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Multimodality language mapping in patients with left-hemispheric language dominance on Wada test

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Abstract

Objective—We determined the utility of electrocorticography (ECoG) and stimulation for detecting language-related sites in patients with left-hemispheric language-dominance on Wada test.

Methods—We studied 13 epileptic patients who underwent language mapping using event-related gamma-oscillations on ECoG and stimulation via subdural electrodes. Sites showing significant gamma-augmentation during an auditory-naming task were defined as language-related ECoG sites. Sites at which stimulation resulted in auditory perceptual changes, failure to verbalize a correct answer, or sensorimotor symptoms involving the mouth were defined as language-related stimulation sites. We determined how frequently these methods revealed language-related sites in the superior-temporal, inferior-frontal, dorsolateral-premotor, and inferior-Rolandic regions.

Results—Language-related sites in the superior-temporal and inferior-frontal gyri were detected by ECoG more frequently than stimulation ($p < 0.05$), while those in the dorsolateral-premotor and inferior-Rolandic regions were detected by both methods equally. Stimulation of language-related ECoG sites, compared to the others, more frequently elicited language symptoms ($p < 0.00001$). One patient developed dysphasia requiring in-patient speech therapy following resection

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Appendix A. Supplementary data Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.clinph.2012.01.027>.

of the dorsolateral-premotor and inferior-Rolandic regions containing language-related ECoG sites not otherwise detected by stimulation.

Conclusions—Language-related gamma-oscillations may serve as an alternative biomarker of underlying language function in patients with left-hemispheric language-dominance.

Significance—Measurement of language-related gamma-oscillations is warranted in presurgical evaluation of epileptic patients.

Keywords

Pediatric epilepsy surgery; Speech; Intracranial EEG; Electrical stimulation

1. Introduction

Cortical stimulation via chronically-implanted intracranial electrodes is performed to localize sites essential for language function in epileptic patients undergoing surgical resection (Zijlmans et al., 2009b; Lesser et al., 2010). Yet, stimulation is not an ideal gold standard method, since it carries the inherent risk of electrically-induced seizures, can take hours to complete, frequently relies upon subjective interpretation, and sometimes fails to detect language-related sites, especially in uncooperative or young patients (Schevon et al., 2007). Investigators have hypothesized that event-related gamma-oscillations on electrocorticography (ECoG) might serve as an alternative biomarker of underlying functions; augmentation of gamma-oscillations at 50 Hz is considered to represent task-related cortical activation (Sinai et al., 2005; Tanji et al., 2005). Previous ECoG studies of gamma-oscillations modulated by picture naming and word repetition tasks found that sites showing gamma-augmentation predicted language-related sites based on stimulation with 40–90% sensitivity and 40–80% specificity (Sinai et al., 2005; Towle et al., 2008; Wu et al., 2010; Miller et al., 2011). The present study employed a language task and analytic approach different from those applied in these previous ECoG studies. First, our patients were asked to comprehend full length auditory questions and overtly vocalize relevant nouns in response (Brown et al., 2008); such an auditory-language task requires not only semantic but also syntactic comprehension. Second, cortical stimulation was not treated as the sole gold standard (Schevon et al., 2007). All study patients had left-hemispheric language dominance based upon the Wada test; thus, it was presumed that the left superior-temporal gyrus (defined as Brodmann Area [BA] 22/41/42), inferior-frontal gyrus (BA 44/45), and dorsolateral-premotor region (BA 6) should contain sites essential for language comprehension and production with some degree of inter-subject spatial variability (Hickok and Poeppel, 2007; Menenti et al., 2011). We then determined whether ECoG mapping revealed language-related sites more frequently than direct cortical stimulation in the aforementioned regions. We also determined if patients developed dysphasic symptoms requiring speech therapy following cortical resection of language-related ECoG sites not otherwise detected by cortical stimulation.

2. Methods

2.1. Patients

This study has been approved by the Institutional Review Board at Wayne State University. The inclusion criteria consisted of: (i) patients with intractable focal epilepsy who underwent extraoperative subdural ECoG recording of the left cerebral hemisphere as a part of presurgical evaluation in Children's Hospital of Michigan or Harper University Hospital in Detroit; (ii) left-hemispheric language dominance determined by a Wada test (Shah et al., 2010); (iii) language mapping using cortical stimulation and measurement of gamma-

oscillations modulated by an auditory-language task (Brown et al., 2008); and (iv) written informed consent obtained before the study. The exclusion criterion consisted of: presence of massive brain malformations (such as perisylvian polymicrogyria or hemimegalencephaly) which confound anatomical landmarks for the central sulcus and Sylvian fissure. This cohort study included a consecutive series of 13 patients satisfying both inclusion and exclusion criteria (age range: 8–37 years; six females) (Table 1). Our study patients were younger than those in previous ECoG studies (median age: 14 years vs 27 years; $p = 0.001$ on Mann–Whitney U test; Sinai et al., 2005; Towle et al., 2008; Wu et al., 2010; Miller et al., 2011).

2.2. Wada test

All study patients had left-hemispheric language dominance as determined by Wada test, which was performed prior to subdural electrode implantation. Sodium amobarbital (2 mg/kg; maximum 125 mg per side) was injected into each internal carotid artery, separately; spontaneous speech, naming, repetition and ability to follow complex commands were evaluated following each injection (Shah et al., 2010). Language impairment not attributable to unilateral facial weakness was noted upon left-hemispheric sodium amobarbital injection in all patients, with language function largely unaffected by right hemispheric injection. All results are as reported by well-trained Clinical Neuropsychologists (R.R. and D.F.).

2.3. Subdural electrode placement and extraoperative video-ECoG recording

Platinum electrodes (intercontact distance: 10 mm; diameter: 4 mm; electrode contacts: 70–128 per patient) were surgically placed in the subdural space over left hemisphere cortical regions, involving the superior-temporal gyrus, inferior-frontal gyrus, dorsolateral-premotor region, and inferior-Rolandic region (defined as BA 4/3/1/2 not more than 4 cm superior from the sylvian fissure; Haseeb et al., 2007; Fukuda et al., 2008). All electrode plates were stitched to adjacent plates or the edge of dura mater, to avoid movement of subdural electrodes after placement. In all patients, intraoperative pictures were taken with a digital camera before dural closure as well as after re-opening (Asano et al., 2009). All electrodes were displayed on the three-dimensional brain surface reconstructed from high-resolution MRI (Wu et al., 2011). ECoG signals were obtained for 3–5 days with a sampling rate of 1000 Hz, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc., Foothill Ranch, CA, USA). The averaged voltage of ECoG signals derived from the fifth and sixth intracranial electrodes on the amplifier was used as the original reference; ECoG signals were then re-montaged to a common average reference. Channels contaminated with large interictal epileptiform discharges or artifacts were visually identified and excluded from the common average reference (Wu et al., 2011; Nagasawa et al., 2011). Surface electromyography electrodes were placed on the left and right deltoid muscles, and electrooculography electrodes were placed 2.5 cm below and 2.5 cm lateral to the left and right outer canthi. ECoG traces were visually inspected with a low-frequency filter at 53 Hz and a sensitivity of 20 μ V/mm; thereby, broadband signals synchronized with facial and ocular muscle activities seen on electrooculography electrodes were treated as artifacts (Jerbi et al., 2009; Kovach et al., 2011).

2.4. Language mapping using ECoG

While awake and comfortably seated with intracranial electrodes in place, each patient submitted to an auditory-language task. Patients were instructed to overtly verbalize a one- or two-word answer (e.g.: ‘Ears’) to a given auditory question (e.g.: ‘What do you hear with?’). Each ECoG trial was transformed into the time–frequency domain using complex demodulation via BESA® software (BESA GmbH, Gräfelfing, Germany; Hoehstetter et al., 2004). A given ECoG signal was assigned an amplitude (a measure proportional to the square root of power) as a function of time and frequency (in steps of 10 ms and 5 Hz). The

time–frequency transform was obtained by multiplication of the time-domain signal with a complex exponential, followed by a low-pass filter. The low-pass filter used here was a finite impulse response filter of Gaussian shape, making the complex demodulation effectively equivalent to a Gabor transform. The filter had a full width at half maximum of 2×15.8 ms in the temporal domain and 2×7.1 Hz in the frequency domain. The corresponding time–frequency resolution was ± 15.8 ms and ± 7.1 Hz (defined as the 50% power drop of the finite impulse response filter). ECoG traces were aligned to: (i) stimulus (question) onset; (ii) stimulus offset; and (iii) response (answer) onset. We determined ‘when,’ ‘where,’ and ‘how much’ gamma-oscillations at 50–120 Hz (averaged across trials) were augmented compared to the resting periods. Further methodological details (such as the reference periods) are described in Supplementary Fig. S1. We also determined whether the degree of such gamma-augmentation reached significance using studentized bootstrap statistics followed by Simes’ correction (Brown et al., 2008; Koga et al., 2011). Sites surviving correction showing significant gamma-augmentation spanning (i) at least 20-Hz in width and (ii) at least 20-ms in duration (Wu et al., 2011) were defined as ‘language-related ECoG sites’ in the present study.

2.5. Language mapping using electrical stimulation

Following the above-mentioned auditory-language task, language mapping by cortical stimulation was performed (Brown et al., 2008; Koga et al., 2011; Wu et al., 2011). Patients and Clinical Neuropsychologists (R.R. and D.F.) were blinded to the results of language mapping using ECoG. A pulse-train of repetitive electrical stimuli was delivered to subdural electrode pairs, using the Grass constant-current stimulator (Astro-Med Inc., West Warwick, RI, USA). The stimulus frequency was 50 Hz, the pulse duration was 300 μ s, and the train duration ranged from 5 to 10 s. Initially, stimulus intensity was set to 3 mA, and stimulus intensity was increased up to 9 mA in a stepwise manner until a clinical response or after-discharge was observed. During each period of stimulation, each patient was asked to answer brief auditory questions similar to those used for ECoG mapping. Other tasks such as picture naming, counting, and reciting ABC’s were also performed. Sites at which stimulation reproducibly resulted in auditory perceptual changes, failure to verbalize correct responses, or sensorimotor symptoms involving the mouth or throat were determined by at least two investigators, always including at least one Clinical Neuropsychologist. It is plausible to assume that auditory perceptual changes induced by stimulation would reflect the underlying function of auditory analysis and stimulation-induced failure to verbalize correct responses would reflect the underlying function necessary for auditory naming; stimulation-induced sensorimotor symptoms involving the mouth or throat would reflect the underlying function involved in articulation. In the present study of patients with ECoG sampled from the left hemisphere, all sites at which stimulation induced such clinical symptoms were uniformly defined as ‘language-related stimulation sites’. Sites were declared ‘not proven to be language-related’ if after-discharges were elicited without a clinical symptom, clinical responses failed to be elicited by maximal stimuli, or baseline language performance between electrical stimuli was too poor to clearly distinguish inducible language deficits.

2.6. Validation of language-related ECoG sites

2.6.1. Anatomical correlation—We determined how frequently ECoG and stimulation identified language-related sites in the superior-temporal, inferior-frontal, dorsolateral-premotor, and inferior-Rolandic regions. We then compared the sensitivity in identifying language-related sites between ECoG and cortical stimulation in the aforementioned regions of interest using Fisher’s exact probability test.

2.6.2. Stimulation correlation—We determined whether stimulation of a pair including language-related ECoG sites elicited language-related symptoms more frequently than that not including language-related ECoG sites using Fisher's exact probability test.

2.6.3. Language symptoms after surgery—As previously described (Asano et al., 2009), the extent of cortical resection was determined after the team and the patient (or the guardian) had extensive discussions regarding the risks and benefits of surgical resection of eloquent areas including language-related stimulation sites. The results of language mapping using ECoG were not used for surgical decision-making; each language-related ECoG site was considered to be involved but not necessarily essential for language function unless cortical stimulation proved it to be essential (Crone et al., 2006). We determined whether cortical damage involving language-related ECoG sites in the superior-temporal, inferior-frontal, dorsolateral-premotor, or inferior-Rolandic regions was associated with the occurrence of new-onset post-operative dysphasic symptoms requiring speech therapy. The necessity of speech therapy was determined by a speech therapist, who was blinded to the results of language mapping using ECoG. We could not correlate between the extent of cortical damage and the results of neuropsychological tests in this cohort of patients, since we failed to systematically conduct neuropsychological assessments before and after surgery.

3. Results

3.1. Sensitivity of ECoG and stimulation in identifying language-related sites

ECoG and stimulation detected language-related sites in the superior-temporal gyrus with sensitivity of 13/13 and 8/13, respectively (Figs. 1 and 2). Likewise, sensitivity of ECoG and stimulation was 12/13 and 6/13 in the inferior-frontal gyrus, 12/13 and 10/13 in the dorsolateral-premotor region, and 13/13 and 11/13 in the inferior-Rolandic region. Language-related sites in the superior-temporal and inferior-frontal gyri were detected by ECoG more frequently than stimulation; $p = 0.04$ and $p = 0.005$, respectively.

3.2. Accuracy of ECoG in identifying language-related stimulation sites

In the left temporal lobe, 21 out of 66 electrode pairs (31.8%) involving language-related ECoG sites as well as 2 out of 75 electrode pairs (2.6%) not involving language-related ECoG sites turned out to be language-related cortical stimulation sites (Table 2). Stimulation of an electrode pair involving language-related ECoG sites elicited language-related symptoms 11.9 times more frequently than those not involving language-related ECoG sites ($p < 0.00001$). The sensitivity and specificity of language-related ECoG for identifying language-related stimulation sites in the left temporal lobe were 0.91 and 0.62, respectively.

In the left frontal lobe, 34 out of 110 electrode pairs (30.9%) involving language-related ECoG sites as well as 7 out of 141 electrode pairs (2.7%) not involving language-related ECoG sites turned out to be language-related stimulation sites (Table 2). Stimulation of an electrode pair involving a language-related ECoG site elicited language-related symptoms 6.2 times more frequently than that not including language-related ECoG sites ($p < 0.00001$). The sensitivity and specificity of language-related ECoG for identifying language-related stimulation sites of the frontal lobe were 0.83 and 0.64, respectively.

3.3. Temporal characteristics of language-related gamma-augmentation

Maximal language-related gamma-amplitudes were observed during the stimulus at superior-temporal sites, about stimulus offset and between stimulus offset and response onset in the inferior-frontal gyrus and dorsolateral-premotor region, and immediately following response onset in the inferior-Rolandic region (Fig. 3). Regardless of locations of

interest, language-related gamma-augmentation most commonly involved the frequency band of 80–100 Hz, as previously reported (Sinai et al., 2005; Towle et al., 2008; Koga et al., 2011).

3.4. Observations during language mapping procedures and following surgery

An unwanted generalized tonic-clonic seizure was induced by cortical stimulation of sites outside of seizure onset zones in patient #13; stimulation mapping was resumed no sooner than 4 h following this seizure.

The postoperative language outcome for each patient is summarized in Table 3. Four patients developed at least transient but clinically observable language disturbance that requiring either inpatient or outpatient speech therapy. Cortical damage involving language-related ECoG sites in the superior-temporal, inferior-frontal, or dorsolateral-premotor regions was associated with the requirement of post-operative speech therapy ($p = 0.007$ on Fisher's exact probability test). Patient #2 developed expressive dysphasia requiring speech therapy following cortical resection involving language-related ECoG sites in the dorsolateral-premotor region, while stimulation mapping failed to identify language-related stimulation sites due to uncooperativeness (Fig. 1).

4. Discussion

In the present study of patients known to have left-hemispheric language dominance on Wada test, we found that ECoG mapping, more frequently than stimulation mapping, detected language-related sites in the left superior-temporal gyrus (widely known to be part of Wernicke's speech region) as well as the left inferior-frontal region (also known to typically contain Broca's speech region). This observation cannot be explained by chance detection of language-related ECoG sites in widespread regions, because of the following reasons: (i) stimulation of language-related ECoG sites more frequently elicited language symptoms compared to that of others; (ii) language-related gamma-amplitudes in the superior-temporal gyrus peaked during auditory stimuli, while those in the inferior-frontal region peaked about stimulus offset or between stimulus offset and response onset; and (iii) cortical resection of language-related ECoG sites not otherwise detected by cortical stimulation resulted in dysphasic symptoms requiring speech therapy in one patient. Language-related gamma-oscillations on ECoG may serve as an alternative biomarker of underlying language function in patients with left-hemispheric language dominance.

Language-related gamma-oscillations on ECoG cannot be used as a stand-alone biomarker. Significance of gamma-augmentation may vary across anatomical locations. For example, we still don't know what function is reflected by or the necessity of gamma-augmentation in the medial-temporal region, of which temporal characteristics were similar to those seen in the inferior frontal and dorsolateral-premotor regions. In four patients, the posterior medial temporal region showed gamma-augmentation not attributable to subtle EMG artifacts (Jerbi et al., 2009; Kovach et al., 2011; Nagasawa et al., 2011). All four patients underwent anterior temporal lobe resection including language-related ECoG sites in the posterior medial-temporal region, but none developed objectively noticeable dysphasia (Table 3). A previous study of 33 patients with left temporal lobe epilepsy suggested that resection of intact medial-temporal structures resulted in not aphasia but naming decline detected by neuropsychological tests, while stimulation failed to evaluate the integrity of medial-temporal structures (Hamberger et al., 2010). Further studies of a larger cohort of patients using pre- and post-operative neuropsychological tests are warranted to determine the significance of language-related gamma-augmentation in each anatomical region. Such studies could also determine the dose-dependent relationship between the degree of gamma-augmentation and the severity of language declines following resection of such sites.

The temporal characteristics of gamma-augmentations in our regions of interest were consistent with the literature. Gamma-augmentation in the superior-temporal gyrus reached the maximum during auditory questions and is likely to reflect perception of acoustic or phonetic information (Sinai et al., 2005; Towle et al., 2008; Brown et al., 2008). Gamma-augmentation in the inferior-frontal and dorsolateral-premotor regions reached the maximum around the offset of questions or between question offset and response onset and is likely to reflect working memory engagement following question delivery, generation of semantically appropriate nouns, or preparation of overt vocalization (Blank et al., 2002; Hickok and Poeppel, 2007). Gamma-augmentation in the inferior-Rolandic region reached maximal amplitude immediately after the onset of response vocalization and is likely to reflect execution of motor commands, processing of somatosensory feed-back, or both (Fukuda et al., 2010).

Gamma-augmentation on ECoG does not directly differentiate ‘sites necessary for language’ from ‘those involved in language.’ Thus, other measures should be integrated to determine the clinical significance of gamma-augmentation at a given site. In the present study, all patients had left-hemispheric language dominance on Wada test; thus, we could assume that the left superior-temporal, inferior-frontal, and dorsolateral-premotor regions should contain sites essential for language (Hickok and Poeppel, 2007). Repetitive transcranial magnetic stimulation (rTMS) is potentially an alternative noninvasive diagnostic modality to localize the cortical regions essential for language function, though the reported accuracy has been variable across centers and rTMS results may vary even within individuals (reviewed in Pelletier et al., 2007). Handedness (Möddel et al., 2009), location and nature of lesions on MRI (Rasmussen and Milner, 1977), functional MRI (Binder, 2011), and diffusion tensor imaging (Tiwari et al., 2011) could be integrated to estimate the language dominant hemisphere, though none of these modalities necessarily localize ‘essential’ language sites. Further studies are warranted to determine the diagnostic utility of ECoG mapping combined with the aforementioned noninvasive modalities in the prediction of language outcome following epilepsy surgery.

The benefits of ECoG mapping include the lack of risk for electrically-induced seizures during recording. ECoG mapping could be done while antiepileptic medications were discontinued or reduced and clinicians were waiting for seizures to occur. Patient participation time was less than 20 min even though ECoG data processing required hours to determine the statistical significance of gamma-augmentations (Brown et al., 2008). Conversely, stimulation mapping was done once the seizure onset zone was localized and antiepileptic drugs such as phenytoin were loaded, in order to reduce the risk of electrically-induced seizures. Nonetheless, patient #13 developed an unwanted generalized tonic-clonic seizure following stimulation of sites outside of seizure onset zones. Patient #2 failed to satisfactorily co-operate with the stimulation mapping procedures due to a prolonged postictal state following a spontaneous seizure. Stimulation mapping took at least 1 h of participation in the majority of patients and the results may have been affected by variance in fatigue across stimulated sites.

Inherent limitations of ECoG and stimulation mappings include: sampling limitation, antiepileptic drugs, and inability to study healthy volunteers. Many of our patients had subdural electrodes placed only on the cortical surface of the presumed epileptogenic hemisphere; we were not able to evaluate the non-dominant hemisphere or subcortical structures. Chronic usage of antiepileptic drugs might have affected the results of language mappings, although such medications were discontinued during the language tasks. Phenytoin was reported to elevate motor thresholds to TMS but had no effect on motor-evoked potential amplitudes (Chen et al., 1997). A human study using macro-electrodes showed that reduction of antiepileptic drugs was followed by a 3% increase in duration of

epileptogenic high-frequency oscillations at 80 Hz spontaneously arising from the seizure onset zone (Zijlmans et al., 2009a). The possible effects of interictal epileptiform discharges on language-related gamma-augmentation were not evaluated in the present study. A previous fMRI study showed that interictal spike-and-slow wave discharges, especially those with large slow wave components, were followed by a lingering decline in cerebral blood flow (Kobayashi et al., 2006). Further studies using a trial-by-trial analysis are warranted to determine the transient effects of interictal epileptiform discharges on language-related gamma-oscillations.

A main difference from previous studies is the difference in patient age. The median age of our patients was 14 years, while that of previous ECoG studies was 27 (Sinai et al., 2005; Towle et al., 2008; Wu et al., 2010; Miller et al., 2011). We still don't know how the age influenced the ECoG findings; nearly all patients showed language-related gamma-augmentation in each of the four regions of interest in the present study. A previous behavioral study using eye tracking suggested that children, by age of 8 years, begin parsing ambiguous phrases delivered auditorily in a context-contingent manner as young adults do (Trueswell et al., 1999). Indeed, newborns have been shown to have a stronger left-dominance in superior temporal regions in response to the mother's native language compared to unknown foreign languages (Sato et al., 2011). Although adults exhibited a larger cortical area of activation in left inferior and middle frontal gyri, a previous fMRI study of healthy subjects demonstrated that measures of language lateralization between the hemispheres do not differ between children and adults during a semantic fluency task; it appears that such activation was strongly lateralized to the left hemisphere by 7 years of age (Gaillard et al., 2003). Likewise, a longitudinal fMRI study of healthy children enrolled at ages 5–7 years for 5 years demonstrated evidence of progressive participation in language processing by the inferior and middle frontal gyri of the left hemisphere with increasing age (Szaflarski et al., 2006).

We cannot rule out the possibility that the testing order may have favorably influenced the ECoG findings in the present study. Epileptologists (A.S., M.A., and E.A.) but not Clinical Neuropsychologists were aware of the results of time–frequency analyses prior to electrical stimulation; epileptologists clinically determined the electrode stimulation sequence and neuropsychologists determined the effects of stimulation on language performance during each stimulation trial. Further studies with a double-blind design are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Measurement of event-related gamma-oscillations at 50–120 Hz detected language sites more frequently than electrical stimulation in epileptic patients with left-hemispheric language dominance on Wada test.
- Stimulation of sites showing event-related augmentation of gamma-oscillations more frequently resulted in temporary language-related symptoms, compared to that of the other sites.
- Cortical resection of sites showing event-related augmentation of gamma-oscillations resulted in dysphasic symptoms in an epileptic patient, while electrical stimulation failed to identify the language sites.

Fig. 1.

Language mapping for an 8-year-old boy with medically-uncontrolled epilepsy (patient 2). (A) Language-related ECoG sites involved the left superior temporal, inferior-frontal, dorsolateral-premotor and inferior-Rolandic regions. Nine pairs of frontal sites and 2 pairs of parietal sites were stimulated and we failed to detect language-related sites, since the patient was uncooperative. Stimulation successfully found the primary sensorimotor cortex for the hand. Cortical resection involved the left dorsolateral-premotor and inferior-Rolandic regions. Following surgery, the patient developed an expressive dysphasia. (B) Gamma-augmentation occurred during questions and answers in the superior temporal gyrus (electrode 1), around the offset of questions in the inferior-frontal gyrus (electrode 2), before the onset of answers in the dorsolateral-premotor region (electrode 3) and during answers in the inferior Rolandic region (electrode 4).

Fig. 2.

Language mapping for a 14-year-old girl with medically-uncontrolled epilepsy (patient 6). (A) Language-related ECoG sites involved the left superior temporal, inferior-frontal, dorsolateral-premotor and inferior-Rolandic regions. Twenty-seven pairs including at least one frontal site were stimulated, while 12 pairs of temporal lobe sites were stimulated. Thereby, electrical stimulation detected language-related sites in the left superior-temporal, dorsolateral-premotor and inferior-Rolandic regions but not in the inferior-frontal gyrus. Cortical resection involved the left anterior temporal region. No dysphasic symptoms were noted postoperatively. (B) Gamma-augmentation occurred during questions and answers in the superior-temporal gyrus (electrode 1), around the offset of questions in the inferior-frontal gyrus (electrode 2) and dorsolateral-premotor region (electrode 3) and during answers in the inferior Rolandic region (electrode 4).

Fig. 3.

Temporal characteristics of language-related gamma-augmentation. The timing of maximal gamma-augmentation at 80–100 Hz (Sinai et al., 2005; Towle et al., 2008; Koga et al., 2011) was plotted as a function of time, using box plots showing the maximum, 75% percentile, median, 25% percentile and minimum across all language-related ECoG sites in each region. (A) The box plots relative to the onset of question stimuli showed that the maximal gamma-augmentation in the superior-temporal gyrus generally occurred during questions. (B) The box plots relative to the offset of question stimuli showed that the peaks of gamma-augmentation in the inferior-frontal and dorsolateral-premotor regions generally occurred around the offset of question stimuli. (C) The box plots relative to response onset showed that the maximal gamma-augmentation in the inferior-Rolandic region as well as reactivations in the superior-temporal gyrus occurred soon after response onset.

Table 1

Patient characteristics.

Patient/ Gender	Age (years)	Antiepileptic medications	Surgical resection	MRI	Pathology	Pre-op VCI	Post-op VCI
1/M	8	CBZ	Lesionectomy only in Lt T	Tumor	Tumor	91	NA
2/M	8	OXC, TPM	Cortical resection in Lt FP	Non-lesional	Gliosis	87	77 (17 months after surgery)
3/F	9	VGB, CBZ, VPA	Lesionectomy + surrounding cortical resection in Lt F	Tubers	Tubers	99	NA
4/M	12	OXC, LCM, VPA	Cortical resection in Lt T	Focal cortical dysplasia	Focal cortical dysplasia	83	NA
5/M	14	OXC, LEV	Cortical resection in Lt F	Post AVM resection	Gliosis	100	96 (19 months after surgery)
6/F	14	OXC, LTG	Cortical resection in Lt T	Increased FLAIR signals in Lt medial frontal region	Gliosis	55	NA
7/F	14	OXC	Lesionectomy + surrounding cortical resection in Lt T	Tumor	Tumor	74	NA
8/M	15	LEV, LTG	Lesionectomy + surrounding cortical resection in Lt T	Tumor	Tumor	77	NA
9/F	16	OXC, LEV	Cortical resection in Lt PO	Non-lesional	Gliosis	121	NA
10/M	17	OXC, LTG	Cortical resection in Lt F	Post-trauma	Gliosis	78	72 (11 months after surgery)
11/M	20	CBZ, LCM	Cortical resection in Lt T	Non-lesional	Gliosis	82 ^a	NA
12/F	28	LCM, CBZ	Cortical resection in Lt T	Non-lesional	Gliosis	75 ^a	NA
13/F	37	LTG, LCM	Cortical resection in Lt T	Increased FLAIR signals in Lt cingulate cortex	Gliosis	72 ^a	NA

LEV: levetiracetam, LTG: lamotrigine, LCM: lacosamide, CBZ: carbamazepine, OXC: oxcarbazepine, TPM: topiramate, VPA: valproate, F: frontal, T: temporal, O: occipital, P: parietal, Pre-op: preoperative, Post-op: postoperative, VCI: verbal comprehension index.

^aVerbal IQ. All patients were right-handed.

Table 2

Probability of stimulation-induced language symptoms.

Patient	Temporal lobe		Frontal lobe	
	Pairs containing language-related ECoG sites	Pairs not containing language-related ECoG sites	Pairs containing language-related ECoG sites	Pairs not containing language-related ECoG sites
1	33% = 2/6 pairs	Not stimulated	33% = 2/6 pairs	0% = 0/10 pairs
2	Not stimulated	Not stimulated	0% = 0/4 pairs	0% = 0/5 pairs
3	0% = 0/6 pairs	0% = 0/7 pairs	33% = 2/6 pairs	7% = 1/15 pairs
4	25% = 1/4 pairs	0% = 0/8 pairs	0% = 0/9 pairs	0% = 0/13 pairs
5	100% = 1/1 pair	0% = 0/2 pairs	25% = 1/4 pairs	10% = 3/29 pairs
6	67% = 4/6 pairs	0% = 0/6 pairs	13% = 2/15 pairs	8% = 1/12 pairs
7	71% = 5/7 pairs	0% = 0/7 pairs	56% = 5/9 pairs	25% = 1/4 pairs
8	33% = 2/6 pairs	0% = 0/6 pairs	33% = 1/3 pairs	0% = 0/12 pairs
9	33% = 2/6 pairs	0% = 0/2 pairs	55% = 6/11 pairs	0% = 0/2 pairs
10	0% = 0/5 pairs	0% = 0/6 pairs	14% = 2/14 pairs	0% = 0/16 pairs
11	50% = 2/4 pairs	9% = 1/11 pairs	42% = 5/12 pairs	0% = 0/3 pairs
12	33% = 1/3 pairs	0% = 0/11 pairs	33% = 1/3 pairs	10% = 1/10 pairs
13	8% = 1/12 pairs	11% = 1/9 pairs	50% = 7/14 pairs	0% = 0/10 pairs
Total	32% = 21/66 pairs	3% = 2/75 pairs	31% = 34/110 pairs	5% = 7/141 pairs

Table 3

Relationship between cortex affected by surgery and postoperative language symptoms.

Patient	Language-related ECoG sites	Language-related stimulation sites	Postoperative language symptoms	Speech therapy
1	Superior-temporal	Superior-temporal	(-)	(-)
2	Dorsolateral-premotor ^b	(-)	Expressive dysphasia (initially no spontaneous speech)	Inpatient & outpatient
3	(-)	(-)	(-)	(-)
4	(-)	(-)	(-)	(-)
5	Inferior-frontal ^c	Dorsolateral-premotor ^b	Temporary expressive dysphasia (initially limited spontaneous speech)	Outpatient
6	(-) ^d	(-)	(-)	(-)
7	Superior-temporal	Superior-temporal	Temporary receptive dysphasia	Outpatient
8	Superior-temporal ^d	Superior-temporal	Receptive dysphasia	Inpatient & outpatient
9	(-) ^a	(-)	(-); visual field deficits	(-)
10	(-) ^b	(-)	(-); temporary hemiparesis	(-)
11	(-) ^{d,e}	(-) ^e	Mild and subjective difficulty in retrieving words	(-)
12	(-) ^d	(-)	Mild and subjective difficulty in retrieving words	(-)
13	(-) ^{d,e}	(-)	Mild and subjective difficulty in retrieving words	(-)

In patient 1, a tumor in the posterior portion of the superior temporal gyrus was located under an electrode classified as a language-related site, and the patient underwent lesionectomy alone.

^aOccipital.

^bSuperior-dorsolateral-prefrontal.

^cMedial-frontal.

^dMedial-temporal.

^eInferior-temporal.