

Electrical Cortical Stimulation Mapping for Function and Seizures



Gonzalo Alarcon, MD, PhD^{a,b}, Lovena Nawoor, BSc, MSc^c,
Antonio Valentin, MD, PhD^{d,e,*}

KEYWORDS

- Functional electrical stimulation • Epilepsy • Brain tumors • Mapping • Motor cortex
- Sensory cortex • Auditory cortex • Language cortex

KEY POINTS

- Functional electrical stimulation with intracranial electrodes can help to identify functional brain regions in humans.
- Cortical mapping with functional electrical stimulation is considered the most reliable method to localize eloquent brain cortex.
- Functional electrical stimulation can help surgical teams to define the largest possible resected area with minimal postoperative motor, sensory, or language deficits.
- Functional electrical stimulation consists of direct application of electrical currents to the cortex while monitoring function, clinical responses, electroencephalogram responses, and evoked seizures.

INTRODUCTION

The main aim of presurgical assessment in patients with epilepsy or brain lesions is to achieve good seizure or tumor control, while ensuring preservation of functional areas to prevent neurocognitive deficits.^{1,2} In order to achieve this aim, it is often necessary to extend the resection beyond the margins of the structural brain lesion to optimize surgical outcome. Because those regions could be near or merged with functional cortex, techniques should be performed to identify functional cortex in order to minimize brain function loss. Traditionally, brain organization has been thought of as a fixed topological distribution where functions are attributed to discrete cortical areas.³ Although a limited resection of the

association cortex can be performed without significant postsurgical deficits, resection of primary motor, primary sensory, hippocampi, or language regions can be associated with severe transient or permanent neurologic, functional, or cognitive deficits. The initial approach to localize motor, sensory, or language areas is based on functional anatomy.⁴ However, because the exact regions responsible for brain function vary among individuals and there is potential reorganization of functional areas around the lesions, detailed anatomic identification of functional areas may be imperative before resection to avoid postoperative deficits.^{5–14}

At present, functional mapping with runs of electrical pulses is considered the most reliable

^a Department of Neurology, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar; ^b Weill Cornell Medicine, Doha, Qatar; ^c King's College London, London, UK; ^d Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, UK; ^e Department of Clinical Neurophysiology, King's College Hospital, London, UK

* Corresponding author. Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), Academic Neuroscience Centre, London SE5 8AF, UK.

E-mail address: antonio.valentin@kcl.ac.uk

method to localize eloquent brain cortex. However, new noninvasive approaches such as functional MRI or transcranial magnetic stimulation can provide valuable additional information.

HISTORY OF FUNCTIONAL MAPPING WITH ELECTRICAL STIMULATION

The localization of cortical functions with electrical stimulation was first performed in the nineteenth century by Fritsch and Hitzig,¹⁵ Ferrier,¹⁶ and Luciani.¹⁷ Electrical stimulation of motor cortex in animals elicited movements and sometimes generalized seizures when increasing current intensity. Cortical electrical stimulation was also performed in humans to induce contralateral movements or generalized seizures, either during experiments¹⁸ or during brain surgery.^{19–21} At the beginning of the twentieth century, Brodmann²² defined and numbered different brain regions and published maps of cortical areas in humans and monkeys, mainly based on the cytoarchitectural organization of neurons using Nissl method of cell staining. Between 1901 and 1917, Sherrington²³ stimulated precentral gyrus in apes and reported contralateral limb movement. He also stimulated anterior frontal areas and occipital cortex near the calcarine fissure, provoking conjugate

contralateral eye movements. These findings were replicated by Vogt and Vogt,²⁴ who called such movements adverse because it seemed as if the ape was looking at or listening to something happening away from the stimulation, on the contralateral side. Furthermore, when Brodmann area 4 was stimulated, they found motor responses at lower intensities than when stimulating area 6 (posterior to area 4), and responses could be abolished by severing fibers between both areas. Based on these results, they designated area 4 as the primary motor field and area 6 as secondary and tertiary motor fields. Foerster²⁵ induced bilateral movements and turning when stimulating at higher intensities over area 6, area 5 (parietal), and area 22 (temporal). He called these regions extrapyramidal and secondary motor areas, different to the primary motor region (area 4). The first systematic study of human cortical functions was published by Penfield and Jasper⁴ during the presurgical assessment of epilepsy. They confirmed that area 4 was the primary motor cortex in humans, and that areas 1 to 3 (postcentral) were primary somatosensory, drawing the well-known homunculus (Fig. 1). In addition, they described how stimulation of the supplementary motor cortex could provoke arrest of voluntary movements. They found that functional

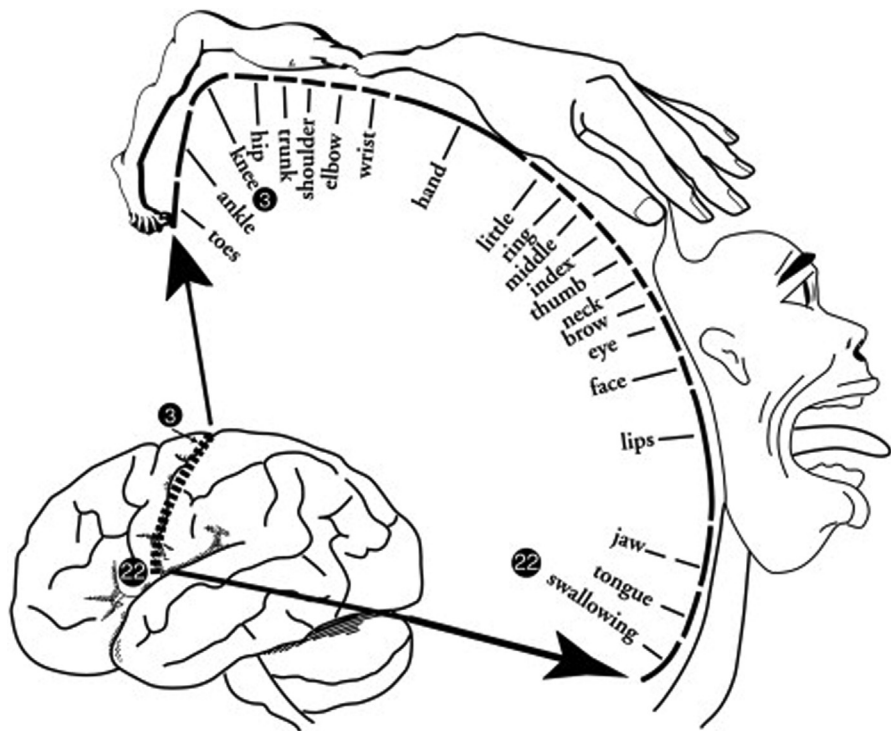


Fig. 1. History of cortical mapping in humans: motor homunculus. (From Sontheimer H. Parkinson disease. In: Diseases of the nervous system. London: Academic Press; 2015. p. 142; with permission.)

connections exist between precentral and post-central regions, considering the area as a sensorimotor unit, as recently confirmed.^{26,27}

METHODS OF FUNCTIONAL ELECTRICAL MAPPING

Functional electrical mapping is usually performed with the patient awake and relaxed, either intraoperatively under local anesthesia, or extraoperatively in the clinical ward in patients implanted with intracranial recordings (**Fig. 2**).

Intraoperative Functional Mapping

Most centers perform intraoperative functional mapping (IFM) in 2 consecutive days. During the first day, a craniotomy is performed under general anesthesia, and, during the second day, the craniotomy is reopened and the patient is then kept awake for mapping. Other centers prefer to complete the procedure in 1 session, including periods of general and local anesthesia. Propofol and dexmedetomidine sedation seems to be a good combination for transitioning patients from asleep to awake periods.²⁸

During IFM, the patient should be made aware of the potential clinical responses of stimulation, because these can be distressing or uncomfortable if unexpected (eg, provoked seizures, forced movements, speech or memory arrest). IFM must be performed with simultaneous electrocorticographic recordings in order to record afterdischarges and minimize the risk of inducing

seizures, in addition to detailed neurologic and neuropsychological assessment. During IFM, the anesthetist controls sleep periods, waking up the patient when needed for the procedure of functional mapping. Potential problems are related to pain or emotional disturbances experienced by the patient during the operation. A highly undesirable side effect is induction of seizures in the operating theater with open craniotomy,²⁹ which should be minimized by using current intensities at or below the threshold to induce afterdischarges on simultaneous electrocorticographic recordings. When it is not adequate to keep the patient fully awake, it is also possible to perform functional mapping with motor or sensory evoked potentials under anesthesia.

Extraoperative Functional Mapping

Extraoperative mapping with subacutely implanted intracranial electrodes involves more than 1 surgical procedure to achieve resection.³⁰ After the initial electrode implantation (**Fig. 3**), functional mapping is performed in the ward. The advantages of this procedure are that it is possible to repeat or continue stimulation in different sessions, which allows a larger variety of stimulation parameters, having more time to further assess clinical findings, performing a larger number of specific functional and neuropsychological tasks, and identifying the regions whose stimulation induces the patient's habitual seizures (which can be particularly dangerous during IFM in the theater with open craniotomy).

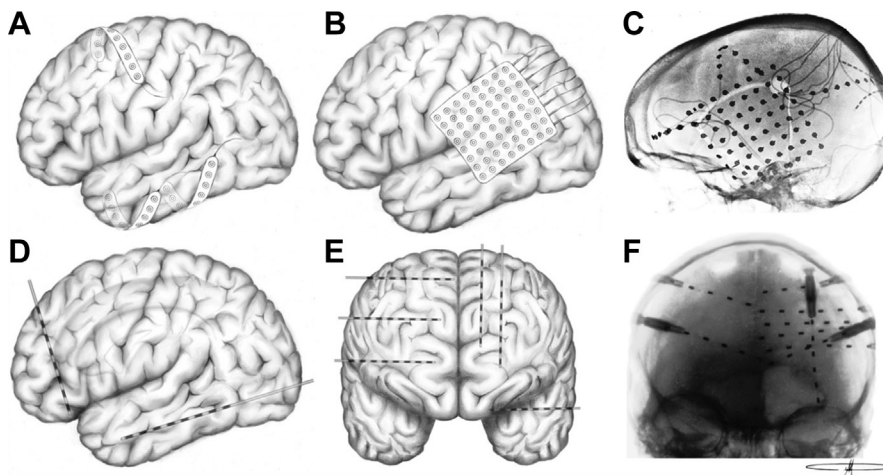


Fig. 2. Types and possible positions of intracranial electrodes. (A) Lateral brain view of 9-contacts subdural electrodes in subtemporal and frontal structures. (B) Lateral view of a 64-contact mat over the parietoposterior temporal region. (C) Lateral radiograph from a patient with a 64-contact mat and four 8-contact subdural electrodes. (D) Lateral view with depth electrodes located in orbitofrontal cortex, and 1 electrode at the hippocampus (posterior approach). (E) Anterior posterior view with depth electrodes over frontal and temporal structures (lateral approach). (F) Anterior posterior radiograph from a patient with depth electrodes in frontal structures. (Courtesy of David Martín López, MD, PhD, King's College London, UK.)

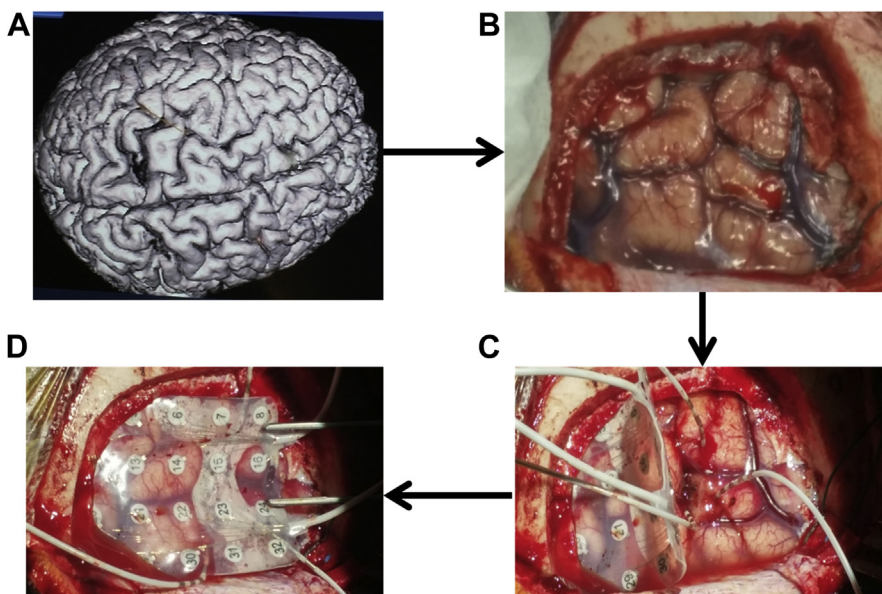


Fig. 3. Preparation and location of intracranial electrodes for functional mapping in telemetry in a 16-year-old patient. (A) Three-dimensional brain MRI showing a lesional region over the posterior aspect of the left frontal lobe. (B) Opening of the bone and dura. (C) Initial positioning of a combination of depth electrodes and a subdural mat to cover the supplementary and primary motor cortex. (D) Final position of electrodes.

Functional Mapping Parameters

Subdural electrodes (mats or strips) provide good spatial sampling of cortical surface. Although having less regular spatial sampling than subdural mats, depth electrodes can also be used to reach and stimulate deep structures. The standard parameters used during functional stimulation are trains of 0.45-millisecond to 1-millisecond biphasic electrical pulses at a frequency of 50 Hz or 60 Hz delivered during 1 to 10 seconds. Other stimulation parameters have also been used for motor cortex (eg, frequencies of 1 Hz). Stimulation should start at a low intensity (0.5–1 mA) with a short duration (1 second). If no clear functional responses are noted, the stimulation duration is gradually increased up to 5 to 10 seconds, followed by progressive increments in stimulation intensity and duration up to 10 mA for 6 seconds in adults and up to 15 mA in pediatric centers.^{31–33} More specifically, for each pair of stimulating electrodes, if no clinical responses are noted, stimulation should be progressively increased (first current intensity and, for each intensity, progressively increase duration in 2-second steps) until at least 1 of the following circumstances occurs: (1) positive clinical signs or symptoms; (2) negative clinical signs; (3) after-discharges on electroencephalogram (EEG); (4) the upper limits of stimulation intensity and duration described earlier are reached. Once a clinical response is noted, functional stimulation must be repeated at the same

position and stimulation parameters after at least 30 seconds, in order to confirm the findings. The standard parameters of functional stimulation seem to be clinically safe. Stimulation with charge density at $55 \mu\text{C}/\text{cm}^2/\text{phase}$ is not associated with pathologic changes.³⁴ Stimulation threshold does not seem to decrease significantly after successive stimulation trials. Kindling of the neocortex has not been observed in humans or higher primates.

An alternative technique for functional mapping includes single-pulse electrical stimulation (0.1–1 Hz) to map the primary motor cortex. It has lower risk of provoking seizures and the induced movements are very localized.^{35–37} However, likelihood of inducing discernible clinical responses is also reduced when single electrical pulses are used. High-frequency monopolar stimulation has also been tried under general anesthesia.³⁸ This technique uses 5 monopolar pulses (0.5 milliseconds) at 300 to 500 Hz with a repetition rate of 1 to 3 Hz. This technique is mainly used for motor evoked potentials, and it can be used in children³⁹ and epileptic patients.⁴⁰

After-Discharges During Functional Electrical Stimulation

After-discharges are runs of epileptiform discharges or ictal patterns induced by functional stimulation (Fig. 4), usually localized to areas close to the stimulated cortex. They are usually short (a

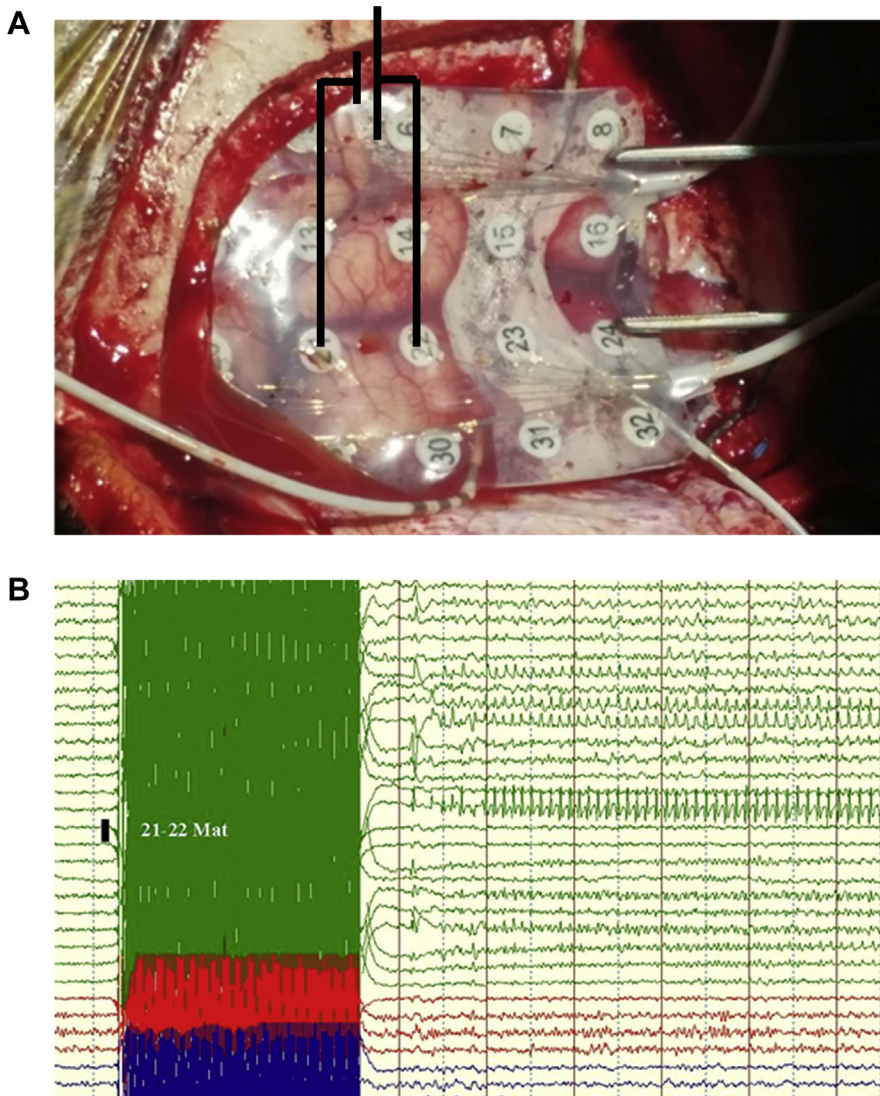


Fig. 4. Examples of after-discharges in a patient with a 32- contact mat. Stimulation through electrodes 21 and 22 of the mat for 3 seconds (A) induced sustained afterdischarges for several seconds at nearby electrodes (B).

few seconds) and asymptomatic if they are restricted to noneloquent cortex. However, they can propagate to eloquent regions, complicating the clinical interpretation of functional mapping because the clinical signs could be provoked by involvement of regions far away from the stimulated cortex. Occasionally, after-discharges last longer, evolving into clinical seizures not necessarily resembling the patient's habitual seizures.

CLINICAL RESPONSES DEPENDING ON THE STIMULATED AREA

The clinical responses to functional stimulation described later are reproducible and are usually

restricted to the duration of stimulation, unless a seizure or after-discharges are induced. As mentioned earlier, if responses are associated with after-discharges, they could be caused by propagation to regions distant from the stimulated cortex, leading to mislocalization of function.⁴¹ Consequently, the gold standard for correct identification of eloquent cortex is the evaluation of the clinical responses described later in the absence of EEG after-discharges.

The location and distribution of eloquent cortex is evaluated by direct visual observation of clinical signs described later. Clinical signs can be positive (movement, sensations) or negative (speech or motor arrest). The cortex responsible for each

sign is assumed to be located under the electrodes used for stimulation to induce the specific response. The stimulation threshold to induce functional responses can show day-to-day fluctuations. The responses most commonly seen when stimulating each eloquent cortical region are described below.

Motor (Largely Precentral) Cortex

Trains of pulses induce contralateral muscle contractions and limb movements such as clonic contractions or dystonic limb postures (**Fig. 5**), most commonly involving the contralateral hand and face because these regions have the largest cortical representation. Stimulation of the primary motor cortex between upper face and finger areas, or at premotor cortex anterior to this region, can elicit turning of the head and eye (frontal eye field area) in the direction contralateral to stimulation (adverse rotation).^{4,42} Unilateral stimulation of mouth, tongue, or throat areas can induce bilateral movements or contralateral unilateral responses. Neck movements (aside from turning) can be induced by stimulation of 2 regions, below and above the face area. Stimulation of the lip/mouth area can elicit a vocalization consisting in a long, drawn-out vowel sound made by symmetric contraction of mouth, pharynx, larynx, and respiratory muscles. Single electrical pulses can induce localized motor responses, often restricted to 1 finger or muscle.³⁶

Somatosensory (Largely Postcentral) Cortex

Stimulation of the somatosensory cortex can induce contralateral paresthesiae such as tingling, numbness, burning, or electrical sensations, and

occasionally pain sensations or a sense of movement. They most commonly involve the contralateral hand and face because these regions have the largest cortical representation. Sensory responses are contralateral except for throat, face, and tongue areas, which can be bilateral. Stimulation of the tongue and mouth areas can induce numbness or tingling, but not taste sensations. A second sensory area is located at the suprasylvian cortex, covering precentral and postcentral regions.⁴ Stimulation of this area induces responses usually associated with desire to move, loss of strength, or temporary paralysis in the contralateral (or ipsilateral) region. Cortical stimulation has been reported to induce somatosensory sensations in phantom limbs.⁸

Mixed Motor and Sensory Responses

Occasionally, functional electrical stimulation can induce both motor and sensory responses, probably because of stimulation of secondary cortex or association fibers. Interestingly, sensory responses can be elicited precentrally and motor responses postcentrally in 25% of patients. When stimulating the lateral lower end of the sensorimotor strip, respiratory arrest can also be provoked.⁴

Supplementary Motor Cortex

In humans, the supplementary motor cortex is the region anterior to the leg area in the interhemispheric fissure and dorsal aspect of the superior frontal gyrus. Stimulation of this region can provoke a variety of clinical responses: aversive movements, dystonic postures (often bilateral, aversive head rotation, and posturing of shoulders and elbows), arrest or slowing of voluntary

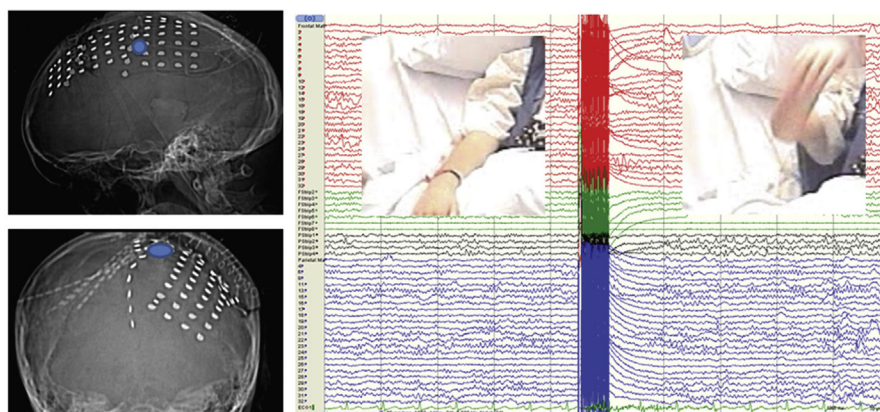


Fig. 5. Functional stimulation of the primary motor hand area with subdural mats and strips over the frontal and the parietal lobe. (A) Lateral radiograph view. (B) Anterior posterior radiograph view. (C) Functional stimulation of contacts 7 and 9 of the subdural strip provoked elevation of the right hand. (Courtesy of International League Against Epilepsy, Flower Mound, TX)

movements and speech, vocalization, sensations (general body sensation, sensation of flush, cephalic, epigastric or indescribable sensations, contralateral or bilateral leg sensations), and autonomic changes (pupillary dilation and changes in heart rate). The supplementary motor cortex also shows somatotopic organization.⁴³

Occipital Visual Cortex

Phosphenes (flickering lights, dancing lights, stars, colors, shades, gray spots) or elementary visual shapes (lines, whirling circles) seen in the contralateral visual field can be induced by stimulation of the visual field. Occasionally, shapes are seen in front of the eyes. Complex visual shapes (faces, people, multisensorial) can be seen when stimulating posterior temporal and parietal regions, close to the occipital lobe. In the human brain, areas 18 and 19 are most easily accessible with subdural electrodes, but area 17 and the calcarine fissure (primary visual cortex) are rarely accessible, except the macula, which is represented at the occipital pole. Stimulation of the parieto-occipital region can induce adverse eye movements. If possible, resections should also avoid visual pathways, such as optic radiations, which can also be identified by electrical stimulation.⁴⁴

Uncus, Olfactory Bulb, and Amygdala

Olfactory and gustatory sensations, such as disagreeable smells, are often elicited by stimulation. A sensation of fear and anxiety has also been described when stimulating the amygdala.⁴⁵

Insula and Sylvian Fissure

The insular cortex is connected to 2 different cortical networks. The anterior insula is primarily connected to the visceral network extending to the temporomesial structures, and its stimulation induces visceral autonomic changes, salivation, taste, and abdominal sensations such as nausea or epigastric sensations. Stimulation of the posterior insula tends to induce somatosensory sensations because it is connected to the somesthetic network reaching the opercular cortex.⁴⁶ A sensation of usually disagreeable taste can be induced by stimulating the insula.

Auditory Cortex (Posterior Half of the Superior Temporal Gyrus)

Stimulation induces perception of ringing, humming, buzzing, and other sounds, as well as deafness and distortion of incoming sounds. Because each

hemisphere receives information from both ears, sounds can be referred to the opposite ear or to both ears. Stimulation of the superior temporal gyrus can also be associated with suppression of hearing.⁴⁷

Language Cortex

Although stimulation of most previously described areas induces the appearance of movement or sensation (positive signs), stimulation of the language area halts function (negative signs), which means that the patient needs to be collaborative and perform a language-related task during stimulation. An area is considered language eloquent if stimulation elicits language impairment (eg, speech arrest, hesitation, semantic errors) during a language task.

The brain areas responsible for language function were some of the first functional areas to be identified in patients who developed disruption of executive speech and writing after brain lesions located in the inferior frontal gyrus.⁴⁸ Patients with lesions over the posterior and superior aspects of the lateral temporal lobe developed problems in the analysis and interpretation of language.⁴⁹ The region described by Broca was associated with speech production (the Broca area or motor speech area), and the area described by Wernicke was related to speech comprehension (the Wernicke area or receptive speech area). The Wernicke area borders the primary auditory cortex in the lateral superior temporal sulcus, at the temporoparietal junction. The Wernicke area also refers to the gyri that form the lower sylvian fissure.^{3,50} Broca's and Wernicke's areas are functionally and structurally connected by the arcuate fasciculus (**Fig. 6**),

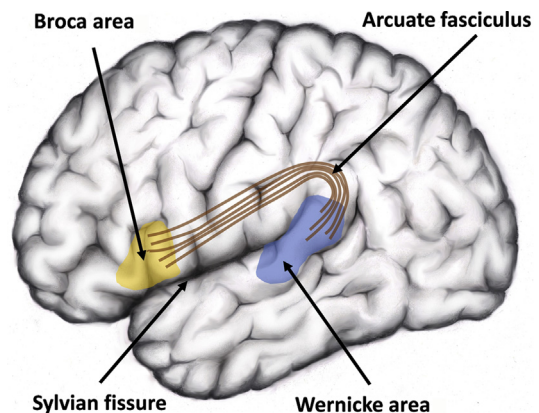


Fig. 6. The arcuate fasciculus connects Wernicke and Broca areas. (Courtesy of David Martín López, MD, PhD, King's College London, UK.)

and they have been associated with the main language function. However, this dichotomy of language processing is now thought to be oversimplified.⁵ For instance, lesion studies show that damage to the Wernicke area can lead to issues with speech production and deficits in speech comprehension.^{3,6} Thus, language networks seem to be more intricately connected than was previously thought.⁵⁰

Language mapping requires participants to engage in specific language tasks (**Table 1**). To localize Broca's area, the traditional task consists in asking patients to read, count, or recite a known song or lullaby while checking for pauses in speech associated with stimulation. Stimulation of Broca's area induces speech arrest while counting, reading, or reciting. Identification of Wernicke's area is more challenging because deficits in speech understanding are more subtle to detect. For example, speech disturbances such as hesitation in Wernicke's area can be less obvious.⁵¹ To identify Wernicke's area, the methods most commonly used are object naming (also called the Boston naming test or grade naming test^{52–56}), verb generation,^{57,58} auditory responsive naming,^{59,60} picture selection, and visual confrontation naming⁶¹ (**Fig. 7A**). However, new techniques are being developed, such as the verb and noun test⁶² and the single-word auditory comprehension test⁶³ (**Fig. 7B, C**). The correct use of these language tests can help clinicians estimate the location of Wernicke's area, limiting potential postsurgical deficits (**Fig. 8**). The language tests currently used to map language areas may be less sensitive or reliable than those used in motor and sensory mapping because postoperative language deficits can still arise in some patients.⁵¹ There are multiple risk factors, including intraoperative complications, preoperative aphasia, and language-eloquent areas linked to epileptogenic areas.⁶⁴

Accurate lateralization of language areas remains inconsistent. For 95% to 99% of right-handed individuals, and approximately 70% of left-handed individuals, language areas are located on the left hemisphere.^{65,66} However, emerging research suggests that the nondominant Wernicke area (often the right homologue) also plays an important role in language, because its stimulation can lead to language disturbance. Differences in the location of language areas between individuals may explain the wide spectrum of language disturbances and differences in recovery, despite similar lesions. This possibility highlights the limitation of defining language-eloquent areas based solely on an anatomic basis.^{5,50}

Memory Cortex

Memory mapping during assessment with intracranial electrodes is mainly performed in patients who failed the Wada test or when preservation of memory after resection is required. In these patients, resection could be limited, avoiding the lateral temporal memory sites and the anterior portion of the hippocampus.^{67,68} Feindel and Penfield⁶⁹ described arrest of memory encoding when stimulating close to the hippocampus. However, disruption of memory when stimulating unilaterally only occurred in a minority of patients and required the induction of after-discharges by the stimulus.^{70–72} Early studies showed that temporary amnesia could be induced when stimulating medial temporal structures bilaterally with trains of electrical pulses lasting 3 to 50 seconds.^{73–75} More recent studies have confirmed these initial findings, showing that short-term memory is processed independently in both hemispheres, mainly by medial temporal structures,^{71,72,76–78} but the lateral temporal neocortex is also implicated,^{79–81} especially for verbal memory in the dominant hemisphere.^{67,82}

Stimulation of the lateral temporal neocortex of the dominant hemisphere can provoke memory recollections or déjà vu,⁴ but it can also induce errors in verbal memory.⁸³ Memory is a complex function that involves a variety of sites and tasks. For this reason, memory mapping with electrical stimulation is nonstandard, and reviews of strategies can be found elsewhere.^{83,84}

FUNCTIONAL ELECTRICAL STIMULATION IN CHILDREN

Myelination in children's brain is incomplete, and functional mapping in children should be performed with extreme caution because it usually requires higher current intensities or pulse durations than in adults. In children under the age of 10, after-discharge threshold is often lower than the threshold for functional response, and functional mapping is then performed by identification of areas showing the lowest functional threshold. Identification of sensory or language areas requires active patient cooperation, and it is not usually possible in infants, toddlers, and children under the age of 4. Functional mapping in children has been extensively reviewed.^{85–87}

AFTER-DISCHARGES AND STIMULATION INDUCED SEIZURES FOR LOCALIZATION OF EPILEPTOGENIC CORTEX

The localizing value of after-discharges provoked by cortical stimulation has long been debated.^{88–90}

Table 1
Summary of different language tests and their respective strengths and limitations

| Name of Test | Brief Description | Strengths/Limitations |
|------------------------------|---|--|
| ONT | Images of objects. The patients are asked to name the object | Widely used as a standard test across studies, allowing comparison. Based on an external stimulus, so there is possible automaticity in naming, which may reduce the amount of semantic processing. Can be a useful and sensitive experimental paradigm in language mapping intraoperatively ^{52–54} |
| Verb generation | Images of actions. The patients are asked to build verbs from these images; eg, eat | Can produce more errors in anterior regions than posterior regions. Difficult to elicit semantic, neological, or phonological errors with this task compared with ONT. ⁵⁴ Can be used in conjunction with action naming task to show differences in language errors between verbs and nouns ^{57,58} |
| Action naming (nouns) | Images of everyday activities. The patients name the actions without saying a noun; eg, sleeping, dancing | May produce fewer hesitation errors, performance errors, semantic errors, and neologism errors than ONT. Evokes a greater number of errors in posterior regions than anterior regions, which may suggest it is more suitable than ONT for mapping posterior language areas ^{52,54} |
| Pseudoword reading | Patients read pseudowords intermixed with real words as controls | This task produces fewer errors possibly because it seems to be less demanding than naming and generation tasks. High number of phonological errors, more frequently evoked in anterior regions ⁵⁴ |
| Auditory comprehension tests | Patients hear a sentence describing a single word and they say the word aloud; eg, "What a book is divided into?" Reply: "Chapters" | Auditory naming may more accurately characterize and lateralize TLE-associated language. May predict seizure focus laterality better than visual confrontational naming. Possibly reflects everyday conversation more accurately, because it requires the expression of an internal idea. Can be used to predict future impairment better than object naming tasks ⁵⁹ |
| SWAT | Patients hear a target word (eg, cat) and they describe the word without using the word itself | Simple and rapid to administer with reliable results to identify Wernicke area. SWAT can identify speech receptive areas and results suggest it can be used as a predictor of postoperative deficits. May be used as a preliminary test in combination with other language tests. Does not test complex language comprehension, so it may not reflect natural speech comprehension ⁶³ |

Abbreviations: ONT, object naming test; SWAT, single-word auditory test; TLE, temporal lobe epilepsy.

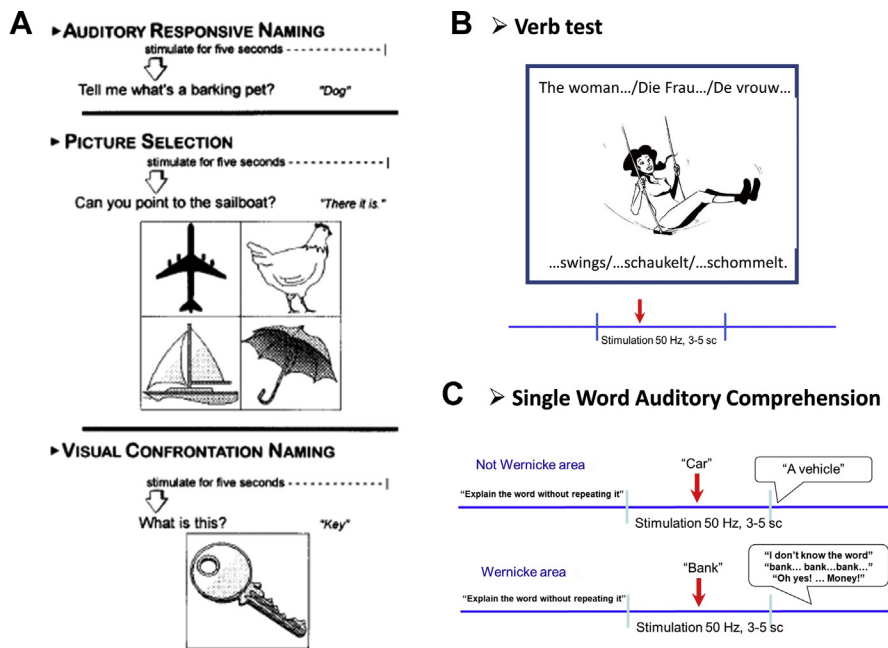


Fig. 7. Language mapping techniques. (A) Paradigms to identify receptive (Wernicke) language areas showing the time course of language task and stimulation. The down arrows indicate the onset of electrical stimulation. (B) Verb test. The red arrow indicates when the figure is shown to the patient during the stimulation period. (C) Single-word auditory comprehension test. The red arrow indicates when the word is said to the patient during the stimulation period. ([A] From Malow BA, Blaxton TA, Sato S, et al. Cortical stimulation elicits regional distinctions in auditory and visual naming. *Epilepsia* 1996;37:245–52; with permission; and [B] Courtesy of YRM Bastiaanse, University of Groningen, Netherlands.)

After-discharges can be induced in areas other than the patient’s seizure onset zone, and their presence is not a clear marker for epileptogenicity. In early studies, it was suggested that the region whose stimulation produced the longest after-

discharges or the only after-discharges was the origin of spontaneous seizures in 75% of cases.⁴ Several large studies have shown 77% to 100% concordance between seizures and after-discharges depending of the brain region.^{89,91}

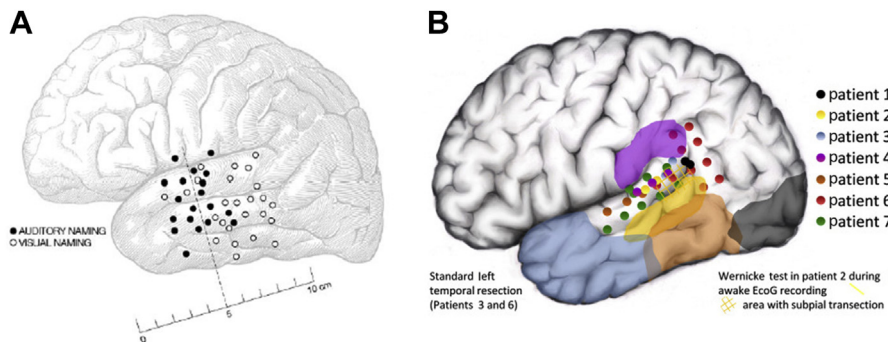


Fig. 8. Language mapping distribution. (A) Auditory (closed circles) and visual (open circles) naming sites in patients with hippocampal sclerosis. (B) Single-word auditory comprehension test sites in patients with intracranial electrodes over the left temporal lobe. EcoG, electrocorticography. (From [A] Hamberger MJ, McClelland S, 3rd, McKhann GM, 2nd, et al. Distribution of auditory and visual naming sites in nonlesional temporal lobe epilepsy patients and patients with space-occupying temporal lobe lesions. *Epilepsia* 2007;48:531–8; with permission; and [B] Alarcon G, Pedersen MB, Juarez-Torres N, et al. The Single Word Auditory Comprehension (SWAC) test: A simple method to identify receptive language areas with electrical stimulation. *Epilepsy Behav.* 2019;90:269; with permission.)

However, the areas showing lowest current intensity required to induce after-discharges (lowest after-discharge threshold) do not seem to be related to the areas generating spontaneous seizure onset. After-discharge threshold is usually lower at the area of seizure onset, but it can be higher in about 25% of patients, presumably because of the neuronal loss inherent to some disorders.⁸⁹ The areas whose stimulation induces the patient's habitual aura or habitual seizures may be a more reliable marker for epileptogenicity. A study of 72 patients reported a high correlation between ictal onset zone for spontaneous seizures and the sites stimulated to induce the patient's habitual auras or seizures, particularly for medial temporal lobe epilepsy.⁹² Interestingly, stimulation with single electrical pulses (0.2–1 Hz) can rarely induce seizures, but, when it does, it could be an useful clinical tool to identify epileptogenic cortex.^{93,94}

SUMMARY

Functional electrical cortical stimulation is a reliable technique for identification of functionally eloquent cortex in presurgical assessment of epilepsy and tumors. It has clinical value to prevent motor and language deficits after surgery. Although invasive, it has been used in humans since Penfield and Jasper⁴ in the 1950s and continues to be one of the most reliable techniques to identify functionally eloquent cortex. Noninvasive alternatives such as functional MRI and transcranial magnetic stimulation are presently being developed and evaluated. Functional stimulation can also aid in the identification of epileptogenic regions if habitual seizures are provoked.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Thijs RD, Surges R, O'Brien TJ, et al. Epilepsy in adults. *Lancet* 2019;393:689–701.
2. Zijlmans M, Zweiphenning W, van Klink N. Changing concepts in presurgical assessment for epilepsy surgery. *Nat Rev Neurol* 2019;15:594–606.
3. Tremblay P, Dick AS. Broca and Wernicke are dead, or moving past the classic model of language neurobiology. *Brain Lang* 2016;162:60–71.
4. Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain*. Boston: Brown; 1954.
5. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. *J Neurosurg* 2015;122:250–61.
6. Mirman D, Chen Q, Zhang Y, et al. Neural organization of spoken language revealed by lesion-symptom mapping. *Nat Commun* 2015;6:6762.
7. De Tiege X, Connelly A, Liegeois F, et al. Influence of motor functional magnetic resonance imaging on the surgical management of children and adolescents with symptomatic focal epilepsy. *Neurosurgery* 2009;64:856–64 [discussion: 64].
8. Ojemann GA, Sutherling WW, Lesser RP, et al. Cortical Stimulation. In: Engel J Jr, editor. *Surgical treatment of the epilepsies*. 2nd edition. New York: Raven Press, Ltd; 1993. p. 399–414.
9. Kakita A, Hayashi S, Moro F, et al. Bilateral periventricular nodular heterotopia due to filamin 1 gene mutation: widespread glomeruloid microvascular anomaly and dysplastic cytoarchitecture in the cerebral cortex. *Acta Neuropathol (Berl)* 2002;104:649–57.
10. Nii Y, Uematsu S, Lesser RP, et al. Does the central sulcus divide motor and sensory functions? Cortical mapping of human hand areas as revealed by electrical stimulation through subdural grid electrodes. *Neurology* 1996;46:360–7.
11. Little AS, Ng YT, Kerrigan JF, et al. Anterior motor strip displacement in a boy with right frontal gray matter heterotopia undergoing epilepsy surgery. *Epilepsy Behav* 2007;11:241–6.
12. Breier JI, Castillo EM, Simos PG, et al. Atypical language representation in patients with chronic seizure disorder and achievement deficits with magnetoencephalography. *Epilepsia* 2005;46:540–8.
13. Duffau H. Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping. *J Neurol Neurosurg Psychiatry* 2001;70:506–13.
14. Devaux B, Chassoux F, Landre E, et al. Chronic intractable epilepsy associated with a tumor located in the central region: functional mapping data and postoperative outcome. *Stereotact Funct Neurosurg* 1997;69:229–38.
15. Fritsch G, Hitzig E. Über die elektrische Erregbarkeit des Grosshirns. *Arch Anat Physiol Wissen* 1870;37:300–32.
16. Ferrier D. Experimental Researches in Cerebral Physiology and Pathology. *J Anat Physiol* 1873;8:152–5.
17. Luciani L. Sulla patogenesi della epilessia. Studio critico-sperimentale. *Riv Sper Freniatr Med Leg Alien Ment* 1878;4:617–46.
18. Bartholow R. Experimental investigation into the functions of the human brain. *Am J Ment Sci* 1874;305–13.
19. Keen W. Three successful cases of cerebral surgery. *Am J Med Sci* 1888;96:452–65.
20. Francois-Frank CE, Pitres A. Recherches expérimentales et critiques sur les convulsions

- épileptiformes d'origine corticale. *Arch Physiol Norm Pathol* 1883;15:1–40.
21. Rosenbach P. Ueber die Pathogenese der Epilepsie. *Virchows Arch* 1884;97:369–409.
 22. Brodmann K. Verleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien Dargestellt auf Grund des Zellenbaues. Leipzig (Germany): Johann Ambrosius Barth; 1909.
 23. Sherrington CS. The integrative action of the nervous system. New York: Charles Scribner's Sons; 1906.
 24. Vogt C, Vogt O. Die vergleichend-architektonische und die vergleichend-reizphysiologische Felderung der Großhirnrinde unter besonderer Berücksichtigung der menschlichen. *Naturwissenschaften* 1926; 14:1192–5.
 25. Foerster O. The cerebral cortex in man. *Lancet* 1931;218:309–12.
 26. Matelli M, Luppino G. Parietofrontal circuits: parallel channels for sensory-motor integrations. *Adv Neurol* 2000;84:51–61.
 27. Freund HJ. Sensorimotor processing in parietal neocortex. *Adv Neurol* 2000;84:63–74.
 28. Souter MJ, Rozet I, Ojemann JG, et al. Dexmedetomidine sedation during awake craniotomy for seizure resection: effects on electrocorticography. *J Neurosurg Anesthesiol* 2007;19:38–44.
 29. Nossek E, Matot I, Shahar T, et al. Intraoperative seizures during awake craniotomy: incidence and consequences: analysis of 477 patients. *Neurosurgery* 2013;73:135–40 [discussion: 40].
 30. Hamer HM, Morris HH, Mascha EJ, et al. Complications of invasive video-EEG monitoring with subdural grid electrodes. *Neurology* 2002;58:97–103.
 31. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med* 2008;358:18–27.
 32. Szelenyi A, Bello L, Duffau H, et al. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. *Neurosurg Focus* 2010;28:E7.
 33. Kayama T. Guidelines committee of the Japan awake surgery c. The guidelines for awake craniotomy guidelines committee of the Japan awake surgery conference. *Neurol Med Chir (Tokyo)* 2012;52:119–41.
 34. Gordon B, Lesser RP, Rance NE, et al. Parameters for direct cortical electrical stimulation in the human: histopathologic confirmation. *Electroencephalogr Clin Neurophysiol* 1990;75:371–7.
 35. Ikeda A, Miyamoto S, Shibasaki H. Cortical motor mapping in epilepsy patients: information from subdural electrodes in presurgical evaluation. *Epilepsia* 2002;43(Suppl 9):56–60.
 36. Valentin A, Alarcon G, Garcia-Seoane JJ, et al. Single-pulse electrical stimulation identifies epileptogenic frontal cortex in the human brain. *Neurology* 2005;65:426–35.
 37. Sanai N, Berger MS. Mapping the horizon: techniques to optimize tumor resection before and during surgery. *Clin Neurosurg* 2008;55:14–9.
 38. Taniguchi M, Cedzich C, Schramm J. Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. *Neurosurgery* 1993;32:219–26.
 39. Schucht P, Seidel K, Murek M, et al. Low-threshold monopolar motor mapping for resection of lesions in motor eloquent areas in children and adolescents. *J Neurosurg Pediatr* 2014;13:572–8.
 40. Usui N, Terada K, Baba K, et al. Extraoperative functional mapping of motor areas in epileptic patients by high-frequency cortical stimulation. *J Neurosurg* 2008;109:605–14.
 41. Blume WT, Jones DC, Pathak P. Properties of after-discharges from cortical electrical stimulation in focal epilepsies. *Clin Neurophysiol* 2004;115: 982–9.
 42. Schlag J, Schlag-Rey M, Pigarev I. Supplementary eye field: influence of eye position on neural signals of fixation. *Exp Brain Res* 1992;90:302–6.
 43. Dinner DS, Luders HO. Human supplementary sensorimotor area. Electrical stimulation and movement-related potential studies. *Adv Neurol* 1995;66:261–9 [discussion: 9–71].
 44. Mandonnet E, Gatignol P, Duffau H. Evidence for an occipito-temporal tract underlying visual recognition in picture naming. *Clin Neurol Neurosurg* 2009;111: 601–5.
 45. Inman CS, Bijanki KR, Bass DI, et al. Human amygdala stimulation effects on emotion physiology and emotional experience. *Neuropsychologia* 2018 [pii: S0028-3932(18)30112-X].
 46. Ostrowsky K, Isnard J, Ryvlin P, et al. Functional mapping of the insular cortex: clinical implication in temporal lobe epilepsy. *Epilepsia* 2000;41: 681–6.
 47. Fenoy AJ, Severson MA, Volkov IO, et al. Hearing suppression induced by electrical stimulation of human auditory cortex. *Brain Res* 2006;1118:75–83.
 48. Broca P. Nouvelle observation d'aphémie produite par une lésion de la moitié postérieure des deuxième et troisième circonvolutions frontales. *Bulletins de la Société Anatomique de Paris* 1861;36: 398–407.
 49. Wernicke C. Der Aphasische Symptemenkomplex. Eine Psychologische Studie auf Anatomischer Basis: Breslau (Poland): Cohn & Weigert; 1874.
 50. DeWitt I, Rauschecker JP. Wernicke's area revisited: parallel streams and word processing. *Brain Lang* 2013;127:181–91.
 51. Chang EF, Breshears JD, Raygor KP, et al. Stereotactic probability and variability of speech arrest and anomia sites during stimulation mapping of the language dominant hemisphere. *J Neurosurg* 2017;126:114–21.

52. Hernandez-Pavon JC, Makela N, Lehtinen H, et al. Effects of navigated TMS on object and action naming. *Front Hum Neurosci* 2014;8:660.
53. Krieg SM, Sollmann N, Tanigawa N, et al. Cortical distribution of speech and language errors investigated by visual object naming and navigated transcranial magnetic stimulation. *Brain Struct Funct* 2016;221:2259–86.
54. Hauck T, Tanigawa N, Probst M, et al. Task type affects location of language-positive cortical regions by repetitive navigated transcranial magnetic stimulation mapping. *PLoS One* 2015;10:e0125298.
55. McKenna P, Warrington EK. Testing for nominal dysphasia. *J Neurol Neurosurg Psychiatry* 1980;43:781–8.
56. Kaplan E, Goodglass H, Weintraub S. Boston naming test. Philadelphia: Lea & Febiger; 1983.
57. Rofes A, Miceli G. Language mapping with verbs and sentences in awake surgery: a review. *Neuropsychol Rev* 2014;24:185–99.
58. Corina DP, Gibson EK, Martin R, et al. Dissociation of action and object naming: evidence from cortical stimulation mapping. *Hum Brain Mapp* 2005;24:1–10.
59. Hamberger MJ, Tamny TR. Auditory naming and temporal lobe epilepsy. *Epilepsy Res* 1999;35:229–43.
60. Hamberger MJ, Seidel WT, Goodman RR, et al. Evidence for cortical reorganization of language in patients with hippocampal sclerosis. *Brain* 2007;130:2942–50.
61. Malow BA, Blaxton TA, Sato S, et al. Cortical stimulation elicits regional distinctions in auditory and visual naming. *Epilepsia* 1996;37:245–52.
62. Ohlerth AK, Valentin A, Vergani F, et al. The verb and noun test for peri-operative testing (VAN-POP): standardized language tests for navigated transcranial magnetic stimulation and direct electrical stimulation. *Acta Neurochir (Wien)* 2020;162:397–406.
63. Alarcon G, Bird Pedersen M, Juarez-Torreson N, et al. The Single Word Auditory Comprehension (SWAC) test: A simple method to identify receptive language areas with electrical stimulation. *Epilepsy Behav* 2019;90:266–72.
64. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA* 2015;313:285–93.
65. Ries SK, Dronkers NF, Knight RT. Choosing words: left hemisphere, right hemisphere, or both? Perspective on the lateralization of word retrieval. *Ann N Y Acad Sci* 2016;1369:111–31.
66. Corballis MC. Left brain, right brain: facts and fantasies. *PLoS Biol* 2014;12:e1001767.
67. Ojemann GA, Dodrill CB. Verbal memory deficits after left temporal lobectomy for epilepsy. Mechanism and intraoperative prediction. *J Neurosurg* 1985;62:101–7.
68. Ojemann G. Surgical treatment of epilepsy. *J Child Neurol* 1988;3:154, 66.
69. Feindel W, Penfield W. Localization of discharge in temporal lobe automatism. *AMA Arch Neurol Psychiatry* 1954;72:603–30.
70. Bickford RG, Mulder DW, Dodge HW, et al. Changes in memory function produced by electrical stimulation of the temporal lobe in man. *Res Publ Assoc Res Nerv Ment Dis* 1958;36:227–43.
71. Halgren E, Wilson CL. Recall deficits produced by afterdischarges in the human hippocampal formation and amygdala. *Electroencephalogr Clin Neurophysiol* 1985;61:375–80.
72. Halgren E, Wilson CL, Stapleton JM. Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories. *Brain Cogn* 1985;4:287–95.
73. Brazier M. Evoked responses recorded from the depths of the human brain. *Ann N Y Acad Sci* 1964;112:33–5.
74. Chapman LF, Walter RD, Markham CH, et al. Memory changes induced by stimulation of hippocampus or amygdala in epilepsy patients with implanted electrodes. *Trans Am Neurol Assoc* 1967;92:50–6.
75. Ervin FR, Mark VH, Stevens J. Behavioral and affective responses to brain stimulation in man. *Proc Annu Meet Am Psychopathol Assoc* 1969;58:54–65.
76. Lacruz ME, Alarcon G, Akanuma N, et al. Neuropsychological effects associated with temporal lobectomy and amygdalohippocampectomy depending on Wada test failure. *J Neurol Neurosurg Psychiatry* 2004;75:600–7.
77. Lacruz ME, Valentin A, Seoane JJ, et al. Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. *Neuroscience* 2010;170:623–32.
78. Coleshill SG, Binnie CD, Morris RG, et al. Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. *J Neurosci* 2004;24:1612–6.
79. Ojemann GA. Organization of short-term verbal memory in language areas of human cortex: evidence from electrical stimulation. *Brain Lang* 1978;5:331–40.
80. Ojemann GA. Effect of cortical and subcortical stimulation on human language and verbal memory. *Res Publ Assoc Res Nerv Ment Dis* 1988;66:101–15.
81. Fedio P, Van Buren JM. Memory deficits during electrical stimulation of the speech cortex in conscious man. *Brain and Language* 1974;1:29–42.
82. Akanuma N, Reed LJ, Marsden PK, et al. Hemisphere-specific episodic memory networks in the human brain: a correlation study between intracarotid amobarbital test and [(18)F]FDG-PET. *J Cogn Neurosci* 2009;21:605–22.

83. Perrine K. Future directions for functional mapping. *Epilepsia* 1994;35(Suppl 6):S90–102.
84. Thompson RF. In search of memory traces. *Annu Rev Psychol* 2005;56:1–23.
85. Chitoku S, Otsubo H, Harada Y, et al. Extraoperative cortical stimulation of motor function in children. *Pediatr Neurol* 2001;24:344–50.
86. Gallentine WB, Mikati MA. Intraoperative electrocorticography and cortical stimulation in children. *J Clin Neurophysiol* 2009;26:95–108.
87. Jayakar P, Duchowny M. Invasive EEG and functional cortical mapping. In: *Paediatric epilepsy syndromes and their surgical treatment*. London: John Libbey; 1997. p. 547–56.
88. Gloor P. Contributions of electroencephalography and electrocorticography to the neurosurgical treatment of the epilepsies. *Adv Neurol* 1975;8:59–105.
89. Bernier GP, Richer F, Giard N, et al. Electrical stimulation of the human brain in epilepsy. *Epilepsia* 1990;31:513–20.
90. Ajmone-Marsan C. Focal electrical stimulation. In: Purpura DP, Penry JK, Tower DB, et al, editors. *Experimental models of epilepsy*. New York: Raven; 1972. p. 147–72.
91. Wieser HG, Bancaud J, Talairach J, et al. Comparative value of spontaneous and chemically and electrically induced seizures in establishing the lateralization of temporal lobe seizures. *Epilepsia* 1979;20:47–59.
92. Chauvel P, Landre E, Trottier S, et al. Electrical stimulation with intracerebral electrodes to evoke seizures. *Adv Neurol* 1993;63:115–21.
93. Valentin A, Alarcon G, Honavar M, et al. Single pulse electrical stimulation for identification of structural abnormalities and prediction of seizure outcome after epilepsy surgery: a prospective study. *Lancet Neurol* 2005;4:718–26.
94. Munari C, Kahane P, Tassi L, et al. Intracerebral low frequency electrical stimulation: a new tool for the definition of the "epileptogenic area"? *Acta Neurochir Suppl (Wien)* 1993;58:181–5.