Corticocortical Evoked Potentials in Eloquent Brain Tumor Surgery. A Systematic Review

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Key words
- Brain surgery
- CCEPs
- Corticocortical evoked potentials
- Intraoperative monitoring
- Language network
- Oncofunctional balance

Abbreviations and Acronyms

CCEP: Corticocortico evoked potential
MRI: Magnetic resonance imaging

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Citation: World Neurosurg. (2024) 181:38-51.
https://doi.org/10.1016/j.wneu.2023.10.028

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***

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Eloquent brain tumor surgery involves the delicate task of resecting tumors located in regions of the brain responsible for critical functions, such as language, motor control, and sensory perception. Preserving these functions is of paramount importance to maintain the patient's quality of life. Corticocortical evoked potentials (CCEPs) have emerged as a valuable intraoperative monitoring technique that aids in identifying and preserving eloquent cortical areas during surgery. This systematic review aimed to assess the utility of CCEPs in eloquent brain tumor surgery and determine their effectiveness in improving patient outcomes. A comprehensive literature search was conducted using electronic databases, including PubMed/Medline and Scopus. The search strategy identified 11 relevant articles for detailed analysis. The findings of the included studies consistently demonstrated the potential of CCEPs in guiding surgical decision making, minimizing the risk of postoperative neurological deficits, and mapping functional connectivity during surgery. However, further research and standardization are needed to fully establish the clinical benefits and refine the implementation of CCEPs in routine neurosurgical practice.

INTRODUCTION

Since the early 1990s, there has been a lively debate on how extended the resection of gliomas must be.[1,2] Nowadays it is unthinkable to consider gross total resection in certain eloquent brain areas due to the proximity of functional areas, which increases the risk of permanent postoperative neurological disturbances. In this context, the patient's quality of life must be paramount in the surgeon's choice of the surgical strategy.[3,4] This represents a difficult challenge for the neurosurgeon: to resect as much tumor as possible, leaving the patient unimpaired and ideally independent, finding a compromise between surgical excision of the tumor and preservation not only of motor functions, but also notably neurocognitive tasks. Hence, a new term was coined that describes the core of this ideal: maximal safe resection.[5,6]

Duffau's group has long worked to establish this ideal in modern glioma surgery, considering "gross total tumorectomy as removing only the top of the iceberg."[7,8] Thanks to the progressive technological advances in neuroimaging and neurophysiological monitoring, it has been well established that the nervous system is an interconnected and intercommunicating network of neurons.[9] Mapping the macroscale connections of the human brain (macroscale connections are pathways created by bundles of nerve fibers) and deciphering these networks have allowed the creation of the basis of the human connectome, which describes the comprehensive set of neuronal connections of the human central nervous system.[10,11] If a macroscale exists, however, the presence of a microscale of the gene expression profiles and cytoarchitecture of neurons is implied, and the cross-link between these 2 levels of the connectome hierarchy is permitted by the mesoscale of cortical circuits, a range of different scales that together connect the 2 extremes, creating a deep and thorough, but mainly plastic, network of neurons that collectively define the three-dimensional space in which limbic, motor, and somatosensory functions develop and integrate.[12-14]

Awake surgery associated with other intraoperative neuromonitoring techniques is the gold standard approach in eloquent brain tumors, but not all patients are viable candidates.[15-19] Corticocortical evoked potentials (CCEPs) are a relatively new means for intraoperative monitoring of neurological pathways. CCEP monitoring involves the recording of electrical signals from electrodes implanted in different areas of the brain cortex. By applying single-pulse electrical stimulation to one cortical zone and recording the resulting CCEPs from functionally connected areas, information about the functional connectivity and the interaction between different brain regions can be obtained.[20-22]

The protocol applied for mapping the language cortex has been described by Matsumoto et al.[23,24] The area is preliminarily mapped using preoperative images and anatomical landmarks or through neurophysiological guidance techniques such as direct cortical single-pulse electrical stimulation using probes or subdural electrodes. The parameters for single-pulse electrical stimulation across the studies evaluated involve bipolar mounting, square-wave electrical pulses with a pulse width of 0.3–300 ms, a frequency of 1–1500 Hz, and an amplitude of 1–35 mA. The stimulation is performed until clinical symptoms or afterdischarges are observed.

The mapping is typically performed using 2 subdural electrodes stimulating, for instance, Broca area and recording the evoked responses from another area, such as Wernicke area, known to be connected by the arcuate fasciculus. In this context, CCEP mapping represents a form of evoked effective connectivity, helping neurosurgeons in the safe removal of brain tumors in an eloquent area.[25] The choice of different stimulation parameters is assessed directly by the neurosurgeon based on the specific situation, considering 3 fundamental aspects: the surgical setting, the surgical procedural damage to be avoided to reduce the deficit rate, and the surgeon's own experience in using CCEPs. CCEPs typically consist of 4 consecutive voltage peaks called P1, N1, P2, and N2, where N1 and N2 are negative peaks and P1 and P2 are positive peaks. However, studies on CCEPs have so far mainly focused on monitoring N1, which is attributed to the excitation of pyramidal cells. Moreover, N1 is usually more pronounced in the recorded signal than the other peaks, which designates it as the most characteristic feature to be studied (**Figure 1**).[26]

In this review, we aimed to analyze how CCEP mapping provides crucial insights into the effective connectivity of the nervous system and can assist neurosurgeons in the safe removal of brain tumors, in particular monitoring speech function preoperatively, intraoperatively, and postoperatively.

MATERIALS AND METHODS

Search of the Literature

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (**Figure 2**).[27] We performed a broad systematic literature search in PubMed/Medline and Scopus electronic databases for all studies investigating the usefulness and efficacy of CCEPs in eloquent brain tumor surgery.

We searched all studies published up to March 26, 2023. The following Medical Subject Headings terms were used: "intraoperative monitoring" AND "strategies" AND "brain tumor," "cortico-cortical evoked potentials" AND "brain surgery," "neurophysiology monitoring" AND "brain tumor," "brain mapping" AND "CCEPs" AND "surgery," "CCEPs" AND "brain tumor," "outcome" AND "CCEPs" AND "brain surgery," "CCEPs" AND "brain" AND "tumor "AND "surgery" AND "outcome." To avoid the potential omission of relevant studies, we manually screened reference lists of articles included. Duplicate articles were eliminated using Microsoft Excel Version 16.37 (Microsoft Corp., Redmond, Washington, USA).

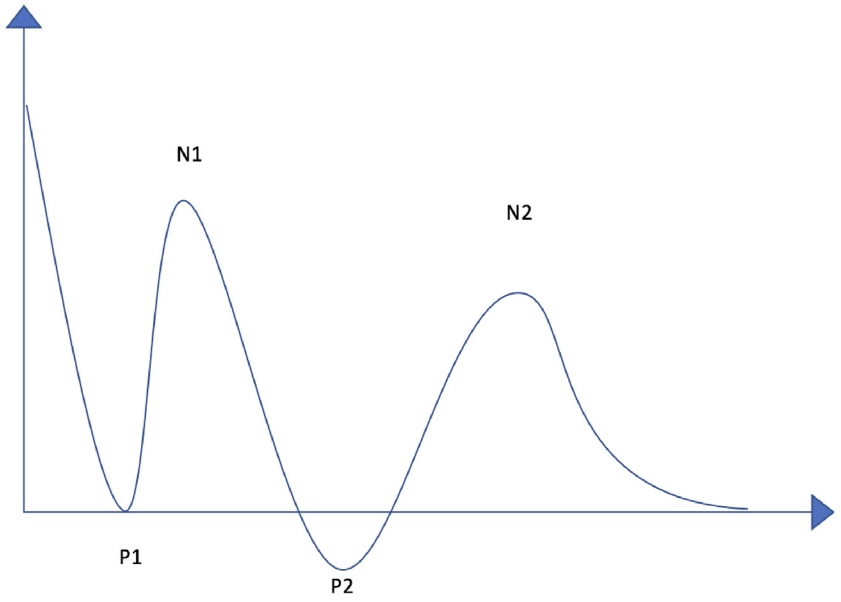

Figure 1. Corticocortical evoked potentials consist of a first negative and a late negative voltage peak, N1 and N2, respectively. The N1 peak is visually identified as a first negative deflection distinguishable from a stimulus artifact. The amplitude of N2 is measured from the preceding positive peak. P1 and P2 refer to positive voltage peaks.

Study Selection and Risk of Bias Assessment

The research strategy initially relied on title and abstract analysis. The full text of an article was retrieved for further investigation if the title and abstract met the inclusion criteria. The data collection process was conducted without the use of any automated tools. Two independent reviewers (C.A. and V.G.) screened all titles and abstracts for eligibility. Disagreement was resolved with discussion and consensus, and when discussion failed to lead to consensus, a third researcher mediated (L.B.). We used the JBI critical appraisal tool for the risk of bias assessment of included studies.[28] The JBI critical appraisal tool was developed by an international working group and approved by the JBI Scientific Committee following extensive peer review.[28] It consists of a 10-question checklist for case series or cohort studies. The reviewer can answer "yes," "no," "unclear," or "not applicable." No automatic tools were used in the screening and selection phases. Ethical approval and patient consent were not required for this study.

Study Eligibility Criteria

Inclusion criteria were the following.

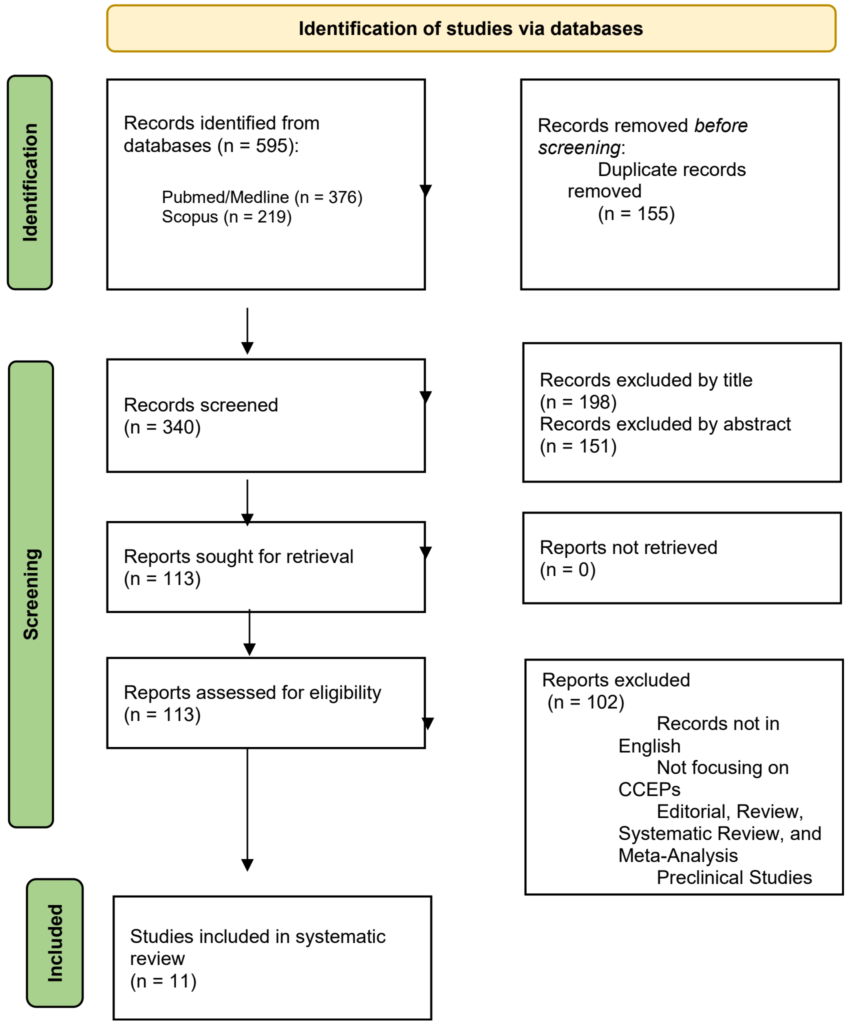

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. CCEP, corticocortical evoked potential.

- Articles focusing on the use of CCEPs in brain eloquent tumor surgery
- Articles written in English
- Clinical studies
- Studies including a main population of patients >18 years old.

Exclusion criteria were as follows.

- Articles not in English
- Reviews, systematic reviews, meta-analyses, and editorials
- Preclinical studies
- Pediatric population
- Studies evaluating intraoperative monitoring techniques other than CCEPs.

Data Extraction

After selecting relevant studies according to the above-listed criteria, the data extracted from each article were first author and publication year, country, study design, number of patients examined, patient demographics (age and sex), function monitored, lesion location and histology, preoperative neurological status, type of anesthesia, CCEP parameters, neurological outcomes, and follow-up time.

RESULTS

Data Selection and General Features of Studies

A total of 595 articles were collected. After removing 155 duplicates, 440 articles were reviewed. Of these, 198 were excluded by title, and 151 were excluded by abstract. Finally, the literature search yielded 11 eligible articles for data extraction. These studies, conducted between 2014 and 2023, spanned multiple countries, indicating a widespread interest in exploring the potential of CCEPs in brain tumor surgery. Most of the included articles (8 of 11) were case series (Tables 1 and 2).

Study Characteristic and Data Analysis

Data of 125 patients were collected. Mean age was 48 ±10.6 years, with a male predominance (males/females = 59/40; not specified for 26 patients in 1 study). The postoperative follow-up periods varied across the included studies, ranging from 2 weeks to 2 years.

The linguistic component was the function through which patients' outcomes were assessed across the preoperative, intraoperative, and postoperative phases in all included studies. Therefore, it appears to be the domain that at the present time can be monitored more precisely throughout the surgical process allowing neurosurgeons to monitor safe resection while performing brain tumor surgery.

The histology and the location of the lesions described were very heterogeneous, spanning from high-grade to low-grade tumors and benign lesions as well. These lesions were located within different areas. These findings suggest the necessity for individualized surgical approaches and the importance of tailored intraoperative monitoring techniques for each patient. Data regarding tumor histology and location, and preoperative neurological symptoms are summarized in Figures 3–5.

Interestingly, in most cases, the speech disorders that were present preoperatively or that appeared immediately after surgery recurred after about 6 months. In many cases, the disorder appeared later in a transient manner. The repetition disorder and phonemic paraphasia continued until the final follow-up in only 1 case. These findings emphasize the importance of

Table 1. Demographic Features of Included Studies

Author, Year	Country	Study Design	Number of Patients	Age (years), Mean ± SD (range)	Sex
Yamao et al., 2014[29]	Japan	Case series	6	33 ± 9 (19—44)	2 M, 4 F
Saito et al., 2014[25]	Japan	Case series	12	35 ± 12 (21—58)	10 M, 2 F
Tamura et al., 2016[30]	Japan, Austria, and USA	Case series	5	54 ± 17 (28—75)	3 M, 2 F
Yamao et al., 2017[31]	Japan	Case series	19	46 ± 16 (19—72)	10 M, 9 F
Ookawa et al., 2017[32]	Japan	Case series	7	57 ± 21 (22—82)	5 M, 2 F
Nakae et al., 2020[33]	Japan, USA, and England	Case series	12	48 ± 18 (25—79)	6 M, 6 F
Cattaneo et al., 2020[34]	Italy	Case series	17	63 ± 14 (39—79)	10 M, 7 F
Filipiak et al., 2021[26]	France	Pilot study	8	39 ± 14 (23—66)	3 M, 5 F
Saito et al., 2022[35]	Japan	Case series	7	45 ± 10 (34—63)	5 M, 2 F
Ishankulov et al., 2022[36]	Russia	Pilot study	26	Not specified	Not specified
Vega-Zelaya et al., 2023[37]	Spain	Prospective	6	52 ± 4.2 (31—62)	5 M, 1 F

M, male; F, female.

long-term monitoring and the need to assess speech outcomes beyond the immediate postoperative period.

In 4 studies, all patients underwent general anesthesia, including the prospective study Vega-Zelaya et al.[37] In 4 other studies, patients were operated on using an awake technique. Furthermore, 3 studies described a mixed cohort in which some of the patients were operated on under full sedation and some underwent awake surgery. Finally, in 1 study the anesthesia protocol was not outlined.

In 9 studies analyzing language lateralization, dominancy was found in the left hemisphere, while hemisphere dominancy was not specified in 2 studies. The preoperative investigations used for preoperative planning were also evaluated as well as the use of diagnostic imaging such as multimodal magnetic resonance imaging (MRI) with any three-dimensional reconstructions (2 studies); tractography (5 studies); spectrography (2 studies); functional MRI (6 studies); and positron emission tomography with ^{11}C-methionine, ^{11}C-choline, and ^{18}F-fluorodeoxyglucose (1 study). In 1 study, a speech therapy evaluation was conducted to evaluate the initial language deficit. Details on the recording methods used in each study are shown in Table 2.

Parameters Evaluation

The analysis of CCEP parameters, particularly the amplitude of the N1 wave, provided insights into the effective connectivity of the brain regions involved. Many studies have considered the N1 wave amplitude of CCEP as a standard marker of effective connectivity, defining it as an

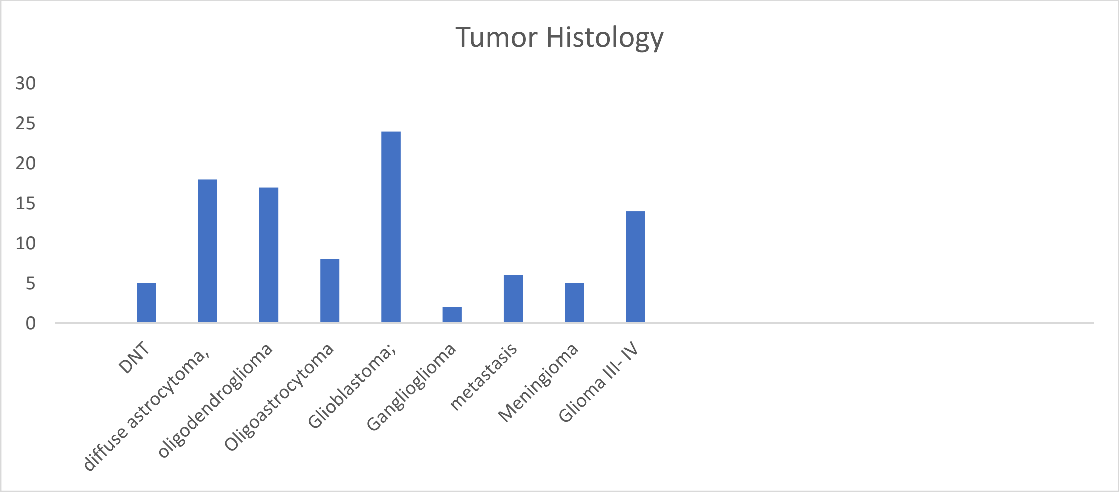

Figure 3. Vertical bar chart showing tumor histology of selected studies. DNT, dysembryoplastic neuroepithelial tumor.

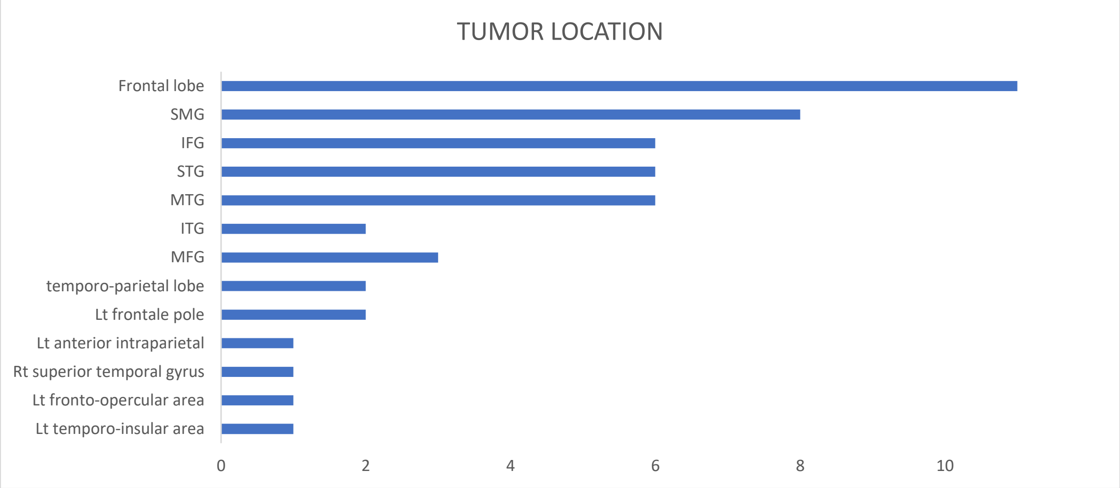

Figure 4. Horizontal bar chart on tumor location of selected studies. SMG, supramarginal gyrus; IFG, inferior temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior frontal gyrus; MFG, middle frontal gyrus; Lt, left; Rt, right.

early negative signal deviation with a peak latency of 10–30 ms. This marker of connectivity has promise as a valuable indicator of postoperative outcomes, and it has been described as a useful tool to help surgeons in optimizing resection strategies, while minimizing the risk of postoperative language deficits. The frequency of stimulation was highly heterogeneous with a mean of 46.5 ± 248.2 Hz. Of 11 studies, 4 set the stimulation frequency at 50 Hz, 4 set the stimulation frequency at 1 Hz, and 2 set the stimulation frequency from 1 to 1500 Hz. The mean intensity of stimulation was set at 11 ± 6.2 mA. In 1 study, the intensity was increased gradually from 5 mA until the effect was attained. Amplitude of stimulation data was heterogeneous (34 ± 90.6 ms), although most studies were set 0.3 ms. Another wave that has been studied for its clinical interest is the N2 wave. This is a later negative deflection that occurs approximately 200–350 ms after the stimulus has been delivered. The N2 wave is often observed while performing higher-level cognitive processes, such as tasks requiring cognitive control or response inhibition. Matsumoto et al.[22] reported a larger distribution of the N2 wave compared with the N1 wave suggesting the existence of a broader neuronal network underlying the speech function than previously described.

However, in a subsequent study by the same group, while performing CCEP

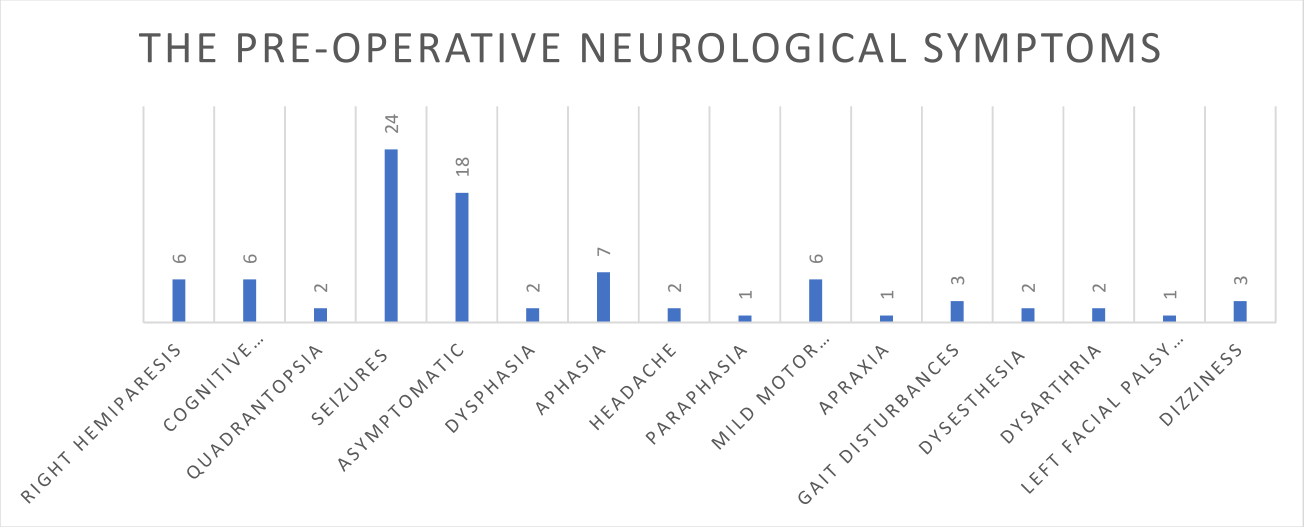

Figure 5. Vertical bar chart showing preoperative neurological symptoms.

recordings the authors decided to consider only the N1 wave, as the N2 wave did not show a clear peak that could be used for standardized recording.[23] Evaluating the findings from other international groups, it emerges that for an unequivocal interpretation of the link between N1 and N2, implementing techniques to silence the N2 wave obtains a better recording of the N1 wave. In this context a novel approach for enhancing the signal-to-noise ratio and automatically detecting event-related potentials in single trials could overcome this issue.[38] Therefore, as discussed above, from our review it appears that the most important wave to predict neurological outcome after surgery is the N1 wave. However, further studies are ongoing, and new possible interactions are under evaluation that show promising applications in brain surgery for tumor resection.

Risk of Bias Assessment

Through the JBI checklist for assessment of study risk of bias, we stratified the quality of each included article into 3 groups: low, moderate, and high quality. The bias risk assessment showed that, among the included articles, 11 respected the JBI criteria for a high-quality study (with ≥7 positive answers). However, it should be emphasized how most studies did not evaluate the presence of confounding factors and a strategy to deal with them. Furthermore, some of the included studies did not report adequate complete and consecutive inclusion of the participants, thus creating a possible bias in the patient selection process. Finally, another aspect to consider in the possible genesis of bias lies in the fact that the JBI checklist was compiled by one of the authors and thus itself subject to possible interpretive bias. However, because each article summarized key lessons regarding the background of diseases, clinical practice, and outcomes, we decided to include all screened studies in our review.

Modality of CCEP Recording

All the studies shown in **Table 2** used CCEPs to monitor language function except for the study by Cattaneo et al.,[34] which focused on motor function. Cattaneo et al.[34] evaluated motor evoked potentials using transcranial electrical stimulation. Motor evoked potential monitoring, from the dura mater opening onward, was performed using a strip electrode (6-contact strip electrode with a diameter of 2.5 mm, distance of 10 mm; contact strip 0.7 mm thin, 10 mm wide). Direct cortical electrical stimulation was applied to the precentral gyrus and to the parietal cortex using a 6- or 8-contact strip electrode, demonstrating by dual cortical stimulation the existence of a distributed system of connections from the posterior parietal cortex to the ipsilateral primary motor cortex. In the studies by Saito et al.,[25,35] Tamura et al.,[30] Yamao et al.,[31] and Ookawa et al.,[32] 2 adjacent electrodes were used in bipolar mode with a square wave of constant current with alternating polarity (pulse width 0.3 ms, frequency 1 Hz). The electrodes had a recording diameter of 3 mm and were spaced 1 cm apart. In the study by Filipiak et al.,[26] the electrodes, with a diameter of 4 mm, were positioned with a center-to-center distance of 10 mm between the electrodes, and depending on the space, 2 or 3 recording strips were placed. Their configuration comprised 1 or 2 short strips with 4 electrodes each and/or a longer strip with 6 electrodes, for a total of 8, 10, or 14 recording electrodes. In the studies by Tamura et al.[30] and Yamao et al.,[31] the maximum intensity was 15 mA. The bandpass filter for data acquisition was between 1 and 1000 Hz, with a sampling rate of 2000 Hz per channel. Responses were averaged using stimulus onset as a trigger, with prestimulus and poststimulus periods of 100 ms and 800 ms, respectively. In each session, at least 5 points in the temporal region were stimulated, and at least 2 trials of 30 responses were recorded to test the reproducibility of CCEPs. In the studies by Vega-Zelaya et al.[37] and Saito et al.,[25,35] the bandpass filter for data acquisition was set to 5–1500 Hz with a sampling frequency of 5000 Hz for each channel. In both studies by Saito et al.,[25,35] the stimulus intensity increased steadily from 2 mA using gradual 1-mA increments until a response was obtained or abnormalities were detected on electrocorticography. Vega-Zelaya et al.[37] also used electrocorticography to monitor brain responses during electrical stimulation to identify the presence of epileptiform patterns (postdischarge). Electrical stimulation was performed with direct cortical stimulation using a grid of 4 × 5 electrodes 1.2 mm in diameter and 1 cm center to center using 3 single monophasic pulses of 1-ms duration and separated by 1 second. Finally, in the study by Ookawa et al.,[32] the sampling frequency was set at 2000 Hz. In each session, the average of at least 2 trials of 50 responses was calculated separately to confirm the reproducibility of the responses.

DISCUSSION

Language Brain Network: Wiring Across Cortical and Subcortical Areas

Until about the end of the 20th century, some specific functions, including language, were thought to be localized and carried out by precise cortical brain areas.[39,40] However, with the introduction of dynamic neural network theory and the advent of connectomics, it became increasingly apparent that the localizationist theory was partial and insufficient to explain all the nuances of language.[41,42] Since then, many studies have been conducted to assess the brain areas and white matter bundles implicated in the genesis and comprehension of language, emphasizing how this function is performed by multiple actors, each implicated in certain aspects of language.[43] This new vision led to the development of the dual stream model of the language. As this topic is beyond the scope of our review, we refer readers to other texts for a better definition of it.[43-47] Briefly, the language brain network consists of complex interconnected areas that together support different aspects of language processing and production. This network understands and generates spoken and written language as well as higher-level language processes such as semantic comprehension and sentence analysis. Several key components of the language brain network play an important role, such as Broca and Wernicke areas, arcuate fasciculus, inferior fronto-occipital fasciculus, frontotemporoparietal network, basal ganglia, cerebellum, and many others.[48-52] These components, among others, are distributed networks

Table 2. Clinical and Monitoring Corticocortical Evoked Potentials Features of Included Studies

Author, Year	Tumor Location	Function Assessed	Language Dominancy	Histology	Preoperative Neurological Status	Preoperative Imaging	Type of Anesthesia	Frequency, Intensity, and Amplitude	CCEP Registration Modes	Clinical and Neurophysiological Outcomes, Range of Functional Damage	Follow-Up
Yamao et al., 2014[29]	INS, STG (1); Ins, STG MTG (1); AG, SMG, PoCG (2); IFG (1); SMG (1) All left	Language	All left dominancy	Anaplastic astrocytoma (1); astrocytoma grade II—III (1); DNT (2); diffuse astrocytoma (1); oligodendroglioma (1)	Right hemiparesis (1); cognitive impairment (1); quadrantopsia (1); seizures (4); asymptomatic (1)	fMRI and tractography	General anesthesia	50 Hz, 12 mA, 0.3 ms to 5 seconds	Conventional cortical electrical stimulation at 50 Hz (square-wave pulse of alternating polarity with a pulse width of 0.3 ms, 3—5 seconds, 5—12 mA)	Postoperative speech impairment occurred in 2 cases, for which they followed up at 3 and 6 months. N1 amplitude increased by average of 116 μV (96—139), increased by 60% at the site of maximum CCEP response. Onset latency changed by average of 1.0 ms and peak latency changed by average of 0.7 ms In 4 cases there was no reduction of N1 amplitude; in 10 cases it was reduced by 12% and 32% after tumor resection	3 months
Saito et al., 2014[25]	Middle frontal (3); insula (3); inferior frontal (2); inferior parietal (4) All left	Language	All left dominancy	Anaplastic oligodendroglioma (3); oligodendroglioma (4); anaplastic oligoastrocytoma (3); glioblastoma multiforme (1); oligoastrocytoma (1)	Asymptomatic (10); mild dysphasia (2)	MRI precontrast and postcontrast and PET with ^{11}C-methionine, ^{11}C-choline, and ^{18}F-FDG	Awake	5—1500 Hz, 3—12 mA, 48—98 ms	CCEPs were used and continuous digital ECoG activity was recorded to detect seizures	In the immediate postoperative period, 10 of 13 patients had speech impairment, all of whom recovered within 6 months (on average) after surgery During removal of the neoplasm, CCEP response was unchanged in 5 cases, decreased (up to 20%—40%) in 4, and disappeared in 3 A decrease in CCEP response was considered to occur when its amplitude reduced approximately $\geq$20%	15 months
Tamura et al., 2016[30]	Left frontal lobe (3); left temporal lobe (1); bilateral frontal lobe (1)	Language	All left dominancy	Glioblastoma (2); anaplastic oligoastrocytoma (1); diffuse astrocytoma (1); ganglioglioma (1)	Motor aphasia (1); mild right hemiparesis (2); convulsive seizure (1); asymptomatic (1)	In 4 cases fMRI was used. In 1 case this was not possible due to severe motor aphasia	Awake	50 Hz, 3—15 mA, 0.3 ms	CCEPs and ECoG	In 1 case aphasia had not worsened; in 2 cases transient naming difficulty occurred for 2 weeks. Postoperative courses of 2 other patients were uneventful	2 weeks

Yamao et al., 2017[31]	INS, STG (1); INS, MTG, STG (1); AG, PoCG, SMG (2); IFG (1); SMG (1); INS, ITG, MTG, STG (1); IFG, MFG, SFG (2); IFG, MFG (2); IFG, MFG, SFG(1); INS, ITG, MTG, STG (1); ITG, MTG (2); AG, SMG, SPL (1); AG, SMG (3)	Language	All left dominancy	Anaplastic astrocytoma (2); astrocytoma WHO II—III (1); DNT (2); diffuse astrocytoma (2); oligodendroglioma (2); GBM (6); oligoastrocytoma (1); metastasis (2)	Right hemiparesis (3); cognitive deterioration (5); quadrantopsia (1); convulsions (8); asymptomatic (1); headache (1); aphasia (4)	fMRI and tractography	15 awake and 4 general anesthesia	50 Hz, 7—15 mA, 0.3 ms	Using cortical electrical stimulation and CCEPs	No patients with CCEP N1 amplitude increase had further language dysfunction after surgery. A decrease in N1 amplitude by <50% led to transient language impairment except for 1 case. One case had a 32% decrease and showed transient phonemic paraphasia probably due to partial resection of SMG. Another case with a 32% decrease had a decline in verbal fluency, but repetition was preserved. Her transient postoperative symptoms were most likely due to partial resection of IFG or subcortical resection just beneath the cortex. In 1 case with a 51.5% decrease, disturbance of repetition and phonemic paraphasia continued until final follow-up. CCEP and SCEP findings provided evidence that the surgical procedure invaded the AF In 15 patients N1 amplitude increased by average of 24.1% (2.2%—68.6%); in 5 patients N1 amplitude decreased by average of 27.5% (9.8%—51.5%). One patient had a decrease of 32% and showed phonemic paraphasia soon after surgery; she made a full recovery 3 months after the surgery. In 1 case N1 amplitude decreased from 233 μV to 158 μV (−32%) after tumor resection. In 1 case N1 amplitude decreased from 446 μV to 403 μV (−9.8%) CCEP N1 amplitude decline of 50% could be a limit value to prevent permanent speech dysfunction due to AF impairment	6 months

CCEP, corticocortical evoked potential; INS, insula; STG, superior temporal gyrus; MTG, middle temporal gyrus; AG, angular gyrus; SMG, supramarginal gyrus; PoCG, postcentral gyrus; IFG, inferior frontal gyrus; DNT, dysembryoplastic neuroepithelial tumor; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; FDG, fluorodeoxyglucose; ECoG, electrocorticography; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule; WHO, World Health Organization; GBM, glioblastoma multiforme; SCEP, subcortico-cortical evoked potentials; AF, arcuate fasciculus; pO/pT, pars Opercularis/pars Triangularis; 3D, three-dimensional; TIVA, total intravenous anesthesia; EEG, electroencephalography; IOM, intraoperative monitoring; FLA, frontal language area.

*BrainSuite software (https://brainsuite.org/).

Continues

Table 2. Continued

Author, Year	Tumor Location	Function Assessed	Language Dominancy	Histology	Preoperative Neurological Status	Preoperative Imaging	Type of Anesthesia	Frequency, Intensity, and Amplitude	CCEP Registration Modes	Clinical and Neurophysiological Outcomes, Range of Functional Damage	Follow-Up
Ookawa et al., 2017[32]	Left SFG (2); left IFG (2); left anterior frontal (1); left frontal pole (1); left sphenoid ridge (1)	Language	All left dominancy	Oligodendroglioma (4); glioblastoma multiforme (1); metastatic brain tumor (1); meningioma (1)	Mild paraphasia (1); mild motor weakness (1); asymptomatic (5)	fMRI and tractography	6 awake and 1 general anesthesia	1 Hz, 10 mA, 0.3 ms	Subdural strip or grid electrodes were placed on lateral and medial frontal cortex	During early postoperative period, transient impairment of speech was noted in 3 patients, and mild verbal apraxia was noted in 1 patient. Among these patients, 1 patient showed an impairment of object naming during awake surgery, whereas no language deficit was detected in 2 patients; language symptoms were unable to be evaluated owing to insufficient arousal state in 1 patient during the surgeries. All patients recovered language function within 8 weeks Amplitude of N1 was 20.3—174.9 mV (median 49.0 mV) in SFG from pO/pT stimulation, whereas it was 28.8—312.0 mV (median 101.9 mV) in pO/pT from SFG stimulation. Amplitudes of N1 tend to be larger in pO/pT from SFG stimulation than in SFG from pO/pT stimulation; however, the difference was not significant	8 weeks
Nakae et al., 2020[33]	Not specified	Language	All left dominancy	Diffuse astrocytoma (2); glioblastoma (5); anaplastic astrocytoma (2); dysembryoplastic neuroepithelial tumor (1); anaplastic oligoastrocytoma (2)	Motor aphasia (1)	fMRI	General anesthesia	1 Hz, 15 mA, 0.3 ms	32 channels; square-wave electrical pulses of alternating polarity with a pulse width of 0.3 ms were delivered at 1 Hz	—	—

Cattaneo et al., 2020[34]	Right postcentral (1); right frontal (1); right postrolandic (1); left anterior intraparietal (1); left prerolandic gyrus (1); left frontal parasagittal (2); right parietotemporal lobe (3); right prerolandic gyrus (1); right rolandic gyrus (1); left SFG (1); right STG (1); left temporal lobe (1); left temporopolar (2)	Motor	All left dominancy	Glioma IV (9); meningioma I (3); meningioma II (1); metastatic melanoma (1); metastatic lung adenocarcinoma (2); ganglioglioma I (1)	Apraxia, gait disturbances, dysesthesia, weakness on right side (1); gait ataxia, dysarthria (1); left facial palsy of central type (1); dysesthesia and weakness of right arm and face, mild language deficits (1); leg weakness (1); headache (1); right leg weakness (1); generalized seizures (2); mood change (1); dizziness, gait ataxia (1); focal seizures, dizziness, left homonymous hemianopia (1); dizziness (1); focal seizures (1); focal seizures, mild language deficits (1); right-side weakness, mild language deficits (1)	MRI with 3D reconstructions (with BrainSuite*)	General anesthesia (TIVA)	250 Hz, 15—35 mA, 0.5 ms	Simultaneous acquisition of EEG, ECoG, EMG, and IOM	—	—
Filipiak et al., 2021[26]	Left fronto-opercular; left frontal; right frontotemporo-insular; left frontal; left temporal; left temporo-insular; left temporal; left supplementary motor area	—	Dominant hemisphere not specified	Glioblastoma *IDH* wild type (grade IV) (3); astrocytoma *IDH* mutant (grade II) (2); oligodendroglioma *IDH* mutant (grade II) (2); astrocytoma IDH wildtype (III)	Not specified	MRI and tractography	Awake	2—5 Hz, 2—5 mA, 1 ms	Strips were used in alignment with cortical endings of AF and superior longitudinal fasciculus III. A 32-channel signal amplifier and a sampling frequency of 2 kHz were used	Positive correlation between streamline lengths and counts with delays and amplitudes of N1 peaks in the vicinity of stimulation sites	—
Saito, et al., 2022[35]	MFG; precentral gyrus; IFG; FLA	Language	Dominant hemisphere not specified	Grade III gliomas in 5 of 7 patients; 2 patients had a glioblastoma, *IDH* wild type and astrocytoma, *IDH* mutant, grade IV	Mild dysarthria (1); partial epilepsy (1)	MRI, fMRI and speech therapy evaluation	Awake	50 Hz, 6 mA, 0.2 ms, 1—2 seconds	6-wire strip electrodes, placed just above FLA and on temporal lobe, parallel to sylvian fissure	Speech disorders occurred in all 6 patients post-operatively (even in the 4 patients who had none pre-operatively). They all recovered their speech function between 15 days and 24 months. CCEP decreased to 10% in 1 patient, who recovered language function after 24 months. CCEP decreased 80% in 1 case; in 5 cases, CCEPs did not change. These 5 patients soon recovered language function within 2 weeks to 1 month Stop the resection of the tumor with a 50% or more reduction of CCEP as a guide.	24 months

CCEP, corticocortical evoked potential; INS, insula; STG, superior temporal gyrus; MTG, middle temporal gyrus; AG, angular gyrus; SMG, supramarginal gyrus; PoCG, postcentral gyrus; IFG, inferior frontal gyrus; DNT, dysembryoplastic neuroepithelial tumor; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; FDG, fluorodeoxyglucose; ECoG, electrocorticography; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule; WHO, World Health Organization; GBM, glioblastoma multiforme; SCEP, subcortico-cortical evoked potentials; AF, arcuate fasciculus; pO/pT, pars Opercularis/pars Triangularis; 3D, three-dimensional; TIVA, total intravenous anesthesia; EEG, electroencephalography; IOM, intraoperative monitoring; FLA, frontal language area.

*BrainSuite software (https://brainsuite.org/).

Continues

Table 2. Continued

Author, Year	Tumor Location	Function Assessed	Language Dominancy	Histology	Preoperative Neurological Status	Preoperative Imaging	Type of Anesthesia	Frequency, Intensity, and Amplitude	CCEP Registration Modes	Clinical and Neurophysiological Outcomes, Range of Functional Damage	Follow-Up
Ishankulov et al., 2022[36]	Eloquent areas (not otherwise specified)	Language	Dominant hemisphere not specified	Brain gliomas in eloquent areas	Not specified	Not specified	Not specified	1 Hz, 300 ms	32-channel CCEPs and a pair of subdural electrode strips. One electrode was placed in Broca area; the second electrode was located on the surface of the upper temporal gyrus in its posterior parts and supramarginal gyrus. Duration of signal recording after stimulation was 300 ms	Demonstrated possibility of predicting speech dysfunctions based on CCEP data obtained before main stage of glial tumor resection	—
Vega-Zelaya et al., 2023[37]	Frontal (3); frontoparietal (2); temporoparietal	Language	Left dominant hemisphere	Astrocytoma IV, glioblastoma IV (3); oligodendroglioma II, glioblastoma II	Seizure (7); aphasia	MRI, spectroscopy and tractography	General anesthesia	10—1500 Hz, from 5 mA using stepwise increments of 5 mA until effect was attained, 1 ms	CCEPs and ECoG	One years after surgery; 5 of 7 patients were asymptomatic; in 1 patient seizures persisted, and in 1 patient the same mild dysarthria as before surgery persisted. None of the patients had aggravated symptoms due to iatrogenic damage At 1-year follow-up, 5 patients were asymptomatic; 1 still had mild dysarthria and 1 still had seizures CCEP alert criterion was set at a reduction in amplitude of >20%	12 months

CCEP, corticocortical evoked potential; INS, insula; STG, superior temporal gyrus; MTG, middle temporal gyrus; AG, angular gyrus; SMG, supramarginal gyrus; PoCG, postcentral gyrus; IFG, inferior frontal gyrus; DNT, dysembryoplastic neuroepithelial tumor; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; FDG, fluorodeoxyglucose; ECoG, electrocorticography; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule; WHO, World Health Organization; GBM, glioblastoma multiforme; SCEP, subcortico-cortical evoked potentials; AF, arcuate fasciculus; pO/pT, pars Opercularis/pars Triangularis; 3D, three-dimensional; TIVA, total intravenous anesthesia; EEG, electroencephalography; IOM, intraoperative monitoring; FLA, frontal language area.

*BrainSuite software (https://brainsuite.org/).

that work together to support different aspects of language processing and production. With the increasingly well-established combination of neurosurgery, neuroscience, and neuropsychology, there appears to be a clear need to be able to assess all the various nuances of language more and more accurately, to trace the structural and functional bases to safeguard them, where possible, during tumor surgery in eloquent areas.[49,53,54]

Usefulness of CCEPs in Monitoring Language Function

CCEPs have emerged as a valuable tool in intraoperative monitoring of eloquent brain tumor surgery. In this review, we have shown that in the discussion of surgical treatment of brain lesions, the concept of connections at different levels of complexity going from macroscale to microscale systems that operate as an extremely highly interconnected networks has become central.[55] This understanding has led to the development of the concept of the human connectome, which describes the comprehensive set of neuronal connections within the central nervous system.[10,56-59] When awake surgery was introduced, it demonstrated a good precision to predict postoperative outcomes regarding motor function, especially when surgery was performed in areas such as the precentral gyrus. Furthermore, when awake surgery is combined with other techniques such as navigated transcranial magnetic stimulation,[60] intraoperative voluntary movement estimation, and transcortical motor evoked potentials, it has proven over the years to be valuable even in preserving motor neurological function.[61,62] However, not all patients are suitable candidates for awake neurosurgery, highlighting the need for alternative approaches. In this scenario, CCEPs have been successful and gained attention for their ability to monitor neurological function, especially language function, even in sedated patients. In fact, patients can be either awake or asleep during CCEP monitoring, depending on the specific circumstances and surgical requirements. Continuous monitoring of CCEPs helps to assess the functional integrity of the language pathways during the lesion removal process, minimizing the risk of damage to critical language-related areas. Deflections of the N1 wave have been described as a reliable criterion to evaluate speech function. Yamao et al.[31] reported that to avoid permanent speech function deficit, the N1 amplitude should not decrease by >50%. Filipiak et al.[26] demonstrated the relationship between the structural connectivity measures obtained from diffusion MRI and the effective connectivity measures based on the propagation of CCEPs in patients with brain tumors, finding a positive correlation between streamline lengths and the delay time and amplitudes of N1 peaks. These authors pointed out that brain tissue microstructure features were strictly related to the propagation of CCEPs, particularly the N1 delays and N1 amplitudes, aiming to link macrostructure and microstructure measures of brain white matter with effective connectivity measures based on CCEP monitoring.[26] Finally, in a recent study by Vega-Zelaya et al.,[37] they demonstrated how CCEPs represent a reliable neurophysiological technique to map and monitor regions associated with language function in a small group of anesthetized patients. The high correlation between alarm events and postsurgical outcomes suggested high sensitivity and specificity and that CCEPs can be used routinely in patients under general anesthesia.

Regarding the complexity of the language network, particularly interesting are the results obtained by Nakae et al.[33] First, they showed how the anterior inferior frontal gyrus is connected to the anterior medium and inferior temporal gyrus. From their results, it also emerges that a parcellation based on CCEP connectivity could be clinically crucial for an eloquent area such as the inferior frontal gyrus, as it allows functional mapping without requiring the conscious cooperation of the patient. However, they also point out that at present the poor spatial resolution of CCEP-based parcellation is a limitation compared with classical MRI-based parcellation. Similarly, Ookawa et al.[32] also highlighted the role of the frontal aslant tract, especially concerning speech initiation and spontaneity. In their study, through CCEP monitoring, they demonstrated a corticocortical network connecting Broca areas and superior frontal gyrus in a reciprocal manner.

Limitations and Future Perspectives in the Use of CCEPs

Although the results so far are encouraging, there are limitations and challenges associated with the use of CCEPs in clinical practice as well as exciting future possibilities. As an important limitation, it is necessary to mention the need for specialized expertise in neurophysiology and neurosurgery and the variability of signal interpretation. Not all surgical centers have access to experts who can accurately analyze and interpret the CCEP signals. Therefore, the availability of CCEP mapping may be limited to certain specialized centers, which restricts its widespread use. On the other hand, standardized protocols for CCEP mapping still need to be established. Developing standardized protocols will facilitate the adoption of CCEPs in routine clinical practice. Lastly, CCEP mapping is an invasive procedure and therefore by definition carries potential complications such as infection or hemorrhage. Minimizing the invasiveness and optimizing the safety of electrode implantation is an area of ongoing research. Despite these limitations, there are exciting future possibilities for CCEPs in brain surgery. As technology continues to advance, the quality and resolution of CCEP recordings are expected to improve. Higher-resolution electrode arrays, improved signal processing techniques, and advanced imaging modalities will enhance the accuracy and reliability of CCEP mapping.[62] Another interesting future development will be to combine CCEPs with functional MRI or diffusion tensor imaging to provide more comprehensive understanding of the brain's functional and structural connectivity.[30,63,64]

Moreover, further developments in real-time signal processing and analysis will enable neurosurgeons to monitor CCEPs during surgery and receive immediate feedback. This real-time information can guide surgical decision making, allowing surgeons to modify their approach dynamically and optimize the preservation of critical brain regions. Finally, probably the most interesting development is that while CCEPs have shown promise in tumor resection in eloquent areas, their potential extends beyond this specific application. CCEP monitoring can be explored in other neurosurgical procedures, such as epilepsy surgery or deep brain stimulation, where preserving functional connectivity is crucial.

CCEPs offer valuable insights into the functional connectivity of the brain during surgery. Despite limitations related to expertise, standardization, patient selection, and invasiveness, ongoing research and technological advancements have the potential to overcome these challenges. The future of CCEPs in brain surgery looks promising, with the possibility of improved patient outcomes, enhanced surgical precision, and expanded applications in various neurosurgical procedures. However, despite the promising results reported in the selected studies, it is essential to acknowledge the limitations of this systematic review. Many of the included articles were case series, which inherently carry a lower level of evidence compared with controlled clinical studies. Moreover, the number of studies available for inclusion was relatively small, indicating a scarcity of research in this specific area.

CONCLUSIONS

The findings of this systematic review highlight the potential of CCEPs as a valuable tool in brain tumor surgery, particularly in preserving speech function. The evaluation of linguistic components and the assessment of effective connectivity provide crucial insights for surgical planning and decision making. However, further well-designed studies, including larger cohorts and controlled clinical trials, are warranted to strengthen the evidence base and establish the efficacy of CCEPs in optimizing language outcomes in patients with brain tumors.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Lapo Bonosi: Conceptualization, Validation, Writing – review & editing, Supervision. **Angelo Torrente:** Conceptualization, Writing – review & editing. **Filippo Brighina:** Project administration. **Cateno Concetto Tito Petralia:** Investigation, Writing – original draft. **Pietro Merlino:** Writing – original draft.

Chiara Avallone: Methodology, Formal analysis, Data curation, Writing — original draft, Visualization. **Vincenzo Gulino:** Methodology, Formal analysis, Writing — original draft, Visualization. **Roberta Costanzo:** Visualization. **Lara Brunasso:** Visualization. **Domenico Gerardo Iacopino:** Project administration. **Rosario Maugeri:** Supervision, Project administration.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 29 August 2023; accepted 5 October 2023

Citation: World Neurosurg. (2024) 181:38-51.
https://doi.org/10.1016/j.wneu.2023.10.028

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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