

D. L. Miglioretti · D. Boatman

Modeling variability in cortical representations of human complex sound perception

Received: 3 September 2002 / Accepted: 2 September 2003 / Published online: 8 October 2003
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Abstract This study investigated methodological (task, stimulus) and intersubject variability in the cortical representation of auditory processing of complex sounds, including speech. Subjects were adult seizure patients undergoing left hemisphere electrocortical mapping (ECM). We tested auditory discrimination of complex sounds, including frequency-modulated tones and speech syllables (digitized, synthesized) contrasted by phonetic features and lexical status. To measure task effects, auditory comprehension was also tested. Within- and across-patient differences in the distribution of deficits induced by ECM were modeled statistically using the recently developed method of Template Mixture Modeling. Cortical representations of auditory discrimination were smaller, more localized, and less variable across subjects than auditory comprehension. Stimulus effects were observed only for speech-tone contrasts. When tasks and stimuli were held constant, two auditory discrimination centers were identified in the posterior temporal lobe. There was also an interaction between task and intersubject effects, with more intersubject variability in cortical maps of auditory comprehension than auditory discrimination. These results demonstrate the utility of

using the statistical modeling approach of Template Mixture Modeling to quantify sources of variability in cortical functional organization.

Keywords Statistical modeling · Brain mapping · Speech perception · Electrocortical mapping · Template mixture modeling

Introduction

There is little convergence among brain mapping studies on the cortical resources that support auditory processing of complex sounds, including speech. Auditory processing of speech has been associated with non-overlapping cortical regions within the left lateral temporal lobe, including the posterior superior temporal gyrus (Wise et al. 1991; Demonet et al. 1992; Zatorre et al. 1992; Binder et al. 2000), the anterior superior temporal gyrus (Price et al. 1996; Scott et al. 2000), the superior temporal sulcus (Binder et al. 2000), and the middle temporal gyrus (Mazoyer et al. 1993; Vouloumanos et al. 2001). Other left hemisphere regions identified include the inferior frontal lobe (Zatorre et al. 1992; Burton et al. 2000), supramarginal gyrus (Celsis et al. 1999), and dorsolateral prefrontal sulcus (Benson et al. 2001). The heterogeneity of brain mapping results has been attributed to methodological differences in mapping techniques, tasks and stimuli, and to intersubject differences (Poeppel 1996; Benson et al. 2001).

While direct comparisons between brain mapping techniques are still emerging (Bookheimer et al. 1997; Lurito et al. 2000), divergent findings have persisted independent of mapping method (Poeppel 1996). Task differences are one source of the observed variability, reflecting variation in response modality, attention, auditory memory, and functional complexity (Wise et al. 1991; Pugh et al. 1996; Burton et al. 2000). Independent of task, stimulus effects have occurred for speech versus non-speech sounds, suggesting functional specialization within the left temporal lobe (Benson et al. 2001; Vouloumanos et

D. L. Miglioretti
Center for Health Studies, Group Health Cooperative,
Seattle, WA, USA

D. L. Miglioretti
Department of Biostatistics, University of Washington,
Seattle, WA, USA

D. Boatman
Departments of Neurology and Otolaryngology, Johns Hopkins
University School of Medicine,
Baltimore, MD, USA

D. Boatman (✉)
Department of Neurology, Johns Hopkins University School of
Medicine,
600 North Wolfe Street/Meyer 2–147,
Baltimore, MD 21287, USA
e-mail: dboatma@jhmi.edu
Tel.: +1-410-955-0221
Fax: +1-410-955-0751

al. 2001). Alternatively, this cortical specialization may be for acoustic features of speech also present in other complex sounds, such as acoustic transients (Johnsrude et al. 1997; Binder et al. 2000). Additional dissociations have been reported for speech stimuli contrasted by lexical status (Mazoyer et al. 1993), phonetic features (Miceli et al. 1978), and natural versus synthesized sources (Benson et al. 2001).

Intersubject differences are another potential source of variability. Although individual variation in brain morphology is well recognized, individual variation in functional brain organization is poorly understood. Brain mapping data are often measured with standard templates and collapsed across individuals, precluding accurate estimates of individual variability. Moreover, averaged brain maps reflect the maximum observed area across individuals, potentially overestimating regions of interest. Although stroke studies have reported individual variability in cortical organization, evidenced by the lack of speech perception deficits in some patients with left temporal lobe lesions (Basso et al. 1977), most stroke patients are studied chronically making it difficult to rule out cortical reorganization as a potential confound.

Electrocortical mapping (ECM), also known as cortical stimulation, is an alternative brain mapping technique that is well suited for studying intrahemispheric functional variability. ECM produces temporary, reversible, relatively localized (~10 mm) functional lesions and is used, intraoperatively or extraoperatively, in planning resection surgery for treatment of seizure disorders (Ojemann 1983; Lesser et al. 1984). ECM is performed unilaterally, usually in the language-dominant (typically left) hemisphere. Because ECM effects are temporary (~5 s), multiple cortical sites can be tested in the same individual with each individual serving as his own control. Although ECM studies have relied largely on picture naming paradigms, other communicative functions have been investigated recently, including auditory speech processing. These studies have identified left posterior temporal lobe resources as critical for basic auditory functions such as syllable discrimination, with other temporal, frontal, and parietal lobe areas recruited for more complex auditory speech functions, such as those involving phonological segmentation and/or lexical-semantic processing (Ojemann and Mateer 1979; Ojemann 1983; Boatman et al. 1997, 2000; Corina et al. 1999; Bhatnagar et al. 2000; Lurito et al. 2000). Several ECM studies have suggested that individual differences contribute to the observed variability in cortical representations (Ojemann 1979; Lesser et al. 1984). However, there have been no attempts to systematically quantify individual variability or potential interactions with methodological factors. One reason is that previous ECM studies, including our own, have been hampered by ad hoc statistical analyses based on visual inspection and simple electrode counts within regions of interest, precluding accurate spatial delineation.

In this study, we modeled ECM data from a new series of patients using the recently developed statistical method of Template Mixture Modeling (Miglioretti et al. 2002).

This statistical approach incorporates estimates of inter-subject variability and is not constrained by sample size or a priori assumptions about regions of interest. For this initial study, we used an established auditory discrimination paradigm to investigate potential stimulus effects of discriminating acoustic transitions in speech versus tones, lexical status and phonetic feature contrasts, and speech generated from different sources (natural versus synthesized). To investigate task-related differences, we included measures of auditory comprehension, representing the other end of the processing continuum from auditory discrimination. Within-subject differences were modeled to identify task and stimulus effects. Between-subject differences were used to quantify individual variability when task and stimuli were held constant.

Subjects and methods

Subjects

Fourteen consecutive seizure patients (ages 20–55 years), nine females and five males, undergoing ECM of the left hemisphere, gave informed consent to participate in this study as approved by The Johns Hopkins Institutional Review Board for ethical treatment of human subjects. All were right handed and left-hemisphere dominant for language on the Wada test (Boatman et al. 1998). Selection criteria included full-scale IQ scores >80 and no history of hearing, motor, speech-language, or comorbid neurological (e.g., tumor) disorders. Patients with bilateral seizures or seizure onset before age 5 years were excluded, as were patients with seizure foci in perisylvian areas, including the superior or middle temporal lobe, or inferior frontal or parietal lobes. Continuous intracranial EEG recordings localized seizure foci to the anterior inferior temporal lobe (ten patients), the basal temporal lobe (four patients), and the superior frontal lobe (two patients). Two patients had multiple seizure foci.

Surgical procedures

Electrode arrays of 3-mm platinum iridium disks, spaced 10 mm apart, were implanted over lateral left cortex (Lesser et al. 1984). Electrode coverage, confirmed by intraoperative photographs and CT scans, included the superior, middle (14 patients), and inferior (9 patients) gyri of the temporal lobe, the frontal lobe (10 patients), and the parietal lobe (11 patients). To control for normal anatomic differences in brain morphology, electrode locations were normalized (Toga et al. 1993).

Auditory discrimination task

A binary AX, forced-choice (same-different) paradigm was used to present 52 stimulus pairs that patients responded to by pressing a button, as in other studies (Miceli et al. 1978; Boatman et al. 1997; Burton et al. 2000). Pairs were blocked by stimulus type, including 30 digitized (44 kHz, 16 bit sampling) monosyllabic word and non-word pairs contrasted by initial consonant voicing or place-of-articulation (e.g., pat-bat, tet-ket), 12 synthesized syllable pairs (e.g., pa-ba) based on published parameters (Klatt 1980), and 10 frequency-modulated tone pairs (500–2000 Hz, modulation rates 5–15 Hz). All stimuli were 400 ms long, separated by fixed intrapair (400 ms) and interpair (5 s) intervals, and presented binaurally by insert earphones at 40 dB SL.

Auditory comprehension task

One-step verbal directions from the Token test (De Renzi and Vignolo 1969) were presented live-voice as part of the clinical ECM test battery (Boatman et al. 2000). Patients responded by manipulating tokens of different shapes and colors (e.g., touch the green square). To control for task differences in motor response complexity, stimulus length, auditory memory, or live versus recorded speech, a second test of auditory comprehension was administered using 20 digitized single words, and a picture-pointing matching response.

Electrocortical mapping

An electrical current of 300-ms square-wave pulses, of alternating polarity, was generated at a rate of 50 pulses/s, for 5-s intervals, between adjacent electrode pairs (Boatman et al. 2000). Testing was performed at threshold current levels between 13–15 mA and in the absence of afterdischarges, sensory and/or motor effects. Clinical constraints limited the number of auditory phrasal comprehension stimuli to eight to ten per electrode pair and the testing of synthesized syllable and tone discrimination to eight patients. A deficit was defined as a significant decrease relative to the patient's baseline performance. For each patient, a comprehensive cortical map of binary (\pm deficit) data was generated. Because the smaller number of auditory comprehension stimuli precluded statistical comparison, impairment was defined using the clinical criterion of more than one deviation from baseline. Test-retest reliability was measured for all experimental conditions by retesting ten electrode sites, at 2-day intervals, in four patients.

Template mixture modeling

Distributions of auditory discrimination and comprehension deficits were modeled separately using Template Mixture Modeling (TMM). TMM has three components (Miglioretti et al. 2000, 2002): (1) a model representing cortical regions of interest in the population, (2) a model of cortical regions within each individual, and (3) a model of the observed data (i.e., whether or not an electrode pair was associated with a deficit). Population regions represent those cortical regions that remain after accounting for random variability in individual regions. Both the population and individual regions were represented as mixtures of an undetermined number of circular templates specified by two location parameters (μ_{1k} , μ_{2k}) and a radius (ρ_k). Templates used to model individual patient data were derived from a distribution centered at one of the population templates. Observed binary values (i.e., \pm deficit) at each electrode site were modeled as a function of the regions delineated by the circular templates using logistic regression (McCullagh and Nelder 1989):

$$\log \text{it}(E(y_{ij}|\mu_i, \rho_i)) = \alpha_0 + \alpha_1 H(\mu_i, \rho_i, x_{ij})$$

Regression parameters α_0 and α_1 describe error rates for auditory discrimination and comprehension. Specifically, α_0 is the log odds of observing a deficit when the j th site does not overlap with a critical cortical region. The slope parameter α_1 describes the chance, in log odds, of inducing a deficit as the location of electrocortical mapping increasingly overlaps the cortical region necessary for the task. The amount of electrical current from the j th electrode site that overlaps the cortical region of interest, standardized to be between 0 and 1, is represented as $H(\mu_i, \rho_i, x_{ij})$. The distribution of the electrical current was modeled using a mixture of three bivariate Gaussian densities to closely approximate the distribution given by Nathan et al. (1993). Given this distribution, Monte Carlo integration was used to calculate $H(\mu_i, \rho_i, x_{ij})$.

The numbers of individual and population templates were considered unknown parameters that were estimated from the

data. Prior distributions were the same as those used in Miglioretti et al. (2002). The model was fit using the Bayesian approach of Reversible Jump Markov Chain Monte Carlo (Green 1995) to simulate parameter values from their joint posterior distribution. Individual probability contours were derived for each patient from the posterior distribution to determine the location, shape, and size of cortical regions associated with auditory discrimination and comprehension. Probable locations of deficits in the study population were also estimated by pooling information across patients. The estimated size of individual and population regions was based on the computed area of regions having at least a 5% posterior probability of being critical for the function tested. The 95% highest posterior density intervals (HPD), similar to 95% confidence intervals (Gelman et al. 1995), were calculated from the posterior distributions using PROC KDE (SAS Institute 2000). We implemented each model for 40,000 sweeps, discarded the first 20,000 sweeps for burn-in, and saved every fifth sweep. To assess convergence of the sampler, we ran multiple chains starting at different initial values to ensure the model was converging to the same estimates.

Results

A total of 216 electrode pairs were tested across the 14 patients (mean 15 pairs/patient; range 9–25 pairs/patient). ECM induced auditory discrimination deficits at a single electrode site in 13/14 patients (Fisher's exact test, $p < 0.001$ in all cases). These sites were localized to the posterior half of the superior and middle temporal gyri (Fig. 1). Analysis of patients' syllable discrimination errors revealed no dissociation for words versus non-words, or consonant voicing versus place-of-articulation (Fisher's exact test, $p > 0.35$). Similarly, discrimination of synthesized syllables was significantly impaired at the same sites as discrimination of digitized syllables in seven patients (Fisher's exact test, $p < 0.05$ in all cases) and borderline significantly impaired in one patient ($p = 0.093$). The only stimulus-related dissociation observed was for syllable versus tone discrimination, with the latter remaining intact at all sites, including those where syllable discrimination was impaired (Fisher's exact test, $p = 1.0$ in all cases).

Auditory comprehension was impaired in all patients at a total of 70 electrode pairs (mean 5.7 pairs/patient; range 1–12 pairs/pairs), with no dissociations observed for phrases versus single words. Because patients' baseline comprehension was at ceiling, the proportion of correct responses at each electrode was compared to one by calculating exact binomial 95% confidence intervals. For all patients, confidence intervals excluded the value of one, indicating a significant impairment ($p < 0.05$, in all cases). Auditory comprehension was always impaired at more electrode sites than auditory discrimination (sign test, $p < 0.0001$). Auditory comprehension was impaired at the same sites as auditory discrimination and at other sites in the temporal (14 patients), frontal (7 patients), and parietal (2 patients) lobes.

Template Mixture Models showed differences in the estimated population regions for auditory discrimination and comprehension (Fig. 1). The estimated population region for auditory discrimination was 2.00 mm^2 (95% highest posterior density (HPD) = $0.05\text{--}6.08 \text{ mm}^2$), while

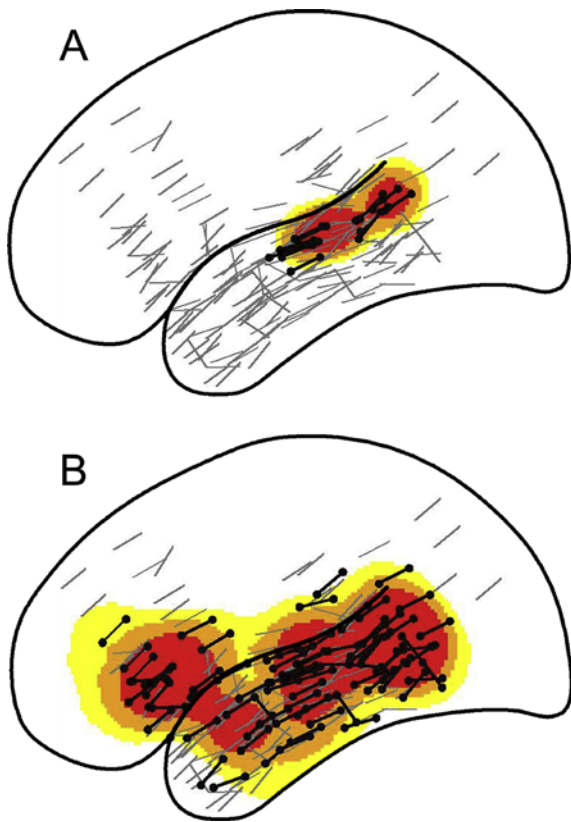


Fig. 1A, B Population probability densities of **A** auditory discrimination and **B** auditory comprehension deficits induced during electrocortical mapping in 14 patients. The *larger black dots* represent sites where auditory discrimination and auditory comprehension were impaired. *Gray lines* represent sites where performance on both auditory tasks remained intact. *Yellow contours*: $0.05 \leq p < 0.10$; *orange contours*: $0.10 \leq p < 0.20$; *red contours*: $p > 0.20$

auditory comprehension was 13.12 mm^2 (95% HPD = $7.78\text{--}18.76 \text{ mm}^2$). The probability that auditory comprehension mapped to a larger cortical area than auditory discrimination was 0.991 (estimated difference = 7.98 mm^2 , 95% HPD = $4.72\text{--}11.43 \text{ mm}^2$). Repeat testing, at 2-day intervals in four patients, yielded identical patterns of deficit for all experimental conditions.

TMM also revealed intersubject differences when task and stimulus variables were held constant. Two distinct auditory discrimination centers emerged from the estimated population regions, both overlaid on the superior and middle temporal gyri and distinguishable along the anterior-posterior axis (Fig. 1). The 13 patients with auditory discrimination deficits were roughly divided between the two centers (7 versus 6), with no evidence of gender stratification: anterior center (two males, five females), posterior center (two males, four females). The lack of discrimination deficits in one patient initially suggested additional intersubject variability. However, inspection of cortical regions associated with the maximum probability of a discrimination deficit revealed no corresponding electrode coverage in this patient.

Individual subject differences also interacted with task effects. Individual regions associated with auditory

comprehension (intersubject variation (VAR) = 2.69, 95% HPD 1.74–4.05) were consistently more variable in size than those associated with auditory discrimination (VAR = 1.04, 95% HPD = 0.42–1.96). Moreover, the sums of intersubject variances associated with the 2-dimensional template locations were 7.9 and 7.8 for comprehension (95% HPD = 4.7–13.4 and 4.8–12.1) compared to only 1.3 and 1.1 for discrimination (95% HPD = 0.4–4.3 and 0.2–3.8).

Discussion

Statistical modeling of ECM data revealed consistent task, stimulus, and interpatient effects on left hemisphere cortical representations of auditory speech processing. Template Mixture Models showed the distribution of auditory discrimination deficits to be smaller, more localized, and less variable across patients than that of auditory comprehension. Localization of auditory discrimination deficits to the posterior half of the superior and middle temporal gyri is consistent with other brain mapping studies (Demonet et al. 1992; Zatorre et al. 1992; Binder et al. 2000; Benson et al. 2001; Vouloumanos et al. 2001). The highly localized and invariant nature of the auditory discrimination deficits observed is consistent with the lack of deficits in one patient with no electrode coverage of this region and with the reported lack of speech perception deficits in some stroke patients with posterior temporal lobe lesions, a finding previously attributed to individual variability (Basso et al. 1977). In contrast to other brain mapping studies, auditory discrimination was not mapped to regions outside the temporal lobe, including the inferior frontal or parietal lobes (Ojemann and Mateer 1979; Zatorre et al. 1992; Celsis et al. 1999; Burton et al. 2000). This may reflect subtle differences in the phonological processing requirements of the discrimination tasks administered. Discrimination tasks that involve phonological segmentation of intrasyllabic components (e.g. syllable initial or final consonants) are thought to recruit inferior frontal and parietal lobe resources, in contrast to whole-syllable discrimination paradigms, like ours, that do not require explicit phonological segmentation (Zatorre et al. 1992; Celsis et al. 1999; Burton et al. 2000). Lack of evidence for involvement of the superior temporal sulcus is also at odds with recent reports (Binder et al. 2000). However, ECM electrodes were implanted over lateral cortex, precluding mapping of cortical sulci.

Stimulus effects were observed only for auditory discrimination of syllables versus frequency-modulated tones. At sites where syllable discrimination was impaired, tone discrimination remained intact and was not impaired elsewhere. This finding supports the view that speech is processed selectively by some cortical resources (Benson et al. 2001; Vouloumanos et al. 2001). However, we cannot rule out differences in acoustic complexity, as recently suggested (Johnsrude et al. 1997; Binder et al. 2000). Although the tone stimuli were matched to speech

in their frequency transitions, they lacked the spectral harmonics and other acoustic feature combinations of the speech stimuli.

No cortical dissociations were observed for the other speech contrasts tested, including phonetic features of voicing versus place-of-articulation, lexical status, or synthesized versus natural speech sources. These findings are in agreement with other studies that have argued against the existence of individual phonetic feature detectors in auditory association cortex (Boatman et al. 1997; Binder et al. 2000). The lack of word-nonword dissociation suggests overlap in their cortical resources during simple auditory discrimination tasks. Similarly, reported dissociations for natural versus synthesized speech are rare and largely limited to dorsal prefrontal sulcus, which could not be tested with ECM (Benson et al. 2001).

TMM revealed individual variability in the cortical representations of auditory speech processing. When task and stimulus variables were held constant, two spatially distinct auditory discrimination centers were identified within the posterior superior and middle temporal gyri. Participation in either center was stratified by patient, suggesting effects of individual subject differences. Although gender differences were ruled out, other sources of individual variation, including genetics, learning, and environment, warrant further consideration (Benson et al. 2001). Identification of a functional subdivision within the posterior half of the superior and middle temporal gyri, independent of task and stimulus effects, may account for the lack of cortical overlap in this region among previous brain mapping studies. The presence of two distinct centers within the posterior temporal lobe was not evident from visual inspection of the electrode maps, underscoring the utility of using probability contours to analyze ECM data.

Individual variability was also evident in the cortical representations of auditory comprehension, consistent with the known influence of individual experience. In contrast to recent reports, however, we found no dissociation for comprehension of phrases versus single words in the anterior temporal or frontal lobes (Scott et al. 2000; Humphries et al. 2001). However, phrasal stimuli from the Token test, while clinically useful, are relatively simple and likely to require less semantic processing and more motor output than normal conversation. Compared with auditory discrimination, the cortical representation of auditory comprehension was also affected more by individual variability, suggesting an interaction between task and subject differences. This has implications for planning brain mapping studies, with fewer subjects needed for studies of low level auditory speech functions, such as syllable discrimination, and larger numbers of subjects needed for studies of auditory comprehension.

ECM provides comprehensive mapping of lateral cortex within one hemisphere. However, the contribution of other neural resources, including cortical sulci and the contralateral hemisphere, cannot be assessed. Another potential limitation is that ECM is performed in patient populations

with neurological disorders, constraining generalization of results to the normal population. Although our patients were screened for known sources of atypical language organization (e.g., early seizure onset, comorbid neuropathologies), other as yet unrecognized consequences of long-term seizure disorders might have affected their cortical organization.

In summary, these results confirm the utility of using TMM to quantify within- and between-subject sources of variability in brain maps derived from ECM. The Template Mixture Model is formulated using a generalized linear framework that is readily adapted to other sources of brain mapping data, including functional MRI, for direct comparisons of brain maps derived from multiple mapping techniques.

Acknowledgements This study was supported by NIDCD grant R01-DC005645. We thank G. Qian and N. Bardhan for technical assistance; Drs. B. Gordon, S. Zeger, C. McCulloch, and S. Reich for helpful discussion; and the reviewers for thoughtful comments.

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