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Evaluation of the predictive value of intraoperative changes in motor evoked potentials of caudal cranial nerves for the postoperative functional outcome

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Abbreviations

ACh:	Acetylcholine
AMP:	Amplitude
CN:	Cranial nerves
CCN:	Caudal cranial nerves
CN.I:	Olfactory nerve
CN.II:	Optic nerve
CN.III:	Oculomotor nerve
CN.IV:	Trochlear nerve
CN.V:	Trigeminal nerve
CN.VI:	Abducens nerve
CN.VII:	Facial nerve
CN.VIII:	Vestibulocochlear nerve
CN.IX:	Glossopharyngeal nerve
CN.X:	Vagus nerve
CN.XI:	Accessory nerve
CN.XII:	Hypoglossal nerve
CPA:	Cerebellopontine angle
EEG:	Electroencephalography
FMEP:	Facial motor evokes potential
GABA:	Gamma aminobutyric acid
HB:	House-Brackmann
IOM:	Intraoperative neuromonitoring
ISI:	Interstimulus interval
LAT:	Latency
MEP:	Motor evoked potential
n:	Number
OR:	Operating room
Post-op:	Postoperatively
RMS:	Root mean square
SD:	Standard deviation
SEP:	Somatosensory evoked potential

TES: Transcranial electrical stimulation

TMS: Transcranial magnetic stimulation

1. Introduction

In the 20th century, mortality rates of patients who had to undergo brain surgery were extremely high. Advances in medicine, like microsurgical techniques and advances in the field of neuroanesthesia as well as intraoperative neuromonitoring, have significantly reduced morbidity and mortality in patients (Acioly et al. 2011). At the beginning of the 21st century, neurological complication rates after brain surgery still varied between 23 and 44% (Cabantog et al. 1994, Di Larazzo et al. 1999, Ohue et al. 1998). These numbers have dropped over the past decade due to further refinements of neurosurgical techniques, introduction of a microscope and to a great extend due to the introduction of neuromonitoring.

Today Intraoperative neuromonitoring (IOM) is routinely used in most neurosurgical centers around the world. Complications of the motor neural system are especially likely to develop if the treated tumor is located close or within the primary motor cortex or the motor pathway (Zhou et al. 2001). However, IOM plays a role not only for brain mapping during surgery of tumors in eloquent areas of the brain, but also for monitoring of cranial nerves (CN) during surgeries in the cerebellopontine angle (CPA). The anatomical preservation of CNs, such as the facial nerve, is currently around 95% and the functional preservation of the facial nerve as high as 70% (Acioly et al. 2011). As of today, dysfunction of postoperative nerve function resulting in facial weakness, tongue deviation, extinct gag reflex and difficulties swallowing are still complications of major concern when patients undergo brain surgery. Therefore cranial nerve injury leads to a severe negative impact on the patient's quality of life.

1.1 Anatomy and physiology of the peripheral nerve system

The peripheral nerve system lies outside the central nerve system and communicates with it and the other parts of the body and consists of nerve endings, peripheral nerve trunks, plexuses and ganglia (Crossman and Neary 2000). It contains the caudal nerves which are describes in further detail below, the spinal nerves and the autonomic nerve system (Garzorz 2009). The neurons of the peripheral nerve system are either afferent (leading to the central nerve system) and contain sensory receptors, which recognizes sensory changes in the environment or efferent (leading away from the central nerve system) to innervate and control muscle function (Crossman and Neary 2000).
The nerve fibers consist of axons, which are the extension of the nerve cells, and neuroglial cells, also called Schwann cells that cover the axons. The myelinated nerve fibers are covered by a myelin sheet which is disrupted by the so called node of Ranvier where the axon is exposed and the saltatory conduction of the action potentials (explained in detail below) takes place. There are also nerve fibers that do not have a myelin sheet and therefore do not form nodes of Ranvier. Hence, a saltatory conduction is not possible resulting in a slower nerve conduction velocity (Garzorz 2009). The nerve fibers are divided into seven categories according their function (see table 1).

Table 1: Classification of the nerve fibers adapted from Erlanger and Gasser 1937

Fiber (type/group)	Mean diameter (µm)	Mean conduction speed (m s^{-1})	Function (example)
Erlanger /Gasser Classification (type)			
Aα	15	100	Motor neurons
Aβ	8	50	Skin touch afferents
Aγ	5	20	Motor to muscle spindles
Aδ	4	15	Skin temperature afferents
B	3	7	Unmyelinated pain afferents
C	1	1	Autonomic postganglionic neurons

The neurotransmitter chemicals are released from the presynaptic ending of a neuron, where they are stored in vesicles, into the synaptic cleft. There, the neurotransmitters are received by the post-synaptic neuron that has chemical gated ion channels within its membrane, so called neuroreceptors (see figure 1) (Garzorz 2009). There are numerous types of neurotransmitters within the different parts of the nervous system. Acetylcholine (ACh) has been known for a long time and is the transmitter between the motor neurons and the striated muscle. ACh is also used as a neurotransmitter in the autonomic ganglia released from the postganglionic parasympathetic neurons. A plethora of other transmitters exist such as the amino acids glutamic acid and gamma aminobutyric acid, knows as GABA that are distributed throughout the central nervous system. Noradrenaline is another neurotransmitter and is released by postganglionic sympathetic neurons within the peripheral nervous system and the central nervous system. Dopamin and serotonin are further transmitters mostly in the brain and the spinal cord (Crossman and Neary 2000).

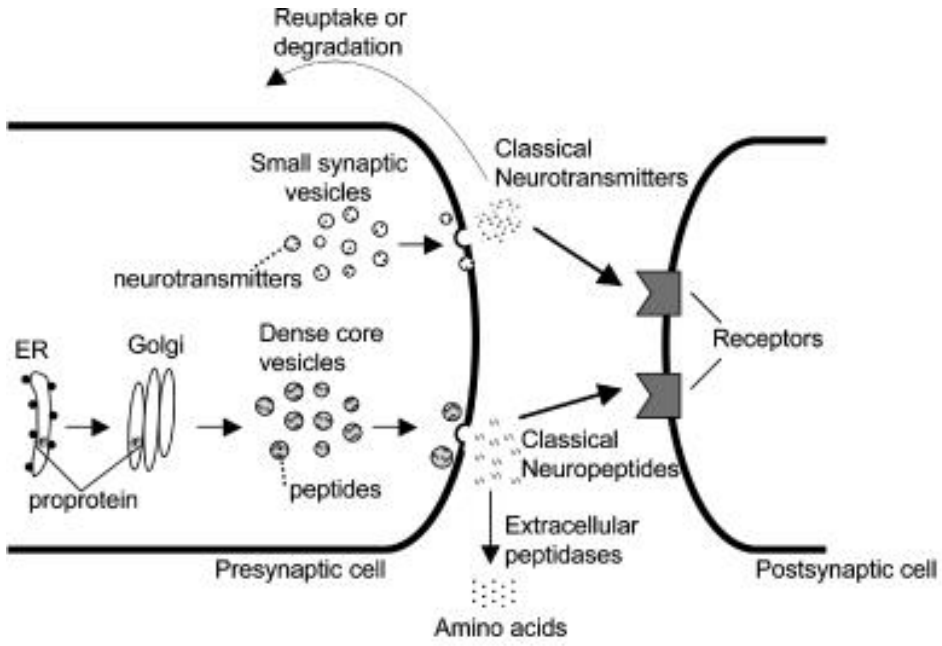


Figure 1. The neurotransmitter chemicals are released from the presynaptic cell where they are stored in vesicles into the synaptic cleft. There the neurotransmitters are received by the post-synaptic cell that has chemical gated ion channels within its membrane, so called neuroreceptors (Gelman and Fricker 2010).

Every nerve cell is excited with an action potential. Hereby voltage-dependent sodium channels in the muscle cell are responsible for generating an action potential by depolarization. If the cell is depolarized, these sodium channels open quickly and a massive sodium intake takes place that further depolarizes the cell and the muscle is activated by opening of the calcium channels. Immediately after depolarization, the cell membrane hyperpolarizes which is called after-potential when potassium channels are opened and the Na+/K+-ATPase pumps the sodium out of the cell. Instantaneously after the depolarization, while the sodium channels are still inactive, the cell cannot be excited which is called refractory-time (Lang 2007).

1.2. Anatomy and Function of the Cranial nerves

The human body consists of twelve cranial nerves. Together with the spinal nerves, the cranial nerves are part of the peripheral nervous system; however, they are not structured segmentally and may only have one quality of fibers (Garzors 2009).

With exception of the first two cranial nerves, the olfactory (CN.I) and the optic nerve (CN.II), all have their origin within the brain stem and send out motor and parasympathetic fibers to muscles and glands or receive viscerosensory or somatosensory fibers from mainly the neck and head. While some cranial nerves consist of mixed fibers, the olfactory nerve and the optic nerve only send out sensory fibers to the bulbus olfactorius and corpus geniculatum laterale and have no nuclei. Since it is embryologically an extension of the mid-brain, CN. II is by definition not a peripheral nerve but part of the central nervous system. The vagus nerve (CN.X) also innervates smooth muscles and glands of the gastrointestinal tract and the cardiovascular system (Kandel et al. 2000). The table and figure below give a general overview of the functional classes of the cranial nerves (table 2; figure 2):

The cranial nerves play a major role in the autonomic and voluntary functions of the body. For this reason, special attention is given to the preservation of these nerves during surgery. This work focuses on preserving function of the glossopharyngeal (CN.IX) and hypoglossal nerve (CN.XII) with the use of neuromonitoring during neurosurgery, which are also called the caudal cranial nerves (CCN). Thus, the anatomy, physiology and pathophysiology of these two cranial nerves are discussed in further detail.

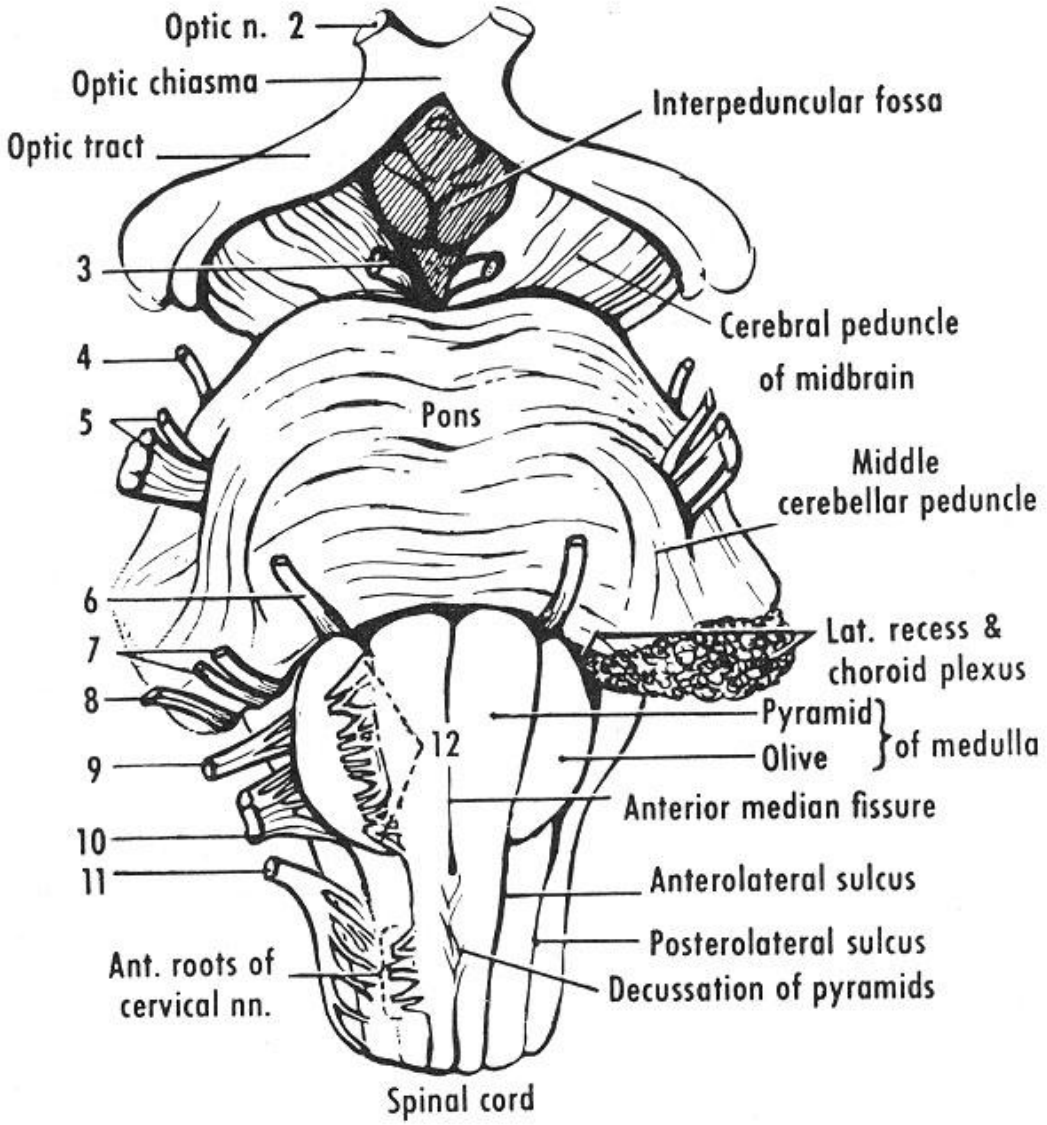


Figure 2
The anatomy of the brain stem with the cranial nerves numbered from 3 to 11 exiting the brain stem (O`Rahilly et al. 2004).

Table 2. Functional Classes of the cranial nerves

Classification	Functions	Structures innervated	Cranial Nerve
Sensory			
General Somatic	Touch, pain and temperature Proprioception	Skin, skeletal muscles of head and neck, mucous membrane of mouth and teeth	V,VII,IX,X
Special somatic	Hearing, balance	Cochlea, vestibular organ	VIII
General visceral	Mechanical Chemosensory	Pharynx, larynx, neck, gut	V, VII. IX, X
Special visceral	Olfactory, taste	Taste buds, olfactory Epithelium	I, VII, IX, X
Motor			
General Somatic	Skeletal muscle control (somites)	Extraocular and tongue muscles	III, IV, VI, XII
General visceral	Autonomic control	Tear glands, sweat glands, gut	III, VII, IX, X
Special visceral	Skeletal muscle control (branchiomeric)	Muscle of facial expression, jaw, neck, larynx, and pharynx	V, VII, IX, X, XI

(Table adapted from Kandel et al. 2000)

1.2.1 Glossopharyngeal nerve

1.2.1.1 Anatomy and physiology

The glossopharyngeal nerve (CN.IX) is the ninth of the twelve cranial nerves and consists of four different nuclei, which lie in the ventrolateral part of the medulla oblongata (Schünke et al. 2006). The nucleus ambiguus sends, together with the vagus nerve, motoric fibers to the muscles of the pharynx and the soft palate. The nucleus salivatorious inferior innervates with its parasymphatic fibers the parotic gland. The nucleolus tractus solitarii receives viscerosensory fibers from the carotic sinus and the posterior part of the tongue and the nucleus spinalis n. trigenimi with its somatosensory fibers coming from the tympanic cavity, tuba auditiva, posterior third of the tongue and the pharynx mucosa (Kandel et al. 2000; Schünke et al. 2006; Garzors 2009; Ong CH et al. 2010).

Leaving the medulla oblongata from postolivary sulcus, the glossopharyngeal nerve enters the cranial cavity through the jugular foramen in which the nerve fibers form the superior and inferior ganglion (Ong CH et al. 2010; Özveren MF et al. 2003). From the inferior ganglion, the tympanic nerve enters the tympanic cavity through the inferior tympanic canaliculus and forms the tympanic plexus with fibers coming from the internal carotic plexus. In it, the lesser petrosal nerve origins and enters the cranial cavity again and innervates with its parasympathetic fibers the parotid gland (Schünke et al. 2006; Garzors 2009; Özveren et al. 2003).

Within its course, the glossopharyngeal nerve leaves also motoric branches to the stylopharyngeal and the pharyngeal constrictor muscle of the pharynx, the palatoglossus, palatopharyngeus, levator veli palatini and uvulae muscle of the soft palate and somatosensory branches to the mucosa of the pharynx and viscerosensory branches to the posterior third of the tongue (Schünke M et al. 2006; Garzors 2009; Özveren MF et al. 2003). Another, yet not as important branch as the latter ones to this work is the carotid sinus nerve measuring oxygen and carbondioxide levels of the blood in the carotid sinus and

subsequently adjusts breathing frequency and blood pressure (Kandel et al. 2000).

1.2.1.2 Symptoms of dysfunction

Injuries of the glossopharyngeal nerve occur mostly not isolated. This is due to its close anatomic relations to the vagus (N.X) and the accessorious nerve (CN.XI) which run together through the jugular foramen exiting the cranial cavity (Bejjani et al. 1998, Gillig et al. 2010; Goldenberg et al. 1991; Garzors 2009; Schünke et al. 2006; Trepel 2012). Pathologic lesions of the glossopharyngeal nerve can be caused by fractures of the skull base, aneurysms, tumors, predominantly schwannomas (Ong et al. 2010; Garzorz 2009), and surgical intervention on which this work focuses on. Since it is anatomically concealed at the infratemporal fossa and the neck (Bejjani et al. 1998; Claes 1986; Goodwin et al. 1993), it is arduous for surgeons to identify the glossopharyngeal nerve (Özveren et al. 2003). For this reason, the nerve is highly endangered to become iatrogenically irritated or injured during surgery. If this occurs, a variety of symptoms can develop depending on the location of the injury. If the motor innervation is interrupted, the function of the stylopharyngeal muscle is decreased or absent resulting in difficulties swallowing. The gag reflex may also be impaired; however, not due to deterioration of the motor innervation but rather the somatosensory fibers (Özveren et al. 2003; Gillig et al. 2010). Deviation of the uvula to the healthy side can be another result of damaging the glossopharyngeal nerve (Garzors 2009):

The loss of taste (bitter) of the posterior part of the tongue are caused by an injury of the viscerosensory fibers (Trepel 2012; Masuhr et al. 2007) and malfunction of the parotic gland by the parasymathic fibers (Garzors 2009).

1.2.2 Hypoglossal nerve

1.2.2.1 Anatomy and physiology

The hypoglossal nerve (CN.XII) is the eleventh of the twelve cranial nerves. It consists only of motor fibers originating from the hypoglossal nucleus located close to the midline of the medulla oblongata just below the rhamboid fossa. The nerve exits the medulla in front of the olive within the anterolateral sulcus and exits the cranial cavity through the hypoglossal canal (Kandel et al. 2000; Schünke et al. 2006). Below the hypoglossal canal the nerve runs behind the vagus nerve to the side and then curves between the internal carotid artery and jugular vein to the root of the tongue (Trepel 2012). Here the hypoglossal nerve innervates the genioglossal muscle and the other muscles of the tongue with the exception of the palatoglossal muscle which is innervated by the glossopharyngeal nerve (Schünke et al. 2006).

1.2.2.2 Symptoms of dysfunction

Injuries to the hypoglossal nerve often occur simultaneously with impairment of the accessory nerve for their close anatomic relations in the periphery (Bademci et al. 2006). Isolated palsy of the hypoglossal nerve are relatively rare (Hui et al. 2009) and are most common caused by metastatic carcinomas, chordomas, gliomas and acoustic neuromas (Keane 1996; Boban et al. 2007) followed by trauma (Hui et al. 2009). Iatrogenic injury of the hypoglossal nerve is rare and most often occurs in patients undergoing carotid endarterectomy (Gutrecht et al. 1988). Unilateral irritation or damage of this nerve will cause paralysis of the genioglossal muscle of the ipsilateral side, resulting in deviation of the tongue at protrusion to the affected side because of the genioglossal preponderance on the healthy side (Gillig et al. 2010).

1.3. Intraoperative Motor Evoked Potential (MEP) monitoring

1.3.1 Historical Overview

In the early part of the 20th century, the German anatomist Korbinian Brodmann produced a cytoarchitectural map of the cerebral cortex that related to the regional histological characteristics, called Brodmann´s areas (see figure 3). Although it has been revised several times over the last decades, there is still some good correspondence between these areas and functionally defined regions of the cortex.

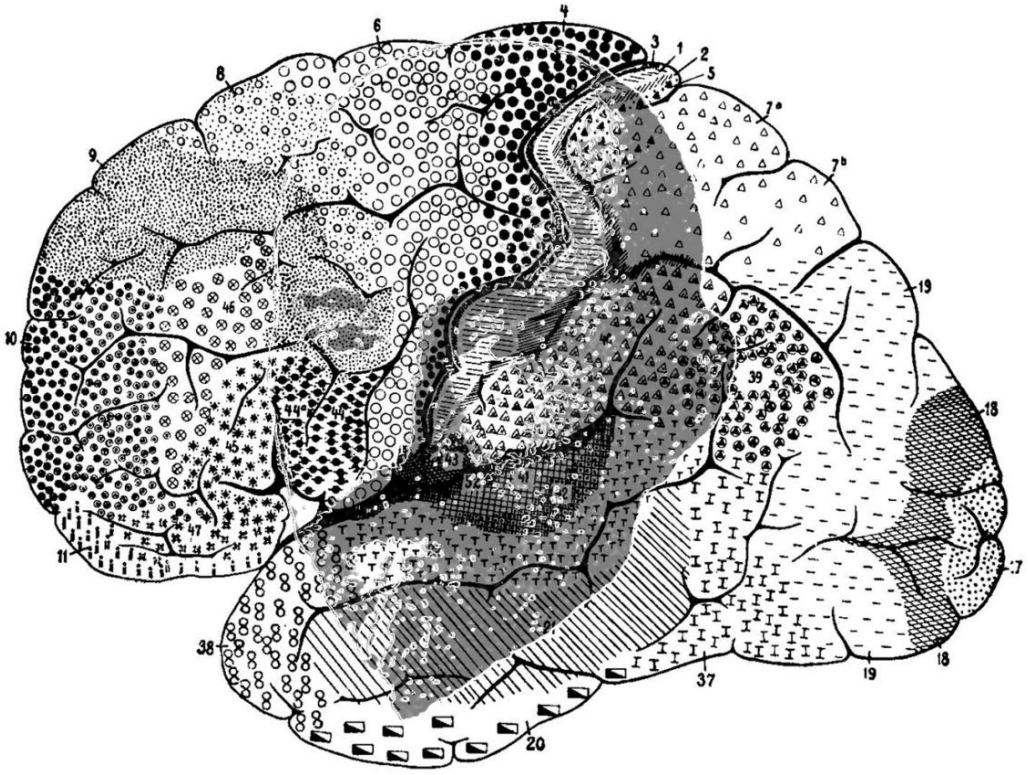


Figure 3: Excerpt from Brodmann´s Areas
Areas 1,2 & 3: Primary somatosensory cortex
Area 4: Primary motor cortex
Area 17: Primary visual cortex
Area 22: Wernicke´s area
Area 41 & 42: Close correspondence to the primary auditory cortex
Area 44 & 45: Broca´s area
(Figure from Benninghoff and Drenckhahn 2004)

The beginning of intraoperative neurophysiologic techniques dates back to 1937 when Canadian neurosurgeon Wilder Penfield and colleagues published their work on electrical stimulation of the motor cortex (Penfield et al. 1937). The contralateral part of the body is represented in an exact somatotopic fashion and pictorially described as a motor homunculus (see figure 4)

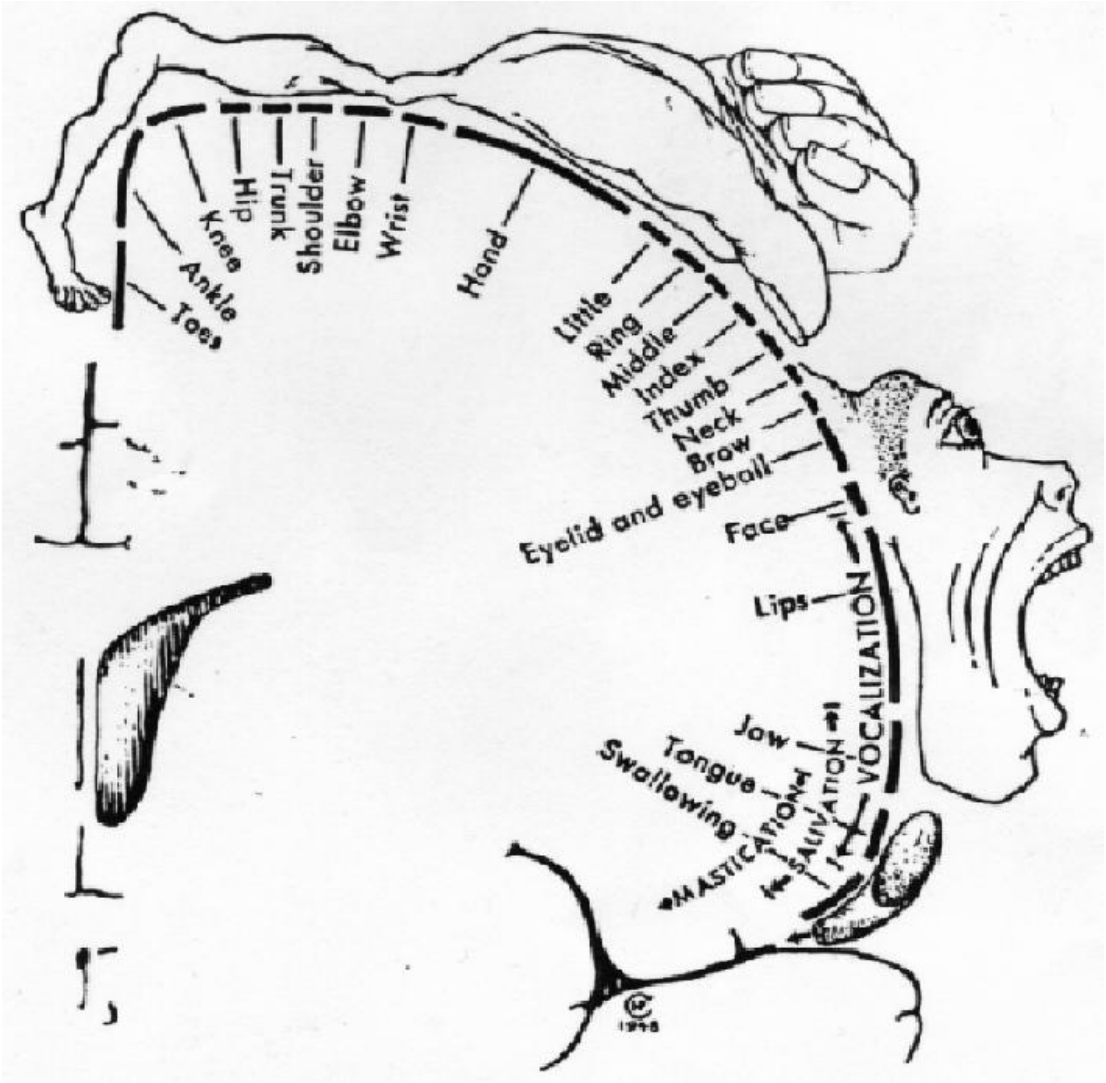


Figure 4
Motor humunculus illustrating somatotopic organisation of the primary motor cortex according to Penfield and Rasmussen 1950.

Several years past by until Patton and Amassian resumed research in this area in the year 1954. Patton and Amassian discovered that the application of a single electric pulse to the motor cortex of monkeys caused various electrophysiological responses in the corticospinal tract (Patton et al. HD 1954). In 1980, Merten and Morton where the first ones being able to evoke MEPs in awake human probands with the use of transcranial electrical stimulation (TES) (Merton et al. 1980). This technique however was not suitable for prolonged research studies due to the discomfort it causes in awake subjects. For this reason, transcranial magnetic stimulation (TMS) replaced the TES technique. Yet, neither TES nor TMS became reliable methods in the operating room since both are not able to consistently evoke MEPs in anesthetized subjects (Sala et al. 2004). It was only when cortical tract monitoring of the motor evoked responses using the direct wave (D-wave) that MEP recording became a useful and regular tool in the operating room. The D-wave is the direct response to a single electrical stimulus applied to the motor cortex (Boyd et al. 1986; Burke et al. 1993; Deletis 1993; Katayama et al. 1988) and the application of a train of stimuli to record motor responses from muscles of the extremities (Jones et al. 1996; Taniguchi et al. 1993; Pechstein et al. 1996), which was discovered by Taniguchi et al. in 1993. Taniguchi et al. showed that a short series of 3 to 5 electric pulses, with an interval between the pulses of 2 to 4 milliseconds, elicited an MEP of the muscles when applied to the motor cortex of anesthetized patients directly (Taniguchi et al. 1993). Only by using this pulse-train technique, TES is effective under general anesthesia as researchers found out in 1993 (Jones et al. 1996; Pechstein et al. 1996; Rodi et al. 1996). Different techniques of intraoperative motor evoked potential monitoring exist today with the pulse-train TES method being the one used in many ORs to minimize mechanical damage to the motor cortex during surgery (MacDonald 2006) and being the one used in this work.

1.3.2 Monitoring of MEPs

There are three objectives using neuromonitoring with MEPs in the operating room: First and most importantly, neuromonitoring gives the neurosurgeon ongoing information of nerve function while operating. Therefore, it can warn the surgeon if necessary to change or adjust the strategy to improve the postoperative clinical outcome (Guerit 1997). Second, it reassures the surgeon that the strategy is adequate and can be continued in this manner without injuring or damaging essential nerve functions.

Thirdly, the operating strategy and technique can be evaluated retrospectively with use of the information provided by neuromonitoring. Looking at the patient`s postoperative clinical outcome, change or adjustment of the surgical procedure in further patients might be implicated to improve nerve functional outcome of these patients.

For these reasons, neuromonitoring has established itself and unquestionably has become an important tool routinely used in most neurosurgical operating rooms today.

To monitor transcranial electrical motor evoked potentials, electrodes have to be placed on or inserted into the scalp. Spiral or straight needles and Electroencephalography (EEG) cup electrodes are useful for this purpose and widely employed (Deletis 2002, MacDonald et al. 2002; MacDonald et al. 2003). The median TES impedance is around 500 Ohms for standard spiral needles, 800 Ohms for straight needles and 1100 Ohms for EEG cup electrodes. This is important to note since impedance over 460 Ohms correlate in proportion to MEP thresholds. To avoid this dependence, larger electrodes with lower impedance than 460 Ohms could be used theoretically (Journee 2004); however, this is not practically employed (McDonald 2006). Corkscrew-like electrodes positioned into the skull are used in TES neuromonitoring at the University of Tübingen and other facilities since they are save and add little impedance despite being invasive (Sala et al. 2004).

Electrodes are positioned on the central (C) sites according to the International 10/20 EEG system. The d-wave maps the anatomic relationship between the motor cortex and the location of the electrodes` position on the skull (Vernon et

al. 1993; MacDonald 2006). The location of the electrodes can be varied to a more anterior site C+1cm or even C+2cm (Deletis 2002; MacDonald 2002; MacDonald 2003; Neuloh et al. 2002). It has not been explored if one or the other site is more efficient. Yet the C+2cm position is thought to be an advantage over the C+1cm position because of its greater distance to electrodes for somatosensory evoked potentials (SEP) (MacDonald 2006), potentially causing stimulus artifacts especially at high voltages that could conceal the responses of muscles (MacDonald et al. 2002). Different positions are applied for the TES electrodes in MEP monitoring (MacDonald 2006) (Figure 5). For the best combination of anode and cathode, an arrangement like C3, Cz-1cm, C2, C4 and Cz+6cm (Deletis et al. 2002) might be used. For electrophysiological reasons, however, the electrode array C1/2 or C3/4 is preferred and has established itself (MacDonald 2006). The cathode is placed at position Cz and the anode on the side contralateral to the corresponding muscle since the motor cortex beneath the anode is most likely to be stimulated (Deletis et al. 2002). If the electrodes are placed at the C1/C2 position, MEPs in limbs of the right side are preferably evoked and at the C2/C1 position MEPs in limbs of the left side. If the muscles of the lower limbs need to be monitored, the electrodes should be placed at Cz-6cm. The Cz electrode is then positioned 1 cm posterior to the usual Cz point (see figure 5, MacDonald 2006, Sala et al. 2004).

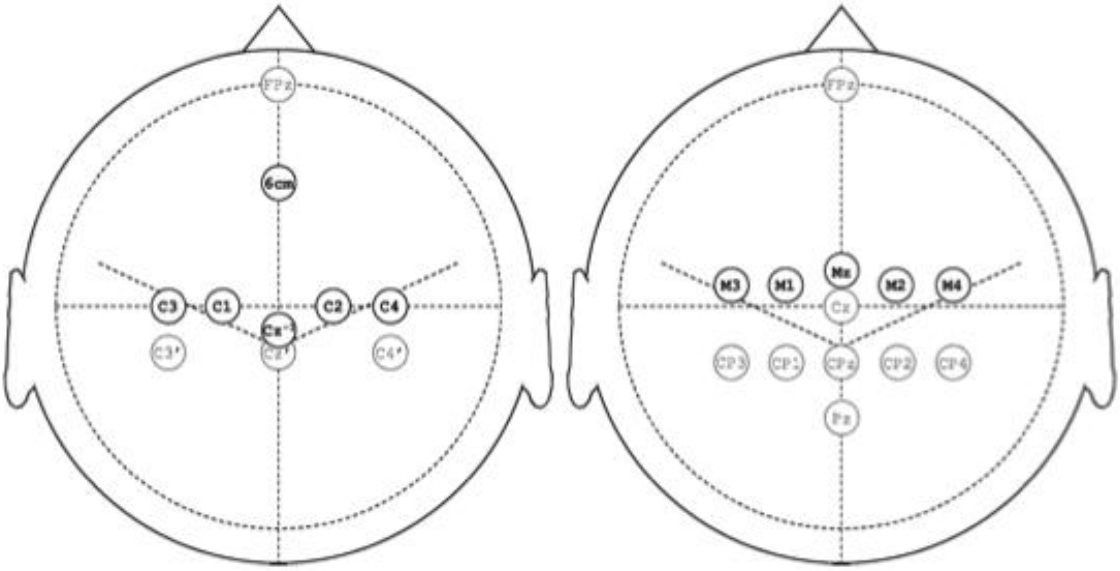


Figure 5. Two transcranial electrocortical stimulation (TES) arrays.
Solid and broken circles are TES and SEP electrode sites. In the left array (Deletis, 2002), Cz^{-1} is 1 cm behind Cz and the frontal site is 6 cm anterior. Anode-cathode combinations can be selected to optimize technique. The author's array on the right increases TES-SEP electrode distance. M sites are 1 cam anterior to C sites except Mz, 2 cm anterior to Cz. Mz is used for hemispheric (e.g. M3-Mz) stimulation. Leg MEPs are usually evoked with M1/2 or M3/4. The additional SEP sites are used for SP optimization (Figure from MacDonald, 2006).

Stimulation is now conducted by the pulse train also known as multipulse TES technique using 3-9 pulses with intervals of 1-5 ms between these pulses (MacDonald 2006). Just a single pulse is not effective in monitoring MEPs in patients undergoing general anesthesia. Only a train of pulses is able to do so (Taniguchi et al. 1993). Pulses applied can either be short (0.05ms) with a current as high as 1500 mA or long (up to 0.5 ms) and a current of only 240mA. There are different types of intraoperative monitoring (IOM) stimulators with the Endeavor® stimulator being one of them and the one used at the University of Tübingen (see figure 6).

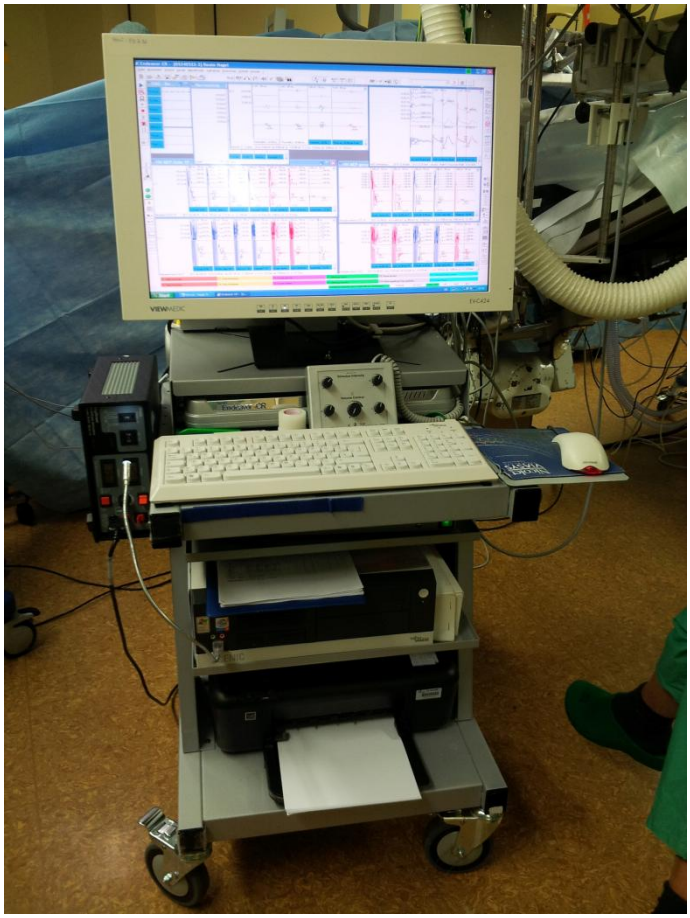


Figure 6
Endeavor® stimulator used to monitor the intraoperative motor evoked potentials, courtesy of the Department of Neurosurgery Tübingen.

It has an output of 200 mA at 400 V when the impedance of the electrode is low making it useful with long pulses up to 0.5 ms (MacDonald et al. 2003; MacDonald 2002). How many pulses are eventually used depend on the preferences of the neurophysiologist, hospital and/or the surgeon (MacDonald 2006). However, there has been studies conducted indicating that 5 pulses are a proper start for MEPs of the leg (Deletis 2002; MacDonald et al. 2003). Three to four pulses might be necessary for MEPs of the hand or facial muscles (Dong et al. 2005; Scheufler et al. 2005). The best inter-puls interval depends on the depths of anesthesia, the muscle recorded and the individual person. Under common general anesthesia, the D-wave needs between 4-5 seconds to fully recover (MacDonald 2006) and can be measured using a catheter electrode which is placed under or on top of the dura mater next to the spinal cord (Sala

et al. 2004). Therefore, the interval between the pulses should be 4-5 ms in duration for MEPs of the muscles (MacDonald 2006; Deletis et al. 2001; Deletis 2002; Bartley et al. 2002). These intervals however can be shortened for hand MEPs as recent studies have shown. An interval of just 1 ms gives the D-wave not enough time to fully recover, yet causes MEP amplitudes of hand muscles to be ample. Thus, a train of 4 pulses with 0.05 ms at 300 V has been proposed for hand muscle MEPs (MacDonald et al. 2003; Scheufler et al. 2005) and longer intervals for leg muscles (MacDonald 2006).

If a single-train MEP cannot be evoked or is insufficient, techniques of facilitation can be used to increase sensitivity of the alpha motor neuron by applying either up to several trains before the actual test train or repeating a series of 2 Hz trains (Quinones-Hinojosa et al. 2005; Deletis 2002; MacDonald et al. 2002; MacDonald et al. 2003). MEP recordings are usually monitored with the use of needle electrodes which are placed to the muscle of interest. If the facial nerve motor function is monitored, the needles are typically placed at the orbicularis oris and the orbicularis oculi muscles (Liu et al. 2007). For monitoring the glossopharyngeal nerve (CN.IX), needles are inserted in the posterior pharyngeal wall and in the tongue for the hypoglossal nerve (see figure 7), (Sala et al. 2004). Special attention has to be given monitoring the glossopharyngeal nerve. It has baroreceptors measuring and adjusting the blood pressure. Disturbances to this nerve can therefore cause disarrangement of this autonomic system (Daube 1991). Depending on which side needs to be stimulated, limb muscles of the contralateral side are used as a control. For the arm, this is in most cases the extensor digitorum communis and abductor pollicis brevis muscle and for the leg it is usually the tibialis anterior and the abductor hallucis muscle (Sala et al. 2004). The control has the purpose to ensure that the muscle to be monitored is not stimulated extracranially (Acioly et al. 2010).

If for any reasons, the needles are not placed correctly into the plug-in position, a false or no response will be the result. Hence, it must be assured and double checked that the needles correspond with the right plug-in position.

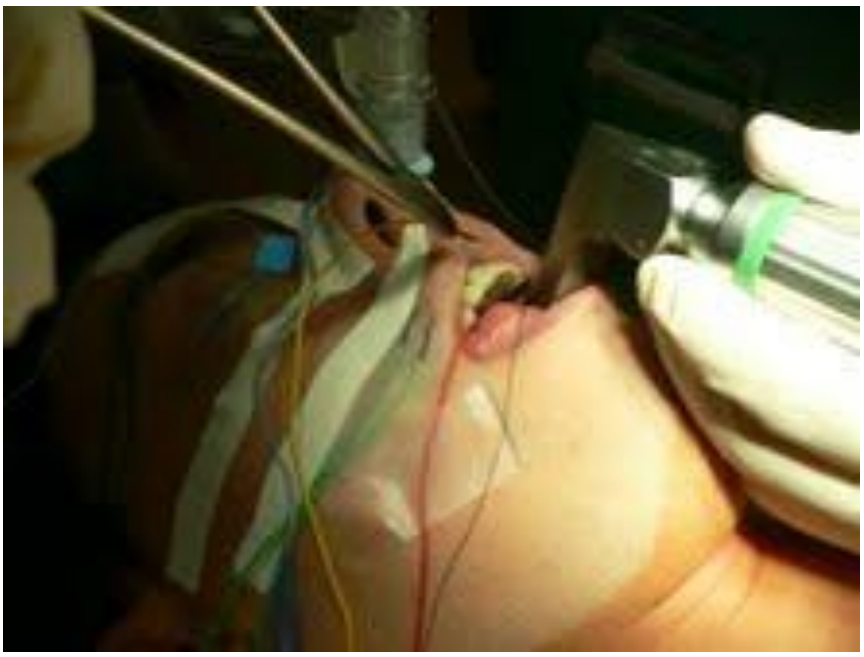


Figure 7
Surgical fixation of the needles in the posterior pharyngeal wall for monitoring CN.IX and in the tongue for CN.XII, courtesy of the Department of Neurosurgery Tübingen.

Anesthetics used during neurosurgery have an influence on MEPs more than on SEPs. SEPs are more stable in an patient undergoing anesthesia. To overcome the higher threshold needed to evoke MEPs under anesthesia, trains of higher voltages can be applied. This however increases the risk of stimulating the cranial nerves peripherally rather than centrally. Isoflurane for example greatly reduces or even abolishes MEPs (Calancie et al. 1991; Kalkman et al. 1991; Schmid et al. 1992; Watt et al. 1996). Barbiturates are also responsible for deterioration of MEPs (Losasso et al. 1991; Schmid et al. 1992) as well as propofol (Peterson et al. 1991; Schmid et al. 1992) and midazolam (Schönle et al. 1989; Kalkman et al. 1992; Schmid et al. 1992). Etomidate are responsible for a decrease in the initial amplitude but shortly afterwards the amplitude returns back to baseline (Kalkman et al. 1992). Fentanyl and ketamine are shown to have no effect on MEPs (Kalkman et al. 1992; Schmid et al. 1992). Anasthetic drugs used in patients that have been monitored in this study are Disoprivan® (Propofol), Ultiva® (Remifentanyl) and Sufentanyl. Propofol reduces the amplitude of MEPs when a multipulse stimulation at a constant

intensity is used. Yet, this affect is only moderate in the clinical range and depends on its dose. Only when Propofol is overdosed MEPs interpretation becomes unfeasible. The latency of MEPs however is not affected by Propofol when its concentration does not exceed common doses (Nathan et al. 2003). In our neuromonitoring, sufentanyl, which is structurally related to Fentanyl, has shown to have a strong influence on MEPs as a double bolus of 0.01 mg/kg body weight decreases MEPs to almost zero. For a meaningful interpretation of intraoperative MEPs, a continuous concentration of Ultiva® is recommended. Worth mentioning and important to take into account is the fact that an anesthetic overhang at the end of the operation leads to increased MEPs. It is therefore recommend monitoring MEPs while this overhang is decreasing but the patient is not yet waking up.

1.4 Aim of study

Recently, the success rate of using facial motor evoked potential (FMEP) and its usefulness in predicting facial nerve outcome has been reported. Hereby the MEPs of orbicularis oculi and oris muscles for facial nerve function monitoring were analyzed (Acioly 2010). This study indicated that stable intraoperative FMEPs can predict a good postoperative outcome of facial function (Acioly et al. 2010).

In this study, we investigated the predictive value of changes in the intraoperative acquired MEPs the caudal cranial nerves, CN.IX (glossopharyngeal nerve) and CN.XII (hypoglossal nerve) for the operative outcome. The main focus here was to correlate the changes of the MEPs to postoperative nerve function such as dysphagia, impairment of the gag reflex and uvula deviation, which are symptoms of glossopharyngeal palsy and dysgesia and tongue deviation, which are symptoms of hypoglossal palsy. It is important to notice that monitoring of these nerves has not been investigated in details thus far. For this reason there is no standardized protocol for MEP neuromonitoring of the CNNs available so far. Furthermore, there are also no

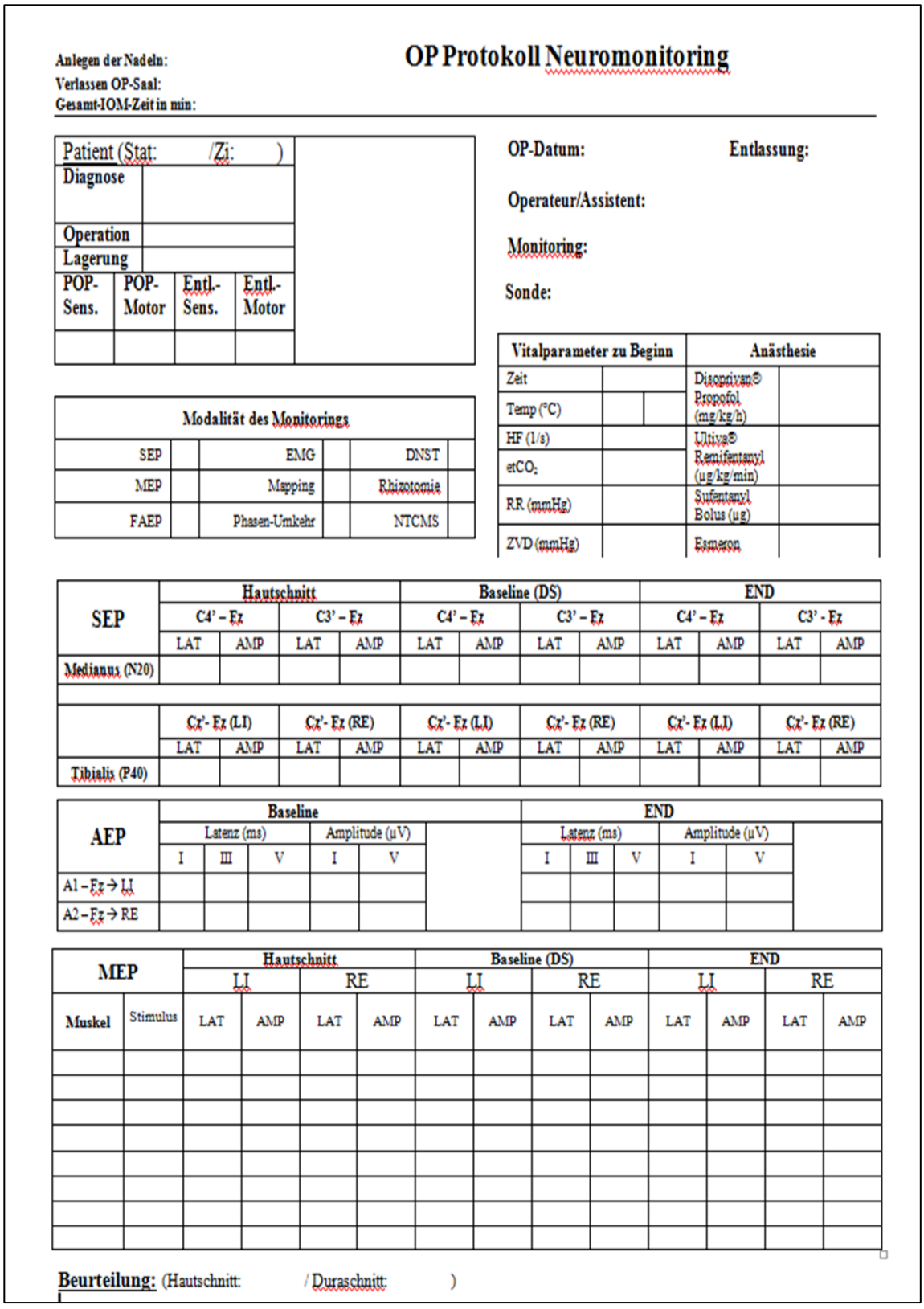
reference values available to compare our results to. This fact created a number of challenges for us which are discussed in detail below.

2. Materials and methods

2.1. Patients

MEPs from the CNNs including the glossopharyngeal (CN.IX) and hypoglossal nerve (CN.XII) were recorded intraoperatively from 63 consecutive patients undergoing brain surgery between April 2007 and April 2010 at the Department of Neurosurgery at the Eberhard Karls University Hospital in Tübingen, Germany. The data that has been collected included the patients age, gender, diagnosis, positioning during surgery, MEP baseline, final and final- to- baseline MEP ratio of the hypoglossal (CN.IX) and glossopharyngeal (CN.XII) nerve and the contralateral abductor pollicis brevis muscle of the hand as a control as well as the pre- and postoperative nerve function of nerve CN.IX and CN.XII. The IOM data was recorded on a special form-sheet (see figure 8).

The diagnoses included astrocytomas stages 1 and 2, acoustic neurinomas stages T3 to T4b (Samii et al 1992), meningeomeas, cavernomas, epidermoid tumors and neurinomas, all together large tumors extending to the CCNs. Special attention of type, size and location of the tumors has not been given in this study. The collected data including patient age, gender, bedding, side, postoperative glossopharyngeal and hypoglossal nerve function and final-to-baseline MEP ratios are illustrated in table 3.



Anlegen der Nadeln:
Verlassen OP-Saal:
Gesamt-IOM-Zeit in min:

OP Protokoll Neuromonitoring

Patient (Stat: /Zi:)			
Diagnose			
Operation			
Lagerung			
POP-Sens.	POP-Motor	Entl.-Sens.	Entl.-Motor

OP-Datum: Entlassung:

Operateur/Assistent:

Monitoring:

Sonde:

Vitalparameter zu Beginn			Anästhesie	
Zeit			Diaprivan® Propofol (mg/kg/h)	
Temp (°C)				
HF (1/s)			Ultiva® Remifentanyl (µg/kg/min)	
$etCO_2$				
RR (mmHg)			Sufentanyl Bolus (µg)	
ZVD (mmHg)			Esmeron	

Modalität des Monitorings					
SEP		EMG		DNST	
MEP		Mapping		Rhizotomie	
FAEP		Phasen-Umkehr		NTCMS	

SEP	Hautschnitt				Baseline (DS)				END			
	C4' – Fz		C3' – Fz		C4' – Fz		C3' – Fz		C4' – Fz		C3' - Fz	
	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP
Medianus (N20)												
	Cz'- Fz (LI)		Cz'- Fz (RE)		Cz'- Fz (LI)		Cz'- Fz (RE)		Cz'- Fz (LI)		Cz'- Fz (RE)	
	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP
Tibialis (P40)												

AEP	Baseline						END					
	Latenz (ms)			Amplitude (µV)			Latenz (ms)			Amplitude (µV)		
	I	III	V	I	V		I	III	V	I	V	
A1 – Fz → LI												
A2 – Fz → RE												

MEP		Hautschnitt				Baseline (DS)				END			
		LI		RE		LI		RE		LI		RE	
Muskel	Stimulus	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP	LAT	AMP

Beurteilung: (Hautschnitt: / Duraschnitt:)

Figure 8
Special self-developed form-sheet of the Neurosurgical department that is filled out during the operation, courtesy of the Department of Neurosurgery, Tübingen.

Table 3: Patients' characteristics

	n	Mean	SD
Gender(female/ male)	38 / 25	--	--
Age (years)	63	49.16	15.29
Postoperative nerve function			
Dysphagia (yes/no)	15/41	--	--
Dysgeusia (yes/no)	7/27	--	--
Gag reflex (extinct/present)	7/47	--	--
Uvula deviation (yes/no)	8/46	--	--
Tongue deviation(yes/no)	7/47	--	--
Glossopharyngeus			
Latency (ms)			
Baseline	55	17.77	4.57
Final	56	16.77	2.99
Final-to baseline ratio	51	0.98	0.17
Amplitude (μV)			
Baseline	54	115.72	132.68
Final	55	204.85	246.32
Final-to baseline ratio	49	2.53	2.81
Amplitude width (ms)			
Baseline	51	12.77	4.63
Final	52	11.95	4.32
Final-to baseline ratio	48	1.09	0.61
Hypoglossus			
Latency (ms)			
Baseline	59	1.25	4.52
Final	59	2.19	2.05
Final-to baseline ratio	58	0.99	0.17
Amplitude (μV)			
Baseline	59	1.25	4.47
Final	59	2.19	13.62
Final-to baseline ratio	59	18.65	129.98
Amplitude width (ms)			
Baseline	55	11.61	3.47
Final	56	11.98	3.18
Final-to baseline ratio	55	1.08	0.34
Hand			
Latency (ms)			
Baseline	63	23.07	2.17
Final	61	22.04	1.94
Amplitude (μV)			
Baseline	63	1331.12	927.72
Final	61	1203.6	668.88

(n=number, SD= Standard deviation)

2.2. MEP Protocol

To monitor glossopharyngeal (CN.IX) and hypoglossal nerve (CN.XII) motor function during surgery using transcranial electrocortical stimulation, corkscrew electrodes were inserted into the scalp of the patients whose heads were fixated the Mayfield® skull clamp. Electrodes were placed at position CZ and C3 for stimulation of the left-side or at position C4 for right-side stimulation. Needles were inserted in the posterior pharyngeal wall for monitoring the glossopharyngeal nerve (CN.IX) and in the posterior pharyngeal wall and in the tongue for the hypoglossal nerve (CN.XII). The contralateral abductor pollicis brevis muscle of the hand was used as a control to make sure that the glossopharyngeal (CN.IX) and hypoglossal nerve (CN.XII) were not stimulated extracranially. To stimulate these nerves, a train of 4-5 pulses with 5 being the standard ranging from 120 to 500 V have been applied. The duration of the pulses were 50 μs and an interstimulus interval (ISI) of 2 ms. The latency in milliseconds, the duration of the amplitude in micro- or milliseconds and the amplitude in μV have been recorded at the beginning of the operation before skin incision called baseline and at the end of the operation called END as shown below (table 4).

How often and at what time it is stimulated, mainly depends on the type of the operation and on the surgeon. When operating close to the motor cortex, a higher frequency of stimulations is recommended to have a continuous control of the nerve function. If only a global monitoring is necessary, stimulation can occur less frequently.

Table 4. Example recording

		C4-CZ Baseline C3-CZ				C4-CZ END C3-CZ			
MEP		**LEFT**		**RIGHT**		**LEFT**		**RIGHT**	
Muscle	**Stimulus**	**LAT (ms)**	**AMP (µV)**	**LAT (ms)**	**AMP (µV)**	**LAT (ms)**	**AMP (µV)**	**LAT (ms)**	**AMP (µV)**
Oculi	5P	17.6	45.1	19.8	36.5	17.9	490	19.4	41.6
Oris	C3-CZ	16.8	199	16.1	171	16.8	110	17.4	29.7
Glosso	C4-CZ	19.6	10.9	19.6	24.9	19.3	32.2	19.0	37.9
Hypo	272V	14.3	780	12.9	1160	14.3	1170	13.1	1600
Hand	296V	22.6	135	23.6	174	22.1	193	24.8	0.85
Foot	5P	37.1	67.3	39.8	153	41.0	42.7	39.4	52.6

Example recording of a patient showing the placement of the electrodes (C3/C4-CZ) and the responses of the stimulated nerves with the number of trains (P) and voltage applied with the resulting latency (LAT) in ms and amplitude (AMP) in µV at the beginning (Baseline) and the end (END) of the operation.

These parameters were monitored during the entire operation (see figure 9). By stimulation of the corresponding muscles, intraoperative changes in the MEPs could have been detected immediately and the surgeon could adjust the strategy. In this present work, we evaluated the *Baseline, END (or final) and* amplitude width data hoping to draw a conclusion to how the changes in the MEPs affected the postoperative outcome in patient´s cranial nerve function.

Focus of this study was the amplitude in µV and the latency in ms represented by a sinusoidal curve which is illustrated below in figure 10.

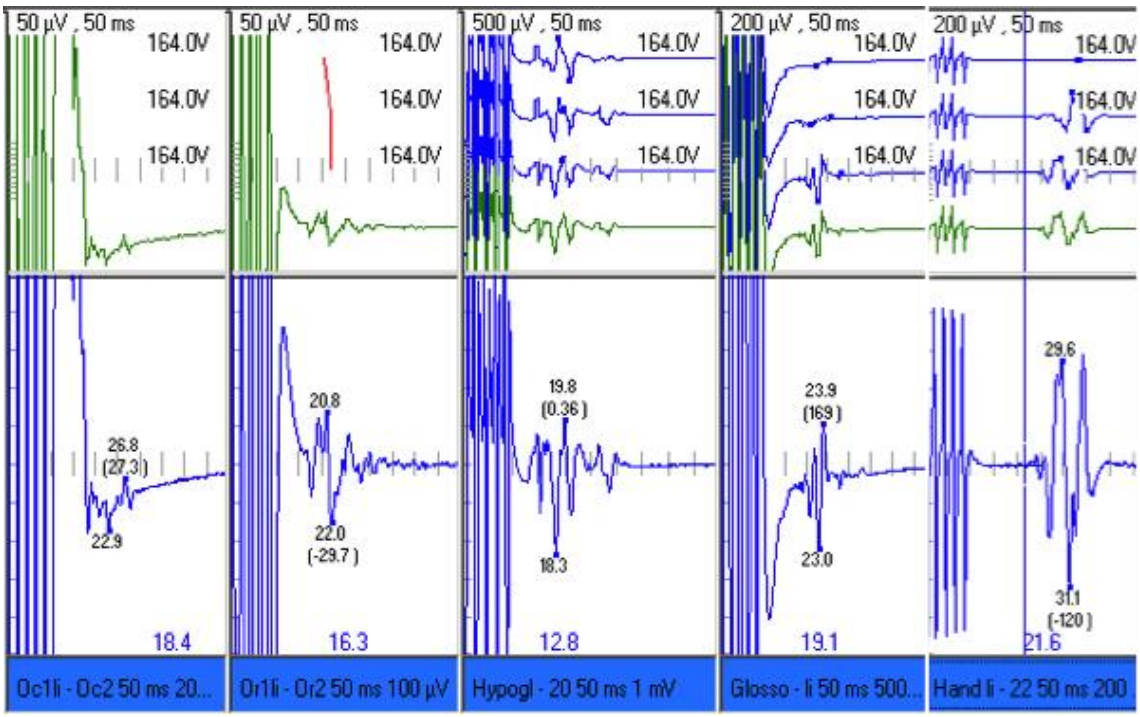


Figure 9
Screenshot from the Endeavor Software of an intraoperative live recording of MEP of the facial, glossopharyngeal and hypoglossal nerve and hand as a control with the amplitude in µV and the latency in ms. The green amplitude is the first one responding to the train pulse, the blue amplitudes the following. The number 164.0V state the intensity of a single train pulse. Courtesy of the Department of Neurosurgery Tuebingen.

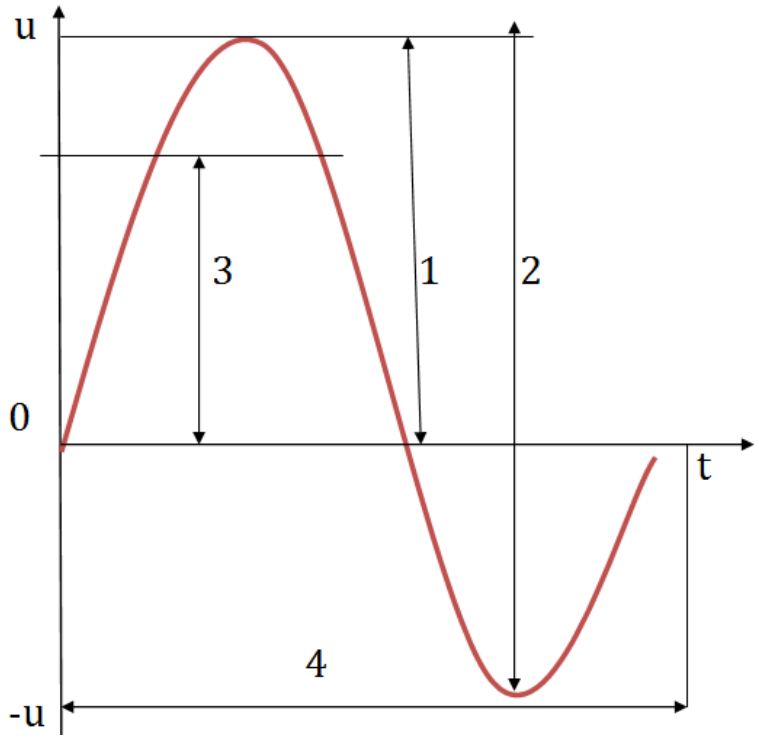


Figure 10: A sinusoidal curve:

1. Peak-amplitude: The peak-amplitude (u) is the maximum absolute value of the signal measured over time (t) that swings below or above zero.
2. Peak-to-peak amplitude: The peak-to-peak amplitude is the difference between the highest amplitude value (peak) and lowest amplitude value (trough).
3. Root mean square (RMS) amplitude: The RMS is the squared median of a physical value and often used in electrical engineering, yet not of importance to this study.
4. Wave-period: The wave-period or latency is the duration of the amplitude.

(figure was self-designed based on www.wikipedia.org)

2.3 Statistical analysis

The statistical analysis was performed with SPSS 19.0 (SPSS, Inc., Chicago, IL). Nonparametric Spearman correlation coefficients were used to evaluate the correlation between MEP final and ratio values and postoperative nerve function outcome. A one-sided p value of <0.05 was considered statistically significant. Odds-ratio and relative risks were calculated for all significant correlations. For the cross tabulations, cut-off values at which there is an increase of risk in postoperative nerve function damage were calculated according the MEP's median. The correlation of the amplitudes with its final-to-baseline ratio values and the latency or duration of the amplitude were aim of the study.

3. Results

3.1. Glossopharyngeal nerve

We found a significant correlation between the amplitude (µV) of the final-to-baseline MEP ratio and uvula deviation (p=0.028; see table 5) and the amplitude duration (ms) of the final MEP and gag reflex function (p=0.027, see table 5), in the way that the higher the MEP (final and ratio) and the longer the MEP END or final duration, the better the postoperative nerve function (see figure 11 and 12)

The analyses of the risk estimate revealed that patients with a final-to-baseline MEP ratio of the glossopharyngeal amplitude ≤ 1.47 V have a 3.4 times increased risk to develop a uvula deviation (see table 6 and 7).

Patients with a final MEP of the glossopharyngeal width ≤11.6 ms have a 3.6 times increased risk for their gag reflex to become extinct (see table 8 and table 9).

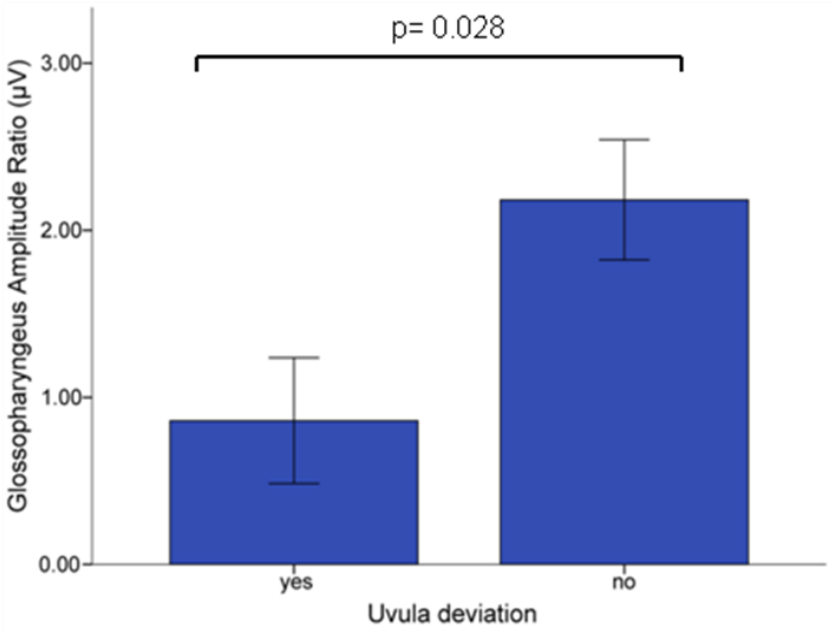


Figure 11
Relationship between the MEP ratio of the glossopharyngeal nerve and postoperative uvula function. The plot shows the mean amplitude (µV) of the final-to-baseline MEP ratio (±SD) in patients with and without uvula deviation revealing that the higher the MEP ratio the better postoperative uvula function.

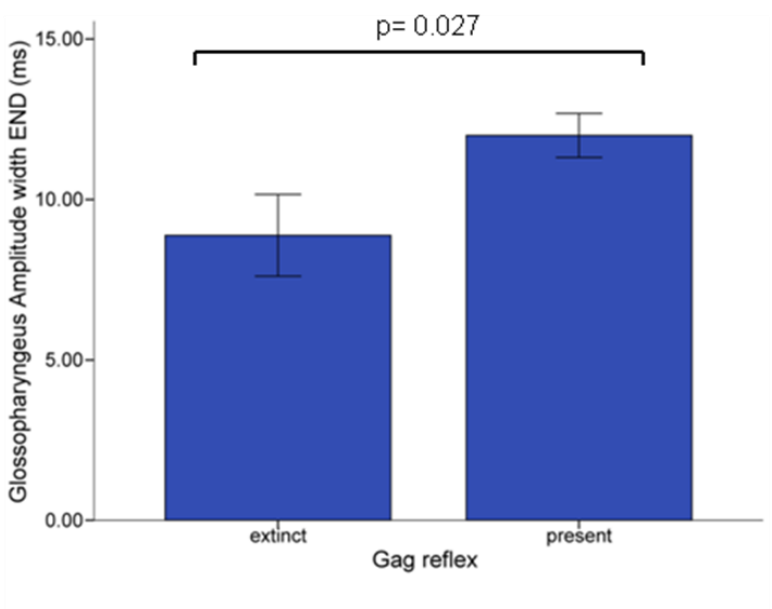


Figure 12.
Relationship between the final MEP of the glossopharyngeal nerve and postoperative gag reflex. The plot shows the mean amplitude duration (ms) of the final MEP (±SD) in patients with and without gag reflex, revealing that the longer the final MEP duration (width), the better the postoperative gag reflex function.

Table 5. Glossopharyngeal MEPs and correlation with post-OP outcome

	Uvula deviation Post-OP (n=42)	**Gag reflex Post-OP (n=42)**
Glossopharyngeal final-to-basline ratio AMP (µV)	r= 0.298; p= 0.028 (1-tailed) p=0.056 (2-tailed)	n.s.
Glossopharyngeal final amplitude width (ms)	n.s	r= 0.3; p=0.027 (1-tailed) p=0.053 (2-tailed)

n.s= not significant

Table 6. Cross tabulation: Glossopharyngeal ratio AMP (µV)* Uvula deviation

		Uvula deviation Post-OP		**Total**
		yes	**no**	
Glossopharyngeal ratio AMP (µV)	**≤ 1.47**	5	20	25
	> 1.47	1	16	17
Total		6	36	42

Table 7. Risk estimate of Glossopharyngeal ratio AMP (µV)

n=42			**95% Confidence interval**	
			Lower	Upper
Odds Ratio		4.00	0.37	33.7
Risk estimate	**For cohort uvula deviation**	3.4	0.39	24.0
	For cohort no uvula deviation	0.8	0.68	1.1

Table 8. Cross tabulation: Glossopharyngeal final AMP width (ms)* gag reflex

		Gag reflex Post-OP		Total
		Extinct	Present	
Glossopharyngeal END AMP width (ms)	**≤ 11.6**	4	18	22
	> 11.6	1	19	20
Total		5	37	42

Table 9. Risk estimate of Glossopharyngeal final AMP width (ms)

n=42			**95% Confidence interval**	
			Lower	Upper
Odds Ratio		4.22	0.43	41.45
Risk estimate	**For cohort gag reflex extinct**	3.6	0.44	29.8
	For cohort gag reflex present	0.86	0.69	1.0

3.2 Hypoglossal nerve

We found a significant correlation between the amplitude width (ms) of the final-to-baseline MEP ratio and swallowing function (p=0.049, table 10), in the way that the higher the MEP ratio the better the postoperative nerve function (Figure 13). The analysis of the risk estimate revealed that patients with a final-to-baseline MEP ratio of the Hypoglossal amplitude width ≤ 1.03 ms have a 1.5 times increased risk to develop dysphagia (Table 11 and Table 12). Additionally, we found a statistical trend between the amplitude width (ms) of the final-to-baseline MEP ratio and tongue function (p=0.07), indicating a possible negative association between final-to-baseline MEP ratio of the Hypoglossal amplitude width ≤ 1.03 ms and tongue deviation (Table 10).

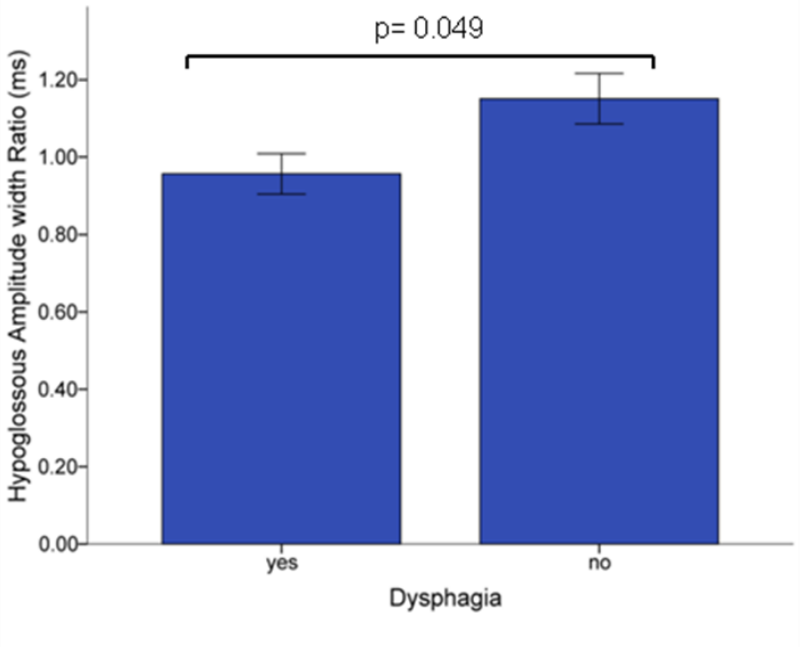


Figure 6

Relationship between the MEP ratio of the hypoglossal nerve and postoperative swallowing function. The plot shows the mean amplitude width (ms) of the final-to-baseline MEP ratio (±SD) in patients with and without dysphagia, revealing that the higher the MEP ratio the better postoperative swallowing function due to the absence of tongue deviation.

Table 10: Hypoglossal MEP and correlation with post-OP outcome

	Dysphagia Post-OP (n=49)	**Tongue deviation Post-OP (n=42)**
Hypoglossal ratio AMP width (ms)	r= 0.239; p= 0.049 (1-tailed)	r= 0.217; p= 0.074 (1-tailed)

Table 11: Cross tabulation: Hypoglossal ratio AMP width (ms)* dysphagia

		Dysphagia Post-OP		**Total**
		yes	**no**	
Hypoglossal ratio AMP width (ms)	**≤ 1.03**	8	17	25
	>1.03	5	19	24
Total		13	36	49

Table 12. Risk estimate of Hypoglossal ratio AMP width (ms)

n=49			**95% Confidence interval**	
			Lower	Upper
Odds Ratio		1.78	0.49	6.52
Risk estimate	**For cohort dysphagia**	1.53	0.58	4.03
	For cohort no dysphagia	0.85	0.61	1.2

4. Discussion

4.1. Protocol of glossopharyngeal and hypoglossal nerve monitoring

Neuromonitoring of facial nerve MEPs (FMEPs) have become a standardized method for monitoring nerve function intraoperatively. Based on the MEPs, it is possible to predict postoperative nerve function of the facial nerve (Dong CC et al. 2005; Akagami et al. 2005; Fukuda et al. 2008). However, neuromonitoring of the CNNs IX. and XII. is relatively new and only few literature is available, due to the following reasons. First, stimulation of the CN.IX and CN.XII nerves is more complicated than of the facial nerve, because electrodes have to be inserted inside the oral cavity into the appropriate muscles. Accessing the tongue and especially the posterior pharyngeal wall intraoperatively is more difficult in an intubated patient than accessing the orbicularis oculi and oris muscles. For the CN.IX, another problem could arise because it contains baroreceptors. This potentially can lead to distress of the autonomic nerve system when stimulated (Daube et al. 1991), which however was not observed in our operating room. Second, the lack of a standardized protocol and parameters makes the field of glossopharyngeal and hypoglossal nerve monitoring a pioneer work, in which these parameters have be established and standardized first. This work is an attempt to do just that and thereby further investigate the wide possibilities in the area of neuromonitoring in the operating room. Finally, postoperative changes in nerve function of CN. IX and CN.XII nerve lack a classification as it has been established for the facial nerve. The House- Brackmann (HB) classification clearly describes six different conditions of facial nerve function indicating the severity of the facial nerve impairment:
Such a classification however does not exist for other caudal nerves such as CCNs IX and XII. Therefore it is quite difficult to determine the level of dysfunction and what impairment will be classified as being mild, strong and severe and what implications this has on the patient’s disability. Since no such classification exists for CN.IX and CN.XII and its establishment would go beyond the scope of this work, we only state whether a palsy of the nerve is

absent or present without making further refinements. We do not yet know at what level of a CCN dysfunction a deterioration of the patient´s ability to swallow, taste and use his or her tongue will begin and how these values will correlate with one another. Further studies focusing on the postoperative nerve function and its classification will have to be conducted.

Since neuromonitoring of CN.IX and CN.XII nerve lacks an already existing standardized protocol, we geared towards the better researched neuromonitoring of FMEPs as described in Acioly`s work „transcranial electrocortical stimulation to monitor the facial nerve motor function during cerebellopontine angle surgery“ (Acioly 2009). As for the facial nerve monitoring, hemispheric electrode montage over C4 and CZ TES were used to stimulate CN.IX and CN.XII nerve, which produces the best nerve responses by minimizing the likelihood of stimulating the contralateral nerve muscle extracranially (Dong et al. 2005). Extracranial stimulation can be ruled out by the absence of the contralateral CN.IX and CN.XII. MEP responses to a single pulse TES and longer latencies (Akagami et al. 2005). The multi-pulse technique with a train of 5 stimuli and pulse duration of 0.5 ms and an ISI of 4 ms has proved itself to be the best stimulation parameters for the abductor pollicis brevis and tibialis posterior muscle by providing the lowest motor thresholds (Szelenyi et al. 2007). An ISI of 4 ms guaranties the entire recovery of each continuing D wave regardless of the intensity of the TES (Deletis et al. 2002; Szelenyi et al. 2007). It has been shown however that there is no statistical significance when comparing an ISI of 4 ms with an ISI of 2 ms (24 in acioly). Hence, an ISI of 2 to 4 can be helpful in accomplishing a complete recovery for CN.IX and CN.XII MEP monitoring (Acioly 2009).

Under general anesthesia, a single-pulse TES is insufficient to generate a muscle response (Sala et al. 2007; Chen et al. 2007). To overcome this suppression, a multi-pulse TES is necessary. It is believed that multiple pulses summate at cortical sites until the influence of anesthesia is overcome (Haghighi 2002). How many pulses should be used is not defined neither for facial MEP monitoring, where pulses as low as 1 pulse (Wilkinson et al. 2005) are described up to a train of 5 pulses, nor for CN.IX and CN.XII MEP

monitoring. Previous FMEP studies have stated however that a train of 3 to 5 pulses provide the best results (Dong et al. 2005; Akagami et al. 2005; Fukuda et al. 2008; Zhou et al. 2001), which is in accordance to what we have demonstrated in our CN.IX and CN.XII monitoring. We suggest that the number of trains ought to be adjustable rather than fixed, since we have seen a relatively significant change in muscle responses by a difference in sometimes only one additional pulse. With 3 to 5 pulses being the average number, it should not be precluded to use a train of 6 or even 7 pulses when lower stimulation stays unsuccessful. Yet caution is called for using too many pulses since excessive electrical stimulation could result in thermal injury of the brain and scalp (MacDonald 2006).

4.2 Recommended reference values

In order to be able to have a quick overview of the reference values we recommend as a result of this study, we designed a table including these values that can be easily used during an operation as a reference to minimize or even prevent nerve damage:

Table 13. Recommended reference values

Nerve	Entity	Recommended reference value	Risk of impairment at deviation
Glossopharyngeal Nerve (N.IX)	Final-to-baseline MEP ratio	> 1.47 V	Risk of uvula deviation at ≤ 1.47 V
Glossopharyngeal Nerve (N.IX)	Final MEP width	> 11.6 ms	Risk of gag reflex extinction at ≤ 11.6 ms
Hypoglossal Nerve (N.XII)	Amplitude width of the final-to-baseline MEP ratio	> 1.03 ms	Risk of dysphagia at ≤ 1.03 ms

4.3 Intraoperative monitoring and postoperative nerve outcome

Various entities can be responsible for pathological reduction of the MEP amplitude such as corticospinal tract injury, trauma of root or peripheral nerves, ischemia or other nerve irritations (MacDonald 2006). Various factors could be interfering with neuromonitoring during surgery: Anesthesia, stimulation errors, edema of the scalp, neuromuscular blockade and intracranial air that can build up especially in patients who are operated in the semi sitting position (MacDonald 2006; Akagami et al. 2005; Zhou et al. 2001; Wiedemayer et al. 2002). MEP reduction or complete loss has proven to be the only trustworthy and generally accepted warning sign in neuromonitoring (MacDonald 2006), which is associated with postoperative nerve palsy (Sala et al. 2007; Dong et al. 2005). Our results concur with these previous findings, as we have also shown that the mean amplitude (μV) of the final-to-baseline MEP ratio of the glossopharyngeal nerve correlates with the postoperative uvula nerve function, such that the higher the MEP ratio of final-to-baseline the lower the chance of having postoperative uvula deviation (see table 13 recommended reference values). Our cut-off value for the final-to-baseline ratio was 1.47 μV. If the amplitude falls below 1.47 μV, patients have a 3.4 times increased risk of developing a uvula deviation. Therefore, surgeons should make a change in their intraoperative strategy or dissection technique, if an MEP reduction is seen and the MEP-ratio has dropped to this value. As for other cranial nerves we have observed that frequently it is helpful to stop the dissection for a short while giving the nerve time to recover. However, if the MEP does not recover after giving the nerve time to recover from the surgical manipulation the injury mechanism could potentially be irreversible, as neuromonitoring most of the time only indicates rather than prevents nerve injuries (MacDonald 2004). There is a medical technician present in the operating room, monitoring the MEPs during the whole operation and advising the surgeon if the MEPs are declining. Dong et al. stated that recovery of MEP after intraoperative deterioration is rarely seen in FMEP monitoring (Dong et al. 2005), as it is observed during operation of the aorta in orthopedic or spinal tumor surgery (MacDonald 2006;

Morota et al. 1997). For this reason, we suggest that the same is true for monitoring of other caudal nerves such as CN.IX and CN.XII. In this respect, there is a general concern that the decrease of MEP is not sufficient enough and might be too sensitive (MacDonals 2006). A further finding of the present study indicates that the glossopharyngeal END amplitude and not just the final-to-baseline ratio have a significant influence on postoperative nerve function. We found that the glossopharyngeal END amplitude duration correlates with the postoperative function of the gag reflex. Patients with a final MEP width of ≤11.6 ms had a 3.6 times increased risk for their gag reflex to become extinct. Yet, we have to act with extreme caution to interpret these results. Only the Final MEP values and not the ratio have shown a correlation with the MEP duration in the past. Furthermore, there are individual differences in MEP responses varying from patient to patient due to various alpha motor neuron excitability (MacDonals 2006), which makes it nearly impossible to propose a general cut-off-value at which predictions of the postoperative nerve function can be made. If we had the Final-to-Baseline values showing the same correlation, we could make such a prediction. Further studies with this attempt have to be conducted to explore the significance of the MEP width with respect to the postoperative nerve outcome of the glossopharyngeal nerve.

In this present study, we also revealed that the MEP duration (i.e. MEP END width (ms)) of the glossopharyngeal nerve correlates with the nerve deficit postoperatively, leading to an increased risk for gag reflex extinction. This can result in dysphagia in affected patients which means difficulty swallowing and laryngeal aspiration of food or fluid, also saliva, entering the larynx with the possibility of causing pneumonia. So far, only MEP amplitude reduction and or loss have been widely accepted warning signs for possible postoperative nerve palsy (Macdonald 2006). Yet persistent MEP loss that cannot be explained by other confounding factors such as anesthesia, ischemia or nerve decompression cannot predict complete or permanent paralysis (Quinones-Hinojosa et al. 2005; Deletis et al. 2002; MacDonald et al. 2002; Calancie et al. 1998; Calancie et al. 2001; Kothbauer 2002). For this reason, it has to be

further investigated how changes in MEPs affect the postoperative outcome in nerve functioning. One such attempt has been done by Acioly 2011. Here the FMEP waveform complexity correlated significantly with the postoperative facial function such as facial paresis, which occurred in all patients in whom waveform deterioration was documented on oris FMEP (Acioly et al. 2011). Due to the observations made in this study, the MEP width could establish itself to be another predicting factor of postoperative nerve palsy. We determined the cut-off value for the MEP END width to be 11.6 ms. If the duration falls below this value, patients have to expect a 3.4 times increased risk to develop a gag reflex extinction. However, these results have to be interpreted with caution, since we are the first in the field of neuromonitoring research to describe a relationship between MEP duration and postoperative nerve function. Therefore no reference values exist for the MEP width.

In the field of thyroid surgery, Lorenz et al. (2010) made such an attempt to establish reference ranges, while investigating normal „quantitative parameters of intraoperative neuromonitoring (IONM).” This study highlighted the importance of establishing reference range values in intraoperative neuromonitoring as a prerequisite for interpretation of results and intraoperative findings (Lorenz et al. 2010). Earlier studies found a duration of the laryngeal muscle of 4 to 5 ms to be normal (Satoh 1978). Lorenz et al. further investigated median durations for the left and right vagal and recurrent laryngeal nerve and showed that there are differences between gender, but hardly differences between the sides of the particular muscle, age and indication (Lorenz et al. 2010). These results imply that medial values must be established in order to interpret possible deviations in amplitude width. Furthermore, it is important to note that falling below or exceeding such defined values may result in impairment or even loss of the nerve’s function due to the underlying physiology. In our case this means that if the duration of an MEP is too short, the action potential could not take place in its proper amount resulting in nerve function deficiency. The same is true when the MEP duration is too long. In this case, the refractory-time was prolonged and the muscle could not be elicited quickly again also resulting in impairment of the muscle function. Hence, there

are median durations (width) of MEP signals serving as reference range values in which a proper muscle function is given. Further studies have to be conducted in order to define such values for the glossopharyngeal and hypoglossal nerve.

A further interesting finding of the present study is that also the hypoglossal nerve showed a significant relationship between the Final-to-Baseline MEP values and postoperative nerve function. We found a significant correlation between the amplitude width (ms) of the Final-to-baseline MEP ratio and swallowing function. The risk estimate revealed that patients with a final-to-baseline MEP ratio width ≤ 1.03 ms have a 1.5 times increased risk to develop dysphagia. Of interest, usually dysphagia is described to be a symptom of impairment when the motor innervation of the glossopharyngeal nerve is interrupted, so that the function of the stylopharyngeal muscle is decreased or absent (Özveren et al. 2003; Gillig et al. 2010). Physiologically, the hypoglossal nerve innervates the genioglossal muscle and the other muscles of the tongue with the exception of the palatoglossal muscle which is innervated by the glossopharyngeal nerve (Schünke et al. 2006). Unilateral irritation or damage of this nerve will cause paralysis of the genioglossal muscle on the same side, resulting in deviation of the tongue at protrusion to the affected side because of the genioglossal preponderance on the healthy side (Gillig et al. 2010). The neurophysiologic underpinnings make a valid interpretation of the correlation between hypoglossal MEP values and swallowing function challenging. We could argue, however that the swallowing act is also highly dependent on a proper functioning tongue. One could easily comprehend that a deviated tongue might be a disruptive factor when processing and swallowing food, even if the tongue does not directly interfere with the muscular involvement of swallowing. Nonetheless, the evaluation of postoperative nerve function was performed by patient's self-report using a subjective questionnaire with a simple "yes" or "no" answer. Therefore a patient might not be able to distinguish between problems of processing the food in the mouth and actually swallowing. Hence further studies are needed to specifically distinguish between processing and

swallowing food. For this purpose an x-ray analysis with Barium-swallowing agent could be used to make future results more objective.

Additionally, we found a statistical trend between the amplitude width (ms) of the final-to-baseline hypoglossal MEP ratio and tongue function ($p=0.07$), indicating a possible negative association between final-to-baseline MEP ratio of the hypoglossal amplitude width ≤ 1.03 ms and tongue deviation. Even though these results only show a statistical trend, they are of high clinical relevance. Firstly, the correlation includes the ratio of MEP values, thereby correcting for individual baseline measures. Secondly, there is a direct neurophysiologic relationship between the hypoglossal nerve and tongue innervation as already mentioned above. Therefore, further studies need to be conducted to obtain a larger sample size, which would also give us the opportunity to evaluate possible gender differences.

5. Summary

Objective: In this present study, we investigated the predictive value of changes in intraoperatively acquired motor evoked potentials (MEPs) of the caudal cranial nerves CN.IX (glossopharyngeal nerve) and CN.XII (hypoglossal nerve) for the operative outcome.

Methods: MEPs of the glossopharyngeal (CN.IX) and hypoglossal nerve (CN.XII) were recorded intraoperatively from 63 consecutive patients undergoing brain surgery. The collected data included the patient's age, gender, diagnosis, positioning during surgery, MEP baseline, final and final- to- baseline MEP ratio of CN.IX and CN.XII and the contralateral abductor pollicis brevis muscle of the hand as a control as well as the pre- and postoperative nerve function of CN.IX and CN.XII. We correlated the changes of the MEPs to postoperative nerve function such as dysphagia, impairment of the gag reflex, uvula deviation, and tongue deviation.

Results: For the glossopharyngeal nerve, we found a significant correlation between the amplitude (µV) of the final-to-baseline MEP ratio and uvula deviation ($p=0.028$) and the amplitude duration (ms) of the final MEP and gag reflex function ($p=0.027$). The analyses of the risk estimate revealed that patients with a final-to-baseline MEP ratio of the glossopharyngeal amplitude ≤ 1.47 V have a 3.4 times increased risk to develop a uvula deviation. Patients with a final MEP of the glossopharyngeal width ≤11.6 ms have a 3.6 times increased risk for their gag reflex to become extinct. For the hypoglossal nerve, we found a significant correlation between the amplitude width (ms) of the final-to-baseline MEP ratio and swallowing function ($p=0.049$). The analysis of the risk estimate revealed that patients with a final-to-baseline MEP ratio of the hypoglossal amplitude width ≤ 1.03 ms have a 1.5 times increased risk to develop dysphagia.

Conclusion: In conclusion, our study greatly contributed to the current knowledge of intraoperative MEPs as a predictor for postoperative nerve function. We were able to extent previous findings on MEP values of the facial nerve on postoperative nerve function to two further cranial nerves. We could

show a significant relationship between the MEP values of the glossopharyngeal nerve and postoperative function of the uvula and gag reflex. For the hypoglossal nerve, we were able to show a significant relationship between the MEP values and swallowing function. Furthermore, we observed a statistical trend for the correlation between the MEP values of the hypoglossal nerve and tongue deviation; further studies including a larger sample size could confirm this result. Finding reliable predictors for postoperative nerve function is of great importance to the overall quality of life for a patient undergoing brain surgery.

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7. Deutsche Zusammenfassung

Ziel der Arbeit: In dieser wissenschaftlichen Arbeit wollten wir herausfinden, wie sich vorhersehbare Veränderungen der Normwerte von motorisch evozierten Potentialen (MEPs) der kaudalen Hirnnerven N.IX (Nervus Glossopharyngeus) und N.XII (Nervus Hypoglossus) auf das zu erwartende postoperative Ergebnis der Funktion dieser auswirken.

Methoden: Die motorisch evozierten Potentiale (MEPs) der Hirnnerven IX. und XII. wurden intraoperativ von 63 konsekutiven Patienten, die sich einer Operation am Gehirn in der Neurochirurgischen Klinik der Universität Tübingen unterzogen, aufgezeichnet. Die erhobenen Daten beinhalteten das Alter der Patienten, das Geschlecht, die Diagnose, die Art Lagerung des Patienten während der Operation, die MEP-Baseline, die Final and Final-to-Baseline MEP Ratio des Nervus Glossopharyngeus (N.IX) und des Nervus Hypoglossus (N.XII) sowie des kontralaterale Musculus Abductor Pollicis Brevis der Hand als Kontrolle und darüber hinaus die Funktion der oben genannten Nerven prä- und postoperativ im Vergleich. Es wurden die Veränderungen der MEPs mit den möglichen postoperativen Funktionseinschränkungen wie Dysphagie, Beeinträchtigung des Schluckreflexes, Deviation der Uvula und der Zunge miteinander korreliert.

Ergebnisse: Für N.IX fanden wir eine signifikante Korrelation zwischen der Amplitude (µV) der Final- to- Baseline MEP Ratio zu einer Deviation der Uvula (p=0.028) sowie der Amplitudendauer (ms) der Final-MEP und der Funktion des Würgereflexes (p=0.027). Die Analyse der Risikoschätzung ergab, dass Patienten mit einer Final- to- Baseline MEP Ratio des N.XI von ≤1.47 V, eine 3,4- fache höhere Wahrscheinlichkeit haben, eine Uvuladeviation zu entwickeln. Patienten mit einer Final- MEP-Breite des N. IX von ≤ 11.6 ms haben ein 3,6-fach erhöhtes Risiko eine Erlöschung des Schluckreflexes zu erleiden. In Bezug auf N. XII fanden wir heraus, dass es eine signifikante Korrelation zwischen der Amplitudenbreite bzw.-dauer (ms) der Final- to Baseline MEP Ratio und der Schluckfunktion gibt (p= 0.049). Die Analyse der Risikoabschätzung ergab, dass Patienten mit einer Final-to-Baseline MEP Ratio der Amplitudenbreite des

N. XII von ≤1.03 ms ein um das 1,5- fache erhöhtes Risiko haben, eine Dysphagie zu entwickeln.

Fazit: Unsere Arbeit trug in sehr großem Ausmaß dazu bei, die bisherigen Erkenntnisse über intraoperative MEPs und deren Veränderungen während einer Operation als Vorhersagewert für die postoperative Nervenfunktion zu erweitern. Wir konnten bisherige Erkenntnisse, die aus dem Monitoring des Gesichtsnerves N facialis und der Beeinflussung auf das postoperative Ergebnis dieses Nervens hervorgingen, auf zwei weitere kraniale Nerven erweitern. Wir waren der Lage, einen signifikanten Zusammenhang zwischen den MEP- Werten des Nervus Glossopharyngeus (N. IX) und dessen postoperativen Funktionseinschränkung bezüglich der Uvulafunktion und des Schluckreflexes heraus zu arbeiten. In Bezug auf den Nervus Hypoglossus (N.XII) konnte ein signifikantes Verhältnis zwischen den MEP-Werten und der Schluckfunktion gezeigt werden. Darüber hinaus war es uns möglich, eine statistische Tendenz für die Korrelation zwischen MEP-Werten dieses Nerven und einer aufgetretenen postoperativen Zungendeviation herzustellen. Diese Resultate konnten durch weitere Studien bekräftigt werden. Es ist von großer klinischer Bedeutung, verlässliche Vorhersagewerte für die postoperative Funktion von Nerven zu entwickeln um somit einen positiven Einfluss auf die Lebensqualität der Patienten, die sich einer Gehirnoperation unterziehen, auszuüben.

8. Erklärung zum Eigenanteil

Eigenanteil

Marcel Kullmann

Diese Studie wurde von Herrn PD.Dr. Dr. med. G.C. Feigl und mir konzipiert und durchgeführt.

Die Datenerhebung wurde von Frau M. Liebsch, Herrn PD.Dr. Dr. med. G.C. Feigl und von mir durchgeführt. Im Anfangsstadium (die ersten 4 Wochen) wurde ich von Frau M .Liebsch und Herrn PD.Dr. Dr. med. G.C. Feigl unterstützt.

Die für diese Studie benötigten Patientendaten wurden von mir zusammengetragen. Noch notwendige klinische Untersuchungen zur postoperativen Beurteilung von Patienten wurden von mir selbständig durchgeführt.

Die intraoperativen Daten des Neuromonitorings wurden von Frau M. Liebsch aufgezeichnet und in die dafür vorgesehenen Datenblätter eingetragen.

Alle Ergebnisse der prä-und postoperativen Untersuchung der Patienten wurden von mir zusammengetragen und zusammen und mit Herrn PD.Dr. Dr. med. G.C. Feigl besprochen. Die Tabellen mit den Daten der Patienten und dem intraoperativen Monitoring wurden von mir mithilfe von Frau M.Liebsch erstellt.

Die Verfassung dieser Dissertation ist selbständig von mir durchgeführt worden. Wenn Material von dritten benutzt wurde, ist es dementsprechend im Literaturverzeichnis vermerkt.

Anteil der Koautoren

Frau Marina Liebsch

Sie war maßgeblich bei der Datenerhebung beteiligt und hat mich in das intraoperative Monitoring durch den Endeavor® Stimulator und dessen Programm eingeführt. Sie half mir ebenso bei der Interpretation dieser Daten.

Herr PD Dr.Dr.med. G.C.Feigl

Er war, zusammen mit mir, der Hauptverantwortliche in der Konzipierung, Planung und Durchführung dieser Studie. Er hat meine Arbeit betreut und bis zum Ende unterstützt.

Er hat die Publikation Korrektur gelesen.

9. Danksagung

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10. Lebenslauf

ANGABEN ZUR PERSON

Name	Marcel Kullmann
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SCHULBILDUNG

09/1998 – 06/2001	Mildred-Scheel-Gymnasium, Böblingen

STUDIUM

01/2003 – 07/2005	Studium der Biologie an der Lee University, Cleveland, TN, USA
10/2005 – 06/2012	Studium der Humanmedizin an der Universität Tübingen

ABSCHLUSS

06/2001	Allgemeine Hochschulreife
07/2005	Bachelor of Science (B.S.) in Biological Science
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01/10/01 – 01/10/02	Zivildienst Olgahospital Stuttgart
01/2003 – 07/2005	Wissenschaftliche Hilfskraft (Lee University, Cleveland, TN, USA)
05/2009 – 10/2011	Nachtwache häusliche Intensivpflege
02/2011 – 01/2012	Praktisches Jahr Universitätsklinikum Tübingen

<u>Wahlfach Neurochirurgie</u>
Ausgeführte Tätigkeiten:

- Aufnahme und Betreuung von neurochirurgischen Patienten
- Assistenzen bei neurochirurgischen Eingriffen
- Lumbalpunktionen und Anlegen von lumbalen Dauerdrainagen
- Teilnahme am neurochirurgischen Bereitschaftsdienst
- Teilnahme an Früh-und Mittagsbesprechungen sowie der interdisziplinären Tumorkonferenz

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12/2005 – 12/2007	Jugendleiter CVJM Nufringen
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PROMOTION

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BESONDERE KENNTNISSE

Sprachen	Englisch – fließend in Wort und Schrift
EDV	Sehr gute Kenntnisse in: MS-Office Brainlab 3.0