Chapter 2

Functional MRI, Diffusion Tensor Imaging, Magnetic Source Imaging and Intraoperative Neuromonitoring Guided Brain Tumor Resection in Awake and Under General Anaesthesia

Zamzuri Idris, W M Nazaruddin W Hassan,
Muzaimi Mustapha, Badrisyah Idris,
Rahman Izaini Ghani and Jafri Malin Abdullah

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52032

1. Introduction

Neuroimaging has evolved from Computed Tomography (CT), CT-Positron Emission Tomography (CT-PET) and Magnetic Resonance Imaging (MRI) scanner in 1970s and 1980s to functional MRI (fMRI), Diffusion Tensor Imaging (DTI) and Magnetic Source Imaging (MSI) or Magnetoencephalography-MRI (MEG-MRI) fusion in 1990s and 2000s. Anatomical and functional neuroimages are currently regarded by most as vital in planning for brain tumors surgery. These anatomical and functional neuroimages can be fused and exported to the neuronavigation system in the operating theatre (Figure 1). Collectively, these images are known as extraoperative neuroimages. On the contrary, intraoperative neuroimages are images that obtained intraoperatively and can be exported regularly to the navigation system. The intraoperative images can be obtained by using either intraoperative CT (iCT), MRI (iMRI) or ultrasound [3D-iUS) [1-3]. Safer and successful brain tumors surgery requires not only neuroimages-guided surgery but also properly defined the eloquent (important and functional) cortices and monitoring of the vital areas of the brain and other organs. Awake surgery with intraoperative brain mapping, and surgery under general anaesthesia with intraoperative monitoring (IOM) which are guided by neuroimages are two operative techniques for brain tumors that are currently regarded by most as gold standard [4-8]. This chapter describes the current functional neuroimaging modalities (fMRI, DTI and MSI), brain mapping, surgery

INTECH
open science | open minds

© 2013 Idris et al.; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

under awake and unconscious states with intraoperative neuromonitorings as adjuncts and techniques to plan and guide the surgeon to resect the brain tumors successfully. We also describe briefly the current treatment modalities for residual brain tumors after the surgery and new concept of brain oscillations and networks as derived from the functional neuroimagings and awake surgery.

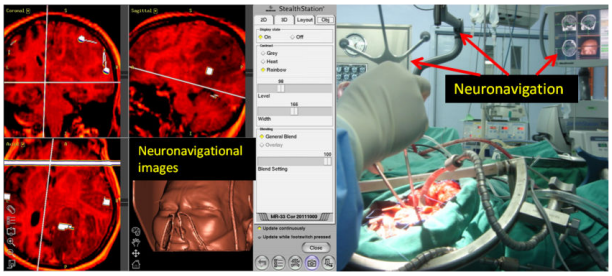

Figure 1. Neuronavigation system in the operating theatre (Medtronic StealthStation TREON™ cranial software; Medtronic Inc., Minneapolis, USA)

2. Neuroimaging

Functional MRI, MSI (MEG-MRI) and transcranial magnetic stimulation (TMS) are three current extraoperative methods that are widely used to locate the eloquent areas of the brain. Functional MRI is based on the increase in cerebral blood flow that accompanies neural activities. The primary form of fMRI uses the blood-oxygen-level-dependent (BOLD) contrast (Figure 2A). In contrast, functional mapping of the brain by using MSI is based on measuring the magnetic fields generated by brain activity (Figure 2B). A basic neural generator of MEG is a magnetometer which consists of a pickup coil paired with a superconducting current detector or better known as superconducting quantum interference device (SQUID). MEG consists of a rigid whole-head helmet containing up to 306 sensors. The sampling rate can reach up to 5 kHz on all channels. The superconducting sensing technology necessary to keep instrumental noise levels at less than a few femtotesla per square root hertz requires cooling at -269°C with liquid helium [9]. A magnetically shielded room made of layers of metal alloys attenuates external perturbations and makes MEG recordings possible (Figure 2C). The equivalent current dipole (ECD) method has been the primary means of analyzing clinical MEG data to identify the location of source activity. Beamforming is a relatively new technique introduced to analyse the brain signals. It is useful to analyse brain activity that may involve multiple active brain regions or networks [10]. Transcranial magnetic stimulation brain mapping is performed by stimulating the cortex with the external figure-of-eight coil (is preferred than circular coil) and single pulse technique, and recording the resulting motor or language responses

http://dx.doi.org/10.5772/52032

(note: repetitive pulses or rTMS is preferred than single pulse technique for language mapping) on the navigated anatomical MRI, MSI or fMRI images (see subheading 4.4).

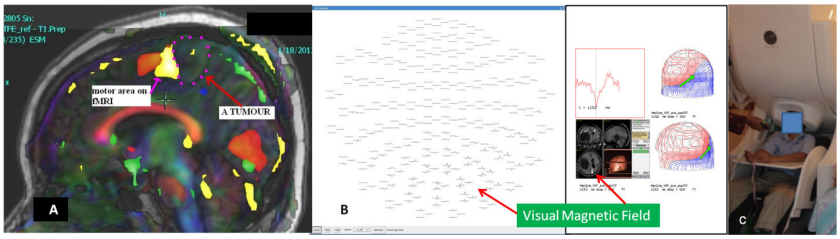

Figure 2. A: Functional MRI depicts the motor hand area lies anterior to the tumor. B: Magnetoencephalography localizes the area for visual evoked magnetic field. C: MEG recording.

Diffusion Tensor Imaging is an anatomical white matter imaging that is useful to elucidate details of the white matter fibres and tracts (Figure 3A). It is an MRI-based technique that can demonstrate white matter anatomy by measuring the directional anisotropy of water (~ non-uniform water flow) [11]. Essentially, in the analysis of the DTI data, a tensor model is used to represent the orientation of the fibers. If there are areas where single fiber population is predominant, the principal diffusion direction is aligned with the white matter fiber tract direction. By following the principal diffusion directions, we can estimate the main directions and reconstruct the fiber tracks, process known as tractography. These reconstructions may then be displayed in 3D, providing a detailed map of the configuration of the tracts and their relationship to other structures [12, 13]. A variety of summary statistics have been proposed to describe the degree to which anisotropy is evident, one of the most common being fractional anisotropy (FA). FA tells the integrity of the fibres and ranged from 0 to 1 (Figure 3B). Nonetheless, one should aware of possible erroneous tractography or erroneous FA values for crossing, kissing, merging or diverging fibres which commonly occurs at subcortical short U fibres and callosal-corona radiata-junctional areas.

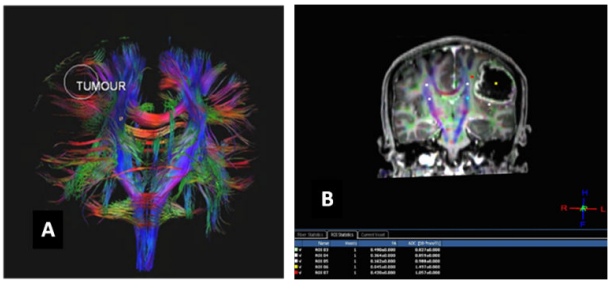

Figure 3. A: Tractography shows various tracts inside the white matter. Blue signifies up-down or down-up fibres, red signifies right-left or left-right fibres and green signifies anterior-posterior or posterior-anterior orientated fibres. B: DTI with FA values.

2.1. Intra- and extraoperative neuroimages and neuronavigation

fMRI, MSI and DTI images are regarded as extraoperative images. They can be fused with anatomical images such as MRI or CT and exported to the neuronavigation. Neuronavigation is a large computer commonly located inside the operating theatre. It helps the surgeon to correlate and localize the eloquent areas of the brain and quickly identify the area of the lesion [14, 15]. Nonetheless, extraoperative images are limited in several ways. They could not give an imaging-update to the operating surgeon with the new images and they may become invalid due to brain shift whenever there is cerebrospinal fluid leak [16]. To solve these problems, an intraoperative imaging modality such as 3D-iUS, iCT (Figure 4) and iMRI can update the operating surgeon with the new and current images. The ultrasound based neuronavigation is interesting and cost a lot less than iCT or iMRI. Combination of these neuroimages with awake brain mapping surgery is regarded by most as a gold standard for brain tumor surgery which lies near the eloquent area of the cortex [17-23].

Figure 4. Intraoperative CT with endoscopic and neuronavigational systems.

2.2. Archimedes principle, brain shift and validness of extraoperative neuroimages

The CSF baths the brain and spinal cord, and occupies the ventricular system as well as the subarachnoid spaces or cisterns. The average brain weights 50 g in CSF and 1400 g without CSF [24]. The reduction in brain weight is believed to have resulted from the antigravity effect of CSF buoyancy. In this respect, we motion that there are three ways to overcome gravity: a) acceleration or aerodynamic force b) buoyant force and c) object with no (or negative) mass or time. Speeding rocket or aeroplanes, with their force of accelerations, is the obvious examples of resisting the earth gravity, whilst buoyant force achieves the same effect by reducing the weight of an object within a buoyant setting, say in a fluid or water environment. Archimedes in 212 BC had first coined the buoyant force as “any submerged object is subject to a greater

http://dx.doi.org/10.5772/52032

pressure force on its lower surface than on its upper surface, creating a tendency for the object to rise. This tendency is counteracted by the weight of the object, which will sink if it is heavier than the surrounding fluid and will rise if it is lighter. If the object weights the same as an equivalent volume of the fluid, it will be in equilibrium and remains motionless" (Figure 5). Since we know that the average brain's weight is only 50 g in CSF (and the actual weight is 1400 g), buoyant force created by CSF has succeeded to overcome the gravity force. In this context, buoyant force exerts a lifting effect against gravity and creates a "floating brain". The buoyant environment is disturbed once either there is communication between our normal atmosphere with intracranial compartment (gradual obliteration of buoyant environment) or in presence of CSF leak (fast obliteration of buoyant environment)[25, 26]. During craniotomy for brain tumor surgery, brain shift normally happens when there is removal of CSF. Shift in the brain makes the extraoperative images used in neuronavigation fast to be invalid. In conclusion, despite different patient's positioning adopted during imaging and surgery, the extraoperative images incorporated to the neuronavigation system would remain reliable as long as no CSF leak or removal occurs at the actual surgery.

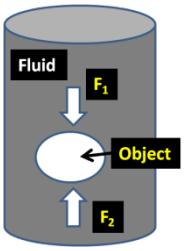

Figure 5. The Archimedes principle: any submerged object is in equilibrium and remains motionless whenever weight of the object (F1) equals to object lower surface fluid pressure (F2).

2.3. Intraoperative neuroimages

The microgravity or buoyant environment created by CSF vanishes once the brain becomes a non-floating organ. At time of actual surgery, opening in CSF cisterns would irrevocably lead to leakage of CSF and hence conversion of buoyant to non-buoyant environment of the brain. Consequently, the localisation onto or into the brain as guided by the extraoperative neuroimages would become imprecise. Thus, surgery that requires precise brain localisation should pay meticulous attention to avoid CSF leak by appropriate positioning of the patient or by using intraoperative neuroimages [27, 28]. Intraoperative neuroimages give updated images to the operating neurosurgeon which can be done on a regular basis. However, note that any extraoperative functional images that are fused with intraoperative images remain inaccurate because of distortion of the brain in the non-buoyant environment and the brain contour itself tends to be different in shape due to the surgery. Therefore, iCT, iMRI or 3D-iUS such as SonoWand system (SonoWand InviteTM Elekta) appears crucially useful to guide the surgeon on the amount and site of the residual (Figure 6), but for a precise functional brain mapping, it is best done under awake state [15, 16, 21].

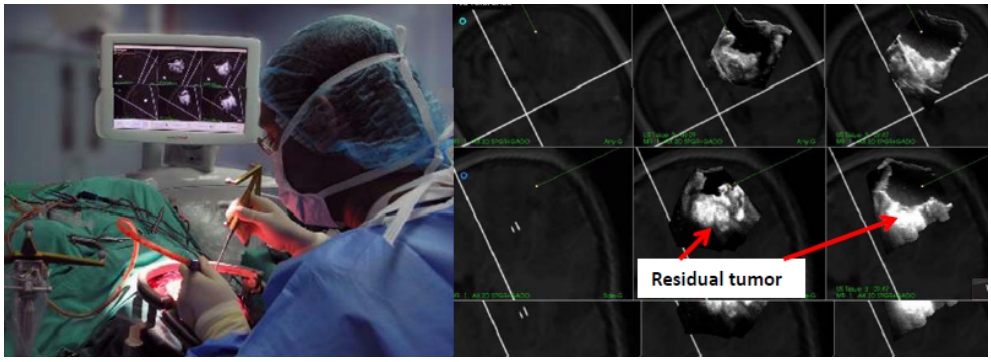

Figure 6. Intraoperative ultrasound using SonoWand system (Elekta) by which the neurosurgeon was informed with the new updated-brain-tumor images.

3. Brain mapping

Mapping the eloquent areas of the brain is vital prior to the definitive tumoral resection. This is especially true for tumors located close to or within the eloquent areas of the brain. Lately, as a result from knowledge gained from intraoperative brain mapping, the previously labeled non-eloquent areas of the brain are no longer considered *silent* brain areas. These areas appeared to be active and and involved in various loops for many brain functions including language, movements and neurocognition. De Benedictis and Duffau in 2011 highlighted the relatively new concept whereby the entire cerebral cortex is involved in execution of functions. The *one-to-one* correspondence between cortical location and function seems inappropriate to explain the complexity of brain processing, especially for higher functions. The brain processing is currently viewed as *many-to-one* or *one-to-many* correlations. Many-to-one concept means multiple brain areas are able to process a single function whilst one-to-many refers to the concept of one region of the brain is capable in eliciting more than one brain functions [30, 31]. Intraoperative brain mapping can be done by using either intraoperative cortical stimulating electrodes such as Ojemann bipolar neurostimulator (Radionics, Inc., Burlington, MA) or grid/strip electrodes, and either done under general anaesthesia or awake state. As a common practice, brain mapping is done under fully awake state using bipolar neurostimulator.

3.1. Technical aspects of brain stimulation

Brain stimulation is currently regarded as important. Brain stimulation is commonly divided into extracranial (or transcranial) and intracranial stimulations. Intracranial stimulation can be further divided into superficial brain stimulation such as cortical-subcortical stimulation and deep brain stimulation. The cortical-subcortical stimulation is commonly used to detect the functional areas of the cortex and subcortical pathways (white matter tracts) prior to and after removal of brain lesions. In contrast to superficial brain stimulation, deep brain stimulation is currently used to treat some neurological or psychiatric diseases. Treating those diseases by giving electrical stimulation works by altering the oscillation rates and amplitudes of the in-

http://dx.doi.org/10.5772/52032

volved networks [32-35]. Transcranial or extracranial stimulation can either be transcranial electrical-digitimer (transcranial electrical stimulation) or magnetic stimulation coil, better known as transcranial magnetic stimulation (TMS) which uses to map the brain motor and language cortices and to treat some neurological or psychiatric diseases [36-38] (see subheading 4.40). Table 1 and figure 7 depict those three common methods of brain stimulation.

Parameters commonly used in electrical brain stimulation (Type of macrostimulation) [note: microstimulation uses glass pipette to penetrate single cell]		
Direct cortical electrical stimulation (source: neurostimulator such as Ojemann neurostimulator)	Deep brain stimulation (DBS) (source: Internal Pulse Generator or IPG)	Transcranial electrical stimulation (TES) [alternative is Trancranial Magnetic Stimulation (TMS).
a) Pulse type can either be monophasic or biphasic pulses.	a) Continuous or reverse pulse type [this differs from mode of stimulation commonly called: unipolar (the case or IPG is positive and a single contact on the lead as cathode. Commonly use because greater current spread typically allows lower stimulation settings) or bipolar mode [2 contacts on the leads as anode and another as cathode – produces narrower field of current spread or more focus effect).	a) Bidirectional square waves (with each cycle, one negative and one positive pulse) or some other pulse type such as brief pulses etc.
b) Frequency: 25 – 60 Hz (low frequency < 30 Hz; intermediately high frequency 30 – 100 Hz: Both normally cause stimulatory effects).	b) Frequency range of 2 - 185 Hz (high frequency > 100 Hz). In DBS, high frequency stimulation or 'hyperstimulation' is used (inhibitory effect on neuronal firing) and mostly at 130 - 185 Hz.	b) Commonly, the frequency ranges from 50 – 130 Hz.
c) Pulse width 0.5 – 1 msec and pulse intervals (length of time between individual impulses; but sometimes it can also mean pulse width) of 1 - 4 msec.	c) Pulse width of 60 – 450 μsec.	c) Single pulse or 2 - 5 train of pulses [0.2 – 0.5 msec pulse width) with 2 - 4 msec interstimulus interval (pulse interval)
d) Intensity of stimulation: microscale [0 – 0.9 mA) to macroscale stimulation [1 – 20 mA).	d) Intensity of stimulation: 0 - 10.5 V (voltage is mostly used) or 0.5 – 2.5 mA (current).	d) Intensity of maximum stimulation is 200 mA [100 to 750 V) (note: for TMS, the stimulus intensity is in the percentage [0-100%], normally at 70 – 90% of magnetic tesla)

Table 1. Comparison among three brain stimulation methods.

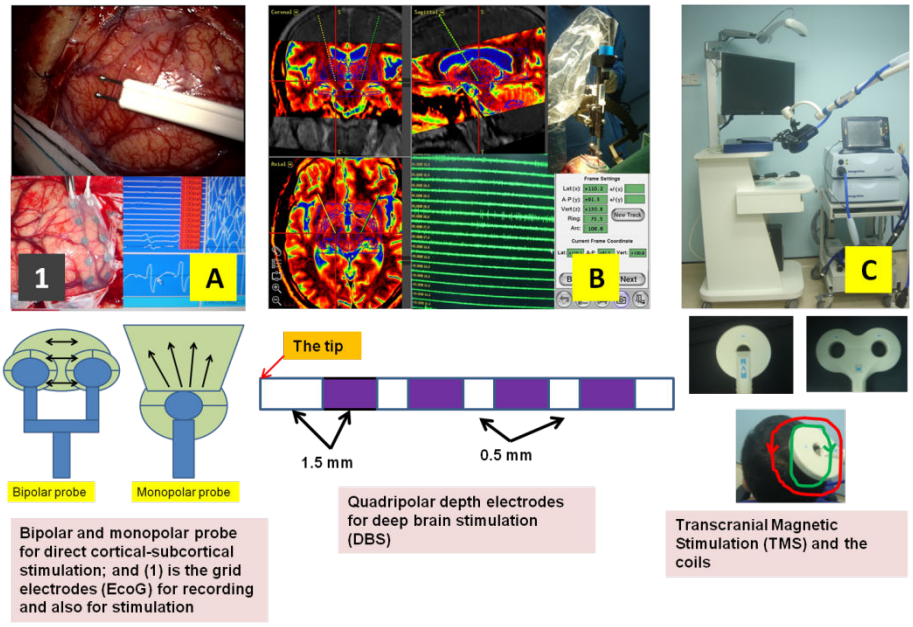

Figure 7. Three methods of brain stimulation. A: Direct cortical stimulation. B: Deep brain area stimulation (in this case, bilateral subthalamic nucleus stimulation or STN-DBS). C: Transcranial Magnetic Stimulation (TMS) using magnetic coils. Note, the induced current in the neural tissues flows in opposite direction to the current generated in the coils and electric energy always coexist with magnetic force (electro-magnetic force).

The most crucial part of brain stimulation is the technical aspects. The elements to this include the stimulator device, the stimulation parameters consisting of pulse type, pulse width (pulse interval), frequency of stimulation, intensity of the stimulation and the stimulation probe. The followings are key points mentioned by Szelenyi et al. that any neurosurgeon who practices direct cortical electrical stimulation need to be familiar with [4]:

i. Stimulator device - Constant-current stimulators are considered safer and more reliable than the constant-voltage stimulators. Unlike the constant-voltage stimulators, constant current stimulators deliver the current independently from the impedance or resistance of the cortical-subcortical surface. Therefore, it is safer and more reliable because constant current is delivered irrespective of possible changes in resistance of brain tissues.

ii. Pulse type – It can be monophasic or biphasic pulse (Figure 8). The first phase of the pulse should be anodal because a lower stimulation intensity is needed to see a stimulation effect. If a monophasic pulse is used, it should be anodal or positive and if biphasic pulse is used, it should be in an anodal/cathodal mode.

iii. Pulse width – The monophasic anodal pulse duration can vary between 0.1 – 2 msec. For biphasic current, the duration of the pulse includes both, the positive and negative

http://dx.doi.org/10.5772/52032

phases. Therefore, only half of the pulse duration is anodal and effective for stimulation.

iv. Frequency of stimulation – Transcortical stimulation requires only a low frequency stimulation ranges from 25 – 60 Hz. The most commonly applied frequency is 50-60 Hz.

v. Intensity of the stimulation – For safety reason, the maximum transcortical stimulation intensity should not exceed 40 μC/cm^2/phase and is commonly limited to 16 - 20 mA.

vi. Stimulation probe – Bipolar probe with two ball tips separated by 6 – 10 mm is our probe of choice (Ojemann neurostimulator), the current density appears homogenous and well concentrated at the stimulation site. In contrast, monopolar electrode (single tip) with a frontal reference electrode would cause wider or spacious stimulation effects that leads to the probability of stimulating brain tissues at a more distant site.

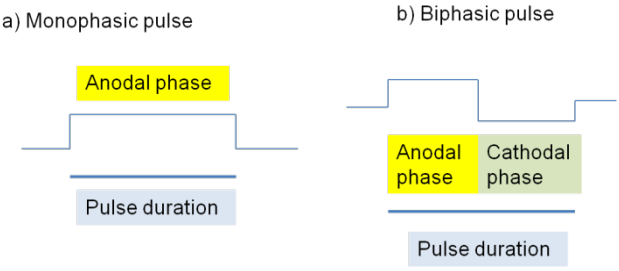

Figure 8. Monophasic and biphasic pulse type.

3.2. Intraoperative brain mapping and awake tumoral surgery

Prior to proper positioning, scalp block is performed at six sites of scalp nerve innervations using mixture of 25 mls ropivacaine 0.75% and adrenaline 5 ug/ml. Additional 20 mls of the same local anaesthetic is infiltrated at the pinning and incision site. Then, the patient is positioned supine with in-situ bladder catheterisation, head fixation in flexed position with the pins and Mayfield head clamp and the thorax is elevated to 40 degrees to ensure comfort to the patient (Figure 9A). Neuronavigation system is arranged such that the monitor is situated at the feet end. Prior to craniotomy, conscious sedation is achieved with dexmedetomidine infusion between 0.2 – 0.5 ug/kg/hr and remifentanil target controlled infusion between 0.25 – 1 ng/ml. Oxygen is only supplied via nasal prong throughout the surgery and the patient is not intubated at all. Needles electromyography (EMG) (or surface EMG electrodes) are inserted into muscles thought to be related to brain mapping (Figure 9B). For the upper limbs, dorsal interrosseus, thenar or hypothenar muscles, brachioradialis, biceps, deltoid and pectoralis major are commonly selected. For the lower limbs, common ones include first dorsal interrosseus, anterior tibialis, gastrocnemius, soleus and anterolateral thigh muscles. For facial

muscles, frontalis and orbicularis oris are preferred. In addition to the above mentioned sites for either surface or needle EMG, surface EMG electrode is commonly used for mapping of pharngeal region (anterior neck). Needles EMG are considered important because of their ability to detect muscular response with low amplitudes of stimulation parameters. With that low stimulation parameters, afterdischarges will unlikely occur, intraoperative seizures are prevented and true effect of stimulation is identified. This principle is thought as important for cases with history of focal seizures and tumor is located near the cortical areas which elicit spikes, polyspikes or spike- or sharpwaves on MEG [39, 40]. Registration of neuronavigation system is made after the head is fixed to the Mayfield head clamp. Extraoperative neuroimages are then used to localise the tumor and functional cortical areas. The planned skin incision is marked to cover the tumor and the identified eloquent areas noted on fMRI, DTI and/or MEG. The craniotomy is made large enough to expose brain cortex for mapping purposes. Surgical patties that are soaked with lignocaine are placed onto the dura for few minutes and all sedative medications are stopped. Patient is started to be fully alert on opening the dura layer. Neuronavigation probe is then used to confirm the tumor, eloquent cortex and areas identified on extraoperative neuroimages. CSF leak is kept minimal by proper positioning of the patient's head and no arachnoid opening is made until tumoral resection begun.

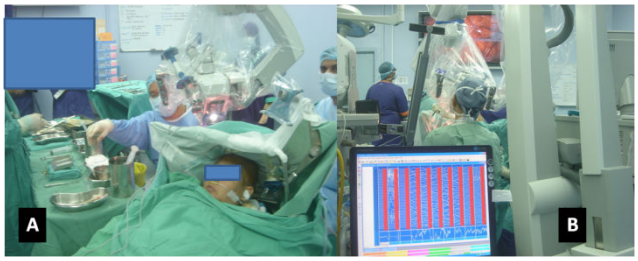

Figure 9. A: Awake craniotomy procedure and B: Intraoperative neuromonitoring with EMGs or motor evoked potentials (MEPs).

Brain mapping is acquired using Ojemann cortical neurostimulator. Stimulating parameters are set normally at anodal biphasic pulse polarity, 50-60 Hz pulse frequency, 0.5-1 milliseconds pulse width/duration (ranges from 0.1 to 2 ms) or pulse intervals and current starting at 1 mA, then increasing gradually until the response is obtained. The sensory response in forms of abnormal sensations is normally noted at 3 – 4 mA stimulus intensity, the motor response is higher at around 3 – 5 mA, manifested as movements or contractions (important to ask the feeling of pharyngeal muscles contraction inside the throat) and EMG responses. If negative motor phenomenon is suspected, especially mapping at the region of association motor cortex, the stimulation induced muscle inhibition can be done by asking the patient to continuously extend and flex the wrist while doing the stimulation (the movement is inhibited by the stimulation). For the language assessment, the longer duration of stimulation is oftenly needed [2 msec pulse width) and every stimulation should start after the patient has said an introductory sentence. The speech or counting arrest is normally noted at 4 – 6 mA. Although no

http://dx.doi.org/10.5772/52032

convincing data to support the association between preoperative epilepsy and intraoperative seizures, in the case of a patient known to have seizures or epilepsy, the following precautions are undertaken for cortical stimulation [39, 41]:

i. The antiepileptic drugs must be served prior and on day of surgery (Consider to load the antiepileptic prior to craniotomy in operating theatre if anti-epileptics were missed).

ii. Get the anaesthetist prepared for intravenous diazepam or lorazepam throughout the procedure.

iii. The operating neurosurgeon must ensure the cold isotonic saline or Hartmann's/ Ringer solution is available when needed.

iv. The bipolar stimulating parameters should be started at low values. For patient with history of focal seizure, stimulation is started at low values, example: 20 - 50 Hz pulse frequency, highest micro or lowest macroscale stimulation intensity which subsequently increase to higher values. Needle EMG to detect the responses and nearby grid or strip electrodes to detect afterdischarges are preferred.

v. Short train or train-of-two to five stimulation technique by using monopolar probe or strip electrodes [which commonly used for continuous motor evoked potential (MEP) monitoring] thought to reduce the risk (anodal constant current, or 2-5 pulses, individual pulse width of 0.3 – 0.5 msec and stimulus interval 3 - 4 msec).

vi. Given enough resting time prior to restimulation (or bath the cortex with cold saline prior to restimulation). Never stimulate same cortical area twice successively [stimulate the cortex which is located closed to and far from the lesion alternately].

Cold irrigation of brain surface is made possible by preparing cold isotonic saline or cold Hartmann's/Ringer solution. This is important to treat episode of seizures or afterdischarges during cortical stimulation. Afterdischarges are type of clinical or subclinical seizure recordings which persist despite stopping the stimulation. These can be in the form of polyspike bursts, spike-waves, sequential spikes, rhythmic waves or mixed, usually with more than 10 seconds duration or with clinical seizures. Figure 10 and 11 show the intraoperative brain mapping procedures in our centre and table 2 shows the summary of stimulation effects of various common brain areas as reported by Duffau [42].

The removal of the tumor is made after confirming the functions of identified cortex. Additional knowledge to the operating surgeon regarding the functions of the adjacent cortices would remind him not to injure them during tumoral resection. In addition, knowledge gained from brain mapping can be used to supplement knowledge in neurosciences [43, 44]. For tumor that involves eloquent cortices such as motor cortex, maximal tumoral resection is the aim since most patients already presented with gross neurological deficits secondary to the tumor. If no or minimal deficit is noted prior to definitive surgery, tumoral resection should be made less aggressive by sparing those in the eloquent cortices. Depending upon the intraoperative fresh frozen biopsy results (if no biopsy done prior to excision), this tumoral residual volume

Site of electrical stimulation	Effects
Left Insula	Articulatory disturbances or autonomic disturbances
Left dominant supplementary motor area	Transient speech disorders or mild objective language deficits. Later mild word finding difficulty. Other possibility: agraphia
Left superior longitudinal fascicle (subcoritcal and lateral to the ventricle)	Conduction aphasia (poor repetition), disconnection syndrome
Left inferior frontal gyrus	Reduce capacity for articulate speech/Broca or motor aphasia
Left superior posterior temporal gyrus	Wernicke aphasia/Disturbance in speech comprehension
Left angular gyrus	Alexia with agraphia
Right hemispheric language cortex (language disturbances noted during patient having seizures or on presurgical neuropshychological assessments or language activation in the right hemisphere noted on fMRI)	Crossed aphasia
Temporo-parietal-occipital or optic radiation areas	Transient visual disturbance such as perception of shadow or illusion at certain visual field quadrant
Right angular or temporal gyrus	Complex vestibulo-somatosensory sensations such as out-of-body sensory illusion
Right superior temporal gyrus or supramarginal gyrus or superior longitudinal fascicle	Deficit in visual search (transient spatial neglect)
Left parietal lobe (near left angular gyrus)	Impaired calculation (multiplication and substraction)
Temporo-parietal or frontal areas	Recent memory can be affected (especially, left temporal cortex)
Anterior temporal lobe or dominant frontal premotor area	Famous face recognition affected
Frontal eye field	Ocular deviation or saccade suppression (inattention)
Right posterior perisylvian cortex	Facial emotion recognition
Primary motor cortex	Movements or motor evoked response
Primary sensory cortex	Abnormal sensations

Table 2. The stimulation effects of various common brain areas.

can mostly be treated conservatively with regular clinical assessment and imaging (mostly for low grade tumors) or by precision radiation therapy (for high grade tumors) either using stereotactic radiotherapy (SRT), radiosurgery (SRS) or intraoperative radiotherapy (IORT) and chemotherapy. Sometimes, patient presents with focal seizures and radiologically as well as histologically confirmed benign looking tumor is found at the eloquent area of the cortex, resection of this tumor should be done after thorough investigation to determine if the epileptic focus arises outside the tumoral and eloquent areas. If so, resection of the tumor (simple surgery) is made together with resection of normal looking and non eloquent cortical epileptic

http://dx.doi.org/10.5772/52032

focus (epilepsy surgery). However, if the adjacent normal looking cortical epileptic focus is an eloquent area, multiple subpial transections by using epilepsy knife is a more appropriate choice [45]. The tumoral edge, margin between abnormal and normal looking cortices are stimulated to identify eloquent cortices and important white matter fibres. Information gained from DTI can be used to identify white matter fibres which normally located at the base of the tumor. Therefore, neurostimulation should also be made at the base to identify and confirm those tracts which normally feasible at the end of the surgery. Hemostasis was properly secured prior to closure of the dura. Closure is made in layers after resedation. The patient is normally observed for 24 hours in neurointensive care prior to discharge to a normal ward.

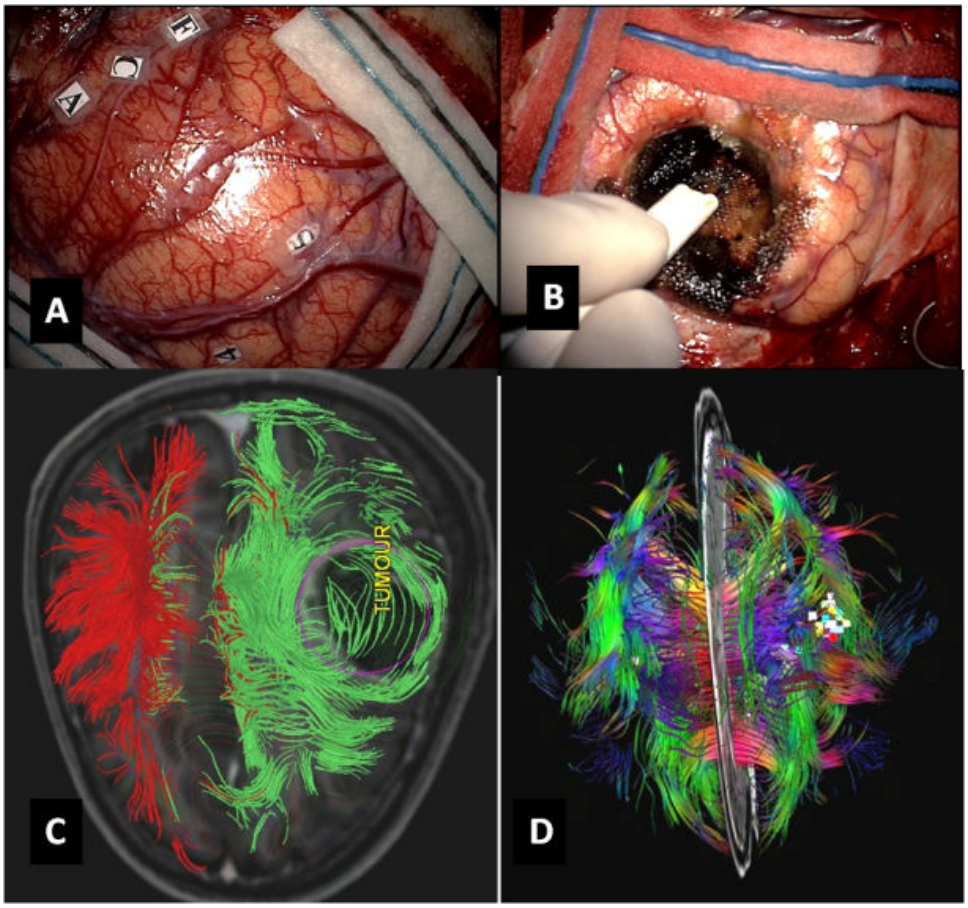

Figure 10. A: Intraoperative brain mapping prior to tumor resection. When areas labeled as A, C, 4 and 5 are stimulated, one would note facial twitching and EMG responses. B: After tumor resection, subcortical stimulation should be done to assess the white matter tracts. C: DTI shows splaying of white matter fibres around the tumor. D: DTI taken months after the surgery revealed more white matter fibres at previous tumor site.

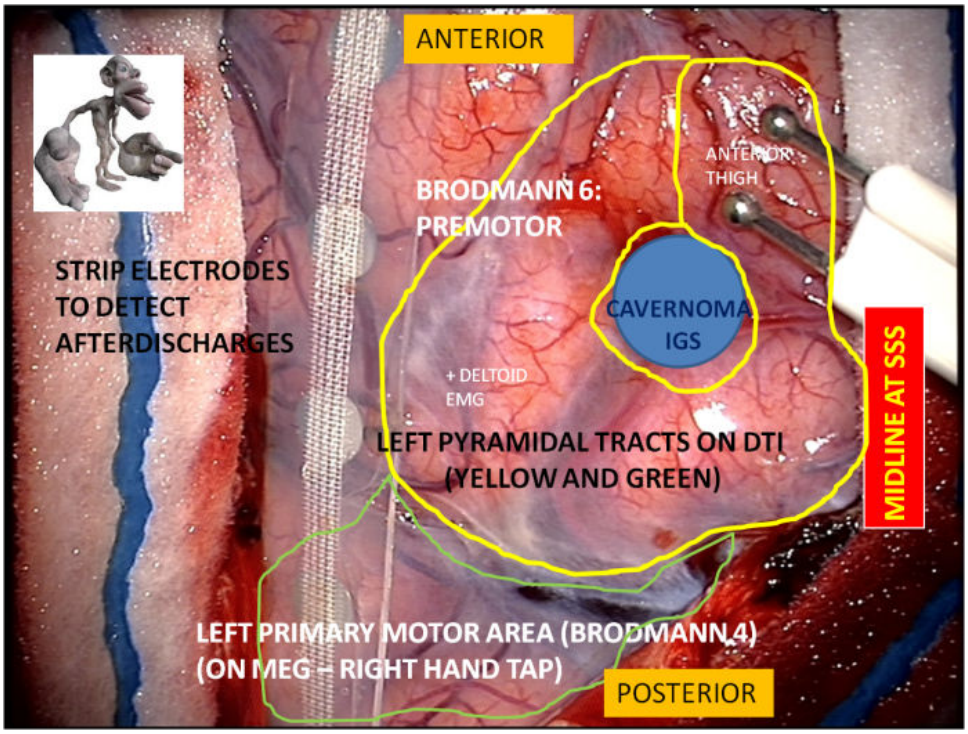

Figure 11. Intraoperative brain mapping under awake state. Cavernoma is identified on image guided system (IGS) or neuronavigation which then resected after complete mapping of adjacent cortical areas.

3.3. Extraoperative brain mapping

Other method of brain mapping is known as extraoperative brain mapping which can be done by using extraoperative neuroimages such as fMRI, MSI, transmagnetic stimulation (TMS) and subdural electrodes (Figure 12A). Subdural grid or strip electrodes (*electrocorticography [EcoG] or intracranial EEG [iEEG*]) are commonly used to record the epileptic discharges and hence identify the epileptic focus prior to resection (mapping the epileptogenic zones) [46]. They can also be used to stimulate the cortex to identify the functional areas of the cortex and to detect afterdischarges during cortical stimulation (functional brain mapping). Brain mapping using grid or strip electrodes are commonly used to identify the language functional areas in cases where the tumor lies closed to language cortices [47]. The electrodes are implanted and secured adequately, clear intraoperative surgical images captured and a thorough language assessment is completed outside the operating theatre. This method is preferred because: a) calmer and appropriate environment outside the operating theatre, b) absence of any residual sedative effects from the drugs used during craniotomy and c) ample time to assess various language functions optimally.

http://dx.doi.org/10.5772/52032

Combined extra- and intraoperative brain mapping is used in our institution. Our findings in comparing extra- with intraoperative brain mapping are in agreement with others, yielding MSI or MEG-MRI signals correlated better with intraoperative cortical stimulation for motor cortices (Figure 12B)[48]. The maximum intraoperative motor response is noted at area which corresponds with area of maximum magnetic signal or vector for motor evoked task. Nonetheless, the information obtained from fMRI should not be regarded as totally unreliable, this is because multiple areas or networks have been shown to be involved in cognitive or motor tasks at different scales [31, 49]. Our experience in awake surgery did show similar findings whereby multiple areas at opposite hemisphere recorded using scalp EEG had shown multiple evoked responses to the electrical stimulation. This finding is further elaborated under the heading of brain waves, oscillations and networks.

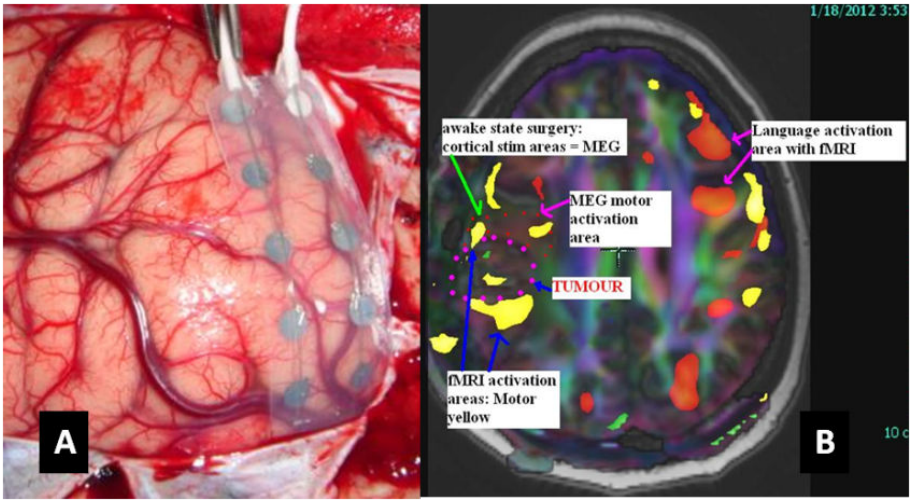

Figure 12. A: Grid electrodes are commonly used to map, stimulate the cortex and to detect afterdischarges. B: Combined extra- and intraoperative information gained from various modalities.

The drawback of brain mapping using fMRI, MSI, TMS is anatomical inaccuracy due to brain shift during surgery and technologically speaking, they lack reliability at an individual scale [42]. Likewise, extraoperative brain mapping with subdural electrodes is limited in terms of inability to stimulate or map the subcortical areas (Figure 12A). Therefore, intraoperative brain mapping of cortical-subcortical brain areas using bipolar probe neurostimulation is regarded as more valid and adaptable than extraoperative brain mapping methods [50]. Nonetheless, not all patients with brain tumors can be operated in awake state. The exclusion criteria include: a) deep seated tumor, b) very young (< 14 years old) or elderly patient (> 65 years old), c) non-educated or non-motivated patients, d) agitative or fretful patients, e) demented patients, and f) presence of other co-morbidity. In such cases, surgery under general anaesthesia is frequently undertaken and therefore new methods in ensuring safety to the patients are required. In that respect, intraoperative monitoring (IOM) seems as an ideal option where it can monitor

the functions of the neurons and nerve tracts of the nervous system during state of unconsciousness [6, 7, 51].

4. Intraoperative neuromonitoring for brain tumor surgery

Intraoperative monitoring or neuromonitoring (IOM) is an electrophysiological technique to monitor the functions of neurons and/or nerve tracts during surgery which provides information regarding functional integrity of nervous system in a patient who is anaesthetized and otherwise could not be examined neurologically. IOM consists of somatosensory evoked potential (SSEP), motor evoked potential (MEP), brainstem auditory evoked potential (BAEP), visual evoked potential (VEP), electromyography (EMG) and electroencephalography (EEG).

IOM records spontaneous activity for averaged EEG and non averaged EMG, and evoked response resulted from external stimulation for averaged values of VEP, BAEP, SSEP and MEP. The recorded spontaneous activities are affected by factors such as ischaemia, mechanical injury, blood pressure, body temperature, anaesthetic regime, electrocardiography, electrical interference and muscle activity. During monitoring, ones should be watchful of: a) drop in the amplitude of the response, b) increase in the latency of the response and c) change in the waveform. The goals of IOM are therefore to identify impaired function along the monitored pathways, to alert the surgeon to any impending complications and to reduce risk of postoperative neurological sequelae.

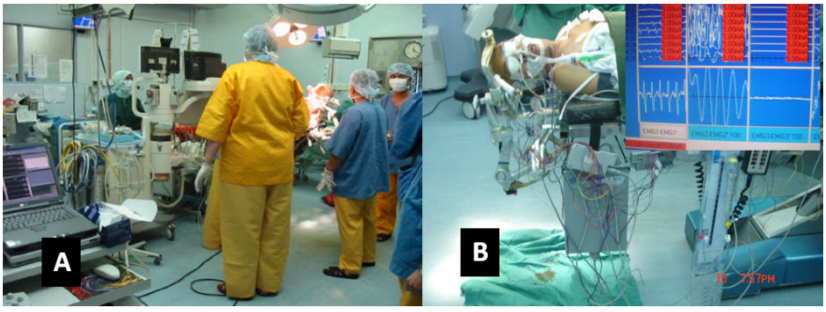

Figure 13. A: Intraoperative neuromonitoring set-up in our operating theatre B: Patient was operated under general anaesthesia with various neuromonitorings.

In general, alarms in neuromonitoring include evoked potentials of ≥ 50% reduction in amplitude and/or increment in latency of ≥ 10%; for EMGs, a change in morphology; and for EEGs monitoring as hints for impending ischaemia or mechanical compression, a decrease or loss in high frequency component, an increase in high amplitude of slower component, burst suppression (periods of silence alteration with periods of activity) which occurs typi-

http://dx.doi.org/10.5772/52032

cally in more severe ischaemia and finally flat EEG which is the severest form of an insult. Figure 13A and B show typical IOM set-up in our operating theatre.

4.1. Upper and lower limbs SSEP

Somatosensory evoked potentials monitor the status of ascending white matter fibres from upper or lower limbs. The recording electrodes are situated strategically at certain points along the monitored pathways, for instance, the Erb point for upper limb SSEP commonly records the N9 waveform generated at the brachial plexus (N for negativity - the wave is deflected upwards and P for positivity - the wave is deflected downwards, its amplitude or shape is important; values 9 signifies the expected time for electrical wave to reach the recorded point from the stimulation site in 'milliseconds' or better known as *latency*. *Velocity* is therefore value of measured distance with a tape from the stimulus site to the recorded site and divided with its latency). Table 3 summarises the stimulation parameters, stimulation and recording sites and examples of surgeries that require these types of monitoring.

Upper limb SSEP (ULSSEP)		
Stimulation parameters	**Stimulation and Recording Sites**	**Surgeries requiring ULSSEP and tips**
Stimulus duration: 250 usec. Stimulus intensity: 20 - 30 mA Stimulus rate: 4 - 5 Hz. (note: distal stimulation and recording proximally in the direction in which physiological sensory conduction occurs is known as *orthodromic*. Antidromic study or method is the reverse)	Stimulation site: Median nerve has the most sensory connections within the palm of the hand therefore optimal choice for obtaining ULSSEP. Stimulate the ulnar nerve for cases where T1 nerve root is at risk since median nerve is only innervated by C6 - 7 nerve roots. Recording site: a) Erbs - Generator site is Brachial plexus: waveform N9 b) C2 (cervical level 2) Cervical/medullary: wavefrom N13 c) CP3 - Left somatosensory cortex: wavefrom N20 - P25 d) CP4 - Right somatosensory cortex: waveform N20-P25	Intracranial tumor, chiari malformation, acoustic neuroma, AVM, aneurysm, carotid endarterectomy, spinal decompression, fusion, instrumentation, tethered cord, syringomyelia, intra and extra dural spinal tumors. Damage to the spinal cord or cortex should never result in a loss of the Erbs point. Loss of the Erbs point (N9) indicates a peripheral injury or decrease temperature of the arm. Always be sure of exactly where the lesion is located on the patient you are about to monitor. It helps predicting when and where a change may occur during surgery (*peak monitoring hours*)

Lower limb SSEP (LLSSEP)		
Stimulation parameters	**Stimulation and Recording Sites**	**Surgeries requiring LLSSEP and tips**
Stimulus duration: 250 usec. Stimulus intensity: 20 - 30 mA Stimulus rate: 4 - 5 Hz.	Stimulation site Posterior tibial nerve. Recording site a) C2 (cervical level 2) - Generator site is cervical/medullary: waveform N31 b) CPz - Midline somatosensory cortex: waveform N37-P45 c) CP3 - Left somatosensory cortex: waveform N37-P45 d) CP4 - Right somatosensory cortex: waveform N37-P45	Intracranial tumor, chiari malformation, acoustic neuroma, carotid endaterectomy, AVM, aneurysm, spinal decompression, fusion, instrumentation, tethered cord, syringomyelia, spinal tumor. LLSSEP can be difficult to obtain especially in older patients or those with oedema surrounding the ankles. In this context, do increase the stimulus intensity to 40 - 50 mA [2X) Loss of LLSSEP is not always an indicator of spinal cord or brain injury, decrease in response can be due to peripheral injury. If U/LLSSEP showed partial or total recovery of the responses by the end, often indicates a positive outcome.

Table 3. Summary of stimulation parameters, stimulation and recording sites and examples of surgeries that require SSEP monitorings.

4.2. Brainstem auditory evoked potentials (BAEP)

BAEP monitors the auditory pathways from peripheral to central components. Auditory clicks are delivered directly to the external auditory canal via the foams that are firmly secured and the responses were recorded at A1 and A2 sites (superior to the ears). In BAEP, there are 7 waves generated, each wave or peak has a specific generator site, loss of a particular peak can help you locate where the intraoperative injury has occurred. Figure 14 shows the pattern of BAEP waveforms. The putative generator sites of the major components of the BAEPs are as follows: Peak I - post-synaptic distal cochlear nerve; Peak II - ipsilateral cochlear nucleus in the upper medulla; Peak III - superior olivary complex in the pons (ipsi and contralateral); Peak IV - ascending lateral lemniscus in the pons (ipsi and contralateral); Peak V - inferior colliculus in the midbrain (ipsi and contralateral); Peak VI - medial geniculate in the thalamus and Peak VII - thalamo-cortical auditory radiations or auditory cortex. BAEPs are primarily analyzed for the presence of waves I, III, and V; waves II and IV have been found to be inconsistent even in normal adults, therefore not considered significant for clinical interpretation [52]. Wave V is the most clearly defined because it has the largest amplitude and a characteristic sharp drop immediately after it and the wave that most likely to be present

http://dx.doi.org/10.5772/52032

despite hearing deficits and manipulation of stimulation and recording parameters. Wave V of the BAEP is therefore considered as the most important component of BAEP [52, 53].

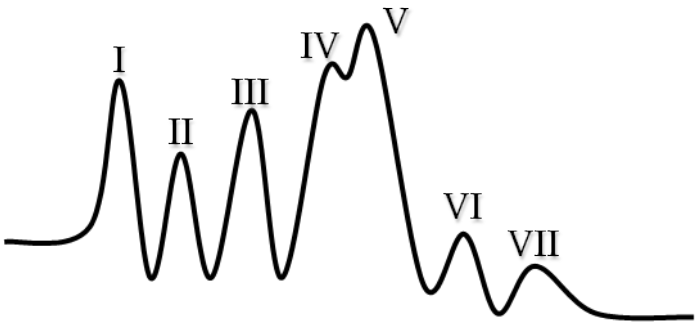

Figure 14. Brainstem auditory evoked potential (BAEP) waveforms.

Interpreting BAEP (also SSEP/MEP) requires baselines waveforms. Baselines are ideally obtained *just prior* to surgical manipulation and after positioning in the operating theatre as a mean of comparison to subsequent averages throughout the case in order to detect any changes. BAEPs that are reliably recorded intraoperatively provide good indication of good neurological outcome. Transient changes are often associated with good prognosis, examples: retraction, manipulation, or compression of the auditory nerve, cerebellum, or brainstem tend to produce transient and reversible changes. Note that these changes usually manifest as increases in latency but with persistence of the insult, loss of BAEP components may occur that could lead to signficant neurological deficits. Specifically, criteria for evaluation of BAEP changes are based on two variables:

i. Latency (timing) - Absolute latency for waves I, III, and V and interpeak latency for waves I-III, III-V, and I-V

ii. Amplitude - Amplitude of waves I and V and amplitude ratio of wave V/I

Generally accepted standard of significant change is a latency increase of peak V exceeding 1.5 ms and a decrease of 50% or more in amplitude [52, 53]. Good *communication* between the surgeon and neurophysiologist is vital to detect early any significant changes which can urge fast intervention by the surgeon and a subsequent change in the surgical procedure and outcomes. Table 4 summarises the stimulation parameters, stimulation and recording sites and recommended types of surgery for BAEP.

Brainstem auditory evoked potentials (BAEP)		
Stimulation parameters	**Stimulation and Recording Sites**	**Surgeries requiring BAEP**
Stimulus duration: 100 usec. Stimulus intensity: 100 – 120 peSPL. Stimulus rate: 11 to 30 Hz.	Stimulation site Auditory clicks delivered directly to the external auditory canal. Recording site a) A1 - Left auditory pathway and brainstem b) A2 - Right auditory pathway and brainstem	Skullbase tumor, posterior fossa tumor, acoustic neuroma, CPA tumor, microvascular decompression, basilar aneurysm, post fossa AVM and EC-IC bypass.

Table 4. Summary of stimulation parameters, stimulation and recording sites and recommended types of surgery for BAEP.

4.3. Electromyography (EMG) and F-wave

Any electrical or magnetic stimulation along the motor pathways will generate involved muscles compound evoked or action potentials, better known as CMAP [compound muscles evoked/action potential – a type of motor evoked potential (MEP) and/or EMG (muscle activity). IOM that uses EMG does monitor wave as well as its sound. On some occasions, muscles twitching, contraction or movement can be noted during the monitoring. It is used during resection of tumor that is located close to motor nerves, for instances, cerebellopontine angle (CPA) tumoral surgery whereby muscles innervated by the facial nerve (orbicularis oris, oculi and nasalis) are monitored using EMGs. The most important factor affecting EMG monitoring is the depth of muscle paralysis. This can be determined by delivering a train of four electrical pulses at approximately 25 mA to usually median or facial nerve, and observing resulting number of twitches: four twitches suggesting no paralysis whereas zero twitches suggesting complete paralysis. For monitoring purposes, ones should have at least 3 twitches in order to detect EMG activity. Interpretation criteria for significant EMG activity are:

i. Sustained firing of a high frequency train lasting for tens of seconds

ii. Large bursts of EMG activity of complex morphology

iii. Sudden bursts of high amplitude spikes

These patterns of activity are usually indicative of nerve irritation but also confirm that the pathway to the specific muscles are intact. Other tips during monitoring are always helpful to turn the volume up high on EMG monitoring machine so that one can hear the EMG activity. If a nerve root can not be electrically stimulated after repeated trials, it may be safe to conclude that the nerve is no longer functionally intact. Figure 15 illustrates the muscle responses that you might get from stimulating the motor cortex, motor pathway, root or nerve.

http://dx.doi.org/10.5772/52032

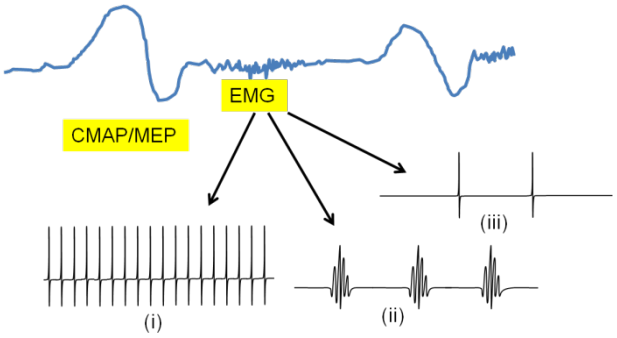

Figure 15. Muscle recording from motor cortical stimulation produces CMAP (which is a type of MEP) or 3 subtypes EMG responses (note: the MEP and EMG monitorings normally display on two different monitors).

F waves (F for foot where they were first described) are a type of late motor response. When a motor nerve axon is electrically stimulated at any point, an action potential is propagated in both directions away from the initial stimulation site. The distally propagated impulse gives rise to the CMAP or M response. However, an impulse also conducts proximally to the anterior horn cell, depolarising the axon hillock and causing the axon to backfire which leads to a small additional muscle depolarisation (F wave) at a longer latency (Figure 16). Because of the long pathway, normal values have to be related to limb length or body height. F waves allow testing of proximal segments of the nerves or roots that would otherwise be inaccessible to routine studies.

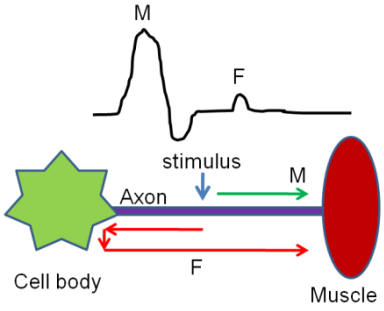

Figure 16. Schematic representation of M and F waves.

4.4. Transcranial electrical and magnetic stimulation and transcortical stimulation

Transcranial electrical stimulation (TES) can be done by using electrical-digitimer stimulation which normally sets at stimulus intensity of 100 to 750 V (max 200 mA), stimulus duration of 0.3-0.5 msec and train of 2 - 5 pulses with 2-4 msec interstimulus interval. On the contrary, the transcranial magnetic stimulation (TMS) uses magnetic stimulation coil to generate electrical

current in the brain tissue [54, 55]. The stimulus intensity can be adjusted from 0 to 100% of the magnetic tesla (normally for single pulse motor mapping, 80-90 % stimulus intensity is needed). The stimulation sites can be determined by image guided system (preferred) or based on the scalp EEG 10-20 system electrodes: the left and right motor cortex correspond to C3 and C4 electrode regions (sometimes use C1 and C2 electrode areas). Recordings are made at the spinal cord or nerve level in forms of motor evoked potentials *(MEP:wave forms/neurogenic potentials – repetitive or train of pulses are needed to produce MEPs for continuous monitoring of the waveforms/pathway, therefore transcortical method, strip or grid electrodes are preferred to create persistent stimulation)*, or on the surface (surface electrode) or inside (needle – well tolerated) the muscles in forms of either MEP *[note: when MEP is recorded in or on the surface of the muscle, it is commonly called as CMAP. This can be either at rest - resting MEP or with grip – facilitated MEP]* or EMG responses *(EMG:muscle activity/myogenic potentials)* [56, 57]. Examples of recorded muscles are dorsal interrosseus, abductor pollicis brevis, brachioradialis, biceps, deltoid, thenar or hypothenar muscles or extensor digitorum longus for upper limb and first dorsal interrosseous, extensor hallucis longus, tibialis anterior, gastrocnemius, soleus, anterolateral thigh groups of muscles for the lower limb and for the face; frontalis and orbicularis oris in awake state and orbicularis oculi, oris or nasalis in unconscious state. Examples of Surgeries requiring MEP are for tumors located along the pyramidal-descending pathways *(transcranial stimulation is better since craniotomy is not desired just for the purpose to only stimulate the motor cortex)* or those near or embedded within the motor strip and cortex *(transcortical stimulation is better because craniotomy for tumor resection can also incorporate the motor strips)*. Eventhough transcranial magnetic stimulation is less painful, transcranial electrical stimulation is the optimal choice for obtaining MEPs because it is capable of delivering a more stable stimulus. Total intravenous anaesthesia (TIVA) should be requested before the case begins, since inhalational anaesthetics will reduce the MEPs amplitude. It is helpful to be in constant communication with anaesthesiologist in order to know level of paralysis as an aid in interpretation.

Transcranial Magnetic Stimulation (TMS) is a method to non-invasively probe and reversibly alter neural processing in the human brain. TMS relies on the Faraday principles of electromagnetic induction to generate electrical currents in neural tissue [58]. The direct impact of a TMS is limited to a patch of cortex of a few square centimetres and the induced field falls off exponentially with distance. The effective penetration depth of TMS is estimated to be ~ 2 cm [59]. The intensity of the stimuli can be controlled by changing the current intensity flowing in the coil, thus changing the magnitude of the induced magnetic field and of the secondarily induced electrical field. The focus of the magnetic field depends on the shape of the stimulation coil: figure-of-eight shaped coil (preferred for mapping) or circular coil. The former provides a more focal stimulation, allowing proper mapping of the cortex and the latter induces a more widely distributed electric field allowing for bihemispheric stimulation [60]. The operator can also control the frequency of the delivered stimuli which will determine the effects of TMS on the targetted region of the brain. Frameless stereotactic system helps to precisely localise the brain region during the procedure (Figure 17). Technique for TMS can be either single pulse TMS (spTMS) which can be used to study motor evoked potentials and map the brain cortex, paired-pulse TMS (ppTMS) to study the inhibitory and facilitatory interactions in the cortex

http://dx.doi.org/10.5772/52032

and repetitive TMS (rTMS) whereby a train of TMS pulses of the same intensity applied to a single brain area at a given frequency that can range from 1 – 20 Hz. Lower frequencies of rTMS in the 1 Hz range, can suppress excitability of motor cortex, while 20 Hz stimulation can cause temporary increase in cortical excitability [61, 62]. rTMS is mainly used to study the brain-behaviour relationship and mapping the language cortex. Important to note that in a child of less than 10 years old, it may not yield localising response due to relative inexcitibility of child cortex [63]. The contraindication to brain stimulation is presence of pacemaker; and relative contraindication for transcranial stimulation is presence of holes or fracture of skull.

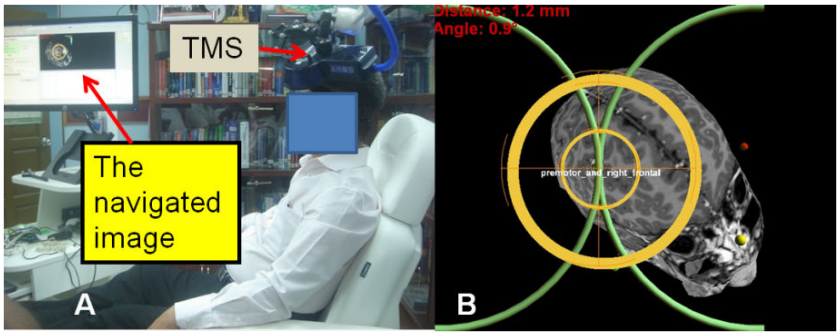

Figure 17. A: The navigated transcranial magnetic stimulation. B: The site of the stimulation is identified on the navigation image.

Transcortical stimulation has been discussed in details at earlier headings and commonly applied in awake surgery. It is a direct method for cortical stimulation which commonly uses neurostimulator *(more precised to elicit EMGs: for brain mapping – tumor within or closed to eloquent cortices)* or strip/grid electrodes for repetitive firing of stimuli to elicit MEP-waves for continuous motor tract monitoring *(example: use for insular region tumor where the surgical approach is at the inferior part relative to the strip/grid electrodes-continuous-stimulation site)* rather than coils *(non-focal and need larger craniotomy than usual).* In general, it requires craniotomy and commonly applies for tumour at region of motor cortex, subcortical motor areas or adjacent to the descending motor pathways. The Penfield technique using neurostimulator is used for transcortical brain mapping: 50-60 pulses per second (frequency 50 – 60 Hz) on motor cortex or subcortically via continuous cortical stimulation over few seconds, with initial current of 1 mA, if no movement or contraction elicited, increase by 1 mA till 16 mA [64]. If no response, then consider non-functional (*Rules of maximum stimulation: < 20 mA for direct (transcortical) and < 200 mA for transcranial/indirect stimulation).*

4.5. Visual evoked potential (VEP)

Goggles containing light emiting diode stimulates retina by light produces evoked responses of occipital cortex at O1 and O2 electrodes or better known as visual evoked potentials (VEPs). P100 of positive polarity and has 100 msec latency is usually used for IOM. Because of high percentage of false positivity associated with VEP, It is mainly used in chiasmatic, optic nerve or sellar region tumour surgery and requires very conservative interpretation (note: patient can close the eyelids during VEP monitoring).

4.6. Tips on anaesthesia

Our IOM anaesthetic protocol encourages use of propofol infusion, opiod infusion (alfentanil etc), with or without inhalational N_2O of less than 50% and intravenous infusion of muscle relaxant with limited dosage, during EMG and/or MEP procedures. Bispectral EEGs (BIS) is good to monitor level of anaesthesia during IOM. Table 5 lists out the anaesthetic tips for IOM procedure.

Intraoperative monitoring (IOM)	Tips for anaesthesia
SSEP	Both techniques of anaesthesia, either inhalational anaesthesia or total intravenous anaesthesia (TIVA) can be used. TIVA can be done with combination of propofol infusion and opioid infusion (remifentanil, sufentanil, alfentanil or fentanyl). Propofol and remifentanil combination is preferable TIVA technique because it can be delivered using target-controlled infusion (TCI) technique. TCI is a technique to deliver certain drugs using special infusion pump incorporated with a software that contains a pharmacokinetic profile of the drugs. If only SSEP is monitored, muscle relaxant can be used if necessary.
EMG	Both techniques of anaesthesia, either inhalational anaesthesia or TIVA can be used. The only important thing is to avoid muscle relaxant during the testing. If muscle relaxant is initially used, it needs to be stopped earlier or reversed when necessary during EMG monitoring
MEP	TIVA is the main anaesthesia technique. Inhalational agents are better totally avoided except desflurane supplement just limited between 0.2- 0.3 minimum alveolar concentration (MAC) is reported to be acceptable in combination with TIVA. Muscle relaxant is better avoided. If indicated to be used, paralysis should be minimal or limited: 1 - 2 twitches per 4 train. Bite block may be used to avoid tongue injury.

Table 5. The anaesthetic tips during IOM procedures.

4.7. Brain tumor surgery under general anaesthesia and neuromonitoring

Intraoperative neuromonitoring is commonly utilised to monitor the status of important neurostructures or tracts whenever surgical removal is planned for tumor that lies close to them. This seems important whenever surgery is planned under general anaethesia (GA). Under non-awake state, monitoring neurological status of the patient is impossible, therefore many surgeons rely on alternative techniques of IOM to safeguard those neural

http://dx.doi.org/10.5772/52032

structures. The first example is an elderly lady with right frontal high grade tumor presented with left upper limb weakness. The surgery was done under GA with neuronavigation guided surgery and motor cortex stimulation with EMG monitoring. The MEG-MRI (MSI) extraoperative images were uploaded to the neuronavigation system (Medtronic StealthStation TREON™, Minneapolis, USA) and were used to localise the tumor and left leg motor area (Figure 18A). Prior to removal of the tumor, the transcortical motor stimulation was made to localise the hand and facial areas (Figure 18B). Tumor removal was uneventful and immediately after, she received adjuvant intraoperative radiation therapy (IORT) to the periphery and chemotherapy (Figure 18C).

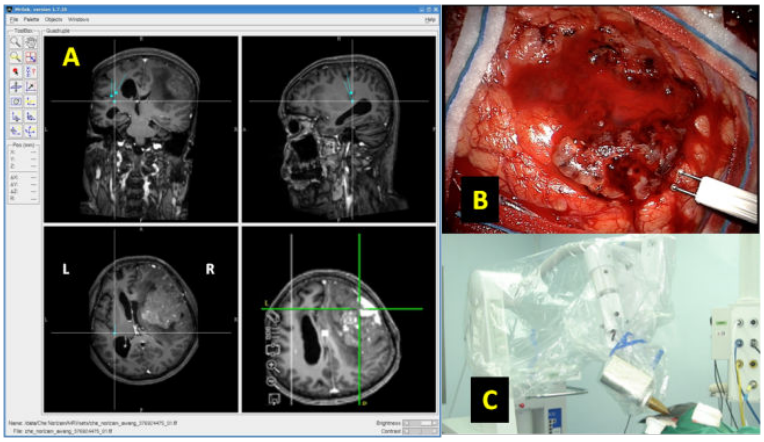

Figure 18. A: MSI was used to localize the eloquent cortices. B: Limited motor cortex stimulation can still be done under general anesthesia as long as no muscle relaxant was given and EMG recordings were made at specific muscles. C: Adjuvant intraoperative radiation therapy (IORT) for residual tumor.

The second case illustration was the ventral brainstem tumor arisen years after radiation therapy to the neck and parotid region for extracranial meningiomas (Figure 19A). The surgery was done under GA and endoscopic true endonasal transphenoidal transclival approach was used to debulk the tumor (Figure 19B). SSEP, BAEP and multiple lower cranial nerve EMGs *(V – Masseter, VI – lateral rectus, VII – nasalis, orbicularis oris and oculi, IX and X – endotracheal tube with adhesive EMG sensors [note: surface EMG electrode at anterior neck is valid for purpose of cortical brain mapping], XI - upper sternomastoid and XII – tongue muscles)* were used to safeguard the important neural structures (Figure 19C). Extraoperative neuroimages were used to localise the tumor and important white matter tracts in the brainstem (Figure 19D). Tumor debulking was completed without causing new neurological deficits (Figure 19E).

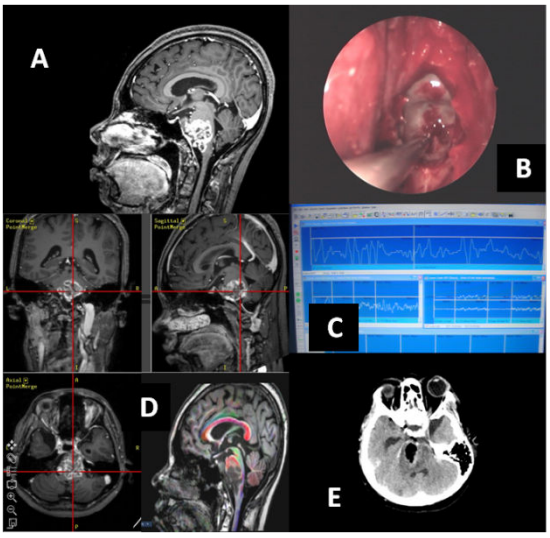

Figure 19. A: Ventral brainstem tumor. B: Endoscopic view during resection. C: Intraoperative neuromonitoring recordings during surgery. D: Neuronavigational images during resection. E: Postoperative image.

5. Brain tumor and adjuvant precision radiation therapy

Several factors known to influence the prognosis of high grade tumors include tumor resection without causing deterioration in patient's neurological functions, adjuvant radiotherapy and chemotherapy [65, 66]. Since high grade tumors tend to be infiltrative in nature, precision radiation therapy should target both the tumor and its infiltrative margin. Hochberg and Pruitt performed series of autopsy studies in patients with high grade brain tumors, where the microscopic margin of tumour was within 2 cm of the enhanced region [67]. This rule of 2 - 3 cm margin from the tumour in radiation therapy seems practical with precision radiation therapy.

Stereotactic radiosurgery (SRS) is an external irradiation technique in which multiple collimated beams of radiation are stereotactically aimed at a radiographically discrete target volume to deliver a single, high dose of radiation to a small volume of tissue (commonly ≤ 3 cm in diameter) (Figure 20A). Stereotactic radiotherapy (SRT) is a technique whereby high precision techniques of SRS with potential radiobiological benefits of fractionation are combined. Therefore SRT involves multiple irradiation sessions and generally used for brain tumors that are irregular in shape and larger than 3 cm in diameter (Figure 20B). Intraoperative or intrabeam radiation therapy (IORT) is a type of intraoperative brachytherapy in which the therapeutic irradiation is administered immeditaley after surgical debulking of brain tumors (Figure 21B). These three techniques of precision radiation therapy are commonly used in our centre to treat high grade tumors after surgical debulking.

http://dx.doi.org/10.5772/52032

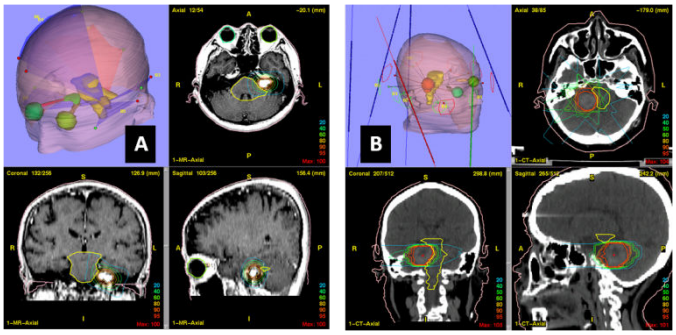

Figure 20. A: Stereotactic radiosurgery (SRS) planning for brain tumor. B: Brain tumor planning for stereotactic radiotherapy (SRT).

In many instances, surgical resection of the tumour is required to reduce the tumor bulk to suit adjuvant therapy, but radiating the *empty* tumoral bed with SRS seems inappropriate. Besides, size of the tumor is also a limiting factor for SRS. As for the time-consuming SRT technique, it is potentially inaccurate because of the different timing of radiation with non-fixed referral points. Thus, such limitations of the two techniques made IORT our most favourable option [66]. The key advantages of IORT are: a) radiation to the tumoral bed can be administered directly after surgical resection; b) radiation can be given circumferentially from the centre of the empty tumoral bed whereby the plan tumour volume is better defined and irradiated; and c) size of the tumor is not a hindrance for high dose irradiation therapy.

At our centre, the IORT procedure had been performed under general anaesthesia immediately after completing the tumoral resection or few days after the surgery. Patient's head was fixed with Mayfield head clamped and rotated adequately so that the tumoral bed localises at the uppermost part. The tumoural bed was measured in all three dimensions and filled up with wet tissue-equivalent cotton strips. Beam directions measured by means of a specially constructed device called the BDI (beam direction indicator). The beam direction was selected according to the shape and depth of the resection cavity and the region presumed at risk of recurrence. The intended beam direction was maintained by using BDI. The BDI consists of a mobile arm with several joints which can be mounted at the edge of the operating table and prepared for the placement of radiation source or better known as Intrabeam Miniature X-ray Source (xRS). The applicator or probe was then fixed to the radiation source. A complete set of spherical applicators or probes from 1.5 to 5.0 cm in diameter are available to enable accurate placement into the tumoral bed, ensuring contact with all surfaces of the treatment area, and uniform dose delivery. The spherical applicator or probe was selected according to the diameter of the resection cavity including a safety margin of at least 1-2 cm. The electron energy was chosen according to the depth of the resection cavity including a margin of at least 1 cm. Dosage of focal irradiation therapy was calculated in Gy and administered intraoperatively (Figure 21A and B).

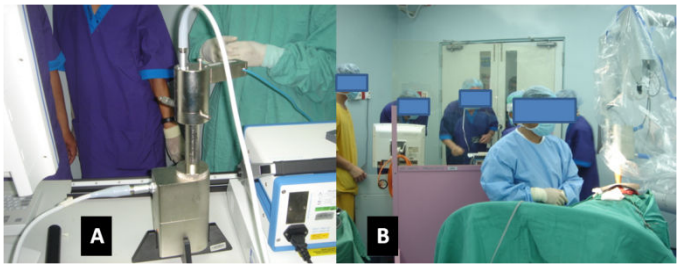

Figure 21. A: Dosage processing prior to irradiation for intrabeam Miniature X-ray Source (xRS). B: Intraoperative radiation therapy procedure, the histologically confirmed tumor bed was irradiated immediately after the surgery.

After completion of the procedure, absolute hemostasis was achieved, dura was closed primarily and the wound was closed in layers. After an interval of 3 – 4 weeks, standard external beam irradiation was started in patients receiving IORT. Besides intracavitary technique of IORT (using spherical applicator as explained above), interstitial IORT is an alternative and commonly used for deep seated high grade brain tumor, such as thalamic gliomas. Initially, tumoral biopsy was made using stereotactic frame (CRW) and once the intraoperative fresh frozen biopsy results confirmed a high grade tumor, the irradiation source was mounted onto the stereotactic frame and the radiation tip was localized into the central part of the tumor for proper irradiation (Figure 22A and B).

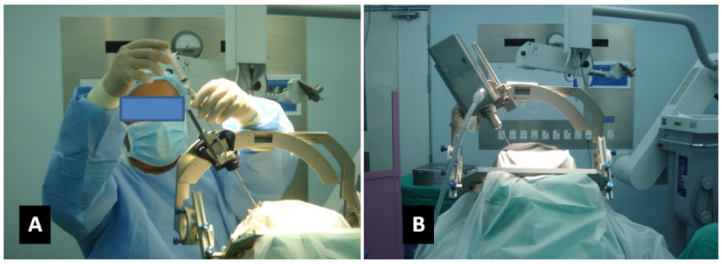

Figure 22. A: Tumoral biopsy procedure completed prior to interstitial IORT. B: An accurate irradiation was administered by using CRW stereotactic frame after knowing the fresh frozen biopsy results.

6. New concept – Brain waves, oscillations and networks

Oscillation with synchronisation does exist inside (~ small universe) and outside (large universe) our brain. Neural oscillation can be stratified into microscale-oscillation (activity of a single neuron), mesoscale-oscillation (activity of local group of neurons or vertices) and macroscale-oscillation (neural activity of different brain regions/networks). Neurons can generate action potentials or spike trains (multiple action potentials in sequence) at microscale oscillation and can be studied using intracellular single-unit recordings. When a group of

http://dx.doi.org/10.5772/52032

neurons firing action potentials, synaptic interactions play major role to synchronise the input to other brain regions. Synchronised firing patterns give rise to large-amplitude mesoscale oscillations of local field potentials which can be detected by using EEG or MEG. Neural oscillations which arise from interactions between or among brain regions are known as macroscale-oscillation. It forms various network loops with edges and vertices inside our brain and it is also best detected by using EEG or MEG [31, 68-72]. Neuronal property of creating oscillation inside our brain is important for normal brain functioning. Neural oscillation contributes to neural coding, brain rhythms with different types or frequency of oscillatory activity *[5 type of brain waves: gamma (above 30 Hz), beta [13 – 30 Hz), alpha (8 – 13 Hz), theta [4 – 8 Hz) and delta [0.5 – 4 Hz); sleep spindles; Mu waves; thalamocortical oscillations; epileptic seizures and bursting]* and fast information processing and transfer. Interestingly, neural oscillations also play an important role in many neurological disorders such as excessive synchronisation during seizure in epilepsy or tremors in movement disorders [69]. Lately, it is also being used in controlling the external devices in brain-computer interface [73-74]. Its principle has a potential basis to invent new devise which can restore the functions of the paretic limbs by implanting the devices and get connected to the residual survived-brain networks *(an example: a case with middle-cerebral-artery infarct with hemiparesis, infarctectomy is performed prior to rewiring using advanced DTI and the procedure is completed with implantation of cortical-subcortical stimulatory device)* and subsequently programming the oscillatory outputs (rhythms and amplitudes) via wireless external computers.

Apart from intrinsic properties of neurons, network properties are also an important source of oscillatory activity. The introduction of modern network theory of small-world or scale-free networks appears plausible to describe the real complex brain networks [49, 69]. Small-world network has high clustering coefficient (many vertices/brain areas/rhythms-generating-brain areas) and short path length (connections or edges between vertices/white matter tracts on DTI), and is therefore regarded as the best and economical network model to explain our extremely efficient brain networks or loops. Oscillations produced by the networks are synchronised-large-scale oscillations which can be recorded by using EEG or MEG and studied for:

i. Evoked and event related potentials (ERPs). Evoked or event activity is the brain responses that are directly related to stimulus-related activity. Evoked potentials are commonly used for sensory or motor stimulus, and ERPs are mainly for cognitive tasks. They are obtained by stimulus-locked averaging (averaging different trials at fixed latencies around the presentation of a stimulus). In this analysis, the spontaneous brain activity is regarded as noise and one only focuses on evoked or event related responses

ii. Resting-state activity or spontaneous activity. Oscillatory activities do exist when subjects do not engage in any activity. It is used to study brain maturiy in different ages or pathology, seizure focus, level of consciousness and many else

iii. Complex analysis for brain networks, using neurodynamics-mathematical models or formula of statistical-physics such as spectral analysis (for large-scale data)

From the experiences at our centre, we presented three clinical examples that display features of brain oscillation which were detected by the aforementioned three main studied methods.

Case 1: This is an example of an *evoked response* to display brain oscillation (Figure 23). A 51-year-old man presented with mild left upper limb and facial weakness without history of focal seizures. The brain MRI disclosed a tumoral lesion at right motor cortex. DTI revealed the lesion was surrounded by important pyramidal tracts. He underwent awake tumoral surgery and the tumor was successfully removed. Prior to tumor removal, cortical stimulation was made at right hand motor cortex [60 Hz, 2 ms pulse interval, at 3 – 4 mA) which was confirmed by EMGs responses in the left hand's muscles. Interestingly, there were also obvious evoked potentials responses detected by the opposite side scalp EEGs. Since there is falx structure at the midline, the transfer of the electrical waves from right to left cerebral hemisphere must have gone through appropriate anatomical pathways or loops (corpus callosum or thalamo-cortical loops). This case example proves that inside our brain, there are networks or loops that play significant role in exhibiting their functions.

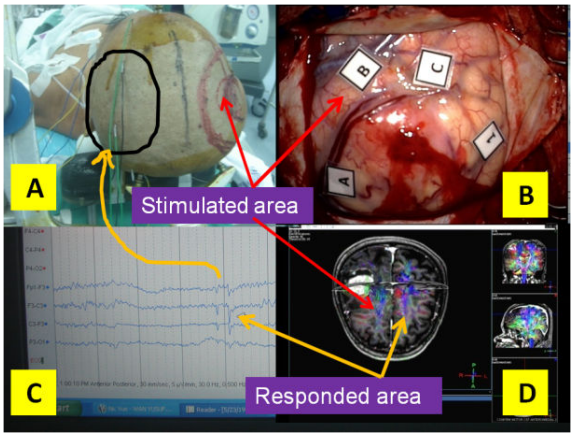

Figure 23. A: Craniotomy for tumor resection was on the right and scalp electrodes were inserted on the left. B: Intra-operative image shows functional brain areas labeled A-C and 1. When area labeled B was stimulated, evoked responses were noted mainly at F3-C3 and C3-P3 at opposite hemisphere (C). D: The stimulated and responded areas seen on DTI.

Case 2: This is an example of resting state or *spontaneous activity* to display brain oscillation (Figure 24). A 41-year-old man who had posterior limb of right internal capsule haemorrhage secondary to cerebral arteriovenous malformation (AVM). He has weakness and dystonia of his left hand. The spontaneous MEG recordings before radiosurgical treatment revealed marked slowings of brain waves at both, right and left motor cortices. This case illustrates lesioning at one point in the network or loop would cause bilateral spontaneous brain waves abnormality. Comparatively similar to above conclusion, it suggests that brain networks or loops do exist in our brain, and they contribute significantly to brain functions.

http://dx.doi.org/10.5772/52032

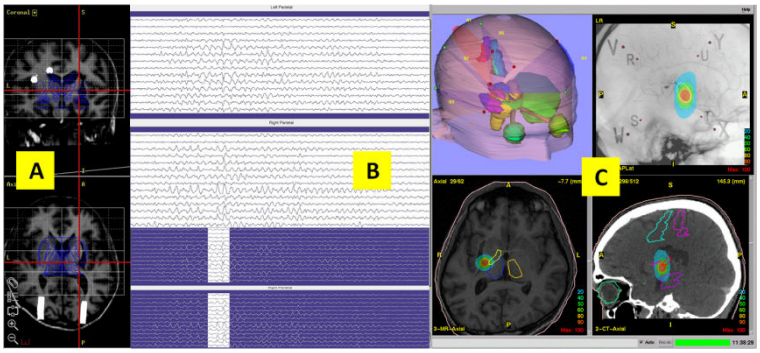

Figure 24. A: The AVM anatomical area was fused with Schaltenbrand-Wahren atlas. B: Spontaneous MEG recordings prior to SRS, shows slowing at bilateral motor cortices. C: Radiosurgical planning for that AVM.

Case 3: This is our third example to display brain oscillation through *complex mathematical model analysis*. Figure 25 disclosed MEG fast-fourier-transformation (fft) analysis for spontaneous brain waves, recorded before and after brain tumor removal in both hemisphere. The tumor was located at frontotemporoparietal brain region. The detail analysis revealed marked changes in brain waves patterns after tumor removal not only in the hemisphere which harbors the tumor, but also in the opposite hemisphere. More activities or less slowing waves patterns were recorded in both hemispheres after tumor resection. This corresponds to marked improvement in patient clinical status. This proves that brain networks or loops do exist in our brain and work via brain waves oscillation.

TUMOURAL HEMISPHERE SIDE

Preoperation	Postoperation
Right frontal	Right frontal
Beta power: 0.14 x 10^{-24} T/cm	0.18 x 10^{-24} T/cm
Alpha power: 0.56 x 10^{-24} T/cm	0.28 X 10^{-24} T/cm
Theta power: 0.29 x 10^{-24} T/cm	0.88 x 10^{-24} T/cm
Delta power: 7.2 x 10^{-27} T/cm	6.11 x 10^{-27} T/cm (less slowing)
Right temporal	Right temporal
Beta power: 0.99 x 10^{-24} T/cm	0.88 X 10^{-24} T/cm
Alpha power: 1.94 x 10^{-24} T/cm	2.08 x 10^{-24} T/cm
Theta power: 1.69 x 10^{-24} T/cm	0.01 x 10^{-21} T/cm (more)
Delta power: 0.03 x 10^{-24} T/cm	0.07 x 10^{-24} T/cm
Right Parietal	Right Parietal
Beta power: 0.53 x 10^{-24} T/cm	0.23 X 10^{-24} T/cm
Alpha power: 0.80 x 10^{-24} T/cm	0.48 x 10^{-24} T/cm
Theta power: 0.01 x 10^{-24} T/cm	0.83 x 10^{-24} T/cm (more)
Delta power: 0.27 x 10^{-24} T/cm	4.76 x 10^{-27} T/cm (less DELTA or slowing waves; more activity after surgery)

OPPOSITE HEMISPHERE SIDE

Preoperation	Postoperation
Left frontal	Left frontal
Beta power: 0.39 x 10^{-24} T/cm	0.15 x 10^{-24} T/cm
Alpha power: 0.87 x 10^{-24} T/cm	0.29 X 10^{-24} T/cm
Theta power: 0.76 x 10^{-24} T/cm	0.26 x 10^{-24} T/cm
Delta power: 5.63 x 10^{-27} T/cm	1.83 x 10^{-27} T/cm (less slowing)
Left temporal	Left temporal
Beta power: 1.66 x 10^{-24} T/cm	0.88 X 10^{-24} T/cm
Alpha power: 4.53 x 10^{-24} T/cm	2.98 x 10^{-24} T/cm
Theta power: 3.51 x 10^{-24} T/cm	0.46 x 10^{-24} T/cm (less ; Oscillate with opposite hemisphere which has more activity???)
Delta power: 0.06 x 10^{-24} T/cm	0.02 x 10^{-24} T/cm (less)
Left Parietal	Left Parietal
Beta power: 0.31 x 10^{-24} T/cm	0.22 X 10^{-24} T/cm
Alpha power: 1.07 x 10^{-24} T/cm	0.69 x 10^{-24} T/cm
Theta power: 0.35 x 10^{-24} T/cm	0.64 x 10^{-24} T/cm (more)
Delta power: 0.01 x 10^{-24} T/cm	6.92 x 10^{-27} T/cm (less slowing/more activity in opposite parietal lobe too!!!!!)

Figure 25. MEG fast-fourier-transformation analysis for brain tumor patient, before and after the surgery for both hemispheres. Analysis revealed enhanced activities in both hemispheres after the surgery.

7. Conclusion

Intraoperative use of anatomical and functional neuroimages plays crucial roles to quickly identify the tumor and to better define the eloquent areas of the brain. This extraoperative-neuroimages guided brain mapping approach commonly combines either with intraoperative brain mapping technique when patients with brain tumors undergo awake craniotomy surgery or with intraoperative neuromonitoring technique when surgery was done under general anaethesia. Both techniques appear to be useful to the neurosurgeons and acceptable to the patients whilst ensuring a safer removal of brain tumors. Besides, information gained from awake surgery, neuromonitoring and functional neuroimagings expands further insights and potential novel understanding in the field of fundamental and cognitive neurosciences.

Acknowledgements

We would like to thanks Mr Azmi Kass Rosman, Dr Saiful Azli Mat Nayan and Dr Gee Teak Sheng from Department of Neurosurgery, Sungai Buloh Hospital, Kuala Lumpur for providing us iCT photo which was depicted in figure 4 in this chapter.

Author details

Zamzuri Idris[1], W M Nazaruddin W Hassan[2], Muzaimi Mustapha[1], Badrisyah Idris[1], Rahman Izaini Ghani[1] and Jafri Malin Abdullah[1]

1 Department of Neurosciences, Universiti Sains Malaysia, Malaysia

2 Department of Anaesthesiology, Universiti Sains Malaysia, Malaysia

References

[1] Lee CC, Lee ST, Chang CN, Pai PC, Chen YL, Hsieh TC, et al. Volumetric measurement for comparison of the accuracy between intraoperative CT and postoperative MR imaging in pituitary adenoma surgery. AJNR Am J Neuroradiol. 2011;32(8): 1539-44.

[2] Shah MN, Leonard JR, Inder G, Gao F, Geske M, Haydon DH, et al. Intraoperative magnetic resonance imaging to reduce the rate of early reoperation for lesion resection in pediatric neurosurgery. J Neurosurg Pediatr 2012;9(3):259-64.

http://dx.doi.org/10.5772/52032

[3] Lindner D, Trantakis C, Renner C, Arnold S, Schmitgen A, Schneider J, et al. Application of intraoperative 3D ultrasound during navigated tumor resection. Minim Invasive Neurosurg. 2006;49(4):197-202.

[4] Szelenyi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, et al. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. Neurosurg Focus. 2010;28(2):E7.

[5] Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. J Neurosurg. 2011;115(2):232-9.

[6] Ritzl EK. Intraoperative neuromonitoring during glioma surgery: bring in the expert neurophysiologists! J Clin Neurophysiol. 2012;29(2):151-3.

[7] Weinzierl MR, Reinacher P, Gilsbach JM, Rohde V. Combined motor and somatosensory evoked potentials for intraoperative monitoring: intra- and postoperative data in a series of 69 operations. Neurosurg Rev. 2007;30(2):109-16;discussion 16.

[8] Duffau H. New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity-a review. J Neurooncol. 2006;79(1):77-115.

[9] Sylvain B. Magnetoencephalography. In: Duffau H. (ed.) Brain Mapping: from neural basis of cognition to surgical applications. 1st ed: Springer-Verlag; 2011.p77-89.

[10] Herdman AT, Cheyne D. A practical guide for MEG and beamforming. In: Handy TC. (ed.) Brain Signal Analysis: advances in neuroelectric and neuromagnetic methods. 1st ed. Cambridge: MIT Press; 2009.p99-140.

[11] Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci. 2008;34(1):51-61.

[12] Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed. 2002;15(7-8):435-55.

[13] Nucifora PG, Verma R, Lee SK, Melhem ER. Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity. Radiology. 2007;245(2): 367-84.

[14] Bello L, Castellano A, Fava E, Casaceli G, Riva M, Scotti G, et al. Intraoperative use of diffusion tensor imaging fiber tractography and subcortical mapping for resection of gliomas: technical considerations. Neurosurg Focus. 2010;28(2):E6.

[15] Gonzalez-Darder JM, Gonzalez-Lopez P, Talamantes F, Quilis V, Cortes V, Garcia-March G, et al. Multimodal navigation in the functional microsurgical resection of intrinsic brain tumors located in eloquent motor areas: role of tractography. Neurosurg Focus. 2010;28(2):E5.

[16] Kuhnt D, Bauer MH, Nimsky C. Brain Shift Compensation and Neurosurgical Image Fusion Using Intraoperative MRI: Current Status and Future Challenges. Crit Rev Biomed Eng. 2012;40(3):175-85.

[17] Rasmussen IA, Jr., Lindseth F, Rygh OM, Berntsen EM, Selbekk T, Xu J, et al. Functional neuronavigation combined with intra-operative 3D ultrasound: initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. Acta Neurochir (Wien). 2007;149(4):365-78.

[18] Schulder M, Maldjian JA, Liu WC, Holodny AI, Kalnin AT, Mun IK, et al. Functional image-guided surgery of intracranial tumors located in or near the sensorimotor cortex. J Neurosurg. 1998;89(3):412-8.

[19] Prabhu SS, Gasco J, Tummala S, Weinberg JS, Rao G. Intraoperative magnetic resonance imaging-guided tractography with integrated monopolar subcortical functional mapping for resection of brain tumors. J Neurosurg. 2011;114(3):719-26. .

[20] Nossek E, Korn A, Shahar T, Kanner AA, Yaffe H, Marcovici D, et al. Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. . J Neurosurg. 2011;114(3):738-46.

[21] Parney IF, Goerss SJ, McGee K, Huston J, 3rd, Perkins WJ, Meyer FB. Awake craniotomy, electrophysiologic mapping, and tumor resection with high-field intraoperative MRI. World Neurosurg. 2010;73(5):547-51.

[22] Benzagmout M, Gatignol P, Duffau H. Resection of World Health Organization Grade II gliomas involving Broca's area: methodological and functional considerations. Neurosurgery. 2007;61(4): 741-52;discussion 52-3.

[23] Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Lopes M, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. J Neurol Neurosurg Psychiatry. 2003;74(7):901-7.

[24] Hartmann P, Ramseier A, Gudat F, Mihatsch MJ, Polasek W. Normal weight of the brain in adults in relation to age, sex, body height and weight. Pathologe. 1994;15(3): 165-70.

[25] Isago T, Nozaki M, Kikuchi Y, Honda T, Nakazawa H. Sinking skin flap syndrome: a case of improved cerebral blood flow after cranioplasty. Ann Plast Surg. 2004;53(3): 288-92.

[26] Coenen VA, Abdel-Rahman A, McMaster J, Bogod N, Honey CR. Minimizing brain shift during functional neurosurgical procedures - a simple burr hole technique that can decrease CSF loss and intracranial air. Cent Eur Neurosurg. 1055;72(4):181-5.

http://dx.doi.org/10.5772/52032

[27] Coenen VA, Abdel-Rahman A, McMaster J, Bogod N, Honey CR. Minimizing brain shift during functional neurosurgical procedures - a simple burr hole technique that can decrease CSF loss and intracranial air. Cent Eur Neurosurg. 2011;72(4):181-5.

[28] Huston OO, Watson RE, Bernstein MA, McGee KP, Stead SM, Gorman DA, et al. Intraoperative magnetic resonance imaging findings during deep brain stimulation surgery. J Neurosurg. 2012;115(4): 852-7.

[29] Vitaz TW, Inkabi KE, Carrubba CJ. Intraoperative MRI for transphenoidal procedures: short-term outcome for 100 consecutive cases. Clin Neurol Neurosurg. 2011;113(9):731-5. .

[30] De Benedictis A, Duffau H. Brain hodotopy: from esoteric concept to practical surgical applications. Neurosurgery. 2011;68(6):1709-23.

[31] Sporns O, Tononi G, Edelman GM. Theoretical neuroanatomy: relating anatomical and functional connectivity in graphs and cortical connection matrices. Cereb Cortex. 2000;10(2):127-41.

[32] Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. Brain. 2007;133(Pt 7):2007-21.

[33] Cohen MX, Axmacher N, Lenartz D, Elger CE, Sturm V, Schlaepfer TE. Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing. J Cogn Neurosci. 2009;21(5):875-89.

[34] Tsang EW, Hamani C, Moro E, Mazzella F, Saha U, Lozano AM, et al. Subthalamic deep brain stimulation at individualized frequencies for Parkinson disease. Neurology. 2012;78(24):1930-8.

[35] Liu X, Wang S, Yianni J, Nandi D, Bain PG, Gregory R, et al. The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia. Brain. 2008;131(Pt 6):1562-73.

[36] Pallanti S, Cantisani A, Grassi G, Antonini S, Cecchelli C, Burian J, et al. rTMS age-dependent response in treatment-resistant depressed subjects: a mini-review. CNS Spect. 2012;17(1):24-30.

[37] Prikryl R, Mikl M, Prikrylova Kucerova H, Ustohal L, Kasparek T, Marecek R, et al. Does repetitive transcranial magnetic stimulation have a positive effect on working memory and neuronal activation in treatment of negative symptoms of schizophrenia? Neuro Endocrinol Lett. 2012;33(1):90-7.

[38] Lefaucheur JP, Drouot X, Von Raison F, Menard-Lefaucheur I, Cesaro P, Nguyen JP. Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. Clin Neurophysiol. 2004;115(11):2530-41.

[39] Niesen AD, Jacob AK, Aho LE, Botten EJ, Nase KE, Nelson JM, et al. Perioperative seizures in patients with a history of a seizure disorder. Anesth Analg. 2010;111(3): 729-35.

[40] Stefan H, Scheler G, Hummel C, Walter J, Romstock J, Buchfelder M, et al. Magnetoencephalography (MEG) predicts focal epileptogenicity in cavernomas. J Neurol Neurosurg Psychiatry. 2004;75(9):1309-13.

[41] Szelenyi A, Joksimovic B, Seifert V. Intraoperative risk of seizures associated with transient direct cortical stimulation in patients with symptomatic epilepsy. J Clin Neurophysiol. 2007;24(1):39-43.

[42] Duffau H. Indications of awake mapping and selection of intraoperative tasks. In: Duffau H. (ed.) Brain Mapping: from neural basis of cognition to surgical applications. 1st ed: Springer-Verlag; 2011.p321-334.

[43] Crone NE, Sinai A, Korzeniewska A. High-frequency gamma oscillations and human brain mapping with electrocorticography. Prog Brain Res. 2006;159:275-95.

[44] Jerbi K, Ossandon T, Hamame CM, Senova S, Dalal SS, Jung J, et al. Task-related gamma-band dynamics from an intracerebral perspective: review and implications for surface EEG and MEG. Hum Brain Mapp. 2009;30(6):1758-71.

[45] Behdad A, Limbrick DD, Jr., Bertrand ME, Smyth MD. Epilepsy surgery in children with seizures arising from the rolandic cortex. Epilepsia. 2009;50(6):1450-61.

[46] Maehara T. Intraoperative Monitoring of epileptic foci: usefulness of multimodality image-guided epilepsy surgery performed in combination with electrocorticography. Brain Nerve. 2011;63(4):321-9.

[47] Crone NE, Hao L, Hart J, Jr., Boatman D, Lesser RP, Irizarry R, et al. Electrocorticographic gamma activity during word production in spoken and sign language. Neurology. 2001;57(11):2045-53.

[48] Korvenoja A, Kirveskari E, Aronen HJ, Avikainen S, Brander A, Huttunen J, et al. Sensorimotor cortex localization: comparison of magnetoencephalography, functional MR imaging, and intraoperative cortical mapping. Radiology. 2006;241(1):213-22.

[49] Sporns O, Tononi G, Edelman GM. Theoretical neuroanatomy and the connectivity of the cerebral cortex. Behav Brain Res. 2002;135(1-2):69-74.

[50] Duffau H. Contribution of cortical and subcortical electrostimulation in brain glioma surgery: methodological and functional considerations. Neurophysiol Clin. 2007;37(6):373-82.

[51] Krammer MJ, Wolf S, Schul DB, Gerstner W, Lumenta CB. Significance of intraoperative motor function monitoring using transcranial electrical motor evoked potentials (MEP) in patients with spinal and cranial lesions near the motor pathways. Br J Neurosurg. 2009;23(1):48-55.

[52] Markand ON. Brainstem auditory evoked potentials. J Clin Neurophysiol. 1994;11(3): 319-42.

[53] Legatt AD. Mechanisms of intraoperative brainstem auditory evoked potential changes. J Clin Neurophysiol. 2002;19(5):396-408.

[54] Lorenzano C, Gilio F, Inghilleri M, Conte A, Fofi L, Manfredi M, et al. Spread of electrical activity at cortical level after repetitive magnetic stimulation in normal subjects. Exp Brain Res. 2002;147(2):186-92.

[55] Levy WJ, York DH, McCaffrey M, Tanzer F. Motor evoked potentials from transcranial stimulation of the motor cortex in humans. Neurosurgery. 1984;15(3):287-302.

[56] Woodforth IJ, Hicks RG, Crawford MR, Stephen JP, Burke DJ. Variability of motor-evoked potentials recorded during nitrous oxide anesthesia from the tibialis anterior muscle after transcranial electrical stimulation. Anesth Analg. 1996;82(4):744-9.

[57] Mallik A, Weir AI. Nerve conduction studies: essentials and pitfalls in practice. J Neurol Neurosurg Psychiatry. 2005;76(Suppl 2):ii23-31.

[58] Nollet H, Van Ham L, Deprez P, Vanderstraeten G. Transcranial magnetic stimulation: review of the technique, basic principles and applications. Vet J. 2003;166(1): 28-42.

[59] Reithler J, Peters JC, Sack AT. Multimodal transcranial magnetic stimulation: using concurrent neuroimaging to reveal the neural network dynamics of noninvasive brain stimulation. Prog Neurobiol. 2011;94(2):149-65.

[60] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol. 2003;2(3):145-56.

[61] Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997;48(5):1398-403.

[62] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res. 2000;133(4):425-30.

[63] Nezu A, Kimura S, Uehara S, Kobayashi T, Tanaka M, Saito K. Magnetic stimulation of motor cortex in children: maturity of corticospinal pathway and problem of clinical application. Brain Dev. 1997;19(3):176-80.

[64] Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electric stimulation. Brain. 1937;60:389-443.

[65] Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys. 1993;26(2):239-44.

[66] Zamzuri I, Rahman GI, Muzaimi M, Jafri AM, Nik Ruzman NI, Lutfi YA, et al. Polymodal therapy for high grade gliomas: a case report of favourable outcomes following intraoperative radiation therapy. Med J Malaysia. 2012;67(1):121-2.

[67] Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. Neurology. 1980;30(9):907-11.

[68] Battaglia D, Witt A, Wolf F, Geisel T. Dynamic effective connectivity of inter-areal brain circuits. PLoS Comput Biol. 2012;8(3):e1002438.

[69] Bullmore E, Sporns O. The economy of brain network organization. Nat Rev Neurosci. 1038;13(5):336-49.

[70] Sporns O, Tononi G, Edelman GM. Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. Neural Netw. 2000;13(8-9):909-22.

[71] Momjian S, Seghier M, Seeck M, Michel CM. Mapping of the neuronal networks of human cortical brain functions. Adv Tech Stand Neurosurg. 2003;28:91-142.

[72] Ahmadlou M, Adeli H, Adeli A. Graph theoretical analysis of organization of functional brain networks in ADHD. Clin EEG Neurosci. 2012;43(1):5-13.

[73] Birbaumer N, Cohen LG. Brain-computer interfaces: communication and restoration of movement in paralysis. J Physiol. 2007;579(Pt 3):621-36.

[74] Prasad G, Herman P, Coyle D, McDonough S, Crosbie J. Applying a brain-computer interface to support motor imagery practice in people with stroke for upper limb recovery: a feasibility study. J Neuroeng Rehabil. 2010;7:60.