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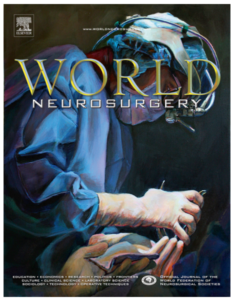

"Cortico-Cortical Evoked Potentials in Eloquent Brain Tumor Surgery. A Systematic Review"

Lapo Bonosi, (Resident), Angelo Torrente, (M.D.), Filippo Brighina, (Ph.D.), Cateno Concetto Tito Petralia, (Resident), Pietro Merlino, (Resident), Chiara Avallone, (Resident), Vincenzo Gulino, (Resident), Roberta Costanzo, (Resident), Lara Brunasso, (Resident), Domenico Gerardo Iacopino, (Resident), Rosario Maugeri, (Resident)

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Title page

Title: "Cortico-Cortical Evoked Potentials in Eloquent Brain Tumor Surgery. A Systematic Review"

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Keywords: Brain surgery, CCEPs, Cortico-cortical evoked potentials, Intraoperative monitoring, Language Network, Oncofunctional balance.

Short Title: "Utility of CCEPs in Brain Tumor."

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"Cortico-cortical Evoked Potentials in eloquent brain tumor surgery. A Systematic Review"

Short Title: "Usefulness of cortico-cortical evoked potentials in monitoring language function during eloquent brain tumor surgery: a valuable tool in the neurosurgeon's armamentarium"

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Abstract: 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. Cortico-cortico 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 aims 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 a total of 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.

Keywords: Cortico-cortical evoked potentials, CCEPs, Oncofunctional balance, Language Network, Intraoperative monitoring, Brain surgery

1. Introduction

Since the early 90's, 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 brain "eloquent" areas, first due to the proximity of functional areas that increases the risk of permanent postoperative neurological disturbances. In this context, patient's quality of life (QoL) must be considered in the surgeon operative decision, becoming paramount in the choice of the surgical strategy [3,4]. This represents a hard challenge for the neurosurgeon: to resect as much tumor as possible, leaving the patient not impaired and possibly independent on others, finding a compromise between the tumor's surgical excision and the preservation not only of the motor functions, but remarkably of the neurocognitive tasks. Hence, a new term was born, a term which describes the core of this ideal: "Maximal Safe Resection" [5,6].

Duffau and others have 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 neurophysiologic 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, has allowed to create the basis of what is called the human connectome, which describes the comprehensive set of neuronal connections of a species' central nervous system (CNS) [10,11]. But if a macroscale exists, the presence of a *microscale*, as the gene expression profiles and cytoarchitecture of neurons is implied, and the cross-link between these two levels of the connectome hierarchy is granted by the *mesoscale* of cortical circuits, a range of different scales that together connect the two 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 (AS) associated with other intraoperative neuro-monitoring techniques is the gold standard approach in eloquent brain tumors, but not all patients are valid candidates [15–19]. Cortico-cortical evoked potentials (CCEPs) are a relatively new means for intraoperative monitoring of neurological pathways. CCEPs involve 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 (SPES) using probes or subdural electrodes. The parameters for SPES across the studies evaluated involve bipolar mounting, square-wave electrical pulses with a pulse width of 0.3 to 300 ms, a frequency from 1-1500 Hz, and an amplitude ranging from 1 to 35 mA. The stimulation is performed until clinical symptoms or afterdischarges are observed.

The mapping is typically performed using two subdural electrodes stimulating, for instance, Broca's area and recording the evoked responses from another area, such as Wernicke's area known to be connected by the arcuate fasciculus. In this context, CCEPs 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 three fundamental aspects: the surgical setting,

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the surgical procedural damage to be avoided to reduce the deficit rate, and his own experience in using them. CCEPs typically consist of four consecutive voltage peaks called P1, N1, P2 and N2, where N are negative peaks and P are positive peaks 1. 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 (Fig. 1) [26].

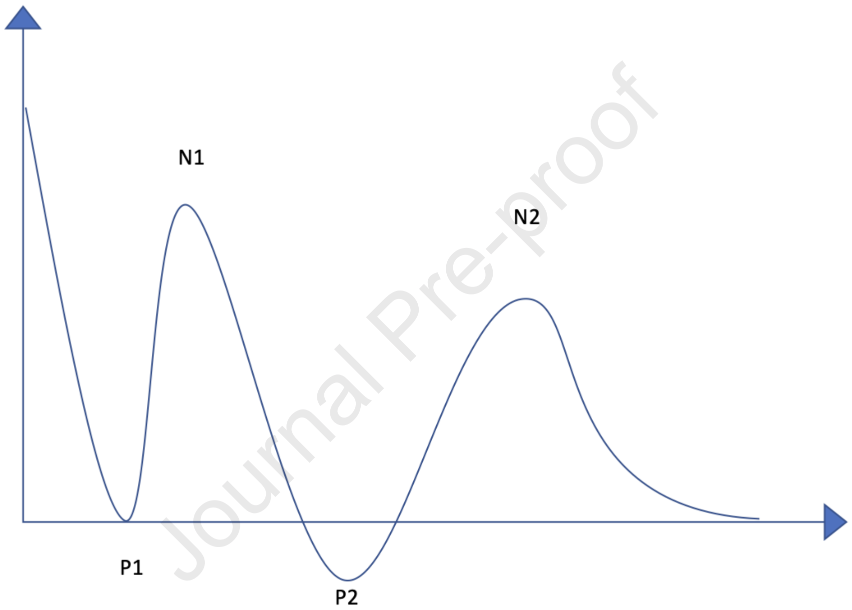

Figure 1: CCEPs consist of a first (N1) and a late negative potential (N2). The N1 peak is visually identified as a first negative deflection distinguishable from a stimulus artefact. The amplitude of N2 is measured from the preceding positive peak.

Our review aims to analyze how CCEPs 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 the speech function pre-, intra, and post-operatively.

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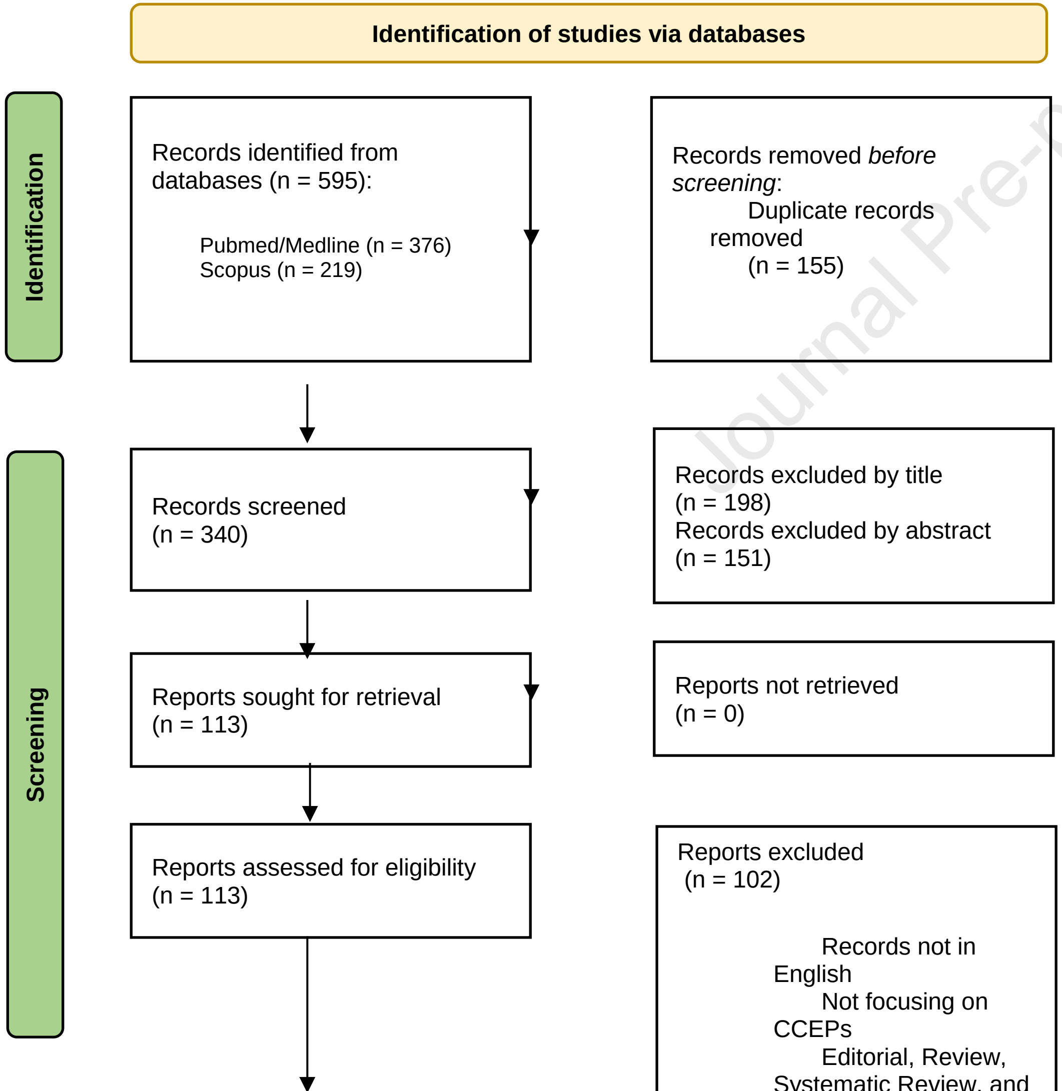
2. Materials&Methods

2.1. Search of the Literature Study selection

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



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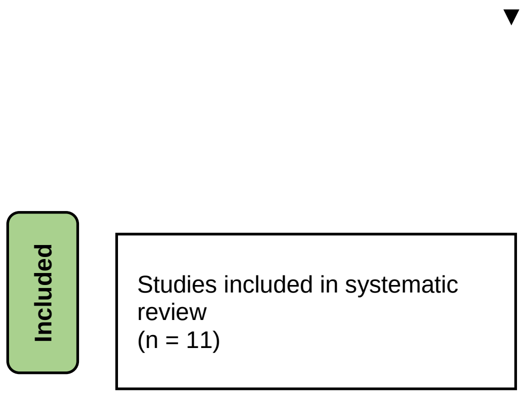

Figure 2.: PRISMA flow diagrams

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We examined for all studies published up to the 26th of March 2023, without backward limits. MeSH terms used were “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 papers were eliminated using Microsoft Excel 16.37 (Redmond, WA, USA).

2.2. Study selection and Risk of Bias assessment

The research strategy initially relied on title and abstract analysis. Article’s full text was retrieved for further investigation if title and abstract met the inclusion criteria. The data collection process was conducted without using 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]. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. 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.

2.3. Eligibility Criteria

Inclusion criteria were the following:

- Articles focusing on the use of CCEPs in brain eloquent tumor surgery.
- Only article in English language.
- Only clinical study;
- Studies including a main population of patients older than 18 years.

Exclusion criteria were as follows:

- Articles not in English language.
- Review, Systematic Reviews, Meta-Analysis, Editorial.
- Preclinical studies.
- Pediatric population.
- Studies evaluating other intraoperative monitoring techniques other than CCEPs.

2.4. Data Extraction

According to the criteria above, after selecting the relevant studies, the data extracted from each paper were: first author, country, publication's year, study design, number of patients examined, patient demographics (age and gender), function monitored, lesion location and histology, preoperative neurological status, type of anesthesia, CCEPs parameters, neurological outcomes, and follow-up time.

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3. Results

3.1. Data selection and studies general features

A total of 595 articles were collected. After removing the duplicates (155), 440 articles were reviewed. Of these, 198 were excluded by title and 151 were excluded by abstract. The literature search yielded a total of 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 out of 11) were case series (Table 1 and 2).

Authors	Country	Year of Publication	Study Design	N° of patient	Age	Gender
Yamao Y et al. [29]	Japan	2014	Case series	6	33±9 y (range 19-44)	2M; 4F
Saito T et al. [25]	Japan	2014	Case series	12	35±12 y (range 21- 58)	10M; 2F
Tamura Y et al. [30]	Japan, Austria and USA	2016	Case series	5	54±17 y (range 28-75)	3M;2F
Yamao Y et al. [31]	Japan	2017	Case series	19	46±16 y (range 19-72)	10M;9F
Ookawa S et al. [32]	Japan	2017	Case series	7	57±21 y (range 22-82)	5M;2F
Nakae T et al. [33]	Japan, USA, England;	2020	Case series	12	48±18 y (range 25-79)	6M; 6F
Cattaneo L et al. [34]	Italy	2020	Case series	17	63±14 y (range 39-79)	10M;7F
Filipiak P et al. [26]	France	2021	Pilot study	8	39±14 y (range 23-66)	3M; 5F
Saito T et al. [35]	Japan	2022	Case series	7	45 ± 10 y (range 34-63)	5M; 2F;

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Ishankulov TA et al. [36]	Russia	2022	Pilot study	26	not specified	not specified
Vega-Zelaya L et al. [37]	Spain	2023	Prospective	6	52 ± 4.2 y (range 31-62)	5M; 1F;

Table 1.: demographics features of studies included.

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Authors	Tumor Location	Function Assessed	Language dominancy	Histology	Pre-op Neurological Status	Pre-Operative Imaging	Type of Anesthesia	Frequency, Intensity and Amplitude	CCEPs registration modes	Clinical and Neurophysiological Outcomes- range of functional damage	FU
Yamao Y et al. [29]	(1) Ins, STG; (1) Ins, STG MTG, (2) AG, SMG, PoCG (1) IFG. (1) SMG All Left	Language;	All left dominancy	(1) Anaplastic astrocytoma, (1) astrocytoma grade II-III, (2) DNT, (1) diffuse astrocytoma, (1)oligodendroglioma.	(1) Right hemiparesis, (1) cognitive impairment, (1) quadrantopsia, (4) seizures and (1) asymptomatic.	fMRI and tractography	General anesthesia	50 Hz, 12 mA, 0.3ms-5s	Conventional cortical Elecrical Stimulation at 50 Hz (square wave pulse of alternating polarity with a pulse width of 0.3 ms, 3-5 s, 5 - 12mA).	Post-operative speech impairment occurred in two cases, for which they followed up at 3 and 6 months. - The N1 amplitude increased by an average of 116 µV (from 96 to 139), increased by 60% at the site of maximum CCEP response. Onset latency changed by an average of 1.0 ms and peak latency changed by an average of 0.7 ms. - in 4 cases there was no reduction of N1 amplitude, only in 10 cases was it reduced by 12% and 32% after	3 m

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										tumor resection.	
Saito T et al. [25]	(3) middle frontal (3) insula (2) inferior frontal (4) inferior parietal. All left.	Language;		(3) Anaplastic Oligodendroglioma (4) Oligodendroglioma; (3) Aanaplastic oligoastrocytoma; (1) Glioblastoma multiforme (1)Oligoastrocytoma	(10) asymptomatic and (2) mild dysphasia	MRI pre- and postcontrast and PET scanning with 11C-methionin	Awake	5-1500 Hz, 3-12mA, 48-98ms	CCEP 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 which recovered within 6 months (on average) after surgery. - During removal of the neoplasm	15 m

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			All left dominancy			e, 11C-choline, and 18F-FDG.				the CCEP response was unchanged in 5 cases, decreased (up to 20%–40%) in 4, and disappeared in 3. - A decrease in the CCEP response was considered to occur when its amplitude reduced approximately 20% or more.	
Tamura Y et al. [30]	(3) Lt frontal lobe; (1) Lt temporal lobe; (1) Bilateral frontal lobe	Language;	All left dominancy	(2) Glioblastoma; (1) Anaplastic oligoastrocytoma; (1) Diffuse astrocytoma; (1) Ganglioglioma	(1) Motor aphasia; (2) Mild rt hemiparesis; (1) Convulsive seizure; (1) Asymptoms	In 4 cases fMRI was used. In one case this was not possible due to severe motor aphasia.	Awake	50 Hz, 3-15 mA, 0.3 ms	CCEPs and ECoG	On one case aphasia had not worsened, on two cases suffered from transient naming difficulty for 2 weeks. The postoperative courses of other 2 patients were uneventful. /	2 week

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Yamao Y et al. [31]	(1) INS, STG; (1) INS, MTG, STG; (2) AG, PoCG, SMG; (1) IFG; (1) SMG; (1) INS, ITG, MTG, STG; (2) IFG, MFG, SFG; (2) IFG, MFG; (1) IFG, MFG,SFG (1) INS, ITG, MTG, STG; (2) ITG, MTG; (1) AG, SMG, SPL; (3) AG, SMG;	Language	All left dominancy	(2) Anaplastic astrocytoma (1) Astrocytoma WHO II-III (2) DNT (2) diffuse astrocytoma (2) oligodendroglioma (6) GMB (1) oligoastrocytoma (2) metastasis	(3) Right hemiparesis (5) Cognitive deterioration (1) Quadrantopsia (8) convulsions (1) asymptomatic (1) headache (4) aphasia.	fMRI and tractography	15 awake and 4 on general anesthesia	50Hz, 7-15 mA, 0.3ms	Using Cortical Electrical Stimulation and CCEPs	No patients with a CCEP N1 amplitude increase had further language dysfunction after surgery in our series. A decrease in N1 amplitude by less than 50% led to transient language impairment, except for one case. On one case had a 32.0% decrease and showed transient phonemic paraphasia probably due to the partial resection of the SMG. Another case had with a 32.0% decrease had a decline in verbal fluency, but repetition was preserved. Her transient postoperative symptoms were most likely due to partial resection of the IFG or subcortical resection just beneath	6 m

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							the cortex. On one case with a 51.5% decrease, the disturbance of repetition and phonemic paraphasia continued until the final follow-up. The CCEP and SCEP findings provided evidence that the surgical procedure invaded the AF. - In 15 patients the N1 amplitude increased by an average of 24.1% (ranging from 2.2 to 68.6%), in 5 patients the N1 amplitude decreased by an average of 27.5% (from 9.8 to 51.5%). One patient had a decrease of 32.0% and showed phonemic paraphasia soon after surgery. She	

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								had made a full recovery three months after the surgery. In one case the N1 amplitude decreased from 233 to 158 μV (-32.0%) after tumor resection. In one case, the N1 amplitude decreased from 446 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.	

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Ookawa S et al. [32]	(2) Left SFG (2) Left IFG; (1) Left anterior frontal; (1) Left frontal pole; (1) Left sphenoid ridge	Language	All left hemisphere dominance	(4) Oligodendroglioma; (1) Glioblastoma multiforme; (1) Metastatic brain tumor; (1) Meningioma	(1) Mild paraphasia; (1) Mild motor weakness (5) asympomatic	fMRI and tractography	6 awake, 1 general anesthesia	1 Hz, 10 mA, 0.3 ms	The subdural strip or grid electrodes were placed on the lateral and medial frontal cortex	During the early postoperative period, transient impairment of speech was noted in 3 patients, and mild verbal apraxia was noted in 1 patient. In these patients, 1 patient showed an impairment of object naming during the awake surgery, whereas no language deficit was detected in 2 patients, and language symptoms were unable to be evaluated owing to the insufficient arousal state in 1 patient during the surgeries. All patients recovered language function within 8 weeks. - Amplitude of N1 ranged from 20.3 to 174.9 mV (median 49.0 mV) in the SFG	8 week

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								from pO/pTstimulation, whereas it ranged from 28.8 to 312.0 mV (median 101.9 mV) in the pO/pT from SFG stimulation. The amplitudes of N1 tend to be larger in the pO/pT from SFG stimulation than in the SFG from pO/pT stimulation; however, the difference was not significant.	

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Nakae T et al. [33]	not specified	Language	All left dominance	(2) Diffuse astrocytoma; (5) Glioblastoma; (2) Anaplastic astrocytoma; (1) Dysembryoplastic neuroepithelial tumor; (2) Anaplastic oligoastrocytoma	(1) motor aphasia	fMRI	General anesthesia	1 Hz, 15mA, 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.	/	/

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Cattaneo L et al. [34]	(1) Right post-central; (1) Right frontal; (1) Right post-Rolandic; (1) Left anterior intraparietal; (1) Left pre-Rolandic gyrus; (2) Left frontal parasagittal; (3) Right parieto-temporal lobe; (1) Right pre-Rolandic gyrus; (1) Right Rolandic gyrus; (1) Left SFG; (1) Right STG; (1) Left temporal lobe; (2) Left temporo-polar.	Motor	All left dominance	(9) Glioma IV; (3) Meningioma I; (1) Meningioma II; (1) Metastatic melanoma; (2) Metastatic lung adenocarcinoma; (1) Ganglioglioma I	(1) Apraxia, gait disturbances, dysesthesia and weakness on the right side; (1) Gait ataxia, dysarthria; (1) Left facial palsy of central type; (1) dysesthesia and weakness of the right arm and face; mild language deficits; (1) Leg weakness; (1) Headache; (1) Right leg weakness; (2) Generalized seizures; (1) 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.	MRI with 3D reconstructions (with Brainsuite).	General anesthesia (TIVA)	250Hz, 15-35mA, 0.5ms	Simultaneous acquisition of EEG, ECoG, EMG and IOM.	/	/

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Filipiak P et al. [26]	Fronto-opercular (L), Frontal (L), Fronto-temporo-insular (R), Frontal (L), Temporal (L), Temporo-insular (L), Temporal (L), Supplementary motor area (L)	–	dominant hemisphere not specified	Glioblastoma IDH wildtype (IV) (3), Astrocytoma IDH mutant (II) (2), Oligodendroglioma IDH mutant (II) (2), Astrocytoma IDH wildtype (III)	not specified	MRI and tractography	Awake	2-5 Hz, 2-5 mA, 1ms	strips were used in alignment with the cortical endings of the Arcuate Fasciculus (AF) and Superior Longitudinal Fasciculus III (SLF3). a 32-channel signal amplifier and a sampling frequency of 2 kHz were used.	Positive correlation between streamline lengths and counts with the delays and amplitudes of N1 peaks in the vicinity of the stimulation sites. /	/

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Saito T et al. [35]	MFG; precentral gyrus; IFG; frontal language area.	Language	dominant hemisphere not specified	grade III gliomas in 5 of the 7 patients and 2 patients had a glioblastoma , IDH-wild type and astrocytoma, IDH-mutant, grade 4	one with mild dysarthria, one with partial epilepsy	MRI, fMRI and speech therapy evaluation	awake	50 Hz, 6mA, 0.2 ms; 1-2s	Six-wire strip electrodes were used, placed just above the FLA and on the temporal lobe, parallel to the 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 slightly 80% in 1, and, in the 5 other 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 m

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Ishankulov TA et al. [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	CCEPs a 32 channels and a pair of subdural electrode strips. One electrode was placed in the Broca's area; the second electrode was located on the surface of the upper temporal gyrus in its posterior parts and the supramarginal gyrus. The duration of signal recording after stimulation was 300 ms.	To demonstrate the possibility of predicting speech dysfunctions based on CCEPs data taken before the main stage of glial tumors resection. /	
Vega-Zelaya L et al. [37]	frontal (3), fronto-parietal (2), temporo-parietal	Language	left dominant hemisphere	Astrocytoma IV, Glioblastoma IV (3), Oligodendroglioma II, Glioblastoma II	Seizure (7), aphasia	MRI, spectroscopy and tractography	General anesthesia	10 to 1500 Hz, from 5 mA using stepwise increments of 5 mA until the effect was attained, 1 ms	CCEPs and ECoG.	5 out of 7 patients were asymptomatic one year after surgery, in 1 seizures persisted and one persisted with the same mild dysarthria as before surgery. None of the	12 m

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							patients had aggravated symptoms due to iatrogenic damage. At the one-year follow-up visit, five patients were asymptomatic, one of them still had mild dysarthria, and one still had seizures. - / - The CCEP alert criterion was set at a reduction in amplitude of more than 20%.	

Table 2: clinical and monitoring CCEPPs features of studies included.

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Abbreviation: DNT=Dysembryoplastic Neuroepithelial Tumor, INS=Insula, PcCG=Postcentral gyrus, SMG=Supramarginal gyrus, AG=Angular gyrus, STG=Superior temporal gyrus, ITG=Inferior temporal gyrus, MTG=Middle temporal gyrus, SFG=Superior Frontal gyrus, IFG=Inferior frontal gyrus, MFG=Middle frontal Gyrus, SPL=Superior parietal lobule, fMRI= functional magnetic resonance imaging, MRI= magnetic resonance imaging, PET= positron emission tomography, FDG= Fluorodeoxyglucose, ECoG=Electro-corticography, FLA=Frontal Language Area.

3.2. Study characteristic and data analysis

A total of 125 patients were collected. Mean age was 48 years ± 10,6, with a male predominance (M:F = 59/40, not specified for 26 patients in one study). The postoperative follow-up periods varied across the included studies, ranging from 2 weeks to 2 years.

The linguistic component has been the function through which patients’ outcomes have been assessed across the pre-operative, intra-operative, and post-surgical phases in all studies included. Therefore, it appears to be the domain that at present can be monitored more precisely throughout the surgical process allowing to monitor safe resection while performing brain tumour surgery.

The histology and the location of the lesions described were very heterogenous, spanning from high grade to low grade tumours 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 pre -operative neurological symptoms are summarized in table 2,3 and 4.

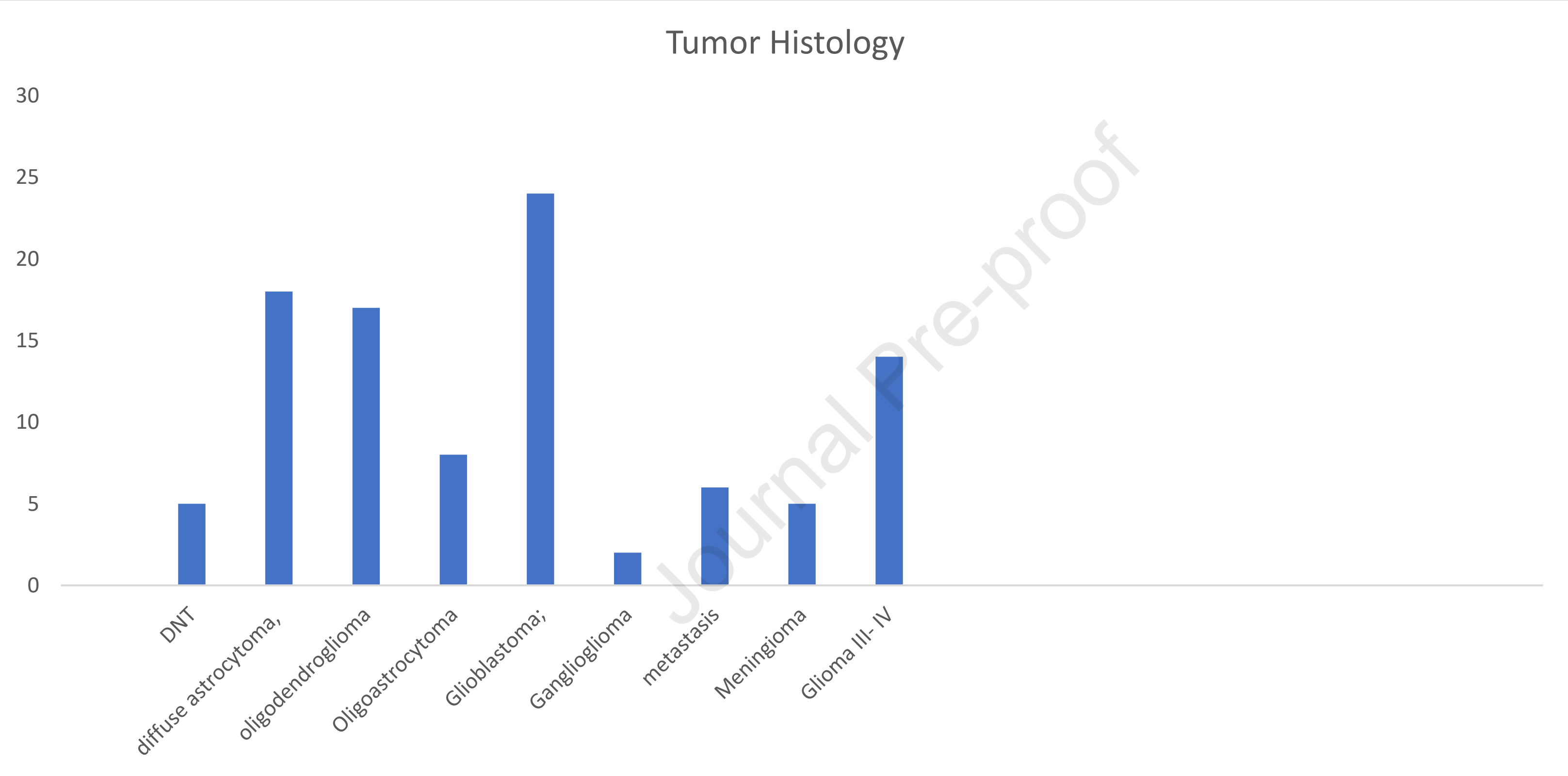

Figure 1: Vertical bar chart about tumor histology of selected studies.

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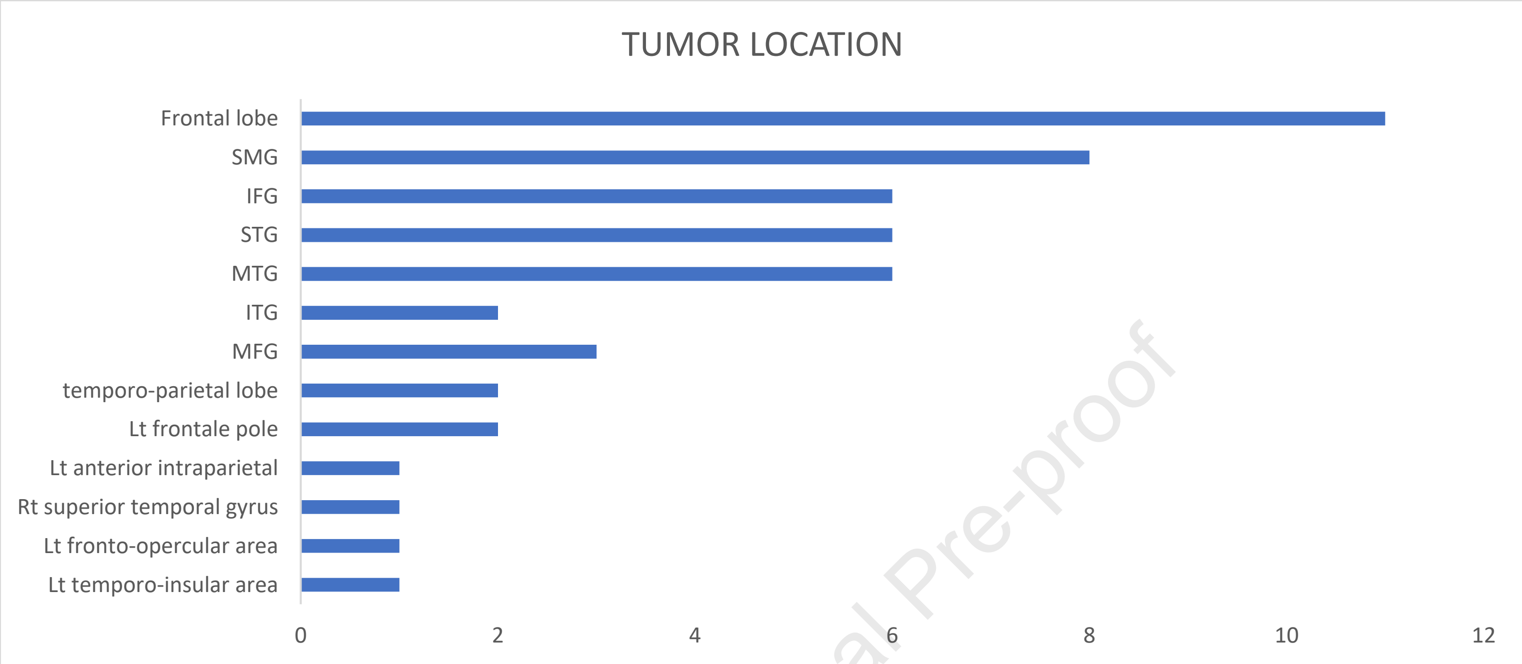

Figure 2: Horizontal bar chart on tumor location of selected studies.
Abbreviations: Lt: Left; Rt: Right; MFG: Middle frontal Gyrus; ITG: Inferior frontal Gyrus: MTG: Middle Temporal Gyrus; STG: Superior Temporal Gyrus; IFG: Inferior Temporal gyrus; SMG: Supramarginal Gyrus

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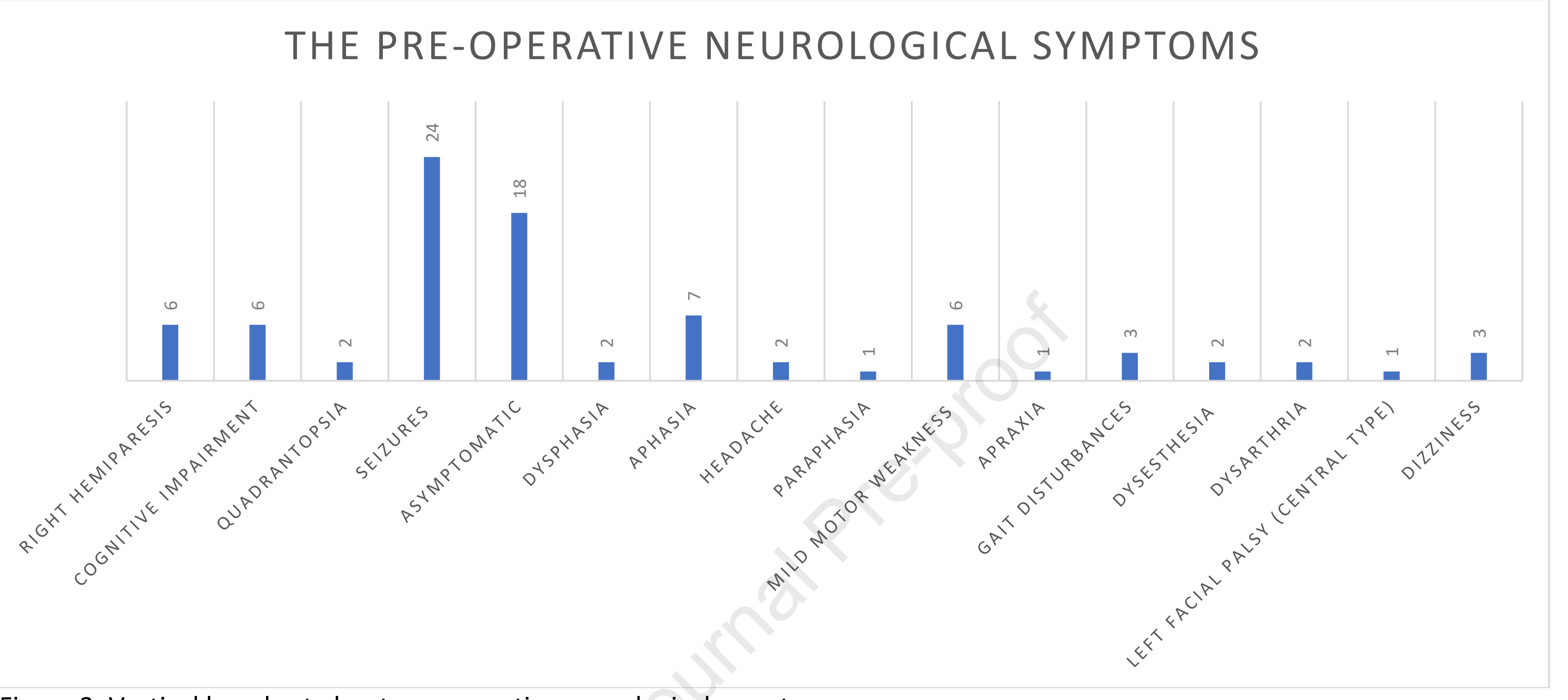

Figure 3: Vertical bar chart about pre-operative neurological symptoms

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Interestingly, in most cases the speech disorders that were present pre-operatively or that appeared immediately after surgery returned after about 6 months. In many cases the disorder appeared later in a transient way. Only in one case did the repetition disorder and phonemic paraphasia continue until the final follow-up. These findings emphasize the importance of 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 work from Vega-Zelaya L et al.

Whereas in 4 other studies out of 11, the patients were operated using awake technique. Furthermore, 3 studies described a mixed cohort in which part of the patients were operated under full sedation and part of them underwent awake surgery. Finally, in one study the anesthesia protocol has not been outlined.

In 9 studies analyzing the language lateralization, dominancy was found in the left hemisphere, while in 2 studies hemisphere dominancy was not specified. The pre-operative investigations used for pre-operative planning were also evaluated, in addition to the use of diagnostic imaging investigations such as: (2) multimodal MRI with any 3D reconstructions, (5) tractography, (2) spectrography, (6) fMRI1, (1) PET with 11C-methionine, 11C-choline, and 18F-FDG, in one 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.

3.3. 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 early negative signal deviation with a peak latency of 10-30 ms. This marker of connectivity holds promise as a valuable indicator of post-operative 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 heterogenous with a mean of 46.5 Hz ± 248.2. Four out of 12 studies have set the stimulation frequency at 50 Hz, 4 out of 12 at 1 Hz, while in two studies frequency was from 1 to 1500 Hz. The mean intensity of stimulation was set at 11 mA ± 6.2. Just in one paper the intensity was increased gradually from 5 mA until the effect was attained. Amplitude of stimulation data were heterogeneous (34 ms ± 90.6), although most studies 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 around 200-350 ms after the stimulus has been delivered. The N2 is often observed while performing higher-level cognitive processes such as tasks requiring cognitive control or response inhibition. The group of Matsumoto et *al*. in study of the 2004 reported a larger distribution of the N2 wave compared to the N1 suggesting the existence of broader neuronal network underlying the speech function than previously described [22].
However, in a subsequent paper the same author, while performing CCEPs recordings decided to consider only the N1 wave since the N2 did not show a clear peak that could be utilized for standardized recording [38]. Evaluating the findings from other international groups it emerges a not univocal interpretation of the link between N1 and N2 implementing techniques to actual silence N2 to obtain a better recording of the N1 wave. A novel approach for enhancing the signal-to-noise ratio and automatically detecting event-related potentials (ERPs) in single trials [39]. Therefore, as discussed above, from our review it appears that the most important wave to predict neurological outcome after surgery is the N1. However, further studies are ongoing and new possible interactions are under evaluation showing promising application in brain surgery for tumor resection.

3.4 Risk of Bias assessment

Through the JBI checklist for assessment of study risk of bias we stratified the quality of each included paper into three groups (low, moderate, and high quality, respectively). The bias risk assessment showed that, among the included studies, eleven respected the JBI criteria for a high-quality study (with seven or more 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 lack in performing adequate complete and consecutive inclusion of the participants, thus determining a possible bias in patients selection process. Finally, another aspect to consider in the possible genesis of bias

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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 of each paper summarizes key lessons regarding the background of diseases, clinical practice, and outcomes, we decided to include all screened studies in our review.

3.4 Modality of CCEPs recording

All the studies shown on the table 2 used CCEPs to monitor language function, except for the study of Cattaneo’s group that focused their attention to motor function [34]. They have evaluated MEPs by means of transcranial electrical stimulation (TES). MEP monitoring, from the dura mater opening onwards, 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 works by Saito T et *al.* [25, 35], Tamura Y et *al.* [30], Yamao Y et *al.* [31], Ookawa S et *al*. [32], two adjacent electrodes were used in bipolar mode with a square wave of constant current with alternating polarity (pulse width 0.3 msec, frequency 1 Hz). The electrodes had a recording diameter of 3 mm and were spaced 1 cm apart. In the study by Filipiak P et *al.* [26], the electrodes, with a diameter of 4 mm, were positioned with a centre-to-centre distance of 10 mm between the electrodes and, depending on the space, and 2 or 3 reconrding strips were placed. Their configuration comprised one or two 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 Y et *al.* [30] and Yamao Y 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 pre- and post-stimulus periods of 100 msec and 800 msec, 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 works by Vega-Zelaya L et *al.* [37], Saito T et *al.* [25, 35] the band-pass filter for data acquisition was set to 5-1500 Hz with a sampling frequency of 5000 Hz for each channel. In both papers by Saito the stimulus intensity increased steadily from 2 mA using gradual 1 mA increments until a response was obtained or abnormalities were detected on the ECoG. Vega-Zelaya L et colleagues [37] also used electrocorticography (ECoG) to monitor brain responses during electrical stimulation to identify the presence of epileptiform patterns (post-discharge). Electrical stimulation was performed with direct cortical stimulation (DCS) using a grid of 4 × 5 electrodes 1.2 mm in diameter and 1 cm centre-to-centre using three single monophasic pulses of 1 ms duration and separated by 1 s. Finally, in the study by Ookawa S 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.

4.0. Discussion

4.1. Language brain network: wiring across cortical and subcortical areas

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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 [40,41]. 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 [42,43]. 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 [44]. This new vision led to the development of the dual stream model of the language. Since this topic is beyond the scope of our review, we refer to other texts for a better definition of it [45–49]. Briefly, 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's and Wernicke's areas, arcuate fasciculus (AF), inferior fronto-occipital fasciculus (IFOF), fronto-temporo-parietal network, basal ganglia, cerebellum, and many others [50–54]. These components, among others, are distributed networks 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, going to trace the structural and functional bases to safeguard them, where possible, during tumor surgery in eloquent areas [51,55,56].

4.2. Usefulness of CCEPs in monitoring language function

CCEPs have emerged as a valuable tool in the intraoperative monitoring of eloquent brain tumor surgery. Through our review we have shown as it has become central in the conversation that pertains the surgical treatment of brain lesions the concept of connections at different levels of complexity going from macro to micro scale systems that operate as an extremely highly interconnected networks [57]. 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 [58–62]. When AS was introduced, it demonstrated a good precision to predict postoperative outcomes regarding motor function, especially when surgery was performed in areas like the precentral gyrus. Furthermore, when AS is combined with other techniques like navigated transcranial magnetic stimulation (nTMS) [63], intraoperative voluntary movement (IVM) estimation and transcortical motor evoked potentials (MEPs), it has proven during the years to be valuable even in preserving motor neurological function [64,65]. However, not all patients are suitable candidates for awake neurosurgery, highlighting the need for alternative approaches. In this scenario, CCEPs have gained success and attention for their ability to monitor neurological function, especially language function, even in the sedated patient. In fact, the patient can be either awake or asleep during CCEPs monitoring, depending on the specific circumstances and surgical requirements. Continuous monitoring of CCEPs helps assessing 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 more than 50%. Filipiak and colleagues have demonstrated the relation between the structural connectivity measures obtained from diffusion MRI and the effective connectivity measures based on the propagation of CCEPs in the brain tumor patients, finding a positive correlation between streamline lengths and the delay time and amplitudes of N1 peaks. They have 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 macro- and microstructure measures of brain white matter with effective connectivity measures based on CCEPs monitoring [26]. Finally, in a recent work by Vega-Zelaya et al., 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 CCEPs can be used routinely in patients under general anesthesia [37].

Regarding the complexity of language network, particularly interesting are the results obtained by the group of Nakae et *al*.[33]; first, they showed how the anterior inferior frontal gyrus (IFG) is connected to the anterior medium and inferior temporal gyrus (MTG/ITG). From their results it also emerges that a parcellation based on CCEP connectivity could be clinically crucial for an eloquent area such as the IFG, 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 CCEPs-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 (FAT), especially concerning speech initiation and spontaneity. In their study they have evaluated through CCEPs monitoring, demonstrating a corticocortical network connecting Broca areas and superior frontal gyrus (SFG) in a reciprocal manner.

4.3. Limitations and future perspectives in the use of CCEPs

Although the results so far are encouraging, there are limitations and challenges associated to the use of CCEPs in clinical practise, 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 CCEPs mapping may be limited to certain specialized centers, which restricts its widespread use. On another hand, there is still needed to establish standardized protocols for CCEPs mapping. Developing standardized protocols will facilitate the adoption of CCEPs in routine clinical practice. Lastly, CCEPs mapping is an invasive procedure therefore by definition carries potential complications such as infection or haemorrhage. 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 CCEPs recordings are expected to improve. Higher-resolution electrode arrays, improved signal processing techniques, and advanced imaging modalities will enhance the accuracy and reliability of CCEPs mapping [66]. Another interesting future development will be to combine CCEPs with functional magnetic resonance imaging (fMRI) or diffusion tensor imaging (DTI) providing more comprehensive understanding of the brain's functional and structural connectivity [30,67,68].

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 eloquent area tumor resection, their potential extends beyond this specific application. CCEPs monitoring can be explored in other neurosurgical procedures, such as epilepsy surgery or deep brain stimulation, where preserving functional connectivity is crucial.

In conclusion, 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 hold 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. 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 to controlled clinical studies. Moreover, the number of studies available for inclusion was relatively small, indicating a scarcity of research in this specific area.

5.0. Conclusion

In conclusion, 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 brain tumor patients.

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Abbreviations list

- CCEPs: Cortico-cortico evoked potentials;
- QoL: Patient’s quality of life;
- CNS: Central nervous system;
- AS: Awake Surgery;
- SPES: Single-pulse electrical stimulation;
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
- MTG: Middle temporal gyrus;
- PoCG: Postcentral gyrus;
- STG: Superior temporal gyrus;
- IFG: Inferior frontal gyrus;
- ITG: Inferior temporal gyrus;
- DNT: Dysembryoplastic Neuroepithelial Tumor;
- INS: Insula;
- PcCG: Postcentral gyrus;
- SMG: Supramarginal gyrus;
- AG: Angular gyrus;
- SFG=Superior Frontal gyrus;
- MFG=Middle frontal Gyrus;
- SPL=Superior parietal lobule;
- Lt: Left;
- Rt: Right;
- IFOF: Inferior fronto-occipital fasciculus;
- AF: Arcuate fasciculus;
- IVM: Intraoperative voluntary movement;
- MEPs: Transcortical motor evoked potentials;
- MTG/ITG: Anterior medium and inferior temporal gyrus;
- FAT: Frontal Aslant tract;
- fMRI: Functional magnetic resonance imaging;
- DTI: Diffusion tensor imaging.

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