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REVIEW

Clinical applications of neurolinguistics in neurosurgery

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Abstract The protection of language function is one of the major challenges of brain surgery. Over the past century, neurosurgeons have attempted to seek the optimal strategy for the preoperative and intraoperative identification of language-related brain regions. Neurosurgeons have investigated the neural mechanism of language, developed neurolinguistics theory, and provided unique evidence to further understand the neural basis of language functions by using intraoperative cortical and subcortical electrical stimulation. With the emergence of modern neuroscience techniques and dramatic advances in language models over the last 25 years, novel language mapping methods have been applied in the neurosurgical practice to help neurosurgeons protect the brain and reduce morbidity. The rapid advancements in brain–computer interface have provided the perfect platform for the combination of neurosurgery and neurolinguistics. In this review, the history of neurolinguistics models, advancements in modern technology, role of neurosurgery in language mapping, and modern language mapping methods (including noninvasive neuroimaging techniques and invasive cortical electroencephalogram) are presented.

Keywords neurolinguistics; language mapping; dual pathway model; neurosurgery

Review of neurolinguistics theory

History of neurolinguistics models and overview of the modern linguistic model

Language function is an important aspect of human cognition and an important research topic in neuroscience and clinical neurology. The study of neurolinguistics helps understand the brain and locate and protect the brain areas related to language function in clinical applications.

The understanding of the neural anatomy of language began with behavior research in patients with brain injury. At the end of the 19th century, Broca and Wernicke found the motor (posterior part of the left inferior frontal gyrus) and the sensory (posterior part of the left superior temporal gyrus (STG)) language cortices, respectively. Wernicke further hypothesized that the motor and the sensory language cortices were connected by fibers passing the lateral fissure and put forward the earliest language model [1]. Lichtheim further proposed the concept center of language. According to his idea, the direct pathway between Broca's and Wernicke's areas was responsible for processing speech information, whereas the language concept center was the indirect connection between the two regions and responsible for processing semantic information [2]. The early language models are conceptual models and lack anatomical basis. In the mid-20th century, Geschwind discovered the language function of the dominant hemispheric parietal lobe and proposed the parietal lobe and the arcuate tract as the connection pathway between Broca's and Wernicke's areas, making great progress on the anatomical basis compared with the previous models. The Broca–Wernicke–Lichtheim–Geschwind model is the traditional language model and forms the neuroanatomical basis of language function [3].

Since the mid-20th century, the cortical electrical stimulation has been used by Penfield, Ojemann, and other pioneers to locate the linguistic cortex of patients with craniotomy. By the end of the century, noninvasive

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brain function localization technologies, such as functional magnetic resonance imaging (fMRI), had been widely used in the study of brain function. In the visual dual-pathway model, the visual system consists of ventral and dorsal pathways, which correspond to "what" and "where" the subject is. Inspired by the visual dual-pathway model, Hickok and Poeppel proposed a dual-pathway language model on the basis of the research results of fMRI brain localization [4]. Ventral and dorsal pathways correspond to the semantic and phonetic systems, respectively. Catani *et al*. used diffusion tensor imaging (DTI) to locate the language-related white matter fibers and explored the connection between functional cerebral areas. Aside from the classical arcuate fasciculus, an indirect pathway connects Broca's and Wernicke's areas. This indirect pathway is composed of an anterior segment connecting Broca's area with the inferior parietal lobule and a posterior segment connecting inferior parietal lobule with Wernicke's area [5]. In the past 10 years, the dual-pathway model of language had become the mainstream of modern language models. The model consists of Broca's area, Wernicke's area, and dorsal and ventral pathways. The dorsal pathway constitutes the superior longitudinal and the arcuate fasciculi and corresponds to phonetic information processing. The ventral pathway constitutes the inferior fronto-occipital (IFOF), uncinate (UF), and inferior longitudinal (ILF) fasciculi and corresponds to semantic information processing (Fig. 1; supplementary video shows the speech production process). However, different scholars have debated the definitions of related brain regions and fiber connections [6]. Compared with the traditional language models, the dual-pathway model has

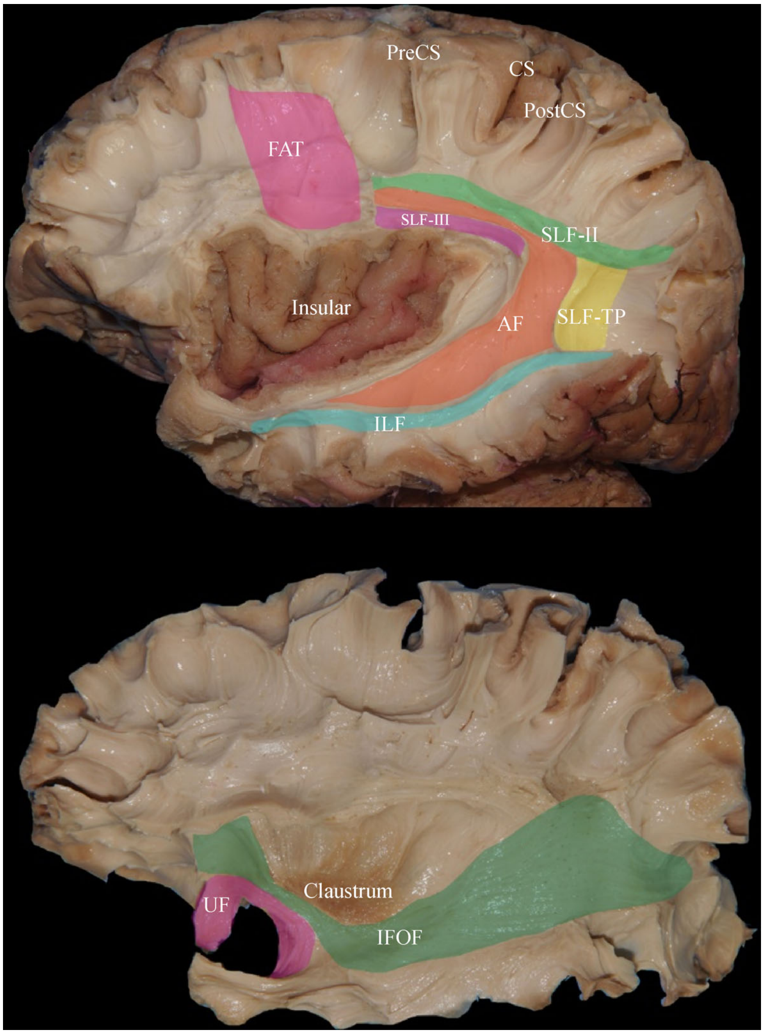

Fig. 1 Fiber anatomy of the dual-pathway language model. The dorsal pathway consists of SLF/AF. The ventral pathway consists of UF, IFOF, and ILF. FAT, frontal aslant tract; PreCS, precentral sulcus; CS, central sulcus; PostCS, postcentral sulcus; SLF, superior longitudinal fasciculus; TP, temporo-parietal; AF, arcuate fasciculus; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; ILF, inferior longitudinal fasciculus.

made evident progress in terms of brain structures and anatomy but still cannot explain all language phenomena, such as those related to the role of cerebellum and other structures [7].

White matter fibers of the dual-pathway language model

Dorsal pathway

The dorsal pathway is composed of the superior longitudinal fasciculus/arcuate fasciculus system.

The arcuate fasciculus originates from the posterior part of the superior and the middle temporal gyri, passes through the supramarginal gyrus and the central lobe, and terminates in the opercular part of the inferior frontal gyrus and the ventral part of the precentral gyrus. The third branch of the superior longitudinal fasciculus originates from the supramarginal gyrus, passes through the central lobe, and ends at the opercular part of the inferior frontal gyrus and the ventral part of the precentral gyrus. The arcuate fasciculus and the third branch of the superior longitudinal fasciculus are not easily distinguishable in DTI, and the two fibers constitute a direct pathway for the dorsal pathway.

The vertical branch of the superior longitudinal fasciculus (also known as the temporal parietal branch) originates from the posterior part of the inferior and middle temporal gyri, passes through the posterior part of the STG, and ends at the angular gyrus. The second branch of the superior longitudinal fasciculus (also known as the horizontal branch of the superior longitudinal fasciculus) originates from the posterior part of the parietal lobe; passes through the angular gyrus, the supramarginal gyrus, and the central lobe; and terminates in the posterior portion of the middle frontal gyrus. The two fiber bundles form an indirect path for the dorsal pathway.

Ventral pathway

The ventral pathway consists of the IFOF, ILF, and UF.

The IFOF originates from the middle and the inferior occipital gyri; passes through the angular gyrus, the STG, the temporal stem, and the anterior part of the insular; and terminates in the triangular part of the inferior frontal gyrus and the anterior parts of the superior and the middle frontal gyri. The IFOF constitutes a direct pathway for the ventral pathway.

The ILF originates from the middle and inferior occipital gyri, passes through the middle and the inferior temporal gyri, and ends at the temporal pole. The UF originates from the temporal pole, passes through the limen of insula, and terminates in the orbital part of the inferior frontal gyrus and the orbital gyri of the frontal lobe. The ILF and the UF constitute an indirect pathway for the ventral pathway.

Auxiliary pathway

The frontal oblique fiber (also known as the Aslant fiber) connects the supplementary motor area in the superior frontal gyrus and the opercular part of the inferior frontal gyrus. The Aslant fiber is the auxiliary fiber bundle of the language pathway. Table 1 summarizes the fibers of dual-pathway language model.

Table 1 Fiber anatomy of the dual-pathway language model [8–11]

Fibers	Originates	Passes	Terminates
Dorsal pathway			
AF	Posterior part of STG/MTG	SMG/central lobe	Opercular part of IFG, ventral part of precentral gyrus
SLF III	SMG	Central lobe	Opercular part of IFG, ventral part of precentral gyrus
SLF II	Posterior part of parietal lobe	SMG/AG/central lobe	Posterior part of MFG
SLF Tp	Posterior part of MTG and ITG		AG
Ventral pathway			
IFOF	MOG/SOG	AG/STG/temporal stem/anterior part of insular	Triangular part of IFG/anterior part of MFG and SFG
UF	Temporal pole	Limen of insular	Orbital part of IFG/orbital gyri
ILF	MOG, IOG	MTG, ITG	Temporal pole
Auxiliary pathway			
FAT	SMA		Opercular part of IFG

AF, arcuate fasciculus; SLF, superior longitudinal fasciculus; Tp, temporo-parietal; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; ILF, inferior longitudinal fasciculus; FAT, frontal aslant tract; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; SMG, supramarginal gyrus; IFG, inferior frontal gyrus; AG, angular gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SOG, superior occipital gyrus; MOG, middle occipital gyrus; IOG, inferior occipital gyrus; SMA, supplementary motor area.

Speech production process

Fig. 2 shows the entire speech production process during picture naming. According to the Levelt–Roelofs–Meyer (LRM) model, speech production is divided into six stages [12–14]. When the picture of a goat is seen, the occipital lobe shows activation after the presentation of the visual information. Next, the visual word form area becomes activated to complete the visual recognition of the image [15,16], and the anterior to the middle part of the middle temporal gyrus becomes activated to complete the conceptual preparation and lemma retrieval process. The time window for the conceptual preparation process, which is responsible for converting the visual information into the concept of a goat, is about 0–200 ms. The time window for the lemma retrieval process, which is responsible for further transforming the concept into the word of goat, is about 200–275 ms. Next, the posterior part of the middle temporal gyrus and the STG become activated to complete the phonological code retrieval process. This step takes approximately 275–390 ms, during which the word goat is translated into the correct phoneme. The phoneme is the smallest phonetic unit in language system that can distinguish a word. Before the end of the phonological code retrieval process, Broca's area becomes activated to complete the phonological encoding process. This step takes approximately 355–455 ms and is responsible for creating the syllable sound and the rhythm information. Before the end of the phonological encoding process, the ventral premotor cortex becomes activated to complete the phonetic encoding process, which has a time window of approximately 410–600 ms. This step is responsible for sequencing syllables and the coordinated movement of articulators. Finally, the ventral sensory motor cortex [17] activates to control the movement of the articulators and complete articulation.

Contributions of neurosurgeons to the study of neurolinguistics

As early as the 19th century, neurosurgeons had made important contributions to neurolinguistics by using the symptom–lesion mapping study. In 1861, Paul Broca defined the left posterior portion of inferior frontal gyrus as the center of articulating speech through the lesion study of two patients with aphasia and showed the foundation for the establishment of the classical language model [18]. However, the lesion study at that time faces several limitations (e.g., extensiveness of lesions, indistinguishable lesion boundaries, and postlesional cortical remodeling), and the initial conclusions are now being questioned [19].

In 1874, Roberts Bartholow first proposed the concept of direct electrical stimulation (DES) mapping of human brain and successfully induced contralateral limb contractions by directly stimulating the cerebral cortex of a patient with a skull defect. Around the beginning of the 1900s, Feodor Krause applied DES during epilepsy surgery and established the first precise map of the motor area in the precentral gyrus [20]. At the same time, Harvey Cushing

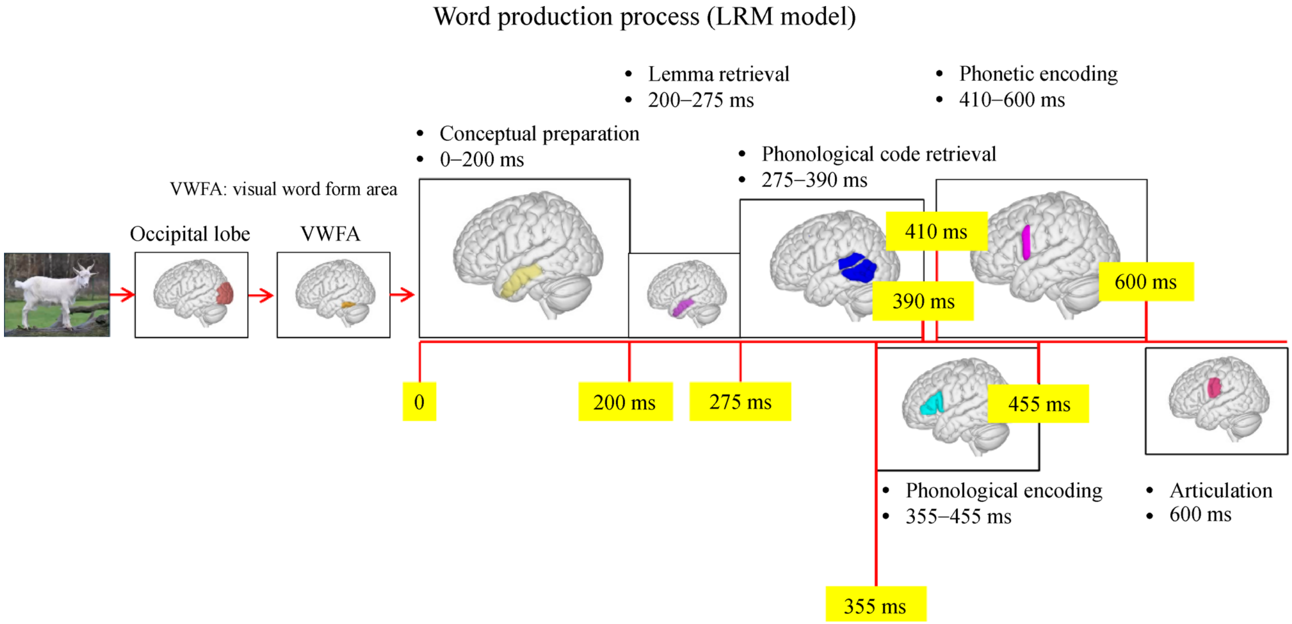

Fig. 2 Process of speech production. The Levelt–Roelofs–Meyer (LRM) model shows the process of picture naming. The LRM model is a basic model to elaborate the whole-word production processing and shows the activation process of different brain regions over time from the beginning of picture onset to speech.

was the first to report sensory mapping by stimulating the postcentral gyrus of two conscious patients under local anesthesia [21]. Subsequently, Krause's student, Otfrid Foerster systematically applied DES in epilepsy surgery to locate the epileptogenic foci and map the sensorimotor cortex [20].

In the late 1920s, Wilder Penfield inherited and optimized the techniques of these three neurosurgeons and established "the Montreal procedure," during which neurosurgeons apply DES under awake craniotomy for preservation and research of numerous essential functions [18]. Penfield used this procedure and created a cortical sensorimotor map referred to as a "homunculus" in his seminal paper in 1937 (Fig. 3). The articulators of speech, including lip, tongue, jaw, and laryngeal systems, were mapped to the ventral portions of the precentral and the postcentral gyri [21]. Penfield extended the application of DES to mapping speech cortex and published the first report of large-scale speech mapping of more than 500 patients undergoing awake craniotomy in Montreal Neurological Institute [18]. In this report, Penfield described the intraoperative language task and greatly improved the neurosurgeons' understanding of the cortical representation of language functions to perform excisions in the so-called "forbidden zone" of the speech cortex. However, speech arrest was considered as an inference of motor mechanism and not included in Penfield's speech map [18].

In the 1970s, George Ojemann improved Penfield's DES technique by introducing the biphasic constant-current electrical stimulation and optimizing intraoperative tasks [22]. In 1989, Ojemann identified the huge individual variability in cortical language localization in his DES study of 117 patients, produced the first probability map to describe this variability, and emphasized the irreplaceable role of intraoperative speech mapping [23]. In the 1990s, Mitchel Berger expanded the indications of DES to neuro-oncology surgery [24] and achieved the probability maps of speech arrest, anomia, and alexia in 250 patients with glioma in 2008 [25]. Subsequently, Hugues Duffau and his colleagues reported the first language map of both hemispheres [26]. In China, Wu and his colleagues compared the speech areas of Chinese and English speakers and provided direct evidence to the differences in cross-cultural neurolinguistics [27].

At the beginning of the 21st century, Duffau applied DES mapping at the subcortical level to explore and preserve the axonal pathways. Duffau combined the transient intraoperative language impairment caused by subcortical DES with the anatomical data provided by neuroimaging techniques to investigate the anatomo-functional correlation, which explored the subcortical fibers related to the language process and provided a better understanding of the language mechanism [28].

In the 2010s, Edward Chang and his team began to use the invasive electrocorticography (ECoG) as a supplementary mapping method. The invasive ECoG retains temporal information, which provides neurosurgeons with important insights into the dynamic procedure of language processing and sophisticated linguistic features [29].

Evaluation techniques and clinical application of neurolinguistics

fMRI

fMRI, including task-based fMRI and resting-state fMRI (rs-fMRI), has been used extensively to study the neural basis of language processing in the past 30 years. The fruitful research based on fMRI has deeply expanded our understanding of the functional anatomy of phonological

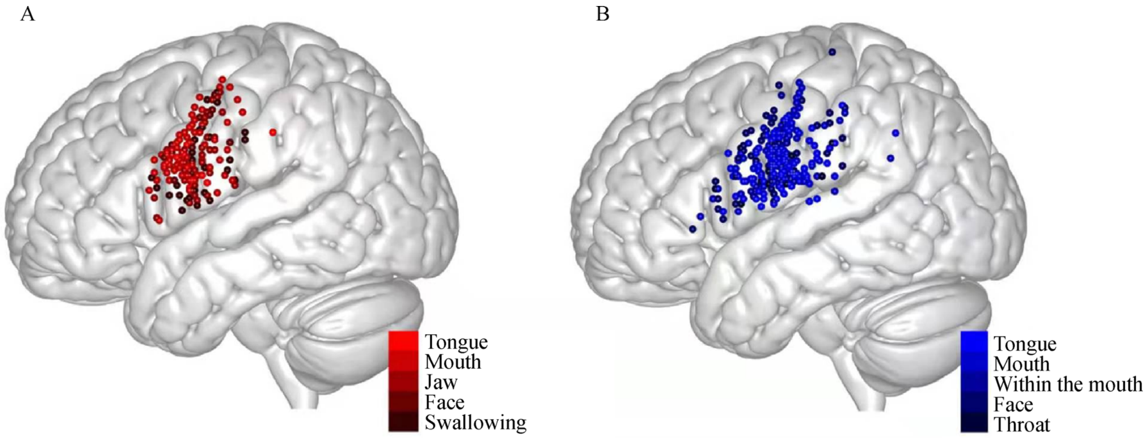

Fig. 3 Somatic sensorimotor map of articulators reconstructed based on Penfield's results [21]. (A) The motor areas of articulators (red) are located in the ventral part of the precentral gyrus. (B) The sensory areas (blue) are located in the ventral part of the postcentral gyrus.

processing, speech production, speech comprehension, and other language processing activities.

The clinical applications of fMRI in language localization include the following specifications.

(1) Language lateralization: The Wada test is considered as the gold standard for the assessment of language lateralization, but noninvasive methods especially fMRI have been increasingly applied recently. Two meta-analyses published in 2011 and 2013 revealed the high concordance between the task-based fMRI (88.69%) and the Wada test (80.55%) [30,31]. In 2015, Doucet *et al.* [32] first proposed rs-fMRI as a reliable method to determine the hemispheric dominance in language processing, and this result was confirmed in further studies [33,34].

(2) Language areas: Compared with the DES during awake surgery, the application of fMRI in language localization is noninvasive, relatively inexpensive, and overcomes the limitation of DES that some patients cannot tolerate due to anxiety, fatigue, or impaired baseline language functions [35]. However, the use of fMRI as a standalone technique in preoperative language mapping to guide resections still has pitfalls. First, fMRI does not distinguish the core areas within all activated areas in language tasks [35,36]. Second, previous research demonstrated that the sensitivity and the specificity of fMRI to locate the language cortex for surgeries were limited compared with those of DES. Lastly, the tumor-related neurovascular uncoupling, which occurs in high- and low-grade gliomas [37,38], has caused false negative bold signal change in fMRI. This phenomenon also affects the reliability of fMRI in language area identification.

High-strength field magnets can increase sensitivity according to research investigating the motor areas [39]. Thus, the application of 7T or higher field MRI devices improves the reliability of fMRI in language localization. The language stimulation paradigm needs to be optimized, and the tasks should differ from different brain regions. Some studies revealed that the combination of tasks increased the sensitivity of fMRI [40,41]. Thus, the optimal combination of tasks needs further investigation.

Transcranial magnetic stimulation (TMS)

TMS detects and locates the cerebral cortex that participates in the task-related response area by applying a time-varying magnetic field to the cerebral cortex for the generation of an induced current to change the action potential of the pyramidal neurons [42,43]. TMS can regulate the excitability of the language cortex, which is conducive to the remodeling of the language function. TMS is also known as “virtual damage” technology [44].

As early as 1991, Pascual-Leone [45] used repetitive TMS (rTMS) in patients with epilepsy for the first time to induce speech arrest. Epstein [46] found that low-frequency rTMS had the same effect as high-frequency rTMS in inducing speech errors. In 2012, Lioumis [47] opened the gate to apply navigation-guided rTMS for mapping the language function by using a subject naming task. The language-eloquent area mapping based on rTMS had high sensitivity and relatively low specificity [48–50].

Compared with noninvasive preoperative mapping techniques, such as fMRI and electroencephalogram (EEG), TMS can locate language-eloquent key areas in which the cerebral cortex participates in a subject naming task response accurately in real time. Compared with the direct cortical stimulation (DCS), which activates cortical axons directly, TMS acts on pyramidal neurons [43] and can be performed without awake anesthesia craniotomy. In a normal brain, a similar degree of interhemispheric inhibition is observed in the bilateral cerebral cortex through the corpus callosum. Contralateral language areas are activated when patients with impaired brain hemisphere dominance have performed language tasks. After the injury of the dominant hemisphere, the inhibition to the contralateral hemisphere is decreased. This phenomenon is called the transcallosal inhibition theory, which is an unfavorable adaptation response. Inhibiting the excessive activity of the contralateral hemispheric language area by low-frequency rTMS can promote the recovery of the dominant hemispheric language network, thereby avoiding the formation of contralateral hemispheric dominance and accelerating the recovery of language function [51,52].

DTI

In recent years, the continuous development of the DTI technology has enabled the noninvasive tracking of the white matter fibers of the human brain. In the brain tissue, the majority of free fluids (such as cerebrospinal fluid) and water molecules in gray matter tend to free dispersion, i.e., isotropy. However, the water molecules in fiber bundles move along the long axis of nerve fibers, which is called anisotropy. By detecting the diffusion parameters in the brain, the DTI can trace the white matter fiber bundles by depicting the easiest direction of water diffusion. The DTI parameters, such as apparent diffusion and partial anisotropy coefficients, are also widely used in the detection of white matter fiber damage caused by various neurological diseases, such as stroke, brain tumor, and multiple sclerosis.

The DTI fiber tracking technology has shown that in addition to arcuate bundles, indirect fiber pathways exist in the language function of brain [53]. Catani *et al.* [5] believe that the arcuate fasciculus is not a fiber bundle but a combination of three fiber bundles, in which the direct pathway connects Wernicke’s and Broca’s areas and is responsible for automatic repetition. The indirect pathway is transferred to the frontal lobe center by the posterior part of the temporal lobe and the parietal lobe to process language understanding, semantic analysis, and other functions. However, disputes about the location and its terminal position of the dorsal pathway remain. Hickok *et al.* [4] proposed the dual-pathway language model on the basis of a previous fMRI study, and Saur *et al.* [54] found the ventral pathway related to the semantic understanding function by combining the DTI results. The DTI [55] and the anatomy study [53,56,57] have identified three ventral pathway fibers, including IFOF, ILF, and UF (Fig. 4).

The DTI technology provides good application in brain tumor resection. Wu *et al.* [58–60] combined DTI fiber tracking and DES to verify the accuracy and the reliability of the DTI pyramidal tract imaging. At present, some shortcomings remain in the application of DTI technology in neurosurgery. In addition to navigation error and brain displacement, the selection of proper model and tracking parameters are difficult. Different parameter settings produce different tractography results. Therefore, comparing and verifying the DTI results with white matter fiber dissection and optimizing the parameters in DTI tractography are needed at present.

Functional near-infrared spectroscopy (fNIRS)

fNIRS is a noninvasive method to probe brain function and uses the measurement of near-infrared light absorption by tissue's hemoglobin. fNIRS obtains the information of event-related hemodynamic changes occurring in the brain cortex and has high temporal resolution [61].

This technology is relatively new and has garnered remarkable research interest due to its wide applications. Watanabe *et al.* were the first to publish the results of clinical application of fNIRS on brain and had shown the hemispheric dominance for language in healthy volunteers and in subjects affected with epilepsy by using a word-generation task [62]. Similarly, other studies had shown the localization of responses to speech stimuli in healthy and neurologically impaired adults [63,64]. fNIRS is noninvasive and has been easily applied in research in the pediatric population. Two studies provided first evidence that the left hemisphere language specialization, like language brain lateralization found in adults, was present at birth in the human brain [65,66].

Majority of clinical studies have generally explored the applications of fNIRS in nonsurgical settings by using scalp probes. However, recently, Qiu *et al.* demonstrated the intraoperative application of fNIRS for mapping language brain regions and concluded that fNIRS is capable of the intraoperative mapping of functional cortical regions and may supplement or even replace DCS with further upgrades [67].

EEG

EEG is a noninvasive method for brain research. Compared with DCS and ECoG, EEG is not limited to awake craniotomy operations. EEG is not limited to the margin of exposure field of surgery and provides information of the whole brain. In contrast to fMRI, which is also noninvasive, EEG directly reflects the state of the neurons and provides a dynamic process of language conduction.

Noninvasive EEG can collect sufficient data and analyze the whole brain function. This method can be used to collect phonetic, semantic, memory, and other language components and study the various processes of language production in detail. The main contribution of noninvasive EEG to the study of brain language function lies in the

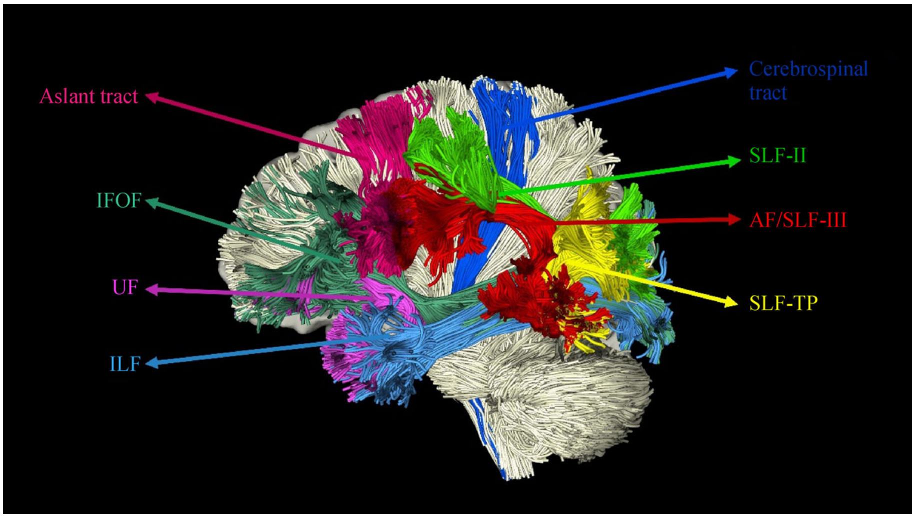

Fig. 4 Dual-pathway language model constructed using DTI. AF, arcuate fasciculus; SLF, superior longitudinal fasciculus; TP, temporo-parietal; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; ILF, inferior longitudinal fasciculus.

study of the occurrence and the conduction process of language at the time dimension of milliseconds by using the method of event-related potentials (ERP), which enables an in-depth understanding of each process of the production of language. A series of studies [68–73] reveals the changes found in the temporal dimension of language generation and transmission, constructs the dynamic process of language generation, and deepens the understanding of the brain language network. However, at the same time, different hypotheses exist about the exact meaning of different ERP components, and further discovery of more ERP components is needed to construct the language process.

EEG has certain advantages in the establishment of the brain–computer interface. Patients with brain injury can use this as an interactive means to control the computer and interact with the external environment. EEG avoids invasiveness to users and has high signal time resolution in favor of real-time signal analysis. Currently, the EEG-based brain–computer interface is based on the P300 ERP. P300 is an ERP induced by a small probability event. In 1988, P300 is used for the "mind typing" of English letters and numbers for the first time [74]. The brain–computer interfaces based on P300, including web browsing, computer operation, and virtual roaming, are extensively developed and used [75–77].

Awake craniotomy

The anesthesia methods for intraoperative awake surgery are divided into two types, namely, the traditional awake–asleep–awake (AAA) anesthesia and the monitored anesthesia care (MAC) methods [78]. During the operation, patients can maintain sedation, analgesia, breathe independently without pain and cooperate with surgeons to manifest the corresponding nervous function in a conscious state. The awake anesthesia during the operation indicates that during the certain stage of the operation, patients are required to cooperate with surgeons to complete certain nerve tests and commanded actions consciously [79]. Awake craniotomy has developed rapidly with its biggest advantage, i.e., the evaluation of neurological status of patients during operation [80].

The AAA anesthesia method is adopted during operation under general anesthesia. Patients are required to complete certain tasks and commanded actions after waking up [81]. The target-controlled infusion of intravenous anesthetics through the laryngeal mask combined with local block anesthesia ensures that patients are under the general anesthesia state from the beginning to the end of the operation. In the key step of resecting tumors in eloquent areas, general anesthesia should be removed, and the laryngeal mask is pulled out to keep patients quiet and awake painlessly [82]. MAC is first applied in the surgical treatment of epilepsy, resecting epileptic nidus located in the pretemporal and the frontal lobes and movement, language, and/or memory areas [83]. During the operation, the cortical mapping stimulation is used to detect and protect these important functional areas. In recent years, conscious anesthesia has been used frequently in glioma resection especially for patients whose tumors are located near the functional brain area (Fig. 5).

Notably, acupuncture anesthesia, an important part of traditional Chinese medicine culture, has been applied in craniotomy for almost 40 years [84]. As related research develops, the acupuncture anesthesia has constantly improved anesthetic effect and been used as one of the effective methods of craniotomy anesthesia. Acupuncture at different stimulation frequencies can promote the secretion of endorphins and dynorphins to generate analgesic and sedative effects. Acupuncture anesthesia, like MAC technology, enables patients to receive the whole operation consciously with combined effect of acupuncture and sedative drugs. However, the depth of anesthesia is hard to control, and discomfort during craniotomy can be caused easily.

ECoG

In addition to the gold standard of brain mapping (intraoperative electrocortical stimulation mapping (ESM) under awake anesthesia), passive ECoG recordings is an alternative invasive tool to rapidly and safely map brain function during or prior to surgery [29]. ECoG focuses on the neural activity in high gamma frequencies by directly recording the electrodes on the surface of cerebral cortex while the patients are engaged in language-related tasks [85]. To date, the studies investigating its feasibility and clinical utility are limited. A recent meta-analysis that summarizes the diagnostic validity of ECoG compared with ESM for presurgical language localization has found that the sensitivity (0.23–0.99) and specificity (0.48–0.96) vary greatly among studies [86]. This finding indicates that this technique should be a supplement to ESM instead of replacement in terms of current evidence for the perioperative mapping.

Cortical representation of speech production

Despite the poor consistency between ESM and ECoG, ECoG especially the high-density ECoG is still widely applied in the investigation of fundamental speech mechanism due to the combination of highly spatial and temporal resolutions. During the past several years, the advent of high-density ECoG provided a unique and direct neural activity recording approach to allow probing further into the functional organization of human brain during speech production and perception.

Speech articulation is the final output stage of speech

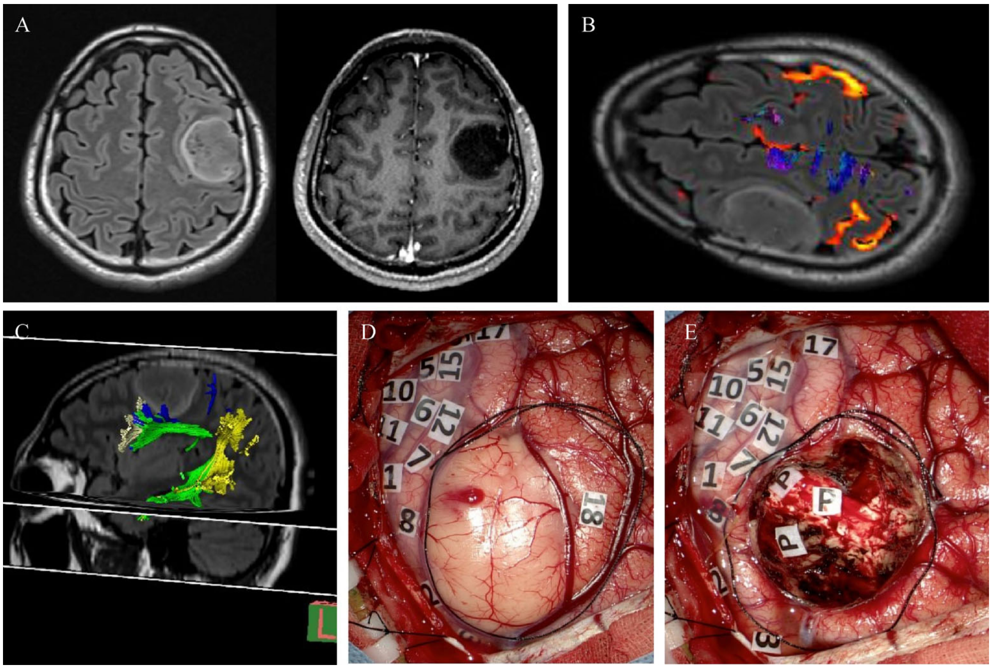

Fig. 5 A case of left middle frontal gyrus low-grade glioma. (A) T2-flair imaging and enhanced T1 MRI imaging show the tumor located at the left middle frontal gyrus without enhancement. (B) Functional MRI shows the bold signal of motor- and language-related cortices. (C) DTI shows the language-related tracts. The green fiber is the arcuate fasciculus, and the white fiber is the Aslant tract. (D) Cortical mapping before tumor resection. Tag 17 shows the anomia site. Tag 18 is the hesitation site of the anomia. Tag 15 shows the speech arrest site. Tags 7, 8, and 12 show the cortex related to lip and jaw movements. Tags 2 and 3 show the hand motor-related cortex. (E) Cortical and subcortical mapping after tumor resection. P tags show the subcortical cerebrospinal fibers. Tag 18 is a hesitation functional site of speech impairment, and the middle frontal gyrus is not a typical language-eloquent site. The area is resected to obtain a good resection rate of the tumor.

production, which requires the precise coordinated movement of over 100 muscles from articulators over rapid time scales. Bouchard *et al.* depicted the spatial organization of ventral sensorimotor cortex (vSMC) by using the ECoG recording during a task, in which the participants read aloud consonant–vowel syllables, to understand the functional representation of different articulators [87]. The articulator representations are organized somatopically on vSMC, and the motor regions of the larynx (dorsal [dLMC] and ventral laryngeal motor cortices) are separate. The dLMC selectively encodes the vocal pitch instead of the nonlaryngeal articulatory movement [88]. These findings provide important insights into the understanding of the representations of articulatory and vocal control.

Cortical representation of speech perception

Speech perception is another important research field investigated using high-density ECoG, which mostly focuses on the posterior STG. Chang *et al.* [89] first revealed the categorical speech representation in STG on the basis of the distinct and invariant cortical neural activity patterns of speech sound. Then, the neural mechanisms of extracting a single speaker's voice in a multispeaker background was demonstrated by recording the STG of subjects who attended to a listening task with two simultaneous speakers. The human auditory cortex selects the perception of the attended speaker and suppresses irrelevant competing speech [90]. Besides, two other predominant discoveries have been found from this state-of-the-art technique about speech perception. First, the cortical activity of STG represents acoustic–phonetic features instead of phoneme [91]. Second, the intonational speech prosody is selectively encoded at single electrodes over the STG, and the representation of intonation contour relies on the encoding of relative pitch, not absolute pitch [92]. In summary, this valuable technique contributes to the clinical treatment and advances the answers of fundamental neuroscience questions.

Summary and perspectives

Neurosurgeons are among the pioneers in neurolinguistics with exceptional advantages and have made major contributions for 200 years [93]. Various invasive and

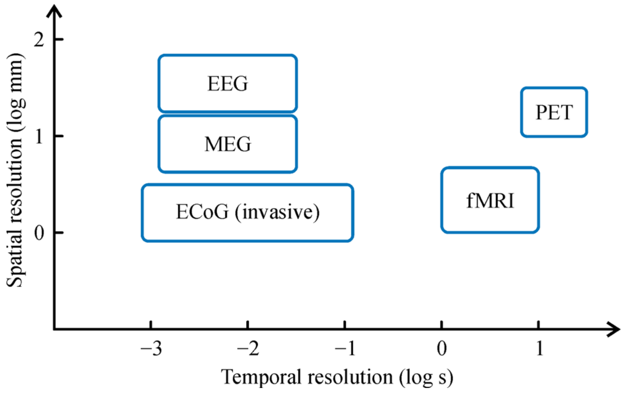

Fig. 6 Comparison of spatial and temporal resolutions in human neurophysiology (created with reference to Chiong *et al.*'s research findings [96]).

noninvasive methods, such as fMRI, TMS, DTI, and EEG, have been developed. The language mapping technology in use today can be divided into two categories. One kind directly reflects the activities of the neurons and includes TMS, EEG, ECoG, and DCS. TMS and DCS have high spatial resolution, and the EEG and ECoG have high temporal resolution. ECoG and DCS are invasive and only used in surgery. Another kind indirectly reflects the activities of the neurons and includes fMRI, rs-MRI, and fNIRS. These techniques are noninvasive and have grown rapidly in the past 20 years, providing a distinct view on brain research, offering evidence for modern neurolinguistics theories, and helping neurosurgeons in understanding and protecting brains. This finding indicates that neurolinguistics and clinical translation are reciprocal and interdependent.

Nowadays, the brain–computer interface, an application of brain function research, is a hot topic. This interface can help patients preserve or improve their bodily function. However, most of the brain–computer interfaces only focus on motor function, and investigators have recently started to conduct studies for the brain–computer interface with vision and speech functions. In 2019, an interdisciplinary team, including neurosurgeons, neuroscientists, speech scientists, and data scientists, has published their results on speech synthesis from cortical local field potential signals [94]. This paper has represented the most advanced brain–computer interface work. Moreover, most brain–computer interface studies are only focused on one function, and comprehensive studies that combine motor, sensory, vision, and speech characteristics are needed.

Approximately 16 billion neurons are contained in the cerebral cortex [95]. However, current technologies cannot balance time resolution, spatial resolution, invasiveness, and brain coverage (Fig. 6). Therefore, combining the advantages and avoiding the disadvantages from these methods and studying brains from multiple perspectives are pivotal for modern neuroscience. Furthermore, a powerful computational method is needed to process and model the brain after recording. Unfortunately, even the latest supercomputer can only model a tiny fraction. In recent years, the surge of machine learning and artificial intelligence has enabled neurolinguistics studies. However, these methods require highly annotated information and a long time. In the forthcoming years, highly automated annotation methods, novel algorithms, and dedicated hardware should be developed for neurolinguistics studies.

Finally, ethical concerns for neurolinguistics studies still need to be addressed. Patient or healthy volunteers participating in studies especially for invasive studies would undergo discomfort unavoidably. Measures are needed to reduce their discomfort and reimburse their devotion from institutions. Neurolinguistics studies usually involve researchers from different backgrounds, and frequent data transfer is a common practice. Thus, the volunteers' privacy should be seriously considered.

Brain function research, including language function, is the core of the future brain research. Brain diseases, which cause brain morphological and functional changes, are the natural model to observe and study the mechanism of brain function. For current clinical medicine participating in the study of brain function, new research methods from neuroscientists and further integrations of comprehensive cognitive evaluation are needed. With the improvement of machine computing capacity, big data have become the norm for most research fields, including brain function research. Brain function research is not a single discipline and not just the deep mining of the data but the deep integration of associated disciplines. Multidisciplinary cooperation has just started. In the future, clinicians, neuroscientists, data analysts, bioengineers, computer scientists, and other experts in related disciplines must work together to advance brain science research.

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Compliance with ethics guidelines

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References

1. Tremblay P, Dick AS. Broca and Wernicke are dead, or moving past the classic model of language neurobiology. Brain Lang 2016; 162: 60–71
2. Ueno T, Saito S, Rogers TT, Lambon Ralph MA. Lichtheim 2: synthesizing aphasia and the neural basis of language in a neurocomputational model of the dual dorsal-ventral language pathways. Neuron 2011; 72(2): 385–396
3. Poeppel D, Emmorey K, Hickok G, Pylkkänen L. Towards a new neurobiology of language. J Neurosci 2012; 32(41): 14125–14131
4. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci 2007; 8(5): 393–402
5. Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. Ann Neurol 2005; 57(1): 8–16
6. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. J Neurosurg 2015; 122(2): 250–261
7. Zhang N, Xia M, Qiu T, Wang X, Lin CP, Guo Q, Lu J, Wu Q, Zhuang D, Yu Z, Gong F, Farrukh Hameed NU, He Y, Wu J, Zhou L. Reorganization of cerebro-cerebellar circuit in patients with left hemispheric gliomas involving language network: a combined structural and resting-state functional MRI study. Hum Brain Mapp 2018; 39(12): 4802–4819
8. Yagmurlu K, Middlebrooks EH, Tanriover N, Rhoton AL Jr. Fiber tracts of the dorsal language stream in the human brain. J Neurosurg 2016; 124(5): 1396–1405
9. Fernandez-Miranda JC, Pathak S, Schneider W. High-definition fiber tractography and language. J Neurosurg 2010; 113(1): 156––158
10. Fernández-Miranda JC, Rhoton AL Jr, Alvarez-Linera J, Kakizawa Y, Choi C, de Oliveira EP. Three-dimensional microsurgical and tractographic anatomy of the white matter of the human brain. Neurosurgery 2008; 62(6 Suppl 3): 989–1028
11. Fernandez-Miranda JC, Pathak S, Engh J, Jarbo K, Verstynen T, Yeh FC, Wang Y, Mintz A, Boada F, Schneider W, Friedlander R. High-definition fiber tractography of the human brain: neuroanatomical validation and neurosurgical applications. Neurosurgery 2012; 71 (2): 430–453
12. Levelt WJ, Roelofs A, Meyer AS. A theory of lexical access in speech production. Behav Brain Sci 1999; 22(1): 1–38
13. Indefrey P, Levelt WJ. The spatial and temporal signatures of word production components. Cognition 2004; 92(1–2): 101–144
14. Indefrey P. The spatial and temporal signatures of word production components: a critical update. Front Psychol 2011; 2: 255
15. Mandonnet E, Gatignol P, Duffau H. Evidence for an occipito-temporal tract underlying visual recognition in picture naming. Clin Neurol Neurosurg 2009; 111(7): 601–605
16. Vogel AC, Petersen SE, Schlaggar BL. The VWFA: it's not just for words anymore. Front Hum Neurosci 2014; 8: 88
17. Breshears JD, Molinaro AM, Chang EF. A probabilistic map of the human ventral sensorimotor cortex using electrical stimulation. J Neurosurg 2015; 123(2): 340–349
18. Penfield W, Roberts L. Speech and brain mechanisms. New Jersey: Princeton University Press, 1959
19. Dronkers NF, Plaisant O, Iba-Zizen MT, Cabanis EA. Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong. Brain 2007; 130(5): 1432–1441
20. Ojemann GA, Whitaker HA. Language localization and variability. Brain Lang 1978; 6(2): 239–260
21. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 1937; 60(4): 389–443
22. Whitaker HA, Ojemann GA. Graded localisation of naming from electrical stimulation mapping of left cerebral cortex. Nature 1977; 270(5632): 50–51
23. 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(3): 316–326
24. Berger MS, Ojemann GA. Intraoperative brain mapping techniques in neuro-oncology. Stereotact Funct Neurosurg 1992; 58(1–4): 153–161
25. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med 2008; 358 (1): 18–27
26. Tate MC, Herbet G, Moritz-Gasser S, Tate JE, Duffau H. Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited. Brain 2014; 137(10): 2773–2782
27. Wu J, Lu J, Zhang H, Zhang J, Yao C, Zhuang D, Qiu T, Guo Q, Hu X, Mao Y, Zhou L. Direct evidence from intraoperative electrocortical stimulation indicates shared and distinct speech production center between Chinese and English languages. Hum Brain Mapp 2015; 36(12): 4972–4985
28. Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, Bitar A, Fohanno D. Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. Brain 2002; 125(1): 199–214
29. Cheung C, Chang EF. Real-time, time-frequency mapping of event-related cortical activation. J Neural Eng 2012; 9(4): 046018
30. Dym RJ, Burns J, Freeman K, Lipton ML. Is functional MR imaging assessment of hemispheric language dominance as good as the Wada test?: a meta-analysis. Radiology 2011; 261(2): 446–455
31. Bauer PR, Reitsma JB, Houweling BM, Ferrier CH, Ramsey NF. Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. J Neurol Neurosurg Psychiatry 2014; 85(5): 581–588
32. Doucet GE, Pustina D, Skidmore C, Sharan A, Sperling MR, Tracy JI. Resting-state functional connectivity predicts the strength of hemispheric lateralization for language processing in temporal lobe epilepsy and normals. Hum Brain Mapp 2015; 36(1): 288–303
33. DeSalvo MN, Tanaka N, Douw L, Leveroni CL, Buchbinder BR, Greve DN, Stufflebeam SM. Resting-state functional MR imaging for determining language laterality in intractable epilepsy. Radiology 2016; 281(1): 264–269
34. Smitha KA, Arun KM, Rajesh PG, Thomas B, Radhakrishnan A, Sarma PS, Kesavadas C. Resting fMRI as an alternative for task-based fMRI for language lateralization in temporal lobe epilepsy

patients: a study using independent component analysis. Neuroradiology 2019; 61(7): 803–810

35. Junck L, Hervey-Jumper SL, Sagher O. Resection of gliomas around language areas: can fMRI contribute? Neurology 2015; 84 (6): 550–551
36. Kuchcinski G, Mellerio C, Pallud J, Dezamis E, Turc G, Rigaux-Viodé O, Malherbe C, Roca P, Leclerc X, Varlet P, Chrétien F, Devaux B, Meder JF, Oppenheim C. Three-tesla functional MR language mapping: comparison with direct cortical stimulation in gliomas. Neurology 2015; 84(6): 560–568
37. Pillai JJ, Zacá D. Clinical utility of cerebrovascular reactivity mapping in patients with low grade gliomas. World J Clin Oncol 2011; 2(12): 397–403
38. Hou BL, Bradbury M, Peck KK, Petrovich NM, Gutin PH, Holodny AI. Effect of brain tumor neovasculature defined by rCBV on BOLD fMRI activation volume in the primary motor cortex. Neuroimage 2006; 32(2): 489–497
39. Krüger G, Kastrup A, Glover GH. Neuroimaging at 1.5 T and 3.0 T: comparison of oxygenation-sensitive magnetic resonance imaging. Magn Reson Med 2001; 45(4): 595–604
40. Bizzi A, Blasi V, Falini A, Ferroli P, Cadioli M, Danesi U, Aquino D, Marras C, Caldiroli D, Broggi G. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology 2008; 248(2): 579–589
41. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. Neurosurgery 2003; 52(6): 1335–1347
42. Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. Neurophysiol Clin 2010; 40(1): 7–17
43. Kombos T, Picht T, Derdilopoulos A, Suess O. Impact of intraoperative neurophysiological monitoring on surgery of high-grade gliomas. J Clin Neurophysiol 2009; 26(6): 422–425
44. Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 2000; 10(2): 232–237
45. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 1991; 41(5): 697–702
46. Epstein CM, Lah JJ, Meador K, Weissman JD, Gaitan LE, Dihenia B. Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation. Neurology 1996; 47(6): 1590–1593
47. Lioumis P, Zhdanov A, Mäkelä N, Lehtinen H, Wilenius J, Neuvonen T, Hannula H, Deletis V, Picht T, Mäkelä JP. A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. J Neurosci Methods 2012; 204 (2): 349–354
48. Picht T, Krieg SM, Sollmann N, Rösler J, Niraula B, Neuvonen T, Savolainen P, Lioumis P, Mäkelä JP, Deletis V, Meyer B, Vajkoczy P, Ringel F. A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery 2013; 72(5): 808–819
49. Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, Negwer C, Droese D, Zimmer C, Meyer B, Ringel F, Krieg SM. Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation. J Neurosurg 2015; 123(1): 212–225
50. Tarapore PE, Findlay AM, Honma SM, Mizuiri D, Houde JF, Berger MS, Nagarajan SS. Language mapping with navigated repetitive TMS: proof of technique and validation. Neuroimage 2013; 82: 260–272
51. Lefaucheur JP. Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rTMS). Neurophysiol Clin 2006; 36(3): 105–115
52. Kapur N. Paradoxical functional facilitation in brain-behaviour research. A critical review. Brain 1996; 119(5): 1775–1790
53. Glasser MF, Rilling JK. DTI tractography of the human brain's language pathways. Cereb Cortex 2008; 18(11): 2471–2482
54. Saur D, Kreher BW, Schnell S, Kümmerer D, Kellmeyer P, Vry MS, Umarova R, Musso M, Glauche V, Abel S, Huber W, Rijntjes M, Hennig J, Weiller C. Ventral and dorsal pathways for language. Proc Natl Acad Sci USA 2008; 105(46): 18035–18040
55. Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 2007; 36(3): 630–644
56. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual *in vivo* dissections. Cortex 2008; 44(8): 1105–1132
57. Martino J, De Witt Hamer PC, Berger MS, Lawton MT, Arnold CM, de Lucas EM, Duffau H. Analysis of the subcomponents and cortical terminations of the perisylvian superior longitudinal fasciculus: a fiber dissection and DTI tractography study. Brain Struct Funct 2013; 218(1): 105–121
58. Wu JS, Zhou LF, Hong XN, Mao Y, Du GH. Role of diffusion tensor imaging in neuronavigation surgery of brain tumors involving pyramidal tracts. Chin J Surg (Zhonghua Wai Ke Za Zhi) 2003; 41 (9): 662–666 (in Chinese)
59. Zhu FP, Wu JS, Yao CJ, Lang LQ, Xu G, Zhang J, Sun S, Mao Y, Zhou LF. Diffusion tensor imaging correlates with subcortical stimulation for intraoperative pyramidal tract mapping: a preliminary study. Chin J Neurosurg (Zhonghua Shen Jing Wai Ke Za Zhi) 2010; 26(9): 795–799 (in Chinese)
60. Zhu FP, Wu JS, Yao CJ, Lang LQ, Xu G, Mao Y. Intraoperative neurophysiological monitoring in low-field MRI environment. Chin J Neurosurg (Zhonghua Shen Jing Wai Ke Za Zhi) 2010; 26(4): 303–305 (in Chinese)
61. Yuan Z. Combining independent component analysis and Granger causality to investigate brain network dynamics with fNIRS measurements. Biomed Opt Express 2013; 4(11): 2629–2643
62. Watanabe E, Maki A, Kawaguchi F, Takashiro K, Yamashita Y, Koizumi H, Mayanagi Y. Non-invasive assessment of language dominance with near-infrared spectroscopic mapping. Neurosci Lett 1998; 256(1): 49–52
63. Kennan RP, Kim D, Maki A, Koizumi H, Constable RT. Non-invasive assessment of language lateralization by transcranial near infrared optical topography and functional MRI. Hum Brain Mapp 2002; 16(3): 183–189
64. Watson NF, Dodrill C, Farrell D, Holmes MD, Miller JW. Determination of language dominance with near-infrared spectro-

scopy: comparison with the intracarotid amobarbital procedure. Seizure 2004; 13(6): 399–402

65. Peña M, Maki A, Kovacić D, Dehaene-Lambertz G, Koizumi H, Bouquet F, Mehler J. Sounds and silence: an optical topography study of language recognition at birth. Proc Natl Acad Sci USA 2003; 100(20): 11702–11705
66. Kotilahti K, Nissilä I, Näsi T, Lipiäinen L, Noponen T, Meriläinen P, Huotilainen M, Fellman V. Hemodynamic responses to speech and music in newborn infants. Hum Brain Mapp 2010; 31(4): 595–603
67. Qiu T, Hameed NUF, Peng Y, Wang S, Wu J, Zhou L. Functional near-infrared spectroscopy for intraoperative brain mapping. Neurophotonics 2019; 6(4): 045010
68. Lee CY, Liu YN, Tsai JL. The time course of contextual effects on visual word recognition. Front Psychol 2012; 3: 285
69. Beres AM. Time is of the essence: a review of electroencephalography (EEG) and event-related brain potentials (ERPs) in language research. Appl Psychophysiol Biofeedback 2017; 42(4): 247–255
70. Boudewyn MA, Long DL, Swaab TY. Graded expectations: predictive processing and the adjustment of expectations during spoken language comprehension. Cogn Affect Behav Neurosci 2015; 15(3): 607–624
71. Nieuwland MS. Do 'early' brain responses reveal word form prediction during language comprehension? A critical review. Neurosci Biobehav Rev 2019; 96: 367–400
72. Hagoort P, Wassenaar M, Brown CM. Syntax-related ERP-effects in Dutch. Brain Res Cogn Brain Res 2003; 16(1): 38–50
73. Brouwer H, Hoeks JC. A time and place for language comprehension: mapping the N400 and the P600 to a minimal cortical network. Front Hum Neurosci 2013; 7: 758
74. Farwell LA, Donchin E. Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials. Electroencephalogr Clin Neurophysiol 1988; 70(6): 510–523
75. Krusienski DJ, Sellers EW, McFarland DJ, Vaughan TM, Wolpaw JR. Toward enhanced P300 speller performance. J Neurosci Methods 2008; 167(1): 15–21
76. Serby H, Yom-Tov E, Inbar GF. An improved P300-based brain-computer interface. IEEE Trans Neural Syst Rehabil Eng 2005; 13 (1): 89–98
77. Zhang H, Guan C, Wang C. Asynchronous P300-based brain-computer interfaces: a computational approach with statistical models. IEEE Trans Biomed Eng 2008; 55(6): 1754–1763
78. See JJ, Lew TW, Kwek TK, Chin KJ, Wong MF, Liew QY, Lim SH, Ho HS, Chan Y, Loke GP, Yeo VS. Anaesthetic management of awake craniotomy for tumour resection. Ann Acad Med Singap 2007; 36(5): 319–325
79. Piccioni F, Fanzio M. Management of anesthesia in awake craniotomy. Minerva Anestesiol 2008; 74(7–8): 393–408
80. Bilotta F, Rosa G. 'Anesthesia' for awake neurosurgery. Curr Opin Anaesthesiol 2009; 22(5): 560–565
81. Hansen E, Seemann M, Zech N, Doenitz C, Luerding R, Brawanski A. Awake craniotomies without any sedation: the awake-awake-awake technique. Acta Neurochir (Wien) 2013; 155(8): 1417–1424
82. Dilmen OK, Akcil EF, Oguz A, Vehid H, Tunali Y. Comparison of conscious sedation and asleep-awake-asleep techniques for awake craniotomy. J Clin Neurosci 2017; 35: 30–34
83. Meng L, McDonagh DL, Berger MS, Gelb AW. Anesthesia for awake craniotomy: a how-to guide for the occasional practitioner. Can J Anaesth 2017; 64(5): 517–529
84. Jin L, Wu JS, Chen GB, Zhou LF. Unforgettable ups and downs of acupuncture anesthesia in China. World Neurosurg 2017; 102: 623–631
85. Wang Y, Fifer MS, Flinker A, Korzeniewska A, Cervenka MC, Anderson WS, Boatman-Reich DF, Crone NE. Spatial-temporal functional mapping of language at the bedside with electrocorticography. Neurology 2016; 86(13): 1181–1189
86. Arya R, Horn PS, Crone NE. ECoG high-gamma modulation versus electrical stimulation for presurgical language mapping. Epilepsy Behav 2018; 79: 26–33
87. Bouchard KE, Mesgarani N, Johnson K, Chang EF. Functional organization of human sensorimotor cortex for speech articulation. Nature 2013; 495(7441): 327–332
88. Dichter BK, Breshears JD, Leonard MK, Chang EF. The control of vocal pitch in human laryngeal motor cortex. Cell 2018; 174(1): 21–31.e29
89. Chang EF, Rieger JW, Johnson K, Berger MS, Barbaro NM, Knight RT. Categorical speech representation in human superior temporal gyrus. Nat Neurosci 2010; 13(11): 1428–1432
90. Mesgarani N, Chang EF. Selective cortical representation of attended speaker in multi-talker speech perception. Nature 2012; 485(7397): 233–236
91. Mesgarani N, Cheung C, Johnson K, Chang EF. Phonetic feature encoding in human superior temporal gyrus. Science 2014; 343 (6174): 1006–1010
92. Tang C, Hamilton LS, Chang EF. Intonational speech prosody encoding in the human auditory cortex. Science 2017; 357(6353): 797–801
93. Colin Phillips KLS. Language and the Brain. McGraw-Hill Publishers, 2005
94. Anumanchipalli GK, Chartier J, Chang EF. Speech synthesis from neural decoding of spoken sentences. Nature 2019; 568(7753): 493–498
95. Collins FS. Reengineering translational science: the time is right. Sci Transl Med 2011; 3(90): 90cm17
96. Chiong W, Leonard MK, Chang EF. Neurosurgical patients as human research subjects: ethical considerations in intracranial electrophysiology research. Neurosurgery 2018; 83(1): 29–37