Do we Need to Wake Patients up during Cortical Surgery?

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Abstract: In recent years, a renewed fashion for awake surgery has appeared. In spite of its undoubted utility for scientific research, this technique has several limitations and flaws, usually not debated by parts of the scientific community.

We will discuss the aims and limitations of cortical surgery, especially the points relevant to protecting the patient. These objectives should define the guidelines that direct clinical practice. We will review the awake technique as well as various tools used in intraoperative neurophysiological monitoring (IONM) to explore and monitor several cortical functions during long surgeries. The main topics discussed include electrocorticography (ECoG) and cortically recorded evoked potentials (EP), including somatosensory, visual and auditory. Later, we will discuss methods to identify and survey motor functions as motor-evoked potentials, although they are elicited trans-cranially. Finally, we will briefly discuss a promising technique to monitor some language functions in anaesthetized patients, such as cortico-cortical evoked potentials (CCEP). We will address in depth some technical questions about electrical stimulation whose full relevance are not always considered.

Finally, we will discuss why, in the absence of empirical facts showing unequivocal superiority in post-surgical outcome, we have to awaken patients, especially when an alternate possibility exists without worst clinical results, as is the case for IONM.

Keywords: Anaesthetized surgery, awake surgery, cortical mapping, cortico-cortical evoked potentials, intraoperative neurophysiological monitoring.

INTRODUCTION

In recent years, there has been a renewed interest in surgery in awake patients [1-3]. This procedure uses the asleep-awake-sleep anaesthetic technique, which consists of induction with propofol + sevoflurane and topical blocking with svedocain + lidocaine around the skin incision. During exploration, the patient must be awoken slowly by removing the sedation. Recently, a new anaesthetic, dexmedetomidine, has been introduced for this type of surgery and is considered the most effective option [4], not only for asleep-awake-asleep technique, but for the conscious sedation one [5].

The scientific interest and relevance of this technique are undisputed. However, its clinical necessity is yet to be demonstrated, the surgery under total anaesthesia with intraoperative neurophysiological monitoring (IONM) is obviously more comfortable for both patients and medical staff. The main question that remains to be answered, therein, is whether the safety of the two techniques is equivalent.

Until now, no systematic comparison has been performed between awake and sedate craniotomy for cortical or subcortical surgery, and a definite answer remains to be established. However, both positions, for and against awake craniotomy, can be argued in this interesting debate, which is the topic of this work.

In our institutions, we have systematically performed IONM on anaesthetized patients for cortical and subcortical surgery for more than fifteen years, and we are firmly convinced of the validity of this approach.

IONM is a set of neurophysiological techniques that cannot evaluate complex functions (i.e., language function, visual or cognitive performance) but can allow the identification primary/eloquent structures with great confidence. Recently, even some parts of the language have been ascertained by cortico-cortical potentials in anaesthetised patients.

Our aim in this review is to show the powerful set of IONM techniques for use during cortical and subcortical surgery and to discuss why we think that a rational use

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ISSN: 1929-2260 / E-ISSN: 1929-2279/18

of them can avoid the stress induced by awakening the patient.

AIMS AND LIMITS OF CORTICAL SURGERY

From a surgical point of view, the cortex can be divided into two classes: i) the primary or eloquent cortex, which cannot be removed or injured because a permanent neurological deficit would appear, and ii) the non-eloquent cortex (secondary and association areas), regions whose function can be supplied by other areas or by means of plasticity.

Cortical surgery, especially neuro-oncology, is a great challenge for neurosurgeons from two perspectives: first, in some types of tumours, gross total resection (GTR) is the best predictor of outcome in terms of life expectancy, mostly for malignant gliomas [6,7]; second, a dominant goal of every surgery is to avoid new iatrogenic lesions. The relative weight of each of these principles can be changed based on individual considerations of the type of tumour, the structures affected, the life expectancy and even the social considerations of each patient. These features are particularly relevant to patients suffering from high-grade gliomas, for whom survival is directly related to the degree of tumour removal. Therefore, to maintain an adequate quality of life, the primary goal of surgery is to achieve GTR without compromising neurological function.

These considerations are extremely relevant at the time of making decisions during the surgery, as sometimes it is more important to remove more tumour, knowing that it is placed in a non-eloquent cortex, thus allowing longer survival without neurological deficits (although some transitory deficit can usually be observed) and preserving non-primary functions at the expense of leaving greater tumour volume, which will ultimately shorten the life expectancy.

With these options in mind, our goals during cortical/subcortical surgeries are two: first, to positively identify the eloquent regions and second, to preserve those structures (cortices and tracts coming from and going to) whose injury would induce permanent deficits. Our approach, therefore, is to maximize tumour resection until a primary/eloquent structure is reached.

CORTICAL AND SUBCORTICAL SURGERY IN AWAKE PATIENTS

After the craniotomy is completed and the anaesthesia is removed, the patient wakes up in the operation room. Usually, this process takes several minutes, and it is not unusual for the patient to become somewhat agitated. After a period of haemodynamical and emotional stabilization, functional mapping begins. Cortical stimulation, which is performed by the neurosurgeon, is usually achieved through a bipolar probe with ball-tips that are separated by 0.5 cm. It is common to use 60 Hz trains over 1-4 s. The pulse width is usually 1 ms, with a current intensity of 2.5-10 mA [8,9]. During stimulation, a set of neurological and neuropsychological tests that are validated by a neuropsychologist or the patient, less commonly, by the neurosurgeon or a neurologist.

Positive responses (e.g., paraesthesia or muscular response) or alteration of complex functions (e.g., language arrest or other kinds of aphasia/paraphasia) are sought during mapping. Usually, no control of the cortex electrical activity by electrocorticography (ECoG) is performed. A low rate of intraoperative seizures has been reported (approximately 3-3.4%) [10], and some authors have concluded that control by ECoG is not mandatory [8]. However, this conclusion has been debated and remains to be validated [11]. Figure **1B** shows how post-discharges appear after electrical stimulation and can be controlled by means of cold serum applied during the cortical surgery.

Subcortical pathways can be assessed by means of the same paradigm. This technique permits the identification of subcortical tracts other than IC or thalamo-cortical radiation [12].

TOOLKIT FOR IONM DURING CORTICAL SURGERY IN ANAESTHETIZED PATIENTS

We briefly expose and analyse the main techniques used by the neurophysiologist during IONM in cortical and subcortical surgery.

Electrocorticography

Several types of tumours that are located in the cortex can induce epilepsy or irritative activity, which are defined by the presence of a spike or sharp waves and combinations thereof. Hence, it is very relevant to assess the presence of these activities. ECoG can discriminate between different functional regions in the cortex, namely [13,14], i) the spiking area, where the irritative activity can be observed; ii) the lesional area, where abnormal slowing or loss of activity is observed; and iii) the non-pathological area, defined by the absence of the abovementioned activities. The identification of these regions is very important

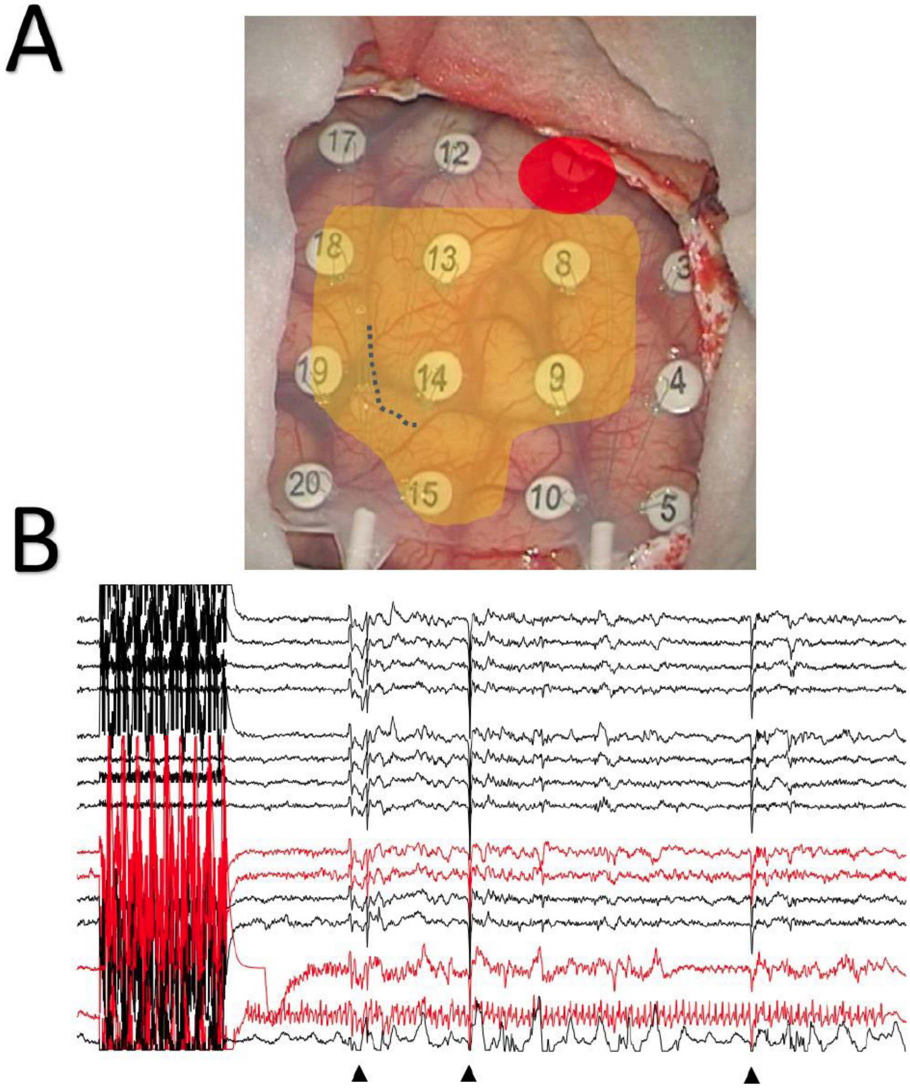

Figure 1: Language mapping in an awake patient with a cavernoma in Wernicke's area. **A**) Image showing the cortical mapping results. Red: Wernicke's area to 13 mA. Orange: region with negative results above 12 mA. The dotted line indicates the cortical incision for approaching the cavernoma. **B**) Recording showing long-term after-discharges following stimulation by electrodes 18/1 to 9 mA. The widespread artefact (arrowhead) corresponds to the moment at which cool serum was administered. Subsequently, the discharges disappeared. The channels affected by after-discharges are shown in red.

because it aids the surgeon in selecting the cortical region through which to approach the tumour, using the more injured region and avoiding the healthiest region [15,16].

As we have stated previously, electrical stimulation can induce irritative activity or even clinical seizures (Figure **2A**). Even electrocautery can inadvertently induce seizures (Figure **2B**) that can then evolve. Thus, it is very important to monitor the presence of this activity during electrical stimulation of the cerebral cortex. Consequently, we propose the use of ECoG to assess the appearance of epileptiform activity not only during functional mapping but also throughout the electrical stimulation during tumour resection.

Some types of mathematical analysis can be helpful for the assessment of ECoG [16,17].

Cortical Somatosensory Evoked Potentials

During surgery of the cortex, it is very common to use the phase reversal of SSEP to identify the transition between motor and somato-sensory areas, which usually occurs at the central sulcus (CS). This recording registers the cortical activity that is generated in the primary somatosensory cortex (Brodmann areas 3, 1 and 2) in response to a stimulus on a peripheral nerve [18], usually the median nerve of the upper limb (although it is not infrequent to stimulate the ulnaris) and the posterior tibialis of the lower limb.

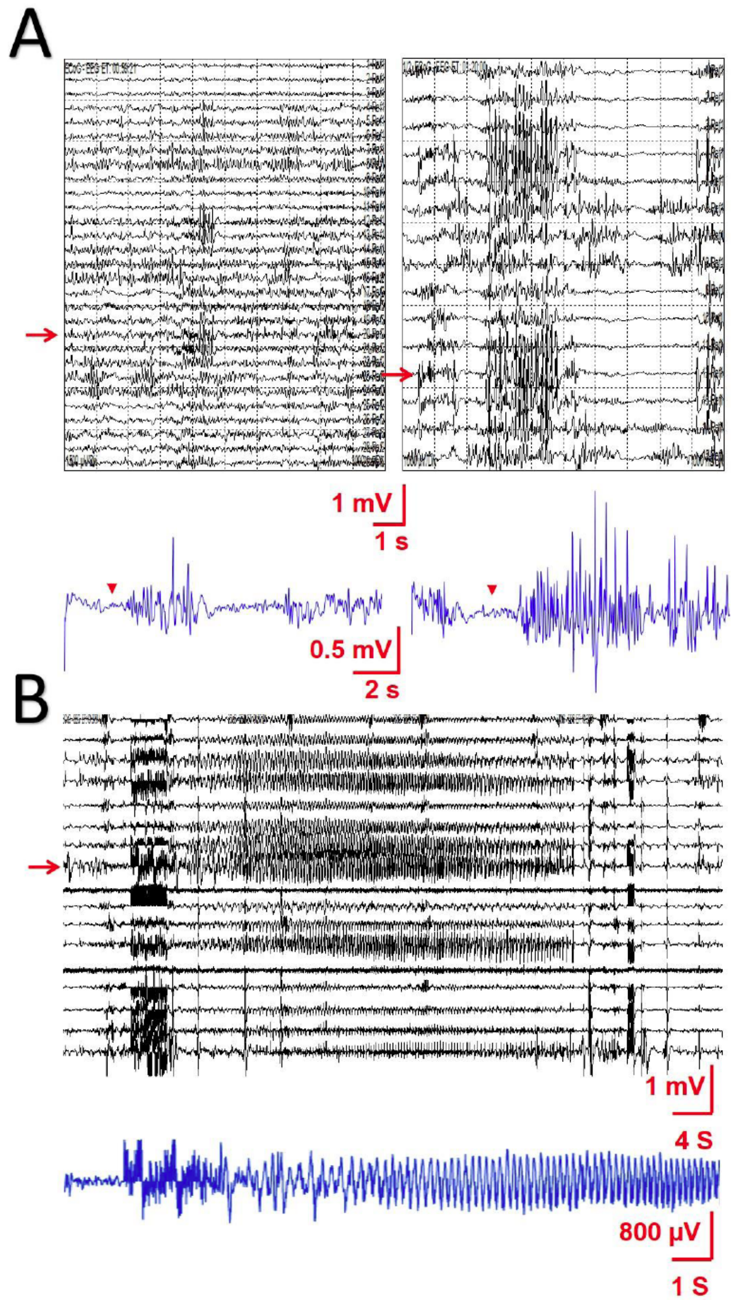

Figure 2: Cortical excitability during cortical surgery. **A**) Cumulative effects of electrical stimulation. ECoG at the beginning (left column) and at 10 min of electrical stimulation during mapping (right column, only with selected channels). Lower row shows selected channel (red arrow at upper row). It's quite clear the intense irritability induced by the same electrical shock (arrowhead). **B**) ECoG recording before starting electrical stimulation for mapping. Artefact shows the use of electrocautery to coagulate a small cortical vessel. A focal seizure appears spreading locally. Irrigation with cold ringer aborts the seizure. Lower row is a detail of the channel indicated by red arrow.

Thalamo-cortical projections from the ventrocaudal nucleus synapse are present in layer IV of the primary somatosensory area. However, the rostral part of Brodmann area 3 is located in the anterior wall of the central sulcus, and thus, the current sources generated by these afferents can be modelled by a dipole oriented parieto-frontally rather than in a normal position relative to the surface. This dipole source results in a reversal of the polarity when registering the potential ahead of and behind the central sulcus. This phase reversal, therefore, determines the actual location of the transition between the motor area (normally anterior to the central sulcus) and the somatosensory regions (habitually posterior).

The somatosensory region corresponding to the forearm can be easily identified by the greater

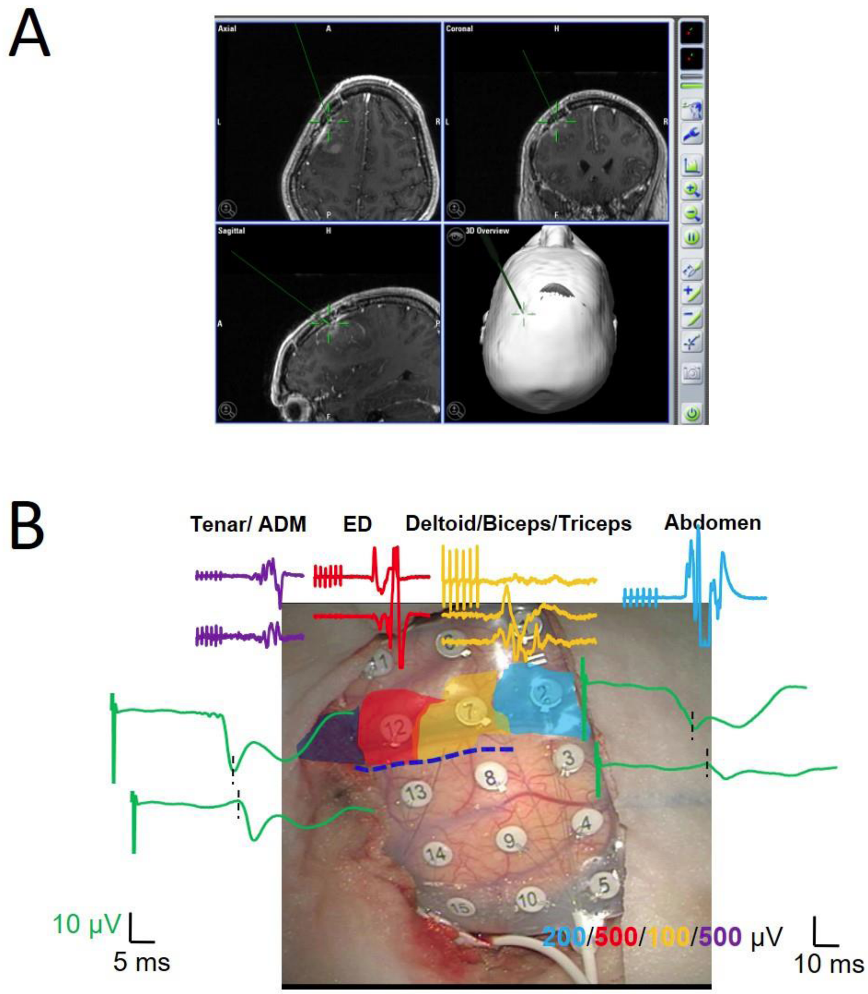

Figure 3: Cortical surgery in a patient with a left frontal glioma. **A**) Neuronavigator showing coronal, frontal and sagittal views of a left cortical tumour. **B**) Placement of the grid over the cortex with sensory and motor mapping. The coloured areas show the motor regions of the abdomen, arm, forearm and hand, and they correspond to the MEP with the same colour. The dashed line in blue shows the area of the central sulcus, with the phase reversal illustrated in SSEP in green.

amplitude of the complex N1/P1/N2 waves [19]. A 20-electrode grid placed at the lateral region of the fronto-parietal transition can be very helpful. By contrast, for the lower-limb SSEP, a 4-8-electrode strip is placed at the medial region. The reference electrode should be placed as far away as possible, i.e., at the contralateral earlobe, whereas the ground electrode should be as close as possible, e.g., at the ipsilateral earlobe [15,17,18]. See Figure **3B** for SSEP performed during a mapping.

It is important to perform a monopolar recording to identify the phase reversal because a differential montage can lead to very serious mistakes (see Appendix).

Cortical Auditory Evoked Potentials (cAEPs)

These potentials were initially thought to be generated in the primary auditory cortex (PAC), located deep in the white matter of the lateral fissure of the transverse gyrus of Heschl. However, other different areas, including the second auditory cortex (SAC) and the insula, are capable of eliciting cAEPs. There is considerable intersubject and interhemispheric variability [20], and the whole structure remains to be elucidated.

cAEPs are characterized by a series of waves, which can be systematized as follows:

- Short-latency waves: N13/P17/N30. These waves are typically recorded from the PAC. This complex is absent in the SAC.
- Intermediate-latency waves: peaks between 60 and 100 ms. These waves, which are always present in the SAC, can also be present in the PAC.

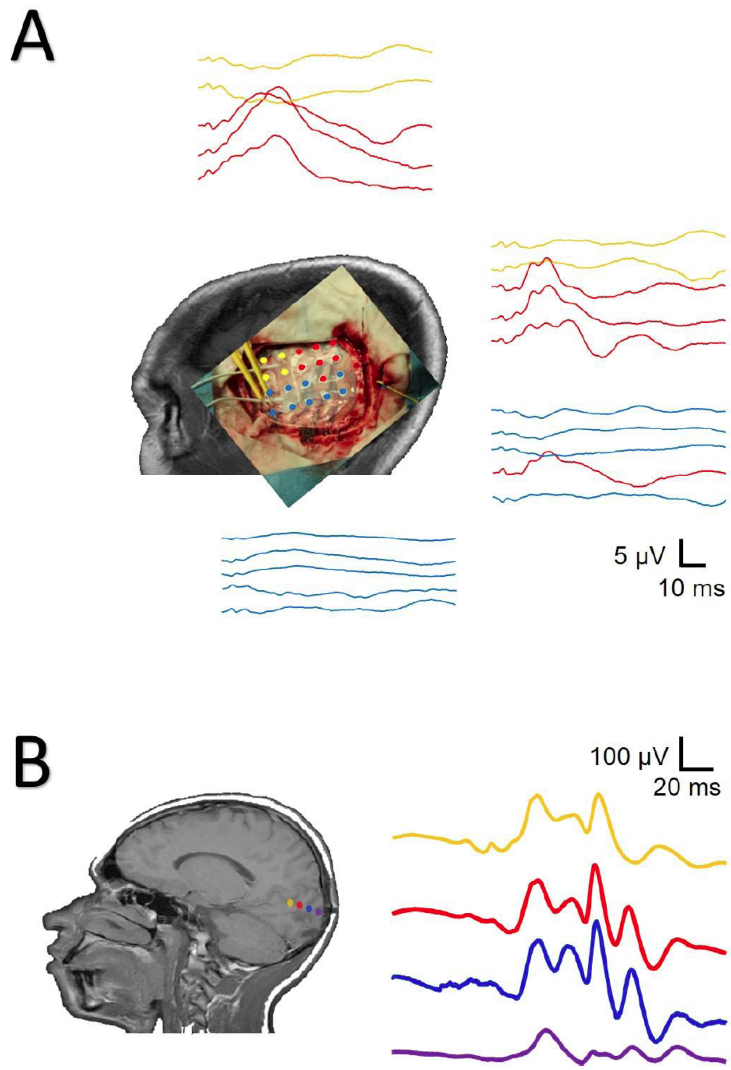

Figure 4: Evoked potentials directly recorded from the cortex. **A**) Auditory Evoked Potentials. Patient with a tumor in the left superior temporal region, with a grid placed over the cortex. Red lines show the response of auditory evoked potentials with a small N13 and a big N60. Yellow lines show the area with loss of activity identified by ECoG. **B**) Visual evoked potentials. Patient with a tumor located near the primary visual cortex. Four electrodes strip was placed near the tumor to mapping and monitor the response to visual stimulation. Each trace corresponding to an electrode is indicated by the same color.

These potentials can be generated by auditory tones through earphones inserted in the external auditory channel. Considering the latencies of some waves, a minimum period of 250 ms should be used to average the signals. Therefore, a stimulation frequency of 2.18 would be adequate. A minimum intensity of 70 dB masking noise (sensation level) is applied to the contralateral ear (Figure **4A**).

It is not uncommon to identify only the SAC, especially when cortical grids are used.

Visual Evoked Potentials (VEPs)

These waves exhibit the characteristics of near-field potentials generated from the primary visual cortex. In the surgery room, the only technique used for stimulation is the application of flashes of light. Although we think that VEP has undeniable utility, there have been some questions about its efficacy, mainly regarding the instability of the recording, the lack of correlation with the postoperative visual function and the high susceptibility to anaesthetic agents. However, more recent results have demonstrated stable recordings and a strong correlation with the postoperative visual function [21,22]. Therefore, intraoperative VEP monitoring will be mandatory for surgeries harbouring a risk of visual impairment [23].

Stimulation is performed by flashing light-emitting diodes stimulated at 2.18 Hz, with 10 μs pulses and a bandwidth of 10–1.000 Hz. We considered an increase in latency of 10% or a reduction in amplitude greater than 50% of the amplitude compared with the baseline as alarm criteria [16].

In some cases, VEP can be directly recorded from the cortical surface. In these cases, the potentials are much more stable, require fewer stimuli (in fact, a very small number of stimuli can induce the response) and are 2-3 orders of magnitude higher than the scalp recording [24] (Figure **4B**).

Motor-Evoked Potentials (MEPs)

MEPs are the recordings that are obtained from muscles in response to stimulation of the motor system at different levels (cortex, inner capsule, cortico-spinal/cortico-bulbar tracts or spinal cord) [25]. Usually, transcranial electrical stimulation is not used, although in some patients, it is an extremely important technique [16,17,26], especially in subcortical surgery. Considering the amplitude of the response, these types of evoked potentials do not need to be averaged.

Transcranial Electrical Stimulation (TES) in Subcortical Surgery

This technique consists of the stimulation of the motor pathway by an electrical current delivered through electrodes placed outside the cranium, usually in the scalp [27].

It is usually believed that TES excites the white matter of the inner capsule (IC) rather than cortical neurons. This distinction must be recognized and kept in mind by the neurophysiologist, especially in the case of surgery at the supratentorial level. However, for subcortical surgery, TES can be safely used under two conditions: i) high voltage (current) is not needed to elicit a response [26,28], and ii) a hemispheric stimulation is performed. With these preventions, TES elicits stable and specific responses that predict the postoperative outcome very well [29] (Figure **5**).

Electrodes can be subdermal needles or cork-screws and are placed at different sites depending on the region to be stimulated.

The parameters used to elicit MEPs through TES are variable [30], but we use trains of 4-6 pulses with a 50-75 µs pulse width, an inter-stimulus interval (ISI) of 2 ms (i.e., 500 Hz) and voltage ranging from 120 to 450 V.

Direct Cortical Stimulation (DCS)

For this technique, electrodes are applied directly to the cortical/subcortical surface. Direct cortical

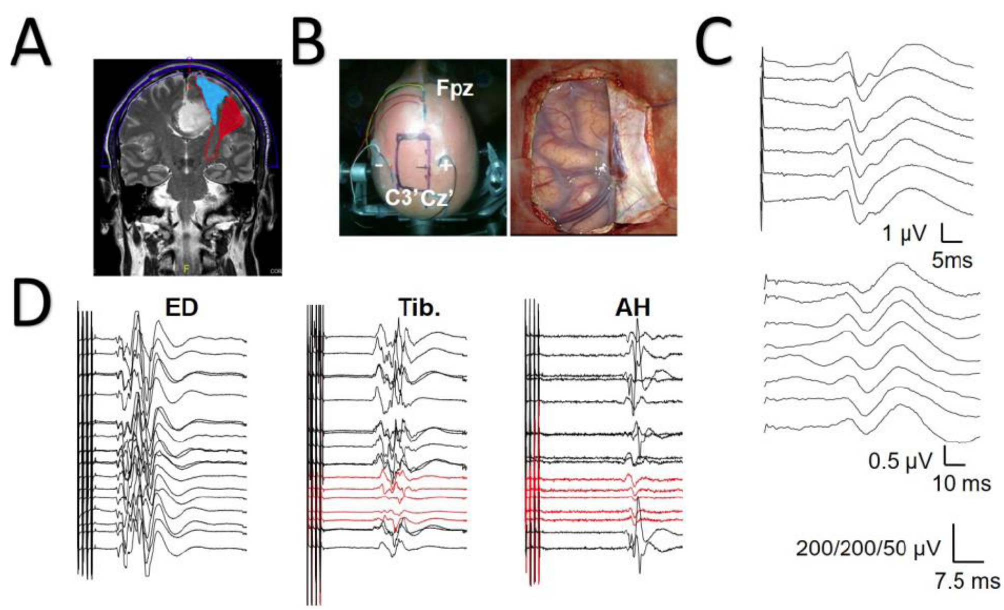

Figure 5: Use of TES in cortical surgery. Patient with a tumor located in the medial frontal region. **A**) Mathematical model used to justify this kind of monitoring (see [28]). The red dashed line represents the outline of the inner capsule. **B**) Configuration of electrodes for SSEP recording from arm and leg and electrodes for transcranial electrical stimulation (left) and view of cortex after dura opening (right). **C**) SSEP of upper and lower members, showing no significant changes during the surgery. **D**) MEP elicited by TES. There was seen a largely stable response during most of the surgery, until a significant alteration of the lower member was observed, with the upper member's response unaffected. Alteration resulted reversible after usual protection measures. After ED = extensor digitorum; Tib = tibialis anterior; AH = abductor hallucix.

stimulation (DCS) to identify the primary motor cortex (PMC) is accomplished using paired electrodes. Stimulation is performed using 4-6 pulse trains at 500 Hz (the reason we call this paradigm high frequency; this technique is also known as multipulse, which is misleading), with bi-phasic pulses of 150-200 μs in the duration/phase. Motor-evoked potentials are assessed using pairs of subdermal needles spaced approximately 2 cm apart that are inserted into the contralateral muscles, but surface electrodes attached to the skin can also be used. Depending on the location of the tumour, it is customary to use the following muscles: the orbicularis oculi, orbicularis oris, deltoid, brachial biceps, extensor digitorum carpal flexor, abductor pollicis brevis, abductor digiti minimi, quadriceps, tibialis anterior and abductor hallucis.

Stimulation is initiated at 4 mA and increased continuously in increments of 1-2 mA until a stable compound muscle action potential (CMAP) is recorded at a minimum amplitude of 30 μV or until an upper limit of 30 mA is achieved without eliciting a CMAP [16,17] (see Figure **2B**).

An alternative strategy entails the use of Ojemann's stimulation or low-frequency stimulation, which consists of a 50-60 Hz train that is 3-5 seconds in length and has a pulse width as high as 0.5 ms [3,31].

Although a systematic comparison between these two strategies remains to be performed, it is important to be aware that neither the electrical thresholds nor the muscle response or electrical safety are equivalent.

In this sense, it is important at this point to consider some electrophysiological variables concerning patient safety. See Appendix for details.

Although there are no well-defined limits for the abovementioned magnitudes, from the table, we can observe that Ojemann's technique is the paradigm with the highest q_{total}/train, and the stimulation for awake craniotomy has the highest ρ_{max}.

Cortico-cortical Evoked Potentials (CCEPs)

As of several years ago, there is evidence that some auditory perceptive functions persist during anaesthesia [32], in addition to the presence of some auditory memory in the context of light general anaesthesia [33] or even the existence of brain responses during sleep [34]. These observations allow the supposition that complex networks associated with language are active during anaesthesia and, therefore, could be used for monitoring.

On the other hand, it is known from the end of the past century that electrical cortical stimulation can elicit responses even in the opposite hemisphere, by means of single-pulse electrical stimulation (SPES) [35]. The specificity for identification of the epileptogenic zone is still debated. However, what is beyond any doubt is that responses are not conducted through volume but driven through specific neural pathways. These cortico-cortical evoked potentials (CCEPs) have been used in IONM for language [36,37].

There are several pieces of evidence showing that complex language function can be monitored in anaesthetized patients.

In fact, during the last two years, we have used these CCEPs in IONM for the language function in patients who refused to be awake during surgery. Until now, our results have been robust but scarce, needing much more work before definite conclusions. However, we have now obtained an excellent agreement between intraoperative results and postoperative outcome.

These preliminary results show the appearing of high-amplitude (> 600 μV) and stable signals during

In the next table, we show some electrical variables of great relevance for cortical responses and patient safety for three different stimulation paradigms (taking from [26]).

Technique	i_{max} (mA)	Pulse width (μs)	Number of pulses	Surface (cm^2)	q_{max}/pulse (μC)	q_{total}/train (μC)	ρ_{max} (μC/cm^2)
HF	25	300	6	0.0133*	7.5	45	563.9
Awake craniotomy	10	1000	1	0.0079**	10.0	10	1265.8
Ojemann	10	500	240	0.0079	5.0	120	632.9

HF: high frequency. *The surface is calculated from a 1.3-mm diameter disc electrode. **The surface is calculated from a 1-mm diameter spherical electrode, assuming that only 1/4th of the surface is in contact with the cortex.

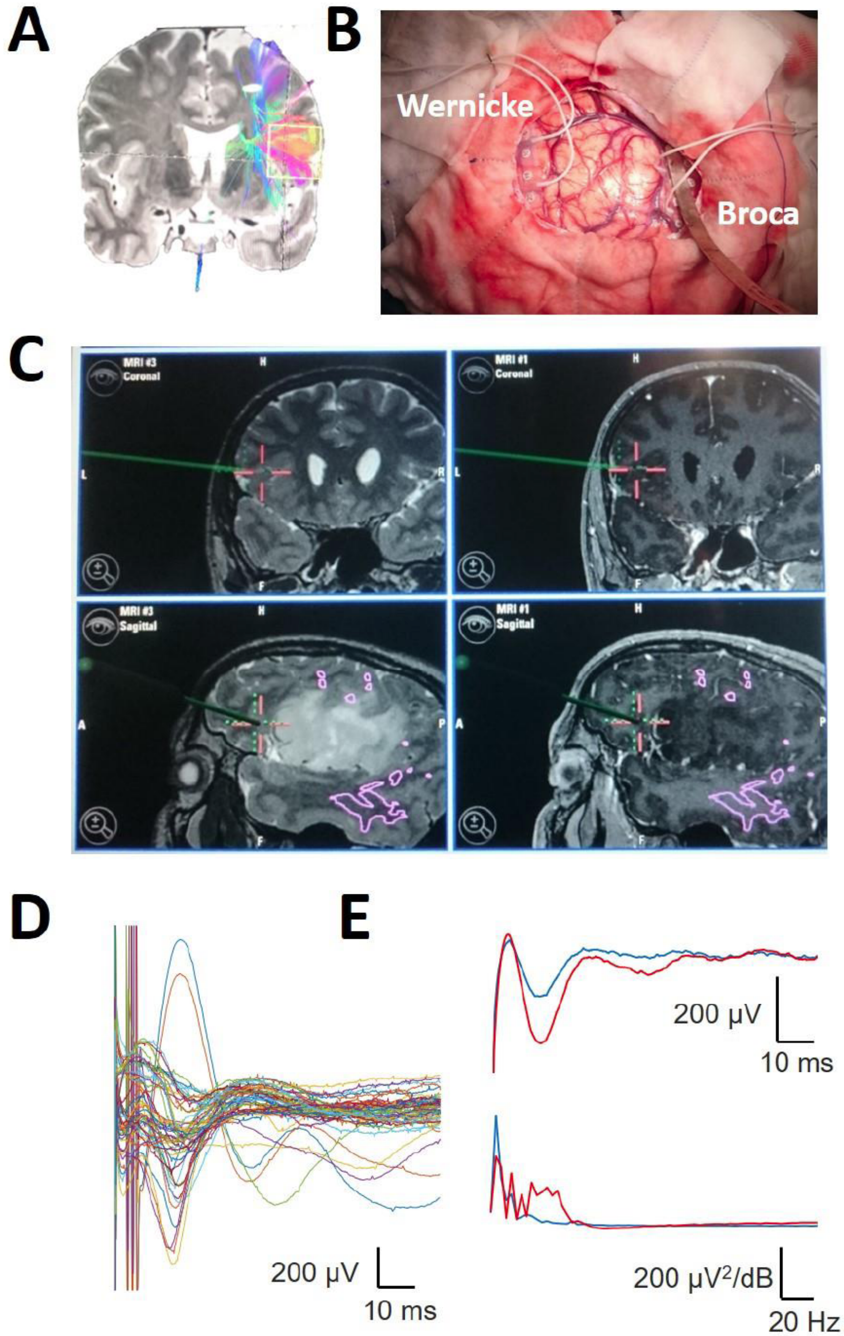

Figure 6: Cortico-cortical evoked potentials (CCEP) in a patient undergoing surgery under complete anaesthesia for refusing awake craniotomy. **A**) Tractography of the left parietal region. **B**) Intraoperative image with the location of the grids in Broca and Wernicke regions. **C**) Image of neuronavigator showing the location of the tumor. **D**) CCEP registered in Wernicke after stimulation in grid located at the Broca's area. Different morphologies are observed. These potentials were stable during the intervention. **E**) Analysis of two CCEP (above) and their corresponding spectra (below) showing how, despite having similar morphologies, the spectral composition is completely different for the faster frequencies.

long periods of time, changing amplitude and/or latency in a reversible way during surgery (Figure **6**).

DISCUSSION

Surgery in awake patients is a fashion that has continuously grown since the last decade of the past century. It has been applied not only to cortical surgery but also to ponto-cerebellar angle surgery and trigeminal surgery. It is beyond the scope of this article to uncover the causes of this fact, which are probably multiple and complex.

Awake surgery is a powerful tool to study the human brain in a way not accessible to other techniques. Nevertheless, for clinical practice, we have other options that can offer sure results without awakening patients. In fact, awake surgery is not free of real and potential problems.

Electrical stimulation of the human cortex can induce seizures even in nonepileptic patients. Therefore, monitoring of the bioelectrical activity of the cortex should be recommended, even if the seizure rates is low, because we can reduce the probability of seizures by detecting post-discharges and impeding their evolution to seizures. In addition to this prevention, some authors have focused on possible secondary effects derived from awake surgery. A normal human response to such an exceptional situation as awake craniotomy can, for instance, result in the delayed appearance of unintentional distressing recollections of the event or some type of post-traumatic stress disorder (as yet undescribed), despite the satisfaction of the patient concerning the procedure [38].

The limitations of awake surgery must be considered seriously. During such surgeries, the patient is awake with the head fixed and covered with cloth and may be kept awake for up to 2 hours. Hence, patients must have both adequate cognitive function and the emotional maturity necessary to withstand such an environment. In fact, the Japan Society for Awake Surgery Guidelines limits the target patient population to those ranging from 15-65 years of age, although with some limitations, awake craniotomy can be used in the paediatric population [39]. Nevertheless, use in mentally handicapped patients remains problematic or impossible. In addition, although it is currently accepted that the intracranial pain-sensitive structures are limited to the dura mater and its feeding, and pain can be adequately controlled by topical anaesthesia of the skin, bone and dura, it has been observed recently that the pia and small cerebral vessels are also pain sensitive, inducing sharp, intense and brief painful events [40].

Probably the most shocking fact about the justification of awake surgery is that no differences in the immediate postoperative motor status, extent of resection have been found between IONM in anaesthetized patients and stimulation during awake craniotomy [41], although no detailed evaluation has been performed for the different techniques or surgeries. If there is not a clear difference in the post-surgical outcome, it is difficult to understand why we need to stress the patient and the medical team when we can instead perform a systematic, calm and reliable mapping and monitoring of most of the brain functions. Obviously, there are some functions, such as cognitive and language functions, that cannot be effectively assessed in anaesthetized patients. In our opinion, these kinds of patients should be the only candidates for awake surgery. However, even this statement must be nuanced. There are some promising data suggesting that some functions related to language can be mapped and monitored in anaesthetized patients. However, this option needs much more work before it can be demonstrated.

Therefore, for selected patients, an awake craniotomy is currently an option to reduce the risk of surgery-related neurological deficits, especially for language mapping. However, the benefits and risks of this type of procedure should be carefully considered, and the decision should serve the interests of the patient.

We have entitled this work with a question. Although we are conscious that a lot of work must be done before to have an unequivocal answer, our feeling and clinical compromise is to answer no.

APPENDIX

The effect of any type of electrical stimulation on the neural tissue is mediated by the total amount of charge applied to the system and the duration of application [42]. The electric current (*i*, in mA) is defined as follows:

$$i(t) = \frac{dq}{dt}$$

where *q* is the charge (in µC), and *t* is time (in ms). Thus, the total charge applied during time t_{pw} (time of pulse width) can be calculated from the above equation as $\int_0^{t_{pw}} i(t)dt$. For square pulses (which are the most common), the integral equals the amplitude x duration, e.g.,

$$q(t) = i \times t_{pw}$$

However, this expression provides information only about the charge/pulse. Therefore, to elucidate the total charge administered to the tissue (q_{total}), we must multiply by the number of pulses (*N*) as follows:

$$q_{total} = i \times t_{pw} \times N$$

Another relevant value concerning safety is the maximum charge density (q_{total}), which is defined as q_{max}/A (µC/cm^2/phase), where A is the area (usually in

cm^2). This parameter directly depends on the size and shape of the stimulation electrode.

The configuration recording for phase-reversal identification during IONM is quite relevant, although no sufficient attention has been payed. The most used model for SSEP is the dipolar one [19]. Therefore, when an array of electrodes is placed in a parallel way to dipole, a phase reversal must appear in monopolar montage because some electrodes are closer to the positive part of dipole, and some electrodes are closer to the opposite polarity. However, when we use a differential montage, algebraic combination of monopolar potentials gives rise to the appearing of two phase-reversals. This fact can induce serious mistakes about the identification of central sulcus.

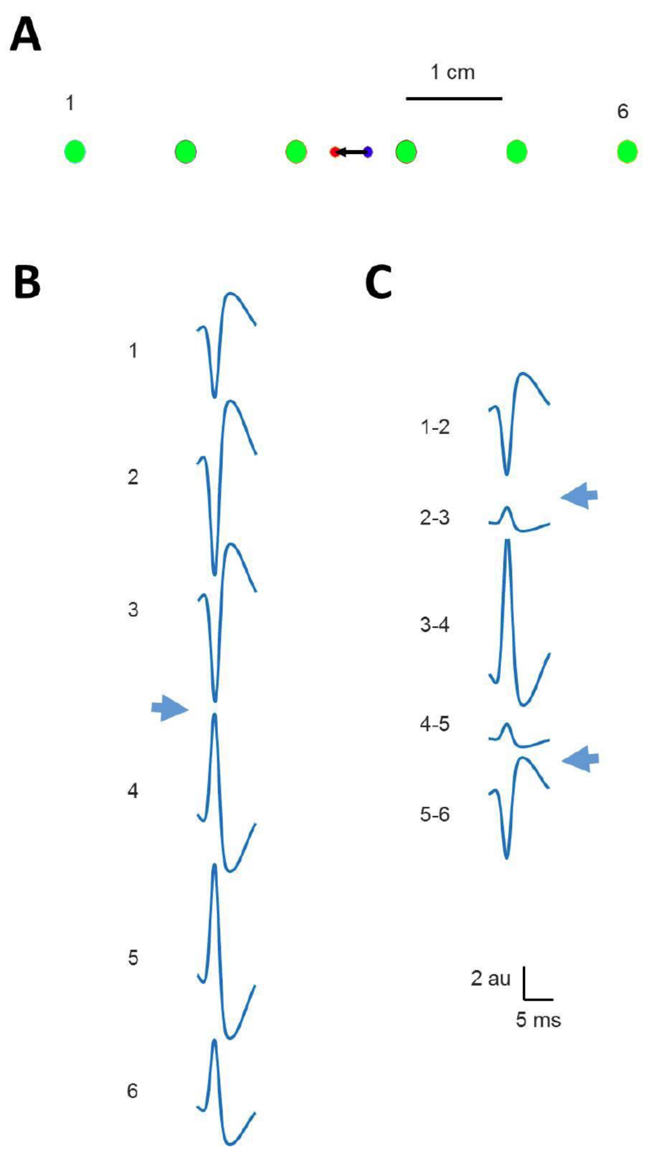

Figure 7: Numerical model of a dipole. **A**) Strip of 6 electrodes (green dots) aligned with a dipole (red/blue dots) located at the middle point and 1.5 mm under surface. **B**) Monopolar recordings showing only one phase reversion (arrowhead) between electrodes 3 and 4 where dipole is truly located. **C**) Differential recordings showing two phase reversals (arrowheads) at electrodes 2 and 5. Numbers correspond to electrodes. Vertical calibration bar is in arbitrary units.

We have addressed this fact (Figure **7**) by means of a simple numerical model performed in Matlab® R2016 (Mathworks, Natick, USA). Dipolar potential (V) to different points $\vec{r}_i$ (namely, electrodes of a strip) can be computed according to this expression

$$V(\vec{r}_i) = \frac{q}{k}\left(\frac{1}{R_i^+} - \frac{1}{R_i^-}\right)$$

Where k is a constant, $R_i^+ = \left\|\vec{r}^+ - \vec{r}_i\right\|$ and $R_i^- = \left\|\vec{r}^- - \vec{r}_i\right\|$ and $\vec{r}^+$ and $\vec{r}^-$ are the radio vectors of positive and negative charge of dipole respectively [43].

Therefore, differential recordings must be strictly avoided during identification of the central sulcus.

ACKNOWLEDGEMENT

This work was financed by a grant from the Ministerio de Sanidad FIS PI17/02193 and was partially supported by FEDER (Fonds Europeen de Developpement Economique et Regional).

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Received on 15-05-2018 Accepted on 18-05-2018 Published on 25-06-2018

DOI: http://dx.doi.org/10.6000/1929-2279.2018.07.03.4