window likely capturing peak N400 responses. Temporoparietal MEG sources within this time window agreed with the IAP 75% of the time, whereas frontal MEG sources agreed in all eight cases. Very high concordance between frontal MEG sources and the IAP has been reported by Bowyer et al. (2005b) using a current source density technique (MR-FOCUSS) during a similar time interval. In their study, this late time interval was superior for eliciting activity within Broca's area, whereas earlier time intervals (∼230–290) were superior for eliciting activity within Wernicke's area and associated temporoparietal cortex. Our results suggest that although initial lexical access within temporoparietal regions may begin ∼240 ms, peak amplitudes and laterality of sources within frontal and temporal perisylvian regions are stronger from 350 to 450 ms. These latter sources likely reflect a combination of language skills, including sustained lexical access, semantic processing, and syntactic analysis (Salmelin, 2007; Fujimaki et al., 2009). Although stronger concordance between frontal lobe MEG sources and the IAP was not anticipated, it should be noted that the IAPs at both institutions are heavily weighted toward the evaluation of expressive rather than receptive language cortex. Therefore, although prefrontal MEG sources, especially within Broca's area, may show somewhat stronger concordance with the IAP, temporal MEG sources may be better predictors of postoperative outcome following language-dominant temporal lobe resections.

Results obtained from dSPM reinforce and expand upon ECD solutions by demonstrating the simultaneous recruitment of temporal, parietal, and frontal lobe regions involved in language processing. Knowledge of simultaneous, distributed activity could assist with tailoring resections in some patients with temporal and extratemporal epilepsy, and could identify patients with hemispheric dissociation in temporal and frontal language cortex (Kamada et al., 2007). It is also possible that the degree of activity within anterior and basal temporal cortex, as observed in the dSPMs of many patients, could help to explain why some patients show language decline following anterior temporal lobectomy (ATL), whereas others do not (Hermann et al., 1999). In particular, cortical stimulation studies have revealed language areas in the basal temporal cortex of the dominant temporal lobe in 40–100% of patients with TLE (Luders et al., 1986, 1991), and there is some evidence of improved neuropsychological outcome when basal temporal language cortex is spared (Mikuni et al., 2006). A systematic evaluation of whether identification of basal temporal sources adds to the prediction of postsurgical language outcome is needed to establish the relevance of these dSPM sources.

Taken together, our data suggest that distributed source modeling of peak N400 responses using a visual, semantic decision task may enhance language lateralization and localization in preoperative evaluations. It is important to note that the dSPM method employed in this study normalizes for noise sensitivity at each location, providing statistical maps that estimate the reliability of observed signals at each location and time point and does not require prior channel selection (Dale et al., 2000). Despite the potential clinical value of our study, there are several additional points that should be addressed. First, the spatial resolution of MEG is limited relative to fMRI or PET (Dale et al., 2000; Dale & Halgren, 2001). Therefore, the localization accuracy of our findings would be greatly

enhanced with convergent data from fMRI. Previous studies that have compared language localization results between fMRI and MEG using ECD models have found poor agreement (Billingsley-Marshall et al., 2007). Perhaps greater agreement would be obtained across modalities using distributed source solutions that produce statistical maps comparable to the ones produced for fMRI (Dale et al., 2000). Second, it is important to note that our results do not contradict current ECD methods for determining language lateralization. Such models have shown strong concordance with the IAP in large, independent cohorts of epilepsy patients (Papanicolaou et al., 2004; Lee et al., 2006). Rather, we propose that dSPM may enhance existing methods by providing additional insight into the distribution of temporoparietal and frontal language cortex. These data may be especially important for identifying dissociations in expressive and receptive language cortex that may not be captured by focal source solutions or the IAP.

Acknowledgments

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Visual semantic judgment task. SOA, stimulus onset asynchrony.

Table S1. Relationship between IAP and MEG language laterality from 350 to 450 ms.

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