History of awake mapping and speech and language localization: from modules to networks

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Lesion-symptom correlations shaped the early understanding of cortical localization. The classic Broca-Wernicke model of cortical speech and language organization underwent a paradigm shift in large part due to advances in brain mapping techniques. This initially started by demonstrating that the cortex was excitable. Later, advancements in neuroanesthesia led to awake surgery for epilepsy focus and tumor resection, providing neurosurgeons with a means of studying cortical and subcortical pathways to understand neural architecture and obtain maximal resection while avoiding so-called critical structures. The aim of this historical review is to highlight the essential role of direct electrical stimulation and cortical-subcortical mapping and the advancements it has made to our understanding of speech and language cortical organization. Specifically, using cortical and subcortical mapping, neurosurgeons shifted from a localist view in which the brain is composed of rigid functional modules to one of dynamic and integrative large-scale networks consisting of interconnected cortical subregions.

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PHRENOLOGISTS of the 1800s, led by Gall and Spurzheim, asserted that the “organ of language” could be found below the eye.⁴² While based on faulty methodology and nonreproducible findings, the idea that brain functions are organized into discrete modules was prescient. Later, lesion-symptom mapping, pioneered by Paul Broca (1861) and Carl Wernicke (1874) demonstrated functional localization of speech and language in the cortex.^{8,44} Specifically, the inferior frontal gyrus is involved in speech articulation, while the posterior temporal lobe localizes language comprehension. Along with advancements in neuroanesthesia, Penfield’s pioneering work in awake craniotomies and speech and language mapping led to a more complicated and integrated understanding of language organization.³⁵ More recently, using similar methods, with particular emphasis on direct electrical stimulation (DES) of subcortical pathways, an even more refined clinical model emerged with 2 parallel processing streams (ventral semantic stream and dorsal phonological stream). Here, we give a general review of the history of cortical localization and awake mapping in the context of speech and language and some of the contributions that have progressed from the classic modular model to a more complicated network of speech and language or-

ganization. This overview is best appreciated in 4 areas of progress: 1) demonstrating cortical excitability and cerebral localization, 2) advancements in neuroanesthesia, and 3) cortical and 4) subcortical DES for functional mapping.

Cortical Excitability and Cerebral Localization

In the 19th century it was thought that the cerebrum was not excitable “by all common physiologic stimuli.”¹⁷ In 1870, developments by Galvani, Volta, and Aldini motivated Gustav Fritsch and Eduard Hitzig to stimulate the cortex of a dog.¹⁷ In these experiments, platinum wires were used with brief pulses of monophasic direct current (current was just sufficient to elicit sensations in the experimenter’s tongue) from a battery (galvanic stimulation). Stimulation of the anterior cortex evoked contralateral movements. These findings confirmed cross-laterality of cerebral function, the electrical excitability of cortex demonstrated for the first time convincing evidence for cerebral localization of function. In 1873, based on these observations and others, Hughlings Jackson theorized that the brain was an aggregate of distinct functional units and that epileptic discharges had their origins in the cortex.²⁵ Dedicated to this notion, David Ferrier replicated these findings, with par-

ABBREVIATIONS DES = direct electrical stimulation; SMA = supplementary motor area.

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ticular attention to using the minimal current necessary to avoid stimulating neighboring structures.¹⁶ Specifically, Ferrier used faradaic current, resulting in more complex and sustained movements. Even still, movements in monkeys were elicited in wide cortical territories both anterior and posterior to the central sulcus.¹⁶ Convincing evidence of the modern view came from the animal studies of Charles Scott Sherrington and Albert Grünbaum.¹⁸ They provided the first detailed map of the motor cortex, which was published in 1917.²⁹ While Ferrier's methods of stimulation were refined, Sherrington went to great lengths to control stimulation conditions. Specifically, he used faradaic unipolar stimulation, lasting 1–2 seconds, taking into consideration local temperature and pricking a small hole in the arachnoid to let out subarachnoid fluid.²⁸ In these experiments, nonhuman primates were anesthetized with chloroform and ether. The anesthesia was lightened with cortical stimulation since profound anesthesia made the cortex unexcitable. Through the meticulous stimulation of 28 nonhuman primates and observation of more than 400 movements, Leyton (changed from Grünbaum) and Sherrington established the first convincing somatotopic representation of the motor cortex, a precursor to similar functional maps in humans. In fact, years later, Wilder Penfield wrote of Sherrington,

It was not the example of Horsley or Cushing that led me into surgery of the nervous system. It was the inspiration of Sherrington. He was, so it seemed to me from the first, a surgical physiologist, and I hoped then to become a physiological surgeon.¹⁵

Human Cortical Stimulation

At the end of the 19th century, several surgeons began using DES for mapping in humans. It is not entirely clear who was the first to stimulate the human cortex, but the clearest and most detailed report is attributed to Robert Bartholow.¹ In 1874, he published "Experimental investigations into the functions of the human brain," a report on a 30-year-old servant with a rapidly expanding epithelioma, eroding through the skull and exposing brain (2 inches in diameter, posterior to the central sulcus). Bartholow applied faradaic current through metal electrodes and observed "distinct muscular contractions" and sensory changes on the contralateral side. These experiments obviously did not serve a clinical purpose and were accordingly met with criticism. In 1886 and 1887, Victor Horsley published his experience with the first 3 (1886) and first 10 (1887) epilepsy operations.^{23,24} While brief in his description, regarding a case of a 20-year-old male with left upper-limb Jacksonian epilepsy, in the footnote he remarked "the exact removal of an epileptogenic focus... could be ascertained by the use of induction current."²³ Before the operation, the patient was given a quarter grain of morphine and put under chloroform anesthesia. Horsley also used local anesthesia in the form of cocaine to block pain from the dura. These patients reported by Horsley were the first examples of cortical excision informed by cortical stimulation. These methods were later replicated by Keen, Bidwell, and Krause.^{4,26,27} Similar to the detailed maps of the motor area by Sherrington, in 1911 Krause

and Schum used monopolar faradaic stimulation in 142 patients, mapping the motor cortex to be anterior to the precentral gyrus with a somatotopic order.²⁷ Cushing visited Sherrington in 1901 and helped map the motor cortex of nonhuman primates. He later used these techniques to confirm Krause's results in motor cortex localization. Cushing also used faradaic stimulation in 2 awake patients under local anesthetic to illicit sensory changes in the postcentral gyrus.¹⁰ The momentum for advancing the concept of cerebral localization using DES continued with the work of Otfried Foerster. Influenced by Wernicke, Foerster operated on patients with epilepsy by localizing epileptogenic foci using traction, hyperventilation, and electrical stimulation.³⁸ Wilder Penfield learned Foerster's method of cortical stimulation under local anesthesia while spending 6 months in Breslau in 1928. Penfield's methods of localization went beyond motor and sensory mapping and detailed areas of cortex subserving speech, hearing, memory, and language. The details of language localization in Penfield's work are detailed below.

Advancements in Neuroanesthesia

In the 19th century, the analgesic properties of nitrous oxide and ether were discovered. Later, in the 1880s the first successful craniotomies using chloroform inhalation emerged.⁵ Chloroform was the anesthetic of choice in Europe due to its ability to reduce systolic blood pressure, though with the significant drawback of causing fatal cardiac arrhythmias. As a result, in the United States there was a preference for ether, although this anesthetic carried its own disadvantages, including augmented bleeding and nausea and vomiting. Furthermore, the airway had to be maintained with jaw thrust during the entirety of the case, leading to a cramped operative field and limited workspace for the surgeon. These inconveniences and dangerous side effects led to a search for alternative methods. Koller introduced the use of cocaine as an anesthetic in 1884. Various derivatives were later synthesized, including procaine (1899), lignocaine (1943), prilocaine (1959), and bupivacaine (1957).³⁶ Cushing further developed the use of local anesthetics with subcutaneous use for peripheral nerve blocks, introducing the term "regional anesthesia." Local anesthetics paved the way for awake craniotomies. While previously intraoperative cortical stimulation allowed for delineation of the motor area with contralateral muscle contraction, regional anesthetic kept patients awake in order to report sensory changes as well as the testing of speech and language. Using these methods, Cushing demonstrated somatosensory function with stimulation of the postcentral gyrus for the first time. The use of local anesthetic only was ideal in that the patients were kept alert and able to alert the operator of the aura of their seizure; however, patient comfort could not always be guaranteed. In 1963, a combination of a neuroleptic (droperidol) and opioid (fentanyl) was introduced, called Innovar.⁴³ This new drug induced "neuroleptanesthesia," a state of tranquilization where the patient was somnolent and indifferent to the surroundings but easily arousable to follow commands. The high incidence of postoperative sedation, restlessness, extrapyramidal, and anticholinergic symptoms discouraged its use.⁶ In 1990, propofol gained

FIG. 1. A: Wernicke's drawings for speech localization included an auditory area "a" and Broca's area "b." The dashed lines designate likely conduction pathways.⁴⁴ Public domain. **B:** "A" designates Wernicke's area (auditory images of words), "B" designates Broca's area (motor images of articulation), and "Pc" designates the area for visual images of words.¹¹ Public domain. **C:** Penfield's speech areas of the left hemisphere using electrical interference with DES. Shaded areas, or speech cortex, include anterior (Broca's), posterior (Wernicke's), and superior (supplementary motor) areas.³⁵ Republished with permission of Princeton University Press, from Penfield W, Roberts L: *Speech and Brain Mechanisms*. Princeton, NJ: Princeton University Press, 1959; permission conveyed through Copyright Clearance Center, Inc. **D:** Ojemann's probability mapping showing significant variability in language localization. The upper numbers denote the number of patients tested in that zone and the lower numbers are the percentage of patients with evoked naming errors in that zone. Reprinted from 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* 71:316–326, 1989, with permission. © AANS. **E:** Hodotopical map incorporating cortical and axonal anatomy and functional correlations from intraoperative DES supporting a 2-stream model.

popularity because of its titratability and quick return to consciousness and its anticonvulsant and antiemetic properties.⁴¹ As it lacks analgesic properties, a short-acting opioid (fentanyl, alfentanil, sufentanil, or remifentanyl) was used in combination. This is the regimen of choice in modern awake craniotomies. More recently, dexmedetomidine, an alpha-2 agonist, has provided many advantages, including moderate sedation, central-derived analgesia, and decreased potential for respiratory depression. It has been used as the sole agent in awake craniotomies.²

From Modules to Networks

Jean Pierre Flourens contested that all parts of the ce-

rebrum were equipotential (1824), functioning globally as a whole.⁴⁵ Bouillaud and later Broca supported the principle of localization. In Broca's first 2 patients, Leborgne and Lelong, speech articulation appeared to be localized to the inferior frontal gyrus.⁷ In 1874, Wernicke published a series of 2 cases that pointed to an auditory word center located in the superior temporal gyrus.⁴⁴ More broadly, he believed that the anterior area (frontal lobe) localized to speech articulation, while the posterior areas were related to perception or language comprehension (Fig. 1A). Later, this region was pushed back to the posterior third of the superior temporal gyrus by Dejerine (1906) and expanded to include the inferior parietal lobule by Marie (1906) (Fig. 1B).^{11,32} These models, based on lesion-

symptom correlations, although pivotal, were inconsistent and inadequate.

Cortical DES

Penfield was the first to systematically study language organization with the use of DES. After visiting Foerster in Breslau in 1928, Penfield adopted his method of DES under local anesthesia to localize the motor area and epileptogenic focus. Specifically, Foerster would use galvanic stimulation to map epileptic foci and, when functionally permissible, do a radical excision to cure patients from their epilepsy. At the time, it was practice to avoid surgery in the dominant hemisphere unless the lesion was anterior in the frontal lobe or posterior in the occipital lobe in fear of removing cortex that would cause an aphasia, termed the “forbidden territory.” Patients continued to present with scars and lesions in these cortical regions without aphasia. As a result, Penfield wrote “we were emboldened gradually to make more and more excision within this forbidden territory.”³⁵ Penfield refined Foerster’s approach and coined the term “Montreal procedure,” which has become the basis for the modern-day awake craniotomy. Specifically, DES was often done with bipolar electrodes using a square wave generator of 0.2- to 0.5-msec duration and 60 Hz. The minimum threshold strength was determined by gradually increasing the voltage until a sensory response was obtained. Speech testing was then done typically using double the threshold intensity. The speech territory was interrogated by assessing naming (patient is presented with a succession of picture cards and responds “that is a ...”), counting, writing, and reading. In an effort to minimize postoperative cognitive morbidity, Penfield also collaborated with neuropsychologists, including Donald Hebb and, later, Brenda Milner.³⁰ During surgery, the patient was encouraged to talk with Hebb, “who drew him out on various subjects while the area of the scar was being removed.” Milner would also later adapt tasks from experimental studies in monkeys to assay the consequences of lesions, revealing insights into executive functions. This experience culminated in Penfield and Roberts’ book *Speech and Brain Mechanisms*, where 190 patients (121 involving the left) undergoing speech and language mapping using DES were reviewed.³⁵ Errors were categorized as a) arrest of speech, b) hesitation or slurring of speech, c) distortion of words or syllables, d) repetition of words or syllables, e) confusion of numbers while counting, f) inability to name with the retained ability to speak, g) misnaming with evidence of preservation, and h) misnaming without preservation. In general, Penfield confirmed that, the closer lesions or stimulation was to the “posterior part of the third frontal convolution,” the more the motor components of speech were affected; the closer to the temporal-parietal-occipital junction, the more reading and writing were affected; and the closer to the posterior superior temporal lobe, the greater difficulty in language comprehension. New in Penfield’s studies was the involvement of the supplementary motor area (SMA) (Fig. 1C). Penfield also highlighted subcortical connections in the proposed “speech hypothesis,” specifically, that the 3 speech areas are coordinated by projections to parts of the thalamus (centrencephalic system). While previously

the consensus was that cortical regions acted as functional units, Penfield came to reject the notion of a static speech and language network and proposed that there were in fact dynamic connections in which a network of cortical areas can compensate for lesions in the classic language areas:

A large part of the cortex and sub-cortex appears to be active during the production of a proposition. The transmission of impulses from the precentral gyrus to all of the complex musculature necessary for speech is certainly occurring; and there is activity in Broca’s area or another speech area. There is, however, no localized area for articulate language in Broca’s convolution. Broca’s convolution is only part of the whole.³⁵

Following Penfield’s seminal studies on language, other authors confirmed the broad cortical distribution of language.¹⁴ The variability in speech and language mapping was rigorously demonstrated in George Ojemann’s seminal study in 1983 of 117 patients.³⁴ Using DES, he mapped a probabilistic representation of speech and language areas (accounting for positive and negative sites of stimulation; Fig. 1D). This distribution was wider than previously described by Penfield. More importantly, there was no language site shared by more than one-half of the patients. The traditional view had held that speech production and language comprehension were localized to the frontal and temporal lobes, respectively. However, picture-naming interruption had been demonstrated in the temporal and parietal regions, likely because this task recruits several cognitive processes. As a result, multimodal word-finding distinction using auditory and visual naming and reading modalities were described for comprehensive language mapping by Hamberger and Tamny and others.^{20,39} This broad cortical distribution and immense variability was also recapitulated by Sanai et al. in a study of 250 patients undergoing glioma surgery.³⁷ These studies revealed that tumor resection > 1 cm from sites with stimulation-induced errors in naming did not result in permanent deficits.^{3,19} The vast majority of deficits were not permanent.

Subcortical DES

A modular and rigid paradigm could not account for recoveries made after insults in the classic cortical regions subserving speech and language. While mapping of the cortical speech and language sites helped preserve patient quality of life, mapping of white matter tracts was also felt to be crucial to avoid permanent deficits. Hugues Duffau reported the first intraoperative mapping of subcortical language pathways. In 30 right-handed patients undergoing resection of low-grade gliomas, several subcortical language pathways were identified, including the subcallosal fasciculus (stimulation resulting in anomia and reduction of spontaneous speech) and arcuate fasciculus (conduction aphasia).¹³ In a follow-up study of 103 patients, using subcortical mapping, no postoperative deficits were encountered due to interruption of white matter tracts.¹² Interestingly, the occurrence of immediate postoperative worsening in speech and language function was 80%, and yet long-term favorable results were 94%. With the addition of diffusion tensor MRI, improved anatomical-functional correlations were made. Duffau proposed an anatomically constrained framework in which parallel distributed corticosubcortical networks served phonologi-

cal, semantic, and syntactic processing. By reviving the use of subcortical stimulation mapping as the only means of exploring the function of connectomal anatomy in humans in vivo, structural-functional correlations were made. The anatomically constrained framework held that speech and language networks are supported by 2 pathways: the dorsal phonological pathway and the semantic ventral pathway, consistent with the Hickock and Poeppel model.²² Using tractography and subcortical DES, the dorsal pathway is supported by the superior longitudinal fasciculus (SLF). This is composed of the arcuate bundle (connects the posterior temporal lobe to the inferior frontal gyrus) which, when stimulated, results in a conductive aphasia, and the lateral portion of the SLF (connects the superior temporal lobe and inferior parietal lobe to the ventral premotor area), which, when stimulated, causes articulation deficits. The ventral pathway is subdivided into a direct bundle, composed of the inferior frontal occipital fasciculus (IFOF), and an indirect bundle, composed of the uncinate and the inferior longitudinal fasciculus (ILF) (see Chang et al. for a thorough review⁹). Beyond Penfield's picture-naming and counting tasks, these subcortical pathways are interrogated using other intraoperative tasks, including the semantic task of association (IFOF), task of cross-modal judgment (IFOF), face-naming task (uncinate), double task (SLF), line bisection task (SLF), and reading task (ILF). Mapping of different languages and translation in multilingual patients has also been performed.⁴⁰ This work has culminated into an alternative view of speech and language organization, one that is interconnected (hodotopy) and dynamic (Fig. 1E). Clinically, the "hodotopical" model explains why resection of presumed eloquent cortex can be done without neurological deficits. This paradigm shift from a previously considered forbidden territory to one of a large dynamic network with adaptive plasticity has resulted in numerous implications, including resection of tumors in crucial cortical regions (e.g., Broca's area, Wernicke's area). Furthermore, the hodotopical model developed through anatomical and DES correlations challenges traditional cerebral localization by claiming that brain processing is not simply the sum of several networks working independently but instead the integration and potentiation of parallel and overlapping subnetworks. This overlap then leads to a multimodal networking brain. For example, using DES, an amodal executive system has been revealed, which is the cognitive control of more dedicated subnetworks such as language switching in multilingual patients.³³ Another example is the control of language planning and selection/inhibition with DES of the SMA (disorders of speech initiation) and caudate nucleus (perseveration), respectively.^{21,31} Consequently, unlike the classic Wernicke-Geschwind model, language production requires dynamic interactions between parallel delocalized subnetwork whose recruitment varies based on the task required.

Conclusions

In 1870, Fritsch and Hitzig confirmed cortical excitability and demonstrated the existence of motor areas using electrical stimulation of the cerebral cortex of dogs.

The localization of speech, a faculty exclusive to humans, remained a concern for clinicians. In the 40 years that followed Broca's description of 2 patients who had lost the ability to articulate speech, a better understanding of speech and language organization emerged with new terms such as aphasia, agraphia, alexia, aphemia, word blindness, word deafness, motor aphasia, sensory aphasia, and global aphasia. Detailed knowledge of these deficits and their cortical localization was later derived by Penfield, in large part due to surgical advancements made in the awake craniotomy and cortical stimulation of conscious patients. Penfield's work largely confirmed postmortem findings that preceded him, supporting the classic Broca-Wernicke model. However, his findings also suggested a more complicated network of interconnected brain areas capable of compensation in case of local damage (e.g., SMA syndrome). Later, Ojemann's findings would find language areas scattered in frontal, temporal, and parietal lobes with significant interindividual variability. With more recent attention to subcortical pathways, Duffau contributed to a newer clinical model in which language and speech consist of 2 parallel processing pathways subserving semantic, phonological, and syntactic processing. While early findings in DES of an awake patient confirmed cortical areas acting as functional units (modules), more recently DES has revealed the speech and language network to be a large-scale, dynamic, and spatially distributed, cortical and subcortical network composed of essential nodes and structures that can be compensated. DES remains as the only means of real-time structural-functional correlation. This has given the surgeon the ability to optimize resections while maintaining a functional balance as well as a unique opportunity to advance fundamental cognitive neurosciences.

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