Epilepsy & Behavior 60 (2016) 124–129

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Functional differences among stimulation-identified cortical naming sites in the temporal region

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ARTICLE INFO

Article history:
Received 14 March 2016
Revised 5 April 2016
Accepted 6 April 2016
Available online 17 May 2016

Keywords:
Cortical stimulation
Language mapping
Naming
Lexical access

ABSTRACT

To preserve postoperative language, electrical stimulation mapping is often conducted prior to surgery involving the language-dominant hemisphere. Object naming is the task most widely used to identify language cortex, and sites where stimulation elicits naming difficulty are typically spared from resection. In clinical practice, sites classified as positive undergo no further testing regarding the underlying cause of naming failure. Word production is a complex function involving multiple mechanisms that culminate in the identification of the target word. Two main mechanisms, i.e., semantic and phonological, underlie the retrieval of stored information regarding word meaning and word sounds, and naming can be hampered by disrupting either of these. These two mechanisms are likely mediated by different brain areas, and therefore, stimulation-identified naming sites might not be functionally equivalent. We investigated whether further testing at stimulation-identified naming sites would reveal an anatomical dissociation between these two mechanisms. In 16 patients with refractory temporal lobe epilepsy (TLE) with implanted subdural electrodes, we tested whether, despite inability to produce an item name, patients could reliably access semantic or phonological information regarding objects during cortical stimulation. We found that stimulation at naming sites in superior temporal cortex tended to impair phonological processing yet spared access to semantic information. By contrast, stimulation of inferior temporal naming sites revealed a greater proportion of sites where semantic access was impaired and a dissociation between sites where stimulation spared or disrupted semantic or phonological processing. These functional–anatomical dissociations reveal the more specific contribution to naming provided by these cortical areas and shed light on the often profound, interictal word-finding deficit observed in temporal lobe epilepsy. Additionally, these techniques potentially lay the groundwork for future studies to determine whether particular naming sites that fall within the margins of the desired clinical resection might be resected without significant risk of decline.

1. Introduction

With the goal of preserving postoperative language function, electrical stimulation cortical mapping (ESM) is often performed prior to surgical resection involving the language-dominant cerebral hemisphere. The procedure involves brief periods of electrical stimulation administered to discrete cortical sites, producing a circumscribed, reversible, functional lesion, during which the effect of stimulation can be tested [1]. Identification of language cortex requires engaging the patient in a language task to determine whether stimulation disrupts performance of the task at hand.

Various tasks have been used to identify language areas; however, object naming evolved as the primary task of choice [2]. This appears to be due, in part, to its ease of administration during the time-constrained procedure of ESM. Additionally, the observation that anomia is present in virtually all aphasic syndromes led to the idea that identification of cortical areas critical for object naming would enable the identification of cortex that played a significant role in language [3].

Although seemingly simple, word production is a complex function involving multiple mechanisms that culminate in the identification of the word that best matches a specific meaning [4–7]. Two primary types of mechanisms – semantic and phonological – are responsible for the retrieval of stored information about word meaning and word sounds. To the extent that naming is a function that captures multiple linguistic processes, it can be disrupted due to impairment in different

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http://dx.doi.org/10.1016/j.yebeh.2016.04.021
1525-5050/

linguistic processes, mediated, potentially, by different brain regions. In addition, despite inability to access a particular word, some information regarding the target word might remain available to the speaker [8]. The same holds true in the ESM setting yet with the addition of a neuroanatomical component. Depending on its location, stimulation that elicits anomia might differentially impede or spare access to linguistic processes that are necessary for successful naming. These considerations suggest that individual naming sites might not be functionally equivalent and that different naming sites might support distinct processes that give rise to naming. Specifically, if distinct neural mechanisms support semantic and phonological retrieval, naming could be disrupted due to difficulty discerning the meaning of an item or accessing the sounds of the item name.

In clinical practice, sites at which stimulation impairs naming are typically classified as positive for language, without further inquiry regarding the underlying cause of naming failure or whether certain linguistic processes nevertheless remain intact [2]. Delineating cortical sites as merely positive or negative for language fulfills an important clinical function; however, more precise characterization of positive language sites could potentially provide further, clinically relevant information, particularly when language sites fall within the boundaries of a planned resection. For example, when the clinical context involves an infiltrating tumor or epileptogenic region, difficult decisions must be made regarding preservation versus resection of positive language cortex. In clinical situations in which one would want to maximize the resection in the hope of prolonging survival or increasing the likelihood of seizure freedom, more detailed information could potentially clarify the relative importance of the site. There might be more of an imperative to preserve a language site that subserves both semantics and phonology than a site for which function is limited to the mediation of word sounds.

Analysis of stimulation-evoked naming errors has been used to infer the linguistic function mediated by the associated cortical areas [9–11]. However, failure to produce any naming response is the most common type of error induced by naming site stimulation (despite preserved speech, e.g., "This is a …"), providing no useful information regarding the nature of the site beyond its involvement in naming. Additionally, error analysis provides only an indirect appraisal of the underlying function. In this study, we aimed to more directly determine the linguistic mechanisms mediated by cortical sites where stimulation disrupts naming. Specifically, we sought to determine whether, and at which sites, semantic or phonological processing remains intact despite impaired naming, by testing these functions during stimulation at clinically identified cortical naming sites.

We hypothesized that cortical stimulation would reveal an anatomical dissociation between naming sites where semantic versus phonological processing remains intact. Based on findings from neuroimaging and lesion studies [12–17], we anticipated greater representation of semantic sparing in the superior temporal region and greater sparing of phonological processing at naming sites in inferior temporal cortex.

2. Method and materials

2.1. Patients

Participants were 16 consecutive, adult patients who underwent cortical language mapping before left temporal resection at Columbia University Medical Center (CUMC), New York University Medical Center (NYU), and North Shore Long Island Jewish Hospital (NSLIJ). Patient participants met the following inclusion criteria: Subjects were required to be left hemisphere language-dominant, to be native English speakers or to have learned English by age five, and to have been fully educated in English. Language dominance was identified by Wada testing (n = 13) or ESM identification of language sites plus postictal speech disturbance consistent with left hemisphere language dominance (n = 3, all right-handed) [18]. Subjects had a minimum of 15 sites tested for language in the lateral temporal region, across all three temporal gyri (mean total sites tested for language: 34.5, SD = 13.5). Additionally, patients were required to perform semantic and phonological mapping tasks at baseline with perfect accuracy (described below). All patients were considered to have unilateral, left hemisphere seizure onset based on preoperative scalp EEG and MRI. The purpose of the clinical language mapping was to identify essential language cortex following identification of the epileptogenic zone based on seizure onset and propagation. All patients signed informed consent for study participation. Patient demographic and clinical information are presented in Table 1. Two patients had vascular malformations, one had a left temporal lobe tumor, one had a left temporal calcification, one had heterotopia along the lateral ventricle, and 11 patients had no abnormalities detected on MRI. This study was approved by the Institutional Review Boards at CUMC, NYU, and NSLIJ.

2.2. Electrodes

All patients underwent extraoperative, clinical language mapping to identify language cortex prior to resection. Subdural grids consisted of eight-by-eight electrodes embedded in a silastic region (trimmed or cut and rearranged if needed) with center-to-center interelectrode distances of 1 cm positioned over the frontal–parietal–temporal region to conform to the covered area. At CUMC, grid position was documented by either digital intraoperative photographs and schematic diagrams drawn at the time of implant and compared to intraoperative photos and postimplant CT or MR imaging and skull films (CUMC, NSLIJ). At NYU and NSLIJ, electrode positions were determined through coregistration of preoperative and postimplantation MRI. Across surgical programs, electrode location was defined by gyrus and distance from the temporal pole.

2.3. Mapping procedures

Mapping was conducted following capture of the required interictal and ictal data for surgical planning. Antiepileptic drugs were restarted prior to mapping and, when clinically appropriate, were administered intravenously. When possible, medications were resumed at least 12 h prior to mapping.

An Ojemann Cortical Stimulator (Radionics, Inc.) was used at CUMC, NYU used a Grass S12 Biphasic cortical stimulator (Warwick, RI), and NSLIJ used a Grass S-12 Isolated Biphasic Stimulator (Astro-Med, Inc.). Stimulation was applied to adjacent electrodes, with a 500-microsecond pulse width, typically at 50-Hz frequency. Stimulation started between 1 and 3 mA and was increased incrementally by 1–3 mA while the patient counted to assess for afterdischarges, functional responses (language or otherwise), and pain due to dural spread of current. Amperage for clinical and research testing ranged from 8 to 15 mA. Positive results were considered valid only if no afterdischarges were elicited. Trials with afterdischarges (and positive findings) were repeated at a lower level of stimulation below the afterdischarge threshold. No patients had seizures during the study tasks.

2.3.1. Language mapping tasks

To identify naming cortex, we routinely use both visual object naming and auditory description naming (e.g., "a household pet that purrs") tasks,

Table 1
Patient information.

	Mean (SD)	Range
Age[a]	31.3 (11.5)	18–53
Education[a]	13.7 (2.3)	8–16
Onset age[a]	12.4 (4.9)	1–20
FSIQ	97.4 (14.0)	76–126

[a] Years, FSIQ = full-scale IQ.

as anterior temporal language sites are not reliably identified with visual object naming alone [19,20]. Additionally, this provides a larger area for investigation in temporal cortex.

For the semantic task, patients manually responded via yes/no placards to orally presented questions regarding the meaning of pictured objects that could not be answered merely from the object's appearance (e.g., Is this something people eat? Is this found in a garden?). For the phonological task, patients indicated yes/no responses to orally presented questions regarding the first phoneme of the object names (e.g., does this start with "t" as in "toy"?). Of note, during the pilot phase of this study, we included an auditory analog of these tasks. However, the auditory tasks required a prolonged stimulation interval, raising concerns of evoking seizures. Therefore, we limited the study to the visual tasks.

Visual naming and auditory description naming were tested with the same number of trials (minimum of two trials per task) at each site. If results were ambiguous, additional trials were administered. For visual naming, patients were shown pictures of common items (e.g., umbrella) and instructed to say "This is a …", to differentiate between sites at which stimulation elicited speech arrest versus naming impairment. For auditory naming, patients were instructed to name the item described as quickly as possible (e.g., "what a king wears on his head"). Stimulation began immediately before presentation of pictured items and auditory descriptions, with a maximum duration of 5 s, terminating immediately upon the production of a correct response. Trials were considered positive if the patient could not name the item during stimulation but responded correctly upon stimulation cessation. Sites were considered positive for language when a minimum of 75% of responses were inaccurate during stimulation. Although there are no formal guidelines for ESM [2], all of the three epilepsy surgery centers in this study routinely use this criterion.

2.3.2. Psycholinguistic tasks

Following completion of the clinical mapping required for surgical planning, the semantic and phonological tasks were conducted at sites identified as naming sites during the clinical ESM procedure. Both tasks (detailed below) required only manual responses. Patients were instructed to respond by pointing to a card showing the responses ("Yes" on the left, "No" on the right) in large font.

2.3.2.1. Semantic task. Patients were presented pictured objects (one per stimulation trial) and instructed to indicate (Yes/No) whether objects have one of the following semantic features: (1) found indoors, (2) something people typically eat, (3) something people can easily carry, (4) often found in a zoo, (5) typically used to sit on, (6) a musical instrument, (7) found in a garden, (8) typically seen in the sky, (9) a tool, (10) a form of transportation, (11) a piece of furniture, (12) found in the ocean, (13) something people typically wear, and (14) found in the woods. This task required access to detailed information about the semantic features of objects that was not directly available from the pictures.

2.3.2.2. Phonological task. Patients were instructed to indicate (Yes/No) whether the pictured objects begin with a particular sound (e.g., "Does this begin with the sound "t" as in toy?"). To discourage subjects from responding based on orthography of the word, some of the words were similar to "photo", i.e., the first letter and first phoneme do not correspond (p vs. /f/). Stimulus presentation and response instruction were identical to that described for the semantic task.

Pictures presented for these trials were color photographs of common items on a white background (e.g., tiger, hammer, carrot). Patients were administered 5 stimuli/trials each for the semantic and phonological tasks at each tested site. Electrocortical stimulation was initiated after the question was presented to the patient, and immediately before picture presentation, and remained on until the patient responded, with a maximum 5-second duration. Given the simple nature of the tasks, responses not provided within the 5-second stimulation interval were considered errors.

Practice trials were administered before mapping began to verify that instructions were understood and that the patient was able to perform the task at baseline with 100% accuracy. Training stimuli were comparable, but not identical, to test stimuli. If any errors occurred during the five semantic or phonological trials with stimulation, the full five trials were subsequently readministered without stimulation to ensure that the error was associated with stimulation and not merely an error that would have occurred without stimulation. If an error occurred without stimulation, these data were excluded from analysis.

2.4. Statistical analyses

2.4.1. Defining the linguistic processes mediated by naming sites

Language mapping requires the use of tasks that are typically performed with perfect or near perfect accuracy so that task disruption coinciding with stimulation can readily be attributed to the effect of stimulation. However, basic language functions, particularly those involving semantics and phonology at the level described above, are generally robust and likely represented in a redundant manner, rendering those functions difficult to disrupt without disrupting other functions as well (i.e., comprehension). Thus, we reasoned that we might not reliably impair task performance with every trial of stimulation, and therefore, disruption of a significant proportion of trials on these highly simple tasks would implicate the site for the function tested.

We considered that the yes–no semantic and phonological questions could be answered correctly, by chance, 50% of the time. Although it was necessary to perform multiple trials per site for each task, this had to be balanced with the risk of evoking seizures due to multiple stimulations at the same cortical site. With 5 trials per task (which we considered reasonable with respect to this concern), the likelihood of all 5 trials correct (or incorrect) by chance would be $(0.5)^5 = 0.031$. Applying binomial probability, the chance of ≥2/5 errors given the baseline probability of .031 is .0008 (whereas a minimum of one error has a probability of .15). Thus, we defined semantic and phonological disruption as the presence of ≥2 errors within the five trials for each task.

2.4.2. Analysis of stimulation testing results

Naming sites from each patient were plotted on a schematic of the temporal lobe region and coded to indicate whether stimulation disrupted auditory naming, visual naming, or both auditory and visual naming. These sites were then coded further, to indicate whether semantic and/or phonological processing remained intact during stimulation. The topographic distribution of semantic and phonological processing sites and their potential relation to auditory and visual naming sites were analyzed by visual inspection followed by Fisher's exact tests because of the sample size and expected cell values. Given our hypothesis, together with the spatial pattern apparent in the schematic (Fig. 1), the primary analysis addressed the distribution of semantic and phonological sites in the superior–inferior dimension. We analyzed the distribution of auditory and visual naming sites in the anterior–posterior dimension only to determine consistency with previously reported findings.

2.4.3. Segmentation of the temporal region and data analysis

To test the hypothesis that semantic and phonological processes distribute differently in the superior–inferior dimension, we compared the distribution of naming sites where semantic and phonological processes were spared above (dorsal) and below (ventral) the superior temporal sulcus. Data were first inspected visually, and Fisher's exact tests were used to more rigorously assess visually apparent topographic patterns. In the anterior–posterior dimension, consistent with previous work, we anticipated that auditory naming sites would be located anteriorly, relative to visual naming sites, as assessed via t-test in cm from the temporal pole [19,21].

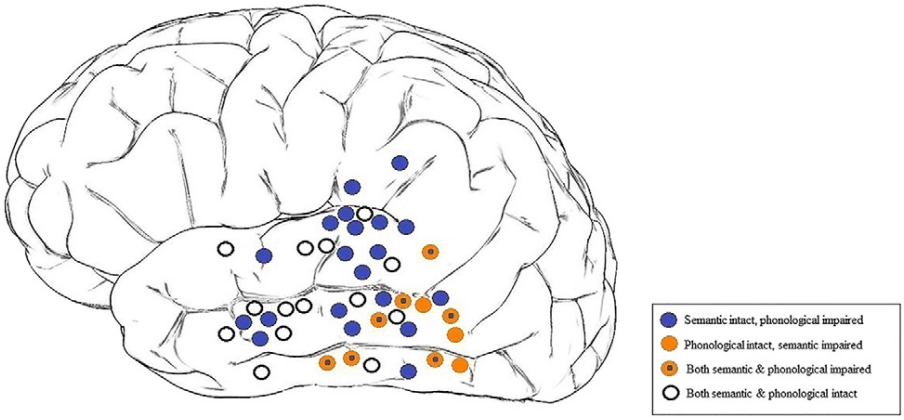

Fig. 1. Differences among stimulation-identified naming sites. Naming sites identified by stimulation mapping. Blue circles: naming sites where stimulation disrupted phonological processing yet spared semantic processing, orange circles: naming sites where stimulation disrupted semantic processing yet spared phonological processing, orange circles with blue center: naming sites where stimulation disrupted both semantic and phonological processing, open circles: naming sites where further testing disrupted neither phonological nor semantic processing.

3. Results

Across the 16 subjects, 44 naming sites were identified (mean: 4.5 (SD: 2.5) per patient). Of these 44 naming sites, 13 were positive for auditory naming only (i.e., stimulation disrupted auditory naming but not visual naming), and 31 were dual naming sites (i.e., stimulation disrupted both auditory naming and visual naming). Consistent with prior results from language mapping studies in patients with TLE [19], naming sites were scattered across the temporal region, with auditory naming sites, on average, located anteriorly to dual (visual–auditory) naming sites (mean (SD): auditory naming = 5.2 cm (SD: 1.7), visual naming = 6.7 cm (SD: 1.4); t (42) = 2.48, P = .01).

3.1. Results of further testing at positive naming sites

Using the criteria described above, results from the semantic and phonological tasks revealed four types of positive naming sites: 1) sites at which stimulation spared semantic processing but disrupted phonological processing (n = 20), 2) sites at which stimulation spared phonological processing but disrupted semantic processing (n = 3), 3) sites at which stimulation spared both semantic and phonological access (n = 14), and 4) sites at which stimulation disrupted both phonological and semantic processing (n = 7) (see Fig. 1). As there were no clear differences in the distribution of semantic and phonological sites between auditory naming and visual naming sites (Fisher's exact: P = 1.0), the data from both auditory naming and visual naming sites were combined and analyzed together as naming sites.

From visual inspection of Fig. 1, it is apparent that stimulation at the vast majority of naming sites above the superior temporal sulcus (STS) spared semantic processing yet disrupted phonological access. On the other hand, stimulation below the STS also revealed many sites where stimulation disrupted phonological yet spared semantic processing; however, semantic processing was impaired at multiple sites in this region. Including only sites where semantic and/or phonological processing were disrupted, the proportions of sites where phonological versus semantic processing remained intact above and below the STS were significantly different (Fisher's exact, P = 0.04, two-tailed). We found no topographical pattern among naming sites where neither semantic nor phonological processing was disrupted.

4. Discussion

Cortical sites considered critical for naming are routinely identified via ESM; however, the granularity of the information obtained is contingent upon the nature of the processing required by the task. We probed clinically identified naming sites to determine whether patients maintained access to meaning or word sounds, despite inability to name the concept at hand.

Consistent with our hypothesis, additional linguistic testing revealed some overlapping yet, notably, anatomical dissociations between naming sites that mediate semantic versus phonological processing. As anticipated, electrocortical stimulation above the STS rarely disrupted semantic processing yet frequently impaired phonological processing. Although we found a higher frequency of phonological disruption at inferior temporal sites than anticipated, results showed the expected, higher frequency of semantic disruption in this region. In considering sites where both semantic and phonological processing were impaired, it is worth noting that disruption of semantic processing can affect the retrieval of word sounds. This assumption is based on the widely accepted idea that semantic information serves as input to phonological processing; consequently, conditions disrupting semantic processing could have cascading effects on the retrieval of a word's sounds [14,22,23].

Overall, this pattern is consistent with evidence from neuroimaging [12,13], ERPs [14,22], and MEG [14], as well as from localization analyses of brain damage causing acquired word production deficits [15–17], suggesting that posterior–superior regions support phonological retrieval, while more inferior regions, especially middle and anterior areas, are engaged in semantic processing. The idea that semantic and phonological processes distribute along an inferior–superior gradient in temporal regions is embodied in current neurofunctional models of language (e.g., the dual stream model [24]). The stimulation-based, topographical patterns from this study provide converging evidence in support of these models, notably, at a time when converging evidence via unique methodologies is considered paramount in the current scientific climate.

Nevertheless, ESM results are limited, spatially, to discrete cortical sites. Emerging work in diffusion tensor imaging (DTI) and corticocortical evoked potentials (CCEPs) underscores the need to consider these results in the context of a more diffuse language network that encompasses both cortical and subcortical areas [25–28]. Thus, these topographical findings do not likely reflect localization of semantic or phonological functions, but rather, cortical locations where disruption of a broader network produces impairments in a reliable manner. Although ESM was limited to the temporal region, Broca's area has been shown to play a role in both semantic and phonologic processing. As DTI and CCEPs have brought to light both functional and structural connectivity between anterior and posterior language areas [24,27], it is possible that the current ESM results might reflect disruption to frontal language cortex or other brain areas remote from the cortical stimulation. Future

work incorporating these technologies can be used to delineate, more specifically, other components of the language network that subserve semantic and phonological processing in the service of accurate word retrieval.

4.1. Clinical relevance

Within the clinical context, more detailed characterization of the naming mechanisms disrupted or preserved during cortical stimulation could potentially aid surgical decision-making. It is generally assumed that ESM-identified naming sites should be spared from resection. There are few, if any, reports of breaching the tacit standard of care of preserving ESM-identified visual naming sites. However, as we have recently found under conditions of anonymous reporting, these sites are sometimes removed, with variable outcomes [2]. Inarguably, it is better to err on the side of caution. Nevertheless, some cortical sites identified as functional via electrical stimulation can be removed without significant risk of permanent postoperative decline. For example, tongue motor sites identified via ESM can be removed because of bilateral representation and resection of supplementary motor cortex results in a transient, but not permanent, postoperative motor deficit [29–31]. Some investigators argue that language sites identified in the basal temporal region can be removed without adverse consequences [32]; however, this remains controversial [33]. Thus, it is worth considering the possibility that more detailed characterization of naming sites carries the potential to differentiate between essential and nonessential language cortex. Prospective, systematic investigation would be needed to determine, empirically, which type(s) of naming sites are more or less likely to result in meaningful postoperative language decline.

In addition to potential surgical relevance, the current results shed some light on the neural bases of the often severe, interictal word-finding deficit observed in individuals with left (dominant) TLE [33,34]. We have previously found that, despite frequent word-retrieval failures, access to meaning is well preserved [35]. Assuming that cortical stimulation provides an accurate reflection of structure–function relations, our results suggest that much of the lateral temporal region, both above and below the STS, is critically involved in access to phonology, and thus, within the lateral temporal lobe, access to phonology might be more vulnerable than semantic processing to disruption induced by epilepsy. We further speculate that the posterior–inferior temporal region, which appears to be most involved in semantic processing, might be least affected by the chronic interruptions related to seizures and interictal epileptiform activity in TLE, thus sparing semantic functioning. This is consistent with reported propagation of EEG discharges in TLE [36].

4.2. Limitations

In virtually all ESM studies, the cortical region available for investigation is determined by the clinical circumstances, specifically, the size and location of the craniotomy for intraoperative mapping and subdural grid placement for extraoperative mapping. Therefore, we were unable to map near the anterior temporal pole in most patients and were unable to map all of the same cortical areas in each patient. Also related to the clinical context is the fact that individuals who require language mapping have structural and/or functional abnormalities in the region under investigation, raising the possibility that the mapping results might not represent neurologically normal cortical organization. Although this must be considered, it should also be noted that most patients who require language mapping, including those in this study, have late onset epilepsy (14/16 at >8 years of age), with the onset of seizures occurring well after language lateralization and localization are thought to be established [37,38]. Finally, one might question the use of such simple linguistic tasks. This may have contributed to finding sites at which neither semantic nor phonological processing was consistently impaired by stimulation. Tasks requiring deeper semantic and phonological processing are probably needed to clarify the association of these negative sites with semantic and phonological processing in naming. However, it is actually crucial that tasks utilized in ESM can be performed perfectly at baseline so that virtually any error in performance can be attributed to stimulation-induced dysfunction [39]. Further, to ensure confidence in the results, we took a highly conservative approach in defining impairment by requiring two errors across the five trials.

In summary, extended linguistic testing at stimulation-identified naming sites provided crucial information for mapping the left temporal areas supporting semantic and phonological processes in object naming. Whereas cortical areas where stimulation impaired semantic processing were topographically limited, stimulation disrupted phonological processing while sparing semantic access more broadly across lateral temporal cortex. These results might explain the integrity of semantic processing in TLE relative to phonological functioning with respect to word retrieval and might ultimately be useful in determining the clinical significance of these different types of ESM-identified naming sites.

Funding

This work was supported by the National Institutes of Health/the National Institute of Neurological Disorders and Stroke (MH) (grant no.: NIH R01 NS35140).

Conflict of interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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