Published in final edited form as:
J Clin Neurophysiol. 2018 March ; 35(2): 86–97. doi:10.1097/WNP.0000000000000440.

ELECTRICAL STIMULATION MAPPING of the Brain: Basic Principles and Emerging Alternatives

Anthony L. Ritaccio, MD,
Department of Neurology, Albany Medical College, Albany, New York, U.S.A.; and National Center for Adaptive Neurotechnologies, Wadsworth Center, New York State Department of Health, Albany, New York, U.S.A

Peter Brunner, PhD, and
Department of Neurology, Albany Medical College, Albany, New York, U.S.A.; and National Center for Adaptive Neurotechnologies, Wadsworth Center, New York State Department of Health, Albany, New York, U.S.A

Gerwin Schalk, PhD
National Center for Adaptive Neurotechnologies, Wadsworth Center, New York State Department of Health, Albany, New York, U.S.A.; and Department of Neurology, Albany Medical College, Albany, New York, U.S.A

Abstract

The application of electrical stimulation mapping (ESM) of the brain for clinical use is approximating a century. Despite this long-standing history, the value of ESM for guiding surgical resections and sparing eloquent cortex is documented largely by small retrospective studies, and ESM protocols are largely inherited and lack standardization. Although models are imperfect and mechanisms complex, the probabilistic causality of ESM has guaranteed its perpetuation into the 21st century. At present, electrical stimulation of cortical tissue is being revisited for network connectivity. In addition, noninvasive and passive mapping techniques are rapidly evolving to complement and potentially replace ESM in specific clinical situations. Lesional and epilepsy neurosurgery cases now offer different opportunities for multimodal functional assessments.

Keywords

electrical stimulation mapping; functional localization; brain mapping; cortico-cortical evoked potentials; electrocorticography; passive gamma mapping

> "A map *is not* the territory it represents, but, if correct, it has a *similar structure* to the territory, which accounts for its usefulness."
>
> Alfred Korzybski (*Science and Sanity*, p. 58)[1]

Corresponding Author: Anthony L. Ritaccio, MD, Department of Neurology, Albany Medical College, 47 New Scotland Ave., MC-70, Albany, NY 12208-3479, T: 518-262-5226; F: 518-262-5261; RitaccA@mail.amc.edu.

Conflicts of Interest
The authors own intellectual property in ECoG-based functional mapping, and may derive licensing income related to it.

Across three centuries, electrical stimulation mapping (ESM) has remained a pivotal method in medicine and systems neuroscience. Historically, the evolution of ESM defined the electrical nature of neural transmission and pioneered the localization of brain function. Despite the development of modern tools such as functional magnetic resonance imaging (fMRI) and diffusion tractography (DT), ESM has survived as a dominant method for delineating cortical function in both clinical and research domains.

Practical application of conventional ESM methods produces specific and reliable outcomes at defined sites. Abundant small and retrospective studies (i.e., level IV evidence) have documented that ESM-guided neurosurgical resective strategies eliminate or minimize sensorimotor and linguistic postoperative deficits.[2–4] Perhaps no other method for delineating brain function possesses both its practical applicability and its proven causality.

Despite its long history and undeniable practical utility, ESM also has clear and broadly acknowledged shortcomings whether performed in an epilepsy monitoring unit (EMU) with dedicated implanted subdural or depth electrodes or intraoperatively in either the anesthetized or awake state. In the semi-chronic setting of the EMU, it is time-consuming and commonly requires hours and sometimes days. It is typically applied late in the course after seizure collections and restoration of antiepileptic drugs, typically on the eve of a patient's epilepsy surgery. In the operating theater, time constraints are even more severe compared to the EMU, and there are the anesthetic challenges of awake craniotomies. The evocation of afterdischarges (AD) and seizures often limits the length of stimulation trains or entirely cancels the utility of the method. This limitation considerably reduces the list of cognitive tasks that can be performed. Finally and curiously, despite its common clinical usage internationally over the past century, the technique is not standardized.

Fundamentally, ESM uses electrical stimuli to inhibit or excite function. Thus, it is a nonphysiological and a "lesional" method. Up to the present, most studies have focused on the discrete effects of stimulation on the stimulated nodes. More recently, attention has also been placed on its summation effects at distant sites. Cortico-cortical evoked potentials represent this most modern innovation of electrical stimulation to express networks beyond local excitatory and inhibitory influences.

Important potential successors to ESM have arisen to challenge conventional mapping strategies that have been somewhat invariant for decades. Novel noninvasive techniques exemplified by transcranial magnetic stimulation (TMS) and passive techniques utilizing electrocorticographic spectral analysis of broadband gamma frequencies are both supplementing, and in some cases supplanting, ESM as the clinical mapping method of choice.

This article attempts to review the historical origins, current applications, and apparent limitations of ESM. Attention will also be paid to current innovations in electrical stimulation techniques and novel methodologies that may complement or replace ESM in the future.

With regard to functional brain mapping, it is best to remember that there is a dichotomy between the accuracy of a map and its usability. In light of this important observation, we discuss not only the theoretical characteristics of each method but also the importance of its practical utility. This dichotomy is commonly referred to as Bonini's paradox,[5] and best interpreted by the French poet Paul Valéry[6]: "Everything simple is false. Everything which is complex is unusable."

HOW DID WE GET HERE?

The interest and fascination with direct cortical electrical stimulation parallel the earliest awareness of the electrical nature of neural transmission. Giovanni Aldini (1756–1826), nephew of Luigi Galvani, used Alessandro Volta's bimetallic pile (a primitive battery) to apply electric current to "reanimate" dismembered bodies of animals and humans.[7] His experiments were highly publicized and became Mary Shelley's main inspiration in the creation of her 1818 novel, *Frankenstein*: "Perhaps, a corpse would be reanimated; galvanism had given token of such things."[8] It was Luigi Rolando who first used galvanic current to stimulate the cerebral cortex of living animals in 1809,[9] but it was Fritz and Hitzig in 1870 who systematically built a body of mapping research by applying electricity to the exposed cerebral cortex of dogs without anesthesia and are credited with the first demonstration of the function of the motor strip.[10] They performed these studies at the home of Fritsch because the University of Berlin would not permit such experimentation on animals. Earlier in his career as a physician in the Danish-Prussian war of 1863, Hitzig had experimented on wounded soldiers whose skulls were fractured by bullets by applying a small electric current to their exposed brains.

The work of David Ferrier was the seed of a cascade of influence and imitators to follow in the late 19th century.[11] Ferrier mapped sensory and motor cortex across a variety of species, and his books were widely disseminated (Fig. 1). In emulation of Ferrier (and to the horror of an emerging bioethics movement), three geographically isolated trials of direct stimulation of exposed human cortex soon followed across three continents.[12,13] The first example of ESM in humans was the single case of Roberts Bartholow in the United States in 1874.[14] His patient had a cancer and infection that had eroded the skull and exposed underlying cortex. The experimental method, which included electrical stimulation with deep penetrating needles in a nonconsenting patient with developmental disability, was rigidly condemned by the American Medical Association and became a cornerstone in the history of American bioethics.[15]

Independently, Ezio Sciamanna, a noted Italian neurologist, localized sensorimotor function in a human demonstration of cortical stimulation mapping shortly thereafter in 1882 (Fig. 1). Sciamanna reported the case of a 49-year-old carriage driver, Ferdinando Rinalducci, who, after falling off his horse, underwent a trepanation procedure for bone fragment removal and repair of parietal region skull fracture.[16] Stimulation was applied via unipolar electrodes placed over regions of interest using galvanic (direct) current ("galvanizzazione sulla dura madre"), producing reliable contralateral motor responses in the face, head, neck, and forearm. A year later, Alberto Alberti, an Argentine neurologist, performed similar experiments on an epilepsy patient.[12] Bartholow, Sciamanna, and Alberti represent the vanguard of ESM in humans. In 1901, Charles Sherrington, along with his American student, Harvey Cushing, spent a month in Liverpool, England performing extensive cortical motor mapping in great apes, including the first stimulation-based proof of Broca's area.[17] Victor Horsley (1857–1916) is credited with the first use of intraoperative electrical brain stimulation.[18,19] In the 1930s, Krause and Foerster published extensively on their large series of systematic human mapping trials, expanding on work previously done in primates.[20,21] Of course, in the 20th century, it was Wilder Penfield (a student of Sherrington and Foerster and an intern under Cushing) who published the most expansive and influential series of clinical-experimental studies in intraoperative mapping that largely defines the methods still in use today.[22]

WHY DO WE DO WHAT WE DO?

Neurosurgical lesional resections are typically performed with two goals in mind: (1) optimization of the extent of resection and (2) minimizing or avoiding deficit, especially when eloquent cortex is at risk.[23] In the context of nontumoral epilepsy surgery, functional mapping informs maximum resection of the epileptogenic zone to achieve seizure freedom in the absence of functional loss. Tumoral surgeries, in contrast, are most commonly performed to increase median survival time, and the purpose of functional mapping is the optimization of quality of life postoperatively.[24]

The justifications for mapping are manifold. While cortical function follows a well-understood general organization,[22] functional zones are commonly distorted or topographically obscured by a lesion or its associated edema. The epileptic zone or intra-axial tumor may reside within eloquent cortex. Congenital abnormalities may obliterate conventional anatomic landmarks. There is well-established normal interindividual variability in the location, duplication, and anatomic extent of eloquent cortex.[25] There is also the potential for variability as a consequence of plasticity driven by lesion location and age of onset.

For mapping precision, bipolar stimulation is used where both cathode and anode are at the level of the target tissue. This may be achieved either through the use of subcortical grid electrodes and depth electrodes in extraoperative mapping (typically within an epilepsy monitoring unit) or through the use of a handheld stimulator wand in the operative setting.

Modeling of current flow in a bipolar paradigm demonstrates a sharp drop in current midway between electrodes commonly in clinical use (e.g., 5 mm for 1-cm interelectrode spacing).[26] The area stimulated depends on the distance from the stimulating electrode and the amount of current applied. Charge density is a function of charge and the cross-sectional area of the electrode surface in contact with the brain (Fig. 2). The established effects of ESM are presumed due to local electrical diffusion. The axon initial segment and nodes of Ranvier have the highest excitability to applied current (the highest concentration of sodium channels).[27]

Potential mechanisms of injury vis-à-vis charge transfer and electrolysis have been largely obviated by the use of stimulators utilizing a biphasic pulse and constant current. Injury from thermal deposition is virtually eliminated by the use of time-tested chronaxie-convergent paradigms in common use for decades. Ceiling limits for maximum stimulation[28,29] (as exemplified by FDA approval of the predicate stimulator device) are based on animal studies under circumstances of continuous stimulation of up to 50 hours, even though stimulation trains in common use rarely exceed 10 seconds (Fig. 2). Histopathological examination after prolonged extraoperative functional mapping has demonstrated no structural damage at the light microscopic level.[30]

WHAT ARE THE ESM STANDARDS?

Extraoperative “semi-chronic” ESM is indicated for epilepsy surgery candidates who have undergone implantation of subdural grid/strip electrodes or stereo-electroencephalographic (SEEG) depth arrays in or near eloquent cortex. Intraoperative ESM may be performed on tumoral or epilepsy resections by a neurosurgeon. Any electrode interface (grid/strip/depth/wand) may be utilized. Any mapping exercise requires electrocorticography (ECoG) to monitor for stimulus-induced ADs that may summate to seizures. Modern stimulator and switching boxes are often integrated into existing EEG video monitoring systems, and provide an intuitive graphical user interface.

Due to a variety of factors, including physioanatomic differences across different functional cortices, electrode configuration (i.e., disc vs. sphere), electrode diameter, inter-electrode distance, current shunting through cerebrospinal fluid (CSF; subdural grid/strip), and individual training idiosyncrasies, there are variations in stimulation paradigms in common use (Fig. 3).

Intraoperative ESM may be performed on a patient under general anesthesia (e.g., for motor responses) or on an awake patient (e.g., for somatosensory, motor, and linguistic responses) where the patient’s cooperation and subjective report are requisite. ESM in the operating theater allows real-time resective guidance of both cortical grey matter and subcortical fiber tracts, as both may be stimulated. This “hodotopic” view takes into account not only nodes but also networks and has demonstrated its superiority among other available techniques in preserving function in large surgical series, particularly glioma patients.[31,32] Both positive responses (regional movement, dysesthesia, phosphenes) and negative responses (motor inhibition, speech arrest, anomia) may be the consequence of eventful stimulation. Mapping is biased to spontaneous positive responses, and negative behavioral responses are detected only if the respective function is explicitly tested.

WHAT ARE OUR BASIC MAPPING NEEDS?

Distinctions have been codified in the literature between eloquent cortex that is obtainable vs. eloquent cortex that is indispensable.[22] Indispensable cortex commonly refers to primary motor cortex/pyramidal tracts, primary sensory cortex, primary visual cortex, and frontal/temporal language regions that generally conform to conventional Broca’s region, Wernicke’s region, and the arcuate fasciculus. Indispensable regions are sacrosanct and are to be preserved in any resective strategy if possible. Whereas mapping the basal temporal language or fusiform gyrus face recognition areas is feasible, avoiding the resection of these areas is not absolutely necessary, because these regions are commonly considered dispensable and are resected without significant morbidity. Likewise, ESM at discrete sites may provoke complex perceptual phenomena such as emotional feelings, illusions, and hallucinations;[33] however, these findings have no established pragmatic value in surgical strategies.

WHY HAS ESM ENDURED THIS LONG?

ESM “evokes reliable and highly specific outcomes that are unlikely to be artefactual and associated with anarchic spread of current.”[34] The probabilistic causation of ESM is the singular aspect that has guaranteed its perpetuation. Intraindividual reliability of ESM was recently demonstrated from initial mapping to repeat mapping of an auditory naming site 11 years later in a patient with an infiltrating temporal lobe glial neoplasm.[35]

The utility of “gold standard” ESM is supported by many contemporary clinical series. In Sanai’s group of 250 cases undergoing resection proximal to eloquent cortex after ESM, fewer than 2% displayed any relevant linguistic deficits.[2] In tumor resections near motor regions, 87% of 55 recovered without motor deficit when mapping nodes were respected. [3] Conversely, partial resection of ESM-verified language sites has been associated with permanent linguistic deficit.[4]

Haglund et al.[4] and others[25,36] have codified the concept of a 10–20 mm “safety margin,” i.e., that the distance of the resection margin from the nearest ESM language site was the most important variable in the duration and permanency of postoperative language deficits. Commonly, if the distance of the resection margin from the nearest language site is >1 cm in frontal lobe language regions, fewer permanent language deficits occur. Higher rates of worsening in eloquent function for the first three postoperative months have been reported when no safety margin was heeded.[23]

WHAT ARE SOME OUTSTANDING ESM CONTROVERSIES?

Complex Mechanisms and Responses

ESM “acts through some unknown saturating, activating, or inhibiting influences at local and/or distant sites.”[34] The effects of ESM are a complex amalgam of excitation and inhibition of neurons, interneurons, and local fiber tracts.[27] Both local and remote influences exist simultaneously beyond the phrenological viewpoint of mapping that existed among early 20th century investigators.[33] This point is dramatically illustrated by the preservation of the subjective memory of the ESM effect in a particular area after its resection.[37] In addition to the direct activation of the axon initial segment and nodes of Ranvier by bipolar stimulation,[38] ESM activates distant sites that suggest monosynaptic transmission in addition to limited local effects. For example, ESM of primary visual cortex in macaque elicits fMRI activation in topographically matched extrastriate cortex V2, V3, V3A, V4, and V5.[39] Although the clinical effect most commonly seen is silencing of ALL areas to which the stimulated area projects, ESM generates a chain reaction of early inhibitory effect that may be overcome by subsequent excitation, depending on current strength and frequency and on the prestimulation firing rate.[40]

Patient Limitations

Preexisting Deficits—Actionable mapping information is generally obtainable only on patients with intact linguistic and sensorimotor abilities. Stimulation trains for mapping are conventionally 1–2 seconds for somatosensory and motor cortex and ≤10 seconds for language identification. Any significant impairment in sensation, motor paresis, or speech hesitancy/anomia will not allow for adequate testing within these temporal constraints.

Pediatric Dilemmas—ESM is safe in children but offers many challenges. Generally, reduced myelination shifts the strength-duration curve to the right, and stimulus thresholds for a function may be beyond AD threshold. Motor responses are typically more difficult to elicit at the standard current settings used in adults. Due to incomplete functional maturation, the sensitivity to identify language nodes approximates that in adults only at the age of 10 years and beyond. Strategies suggested to compensate include increased pulse durations as high as 500 microseconds and increased charge density (up to 25 mA).[41–44] (The practice of ESM is discussed in greater detail in the companion article by P. Jayakar.)

Procedural Issues and Complications

Lack of Standardization—"A negative mapping does not protect, but creates the problem of questionable stimulation reliability."[45] There is a clear lack of consensus on electrical stimulation paradigms and techniques. Striking inconsistencies in ESM methodology and subsequent resection strategies have been illuminated in an international survey that analyzed responses from 56 centers (Fig. 4).[46] Significant variations were noted, not just in stimulation settings but in functions tested and protective margins preserved in resection. Considering that ESM-induced deficits in language may be function specific, only half of the responding centers tested all four commonly testable functions (speech production, comprehension, naming, reading), creating the potential for false negative results related to non-tested function. This may explain why 41% of centers reported persistent postoperative language deficits despite preservation of positive language nodes; 56% of this group named failure to identify crucial language sites as operant.

Correlation analysis, principal component analysis, and sensitivity analysis have been done to identify functional overlap between tasks and identify optimal task order for efficiency.[47] Whereas naming was the most sensitive task, 31% of temporal language sites and 31% of frontal language sites were undetected after naming alone. Multitask ESM is necessary to avoid missing eloquence and risking deficit. (A guide to the most commonly used techniques for ESM using subdural electrodes can be found in the accompanying article by E. So and A. Alwaki.)

Afterdischarges (ADs) and Stimulation-Evoked Seizures—ADs are EEG activity in response to stimulation that resemble spontaneous seizures or may evolve into them. Stimulation intensities for AD production are widely variable among stimulation site, different lobes, adjacent electrodes, or even the same electrode pair from one trial to another.[48] Mapping data from 92 patients undergoing extraoperative mapping were analyzed retrospectively.[49] Thresholds for provoking ADs were not significantly higher than current settings to provoke sensory, motor, or linguistic responses. High interpatient variability as well as intrapatient variability across different brain regions was demonstrated. Multivariate analysis of patient characteristics (e.g., age, duration of disease, electrode location, etc.) failed to find predictive factors of stimulus thresholds. Paradoxically, the adventitious observation[50] that the application of brief bursts of pulse stimulation during ADs could terminate them was a principal motivation in the development of the first commercial device for responsive cortical stimulation in epilepsy.[51]

Induced seizures are interruptive. In a retrospective review of 57 patients who underwent ESM, seizures occurred in 33%.[52] Among a subset undergoing ESM language assessments, 17% had evoked seizures that disrupted mapping attempts.

Problematic Awake Craniotomies—Intraoperative ESM in the awake patient places significant demands on the skill of an anesthesiologist to facilitate typical asleep-awake-asleep procedures and to avoid both inadequate or excessive sedation. Pain, emesis, and emotional intolerance to the technique are infrequently encountered, and of course, seizures may be provoked. In a large series, intraoperative seizures during awake craniotomy occurred in 12.8% of 477 patients.[53] Failure of ESM technique for any reason(s)[54] has been associated with a lower incidence of gross total resection and greater postoperative morbidity.

Searching for the Right Frequency—Established stimulation frequencies for mapping are 60 Hz (North America) and 50 Hz (Europe). In 1993, Taniguchi et al.[55] innovated the novel technique of high-frequency monopolar stimulation (HFMS) for monitoring of motor pathways under general anesthesia. A train of five monopolar pulses are delivered at frequencies typically between 300 and 500 Hz at a repetition rate of 1–3 Hz at a pulse duration of 0.5 millisecond and an interstimulus interval of 2–4 milliseconds (Fig. 5). This method is now commonly used for motor evoked potential monitoring and is capable of eliciting motor responses at lower intensities, with shorter trains (at 10–18 milliseconds), is not affected by preoperative motor status,[56] and is reported to be less ictogenic. The utilization of HFMS parameters for cortical localization (and not monitoring) of motor eloquence has been studied intraoperatively in children[57] and extraoperatively in epilepsy patients.[58] HFMS has also been effective and safe in intraoperative language mapping of glioma patients.[59] The relatively short duration of the stimulus has to be timely presented to interfere with the function being tested.[45]

The efficacy and safety of low-frequency stimulation (LFS) has also been studied.[60] Stimulation at 5 and 10 Hz was determined to be as effective as that at the standard 50–60 Hz with reduced provocation of ADs for typical 3–5 second trains. Zangaladze et al.[60] suggest repeating stimulation at 50 Hz if no responses are elicited with LFS, but exaggerating the time burden of the ESM process does not appear, at first glance, to be a welcome breakthrough.

Diminished Utility in the Era of Stereo-electroencephalography

SEEG stimulation is feasible and safe, and its use may allow mapping of conventionally inaccessible cortex (insula, ventral, and medial cortices).[61] Considering the surface area available for stimulation and the relatively short interelectrode distances in commonly used

SEEG electrodes, as well as the absence of CSF shunting of current, there are no good models of current spread. The clear downside to SEEG mapping is limited sampling compared to typical subdural grid coverage, resulting in the absence of a useable two-dimensional functional map to guide resection. Ultimately, the growing popularity of SEEG techniques may place an increased reliance on intraoperative neurosurgeon-driven ESM. (A guide to ESM using SEEG electrodes can be found in the accompanying article by J. Britton.)

The Role and Utilization of fMRI and DTI Techniques with ESM

fMRI and diffusion tensor imaging (DTI) offer substantial aid in the localization of linguistic and sensorimotor cortex. These data may facilitate optimum placement of grid and strip electrodes in the setting of a typical two-stage epilepsy surgery or offer invaluable initial guidance for choosing intraoperative ESM sites with the highest yield in the surgical arena.

There is a surprising lack of level IV data confirming the predictive abilities of fMRI and DTI in reducing morbidity *apart from* conventional ESM. fMRI suffers from its characteristic limitation of poor temporal resolution and is considered not sensitive and/or accurate enough to be used independently as a localization method.[62] fMRI is extraordinarily useful in language lateralization, but it characteristically identifies the entire network involved in language function, whereas interference mapping with ESM can distinguish between “essential and substitutable epicenters.”[63]

DTI currently suffers from relatively low spatial resolution compared to ESM of white matter for the preservation of motor function in tumor cases approximating pyramidal tracts.[64] In imaging the arcuate fasciculus, current DTI technology also suffers from end-to end-point tracking reliability, making localization of conventional frontal and temporal language termini inaccurate.

Investigators have analyzed relationships between subcortical mapping and DTI.[65,66] A positive correlation has been found between a stimulation intensity of 8–12 mA and a <6-mm distance between the stimulation site and visualized tracts. Nevertheless, the estimated distance between DTI and the location of stimulation is influenced by the inaccuracies of DTI, the invasiveness of the tumor, intraoperative brain shift affecting navigation accuracy, and the various stimulation parameters and probe types used. For the present, only subcortical electrical stimulation allows for the in situ real-time assessment of subcortical tracks.

CAN ESM BE INNOVATED BEYOND ITS PRESENT FORM?

ESM has enjoyed a long history, has been evaluated in many individual and meta studies (e.g., Ojemann et al.[25]), and has undeniable benefits for identifying eloquent cortex and thereby minimizing postsurgical deficits. At the same time, the technology and protocols underlying ESM have not changed in decades, and ESM does have important limiting aspects in patient participation, procedural difficulties, and time consumption as noted in the sections above. These issues provide the motivation to further innovate ESM and/or to complement it with entirely new functional mapping technologies.

To date, the classical use of ESM has been to identify those areas in the cortex that support motor, language, or other important functions by delivering trains of electrical stimuli at a relatively high rate (~50 Hz) to excite or inhibit local cortical population activity. In addition to this classical application of the ESM procedure, recent reports have also described the use of electrical stimulation to identify the termini of anatomical connections projecting from these stimulation sites. This technique, commonly referred to as corticocortical evoked potentials (CCEPs),[67–69] delivers electrical stimuli at a much lower rate (~1 Hz) while electrocorticographic (ECoG) responses to that electrical stimulation are recorded at all other sites (Fig. 6). Functional inferences are based on visual analysis of stimulus-related averaged CCEPs (quantification of strength and latency) to evaluate the measure and directionality of causal influence. This procedurally requires less than a minute for each stimulus site, requires no patient cooperation, and has a negligible chance of seizure provocation. CCEPs have been used to investigate anatomic connectivity in the language system,[67,70–72] motor system,[68] parietofrontal circuits,[69] and the visual system.[73]

WHAT ARE THE ALTERNATIVE MAPPING METHODOLOGIES IN ASCENDANCE?

The practice of preoperative or intraoperative mapping has remained relatively static since the seminal work of Penfield and his contemporaries.[22] Over the past decade, this situation has begun to change. Supported by an increase in understanding of basic brain physiology and increasing technical sophistication of sensing, stimulation, and computing technology, a number of studies have evaluated the clinical applicability of emerging techniques that include passive ECoG-based functional mapping,[74–76] transcranial magnetic stimulation (TMS),[77] and magnetoencephalography (MEG).[78,79] Each of these methods has distinct advantages and disadvantages, including varying degrees of practicality, complexity, and expense.

ECoG-based functional mapping records electrical signals from the brain using the same electrodes placed for ESM and identifies those locations that change ECoG broadband activity in the 70–170 Hz range with specific motor, language, or cognitive tasks. Broadband activity has been suggested by many studies (e.g., Crone et al.[74]) to be the key indicator of cortical population-level activity, has been shown to be a direct reflection of excitation of neurons directly underneath the electrode,[80] and has been shown to drive the BOLD signal identified using fMRI.[81] ECoG-based functional mapping can be achieved in real time (i.e., while signals are being recorded), does not require expertise in signal analysis,[82] and can produce clinically useful results in a few minutes. Because it does not depend on electrical interference, it also does not increase the risk for after-discharges or seizures. To date, ECoG-based functional mapping has been applied in the context of mapping of motor[76,83–85] or language[84,85] function (Fig. 7), in pediatric patients,[86,87] and in the operating room.[84,88]

Transcranial magnetic stimulation (TMS) delivers disruptive magnetic stimuli noninvasively, i.e., from outside the cranium. Just like invasive ESM, TMS temporarily activates or lesions targeted cortical populations and thus can be used to identify eloquent cortex. To perform

TMS, a coil is placed on the scalp. Alternating current flowing through the coil induces a magnetic field that can trigger action potentials in nearby cortical areas (Fig. 8). Variability in placement likely contributes to variability in mapping results[89] and may be the reason that even though TMS was introduced to clinical neurology more than 30 years ago,[90] its adoption in neurosurgery has remained limited until recently. More recent reports (Ruohonen and Karhu,[91] for review) are describing the use of navigated TMS (nTMS), in which MRI images are co-registered with a coil placement system to minimize placement errors. The use of nTMS has attracted increasing attention for presurgical mapping of motor cortex[92–96] and is even approved by the FDA as a sole (and not adjunct) technique for that purpose. More recent reports have expanded the use of nTMS to mapping of language areas.[97–99] Finally, a few select reports[100] have explored the use of TMS for replacement of the intracarotid sodium amobarbital (WADA) test for language lateralization, although the relationship between these two techniques is still somewhat inconclusive.[101]

MEG is a noninvasive electrophysiology method similar to scalp-recorded EEG, except that it is based on detection of magnetic instead of electric fields. In part for this reason, MEG has a somewhat higher spatial resolution than EEG and makes MEG more suitable to functional localization than EEG. At the same time, MEG is typically evaluating the location of sites whose event-related potential (ERP) changes with a motor, language, or other task. In contrast to ECoG-related changes in the broadband gamma range, which are very closely related to neuronal firing underneath the electrode, the physiological basis of ERPs is more complex and undefined.[102,103] Nevertheless, several studies have explored its value for presurgical functional mapping. Indeed, Ganslandt et al.[104] and Cheyne et al.[78] explored the use of MEG for mapping of motor and sensory areas, respectively; Papanicolaou et al.[105] explored mapping of language areas; and Alberstone et al.[106] used MEG to delineate somatosensory, visual, and auditory cortex. These and other studies prompted the American Clinical MEG Society (ACMEGS) to publish a position statement on the value of MEG-based mapping in presurgical mapping of eloquent cortex.[107]

The new techniques described above have different characteristics that are summarized in Table 1. A number of studies have evaluated the differential utility of these techniques for presurgical or intraoperative functional mapping. [76,77,87,108–118]

DISCUSSION

ESM has been used for nearly a century to localize function in the human brain. Its clinical value for preserving eloquence, shortening postoperative motor and linguistic deficits, and increasing quality of life is well established and recognized, and is documented by abundant level IV evidence.[2,25] At the same time, the emergence of alternative methods over the past two decades has helped to highlight the shortcomings of ESM, which include the time required for the procedure, pathological responses (ADs and epileptic seizures) to electrical stimulation, and its difficult or impractical application in different populations (such as children) or in certain clinical situations (e.g., during awake craniotomies).

Alternative methods include fMRI, passive ECoG-based mapping, TMS, and MEG. They differ in cost, required expertise, active or passive interrogation of the brain, and clinical availability. Numerous studies have highlighted the potential advantages of alternative methods but also have routinely acknowledged mapping discrepancies to electrical stimulation. Together, these evaluations highlight several important issues that will likely shape the adoption of these alternative methods in the clinic.

Theoretical vs. Practical Benefits

Proponents for any given method typically highlight the theoretical advantages of that method. However, it is important to recognize that the practicality of a given technique, i.e., its availability to neurosurgical centers, its cost, and the personnel and time requirements of its effective use, is immensely important as well, and, indeed, in part is the reason for the widespread use of ESM. ESM is cheap, relatively easy to use, and widely available, and it only requires mobile equipment that can readily be transported to the patient's room or the operating room. In contrast, it is undeniable that in the hands of experts highly trained in physics, mathematics, and/or cognitive neuroscience and with the right equipment and time, fMRI can produce reliable and useful results. However, people with these skills are not readily available in many medical centers, and fMRI is costly and difficult to reimburse. Thus, the practical impact of any mapping technology depends not only on its capability to produce clinically useful maps of eloquent cortex but also on the practicality of putting this capability to use.

Correlative Passive vs. Causal Active

ESM and TMS are active methods, i.e., they depend on temporarily lesioning a particular area of the cortex. Eloquent cortex is often identified by identifying the stimulating location that reliably interrupts function (e.g., receptive aphasia). Thus, the use of active methods establishes a causal relationship between the disruption of a particular brain area and the disruption of a particular function, and thereby provides a simulation of the effect of a surgical lesion of this brain area. In contrast, fMRI, ECoG, and TMS are correlational rather than causal methods. They identify those areas in the brain whose metabolic/ electrophysiological signature changes with a particular task, such as listening to an auditory speech stimulus. This distinction is often used to highlight the advantage of ESM (and TMS) over passive methods and is cited as one of the primary reasons for the discrepancy of ESM with other methods. However, many factors explain that discrepancy, and some of them are not well recognized.

Discrepancies to ESM

Some of the discrepancies between ESM and other methods are due to methodological differences. For example, fMRI is based on a rather indirect metabolic measurement of brain activity and can, without careful removal of artifacts and careful statistical treatment, highlight erroneous activations of brain areas that are not involved in a particular function. On the other hand, because MEG and TMS are based on extracranial procedures, they have difficulty identifying the exact location of eloquent cortex reliably. Indeed, ESM itself may not reliably isolate eloquent cortex, because it is based on stimulation through electrodes at two sites and because the current between the two sites may spread to distant sites. These method-specific errors are well recognized and can be minimized through careful application. Remaining discrepancies with ESM are usually attributed to shortcomings of the alternative method with which it is compared.

However, there are other reasons that explain these remaining discrepancies, and they have received little attention in contemporary discussions. In this regard, it is important to recognize that ESM and TMS are based on a subjective, qualitative, and coarse evaluation, such as visual observation of the patient's behavior, whereas fMRI, ECoG, and MEG are based on an objective, quantitative, and highly sensitive procedure (i.e., automated statistical evaluation by a computer algorithm). Hence, ESM and TMS identify only those locations that produce deficits that are so pronounced (e.g., complete interruption of speech) that they can be readily identified during the necessarily brief and coarse evaluations during the stimulation procedure, whereas the other methods can identify locations that are responsible for more nuanced aspects of function. Notable in this context, it is well known that the perceptual and language systems are composed of distinct constituent functional areas. All of these areas will be identified by the passive methods. At the same time, without application of detailed psychophysical batteries that are impractical due to the lengthy amount of time required, the ESM and TMS methods will fail to identify those important areas of function. In this view, locations that produce the most substantial deficits in function are defined by the active methods, and these locations are surrounded by a "functional penumbra" of cortex that is also involved in subtler yet still important aspects of function. Thus, excision of sites that show activations with the passive methods but are negative to ESM or TMS may well produce detectable functional deficits. Indeed, a growing number of recent studies are providing initial experimental evidence supporting this view.[119,120]

In sum, different mapping methods have differing theoretical and practical advantages. This suggests that it may be advantageous to combine assessments from different methods to increase the accuracy and confidence in the mapping results. Indeed, the many comparison studies cited above suggest that such multimodal assessments are beginning to be practical. Nevertheless, it is clear that the requirements of different methods may make them more applicable to the extra- or intraoperative scenarios, and those themselves are under constant evolution.

Acknowledgments

Source of Funding: This work was supported by the NIH (EB018783), the US Army Research Office (W911NF-14-1-0440), and Fondazione Neurone.

References

1. Korzybski, A. Science and Sanity: An introduction to Non-aristotelian Systems and General Semantics. 1. Brooklyn, NY: Institute of General Semantics; 1933.
2. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med. 2008; 358:18–27. [PubMed: 18172171]
3. Nossek E, Korn A, Shahar T, Kanner AA, Yaffe H, Marcovici D, et al. Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. Clinical article. J Neurosurg. 2011; 114:738–746. [PubMed: 20799862]

4. Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA. Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery. 1994; 34:567–576. discussion 576. [PubMed: 7516498]

5. Bonini, CP. Simulation of Information and Decision Systems in the Firm. Englewood Cliffs, NJ: Prentice-Hall; 1963.

6. Valéry P. Notre destin et les lettres. Conférencia, journal de l'université des annales. 1937:19.

7. Parent A. Giovanni Aldini: from animal electricity to human brain stimulation. Can J Neurol Sci. 2004; 31:576–584. [PubMed: 15595271]

8. Shelley, MW. Frankenstein; or, The Modern Prometheus. London: Lackington, Hughes, Harding, Mavor & Jones; 1818.

9. Rolando, L. Saggio sopra la vera struttura del cervello dell'uomo e degl animali e sopra le funzioni del sistema nervoso. Sassari: Stamperia Privilegiata; 1809.

10. Fritsch G, Hitzig E. Über die elektrische Erregbarkeit des Grosshirns. Arch Anat Physiol Wissen. 1870; 37:300–332.

11. Ferrier, D. The Functions of the Brain. London: Smith, Elder; 1876.

12. Zago S, Ferrucci R, Fregni F, Priori A. Bartholow, Sciamanna, Alberti: pioneers in the electrical stimulation of the exposed human cerebral cortex. Neuroscientist. 2008; 14:521–528. [PubMed: 18219054]

13. Casciato S, Ritaccio AL. Ezio Sciamanna: The Italian contribution to the origin of cortical stimulation mapping in humans. Epilepsy Behav. 2016; 62:186–188. [PubMed: 27490906]

14. Bartholow R. Experimental investigations into the functions of the human brain. Am J Med Sci. 1874; 134:305–313.

15. Human vivisection (Editorial). Cincinnati Medical News. 1874; III:385.

16. Sciamanna E. Fenomeni prodotti dall'applicazione della corrente elettrica sulla dura madre e modificazione del polso cerebrale. Ricerche sperimentali sull'uomo. Atti della R Accademia dei Lincei Memorie della Classe di Scienze fisiche, matematiche e naturali. 1882; 13:25–42.

17. Leyton SS, Sherrington CS. Observations on the excitable cortex of the chimpanzee, orang-utan and gorilla. Q J Exp Physiol. 1917; 11:135–222.

18. Horsley V. Case of occipital encephalocele in which a correct diagnosis was obtained by means of an induced current. Brain. 1884; 7:228–243.

19. Vilensky JA, Gilman S. Horsley was the first to use electrical stimulation of the human cerebral cortex intraoperatively. Surg Neurol. 2002; 58:425–426. [PubMed: 12517631]

20. Krause F. Die operative Behandlung der Epilepsie. Med Klin Berlin. 1909; 5:1418–1422.

21. Foerster O, Altenburger H. Elektrobiologische Vorgänge an der menschlichen Hirnrinde. Dtsch Z Nervenheilkd. 1935; 135:277–288.

22. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937; 60:389–443.

23. Gil-Robles S, Duffau H. Surgical management of World Health Organization Grade II gliomas in eloquent areas: the necessity of preserving a margin around functional structures. Neurosurg Focus. 2010; 28:E8.

24. Duffau H. Brain mapping in tumors: intraoperative or extraoperative? Epilepsia. 2013; 54(Suppl 9): 79–83. [PubMed: 24328878]

25. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg. 1989; 71:316–326. [PubMed: 2769383]

26. Nathan SS, Sinha SR, Gordon B, Lesser RP, Thakor NV. Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. Electroencephalogr Clin Neurophysiol. 1993; 86:183–192. [PubMed: 7680994]

27. Ranck JB Jr. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res. 1975; 98:417–440. [PubMed: 1102064]

28. McCreery DB, Agnew WF, Yuen TG, Bullara L. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. IEEE Trans Biomed Eng. 1990; 37:996–1001. [PubMed: 2249872]

29. MacDonald, DB., Deletis, V. Safety issues during surgical monitoring. In: Nuwer, MR., editor. Monitoring Neural Function During Surgery Handbook of Clinical Neurophysiology. Amsterdam: Elsevier; 2008. p. 929-945.
30. Gordon B, Lesser RP, Rance NE, Hart J Jr, Webber R, Uematsu S, et al. Parameters for direct cortical electrical stimulation in the human: histopathologic confirmation. Electroencephalogr Clin Neurophysiol. 1990; 75:371–377. [PubMed: 1692272]
31. De Benedictis A, Duffau H. Brain hodotopy: from esoteric concept to practical surgical applications. Neurosurgery. 2011; 68:1709–1723. discussion 1723. [PubMed: 21346655]
32. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012; 30:2559–2565. [PubMed: 22529254]
33. Selimbeyoglu A, Parvizi J. Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. Front Hum Neurosci. 2010:4. [PubMed: 20198130]
34. Desmurget M, Song Z, Mottolese C, Sirigu A. Re-establishing the merits of electrical brain stimulation. Trends Cogn Sci. 2013; 17:442–449. [PubMed: 23932195]
35. Bortnik KE, McKhann GM 2nd, Hamberger MJ. Test-retest reliability of cortical language mapping in a patient with refractory focal epilepsy: 11 years later. J Neurosurg. 2017:1–4.
36. Berger MS, Kincaid J, Ojemann GA, Lettich E. Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. Neurosurgery. 1989; 25:786–792. [PubMed: 2586730]
37. Penfield W, Perot P. The brain’s record of auditory and visual experience. A final summary and discussion. Brain. 1963; 86:595–696. [PubMed: 14090522]
38. Rattay F, Wenger C. Which elements of the mammalian central nervous system are excited by low current stimulation with microelectrodes? Neuroscience. 2010; 170:399–407. [PubMed: 20659531]
39. Tolias AS, Sultan F, Augath M, Oeltermann A, Tehovnik EJ, Schiller PH, et al. Mapping cortical activity elicited with electrical microstimulation using FMRI in the macaque. Neuron. 2005; 48:901–911. [PubMed: 16364895]
40. Pollen DA. Responses of single neurons to electrical stimulation of the surface of the visual cortex. Brain Behav Evol. 1977; 14:67–86. [PubMed: 837212]
41. Jayakar P, Alvarez LA, Duchowny MS, Resnick TJ. A safe and effective paradigm to functionally map the cortex in childhood. J Clin Neurophysiol. 1992; 9:288–293. [PubMed: 1592899]
42. Gallentine WB, Mikati MA. Intraoperative electrocorticography and cortical stimulation in children. J Clin Neurophysiol. 2009; 26:95–108. [PubMed: 19279495]
43. Duchowny M, Jayakar P, Harvey AS, Resnick T, Alvarez L, Dean P, et al. Language cortex representation: effects of developmental versus acquired pathology. Ann Neurol. 1996; 40:31–38. [PubMed: 8687189]
44. Schevon CA, Carlson C, Zaroff CM, Weiner HJ, Doyle WK, Miles D, et al. Pediatric language mapping: sensitivity of neurostimulation and Wada testing in epilepsy surgery. Epilepsia. 2007; 48:539–545. [PubMed: 17284300]
45. Szelenyi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, et al. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. Neurosurg Focus. 2010; 28:E7.
46. Hamberger MJ, Williams AC, Schevon CA. Extraoperative neurostimulation mapping: results from an international survey of epilepsy surgery programs. Epilepsia. 2014; 55:933–939. [PubMed: 24816083]
47. Wellmer J, Weber C, Mende M, von der Groeben F, Urbach H, Clusmann H, et al. Multitask electrical stimulation for cortical language mapping: hints for necessity and economic mode of application. Epilepsia. 2009; 50:2267–2275. [PubMed: 19624716]
48. Lesser RP, Luders H, Klem G, Dinner DS, Morris HH, Hahn J. Cortical afterdischarge and functional response thresholds: results of extraoperative testing. Epilepsia. 1984; 25:615–621. [PubMed: 6479112]

49. Corley JA, Nazari P, Rossi VJ, Kim NC, Fogg LF, Hoeppner TJ, et al. Cortical stimulation parameters for functional mapping. Seizure. 2017; 45:36–41. [PubMed: 27914225]

50. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, et al. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. Neurology. 1999; 53:2073–2081. [PubMed: 10599784]

51. Morrell MJ. Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011; 77:1295–1304. [PubMed: 21917777]

52. Bank AM, Schevon CA, Hamberger MJ. Characteristics and clinical impact of stimulation-evoked seizures during extraoperative cortical mapping. Epilepsy & Behavior. 2014; 34:6–8. [PubMed: 24667479]

53. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, et al. Intraoperative seizures during awake craniotomy: incidence and consequences: analysis of 477 patients. Neurosurgery. 2013; 73:135–140. discussion 140. [PubMed: 23615101]

54. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, et al. Failed awake craniotomy: a retrospective analysis in 424 patients undergoing craniotomy for brain tumor. J Neurosurg. 2013; 118:243–249. [PubMed: 23121432]

55. Taniguchi M, Cedzich C, Schramm J. Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. Neurosurgery. 1993; 32:219–226. [PubMed: 8437660]

56. Tate MC, Guo L, McEvoy J, Chang EF. Safety and efficacy of motor mapping utilizing short pulse train direct cortical stimulation. Stereotact Funct Neurosurg. 2013; 91:379–385. [PubMed: 24108152]

57. Schucht P, Seidel K, Murek M, Stieglitz LH, Urwyler N, Wiest R, et al. Low-threshold monopolar motor mapping for resection of lesions in motor eloquent areas in children and adolescents. J Neurosurg Pediatr. 2014; 13:572–578. [PubMed: 24635135]

58. Usui N, Terada K, Baba K, Matsuda K, Tottori T, Umeoka S, et al. Extraoperative functional mapping of motor areas in epileptic patients by high-frequency cortical stimulation. Journal of Neurosurgery. 2008; 109:605–614. [PubMed: 18826346]

59. Riva M, Fava E, Gallucci M, Comi A, Casarotti A, Alfiero T, et al. Monopolar high-frequency language mapping: can it help in the surgical management of gliomas? A comparative clinical study. J Neurosurg. 2016; 124:1479–1489. [PubMed: 26406788]

60. Zangaladze A, Sharan A, Evans J, Wyeth DH, Wyeth EG, Tracy JI, et al. The effectiveness of low-frequency stimulation for mapping cortical function. Epilepsia. 2008; 49:481–487. [PubMed: 17868054]

61. Trebuchon A, Chauvel P. Electrical stimulation for seizure induction and functional mapping in stereoelectroencephalography. J Clin Neurophysiol. 2016; 33:511–521. [PubMed: 27918346]

62. Austermuehle A, Cocjin J, Reynolds R, Agrawal S, Sepeta L, Gaillard WD, et al. Language functional MRI and direct cortical stimulation in epilepsy preoperative planning. Ann Neurol. 2017; 81:526–537. [PubMed: 28220524]

63. Spena G, Nava A, Cassini F, Pepoli A, Bruno M, D'Agata F, et al. Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes. Acta Neurochir (Wien). 2010; 152:1835–1846. [PubMed: 20730457]

64. Ohue S, Kohno S, Inoue A, Yamashita D, Matsumoto S, Suehiro S, et al. Surgical results of tumor resection using tractography-integrated navigation-guided fence-post catheter techniques and motor-evoked potentials for preservation of motor function in patients with glioblastomas near the pyramidal tracts. Neurosurg Rev. 2015; 38:293–306. discussion 306–297. [PubMed: 25403686]

65. Bello L, Gambini A, Castellano A, Carrabba G, Acerbi F, Fava E, et al. Motor and language DTI Fiber Tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. Neuroimage. 2008; 39:369–382. [PubMed: 17911032]

66. Leclercq D, Duffau H, Delmaire C, Capelle L, Gatignol P, Ducros M, et al. Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. J Neurosurg. 2010; 112:503–511. [PubMed: 19747052]

67. Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. Brain. 2004; 127:2316–2330. [PubMed: 15269116]

68. Matsumoto R, Nair DR, LaPresto E, Bingaman W, Shibasaki H, Luders HO. Functional connectivity in human cortical motor system: a cortico-cortical evoked potential study. Brain. 2007; 130:181–197. [PubMed: 17046857]

69. Matsumoto R, Nair DR, Ikeda A, Fumuro T, Lapresto E, Mikuni N, et al. Parieto-frontal network in humans studied by cortico-cortical evoked potential. Hum Brain Mapp. 2012; 33:2856–2872. [PubMed: 21928311]

70. Conner CR, Ellmore TM, DiSano MA, Pieters TA, Potter AW, Tandon N. Anatomic and electro-physiologic connectivity of the language system: a combined DTI-CCEP study. Comput Biol Med. 2011; 41:1100–1109. [PubMed: 21851933]

71. Tamura Y, Ogawa H, Kapeller C, Prueckl R, Takeuchi F, Anei R, et al. Passive language mapping combining real-time oscillation analysis with cortico-cortical evoked potentials for awake craniotomy. J Neurosurg. 2016; 125:1580–1588. [PubMed: 26991386]

72. Yamao Y, Suzuki K, Kunieda T, Matsumoto R, Arakawa Y, Nakae T, et al. Clinical impact of intraoperative CCEP monitoring in evaluating the dorsal language white matter pathway. Hum Brain Mapp. 2017; 38:1977–1991. [PubMed: 28112455]

73. Matsuzaki N, Juhasz C, Asano E. Cortico-cortical evoked potentials and stimulation-elicited gamma activity preferentially propagate from lower- to higher-order visual areas. Clin Neurophysiol. 2013; 124:1290–1296. [PubMed: 23523110]

74. Crone NE, Miglioretti DL, Gordon B, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. Brain. 1998; 121(Pt 12):2301–2315. [PubMed: 9874481]

75. Leuthardt EC, Miller K, Anderson NR, Schalk G, Dowling J, Miller J, et al. Electrocorticographic frequency alteration mapping: a clinical technique for mapping the motor cortex. Neurosurgery. 2007; 60:260–270. discussion 270–271. [PubMed: 17415162]

76. Brunner P, Ritaccio AL, Lynch TM, Emrich JF, Wilson JA, Williams JC, et al. A practical procedure for real-time functional mapping of eloquent cortex using electrocorticographic signals in humans. Epilepsy Behav. 2009; 15:278–286. [PubMed: 19366638]

77. Picht T, Schmidt S, Brandt S, Frey D, Hannula H, Neuvonen T, et al. Preoperative functional mapping for rolandic brain tumor surgery: comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. Neurosurgery. 2011; 69:581–588. discussion 588. [PubMed: 21430587]

78. Cheyne D, Bostan AC, Gaetz W, Pang EW. Event-related beamforming: a robust method for presurgical functional mapping using MEG. Clin Neurophysiol. 2007; 118:1691–1704. [PubMed: 17587643]

79. Van Poppel M, Wheless JW, Clarke DF, McGregor A, McManis MH, Perkins FF Jr, et al. Passive language mapping with magnetoencephalography in pediatric patients with epilepsy. J Neurosurg Pediatr. 2012; 10:96–102. [PubMed: 22725975]

80. Miller KJ, Sorensen LB, Ojemann JG, den Nijs M. Power-law scaling in the brain surface electric potential. PLoS Comput Biol. 2009; 5:e1000609. [PubMed: 20019800]

81. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001; 412:150–157. [PubMed: 11449264]

82. Kapeller C, Korostenskaja M, Prueckl R, Chen PC, Lee KH, Westerveld M, et al. CortiQ-based real-time functional mapping for epilepsy surgery. J Clin Neurophysiol. 2015; 32:e12–22. [PubMed: 25761260]

83. Su DK, Ojemann JG. Electrocorticographic sensorimotor mapping. Clin Neurophysiol. 2013; 124:1044–1048. [PubMed: 23601701]

84. Roland J, Brunner P, Johnston J, Schalk G, Leuthardt EC. Passive real-time identification of speech and motor cortex during an awake craniotomy. Epilepsy Behav. 2010; 18:123–128. [PubMed: 20478745]

85. Miller KJ, Honey CJ, Hermes D, Rao RP, denNijs M, Ojemann JG. Broadband changes in the cortical surface potential track activation of functionally diverse neuronal populations. Neuroimage. 2014; 85(Pt 2):711–720. [PubMed: 24018305]

86. Korostenskaja M, Chen PC, Salinas CM, Westerveld M, Brunner P, Schalk G, et al. Real-time functional mapping: potential tool for improving language outcome in pediatric epilepsy surgery. J Neurosurg Pediatr. 2014; 14:287–295. [PubMed: 24995815]

87. Korostenskaja M, Wilson AJ, Rose DF, Brunner P, Schalk G, Leach J, et al. Real-time functional mapping with electrocorticography in pediatric epilepsy: comparison with fMRI and ESM findings. Clin EEG Neurosci. 2014; 45:205–211. [PubMed: 24293161]

88. Kamada K, Ogawa H, Kapeller C, Prueckl R, Guger C. Rapid and low-invasive functional brain mapping by realtime visualization of high gamma activity for awake craniotomy. Conf Proc IEEE Eng Med Biol Soc. 2014; 2014:6802–6805. [PubMed: 25571558]

89. Julkunen P, Saisanen L, Danner N, Niskanen E, Hukkanen T, Mervaala E, et al. Comparison of navigated and non-navigated transcranial magnetic stimulation for motor cortex mapping, motor threshold and motor evoked potentials. Neuroimage. 2009; 44:790–795. [PubMed: 18976714]

90. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985; 1:1106–1107. [PubMed: 2860322]

91. Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. Neurophysiol Clin. 2010; 40:7–17. [PubMed: 20230931]

92. Takahashi S, Vajkoczy P, Picht T. Navigated transcranial magnetic stimulation for mapping the motor cortex in patients with rolandic brain tumors. Neurosurg Focus. 2013; 34:E3.

93. Krieg SM, Shiban E, Buchmann N, Gempt J, Foerschler A, Meyer B, et al. Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. J Neurosurg. 2012; 116:994–1001. [PubMed: 22304452]

94. Picht T, Mularski S, Kuehn B, Vajkoczy P, Kombos T, Suess O. Navigated transcranial magnetic stimulation for preoperative functional diagnostics in brain tumor surgery. Neurosurgery. 2009; 65:93–98. discussion 98–99. [PubMed: 19935007]

95. Picht T, Frey D, Thieme S, Kliesch S, Vajkoczy P. Presurgical navigated TMS motor cortex mapping improves outcome in glioblastoma surgery: a controlled observational study. J Neurooncol. 2016; 126:535–543. [PubMed: 26566653]

96. Karhu, J., Hannula, H., Laine, J., Ruohonen, J. Navigated transcranial magnetic stimulation: principles and protocol for mapping the motor cortex. In: Rotenberg, A.Horvath, JC., Pascual-Leone, A., editors. Transcranial Magnetic Stimulation. New York: Springer Science+Business Medida; 2014. p. 337-359.

97. Sollmann N, Kubitscheck A, Maurer S, Ille S, Hauck T, Kirschke JS, et al. Preoperative language mapping by repetitive navigated transcranial magnetic stimulation and diffusion tensor imaging fiber tracking and their comparison to intraoperative stimulation. Neuroradiology. 2016; 58:807–818. [PubMed: 27079196]

98. Tarapore PE, Findlay AM, Honma SM, Mizuiri D, Houde JF, Berger MS, et al. Language mapping with navigated repetitive TMS: proof of technique and validation. Neuroimage. 2013; 82:260–272. [PubMed: 23702420]

99. Krieg SM, Lioumis P, Makela JP, Wilenius J, Karhu J, Hannula H, et al. Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. Acta Neurochir (Wien). 2017; 159:1187–1195. [PubMed: 28456870]

100. Pelletier I, Sauerwein HC, Lepore F, Saint-Amour D, Lassonde M. Non-invasive alternatives to the Wada test in the presurgical evaluation of language and memory functions in epilepsy patients. Epileptic Disord. 2007; 9:111–126. [PubMed: 17525019]

101. Epstein CM, Woodard JL, Stringer AY, Bakay RA, Henry TR, Pennell PB, et al. Repetitive transcranial magnetic stimulation does not replicate the Wada test. Neurology. 2000; 55:1025–1027. [PubMed: 11061262]

102. Makeig S, Westerfield M, Jung TP, Enghoff S, Townsend J, Courchesne E, et al. Dynamic brain sources of visual evoked responses. Science. 2002; 295:690–694. [PubMed: 11809976]

103. Mazaheri A, Jensen O. Asymmetric amplitude modulations of brain oscillations generate slow evoked responses. J Neurosci. 2008; 28:7781–7787. [PubMed: 18667610]

104. Ganslandt O, Fahlbusch R, Nimsky C, Kober H, Moller M, Steinmeier R, et al. Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. J Neurosurg. 1999; 91:73–79. [PubMed: 10389883]

105. Papanicolaou AC, Simos PG, Breier JI, Zouridakis G, Willmore LJ, Wheless JW, et al. Magnetoencephalographic mapping of the language-specific cortex. J Neurosurg. 1999; 90:85–93. [PubMed: 10413160]

106. Alberstone CD, Skirboll SL, Benzel EC, Sanders JA, Hart BL, Baldwin NG, et al. Magnetic source imaging and brain surgery: presurgical and intraoperative planning in 26 patients. J Neurosurg. 2000; 92:79–90. [PubMed: 10616086]

107. Bagic AI, Bowyer SM, Kirsch HE, Funke ME, Burgess RC, Committee APS. American Clinical MEG Society (ACMEGS) Position Statement #2: The Value of Magnetoencephalography (MEG)/Magnetic Source Imaging (MSI) in Noninvasive Presurgical Mapping of Eloquent Cortices of Patients Preparing for Surgical Interventions. J Clin Neurophysiol. 2017; 34:189–195. [PubMed: 28059855]

108. Tarapore, PE., Nagarajan, SS. nTMS, MEG, and fMRI: comparing and contrasting three functional mapping techniques. In: Krieg, SM., editor. Navigated Transcranial Magentic Stimulation in Neurosurgery. Cham, Switzerland: Springer International; 2017. p. 31-49.

109. Picht T, Krieg SM, Sollmann N, Rosler J, Niraula B, Neuvonen T, et al. A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery. 2013; 72:808–819. [PubMed: 23385773]

110. Sinai A, Bowers CW, Crainiceanu CM, Boatman D, Gordon B, Lesser RP, et al. Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. Brain. 2005; 128:1556–1570. [PubMed: 15817517]

111. de Pesters A, Taplin AM, Adamo MA, Ritaccio AL, Schalk G. Electrocorticographic mapping of expressive language function without requiring the patient to speak: A report of three cases. Epilepsy Behav Case Rep. 2016; 6:13–18. [PubMed: 27408803]

112. Genetti M, Tyrand R, Grouiller F, Lascano AM, Vulliemoz S, Spinelli L, et al. Comparison of high gamma electrocorticography and fMRI with electrocortical stimulation for localization of somatosensory and language cortex. Clin Neurophysiol. 2015; 126:121–130. [PubMed: 24845600]

113. Taplin AM, de Pesters A, Brunner P, Hermes D, Dalfino JC, Adamo MA, et al. Intraoperative mapping of expressive language cortex using passive real-time electrocorticography. Epilepsy Behav Case Rep. 2016; 5:46–51. [PubMed: 27408802]

114. Bartos R, Jech R, Vymazal J, Petrovicky P, Vachata P, Hejcl A, et al. Validity of primary motor area localization with fMRI versus electric cortical stimulation: a comparative study. Acta Neurochir (Wien). 2009; 151:1071–1080. [PubMed: 19415166]

115. Suarez RO, Taimouri V, Boyer K, Vega C, Rotenberg A, Madsen JR, et al. Passive fMRI mapping of language function for pediatric epilepsy surgical planning: validation using Wada, ECS, and FMAER. Epilepsy Res. 2014; 108:1874–1888. [PubMed: 25445239]

116. Wang LJ, Lin FX, Zhao B, Wu J, Cao Y, Wang S. Testing the reliability of BOLD-fMRI motor mapping in patients with cerebral arteriovenous malformations by electric cortical stimulation and surgery outcomes. World Neurosurg. 2016; 92:386–396. [PubMed: 26732959]

117. Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, et al. Impairment of preoperative language mapping by lesion location: a functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation study. J Neurosurg. 2015; 123:314–324. [PubMed: 25884257]

118. Babajani-Feremi A, Narayana S, Rezaie R, Choudhri AF, Fulton SP, Boop FA, et al. Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation. Clin Neurophysiol. 2016; 127:1822–1836. [PubMed: 26679420]

119. Kojima K, Brown EC, Rothermel R, Carlson A, Matsuzaki N, Shah A, et al. Multimodality language mapping in patients with left-hemispheric language dominance on Wada test. Clin Neurophysiol. 2012; 123:1917–1924. [PubMed: 22503906]

120. Kojima K, Brown EC, Rothermel R, Carlson A, Fuerst D, Matsuzaki N, et al. Clinical significance and developmental changes of auditory-language-related gamma activity. Clin Neurophysiol. 2013; 124:857–869. [PubMed: 23141882]

121. Ruohonen, J., Ilmoniemi, RJ. Basic physics and design of transcranial magentic stimulation devices and coils. In: Hallett, M., Chokroverty, S., editors. Magnetic Stimulation in Clinical Neurophysiology. 2. Philadelphia, PA: Elsevier; 2005. p. 17-30.

Author Manuscript
Author Manuscript
Author Manuscript

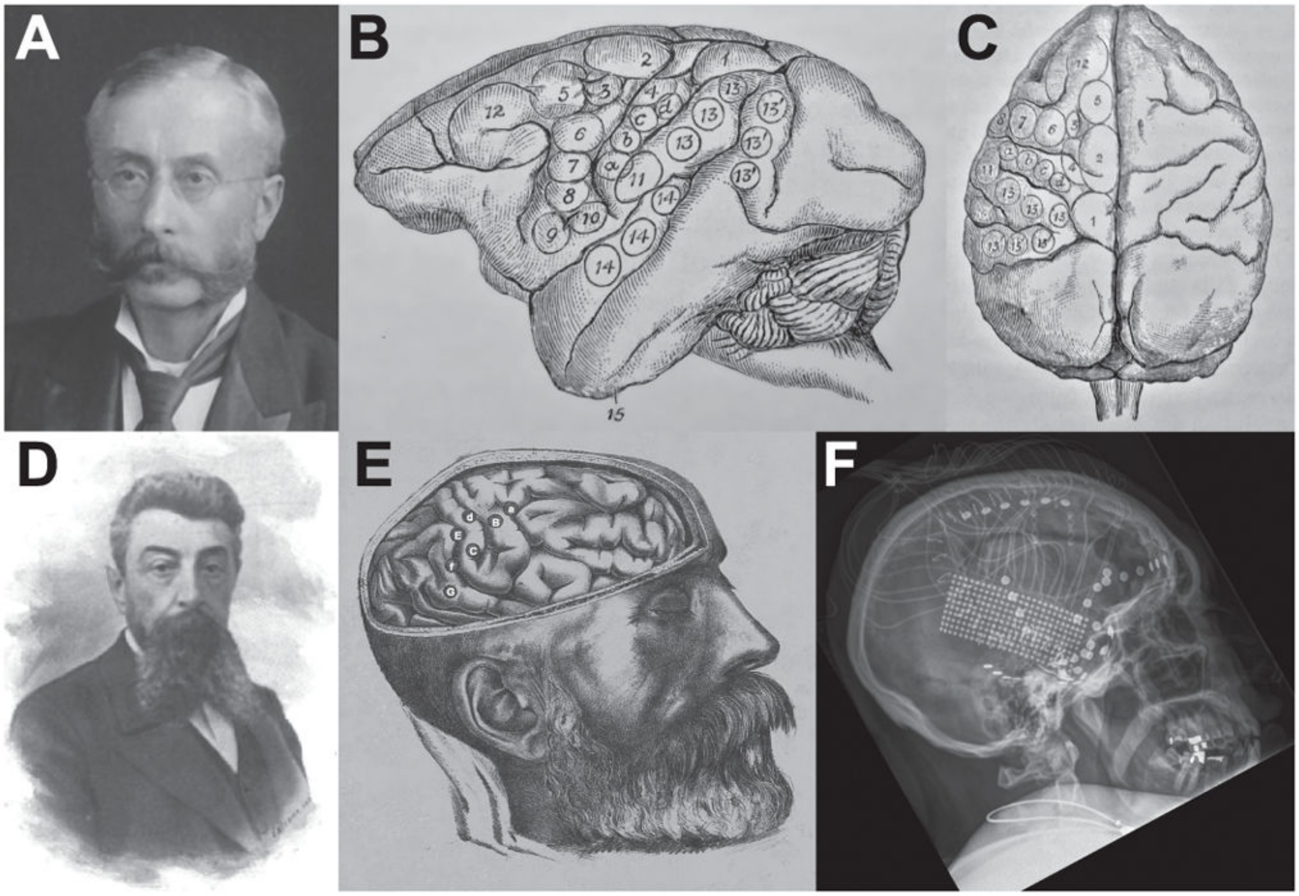

Fig. 1.

Subdural ESM across three centuries. **A,** Sir David Ferrier (1843–1928). His book, *The Functions of the Brain*,[11] published in 1876, is seminal in the history of neuroscience. The extensive electrical stimulation mapping across multiple species contained therein was the principal inspiration for human ESM, including the first isolated attempts at human functional stimulation to shortly follow across three continents.[12] **B** and **C**, Sagittal and axial drawings of ESM in monkey brain from Ferrier's book. **D,** Ezio Sciamanna (1850–1905). Sciamanna was one the founders of what is now the School of Medicine at Sapienza University in Rome. Sciamanna (Italy 1882), along with Bartholow (United States 1874) and Alberti (Argentina 1883), followed Ferrier's work with the first isolated cases of human ESM. **E,** Lateral view of exposed cortex of Sciamanna's patient, Ferdinando Rinalducci. Electrical stimulation sites are numbered. Motor responses comprising contraction of facial, forearm, finger, and neck muscles were obtained after stimulation of gray matter ("galvanizzazione sulla dura madre"[16]) at points B, C, E, and G of his original illustration. **F,** Lateral X-ray of a novel high-density, 250-channel subdural ECoG grid (Albany Medical Center, Albany, NY, 2016).

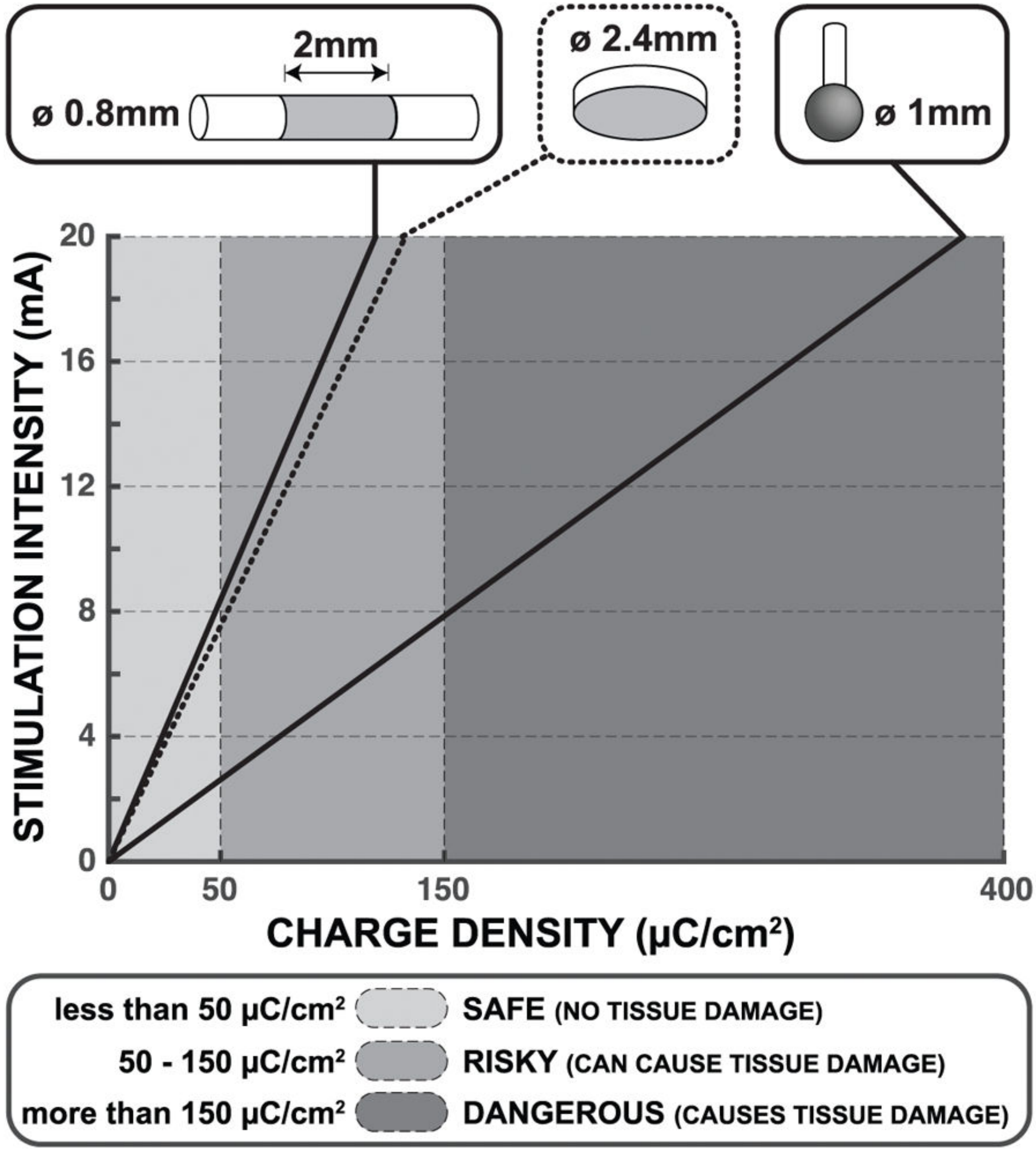

FIG. 2.

Stimulation intensity (mA) plotted against charge density (μC/cm^2) of commonly used SEEG, grid/strip, and intraoperative probe electrodes (top). Charge density is segregated into "safe," "risky," and "dangerous" categories based on criteria used by the FDA for the approval of the predicate stimulator device (bottom).[28,29] These safety criteria do not take into account other important factors in safety, including interelectrode distance, and presence (ECoG) or absence (SEEG) of current shunting through cerebrospinal fluid, for example.

Author Manuscript
Author Manuscript
Author Manuscript

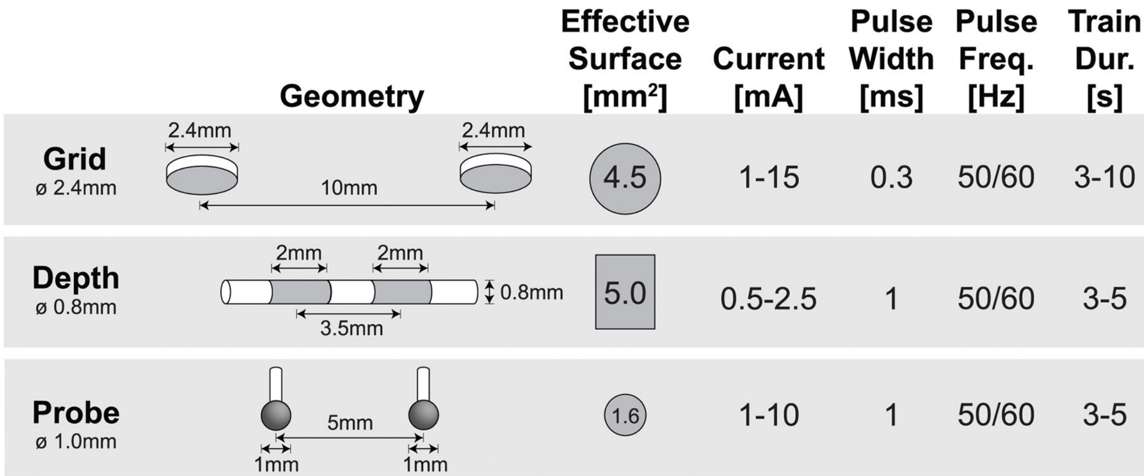

FIG. 3.

Geometry (to scale) of exposed “effective” surfaces available for stimulation of commonly used surface (grid/strip), depth (SEEG), and probe (intraoperative handheld) electrodes. Note relatively equivalent effective surfaces of grid and depth electrodes as compared to significant difference in their respective interelectrode distances. Commonly used stimulation paradigms for each are exemplified, although no current consensus exists.

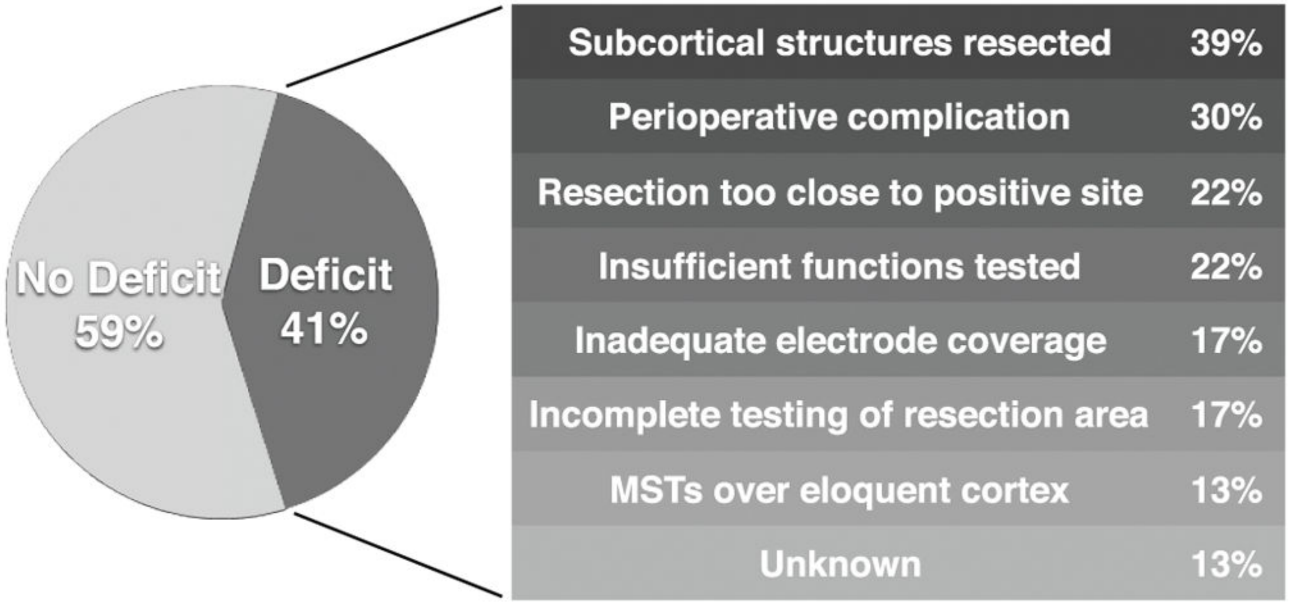

FIG. 4.

Persistent postoperative language deficits reported in an international survey of 56 international epilepsy centers.[46] Percentages listed at right are reported attributions to decline by respondents, including insufficient (22%) and incomplete (17%) testing of resected site. (Reprinted from Hamberger et al.[46])

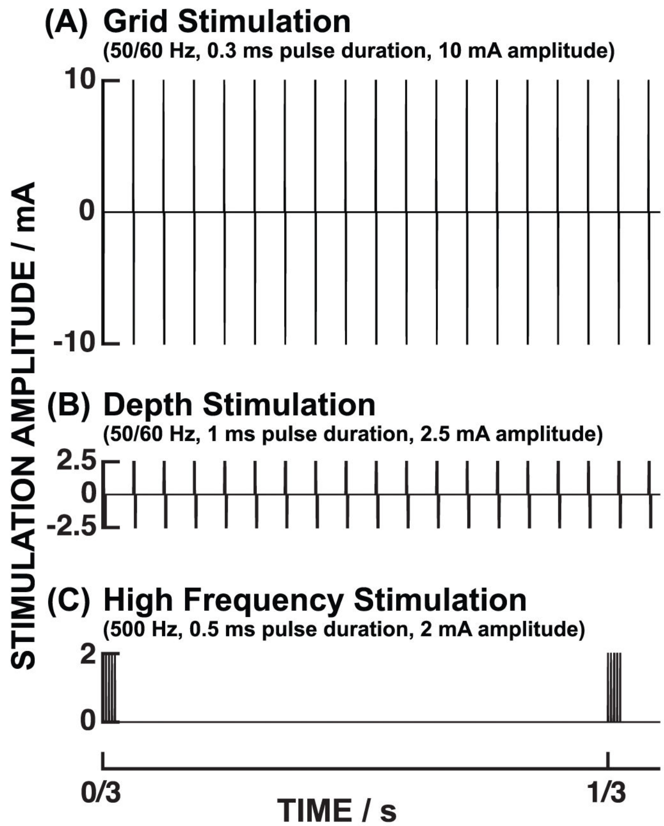

FIG. 5.

Illustration of common stimulation parameters across 1/3 second for grid (**A**), depth (**B**), and alternative high-frequency monopolar stimulation ("train of five" method, **C**).

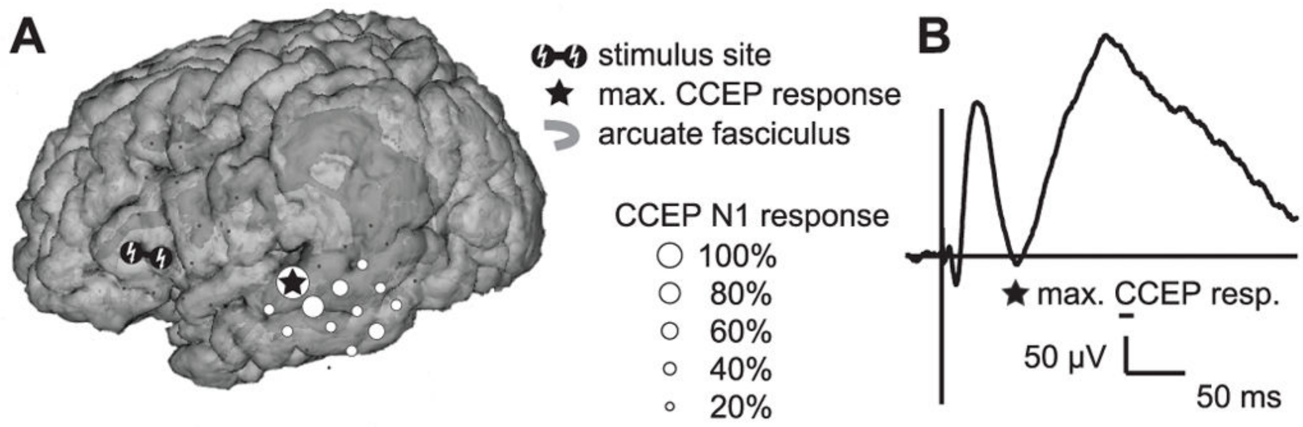

FIG. 6.

CCEP resulting from intraoperative stimulation under general anesthesia. **A,** Stimulation of inferior frontal gyrus yields CCEP responses over middle and posterior parts of superior, middle, and inferior temporal gyri. Maximal CCEP amplitude is observed over the location marked with star. **B,** Corresponding CCEP waveform. (Adapted with permission from Yamao et al.[72])

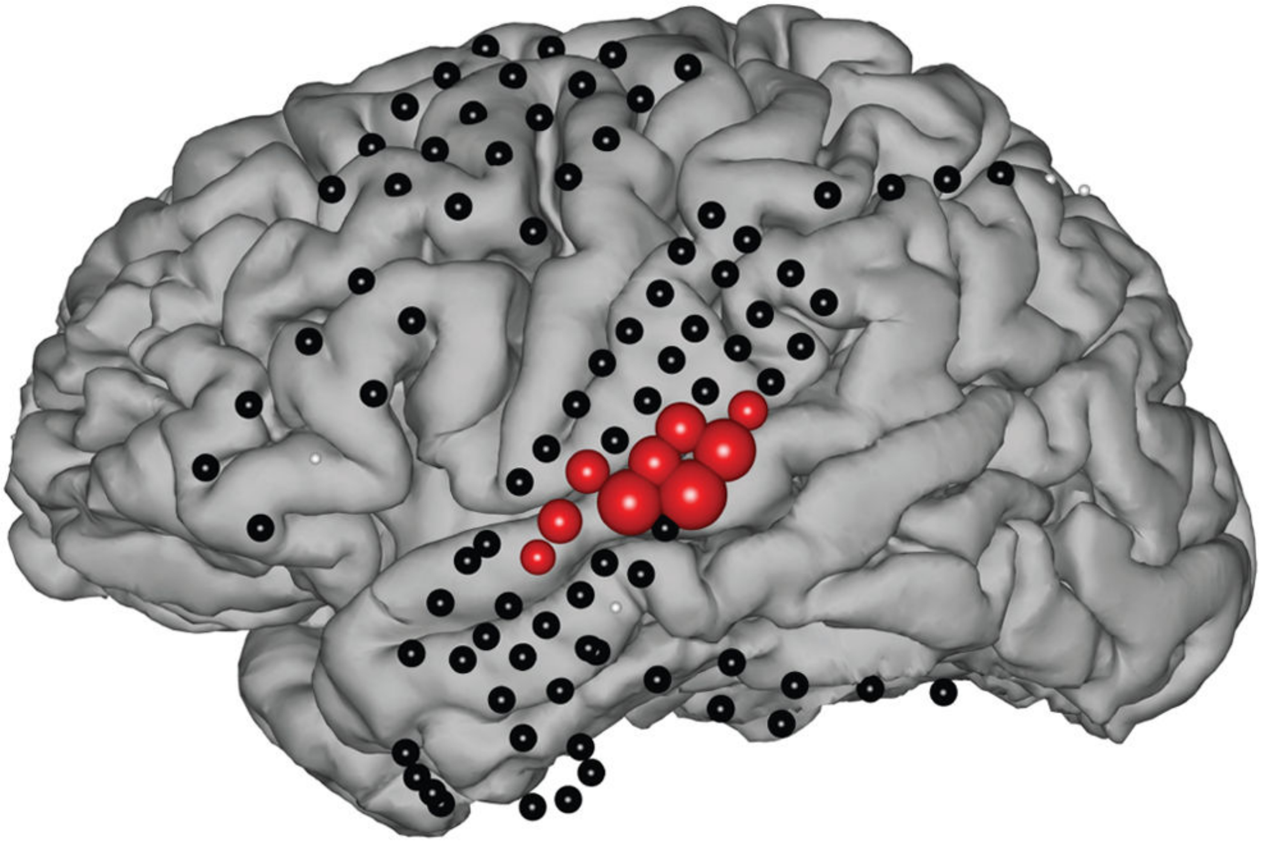

FIG. 7.

Example ECoG-based mapping results of receptive language function. Red circles give those locations whose ECoG broadband activity changes when the patient listens to the Boston Aphasia Battery (unpublished results).

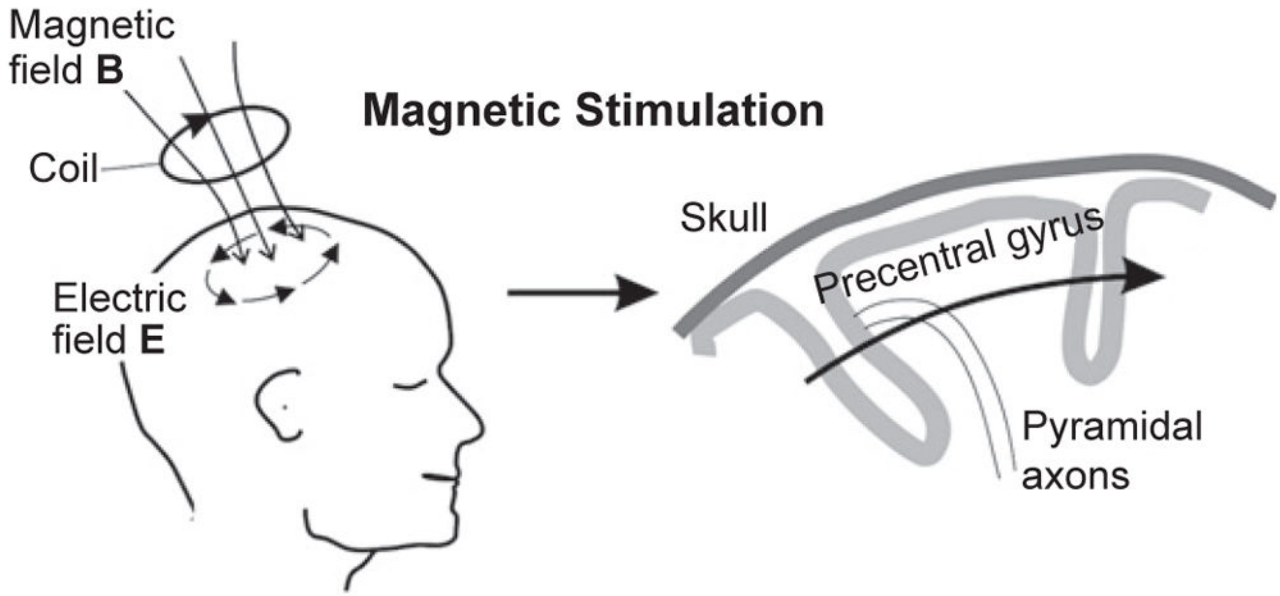

FIG. 8.

Principle of TMS. Current in the coil generates a magnetic field B that induces an electric field E. The drawing on the right illustrates a lateral view of the precentral gyrus in the right hemisphere. Two pyramidal axons are shown with a typical orientation of the magnetic field. The electric field is parallel to the scalp and may induce action potentials in the axons. (Adapted with permission from Ruohonen and Ilmoniemi.[121])

TABLE 1

Characteristics of different functional mapping techniques

Technique	Cost	Expertise	Active/Passive	Availability
ESM	+	+	A	+++
fMRI	+++	+++	P	++
Passive ECoG	++	++	P	++
TMS	++	+++	A	++
MEG	+++	+++	P	+

A, active; ECoG, electrocorticography; ESM, electrical stimulation mapping; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; P, passive; TMS, transcranial magnetic stimulation. +, minimal; ++, average; +++, maximal.