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Estimation of optimal time window for cortical mapping in awake craniotomy, based on intraoperative reaction time

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Summary in English

Awake craniotomy is one of the safest, language-concerning neurosurgical techniques, which has the goal of minimizing the risk of postoperative functional speech impairment during surgery through continuous neurological evaluation (Serletis and Bernstein 2007), (Itoi, Hiromitsu et al. 2015). However, not every patient becomes fully awake at the same time or to same extent after extubation. This makes neurological testing difficult and compromises the safety of the operation. In previous studies, some risk factors for a major disturbances in waking up such as seizures (Nossek, Matot et al. 2013), temporal lobe damage in prior medical history (Shinoura, Yamada et al. 2011), pre-operative anxiety of the patient (Ford, Boulis et al. 2007) and performance in design and computational skills (Itoi, Hiromitsu et al. 2015) were identified.

Our study aims to quantify the wakefulness of the patient by measuring the intraoperative reaction time and to determine the optimal time window for cortical mapping.

The study was built as a prospective single-center analysis, with a cohort of 35 patients. Our team programmed the Application for measuring and documenting the intraoperative reaction times. We used the *Sleep-Awake-Awake* Anaesthesia protocol. The patients were operated under microsurgical technique with 5-ALA (Stummer, Stocker et al. 1998) and intraoperative neurophysiological monitoring with bi- and monopolar cortical stimulation (Beez, Boge et al. 2013), (Kamp, Rapp et al. 2015). The Statystical analysis was performed with SPSS v24.0. Values of *p* less than .05 in T-test and ANOVA were considered significant.

At the time of publication of this analysis, there was no previously published data on an attempt to determine the window of time for optimal intraoperative wakefulness. Although the trends in our data suggest that, after enrolling additional patients in a similar study, the optimal time window for cortical mapping might be proven to be broader in the future, our current data analysis concludes the following: firstly, the preoperative reaction times of our patient cohort were significantly shorter than the intraoperative. Secondly, there is a strong correlation between the preoperative reaction times and age. Thirdly, the patients seem to demonstrate the optimal reaction times after the 20th minute after extubation.

Summary in German

Die Wachkraniotomie ist eine der sichersten sprachbezogenen neurochirurgischen Techniken, Ziel dieser Tecnik ist das Risiko postoperativer funktionaler Sprachstörungen während der Operation durch kontinuierliche neurologische Evaluation zu minimieren (Serletis und Bernstein 2007), (Itoi, Hiromitsu et al. 2015). Allerdings wird nicht jeder Patient nach der Extubation gleichzeitig oder in gleichem Maße wach. Dies erschwert die neurologische Tests und beeinträchtigt die Sicherheit der Operation. In früheren Studien wurden einige Risikofaktoren für schwere Aufwachstörungen wie Krampfanfälle (Nossek, Matot et al. 2013), Temporallappenschäden in der Vorgeschichte (Shinoura, Yamada et al. 2011), präoperative Angststörungen des Patienten (Ford, Boulis et al. 2007) und Leistung in Design und Kalkulation (Itoi, Hiromitsu et al. 2015) identifiziert.

Ziel unserer Studie ist es, die Wachheit des Patienten durch die Messung der intraoperativen Reaktionszeiten zu quantifizieren und das optimale Zeitfenster für das cortical mapping zu bestimmen.

Die Studie wurde als prospektive single-center Analyse mit einer Kohorte von 35 Patienten erstellt. Die Applikation zur Messung und Dokumentation der intraoperativen Reaktionszeiten wurde von unserem Team programmiert. Anästhesie-Protokoll *Sleep-Awake-Awake* wurde verwendet. Die Patienten wurden unter mikrochirurgischer Technik mit 5-ALA (Stummer et al., 1998) und intraoperativem neurophysiologischen Monitoring mit bi- und monopolarer kortikaler Stimulation operiert (Beez, Boge et al. 2013), (Kamp, Rapp et al. 2015). Die statistische Analyse wurde mit SPSS v24.0 durchgeführt. P-Werte von weniger als .05 in T-test und ANOVA wurden als signifikant angesehen.

Zum Zeitpunkt der Veröffentlichung dieser Analyse gab es keine zuvor veröffentlichten Daten über einen Versuch, den Zeitfenster für optimalen intraoperativen Wachheit zu bestimmen. Obwohl die Trends unserer Daten darauf hindeuten, dass sich nach Aufnahme zusätzlicher Patienten in einer ähnlichen Studie, das optimale Zeitfenster für die kortikale Kartierung in der Zukunft als breiter erwiesen werden könnte, kommt unsere aktuelle Datenanalyse zu dem Schlussfolgerungen, dass erstens, die präoperativen Reaktionszeiten unserer Patientenkohorte signifikant kürzer waren als die intraoperativen; zweitens, besteht eine starke Korrelation zwischen den präoperativen Reaktionszeiten und dem Alter; und drittens scheinen die Patienten die optimalen Reaktionszeiten nach der 20. Minute nach der Extubation zu haben.

Abbreviations

1. **5-ALA** – 5-aminolevilinic acid
2. **ACC** – Anterior cingulate cortex
3. **CSF** – Cerebrospinal fluid
4. **DBS** – Deep brain stimulation
5. **EMG** - Electromyography
6. **i.v.** – *intra venam*
7. **iCT** – intraoperative computed tomography
8. **iMRI** – intraoperative magnetic resonance tomography
9. **L/min** – Liters per minute
10. **LMA** – Laryngeal mask airway
11. **MEP** – Motor evoked potentials
12. **mg** – milligrams
13. **mg/kgBW/min** – milligrams per kilogram body weight per minute
14. **mL** – milliliters
15. **mmHg** – millimeter of mercury
16. **NSAID** – non-steroidal anti-inflammatory drug
17. **UKD** – University Hospital Düsseldorf
18. **µg/kgBW/min** – micrograms per kilogram body weight per minute

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1. Introduction

Awake craniotomy is one of the safest, language-concerning neurosurgical techniques, which has the goal of minimizing the risk of postoperative functional speech impairment during surgery (Serletis and Bernstein 2007). In order to monitor the brain function during operation, patients are evaluated neurologically following the intraoperative extubation (Itoi, Hiromitsu et al. 2015).

1.1 Development and techniques of awake craniotomy

The era of modern awake craniotomies began when Penfield and Pasquet published their landmark paper “Combined regional and general anesthesia for craniotomy and cortical exploration” (Penfield, 1986). Six years later, Silbergeld and Mueller published their study using propofol sedation in awake craniotomy (Silbergeld et al., 1992). This work is the second great milestone in the evolution of awake craniotomy for propofol had the desired qualities of rapid onset, easy titrability and short recovery time, lacking in previous sedatives. The single disadvantage of propofol was its lack of analgesic qualities. Introduction of remifentanil, an ultrashort-acting opioid and regional scalp block combined with dural instillation with local anesthetics set the base for the modern standard of awake craniotomy.

There are several versions of awake craniotomy, depending on the intraoperative phases of active and ceased sedation they are widely known as *Sleep-Awake-Sleep, Sleep-Awake-Awake* and *Awake-Awake-Awake*.

1.1.1 Sleep-Awake-Sleep anesthesia technique

Schulz and colleagues describe the *sleep-awake-sleep* technique in the background of neurooncological and epileptological awake craniotomy as well as the technique-of-choice for the electrode implantation for deep brain stimulation (DBS). The anesthesiologic strategies include use of propofol for rapid induction and low interference with the respiratory function of the usually spontaneously breathing patient, hemiscalp block in combination with low-dose remifentanil is chosen for analgesia in trepanation as well as local infiltration for deep brain electrode implantation. Airway control may be achieved by ordinary transnasal placement of Magill tube with its tip underneath the epiglottis. Since there is no effective cuff seal to secure against aspiration, adequate antiemetic prophylaxis is of utmost importance. (Schulz et al., 2006)

1.1.2 Sleep-Awake-Awake anesthesia technique

The standard technique for awake craniotomy in our institution is the *sleep–awake–awake* technique. Most patients receive no premedication or sedative on the day of surgery and no long-acting benzodiazepines on the day before surgery in order not to interfere with wakefulness of the patient during the awake phase of the craniotomy. Dexamethasone is given as a standard neurosurgical preoperative protocol drug, due to its pronounced antiemetic qualities, no additional antiemetics are usually required during the operation. In all patients a scalp block including the supraorbital, temporal, and occipital nerve blocks on both sides was performed. Incision site and Mayfield pin insertion points are additionally infiltrated with 0.5% Bupivacaine and vasoconstrictor Adrenaline solution (Nossek, Matot et al. 2013). All patients by default are provided with two peripheral venous lines, intraarterial line for invasive blood pressure monitoring and urinary catheter. Central venous line and use of Mannitol are not the part of the routine and are used only in obligatory cases.

For the duration of the sleep phase, a Laryngeal Mask Airway (LMA) is inserted for volume-controlled ventilation until the dural incision (Serletis and Bernstein 2007). Ventilation is routinely monitored by capnography, targeted end tidal CO2 is between 35-40 mmHg. Sedation during the sleep phase is ensured with continuous administration of remifentanil (0.25-0.55 µg/kgBW/min) and propofol (4–8 mg/kgBW/min). After the dural incision, the patients are wakened-up and LMA is removed. We usually discontinue Propofol 10-20 minutes before the awakening and maintain adjunct analgesia by 1 g short infusion of Methamizole prior to awakening of the patient. We maintain light sedation, if required by short-term administration of Remifentanil (0.02 -0.08µg/kgBW/min). All patients during the awake phase of the operation receive 6 L/min oxygen through a nasal cannula. In general during the awake phase, patients do not receive any propofol and only minimal doses of remifentanil, if necessary (Sarang and Dinsmore 2003). Patients suffering pain from dural manipulation receive additional topical administration of 5 mL 0.5% bupivacaine on top of the dural leaves.

Mild sedation with propofol and remifentanil as well as additional peripheral analgesia is started direct after the confirmed resection and continued until the wound closure, depending on required depth of anesthesia.

After the operation, patients are given NSAID, usually up to 40 mg parecoxib i.v., for postoperative analgesia before returning to the recovery room.

1.1.3 Awake-Awake-Awake anesthesia technique

When conscious sedation is used without general anesthesia, sedation is administered during the initial painful parts of the procedure, then either stopped or minimized during cortical mapping, and resumed for resection and closure. Conscious sedation is the goal depth of anesthesia, the patient should respond purposefully to verbal or tactile stimulation, the airway ought to be maintained without any intervention, ventilation should be spontaneous and adequate, and hemodynamics stable without support. Excessive sedation should be avoided, as it increases the risk of airway obstruction, aspiration, and respiratory depression including apnea. If necessary, a nasopharyngeal tube is usually well tolerated by patients who undergo moderate sedation. In the retrospective study by Danks and colleagues, neurooncological surgery with conscious sedation was considered a safe technique that allows maximal resection of lesions in close anatomical relationship to eloquent cortex with a low risk of new neurological deficit. (Danks et al., 2000).

However, if primarily intubated, not every patient becomes fully awake at the same time after extubation. More so, even the patients undergoing an *Awake-Awake-Awake* anesthesia may be suboptimal awake. Some patients remain drowsy and slow during the entire waking phase. This makes neurological testing difficult and compromises the safety of the operation. It is therefore desirable to be able to predict whether and when patients are fully awake and neurologically observable during an awake craniotomy.

1.2 Risk factors in awake craniotomy

In previous history no attempts have been made to quantify the wakefulness of the neurosurgical patient prior to or during the awake craniotomy, however the phenomenon of suboptimal wakefulness is well documented in scientific literature. Moreover, certain risk factors for intraoperative drowsiness or incompliance were determined. These factors are associated with major delays of the wake-up phase and, therefore, may be regarded as a relative exclusion criterion in the indication setting for the awake craniotomy. The most prominent risk factors include preoperative seizures or treatment with multiple antiepileptic drugs, involvement of the dorsal part of the anterior cingulate cortex, pre-operative history of anxiety and poor preoperative performance in design and computational skills.

1.2.1 Treatment with multiple antiepileptic drugs

In the study by Nossek and Matot, 424 Patients undergoing awake craniotomies were retrospectively assessed. Twenty-seven out of these craniotomies were considered failures. The two main causes of failure were lack of intraoperative communication and intraoperative seizures. The preoperatively assessable risk factors for lack of intraoperative communication were mixed preoperative dysphasia and treatment with phenytoin, and history of seizures as well as treatment with multiple antiepileptic drugs for intraoperative seizures (Nossek, Matot et al. 2013).

1.2.2 Involvement of the dorsal part of the anterior cingulate cortex

In this two-case study the authors were looking specifically at the significance of the dorsal ACC in the panic disorder. The first patient underwent an awake craniotomy, which had to be aborted because of recurrent panic attacks after each attempt to manipulate or stimulate the tumor on the border of the dorsal ACC. The second patient developed panic disorder six months after prior surgery and the following Cyberknife therapy. Radiological examination revealed that the dorsal ACC size was reduced at six months and absent at two years after surgery, possibly due to radiotherapy-induced damage. Profile of mood states testing, performed for more elaborate analysis of patient mental state, characterized the presence of tension-anxiety as the common abnormal symptom in both cases. Therefore, it was concluded that damage to the right dorsal ACC can supposedly induce panic disorder and that this structure likely plays a pathophysiologic role in development of panic-associated disorders (Shinoura et al. 2011).

1.2.3 Preoperative history of anxiety

Although the single-case report by Ford and Boulis concerns a case of DBS and not a classical awake craniotomy, the incompliance of the patient would have led to an abortion in any case of awake surgery. The patient, who had a known history of mild anxiety, underwent an awake craniotomy procedure for the implantation of bilateral deep brain stimulation electrodes. During the operation, the patient abruptly and persistently requested the discontinuation of a surgery. Subsequently, the surgical team performed the steps necessary to abort the surgery and electrode implantation did not succeed. Conclusively it is stated that a close neuropsychological patient examination could be helpful in selection of appropriate surgery candidates (Ford et al., 2007).

1.2.4 Preoperative performance in design and computational skills

The study of Itoi and colleagues is also concerned with risk factors to inappropriate intraoperative patient wakefulness. The predictive value of a patient's preoperative neuropsychological background in terms of sleepiness during an awake craniotomy was prospectively evaluated in thirty-seven brain tumor patients. Patient cognitive status was evaluated prior to surgery. During the course of the surgery, performance and attitude toward cognitive tasks of each patient were recorded by neuropsychologist. Apparently, the patients' construction and calculation abilities moderately correlated with their wakefulness (Itoi, Hiromitsu et al. 2015).

1.3 Supplementary techniques for enhancement of radicality and safety

Evidence mounts that the extent of tumor removal in intraaxial tumor surgery is related to patient survival time. Therefore, resecting the largest possible tumor volume without leading to permanent neurological damage is the main goal for the neurosurgeon. Electrical stimulation of the brain to detect cortical and axonal areas involved in motor, sensory, speech, and cognitive function located within or along the boundaries of the tumor is one of the main means in order to ensure the safety of the surgery. In year 2007 it was compellingly described in the review by Szelenyi and colleagues (Szelenyi et al., 2007).

The radicality of awake craniotomy was substantially increased after development of intraoperative tumor and site visualization techniques such as 5-aminolevulinic acid (5-ALA), intraoperative MRI (iMRI), intraoperative ultrasound (iUS) and navigation. In the following chapters, the most prominent aspects of assisting techniques in awake craniotomy will be described.

1.3.1 Intraoperative monitoring

In order to understand intraoperative monitoring one should acquaint himself with the different aspects of the system, such as stimulation devices, parameters, probes, mapping procedure and its side effects.

There are two groups of stimulation devices. Constant-current and constant-voltage stimulators. In general, the constant current stimulators are considered safer for cortical mapping because of their quality to elicit the same amount of current independent of the impedance of the tissue. Contrary to the latter, the constant-voltage devices will elicit a dramatically larger amount of current due to decreased impedance of the tissue. This might compromise the safety of the procedure during the Tumor resection in an awake craniotomy, where cortical and subcortical brain tissues are stimulated alternately. A surge in current elicited on the brain tissue might damage the parenchyma.

Stimulation parameters based on short pulse trains with frequencies between 25 and 60 Hz are usually applied. Historically common frequency in Europe is 50Hz and in North America - 60 Hz. The upper limit of stimulation current is 20mA (Agnew and McCreery, 1987).

One could distinguish between two main probe types: bipolar and monopolar. Bipolar stimulator with two tips with interelectrode distance of 6 to 10 mm is routinely used worldwide. Bipolar electrodes with distance between tips larger than 10mm seem to be inducing electrical activity of large pyramidal tract cells (Hern et al., 1962). Bipolar electrodes elicit current that has the greatest local stimulation effect, whereas monopolar electrodes have more spacious stimulation effects due to lower current density surrounding the reference electrode.

In order to map the motor function in primary motor cortex, one to two millisecond duration impulse usually induces either muscle/limb movement or EMG response. One should be observing clonic movements of the limb in that case. This stimulus usually does not suffice for the stimulation of secondary motor area and 2-4 ms duration impulse should be applied. In general, by stimulation of secondary motor area, tonic movements of the limb are observed (Yingling et al., 1999). Not only muscle activation, but also muscle inhibition should be observed during mapping. The absence of movement is usually related to inhibition of movement by electrical stimulation. Associative motor areas are usually detectable via aforementioned inhibition phenomenon (Luders et al., 1995). The located relevant areas should be marked using sterile tags, this facilitates the visualization of overall cortical function including sensory, motor and language *in situ* (Duffau et al., 1999).

Although there are no reported long-term side effects of cortical stimulation, Seizures are the most common short-term side effects (Gordon et al., 1990). These can potentially be harmful. However, there is no documented case of serious injury that was caused by intraoperative seizure. Seizures can be terminated with direct topical application of iced Ringer lactate on cortex (Sartorius and Berger, 1998). Switching from 50-60Hz stimulation to the train-of-five technique can preventively reduce the risk of intraoperative seizure (Szelenyi et al., 2007). This should be considered especially in cases where lesion involves primary motor- and sensor area, as well as premotor area. Patients with aforementioned tumor localization are significantly more prone to intraoperative seizures.

1.3.2 The 5-aminolevulinic acid

5-aminolevulinic acid (5-ALA), is a precursor naturally occurring in the blood heme biosynthesis pathway. Initialy it was described as a photosensitizing agent for the photodynamic therapy of skin, bladder and gastrointestinal tumors (Fritsch et al., 1997), (Grant et al., 1993), (Kennedy and Pottier, 1992), (Kriegmair et al., 1996), (Loh et al., 1993a), (Loh et al., 1993b), (Regula et al., 1995). Malignant tissue has a putative capacity to preferentially accumulate fluorescent and photosensitizing endogenous porphyrins, if excessively administrated.

First described by Stummer et al. in 1998, this phenomenon was used to distinguish human malignant gliomas from normal brain parenchyma. In contrast to previously described intravenous contrast substances, the perorally administrated 5-ALA causes fluorescence only within malignant cells, without contaminating the tumor resection cavity with blood-borne marker. The initial study was performed with 10 Patients under diagnosis of malignant glioma. It showed prominent tumor fluorescence and became one of the landmark papers in neurooncology (Stummer et al., 1998).

1.3.3 Intraoperative MRI

Intraoperative MRI (iMRI) was first introduced to clinical practice in 1990 (Black et al., 1997). Since then low (<=0.5 T) and high (1.5 – 3.0T) field iMRI are being investigated for efficacy in glioma resection (Kubben et al., 2011), (Coburger et al., 2017, Coburger et al., 2014). Senft and colleagues in 2011 proved the implementation of high field iMRI to be superior to conventional microsurgery alone. In the randomized controlled trial gross total resection was 96% in iMRI group, whereas only 68% in the group of conventional microsurgery (Senft et al., 2011). Intraoperative MRI provides relevant real-time momentarily imaging showing the actual status of tumor resection, moreover combined with a neuronavigation system which increases accuracy during resection, makes the brain shift after initial resection even a less burdensome problem (Hatiboglu et al., 2009), (Hall et al., 2006). Nimsky et al. in 2006 was the first one to demonstrate the advantage of combination of iMRI and intraoperative navigation (Nimsky et al., 2006a).

1.3.4 Intraoperative navigation

A predecessor of intraoperative navigation is the implementation of stereotaxis in neurosurgery. The first official use of stereotactic method was published in 1908 by British scientists: neurosurgeon Victor Horsley and physiologist Robert Clarke. The Horsley-Clarke device was used only in animal models and was based on Cartesian system of three orthogonal axes (Rahman et al., 2009). Martin Kirschner was the first author to publish the use of stereotactic device in humans. The article about stereotaxis-based ablation of trigeminal neuralgia was published in 1933 (Appleby and Simpson, 1967). In modern stereotactic surgery, polar coordinates are used instead of Cartesian system, these were introduced by Lars Leksell (Leksell, 1983). Since then stereotaxy, radiosurgery, gamma knife and linear accelerator treatment are based on Cartesian coordination system.

The concept of frameless stereotaxy for neurosurgery was introduced in 1990 by David Roberts. Frameless stereotaxy has the advantage of capability to track the implant or a surgical instrument in real-time, based upon preoperative imaging such as CT or MRI. Moreover, with implementation of functional MRI, tractography and multimodal image fusion, intraoperative visualization of eloquent motor, sensory and language areas, as well as subcortical pathways are possible. This has enabled the advent of functional neuronavigation, which has been shown to improve surgical outcomes in complex cases (Nimsky et al., 2006b). The main limitation of current intraoperative neuronavigation systems is that these systems rely on mere preoperative images for accurate navigation during the operation. Brain is a rather semi-rigid mass and is quite susceptible to volume shifting, especially if ventricular cavities are opened and CSF leakage takes place. This phenomenon is called brainshift. Brainshift also inevitably occurs after drainage of an intracranial cyst or resection of tumor mass, which preoperatively compressed the functional parenchyma. Even mere craniotomy and dural incision may cause a mild brainshift due to CSF leakage and cessation of pressure differences between intra- and extracranial compartments. Although due to the aforementioned phenomena the exact localization of the targets is less accurate, intraoperative navigation remains invaluable for intraoperative orientation. The problem of brainshift is addressed by intraoperative imaging such as iCT/iMRI or intraoperative ultrasound.

1.3.5 Intraoperative ultrasound

In early 1970s, B-mode Ultrasound was added to surgical armamentarium (Christian et al., 2014). In surgical era preceding the magnetic resonance, 2D B-mode grayscale intraoperative ultrasound was routinely used in neurosurgery (Rubin et al., 1980). After introduction of magnetic resonance, it was rapidly adopted into clinical diagnostic routine and, by offering a superior image quality, superseded the intraoperative ultrasound in routine operation planning. Soon afterwards, the brainshift phenomenon was encountered and the evident need for real-time imaging brought the re-emergence of intraoperative ultrasound (Nabavi et al., 2001). In tumor surgery, intraoperative ultrasound has the preeminent role in control of extent of resection in various tumors, including high- and low grade gliomas, meningiomas, pediatric mass lesions and posterior fossa tumors (Solheim et al., 2010), (Rubin and Dohrmann, 1985).

1.4 Vote of Ethics

Our single-center analysis was approved by the local Research Ethics Committee and institutional review board (internal study number: 6076R). Patients over 18-years-old undergoing resection of primary brain tumor or intraaxial metastasis under awake craniotomy in year 2017-2018 were prospectively included. The study was conducted in compliance with the Helsinki declaration and under conditions of good scientific and clinical practice.

1.5 Aim and Objectives

The main aim of our study is to determine the optimal time window for cortical mapping in awake craniotomy. Therefore, our objectives are firstly, to prospectively assess the reaction times of our patient cohort undergoing awake craniotomy, and secondly, to determine the time window during the awake phase of the craniotomy, where the patient reaction times are the shortest.

2. <u>Research Article:</u>

Determination of Optimal Time Window for Cortical Mapping in Awake Craniotomy: Assessment of Intraoperative Reaction Speed.

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ORIGINAL ARTICLE

Determination of optimal time window for cortical mapping in awake craniotomy: assessment of intraoperative reaction speed

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Abstract

Currently, there is no known time frame when the patients are the most responsive during awake craniotomy. The aim of this work is therefore to determine when the patient has the shortest reaction time and so to extrapolate the optimal time window for cortical mapping. In this analytic observational study, our group has recorded the reaction times of 35 patients undergoing an awake craniotomy and compared them with the preoperative baseline. The operations were performed according to a "sleep–awake–awake" protocol. Data collection was performed in parallel with standard methods for evaluation of language and cognitive functions. The preoperative reaction times of our patient cohort (average ± SD = 510 ± 124 ms) were significantly shorter than those measured during the operation 786 ± 280 ms, $p < .001$. A one-factor ANOVA within subjects showed a significant increase in reaction times; $p < .001$. Post hoc comparisons on a Bonferroni-corrected α-error level of .05 showed significant differences between the reaction speed during the 0–10 min time frame and the preoperative baseline, as well as the intraoperative reaction times during the 20–30 min, 30–40 min, and the $t > 40$ min time frames. In conclusion, measurement of intraoperative reaction speed seems to be a technically feasible method that is well tolerated by the patients. The intraoperative reaction speed performance was shown to be significantly slower than on the day before the operation. The patients seem to be the slowest directly after extubation and gradually wake up during the awake phase. The poorest wakefulness is demonstrated during the first 20 min after extubation.

Keywords Awake craniotomy · Cortical mapping · Reaction time · Wakefulness · GBM · Cerebral metastasis

Introduction

Awake craniotomy is a safe neurosurgical technique, which has the goal of minimizing the risk of postoperative language-related and general neurological deficits [6, 7]. After the intraoperative extubation follows a continuous multimodal neurological examination in order to monitor the brain function during this operation [8, 11].

However, not every patient becomes fully awake at the same time after extubation. Some patients remain drowsy and slow during the entire waking phase. This makes neurological testing difficult and compromises the safety of the operation. It is therefore desirable to be able to predict whether and when patients are fully awake and neurologically testable during an awake craniotomy.

In previous studies, factors correlating with the state of awareness such as seizures [14], temporal lobe damage in prior medical history [19], and pre-operative anxiety of the patient [5] were identified. These factors are associated with major delays of the wake-up phase and can therefore be regarded as relative exclusion criteria in the indication setting for the awake craniotomy. Preoperative performance in design and computational skills correlates with drowsiness during awake operation only moderately [8].

Interdependence of reaction time and wakefulness was previously demonstrated by Corsi-Cabrera and colleagues in 1996. The results indicated that total sleep deprivation with high significance ($p < .009$ for all comparisons) induced an increase in reaction time duration and absolute power in

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EEG. Moreover, all the affected variables, including reaction time, returned to baseline values after recovery sleep [3]. Data of this study strongly indicates that reaction speed has a positive correlation with wakefulness of the patient.

Currently, there are no means to quantify the degree of alertness during an awake craniotomy. Therefore, the aim of this study is to assess the feasibility of intraoperative reaction speed measurement and to determine the optimal time window for cortical mapping after the awakening of the patient.

Materials and methods

Patient cohort

The study was built as a single-center analytical observational study. All patients scheduled for awake craniotomy in our department from February 2018 to October 2018 were considered for the study. The intraoperative reaction speed was tested in all scheduled patients if the individuals were 18 years of age or older. Patients with a sufficient amount of data about intraoperative reaction times were included in the study.

Testing of reaction speed, and neurological and cognitive functions

The data collection was carried out in three phases, namely pre-, intra-, and postoperative. The preoperative measurement of the reaction speed was performed on the day before the operation as a part of the routine preparation for the procedure. Within the framework of this routine preparation, an assessment of possible neurological deficits and learning the tasks for the monitoring of motor, language, and cognitive functions are performed.

During the operation, when the scalp incision, craniotomy, and opening of the dura under general anesthesia are completed, the awake phase begins. Sedatives and hypnotics are paused and when sufficient respiratory drive is reached, extubation follows. The moment of extubation is considered to be the reference time ($t = 0$) of the waking phase. The initial reaction speed is registered with the application as soon as possible after extubation and then every 10 min onwards, during the waking phase. This collection of reaction time data is combined with our standard continuous testing of speech, motor, sensory, and cognitive functions (Table 1).

User interface of the application

As soon as the program is activated, the entire screen turns blue (Fig. 1a) and stays that way for a random amount of time (1.5–3 s); the screen changes its color to green and a commando reading "click" appears (Fig. 1b). Now, the proband has to touch the screen as fast as possible. The time between the change of the colors on the screen and the tap on its surface is measured. As soon as the screen is touched, it switches back the blue color and the whole procedure restarts. The sequence is repeated three times during each measurement.

In addition, the following events and their exact time are displayed on the "Operation Timeline": the cessation of anesthetic delivery, eye opening, extubation, epileptic seizures, and any extraordinary events during the awake phase (Fig. 1c).

A possible effect-modifying factor which could distort the measurement of reaction speed was the distance between the tablet screen and the finger of the patient. We addressed the issue by placing the device always in the same place at about 30-cm distance from the eyes and controlling that the finger of the patient was not farther away from the screen than 5 cm during the testing. A second theoretically possible effect-modifying factor is a paresis of the hand due to ischemia, seizure, or damage to eloquent tissue; this would substantially prolong the registered reaction time due to compromised conduction of movement although reaction speed itself might have been not impaired. The issue should be addressed by documentation of such an adverse event and continuation of testing with the contralateral hand, if possible, or else discontinuation of the testing of reaction speed.

Anesthesia protocol

A *sleep–awake–awake* was our standard technique. Most patients received no premedication or sedative on the day of surgery and no long-acting benzodiazepines (flurazepam, diazepam) on the day before surgery. Dexamethasone was given as a standard neurosurgical preoperative protocol drug, which also is known for its pronounced antiemetic quality. No additional antiemetic drugs were given. In all patients, a scalp block including the supraorbital, temporal, and occipital nerve blocks was performed. Additionally, incision site and Mayfield pin insertion points were locally infiltrated with 0.5% bupivacaine and vasoconstrictor adrenaline (1:200,000) solution [13]. All patients by default are provided with two peripheral venous lines, intraarterial line for invasive blood pressure monitoring, and urinary catheter; a central venous line was usually not inserted. Mannitol was not routinely used.

For the duration of the sleep phase, a laryngeal mask airway (LMA) was inserted and volume controlled ventilation was performed at least until the dural incision [18]. Ventilation was monitored by capnography (end-tidal $CO_2 = 35$–40 mmHg). Sedation during the sleep phase was ensured with continuous administration of remifentanil (0.25–0.55 μg/kgBW/min) and propofol (4–8 mg/kgBW/min). After the dural incision, patients were wakened-up and LMA was removed. Propofol was usually discontinued 10–20 min before the awakening, and adjunct analgesia was

Table 1 Cognitive abilities and description of tasks

Language tests	
Pronunciation/chronological order	Counting, letters in alphabetic order
	Sorting weekdays and months chronologically
Reading out loud	Reading aloud words and sentences
Object naming	Word finding: naming objects
Token test	Comprehension of and pointing to geometric forms
Memory tests	
Learning and recall	Immediate recall: learning a list of numbers
	Delayed recall: learning a list of numbers, delayed recall
Motor, attention and executive tests	
Stroop	Mental speed, selective attention: naming colors of printed words denoting another color
Calculating	Reading calculation exercises aloud and answering correctly
Motor	Case-tailored exercises for fine and gross motor functions of the limb

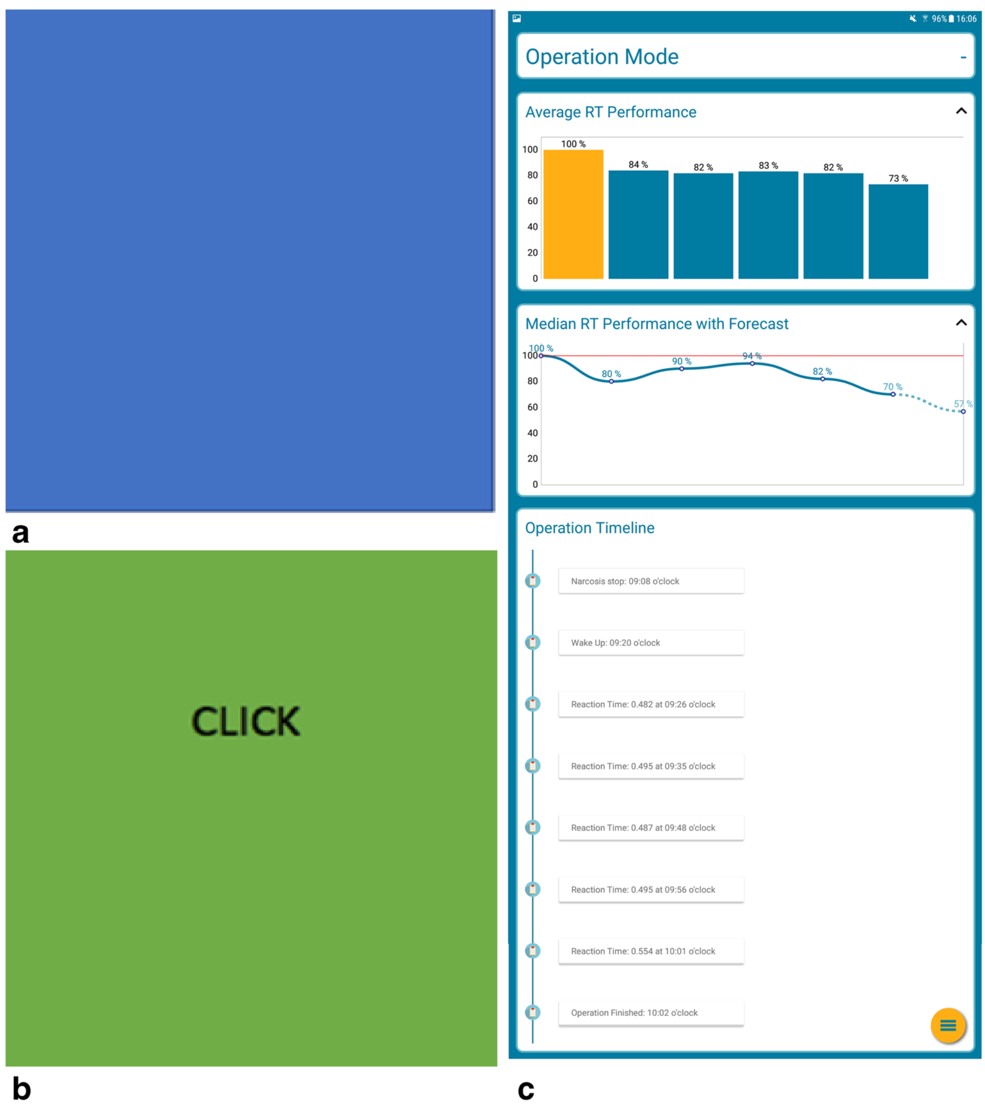

Fig. 1 Example of the user interface of the application

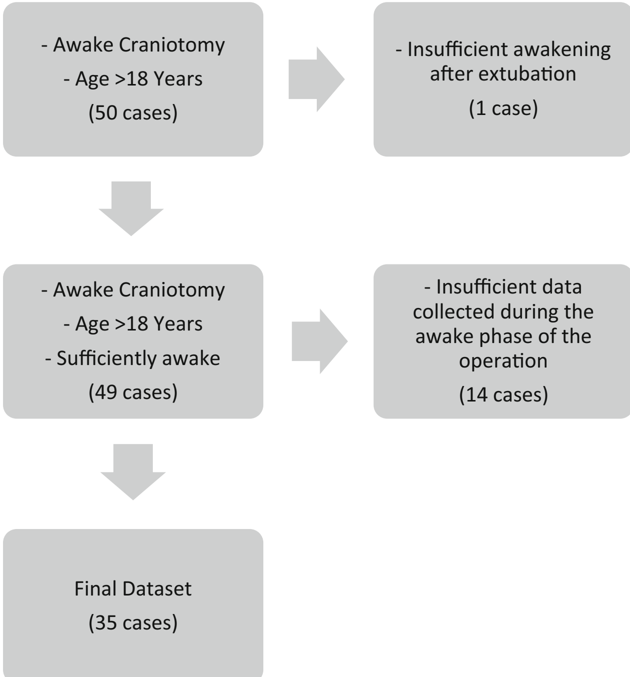

Fig. 2 Flow-diagram illustrating emission of patients through the stages of the study

maintained by short infusion of 1 g metamizole prior to awakening of the patient. Light sedation, if necessary, was maintained by short-term administration of remifentanil (0.02–0.08 μg/kgBW/min). All patients during the awake phase of the operation received 6 L/min oxygen through a nasal cannula. As a general guideline during the awake phase, patients did not receive any propofol and only minimal doses of remifentanil, if necessary [16]. Patients who suffered any pain from dural manipulation received additional topical administration of 5 mL 0.5% bupivacaine on dural leaves.

Mild sedation with propofol and remifentanil as well as additional peripheral analgesia was given after the resection was completed until wound closure, depending on the required depth of anesthesia.

After the operation, patients were given a nonsteroidal anti-inflammatory drug (NSAID), usually up to 40 mg parecoxib i.v., for postoperative analgesia before returning to the recovery room.

Surgical technique and intraoperative monitoring

Preoperative preparation was mainly performed by neurosurgeons or specialized nursing staff in a dedicated session 1 day prior to awake surgery. Twenty milligrams per kilogram body weight of 5-aminolevilinic acid (5-ALA) was administered per orally 3 h prior to surgery. As a standard protocol, operations were performed in a *sleep–awake–awake* technique. For additional safety, all surgeries were performed with intraoperative monitoring (IOM) recording motor-evoked (MEPs) and somato-sensory evoked potentials (SSEPs). Patients were positioned in supine, lateral, or park bench position according to the localization of the tumor. In all cases, local anesthesia was applied to Mayfield pin sites and a regional scalp nerve block, as described above. After opening of the dural skin, patients were awakened for the subsequent cortical mapping [1, 10].

During the surgical approach and resection, cortical and subcortical levels were electrically stimulated with 60-Hz bipolar or monopolar current in order to elicit changes in neurologic functions such as speech, motor movement, and tactile sensation or to cause a perceptible response in electrophysiological recordings [9].

5-ALA-negative tumors were resected using white light–assisted microsurgical technique alone, whereas the 5-ALA-positive tumors were resected by combination with the aforementioned and the fluorescence-assisted microsurgical techniques.

Data collection

Reaction speed was measured three times perioperatively as follows: preoperative baseline reaction speed was measured on the day before operation; intraoperative reaction speed was measured at least five times during the operation at least once during each time frame (0–10 min, 10–20 min, 20–30 min, 30–40 min, $t > 40$ min). Epidemiological data, such as age and gender, and data regarding the tumor location, volume, histology, IDH-1 or ATRX status, duration of induction of anesthesia, and complications associated with awake surgery, if available, were collected.

Statistical analysis and missing data

Descriptive and inference statistics were calculated using the IBM SPSS Version 25.0 and p values of less than .05 in T test, Pearson's correlation, and ANOVA were considered significant. In some cases, up to two intraoperative reaction time datapoints were missing; in order to increase the number of participants in sample, these data points were imputed by using the mean reaction-time value of all other subjects during the given time frame. In 10 cases, there was missing one and in 4 cases, there were missing two data points. In ANOVA, Mauchly's test for sphericity was performed. Sphericity of data could not be accepted; therefore, Greenhouse–Geisser correction was used. A Bonferroni test was used for the post hoc analysis.

Determination of minimal sample size

We have pre-calculated minimal size limit for our population using G*Force software Version 3.1.9.2. Since there is no previously published data concerning the intraoperative reaction time in awake craniotomy, we have aimed for a medium effect size $f = 0.25$ according to Cohen's convention [2], α-

Table 2 Clinical data of 35 patients included in the study

Patient No.	Age	Sex	First diagnosis vs. recurrence	Localization	Tumor size in cm^3	Induction time (min)
1	47	Female	First diagnosis	Left temporomesial	44.7	25
2	50	Male	First diagnosis	Left central	44.6	29
3	72	Female	First diagnosis	Left temporooccipital	17.8	No data
4	59	Female	First diagnosis	Left frontocallosal	64.4	19
5	68	Female	Recurrence	Left postcentral	8	24
6	29	Male	First diagnosis	Left insular	9.6	24
7	42	Male	Recurrence	Right frontal	7.2	14
8	28	Female	First diagnosis	Right postcentral medial	27.3	15
9	47	Female	First diagnosis	Left parietotemporal	25.3	25
10	60	Male	n/a (Haemorrhage without tumor)	Left central	19.4	20
11	67	Male	Recurrence	Left parietal	13.4	15
12	56	Male	First diagnosis	Left parietal	28.1	36
13	32	Male	First diagnosis	Left insular, left frontal	22.3	32
14	67	Male	Recurrence	Left frontal	13.1	20
15	33	Male	First diagnosis	Left frontoopercular	53.8	20
16	62	Female	First diagnosis	Left parietooccipital	34.3	28
17	21	Male	Recurrence	Left frontal	5.8	25
18	60	Male	First diagnosis	Left postcentral	4.8	25
19	57	Male	First diagnosis	Right parietal	27.3	20
20	50	Male	First diagnosis	Right temporoparietal	6.3	32
21	34	Male	First diagnosis	Left frontal	2.2	16
22	27	Female	Recurrence	Left frontal	17.5	21
23	42	Male	Recurrence	Left central	8.8	28
24	40	Female	Recurrence	Right insular	0.7	25
25	71	Female	First diagnosis	Left temporal	19.5	23
26	28	Female	First diagnosis	Left frontal	0.5	38
27	37	Female	First diagnosis	Left central	2.5	29
28	49	Male	First diagnosis	Left temporoparietal	30.9	12
29	65	Female	First diagnosis	Left temporal	2.2	No data
30	23	Male	First diagnosis	Left central	29.4	20
31	23	Male	Recurrence	Left central	18.5	20
32	63	Female	Recurrence	Left central	1.2	24
33	54	Female	Recurrence	Left frontocallosal	18.1	6
34	59	Female	First diagnosis	Right central	41.2	17
35	75	Female	First diagnosis	Right central	33.2	25

error probability of .05 and power (1-β) of 0.8. As determined, our study population must have at least 19 patients. Therefore, statistically significant effects found in our population of 35 patients are to be deemed plausible.

Results

Patient cohort

In this study, reaction pre-, intra-, and postoperative reaction speed of 47 patients (50 awake craniotomies) were assessed. One patient did not sufficiently wake up for safe cortical mapping, and in 12 patients (14 awake craniotomies), reaction speeds during more than two intraoperative time windows were not documented. Thirty-four patients (35 awake craniotomies) provided sufficient data for statistical analysis of intraoperative reaction time, and they were included in the final cohort of the study (Fig. 2). Our final cohort consisted of 17 females and 18 males. The median age of the patients was 48 years and ranged between 21 and 75 years.

Clinical data of our patient cohort is summarized in Table 2.

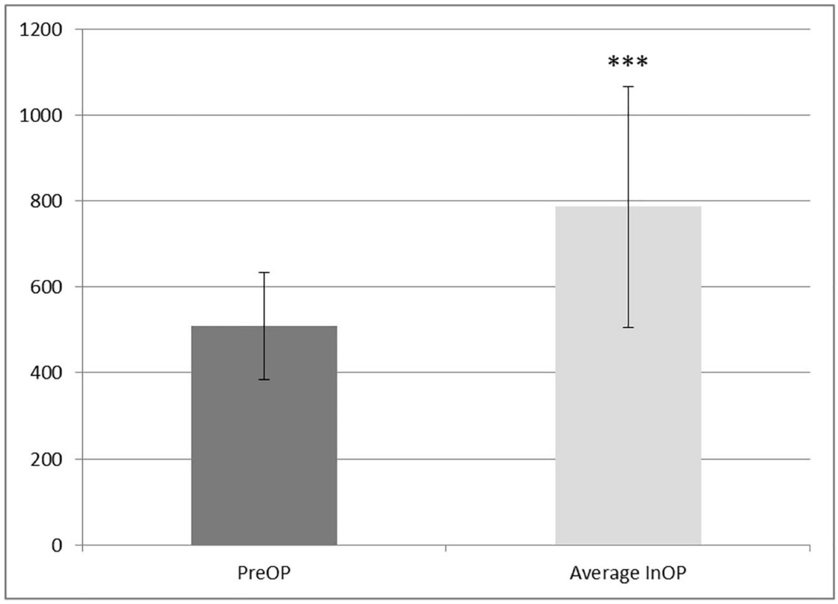

Fig. 3 Bar graph demonstrating that the preoperative reaction times were significantly shorter than the intraoperative reaction times ($p < .001$

Intraoperative reaction speed and optimal window for cortical mapping

All following values are given as average ± standard deviation. The preoperative reaction times of our patient cohort (509 ± 157 ms) were significantly shorter than those measured during the operation (787 ± 270 ms); $t(34) = -6.9$, $p < .001$, one-tailed (Fig. 3).

Descriptively, the average reaction times were as follows: preoperatively 509 ± 157 ms, 1st time frame (0–10 min) 989 ± 507 ms, 2nd time frame (10–20 min) 802 ± 360 ms, 3rd time frame (20–30 min) 698 ± 288 ms, 4th time frame (30–40 min) 672 ± 269 ms, and 5th time frame ($t > 40$ min) 743 ± 280 ms.

A one-factor ANOVA (within subjects) showed a significant increase in reaction times; F (2.5, 85.012) = 12.479, $p < .001$. Post hoc comparisons on a Bonferroni-corrected α-error level of .05 showed significant differences between the reaction time during the 1st time frame (0–10 min) and the preoperative reaction time ($D = 479$, $p < .001$, one-tailed) as well as the intraoperative reaction times during the 3rd (20–30 min) ($D = 290$, $p = .013$, one-tailed), 4th (30–40 min) ($D = 317$, $p = .012$, one-tailed), and the 5th time frame ($t > 40$ min) ($D = 246$, $p = .044$, one-tailed). However, the reaction time

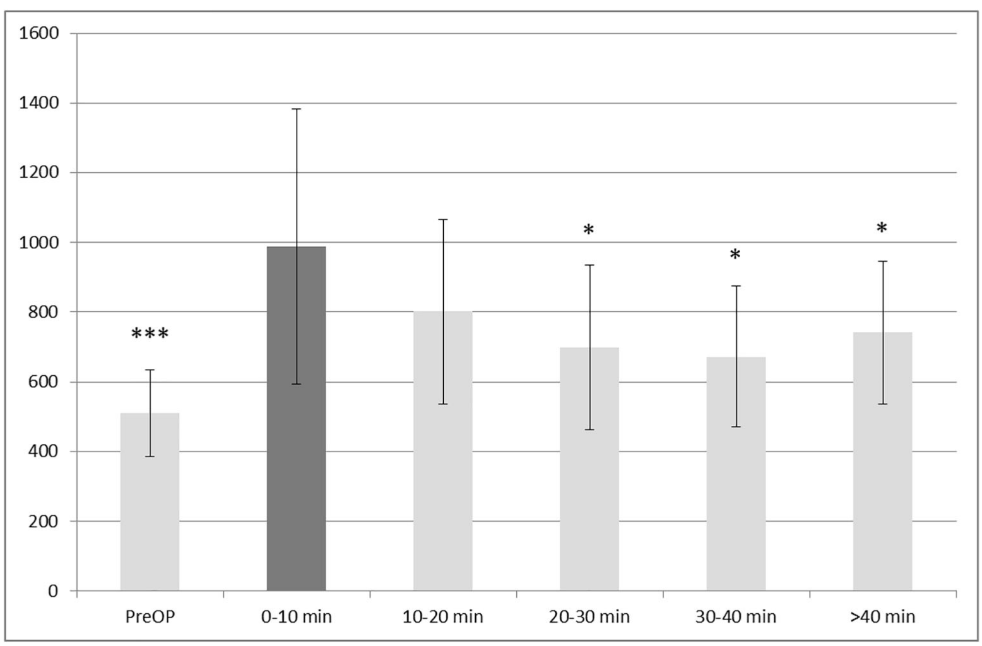

Fig. 4 A bar graph representing the reaction time over the course of the operation. According to our current data, the patients have the worst reaction speed during the first 10 min after extubation. The difference between the first and the second intraoperative time frame is not significant; therefore, the optimal reaction speed during awake craniotomy seems to start after the 20th minute after extubation

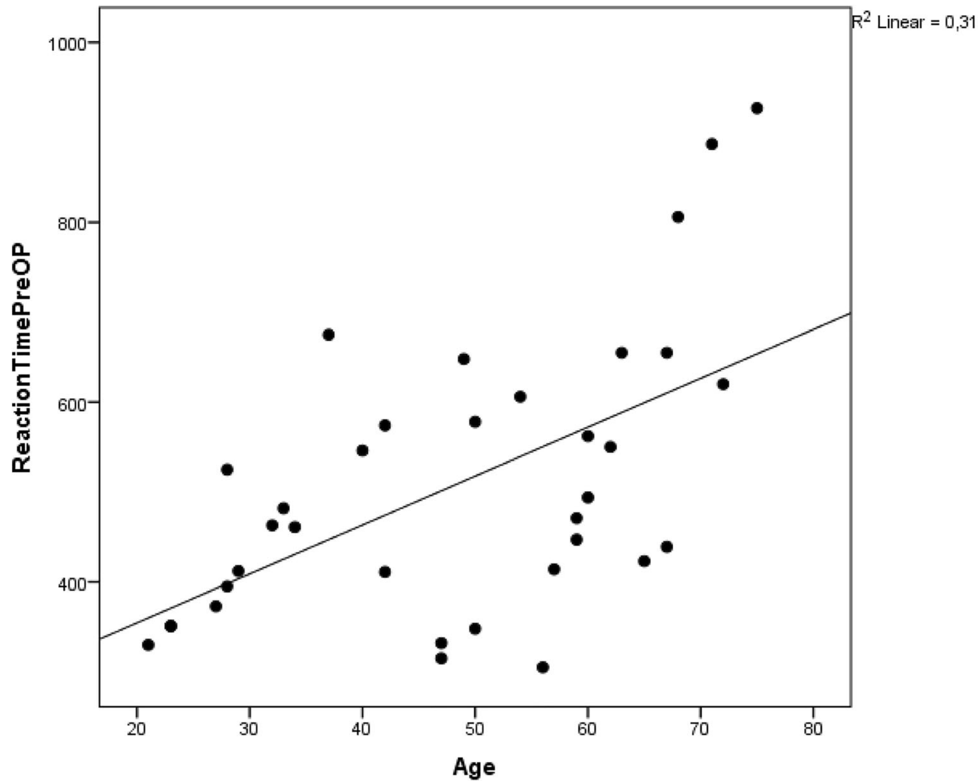

Fig. 5 Correlation diagram indicating that there is a strong correlation between the preoperative reaction times and age ($r = .562$, $p < .001$)

during the 1st time frame (0–10 min) did not statistically significantly differ from the intraoperative 2nd time frame (10–20 min) ($D = 187$, $p = .235$, one-tailed) (Fig. 4).

There is a strong correlation (Fig. 5) between the preoperative reaction times and age ($r = .562$, $p < .001$). The correlations between the intraoperative reaction time during the 1st time frame (0–10 min) and the volumetric tumor mass ($p = .094$), BMI of the patient ($p = .507$), overall anesthesia duration prior to extubation ($p = .176$), and cumulative dose of propofol and remifentanil ($p = .276$) were not significant.

There was no significant difference in the intraoperative reaction time during the 1st time frame between the patients taking antiepileptic home medication ($N = 15$) in comparison with the patients that were taking none ($N = 20$) ($p = .089$). Since antiepileptic drugs were not a part of our standard anesthesia induction scheme, only two patients were given antiepileptic drug, levetiracetam, during the induction phase. The reaction times in these two patients did not significantly differ from the rest of the cohort ($p = .408$).

Side in cerebral hemispheres ($p = .807$) and frontal, occipital/basal, or parietotemporal lobar location of the tumor did not alter the reaction speed during the 1st time frame.

There was no significant difference between reaction times in the aforementioned time frame of different genders ($p = .283$).

Raw data of patient reaction times prior and during the awake operation can be found in Table 3.

Discussion and conclusions

Extent of resection increases survival

It is evident that surgical resection plays the central role in the management of high- and low-grade gliomas. For high-grade glioma, removed tumor volume directly correlates with overall survival. The stepwise improvement in survival is seen even in the range of 95–100% [15]. This approach of maximal safe resection of the tumor mass and infiltrated tissue also applies to low-grade glioma where supra-total resection beyond MRI-defined tumor margin further increases the overall survival [4]. Hence, the techniques that are empowering the neurosurgeon to increase the margin of safe resection are of significant importance.

Awake craniotomy and extent of resection

In modern neuro-oncological surgery, multiple methods allowing for an aggressive resection are established. The extent was substantially increased after the development of intraoperative tumor and site visualization techniques such as 5-aminolevulinic acid (5-ALA) [21], intraoperative MRI (iMRI) [17], intraoperative ultrasound (iUS) [20], and navigation [12].

If the tumor is located near a functional speech area, awake craniotomy also allows for a more aggressive tumor removal in comparison to surgery under general anesthesia. However,

Table 3 Means of patient reaction times during assessed pre- and intraoperative time frames presented as raw data in milliseconds

Patient No.	PreOP	0-10 min	10-20 min	20-30 min	30-40 min	>40 min
1	332	451	526	359	372	530
2	348	802	645	641	761	881
3	620	1006	659	447	551	656
4	447	506	765	508	514	519
5	806	1103	573	629	684	1237
6	412	847	1235	608	588	692
7	411	1006	503	383	396	643
8	395	430	992	1125	1258	702
9	315	354	431	1002	719	435
10	494	1685	803	526	510	425
11	655	1923	1200	904	608	1007
12	305	980	1023	731	851	702
13	463	832	679	742	805	702
14	439	1191	636	596	516	617
15	482	708	935	626	719	811
16	550	1297	859	1046	718	617
17	330	2055	449	394	282	617
18	562	821	561	643	725	544
19	414	1321	602	452	492	617
20	578	620	661	526	511	495
21	461	578	487	395	401	617
22	373	475	491	508	403	588
23	574	988	1046	1369	1220	1071
24	546	983	1480	978	1260	1017
25	887	746	559	586	612	1112
26	525	694	581	650	718	745
27	675	2270	1615	960	816	902
28	648	681	549	493	603	559
29	423	537	820	527	565	806
30	351	788	371	339	381	335
31	351	442	820	384	431	375
32	655	1664	764	1294	742	806
33	606	1363	2019	1282	1365	1755
34	471	580	721	844	491	806
35	927	1883	1011	936	935	1020

maximal compliance and cooperation of the patient is necessary; else, the safety of the procedure is inevitably compromised.

Implications and limitations of the study

In our work, we analyze the feasibility of measuring the reaction time in order to estimate the wakefulness of the patient. Moreover, we sampled the first sizable amount of data about the kinetics of patient reaction speed during awake craniotomy.

The study is limited to evaluating only the first 40 min of awake phase of craniotomy due to the lack of data in the later stages of the phase. This is related to the fact that the awake phase needed for the resection of the language-critical portion of the tumor usually is shorter than 60 min.

The second limitation is a relatively large dispersion of the results, especially in the first intraoperative time frame (0–10 min). This might be explained by the wide age-spectrum (21–75 years old) of our patient group, since our data suggests that there is a trend towards the correlation between age and reaction time during the first 10 min after extubation. Due to this large dispersion, the difference between the reaction speed during the 1st and the 2nd intraoperative time frame is not significant. Therefore, after accumulation of additional data, it is plausible that, in the future, the 2nd intraoperative time frame (10–20 min) will be proven to be significantly different from the reaction time during the first 10 minutes after extubation. Hence, a larger multi-center study is being developed in order to definitely determine the optimal time window for cortical mapping in awake craniotomy.

Our data concludes three following statements about the patients undergoing awake surgery.

Firstly, there is a strong correlation between preoperative reaction times and age. Therefore, one should expect a poorer reaction speed performance in senior patients. The influence of tumor volume, location, side as well as patient's gender, BMI, antiepileptic medication, duration of anesthesia induction, and cumulative dose of propofol and remifentanil are insignificant in our data set.

Secondly, the patients are generally almost two times slower during the operation than preoperatively. It seems that the induction of anesthesia and sedation for the duration of the approach does indeed impair the general wakefulness of the patient, despite the fact that patients subjectively seem to be fully awake and able to communicate.

Lastly, the reaction speed is the most reduced during the first 10 min after extubation. Although there is a trend of increase in speed in the following 10 min, a significant increase in speed can only be detected as of the 3rd time frame (20–30 min) and onwards.

Conclusions

In conclusion, we have proven that measurement of intraoperative reaction speed is a technically feasible method that is well tolerated by the patients.

Elderly patients will usually demonstrate poorer performance of reaction speed; this should be considered in patient selection and during the evaluation of reaction time on the day before operation. The intraoperative reaction time performance is significantly slower than on the day before the operation. The patients seem to be the slowest directly after extubation and gradually wake up during the awake phase of the operation. Therefore, according to our current data, the optimal time window for cortical mapping in awake craniotomy begins 20 min after extubation.

Compliance with ethical standards

Ethical statement The authors declare that there is no conflict of interest. Local ethical committee granted the approval for this study, internal study number: 6076R. It was conducted in compliance with the Helsinki declaration and under conditions of good scientific and clinical practice. Informed consent was obtained from the study participants.

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3. Discussion and Conclusions

3.1 Discussion

Currently there are no options for quantifying the degree of alertness during an awake craniotomy. Interdependence of reaction time and wakefulness is demonstrated in the study by Corsi-Cabrera and colleagues in 1996. In their study, nine young adult male volunteers were subjected to total sleep deprivation for 40 hours. Oral temperature, reaction time in a visual vigilance task, and electroencephalogram while performing the task were recorded every 2 hours during total sleep deprivation and after recovery sleep. The results indicated that total sleep deprivation with high significance ($p < .009$ for all comparisons) induced an increase in reaction time and absolute power the full band in EEG. Moreover, all the affected variables returned to baseline values after recovery sleep (Corsi-Cabrera, Arce et al. 1996). Data of this study strongly indicates that reaction time duration has a negative correlation with wakefulness of the patient.

There have been reported attempts to measure patient reaction times in order to determine the wakefulness or the depth of sedation during an operation or invasive procedure. For example in the study of O’Brien and colleagues “Reaction time-monitored patient-maintained propofol sedation: a pilot study in oral surgery patients’’ (O'Brien et al. 2013) the authors reportedly solved the known problem of oversedation in patient-maintained propofol-based sedation system. In order to reduce the risk of adversely deep sedation, the authors implemented a reaction time monitor into the handset to add an individualized feedback mechanism. It was reported that all twenty healthy volunteer patients received sedation without reaching any unsafe endpoints, which in this study were the cessation of verbal contact throughout the procedure or dangerous drop in peripheral oxygen saturation. The mean (SD) of the latter was 98.0 (2.1)%

under atmospheric air. According to the authors of this study, reaction time based feedback system rendered this type of light propofol sedation safer than previously reported.

In order to determine the safest time window for cortical mapping in the awake phase of the craniotomy, we registered the intraoperative reaction times every ten minutes after extubation and compared them with the baseline reaction time obtained on a day before the operation. These preoperative and intraoperative reaction times, as well as other relevant intraoperative events such as epileptic seizures, patient incompliance or aggression, were documented with an Android-based Application "Reaction Time Sampler" developed and programmed by our team.

According to our data, the preoperative reaction times of our patient cohort were significantly shorter than those measured during the operation ($p < .001$). Therefore, one may argue that in general, patients are significantly slower and therefore less awake during the craniotomy.

There is a strong correlation between the preoperative reaction times and age. Therefore, senior patients are to be expected to have even poorer preoperative reaction time performance.

In order to determine the optimal time window for cortical mapping, we have split the first forty minutes of awake phase of craniotomy to 10-minute intervals and analyzed for statistical significance between reaction times.

A one-factor ANOVA (within subjects) showed a significant increase in reaction times ($p < .001$). Post hoc comparisons on a Bonferroni-corrected α-Error level of .05 showed significant differences between the reaction time during the 1st time frame (0-10 min) and the preoperative reaction time ($p < .001$) as well as the intraoperative reaction times during the 3rd (20-30 min) ($p = .013$), 4th (30-40 min) ($p = .012$), and the 5th time frame (t>40 min) ($p = .044$). However, the reaction time during the 1st time frame (0-10 min) did not statistically significantly differ from the intraoperative 2nd time frame (10-20 min.) ($p = .235$).

3.2 Conclusions

According to our current data, patients during the awake phase of craniotomy are reacting about two-times slower, than they were reacting preoperatively. Secondly, older patients seem to demonstrate poorer preoperative reaction time. Thirdly, the optimal time window for cortical mapping seems to start after the 20th minute after extubation. According to the trends of our data, after inclusion of additional patients in an analogical study, the optimal time window for cortical mapping might be proven wider than stated in our current work.

4. Literature

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