Review

Intraoperative settings for awake surgery: anaesthesiological, neurophysiological and cognitive aspects
Clinical appraisal of methods, classifications and definitions

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SUMMARY: *In order to compare different research papers we reviewed the literature on intraoperative strategies, whereas we emphasized the methodological differences. This is particularly relevant, since the cost-benefit ratio and the optimization of resources are major aims of awake surgery.*

KEY WORDS: *Brain tumours, Complications, Language assessment, Neuropsychological assessment, Surgical treatment.*

Setting intraoperatorio della chirurgia a paziente sveglio: aspetti anestesiologici, neurofisiologici e cognitivi
Valutazione clinica dei metodi, delle classificazioni e delle definizioni

RIASSUNTO: *Al fine di confrontare diversi studi di ricerca abbiamo effettuato una revisione della letteratura in merito alle strategie intraoperatorie, soffermandoci sulle differenze metodologiche. Ciò è particolarmente importante se si considera che il rapporto costo-beneficio e l'ottimizzazione delle risorse rappresentano i principali obiettivi che la chirurgia a paziente sveglio persegue.*

PAROLE CHIAVE: *Tumori cerebrali, Complicazioni, Valutazione del linguaggio, Valutazione neuropsicologica, Trattamento chirurgico.*

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☐ INTRODUCTION

❒ **PREMISE.** Awake surgery and cortical mapping have got a widespread application in the recent years for many different reasons: the introduction of new anaesthetic agents, the improvement of surgical techniques, the introduction and the widespread use of functional Magnetic Resonance Imaging (fMRI) and the growing interest in brain mapping, as shown by refinements and upgrading of different techniques (Magnetoencephalography: MEG; Event Related Potentials: ERP; Electroencephalography: EEG; Positron Emission Tomography: PET; optical imaging; etc.)(15,65,83,84,102,126,135,142,146,148,164). Information technology and the chance to use image-guided surgery have prompted researchers to compare non-invasive with invasive mapping on an awake patient(67,71,81,147). While this practice has rapidly evolved, the technical characteristics of electrocortical mapping have remained essentially the same since Penfield's time. His technique is still considered the gold standard for mapping language(49,137).

Disruption of the task during cortical stimulation is taken to indicate that the underlying cortex is essential for the performance of that task. What has changed is the increasing feasibility of brain mapping in vivo, that is in a safe and acceptable way for the patient, and the opportunity to use a broad variety of selective tasks(17,159,162,163). This has stimulated translational research and cooperation between neuroscientists and neurosurgeons, from basic sciences to clinical applications. Nowadays, the coupling of location and function is analyzed as a complex anatomo-functional scenario, including local cytoarchitectural variability, multimodal pathways, and dynamic compensatory mechanisms, all taking us well beyond the original point of view of localizationism(39,45,46,48). This constitutes a significant difference from Penfield's time, so that there can be no comparison between the two periods. Therefore, developing new high-tech instruments and building multidisciplinary teams are complementary aspects of the same innovation that has led us into a new era, that we will call the *translational era*(169,172).

Thanks to this wide cooperation, we can rely on an enormous amount of data collected earlier, during and after awake surgical procedures. Thus, the criteria used to select parameters of interest, their definition and classification, are of paramount importance, since there is a high risk of invalidating conclusions and a great deal of work.

❒ **RATIONALE FOR CLINICAL REVIEW.** After Penfield's pioneering work, during the 1970s and 1980s reliable concepts for cortical language mapping were established by Ojemann, whose protocol remains a milestone for future studies(106,114,117). In awake patients, the choice for visual object naming, suggested by Penfield's clinical experience, was first supported by findings which recognized anomia as the most sensitive deficit in clinical impairment(149) and validated thereafter by intraoperative(57) and clinical studies(57,116,150). While the initial assumption was that no electrically identified areas should be removed if postsurgical language complications are to be avoided, later it was increasingly assumed that postsurgical language deficits would not occur when resecting only cortical areas that did not generate language deficits after electrical stimulation(22,150). This indirect message is gaining strength, even though most studies lack pre- and postoperative global assessment and objective determination of cognitive complications.

In addition, the original assumption that resection of any essential language areas will result in postoperative aphasia has not been definitively confirmed to date(129,158), nor has the assumption that sparing positive sites for naming task will result in saving other language functions(63,131,173,175,176).

We are moving from intraoperative naming-assisted surgical resection to other language and cognitive tasks. Before relying on new protocols we need a multistaged system of evidence concerning the possibilities and limits of awake surgery for cognitive mapping (feasibility and efficacy) (*addressed in the article "Clinical settings for awake surgery. Critical appraisal of methods, classifications and definitions", at page 61*), its technical standardization (*addressed in this article*) as well as the clinical validity of each single task or battery of tasks (*addressed in the clinical article, at page 61*). Meanwhile, patient security must be guaranteed by an accurate comparative assessment that should be discussed and defined. The aims of tumor surgery and epilepsy surgery are different: minimizing neurological sequelae is only one aspect of the treatment that can be tailored to the characteristics of the lesion, as it was defined by clinical and instrumental studies. Symptoms and impairment constitute the essential difference between the two pathologies. Improvement of a preoperative clinical impairment and radical tumor resection are end-points for tumor surgery, while improvement of the preoperative performance is the end-point in epilepsy treatment(16,59).

In glioma surgery, increased indications for tumor removal, a higher rate of radical tumor resection and a lower rate of postoperative impairments have been described[29], clinical advantages of which need confirmation. It should also be noted that while cortical mapping was originally applied to epilepsy surgery, where resection is essentially limited to the cortex, later indications were extended to tumour surgery, that involves the white matter. Whether these differences result in different clinical and operative settings is still not clear.

Low grade gliomas are the pathology that get most benefits from awake surgery. They represent a considerable challenge in that they have characteristics of both epilepsy and tumours, with a long history that could influence neuro-functional anatomy in patients whose neurological examination is normal[27,30,31].

❒ **Objectives.** The aim of this document is to review and focus on the advisability and modality of intraoperative mapping, discussing inclusion and exclusion criteria, classifications, definitions, timing, modality of evaluation and on how bringing together all of these parameters.

☐ METHODS

❒ **Criteria for considering studies for this review.** In the clinical part we will examine:

- feasibility and efficacy of awake surgery;
- clinical setting and treatment results.

Papers for review were included only if cognitive mapping and awake surgery were applied in clinical series with functional and lesional end-points.

In this article we will discuss:

- anesthesiological management;
- electrical stimulation characteristics;
- representation and reproducibility of specific local language and non-language functions.

These papers analyze cognitive end-points using neurophysiological techniques applied to clinical research.

❒ **Methods of the review.** Full articles were screened independently by four Authors. Papers were submitted for extraction of data and review to all the other Authors, according to their individual experience, using a pre-established format.

Before starting, selected articles were discussed by all Authors together in order to unify basic knowledge, evaluation methods and terminology.

☐ ANAESTHESIOLOGIC MANAGEMENT

Procedures that identify and map specific brain areas are becoming increasingly relevant in these last few years. The anaesthesiologist is involved in providing changing states of analgesia that will not interfere with patient comfort or with the electrophysiological monitoring process and that will yet ensure cardio-respiratory stability. During surgical procedures involving the Broca and Wernicke areas, verbal contact is important and should be maintained. A good anaesthetic technique requires analgesia, anaesthesia or sedation and respiratory and hemodynamic control with no interferences on electrocorticographic and neuropsychological testing. One of the main techniques adopted in the past was asleep-awake-asleep anaesthesia[151]. Patients were fully anaesthetized during a major part of the craniotomy, such as the skull opening, and then awakened for stimulation. One of the foremost intraoperative issues is the airway maintenance through endotracheal intubation or a laryngeal mask. At times anaesthesiologists will use Guedel tubes or naso-pharyngeal tubes. All devices must be removed for cortical mapping. If devices are removed too late patients could experience laryngeal irritation, leading to cough and an increase of intracranial pressure. Another concern is the effect of the anaesthetics on cortical functions and their half-life. For the third part of anaesthesia, patient asleep, positioning of airway devices could be difficult, in particular for the endotracheal tube.

Current techniques include continuous sedation[151] with fast-acting agents and the use of local anaesthesia on the scalp. Airway management remains a concern due to aspiration risks or over-sedation with an oxygen saturation < 90%. In many institutions patients breathe spontaneously during awake surgery. Propofol, fentanyl, remifentanyl and midazolam are commonly used. Volatile anaesthetics should not be used because of their interference with EEG recording (they may cause a dose-dependent EEG distortion) and because of vasodilatation yielding an increase in Intracranial Pressure (ICP)[151]. Propofol can also bias EEG monitoring, but intravenous drugs are, nevertheless, preferable since the ideal anaesthetic for neurosurgery (rapid onset, easily controllable duration of action, no effect on the cardio-vascular or respiratory system, causing no nausea, vomiting and no interfere with neurological and neurophysiological evaluation) does not exist yet. The level of sedation is fundamental, since an over-sedation results in an uncooperative

Score	Responsiveness	Speech	Facial expression	Eyes
5 (*alert*)	Responds readily to voice with normal tone	Normal	Normal	Clear, no ptosis
4	Responds slowly to voice with normal tone	Mild slowing	Mild relaxation	Mild ptosis (*less than half the eye*)
3	Responds after calling loudly or repeatedly	Prominent slowing or slurring	Marked relaxation (*slack jaw*)	Marked ptosis (*half the eye or more*)
2	Responds after mild prodding or shaking	Few recognizable words	_	_
1	Does not respond to mild prodding or shaking	_	_	_
0	Does not respond to pain	_	_	_

Table 1. Modified Observer's Assessement of Alertness/Sedation Scale.

patient and respiratory depression, whereas under-sedation makes the patient uncomfortable.
Anaesthesiologists commonly use a sedation scale, i.e. the *Modified Observer's Assessment of Alertness/Sedation Scale* (Table 1). Patients usually display a score 3 during most of the initial craniotomic procedure, specifically the skull opening; subsequently, while the awake procedure is taking place, they will show a score 5. Pitch et al.[132] in their study referred to *Ramsay Scale* with a target score of 5-6 (weak or no response to pain stimuli) in the first part of craniotomy.
Awake craniotomies can be performed in children and have also found a place in epilepsy surgery[64].

❒ Local anaesthesia

During sedation, blockage of the auricolo-temporal, zygomatico-temporal, supraorbital, supratrochlear, lesser occipital and greater occipital nerves is mandatory to allow a pain-free skin-incision. Long-acting agents are used, and ropivacaine and levobupivacaine seem preferable for their safe action on the heart. Costello et al.[20] described in 2004 the safe dosages of ropivacaine, up to 4.5 mg/kg. For levobupivacaine a 2.5 mg/kg dosage appears safe[21]. At the beginning of the procedure the anaesthesiologist calculates the maximum volume of local anaesthetics. The surgeon assesses how much is needed for the scalp block and reserves 10-15 ml for the dural incision.

❒ Anaesthetics

■ **Propofol.** It has a rapid action onset and is quickly removed from the bloodstream through redistribution and metabolism; this shows that the level of anaesthesia or sedation can be rapidly changed. Nevertheless, propofol can lead to respiratory depression. Skucas et al. demonstrated in 2006, on a cohort of 332 patients, how propofol can be safely used without a need for intubation or positioning of a Laryngeal Mask Airway (LMA)[167]. Propofol should be stopped 15-20 min before electrocorticography. It should also be noted that propofol interacts with Gamma-Amino-Butyric Acid (GABA) receptors, leading, at low dosages, to a central nervous system hyperactivity that will result in movements mimicking tonic-clonic seizures. Propofol has also a neuroprotective action, probably mediated by antioxidant properties, which may play a role in apoptosis, ischemia-reperfusion injury and inflammation-induced neuronal injury.
■ **Narcotis.** Remifentanyl seems to be the most appropriate narcotic during awake surgery because of its rapid onset, rapid half-life and no accumulation even after a long infusion time. Remifentanyl can lead to muscle rigidity, postoperative shivering, low risk of postoperative agitation and seizures, bradycardia.
■ **Dexmedetomidine.** It is a specific alpha2-receptor agonist that gives cooperative sedation, anxiolysis and analgesia without respiratory depression. Dosage is 0.1-0.2 mcg/kg/min. It has sympatholytic and antinociceptive properties, but it can also give a dose-dependent hypotension and bradycardia; for this reason it is not approved in Europe. Dexmedetomidine has also anticonvulsant effects, observed in rats, but no proven data are available in humans.
■ **Neuroleptanalgesia.** It is a combination of droperidol and narcotics. Unfortunately this kind of combination leads to seizures, respiratory depression and postoperative agitation. It has been withdrawn in Europe.

☐ ELECTRICAL STIMULATION

❒ ELECTRICAL PARAMETERS AND NEUROPHYSIOLOGICAL EFFECTS

Although electrical stimulation during cortical mapping - either intraoperatively or from chronically implanted grids/strips - is considered the "gold standard" of mapping procedures, we have a limited understanding of the neurophysiological mechanisms involved. For example, the 50-60 Hz Penfield technique[128] has been used for many years to elicit motor responses, that have been documented mainly through direct visual observation of contralateral tonic limb movements, while Electromyographic (EMG) recordings were uncommon. The first EMG recording from limb muscles by Yingling et al.[179] suggested that latency of an EMG motor response from lower extremities elicited using this technique is about 250 ms. This is much longer than the latency of muscle Motor Evoked Potentials (mMEPs) elicited after direct cortical stimulation using the so-called short train technique (5 to 7 stimuli, 0.5 ms duration, InterStimulus Interval: ISI 4.1 ms = 250 Hz, with train repetition rate of 1 or 2 Hz). Therefore, although we have been using Penfield's technique for more than 50 years, the underlying neurophysiological mechanism is paradoxically less understood than the one involved in the generation of mMEPs after multipulse transcranial or direct cortical electrical stimulation[23,24,127,168].

Similarly, at a first sight, principles of cortical stimulation for language mapping are well established at different institutions (Table 2), where the classical 50-60 Hz bipolar technique is generally employed for historical reasons. Studies on cortical mapping of cognitive functions other than language suggest that neurophysiological parameters similarly to those adopted for language mapping are currently used[39,41,101,130,141]. Yet, a detailed analysis of the methodology adopted by different Authors suggests some inconsistency among protocols (see Table 3).

This diversity among protocols is not trivial because it obviously impacts on the results of the stimulation. Therefore, function localization may vary in different studies as a result of stimulation parameters and mapping strategies. Mapping strategies appear as one of the main variables that may affect the results of stimulation. Two different theories stay behind the choice of either one or the other strategy:

1) some Authors apply the concept that thresholds (the minimum stimulation current required to induce functional changes) vary across the exposed cortex depending on:
   A. the task being assessed, and
   B. the location being mapped. This is in keeping with the observation that even AfterDischarges (ADs) thresholds can vary significantly not only across the population, but in the same subject at different cortical sites[85,137]. Accordingly, these Authors attempt to maximize stimulation currents at each cortical site to ensure the absence of eloquent function[86,138,177]. Doing so, it is more common to exceed ADs thresholds in adjacent cortices, and there is a higher risk of distal activation due to current spreading to adjacent sites;
2) other Authors[8,10,108,118,171] keep stimulation intensity constant while mapping the entire cortex and set the threshold just below the lowest current observed to induce ADs. This strategy is aimed to minimize the risk of inducing ADs (which may invalidate the results) and clinical seizures, but may miss the identification of eloquent cortical sites.

When describing the 50-60 Hz stimulation, most of Authors refer to biphasic square waves, positive-negative square waves, or alternating waves. This may lead to some confusion or ambiguity in the current settings[32,178]. When the pulse output is biphasic, first negative and then positive, if the dial is set at 8 mA, it will first deliver 8 mA in one polarity and then 8 mA in the other polarity. Some Authors may have misleadingly interpreted this to mean the total current is thus 16 mA instead of 8 mA. Actually, the intensity is always that displayed on the stimulator (in this case 8 mA) but, with a biphasic pulse, the total charge applied to the brain is lower because current delivery continues during each phase.

High frequency (50-60 Hz) stimulation is currently used in cortical mapping. However, there is some evidence in transcranial magnetic stimulation[18] and cortical mapping in awake epilepsy patients[180] that low frequency stimulation may be effective. This latter study concludes that:

1. ADs are seen less often at lower frequencies (5-10 Hz);
2. the mean current intensity to produce ADs was higher using lower frequencies (5-10 Hz) than 50 Hz;
3. comparing 5 *versus* 50 Hz and 10 *versus* 50 Hz, no difference in the incidence of positive mapping results was found;

Authors and year	Stim.	Interelec. distance (*mm*)	Electrode diameter (*mm*)	Pulse	Int. (*mA*)	Durat. (*ms*)	Freq. (*Hz*)	Train durat. (*s*)	EcoG	ADs
Alpherts W.C. et al., 2008[1]	probe	7		monophasic square	4-12	0.3	40		x	
Anderson J.M. et al., 1999[2]	grid			alternating	15.5	0.3	50	5	x	x
Bello L. et al., 2007[5]	probe	5	1	biphasic square wave		1	60	4	x	x
Bello L. et al., 2008[6]	probe	5	1		3.5-16	1	60	4	x	x
Benzagmout M. et al., 2007[7]	probe	5	1	biphasic	2-8	1	60	4		
Boatman D. et al., 1995[14]	grid	10	2.3	alternating	15	300 (?)	50	5	x	x
Duffau H. et al., 1999[38]	probe	5		biphasic	3-6	1	60			
Duffau H. et al., 2005[45]	probe	5		biphasic	2-8	1	60	4		
Greenlee J.D. et al., 2007[56]	probe	2	2						x	
Hamberger M.J. et al., 2001[60]	probe /grid			biphasic square wave	3 to 15	0.3	50		x	
Henry R.G. et al., 2004[64]	probe			biphasic square wave	2-6	1.25	60	4-5		
Ilmberger J. et al., 2001[70]	probe				7 to 18	0.2	50	4		x
Krauss G.L. et al., 1996[79]	grid	10	2.3	biphasic	15	0.3	50	2-5	x	x
Kurimoto M. et al., 2006[80]	probe			bipashic square wave	5	1	60	3		
Lesser R.P. et al., 1984[85]	grid			bipolar square wave		0.3	50	5-8	x	x
Luders H. et al., 1988[91]	grid	10	3.2	bipolar square wave	1-15	0.3	50	5-20	x	x
Luders H. et al., 1991[92]	grid			alternating	15	0.3	50	5	x	x
Malow B.A. et al., 1996[95]	grid	5-10		biphasic square	2 to 15	0.5	60	5	x	x
Matsumoto R. et al., 2004[98]	grid	10	3.97	alternating		0.3	50	2-5	x	
Moore T.A. et al., 2006[100]	probe			biphasic square wave	4-6	200 (?)	50	2-5		
Ojemann G.A., 1979[109]	probe	5		biphasic square wave	5 to 10	2.5	60			
Ojemann G.A., 1979[109]	probe	5		biphasic square wave		2.5	60	4 to 8		x
Ojemann G.A. et al., 1989[118]	probe	5	1	biphasic square wave	1.5-10	2.5	60	4	x	x
Otani N. et al., 2005[124]	probe	5	1	bipolar square wave	10	1-4	50-60	1-2	x	x
Perrine K. et al., 2000[130]	grid		4	monophasic square	2-15	0.3	50	10	x	x
Roux F.E. et al., 2003[141]	probe	5	1	biphasic square wave		1	60	4	x	x
Roux F.E. et al., 2004[144]	probe	5	1							
Roux F.E. et al., 2006[143]	probe	6	1						x	
Schaffler L. et al., 1993[155]	grid			positive-negative square wave	2 to 9	0.3	25	5	x	
Schwartz T.H. et al., 1999[157]	grid			biphasic square wave	2 to 15	0.3	50		x	x
Sinai A. et al., 2005[165]	grid	10	4-2.3	alternating	15	0.3	50	1-5	x	x

Table 2. Summary of stimulation parameters for language mapping: literature review. *Legend*: ADs = AfterDischarges, durat. = duration; EcoG = Electrocorticography; freq. = frequency; int. = intensity; interelect. = interelectrodes; stim. = stimulation.

4. higher current intensities were required to alter function when using 50 Hz as compared to 5 and 10 Hz.

It therefore seems that lowering stimulation frequency decreases the probability of inducing ADs without significantly compromising the efficacy of mapping. This is anecdotally confirmed in a case report by Hoshino et al.[68]. The Authors, using an optical imaging technique, compared the metabolic effects of cortical stimulation of the hand area through subdural grids at 5 and 50 Hz, keeping constant stimulation intensity (5 mA) and duration (5 s). This study revealed a localized oxyhemoglobin increase and deoxyhemoglobin decrease after 5 Hz stimulation, while 50 Hz stimulation produced an increase in both oxyhemoglobin and deoxyhemoglobin, suggesting that oxygen

consumption exceeded oxygen delivery and ultimately increases the risk of epileptic discharges in the stimulated cortex. Moreover, at 50 Hz these metabolic changes propagated outside the hand area of the motor cortex.
These preliminary observations warrant further investigation in the intra operative setting but suggest that it would be advisable to start cortical mapping at a lower frequency first.

❒ Side effects: Seizures

The occurrence of intraoperative seizures induced by cortical stimulation is reported in as much as 24% to 27% of cases using the 60 Hz technique(153,179) and it is debated whether or not this risk is higher in patients with symptomatic epilepsy as compared to those with asymptomatic epilepsy. Most of these seizures can be controlled by irrigating the cortex with cold ringer solution(152), and this helps to avoid the administration of antiepileptic drugs that could increase thresholds in electrical mapping. However, it is recommended not to stimulate the cortex again immediately after a seizure both to avoid a new seizure and because hypothermia may cause false negative mapping results. Overall, the occurrence of seizures may affect the mapping strategy and to some extent jeopardize the reliability of mapping. Accordingly, the use of Electrocorticography (EcoG) and the choice of appropriate neurophysiological parameters play a role in reducing the risk of intraoperative clinical seizures.

❒ Neurophysiological probes

Electrophysiological stimulation of the cortex is related to the use of a number of different neurophysiological parameters, which can influence the final effect of mapping. The use of monopolar *versus* bipolar stimulation is one of these variables. The vast majority of Authors use bipolar stimulation either from a probe or from two adjacent electrodes of a strip or grid. Electrodes are usually 5 to 10 mm apart but their diameter varies as much as 4-fold (1 to 4 mm), which - keeping constant the other parameters - can influence the charge density applied to the cortex (this parameter can therefore also affect comparison among different studies). Bipolar stimulation is supposed to produce a higher current density more focally than monopolar stimulation(103). Schekutiev and Schmid(156) convincingly demonstrated that bipolar stimulation with a concentric electrode was more specific than monopolar stimulation with a focal cathode and remote anode, using the same stimulus parameters. However, most of the studies claiming the focality of bipolar stimulation, refer to Haglund's paper on optical imaging(58). Yet, in this study, the maximum current intensity never exceeded 4 mA, while in a clinical setting it goes as high as 15 mA. Therefore, the real dispersion of current when using bipolar cortical stimulation and the related risk of activating distant cortical sites has never been systematically studied and, especially at higher intensities, the lack of selectivity may be a real drawback. It should also be considered that while bipolar stimulation will produce less spread of current at the same intensity, it is also more sensitive to the orientation of the bipolar tips with respect to the axis of the fibers being stimulated(97). Finally, as recently pointed out by Berman et al.(12), no studies could be found in the literature describing the penetration distance of bipolar stimulation current in subcortical white matter.
Up to now, monopolar stimulation with a short train of stimuli has proved to be not inferior to the traditional 60 Hz technique in mapping the primary motor cortex(77). In terms of preventing electrical injury to the cortex, while safety of bipolar stimulation at 50 Hz was previously demonstrated(55), preliminary data in rats suggest that the short train technique does not induce significant morphological or electrophysiological changes up to 30 mA(105). The short train technique, however, is recommended to map motor cortex and subcortical motor pathways, but cannot be used for language and cognitive mapping, as the duration of the train is too short (about 20 ms) to induce any significant inhibition of the cognitive function to be tested.

❒ Subcortical mapping

Intraoperative mapping of subcortical language pathways is also a relatively novel field of investigation with limited literature(5,26,39,43,44,64). Similarly to what emerges from the literature concerning subcortical motor mapping(39,73,93), Authors usually declare the range of stimulation intensities but detailed analyses of subcortical thresholds are missing. Interestingly, most of the Authors state that for subcortical mapping they used the same current intensity which elicited a cortical either sensory or motor response. A clear explanation of this neurophysiological strategy is however missing. The issue of current spreading when increasing intensity and the different impedance of gray and white matter would suggest that a mere translation of the cortical threshold to a subcortical level may not be the most appropriate approach. Clearly this issue has not been addressed yet in the literature but is it foremost critical from a neurophysiological standpoint.

With the advancements in Diffusion Tensor Imaging (DTI) and the increasing interest for subcortical mapping, a trendy issue in functional brain surgery is the correlation and mutual validation of these two techniques. Preliminary reports[6,12,13,64,72,99] suggest a good correlation between these two methods. In terms of validation, a point missed in virtually all papers is the information on current threshold to localize pathways subcortically. Correlation on the neuronavigational system between localization of the corticospinal tract or subcortical language pathways and positive subcortical mapping sites is important[161]. However, stimulation intensities in a range between 3 and 16 mA, as reported by most of the Authors, have significantly different localizing values as the current spreading is obviously different. Consequently, a strict validation of a correspondence between the anatomical information (DTI) and the neurophysiological data (subcortical mapping) should be based on detailed threshold information more than on less specific terminology such as "positive subcortical mapping sites"[33].

The attempt to standardize intraoperative neurophysiological techniques necessarily meets the needs for a validation of their clinical use and this should be based mainly on correlations between intraoperative findings and postoperative outcome of the tested functions. Some attempts, in this perspective, have been performed with regards to motor function by establishing preliminary criteria for the interpretation of Motor Evoked Potentials (MEPs) in brain surgery[76,104].

❒ Interpretation of the interference

For the majority of neurophysiological techniques, the quality of evidence for the benefits of cortical mapping is scarce (mostly class III, some class II studies) and mainly based on non-randomized historical controls studies, analyses of clinical series and expert opinion. In particular for language mapping - when compared to motor mapping - the analysis of results is complicated by the choice of the appropriate task to test a specific language-related function. Even more for cognitive tasks other than language, choice of the appropriate test is crucial because a "negative" mapping result does not allow considering that area as "non-eloquent" if function has not been tested properly[32,61]. Therefore semeiology of language is of outmost importance in the interpretation of the results, and therefore in the correlation with the outcome. For example, a "speech arrest" or a speech disturbance can be induced not only by the inhibition of essential language areas but can be the results of stimulation of nearby negative motor areas in the perirolandic cortex[92,99] or the lower part of the primary motor cortex. Because of the variety of functions that can be tested and of sites identified as relevant in language tasks, a clear terminology and consistency between pre-, intra- and postoperative testing is essential for the validation of the appropriateness of neurophysiological techniques. For example, if during surgery in the posterior superior temporal gyrus visual naming is not tested intra- and postoperatively, this function may be selectively impaired but we will classify the patient as "unchanged" and consider the adopted neurophysiological strategy as valuable.

In conclusion, from a clinical stand-point, efficiency in neurophysiological mapping is becoming a priority because neurosurgeons seek to reduce the time spent mapping to improve patient comfort and tolerance during surgery, and to minimize operating time. Although we are still far from establishing guidelines or substantiate the need for neurophysiological mapping by evidence based criteria, the usefulness of these techniques is proved by countless patients who saw their risk of postoperative language decline minimized thanks to the use of intraoperative neurophysiology. Yet, the following may represent some fields of investigation to improve the reliability of mapping and further support preliminary observations on the "cognitive brain" which, for now, should cautiously be considered as speculative.

☐ VISUAL OBJECT NAMING

❒ Task description and procedure

The *Visual Object Naming* (VON) is a task for measuring anomia, a feature of all types of aphasias, so that it can determine a site essential for language function[106,117]. Furthermore, it applies well to the already limiting conditions of a surgical procedure: it is short and easy for patients.

■ **Procedure.** Current literature shows that all Authors perform the VON task. Ojemann's procedure is a recognized pattern of steps to which Authors refer in preparation for an awake craniotomy. Depending on the aim of the study the procedural steps are described more or less in detail.

Most Authors give a point-by-point description on how they administer the VON task during intraoperative mapping, even if it is a replica of Ojemann's procedure[110,116,119,129,157]. Others simply quote the source giving a brief description of the procedure[4,31,39,57,91,108,121,124,141,144]. Other Authors do not describe and do not quote the source of methodology; this gives evidence of the significant diffusion and recognized validity of the VON task[6]. The following are the main referred Authors: Berger[9,11] e Ojemann[11,106,107,114,120]. In general, all Authors perform awake mapping the same way.

❍ ***Procedure before mapping step by step.*** According to Ojemann[118], techniques of intraoperative stimulation mapping must indicate where the language function is located and where it is not[(a)]. Achieving a wider craniotomy is aimed to define both the areas involved in the surgical resection and those considered as "classic" language locations. Here we summarize the main steps observed before language mapping, according to Ojemann's protocol (excluding the details concerning local anaesthesia):

1. prior to language mapping the Rolandic cortex is identified by stimulation. The sensorimotor cortex is identified by associated evoked motor and sensory responses to tongue, teeth, throat, or face;
2. language mapping for each patient uses the larger current that does not produce an afterdischarge at electrocorticogram;
3. a current range of 1.5-10 mA is administered, delivered from a constant-current stimulator in 4-second trains at 60 Hz across 1-mm bipolar electrodes separated by a 5 mm gap;
4. the chosen sites for mapping stimulation are identified by small tags randomly applied on the cortex (10-20 sites per subject).

As far as point 1 is concerned, the literature shows that some Authors identify the anterior Rolandic cortex. For this purpose, Ojemann investigated the area immediately anterior to the face motor cortex, observing that electrical interferences caused an inability to mimic[(b)] even a single oro-facial movement, which could be essential for speech as well. The purpose of this first step is to distinguish between motor and sensory areas and the Broca's area[106]. In 95.5% of cases Broca's area was found in those locations where a speech arrest was evoked during the task without a simultaneous motor response in the mouth, which is usually sited in the area directly anterior to the face motor cortex (*see successive chapter "Other tasks", section "Counting", at page 129*)[57]. In order to exclude a disturbance due to muscle participation in speech arrest, Schäffler et al.[155] looked for "positive" and "negative" symptoms evoked by the inability to perform motor tasks during stimulation, for example during protrusion and rapid alternating movements of the tongue. Bello et al.[5] determined Broca's area by asking patients to count and also by the use of electromyography (three electrode placements: upper lip, lower lip, cheek).

As regards all other steps (points 2, 3, 4), they have been analyzed elsewhere (see *previous chapter "Electrical stimulation", at page 119*).

❍ ***Language mapping step by step.***

1. Language function is measured by showing the patient a set of achromatic slides, each one a line drawing of a different common object such as a bell, a hand, a car, a ring, introduced by a carrier phrase "That is a..." or "This is a..."[115]. Later in this text (*see successive subsection "Cognitive tasks", at page 124*) a description of which batteries of slides are used for the VON task will be given.
2. Slides are displayed for 4-second intervals, after instructing the patient to name each one as it appears.
3. Current is applied as the slide appears on-screen and continued until the following slide, or until the patient manifests disturbances. The sequence would involve a slide associated to stimulation followed

(a) It is important to underline that Ojemann looks for both positive and negative language sites, leading to a wider craniotomy, an aspect that will be discussed later by Mitchel Berger (2008). The Authors (Sanai et al.) demonstrate that craniotomies tailored to limit cortical exposure, even without localizing positive language sites, allow most gliomas to be totally resected without consequences for language[151].

(b) Patient saw a sequence of three slides with the same simple oro-facial posture (such as protrusion of the tongue) or three different postures and he/she has to mimic them. Stimulation occurs on a randomly selected half of each series. Furthermore, there is a striking association between these motor sites and the ability to discriminate speech sounds (phoneme identification) (Ojemann, 1983)[107].

by at least a "stimulation-free" slide. For each chosen small cortical site a minimum of three stimulations is performed. Regarding the distance between tags, it has been shown that the effects of stimulation on naming may be quite localized, changing within a centimetre, even on the same gyrus[120].
4. Patient responses are recorded by manual scoring in order to provide immediate feedback to the surgeon and by audiotape for further analysis[114].

As regards point 1, the carrier phrase is indispensable to discriminate between anomia and speech arrest and/or motor disturbances (*see also successive subsection "Positive site" of this section, part "Error definition", at page 124, and Table 3*).

Point number 1 and 2 do not show significant differences among Authors. As regards point 3, some Authors start the stimulation immediately before the presentation of slides[5,63].

Here, it must be noted that a learning effect can limit the validity of the test after a certain number of repetitions, specifically more than four[121].

As regards point 4, it will be better described in *chapter "Data Recording" at page 132*.

■ **COGNITIVE TASKS.**

❍ ***BATTERY.*** The source for intraoperative test images varies amongst Authors, as it can be gathered from the literature, and quite often it is not quoted. The main batteries we take into consideration below will show differences from one another based upon various parameters (frequency, familiarity, name category). Some Authors report the sources for line drawing objects. Usually these are:

- the *Boston Naming Test* (BNT)[73]. It represents a measure of object naming from 60 line drawings characterized by different levels of frequency and divided by category: vegetables, wild animals, tools[63,135,136,139]. Some Authors chose a brief version of 50 items[99];
- the *Snodgrass and Vanderwart Test*, consisting of 80 items - from a pattern of 260 pictures - divided in 3 living categories - animals, fruit, vegetables - and 3 inanimate categories - tools, vehicles, furniture; further items are ten musical instruments and ten body parts. Each word has the same number of syllables but different levels of frequency[6,131]. A short version of the Snodgrass Test is also available, where only high frequency items are selected[62];
- the *DO80* (in French: Dénomination Orale de 80 images), involving 80 black and white pictures chosen according to variables such as frequency, familiarity, age of acquisition and level of education. These stimuli are homogeneous along the different categories, with normative data[53,96];
- finally the *Aachner Aphasia Subtest*[52,129].

Other Authors describe black and white line drawings[118,120,121].

❍ ***ITEM SELECTION.*** As a standard procedure, before being performed, an intraoperative test has to be previously verified on each patient.

Ojemann et al.[117] used to choose those items that patients were able to name as quickly as possible without difficulties during the preoperative testing phase. Items that patients were not able to name during the preoperative assessment were deleted[63,118,141]. Ojemann does not specify the cut-off number of items a patient can misname when included into an awake surgery protocol. Only Roux and Lubrano specified a 10% error cut-off[89,145]. By adopting a high cut-off in the item selection, the probability of false-positive answers due to a language variability is reduced. According to Little et al.[88], a preoperative object naming error rate greater than 25% cannot statistically correlate with cortical stimulation and therefore cannot be reliably interpreted as evoked by stimulation. On the other hand, the same Authors suggested it is possible to improve the patients' performance by training them to name objects, in order to allow a reliable intraoperative language mapping. This strategy must be better analysed considering the practice effect on naming distribution that Ojemann found in a previous study on verb generation[121] and the differences between automatic series such as counting[131].

■ **POSITIVE SITE.**

❍ ***ERROR DEFINITION.*** In the absence of stimulation undefined errors could happen. Without a careful preoperative assessment the intraoperative definition of errors remains very uncertain. Ojemann et al. found that the intraoperative range of errors vary between 4.6% and 22%[117,118]. Haglund et al.[57] excluded all patients with an intraoperative baseline (with no stimulation) naming error rate averaging more than 25%. Both Authors confirm that the higher the rate of spontaneous error, the lower the validity of the test. Nevertheless, this finding was not quite taken into consideration later on.

G.A. Ojemann[114], using the single sample binomial test to determine if a site is essential for language, examined the accuracy of response during naming. He gives a non-parametric description to determine if a site can be interpreted as essential: "*a site was determined to be related to language function if the chance probability of errors evoked at that site was less than*

0.05 [...] evoking errors during two of three stimulations at a site often achieved that level of statistical significance...".

Some Authors use different strategies. For instance, Peraud et al. tested all sites at least twice and considered two of two stimulations acceptable to consider a site positive for language function(129). Others chose three of three stimulations to ensure whether a cortical site is essential (3/3 tries)(51,144). Hamberger et al.(63) stimulated a minimum of two times, for both visual and auditory naming, at each site. When one of two attempts was performed inaccurately, two more tries were made. Sites were considered critical for task performance only when at least 75% of responses were inaccurate (3/4 tries). In conclusion, except for few cases, it seems that most surgeons would consider at least two times out of three (2/3 tries) necessary for the validation of a functional site(5,57,144,157). Again, one should note there is a learning effect that limits the validity of a test after a certain number of repetitions, specifically four(121) (*please see also successive section "Distribution of positive sites", subsection "Distribution as regards individual characteristics", at page 128*).

❍ ***Type of errors.*** The VON task is easy to apply but its interpretation is much more difficult. We will here present two levels of description: the definition of errors (Table 3) and the pattern of errors considered by each Author (Table 4).

When classifying the type of errors, the main distinction that needs to be made is between speech arrest, anomia and speech disturbances. Speech arrest has been already mentioned in *chapter "Visual object naming", section "Task description and procedure" and subsection "Procedure", at page 123, and Table 3*. Anomia is the inability to produce the name of the object with a preserved capacity to speak, as demonstrated when reading the carrier phrase "This is a" (Table 3)(118). All other disturbances have been variously named without concordance on the definition.

Since the origin of awake mapping, Penfield and Roberts (1959) listed as aphasic-like errors *distortion* and *repetition* of syllables and words, *confusion of numbers* while counting, inability to name with a preserved ability to speak, *misnaming* and *perseveration*. Previously, Fedio and Van Buren(171) schematized naming responses into four classes:

a) correct;
b) correct but with a significant delay or hesitation;
c) substitution or misnaming;
d) omission or complete failure to name.

The last two, c) and d), were regarded as errors. Ojemann et al. divided errors into: omissions, non-sense word, jargon, other errors not specified(118).

The classification of errors is strongly related to the aim of a study; it can vary from a simple definition of error (every change that occurs during stimulation) to a more articulate definition (Table 4)(5,7,28,35,36,38). In addition, it is difficult to find the same criteria in the pre- and postoperative study results.

■ **Clinical validation.** Ojemann et al. observed that the stimulation of one cortical site can alter a language function such as naming after each single attempt. There is further evidence that a site where only partial disruption has occurred (just one over three) is less crucial to language than the "100%" sites(106).

In 1994 Haglund et al.(57) achieved statistically significant observations regarding the correlation between postoperative worsening and resection distance from a positive site. Since then, 1 cm is the safe critical distance between the resected tissue and the positive site(5,57,144,150,166). Later observations raised doubts on the criterion. Resection carried out at a distance of less than 1 cm from the positive cortical area caused postoperative deficits that spontaneously resolved(78,129). Seek et al.(158), in 2006, made a single case observation that margins of resection do not necessarily need to be respected. Postoperative aphasia did not occur despite the resection of a brain area where language functions were impaired or blocked during electrical stimulation of the left temporo-parietal cortex. A moderate aggravation of the pre-existing word-finding difficulties was noted, but spontaneous speech and oral comprehension remained preserved.

A resection-outcome analysis is performed immediately after the operation (range 3-7 days after) and another assessment at one month and three months. A follow up evaluation takes place usually after six or more months(6,63). Hamberger et al. prolonged the single outcome evaluation time to one year, raising the question on what phenomenon is being observed, whether it is the result of the mapping hypothesis or if it rather is an unrelated event linked to other processes such as brain plasticity(40).

❒ Distribution of positive sites

Here a description of the distribution of sites found using the VON task will follow.

■ **Cortical topography.** Different techniques for describing cortical topography have been used to por-

Error	Definition
Articulatory interferences	• Stimulation evokes a visible face and tongue contraction[141]
Anomia	• The inability to name with a preserved ability to speak, demonstrated by reading the test phrase "This is a"[117] • Patient was unable to name objects but was able to repeat sentences and had fluent speech[150] • Patient is not able to name the object[58,157] • The patient is unable to find the appropriate word for the image. "This is… a ….". Once the stimulation is not longer applied the patient is again able to name the object[144] • Patient can speak but he is not able to name the object: e.g. "I know the name but I can't pronounce it…"[89] • Anomic episodes: preventing the patient from saying the name during stimulation[5] • Anomic episodes: retained ability to speak without the ability to name[88]
Omission	• Same definition as anomia in Ojemann
Speech arrest	• The patient is unable to say anything after the image has been shown and stimulation applied. No visible contraction of face/tongue[144] • No perceptible face or tongue contraction[89] • Arrest of all speech[88] • Patient does not produce utterance[50,129,132,144] • Discontinuation in number counting without simultaneous motor responses (i.e., mouth or pharyngeal-muscle movement)[150] • Interruption in counting or no verbal output during naming[157] • Complete interruption of number counting[58]
Aphasic arrest	• Patient reads the carrier phrase and then he/she does not produce the name[50,129,132,144]
Perseveration	• During the naming task the patient repeated the previous and not the current item[31]
Hesitation (or delay)	• Patient's response latency (seconds) during stimulation exceeded by 2 standard deviation his baseline or pre-stimulation pace[171] • Response time - no more specifications[41,63,144]
Tip-of-the-tongue	• The number of correct responses following phonemic cueing, or that occurred two or more seconds post-stimulus[63]
Kinds of paraphasia	• Phonetic: a disorder of the articulatory realization from one to several phonemes occurs with possible complete anarthria, or speech arrest • Phonemic: disorder of the phonological form of the word • Semantic: disorder of the meaning of the word[7]
Dysarthria	• Distinguished from speech arrest by the absence of involuntary muscle contraction affecting speech[150]

Table 3. Naming: errors definitions considered in literature.

tray the positive cortical sites for naming. The variability in the location of sites that show significant evoked changes in naming was determined by aligning the individual patient maps to Rolandic cortex and sylvian fissure[118]. The Authors divided the brain surface in small squares drawn schematically in relation to surface landmarks. The frontal cortex was divided in: inferior, middle and superior frontal gyri, beginning with the most anterior evoked motor response that identified the anterior limit of the motor cortex. The inferior frontal gyrus was further divided in inferior and superior zones. The temporo-parietal cortex was determined from the posterior end of the sylvian fissure to the projection of the foot of the central sulcus onto that fissure. This region was divided in four zones: superior, middle, inferior temporal gyri and parietal operculum.

Haglund et al.[57] divided the temporal lobe in sectors based on the Superior Temporal Gyrus (STG), Middle Temporal Gyrus (MTG), and Inferior Temporal Gyrus (ITG). Furthermore, each of the three temporal lobe sectors was divided in six zones: one anterior to the projection of central sulcus, one posterior to the end of the sylvian fissure, and four in between. The same

Authors	Pattern of errors
Bello L. et al., 2007[5]	• Anomic episodes, phonemic or semantic paraphasia
Benzagmout M. et al., 2007[7]	• Phonemic, semantic and phonetic paraphasia, slowness with initiation, perseveration
Petrovich Brennan N.M. et al., 2007[131]	• Paraphasic errors, speech arrest, hesitation; word finding difficult, dysarthria, circumlocution, hypophonia (no description)
Corina D.P. et al., 2005[19]	• Anomia, delayed, semantic paraphasia
Duffau H. et al., 2002[41]	• Speech arrest, anomia, dysarthria, spontaneous speech reduction
Fontaine D. et al., 2002[50]	• Aphasic misnaming: defined by semantic paraphasia and confusion of expressions, aphasic arrest defined by carrier phrase uttered but not produce the name
Hamberger M.J. et al., 2005[63]	• Tip of the tongue: correct response after phonemic cueing, time of answer
Ojemann G.A., 1977[111]	• Naming errors: correct name after the slide changed (after stimulation had stopped), substitution (e.g. fork instead of spider)
Ojemann G.A., 1978[113]	• Total arrest of speech, omission
Ojemann G.A., 1979[109]	• A total arrest of speech, anomia
Roux et al., 2004[144]	• Articulatory interferences, pure reading arrest, paraphasias, ocular movements, others (hesitations and perseverations)
Sanai et al., 2008[150]	• Speech arrest, dysarthria, anomia, alexia, expressive and receptive aphasia. Mild deficit: paraphasia were noted but did not influence the resection
Signorelli et al., 2001[160]	• Paraphasias, speech arrest, perseveration, anomia and comprehension troubles

Table 4. Naming: the more common error patterns considered in literature.

cortical topography was adopted by various Authors[95,154].
Roux et al.[144] considered the terms “Broca” and “Wernicke” region imprecise and scarcely informative. These Authors arbitrarily divided the temporal gyri in three segments by drawing an imaginary line extending between the pre- and postcentral gyrus. Schäffler et al.[154] and Schwartz et al.[157], using implanted subdural grids, divided the lateral temporal lobe, inferior frontal lobe and inferior parietal lobe into separated squares (48 one-centimetre squares). The same criteria were used by Sanai et al. (2007)[150] during intraoperative mapping.
In addition, the neuronavigator made the exact location of sites increasingly easier, aiming to a common parameter for site definition.
■ **General distribution.** Ojemann et al.[118,121] attempted to describe a distribution of language. He reported that naming interferences occurred over a wide area of left lateral cortex, extending beyond the limits of the classical model. He also explained that there is a substantial variability in the individual organization[109,117]. Commonly, at least one area was described in the inferior frontal gyrus, and one or more were in the temporo-parietal perisylvian cortex. Sanai et al.[150], undertaking a different approach for language mapping, found a different naming location. Their resection strategy did not require identification of the stimulation-induced positive sites within the field of exposure; thus, they performed the resection of cortical tissue on the basis of negative sites. Consequently less naming sites were found, distributed predominantly in the superior and middle temporal gyrus, when compared to those classically described in previous language studies of the temporal lobe[112]. The Authors state that these data are not due to a site-selection bias, since, despite the use of tailored craniotomies, summing all cortical stimulations from 186 patients with temporal lobe lesions they mapped the entire temporal lobe.
Other studies identified naming locations on specific regions such as the insular lobe, the striatum and opercular region and the basal temporal language area[34,42,44,53,94,131].
Essential areas are commonly localized on one or more rather small cortical surface areas of 1-2 cm^2. Regards the surface areas, most patients show errors evoked in any uninterrupted area of cortex larger than 1.5 cm^2; some cases show uninterrupted areas of language greater than 2.5 cm^2[114]. In some cases these areas have well-defined boundaries, in other they are surrounded by a small rim of cortex where a single error can be evoked. At times a different terminology is adopted by Authors for these cortical regions (e.g. dis-

creteness, nodes[(c)], shell-core[(d)], respectively, in Haglund et al.[(57)], Schwartz et al.[(157)] and Schäffler et al.[(154)].

■ **Distribution as regards individual characteristics.** The location of cortical sites in relationship to demographic characteristics (gender; age; preoperative Verbal Intellective Quotient: VIQ) and practice effect have been described[(10,57,112,157)].

As regards gender, Mateer (1982) found differences in naming distribution. Males were exhibiting a higher proportion of sites in the left anterior temporal cortex than females. All later studies found no correlation between gender and naming site distribution[(25,57,157)]. On the other hand, female patients seem to have a significant larger number of sites than males (mean sites number 3.1 *versus* 2.1)[(57)].

S.G. Ojemann et al.[(122)] compared the results of a previous study[(118)] based on adult population (117 patients, mean age 30.8 years) to a study based on paediatric population (26 patients, < 16 years old). The older age group showed a higher frequency of naming errors and more positive sites; in addition, the paediatric group was more likely to have multiple essential areas in the temporo-parietal regions. The location of essential areas in adults seems not to change over time if further lesions do not occur[(107)].

Differences in language organization are apparently related to VIQ and primarily involve the temporal lobe (VIQ mean scores 93.6 *versus* 99.9). Patients who preoperatively had a lower VIQ score showed larger language areas than patients with a higher preoperative VIQ score[(118)].

Naming changes due to stimulation of the superior temporal gyrus were significantly more likely in patients with a lower preoperative VIQ, while subjects with a high VIQ showed more naming errors when stimulation was applied in the middle temporal gyrus[(118)]. Practice effect due to repeating the *Verb Generation Task* can also influence the frequency of naming sites. Specifically, more sites were found to interfere with novel than with practiced verb generation. It seems that, as the task is performed more efficiently, the cortical area devoted to the task itself decreases; this effect has been found in the frontal, temporal and parietal cortex[(57,121)].

■ **Bilingual patients.** Investigations on multilingual subjects have generated various results depending on multiple factors: the type of spoken language, the tasks applied, the subjects considered. It is not clear whether languages are mediated by multiple and separate cortical areas or shared by common areas. Some studies report that in bilingual patients multiple and separate areas of the cortex mediate different languages[(4,47,75,90,114,141,145,174)]. Other investigations pointed out that common areas of the brain are activated during language tasks[(69,133)].

Globally considered, research recommends performing multiple intraoperative mapping for all languages in which the patient is fluent, in order to avoid the potential confounding effect of language switching between trials, since language switching has been shown to induce cortical activation[(66)].

As regards distribution, naming and reading tasks are known to activate similar or different areas in the brain[(90,139,145,174)]. In bilingual patients language-specific interference was found by all investigating teams in the posterior temporo-parietal regions[(89,90,134,144,145,174)]. Nevertheless, language-specific areas in bilinguals can also be found in frontal regions[(4,89,134,144)]. Those language-specific sites were found no matter what the level of proficiency, the age of acquisition and the type of language tested. Further studies will be needed for validation.

■ **Distribution of visual naming *versus* other language tasks.** Regardless that surgical resection is performed respecting the positive sites margins, patients may still display a postoperative language deficit, such as in comprehension or reading[(131)]. The literature shows that specific sites for different language functions exist and they are often in close relationship to naming sites.

❍ ***Counting.*** Counting is often related to the speech arrest response during electrocortical stimulation and it is often identified in the area directly anterior to the face motor cortex and also in the posterior part of the superior temporal gyrus, extending toward the inferior parietal lobe[(57,157)]. On the other hand, Sanai et al.[(150)] found a 73.9% of frontal lobe sites where speech arrest occurred while counting; none of the patients had a speech arrest during parietal lobe stimulation and nothing is specified as far as the temporal lobe is concerned. In the literature only Petrovich Brennan et al.[(131)] used direct cortical stimulation to compare the sensitivity of the two most common tasks (VON and counting) in the identification of language areas. Results can be summarized as follows: first, a larger

[(c)] Nodes are non contiguous areas where interruption of language function is more likely (Schwartz et al, 1999)[(157)].

[(d)] "Core" language area are cortical sites at which language interference occurred at ≥ 20% of electrodes; "shell" language area are cortical sites with language interferences at 11-19% of stimulated electrodes[(156)].

number of sites is found during object naming than during counting; second, counting errors belong to specific categories (such as speech arrest or hypophonia); finally, in some sites an overlapping is visible; in others only the naming task causes a change in the execution, not vice versa. This could suggest that by choosing only the naming task false negative language localizations may occur.

❍ ***Auditory naming.*** Naming an object after having heard a definition (auditory naming) belongs to a different location then VON[63,95]. In particular, Malow et al.[95], using subdural electrodes on patients with temporal lobe epilepsy, found that stimulation in the anterior and posterior temporal cortex elicited errors in auditory naming, independently from VON. Hamberger et al.[60] found a regular representation of auditory naming sites anterior and close to the visual naming sites, in the mid posterior of the superior temporal gyrus.

❍ ***Verb generation.*** The selective impairment between action naming and retrieving object names, documented by Goodglass (1934) and Miceli et al. (1984), is confirmed in awake surgery[19,121]. The procedure of presentation was the same as VON, using a list of concrete nouns (40 items taken from neuro-imaging studies). Data analysis reveals a double dissociation between action and object naming. In these cases, the region giving rise to an object naming disruption lays anterior to that implicated in action naming[19].

Two different maps emerge from the use of verb generation and visual naming tasks: one in the frontal and one in the temporo-parietal area. The frontal lobe sites where stimulation interfered with verb generation were always located at 1 cm or less from sites responding during object naming task, and posterior. On the contrary, close vicinity and overlapping rarely occurred in temporal and parietal regions[121]. Furthermore, specific sites of verb generation task impairment were more frequently localized in posterior (temporal and parietal) regions, while the middle temporal gyrus seemed to be more specifically associated to object naming.

❍ ***Reading.*** Areas where stimulation mapping causes changes during reading or VON tasks only, and regions where overlapping of both functions occur, have been identified in the temporal regions[150,157]. In particular, the distribution of reading has been found rather adjacent to naming sites (distance of 1 cm or less). Specific sites for reading were often in the posterior temporal lobe, supramarginal gyrus, dominant angular gyrus[144]. An overlapping with speech arrest is rare (21% of cases); this suggests that reading is part of a semantic lexicon that cannot be defined with automatic series.

■ **Distribution as regards pathologies.**

❍ ***Epilepsy and glioma.*** Haglund et al.[57] studied the possibility of differences between brain tumor and epilepsy patients (the same 117 patients from Ojemann's study, published in 1989). The brain tumor group had fewer positive naming sites in the superior temporal gyrus than the epilepsy group. Authors suggested that a slow growing lesion eliminates or alters the existing essential language sites.

❍ ***Low and high grade glioma.*** Despite the fact that high grade gliomas show a higher rate of preoperative clinical deficits, the rate of subcortical language sites in low and high grade gliomas was similar[5,57,123,173]. These data seem consistent with previous research conducted upon high grade gliomas, where an individual variability on eloquent sites location was found, similarly to low grade gliomas[160].

□ OTHER TASKS

Other tasks linked to language function (reading, writing, short-term memory) or other functions (calculation, neglect) were adopted for intraoperative mapping. In some cases these are part of a standard battery[150,157,166], in other they are performed to investigate (for study and clinical reasons), specifically the functions they belong to (e.g. reading).

Also for these tasks the first steps are the same described for mapping the visual naming task. Thus, after having described in detail the VON task and having analyzed the literature regarding other tasks, questions are raised.

❒ Counting

Counting belongs to an "automatic" speech category, together with reciting months of the year and days of the week, nursery rhymes and other well-known and familiar songs. Some Authors refer to this category of speech as "non-propositional", as opposed to "propositional" speech (that is the formulation of a message, like in VON) or "over-learned" serial[131]. It is commonly used preoperatively and intraoperatively together with VON, since it is a simple method for eliciting continuous and fluent motor speech. It is not necessary to explain in detail the procedures of the counting task, but it must be underlined that this task has an important role in defining the "speech arrest" (*as seen in Table 3*), discerning it from the speech arrest caused by motor and sensory areas[58,150,157]. Further details of the distribution in relation to VON have been previously described[131].

❒ COMPREHENSION

Some Authors developed tasks to test comprehension during intraoperative mapping. The *Palm and Pyramid Tree Test* consists of a triad of pictures showed to the patient, that has to pair them by naming the two pictures with conceptual links[51]. Other tasks often used are brief versions of the *Token Test* and of the *Sentence and Word Comprehension Test*[6, 70,135,147]. In general, positive sites are elicited in posterior areas of the superior temporal lobe. The posterior part of the superior temporal gyrus showed a dissociation between sites where anomia occurred after stimulation and other sites where comprehension disturbances - with preserved ability to name the object - are elicited[28].

❒ READING

The *Reading Test* is quite common amongst intraoperative task batteries and subdural electrode stimulations; it is adopted to supplement language mapping[37, 85,106,150,157,166]. Some Authors specifically investigated the reading tasks or compared them to other tasks (e.g. writing, VON, counting, calculation and so forth)[89,144]. As far as the adopted stimulus is concerned, different procedures can be found in the literature: sentences or single words. As regards reading of sentences, Ojemann et al.[117] was the first to describe reading mapping. He assessed this function including it in a sequence of trials for evaluating short-term memory; this procedure will be described later (*see successive section "Working memory", at page 131*). Here we must point out the instrumental role of the "reading" trial - as storage phase or distractor - for assessing another function (short-term memory).
Roux et al.[144] and Lubrano et al.[89] used a set of unrelated sentences, never previously rehearsed by patients. Stimulation was applied randomly on the cortex during reading for the entire duration of one of the slides.
"Single word" stimuli have been also used; items were projected sequentially on a computer screen and the patient was asked to read it[150].
Authors do not specify how they constructed sentences or selected words. The analysis for defining a site as positive was the same as previously seen for VON; testing was conducted at least three separate times and sites that did not show reproducible language interference were not considered eloquent areas[144,150]. In addition, no consensus has been reached upon the definition of errors or of the procedure, so far (Table 5).
As regards distribution, several focal areas where changes occurred during the reading task stimulation were frequently found in posterior middle and posterior superior temporal gyri[86,157]. Sanai et al.[150] described reading sites sparsely located in the temporal lobe, mostly in the inferior parietal lobe, 1-2 cm behind the somatosensory cortex.
For a comparison between reading and naming (*see chapter "Visual object naming", section "Distribution of positive sites", subsection "Distribution of visual naming versus other language tasks", part "Reading", at page 129*).

❒ WRITING

Agraphia was described since the 1860s and in 1881 Exner postulated that lesions on the foot of the frontal lobe (F2) could specifically cause writing deficits. Writing models differentiate a lexical system (based on whole-word retrieval involved in writing regular and irregular words) and a phonological system used to write unfamiliar words or pseudo-words. Nevertheless, in the task construction, a distinction in the writing, as well as in the reading and calculation tasks, was not maintained. Few Authors performed awake surgery with the aim of mapping and sparing areas involved in writing processes[89,144].
Patient positioning is an important aspect during the task for writing functions. Patients is placed supine and a three-point head fixation device is applied. After being fixed and rotated 30° opposite to the side of the craniotomy, the head and shoulders are slightly raised (10°-20°) so that the patient feels comfortable and can see her/his own hands while writing. Patients have to use the dominant hand and a pencil to write horizontally on an A4 sheet of paper[89], that is laid on a stiff pad and handed out vertically by a nurse. The common procedure is made of dictation of sentences at each cortical site and application of di-

Error	Definition
Articulatory interferences	• Including total arrest of speech, production of few intact words, mispronunciations, perseveration[106] • Stimulation evokes a visible face and tongue contraction[144]
Pure reading arrest	• The patient stops reading, e.g. “The car is blue and…”. Once stimulation stops the patient is able to read again. No face or tongue visible contraction[144] • A type of language deficit not due to positive or negative motor effects*[154]
Alexia	• The retention of the ability to write and, but with errors in reading words[150]
Aphasia, receptive	• Impaired ability to understand written language[150]
Paraphasia	• The speech is fluent but the text read by the patient is incomprehensible or the words are inappropriate, e.g. “The tar is cue and straw….”
Jargons	• Production of jargons for substantive parts of sentences - such as nouns or verbs[106] • Reading fluently but with frequent errors in individual words including nouns[118]
Syntactic aspects/grammatical errors	• Errors involving only verb endings, prepositions, pronouns or conjunctions[106] • Production of incorrect words, or deletion of syntactic elements[118]
Miscellaneous findings	• Repeat words, hesitation during reading
Ocular movements	• The patient stops reading because of ocular movements

Table 5. Reading: type of errors definition. *Legend*: * Interference with reading aloud, according to Schäffler, can occur from stimulation of a positive or negative motor area of speech related muscles. To exclude this possibility Authors tested for negative motor effects by asking the patient to perform a tonic motor activity (e.g. protrusion of the tongue) and rapid alternating movements of the tongue. Furthermore, the patient was asked to stick out his tongue and this procedure excluded positive motor effects on the tongue (muscles twitches or movements of the tongue).

rect stimulation for less than 4 seconds while patients are writing[89,140].
Lubrano et al. also asked subjects to copy written material - isolated letters, words, numbers. In the course of the procedure, sites where interference from hand contraction or eye movements were noted were excluded from study. Authors evaluated the type of errors both qualitatively and quantitatively by comparing pre- and postwriting abilities[89].
The following errors were considered, without coupling them with cognitive and descriptive criteria: dyspraxic and dysphasic, writing arrest neographisms, difficulties in letter formation, omission of words or letters, and deterioration of hand writing[89,140].
As regards site distribution, it seems to be extremely localized (within 1 cm) in the angular gyrus[140]. Lubrano et al. identified sites in the superior temporal gyrus and posterior portion of the frontal lobe[89].

❒ Working memory

Working memory has been studied since the beginning of awake procedures. There is evidence of a role for the language cortex in short-term memory[115-117,171].
The procedure for assessing short-term memory is similar among Authors.
As far as the procedure is concerned, it consists of a composition of three slides; stimulation persists for five seconds and each site is stimulated at least three times. Stimulation is applied randomly during each of the three phases and the patient is never cued when it occurs. The memory tasks include encoding, storage and retrieval.
There are three distinct phases:
- *encoding* (or input): naming task;
- *storage*: reading of a sentence or number counting[115];
- *recall*: of the word presented during the input phase.

Ojemann (1978)[113] added a variant for the task, consisting of four achromatic slides. The first three are the habitual slides; the fourth is a recognition task (note that at this point stimulation is never applied. It is to make sure the patient recognized the object).
During the item selection procedure trials during which stimulation caused errors or hesitations were excluded. Trials with naming error are excluded from memory performance analysis to assure that the information to be remembered has been perceived[106].
With reference to the three task phases, the sites iden-

tified during the storing phase seem more frequently located in the temporal and parietal regions, while the recall phase appears more frontal[117].

❒ Calculation

Functions related to arithmetic tasks have been less investigated. Data come from few studies.
Tasks are very simple: addition tasks (e.g. 29 + 30)[140], addition and subtraction[80], multiplications and subtractions[46]. In general, the supramarginal and angular gyri are regions involved in calculus; interestingly, data from a case report suggest that functional areas involved in simple multiplications (learned by multiplication tables) are located at the posterior end of the sylvian fissure (close to the language sites), while subtractions are more likely located in the superior angular gyrus.
As already seen for other tasks, there was a preoperative selection of arithmetical items where no errors occurred.

❒ Intraoperative electrocortical stimulation in the right hemisphere

Although language has been extensively mapped intraoperatively, spatial functions have received less attention in clinical practice. This can be due to the fact that spatial functions are thought not to suffer strong consequences after removal of small portions of brain tissue. Contrary to this idea, it is well known that the presence of spatial neglect has a dramatic effect on the outcome of patients, both in terms of rehabilitation and of their quality of life[54,82,87,125]. In the past years very few papers have been published on intraoperative electrocortical stimulation mapping in the right hemisphere in patients undergoing tumour resection[3,52,171].
Bartolomeo's group in France[3,170,171] studied two patients undergoing tumour surgery in the right hemisphere by means of a very simple task, the *Line Bisection Task*. This task is the most widely used to detect neglect in brain damaged patients. In fact, neglect patients typically bisect the line towards the right side. The Authors found that, when asking patients to bisect a line as their cortex was electrically stimulated, patients showed symptoms of neglect, that is a rightward deviation of the line bisection. The areas stimulated were the right inferior parietal lobe and the right superior temporal lobe. These are areas typically associated to neglect, along with the deep inferior parietal lobe white matter, indicating an involvement of the superior longitudinal fasciculus. This way, functionally important areas could be determined and left intact, sparing patients from spatial neglect postoperatively.
Another paper comes from the Karnath's group in Germany[52]. The Authors studied with a visual search task one patient undergoing tumour resection. While different portions of the cortex were being stimulated the patient was asked to look for and to find L-shaped targets among rotated L-shaped distractors presented on a PC monitor. The Authors found that electrocortical stimulation of the central portion of the right superior temporal gyrus deteriorated the visual search performance to mere guessing; this suggested the crucial role of this area in the mediation of the exploratory behaviour.

☐ DATA RECORDING

The response of patients during awake mapping is an important aspect for the analysis of data also after surgery. Data from literature show different levels of analysis of response depending on the aim of mapping. In particular, response registrations depend upon the presence of a professional figure in the operating room, audiotape or/and videotape devices, blinded or multiple postoperative examiners.
Duffau et al. underline the importance of a speech therapist in the operative room to accurately analyze in real-time the functional responses induced by stimulation[46].
Haglund et al.[57] recorded the patient audiotape during language mapping and had it reviewed later on by a blinded examiner for the final analysis of significant language sites.
A further practice is to audio-videotape the mapping procedures, with patients' answers recorded through a microphone placed near their mouth[95,140]. This is particularly important to check mouth and face muscles and to detect eye movements that - mostly in frontal sites - could interfere with reading. A postoperative evaluation could be more efficiently achieved by more investigators, allowing the validation of intraoperative data[19,1501].
A picture of the brain was systematically taken after each brain mapping along with a written record of the findings during stimulation.

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