Variation in the topography of the speech production cortex verified by cortical stimulation and high gamma activity

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In this study, we have addressed the question of functional brain reorganization for language in the presence and absence of anatomical lesions in two patients with epilepsy using cortical stimulation mapping and high gamma (HG) activity in subdural grid recordings. In both, the expressive language cortex was defined as the cortical patch below the electrode(s) that when stimulated resulted in speech arrest, and during speech expression tasks generated HG activity. This patch fell within the borders of Broca's area, as defined anatomically, in the case of the patient with a lesion, but outside that area in the other, lesion-free patient. Such results highlight the necessity for presurgical language mapping in all cases of surgery involving the language-dominant hemisphere and suggest that HG activity during expressive language tasks can be informative and helpful in conjunction with cortical stimulation mapping for expressive language mapping. *NeuroReport* 25:1411–1417 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

As is well known, the original specification of Broca's area was a result of natural experiments; that is, lesions due to stroke that resulted in suppression of the capacity to produce speech [1]. The inability to produce speech may have other causes besides disruption of the putative networks mediating language, such as disruption of circuits controlling the orofacial musculature (i.e. motor, premotor, and supplementary motor circuitry). Natural lesions, varying in severity and the extent of the cortical area they disrupt, have made precise anatomic demarcation of the language-specific region (as opposed to the premotor and motor regions, resulting in dysarthria) very difficult. During the late 19th century, controversies raged with regard to the topography of the region and its precise significance [2–4]. Slowly, however, a consensus was reached that the areas specific to language production proper are the pars opercularis [Brodmann's area (BA) 44] and triangularis (BA 45) of the left inferior frontal gyrus [5], with distinct cytoarchitectonic characteristics (see Petrides *et al.* [6] for an example).

More precise experimental methods of cortical stimulation mapping (CSM) have amended the original notion of Broca's area in a fundamental manner [7]. Recently, subdural recordings used along with CSM were found to afford a more precise estimation of the extent of the cortex mediating speech production. Namely, it has been shown that the area that is essential for speech production, as well as many other areas involved in different higher functions, may not always have the topography usually associated with it. Such aberrant localization of functional circuits may result from the presence of congenital structural lesions or an acquired structural lesion in their vicinity, resulting in functional reorganization of the cortex for functions such as language [8,9] and even for more basic functions [10].

CSM is currently accepted as the gold standard for language mapping, although it is not without some limitations (see recent work by Papanicolaou *et al.* [11] and Cervenka *et al.* [12]). Accordingly, several investigators have utilized an alternative approach to localizing language-specific regions of the cortex on the basis of intracranial EEG (iEEG) recording [12–16]. It is generally found that enhancement of the power of iEEG recording in the high gamma (>50 Hz) frequency range is a reliable marker of cortical activation and provides functional language mapping of high spatial and temporal resolutions [12,17].

In the current study, we explored the expressive language cortex in two patients with epilepsy and documented the variation in topography of the language production cortex. Subdural electrodes over the putative speech production area were placed on the basis of CSM and high gamma (HG) activity in iEEG recordings during three language tasks: (i) an object naming task involving overt naming of objects; (ii) a syllable articulation task involving overtly repeating simple syllables ('ba' or 'pa')

and (iii) a continuous recognition memory (CRM) task involving listening to words (see Supplemental digital content 1, *http://links.lww.com/wnr/A305* for detailed descriptions of the tasks).

The object naming task is one that has been frequently used in language mapping [7,12,13,18,19]. Several recent studies have shown that enhancement of HG during the object naming task is a reliable marker of the expressive

Fig. 1
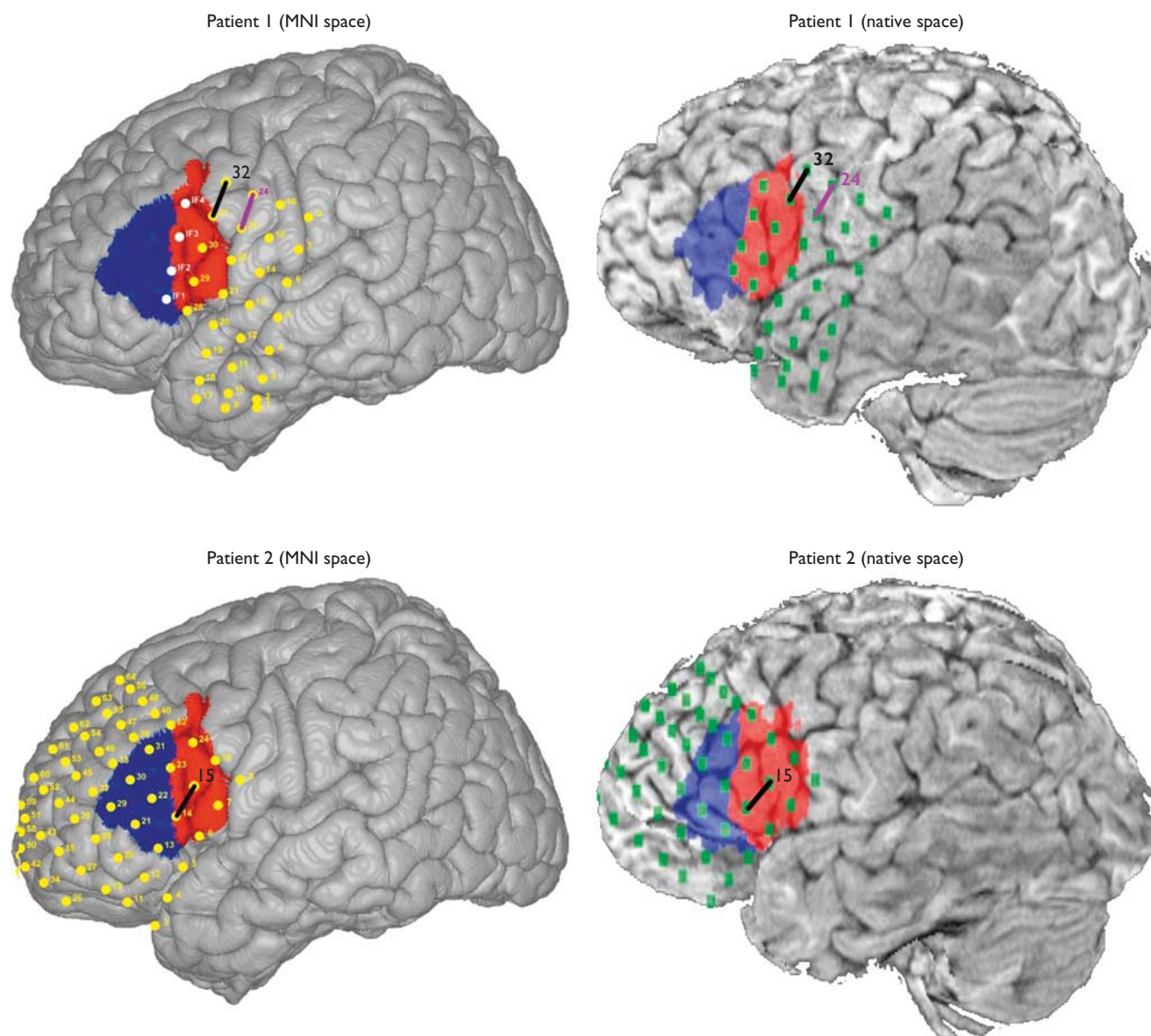
Subdural electrode locations and cytoarchitectonic maps of Broca's areas (BA 44/45) are shown on a rendering of the standard Montreal Neurological Institute (MNI) brain atlas and native (subject) space. The red and blue maps show BA 44 and BA 45 areas, respectively. Subdural electrodes for patient 1 consisted of a modified 32-channel grid placed over the lateral temporal region and a four-contact inferior frontal strip (IF1–IF4). Subdural electrodes for patient 2 consisted of a modified 64-channel grid placed over the frontal region. Interruption of expressive speech was observed during stimulation of pair electrodes (31–32) and (14–15), marked by black lines, in patient 1 and patient 2, respectively. Electrical stimulation of pair electrodes (23–24), marked by a magenta line, resulted in tongue contraction in patient 1.

Fig. 2
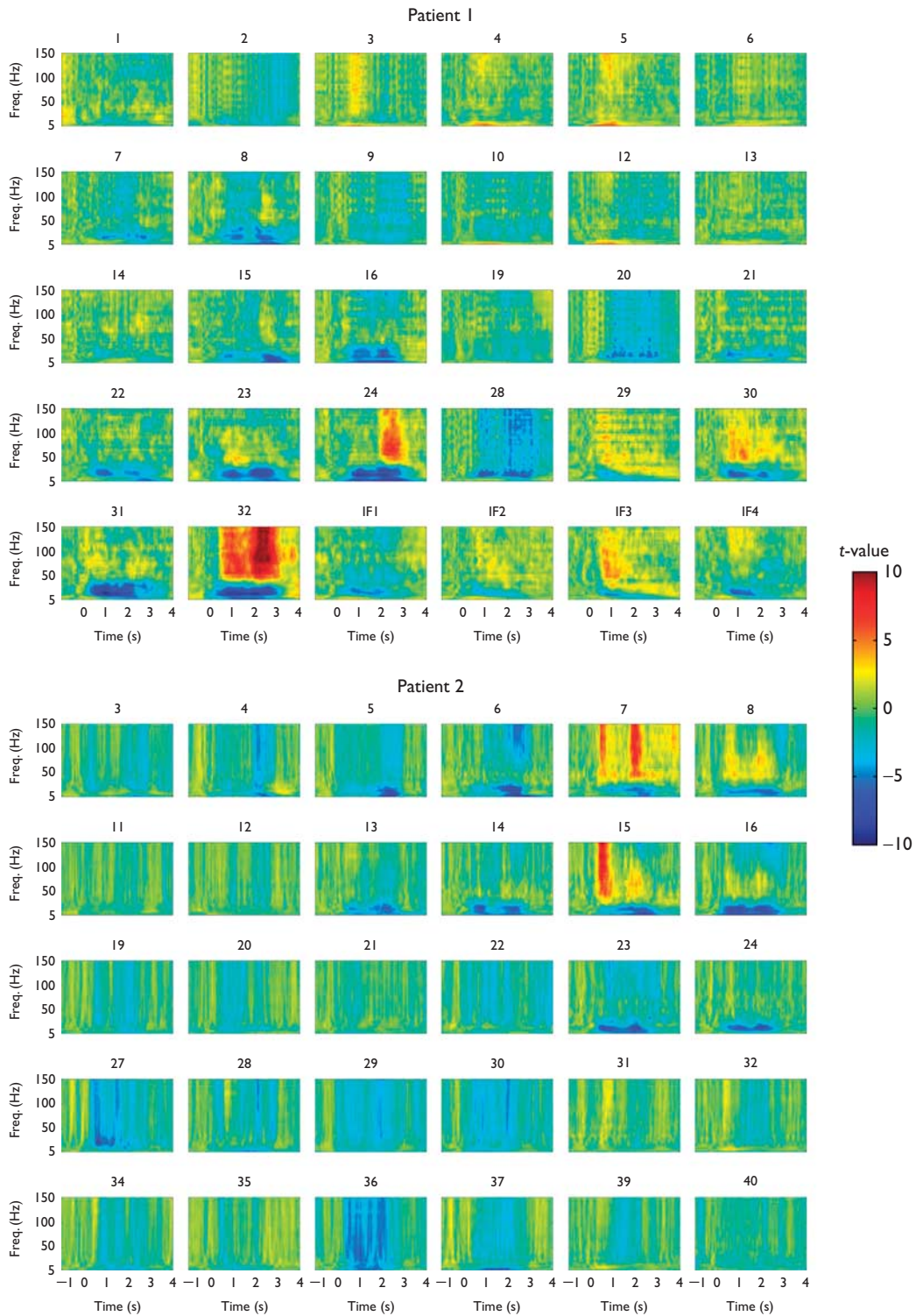
Time–frequency (TF) analysis of recordings during the object naming task in a subset of subdural electrodes. Power in every time–frequency bin was compared with the mean power at baseline (i.e. −0.5 to −0.1 s) to calculate a *t*-value across all trials. The top and bottom parts of this figure show the TF results for patient 1 and patient 2, respectively. The title of each subplot shows the subdural electrode number (see Fig. 1 for locations of the electrodes). As shown in Figs S1 and S2 (Supplemental digital content 1, *http://links.lww.com/wnr/A305*) significant enhancement of the high gamma activity is only present in electrodes 24 and 32 of patient 1, and electrodes 7 and 15 of patient 2. Time 0 indicates the onset of the visual stimulus. Freq., frequency.

language cortex [12,19]. The CRM task is a receptive language task [20] that has also been used for language laterality assessment and for identifying the language-specific cortex within the dominant hemisphere [21]. In the current study, the CRM task was used as a control task. In addition to the object naming task, the syllable production task was used with the expectation of involving the speech production area and distinguishing it from areas possibly involved in semantic retrieval or any other function besides speech production that the object naming task may entail.

Methods

Details of the materials and methods of this study are described in Supplemental digital content 1 (*http://links.lww.com/wnr/A305*), a summary of which is presented here.

Patients

Two patients underwent phase II epilepsy surgery evaluation at Le Bonheur Children's Hospital for the treatment of intractable seizures. A comprehensive neuropsychological evaluation (including WAIS, WRAT-4, D-KEFS, etc.) was performed on both patients, and both of them performed at an average or above-average level. Patient 1 was a right-handed 30-year-old man with partial onset seizures, beginning at 25 years of age, of presumed left temporal lobe origin. Functional MRI and magnetoencephalography provided evidence of left hemisphere localization of receptive and expressive language, and transcranial magnetic stimulation (TMS) results suggested representation of expressive language in the left hemisphere. A subsequent cerebral arteriogram and Wada test confirmed left hemisphere language dominance.

Patient 2 was a 14-year-old right-handed girl. She had a generalized tonic clonic seizure at 4 years of age and was found to have a left frontal brain tumor, which was resected. She continued to have seizures, which were similar to the seizures that she experienced before resection of the left frontal brain tumor. Functional MRI showed a left hemispheric language lateralization of receptive and expressive language. TMS findings were suggestive of left hemisphere representation for expressive language.

Language mapping using cortical stimulation mapping and high gamma activity

Localization of the expressive language cortex was performed by initiating cortical stimulation immediately after sentence reading; the subdural electrodes at which stimulation resulted in speech arrest were identified. Furthermore, subdural electrodes over the putative speech production area were identified on the basis of HG activity in intracranial EEG (iEEG) recordings during the object naming, syllable articulation, and CRM tasks. To this end, time–frequency analysis was carried out on the preprocessed iEEG data, and the power in every time–frequency bin was compared with the mean power at baseline (i.e. -0.5 to -0.1 s) to calculate a t-value across all trials of each task. Thereafter, subdural electrodes showing significant HG activity in the 50–150 Hz frequency range were identified by means of a Monte Carlo randomization test.

Localization of subdural electrodes and map of Broca's area

The postoperative computed tomography scan was co-registered to the preoperative MRI scan and normalized to the Montreal Neurologic Institute (MNI) standard atlas. Thereafter the locations of the subdural electrodes were extracted from the normalized computed tomography images. Figure 1 shows the overlay of the subdural electrodes on the brain surface of the MNI atlas. We used the SPM Anatomy toolbox [22] for the cytoarchitectonic maps of Broca's area (BA 44 and BA 45) in the MNI coordinate (Fig. 1).

Results

Electrical stimulation of pair electrodes (31–32) in patient 1 and pair electrodes (14–15) in patient 2 resulted in complete speech arrest. Electrical stimulation of pair electrodes (23–24) in patient 1 resulted in tongue contraction. Electrical stimulation of pair electrodes (2–3), (3–4), (4–5), (5–6), (6–7), (7–8), (29–30), and (30–31) in patient 1 and pair electrodes (4–5), (5–6), (6–7), (11–12), (12–13), (13–14), (19–20), (20–21), (21–22), (22–23), (23–24), (28–29), (29–30), and (30–31) did not result in either speech arrest or facial motor deficiency (see Fig. 1 for locations of the electrodes).

Electrical stimulation of pair electrodes (31–32) in patient 1 resulted in speech arrest, but stimulation of pair electrodes (30–31) did not result in any speech deficiency. This observation suggests that electrode 32 in patient 1 is within the speech production area and electrode 31 may lie in the vicinity of (or maybe outside) this area. In fact, HG activity during the object naming and syllable tasks confirms this suggestion, in that significant HG activity was observed in electrode 32 but not in electrode 31. In addition, TMS results of speech disruption in patient 1 during the object naming task revealed that the speech production areas were localized superior and close to electrode 32. As shown in Fig. 1, whereas stimulation of electrodes 14 and 15 in patient 2 resulted in speech arrest and these electrodes are clearly within Brodmann's area (BA 44), electrode 32 in patient 1 is outside the anatomically defined Broca's area (BA 44 and BA 45).

The CSM findings were cross-validated with the results of subdural iEEG recordings in both patients for the object naming, syllable, and CRM tasks. Particularly, we analyzed the HG activity in these recordings to identify the electrodes overlaying the expressive language regions. As shown in Fig. 2 and Fig. S1 (Supplemental digital content 1, *http://links.lww.com/wnr/A305*) electrodes

Fig. 3
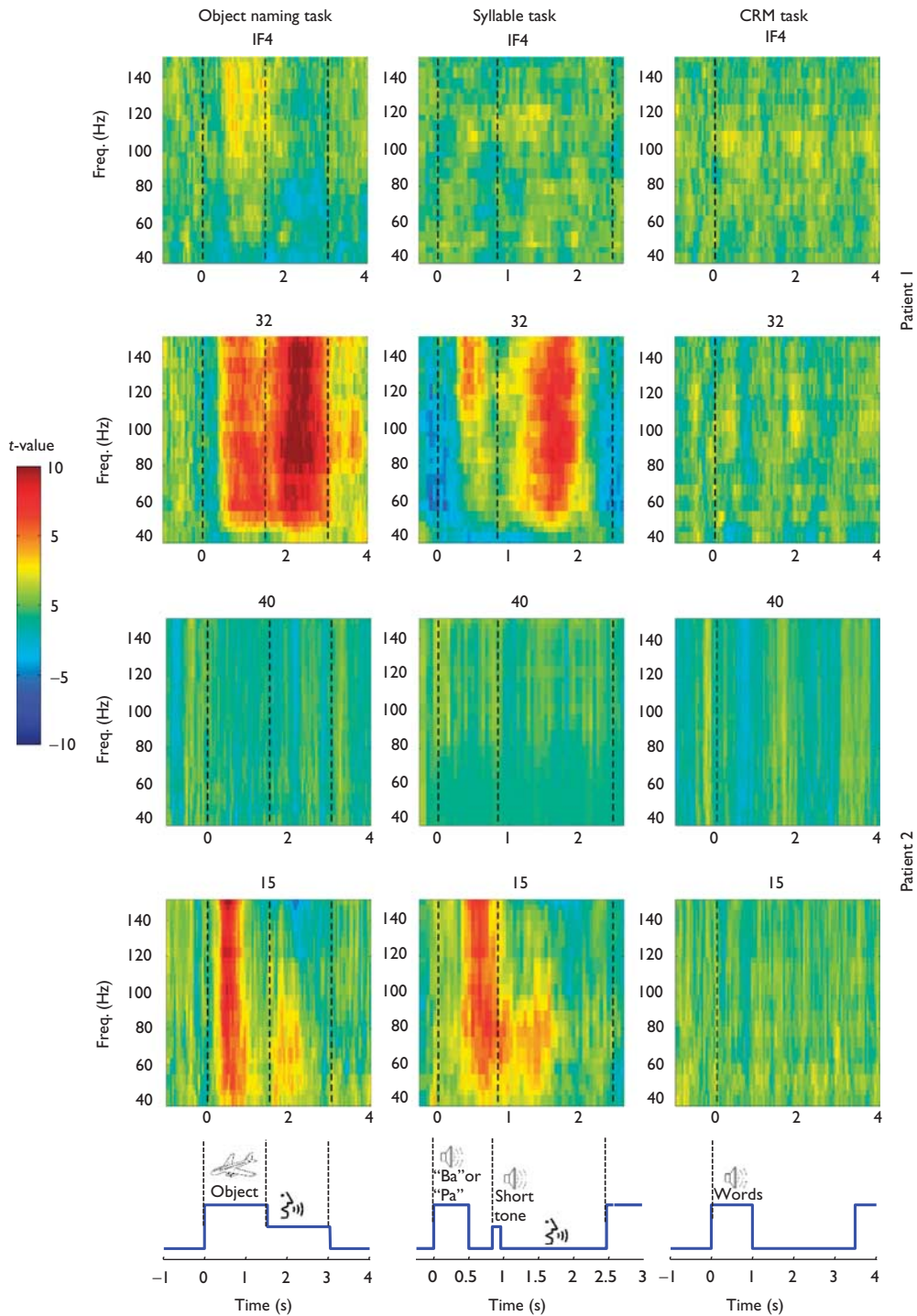
Time–frequency (TF) analysis of the recordings during three tasks from two subdural electrodes in the two patients (see Fig. 1 for locations of the two electrodes). Power in every time–frequency bin was compared with the mean power at baseline (i.e. −0.5 to −0.1 s) to calculate a *t*-value across all trials. Left column: TF analysis of the overt object naming task. Middle column: TF analysis of the repeating simple syllables (/ba/pa/) task. Right column: TF analysis of the auditory continuous recognition memory (CRM) task. The time course of one trial (epoch) of each task is shown at the bottom of this figure. Electrodes 32 in patient 1 and 15 in patient 2 show significant enhancement of high gamma (HG) activity (50–150 Hz) in the object naming and syllable tasks, respectively. Note that the CRM task, which is a receptive language task, does not show HG enhancement in any electrode. Electrodes 40 in patient 2 and IF4 in patient 1, as control electrodes, did not show HG activity in any task. Freq., frequency; IF4, inferior frontal strip 4.

32 and 24 in patient 1 were the only electrodes that recorded significant HG activity during the object naming task. Significant enhancement of HG activity (50–150 Hz) in electrode 32 started at ~ 500 ms following stimulus onset and was sustained during the period through which overt articulation was taking place. These observations suggest that electrode 32 in patient 1 most likely overlaid the speech production area. HG activity at electrode 24 in patient 1 was only present in the latency corresponding to overt articulation and was not significant before articulation or during the presentation of the pictures. These observations suggest that electrode 24 in patient 1 most likely overlaid the motor speech areas. In fact, CSM results confirmed this hypothesis in that they revealed that stimulation of the pair electrodes (23–24) resulted in contraction of the tongue. It is notable that four electrodes on the inferior frontal strip (IF1–IF4) and two lateral temporal electrodes (29 and 30) in patient 1 lay in BA 44/45 (Fig. 1), although none exhibited enhancement of HG activity, and those stimulated during CSM did not cause speech arrest.

Electrodes 15 and 7 in patient 2 were the only electrodes that demonstrated significant HG activity during the object naming task (Fig. 2 and Fig. S2, Supplemental digital content 1, *http://links.lww.com/wnr/A305*). Significant enhancement of HG activity in electrode 15 started before overt articulation, ~ 500 ms following presentation of the pictures. This observation, in addition to the speech arrest observed on stimulation of the pair electrodes (14–15), suggests that electrode 15 in patient 2 was within the speech production area. Significant HG activity at electrode 7 was observed before and after overt articulation. However, most of the significant HG activity was observed after overt articulation. CSM results revealed that stimulation of the pair electrodes (6–7) did not result in speech arrest. These observations suggest that electrode 7 may not lie in the speech production area but it may be within the motor speech area.

Time–frequency analyses of the recordings during the three tasks for the two patients are presented in Fig. 3. The activities of two representative electrodes are shown (one within and one outside the speech production area). As shown in Fig. 3, HG activity during the syllable task yielded similar results as that during the object naming task in identifying the speech production areas in the two patients. Electrode 32 in patient 1 and electrode 15 in patient 2 showed significant HG activity during both the syllable and the object naming tasks. The results of the syllable production task support the notion that the areas identified as speech-specific in both the syllable and the object naming tasks are in fact specific to the preparation and production of speech and not to any other function, such as semantic retrieval that object naming might entail. In contrast, the control CRM task did not result in significant HG activity in any of the electrodes overlying the speech production area in either patient 1 or patient

2, as expected. Moreover, electrodes 40 in patient 2 and IF4 in patient 1, as control electrodes, did not show HG activity during any task.

Discussion

Using CSM and subdural grid recordings, we explored the organization of the expressive language cortex in two patients undergoing epilepsy surgery evaluation. Despite the absence of a lesion that could result in functional reorganization, in one patient we found atypical topography of the expressive language cortex. Moreover, in keeping with our expectations, we found that in both patients the speech production area as defined by CSM was subsequently verified by enhancement of HG activity in subdural recordings from the same electrodes that when stimulated resulted in speech arrest. These findings indicate that the operational specification of the speech production area may not be where it is expected to be on the basis of anatomical landmarks, thus indicating that presurgical language mapping is necessary in all cases of dominant hemisphere surgery.

Anatomofunctional variability in language areas across individuals has been reported in other studies [7,23]. Using CSM and the object naming task in 117 patients, Ojemann et al. [7] observed that there was considerable individual variability in the location of language function, although the language areas were highly localized in a given patient. In fact, the expressive language areas in both patients of the current study lay within the language areas reported by Ojemann et al. [7].

The location of the expressive language cortex in patient 1 was in the precentral gyrus (BA 6). Electrical stimulation of this region could result in speech arrest by spreading of current to the neighboring Broca's area, or be mediated by U fibers connecting the two regions [24]. However, we think that this is unlikely because electrodes within BA 44/45, namely, IF1, IF2, IF3, IF4, 29, and 30 (Fig. 1), did not show significant HG activity during language tasks, and those stimulated during CSM did not result in speech arrest. Another explanation for the atypical localization of the speech production region could be lesion-induced functional reorganization of the brain. However, this patient did not have any visible structural abnormality. Therefore, it is unlikely that there was functional reorganization of the language areas in this patient. This is in contrast to that observed in the second patient, who exhibited normal localization of expressive language despite having a structural abnormality in the left frontal lobe.

CSM is currently accepted as the gold standard for language mapping, although it is not without some limitations [12]. It is often not practical to administer a comprehensive battery of language tasks during CSM. In addition, CSM is time consuming and can also produce after-discharges and seizures, especially during

stimulation of regions close to the ictal onset zone, which is typically the area of greatest interest with regard to functional mapping for surgery planning. Recent studies have shown that enhancement of HG activity has sensitivity and specificity comparable to CSM for receptive and expressive language mapping [13,25]. Considering the limitations of CSM [12], the presence of HG activity during language tasks can be used in conjunction with CSM to improve the performance of language mapping. An example approach is to use the HG activity during language tasks as an aid to reduce the time requirements of CSM by providing information in advance on which electrodes are likely overlying the speech production area. Specifically, at present, CSM involves stimulation of electrodes in a sequence that is either random or guided by guesses as to the topography of the language-specific cortex. Instead of this blind and time-consuming search, CSM can be optimized by starting the stimulation of those electrodes that showed significant HG activity in previous recordings during language tasks.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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