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Epilepsy Surgery Around Language Cortex

A study with indepth discussion of cortical stimulation mapping as a gold standard for detecting language cortex and a comparison of two different cortical mapping techniques to ensure postoperative language function and seizure control in this group of epilepsy surgery patients

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1 INTRODUCTION

Epilepsy surgery is any neurosurgical intervention, whose primary objective is to relieve medically intractable epilepsy [32]. Its aim is to reduce the number and intensity of seizures, minimize neurological morbidity and antiepileptic drug toxicity, and improve the patient's quality of life [46]. The main challenge of neurosurgery has always been to preserve maximal physiological, neuronal functions during the operation. This is even of more concern in epilepsy surgery, which is normally an elective surgery without any vital indications for resection of the epileptogenic zone.

The epileptogenic zone is a region of the cortex that can generate epileptic seizures. By definition, it is the "minimal area of cortex that must be resected to produce seizure freedom" [62].

The concept of the epileptogenic zone is a purely theoretical one. Some are of the opinion that its extent and location cannot be fully determined until the patient is actually made seizure free by resective surgery [14]. As the epileptogenic zone is often located near functionally significant cortical regions, a major concern is to preserve the higher cortical functions located there. Often it is their preservation that conflicts with the resection of the entire epileptogenic cortex in order to also achieve seizure freedom or reduce the seizure frequency after the operation. Those patients with a potential overlap of pathological alterations and neurophysiological function pose the frequently observed dilemma of a necessary tradeoff between seizure relief and permanent neuropsychological deficits [49], [51], [105].

One of the most significant higher cortical functions, of great importance for neurosurgeons and their patients, has always been and remains speech. According to Ojemann and colleagues, the location of language zones varies from one individual to the next. They are found in a wide area of the left lateral cortex, extending beyond the traditional anatomical limits of the Broca and Wernicke areas [84], [86], [88], [89], [120]. Thus, the location of the epileptogenic zone should more frequently be suspected to lie around the speech cortex. Extensive investigations must often be performed to clarify this.

Therefore epilepsy surgery close to the speech cortex has become a special, independent, and even more problematic subgroup of epilepsy surgery as regards the

successful surgical treatment of medically refractory seizure activity. To better explain the actual investigation and treatment options for this epilepsy surgery subgroup, we compiled an overview of our 10 years of experience with such patients in Munich University Hospital, Grosshadern. This overview comprises descriptions of current examinations used in our work, especially focusing on the invasive language mapping method, the current gold standard for language localization. It also includes our data on 22 left hemisphere epilepsy surgery patients whose epileptogenic zone was located around the speech cortex and who underwent operations in our clinic between 1997 and 2007. We also assess two different tactics of language mapping in those patients and appraise our indications for their use.

1.1 Statistical data on epilepsy and epilepsy surgery

Almost one percent of the world's populace suffer from epilepsy. There are approximately 50 million epilepsy patients in the whole world [54]. In Germany there are 6 to 7 epilepsy patients per 1 000 inhabitants, thus about 500 000 in the entire country. Every year 30 to 50 persons out of 100000 in Germany are diagnosed to have epilepsy, making all together about 30 000 new epilepsy cases each year [54].

According to data of the National Society for Epilepsy (United Kingdom), up to 70% of persons with epilepsy achieve full seizure freedom through medication [73].

Sixty percent of all epilepsies are of focal onset. In about 30% of focal epilepsy cases the seizures continue in spite of adequate antiepileptic (AED) medication or patient develops intolerable side effects [21]. If half of these patients were evaluated for epilepsy surgery and half of those evaluated would eventually benefit from epilepsy surgery, this means that about 4.5% of all patients with epilepsy (0.03% of the total population) could profit from epilepsy surgery [31]. There is currently a considerable backlog of 5,000 people waiting for surgery and between 300 to 500 new cases each year in the United Kingdom [73].

1.2 Criteria for including an epilepsy patient in pre-surgical investigation

On the basis of the above-mentioned definition of epilepsy surgery, a potential epilepsy surgery patient must have medically intractable epilepsy.

Although the definition of medical intractability differs among the various epilepsy centers, it mainly refers to patients whose seizures have continued despite adequate monotherapy in trials of at least two antiepileptic drugs (AEDs) with or without one trial of combination of two drugs [25], [121]. Medical intractability can also indicate that control of seizures is achieved, but the necessary medication is accompanied by intolerable side effects. Another criterion of medical intractability is that seizures are of sufficient severity and/or frequency to interfere with the patient's quality of life [33]. The impact of epileptic seizures on a patient's quality of life is assessed during several visits to an epileptologist.

2 Examination of surgery candidates

2.1 Introduction

If the above-mentioned criteria for medical intractability are met, the patient is included in our epilepsy surgery program and specific investigations are initiated to find the epileptogenic zone.

Per definition epilepsy surgery does not include normal surgical treatment of intracranial lesions, where the primary goal is to diagnose and possibly remove the pathological target, often a progressing tumor. In these patients, epileptic seizures are only one symptom of the lesion and are treated as part of the procedure [46]. However, a few tumor patients in whom the primary goal of operation was still to decrease an intolerable seizure frequency were also included in our epilepsy surgery program**.**

2.2 The goal and structure of pre-surgical investigations

The goal of pre-surgical evaluation is to precisely define the location and extent of the epileptogenic zone together with nearby functional zones using both non-invasive and invasive investigation methods.

Pre-operative investigations are of great significance in surgery of the dominant hemisphere. Their ability to precisely localize the functionally significant (dominant)

cortex and to specify its relation to the epileptogenic cortex (epileptogenic zone) determines the objectives and results of surgery as regards seizure control and post-surgical neuropsychological/ neurological morbidity.

Like many other epilepsy surgery centers, we begin with relatively less expensive and simple, non-invasive methods and progress to invasive investigations only if non-invasive investigations do not provide enough information to define an epileptogenic zone and determine its relation to functionally significant cortex. We then proceed with resective surgery.

2.3 Non-invasive investigations

Non-invasive or extra-cranial investigations are relatively safe methods that provide sufficient information in the majority of medically intractable epilepsy cases regarding the localization of the epileptogenic zone. They often allow us to proceed with resective surgery, without requiring more invasive (intracranial) examinations.

The following list gives short descriptions of non-invasive investigational methods used in the pre-surgical evaluation.

2.3.1 History and neurological examination

A detailed history of epileptic attacks and a neurological examination are essential to differentiate between epileptic and non-epileptic attacks. Both are also important for understanding the seizure semiology, which can indicate the possible seizure origin [65].

2.3.2 Ictal and interictal electroencephalographic recordings

The electroencephalogram (EEG) is a graphic recording of the brain's electrical activity. By registering epileptogenic potentials in some of the head-surface electrodes, we can narrow down the possible localization of an epileptogenic zone.
Hans Berger (1873 – 1941) first described an EEG in 1929. The following ten years witnessed revolutionary changes in the diagnosis of epilepsy, mainly due to the

implementation of EEG in clinical practice [11]. The first purely EEG-directed temporal lobe resection was performed in 1942 (Boston, USA) by Percival Bailey (1892 – 1973) and Frederick Gibbs (1903 – 1992) [111].

Although surface EEG recordings are less sensitive than invasive studies, their role has continued to evolve with the advent of high resolution volumetric magnetic resonance imaging (MRI) and other imaging techniques. They provide the best overview and therefore the most efficient way of defining the approximate localization of the epileptogenic zone [75], [107].

As already mentioned, the main limitation of extra-cranial EEG is its decreased sensitivity to cortical generators [40], [108]. Surface recordings also have significant difficulty "seeing" seizure onsets occurring in cortical regions located relatively deep with respect to the scalp (interhemispheric, mesial temporal, etc.). This lack of sensitivity implies that surface recordings only detect EEG seizures after they have spread to involve extensive areas of cortex. EEG also has a spatial limitation - it can only record electrical activity of the brain in an area of approximately 6 cm^2 [62].

For proper investigation both ictal and interictal EEG have to be recorded.
Interictal EEG gives evidence of the region of cortex that generates epileptiform discharges in the EEG (some authors also call this zone the epileptogenic focus [70]). Many patients have, however, multiple, bilateral, fronto-temporal, or poorly localizing interictal irritative abnormalities. The definition of interictal epileptiform discharge, which is highly subjective and varies among electroencephalographers, poses a major limitation of the method. Thus, ictal electroclinical documentation of seizures is considered the gold standard in non-invasive electroencephalography [46].

In about 80% of adult patients with temporal lobe epilepsy, extracranial ictal EEG video- monitoring, in combination with MRI, sufficiently localizes the seizure origin to permit a decision about surgery [34]. If the patient has a mesial temporal lobe epilepsy, then the percentage rises to 90% [46], [107].

2.3.3 Magnetic resonance imaging (MRI)

MRI is a sensitive and specific method for detecting various abnormalities of the brain structures. As mentioned earlier, if a structural lesion is found and its location is

consistent with clinical and EEG data on the epileptogenic zone, the removal of the lesion may be sufficient to control seizures [16]. Most epilepsy surgery centers use high-resolution MRI images on 1,5-Tesla systems with standardized protocols that consider seizure semiology and EEG findings to detect lesions [115]. The potential usefulness of 3-Tesla high-field MRI is currently being investigated [19]. When augmented by special techniques, image algorithms, and increasing experience, the sensitivity of MRI is now close to 98% [20], [80], [115].

In those patients in whom scalp EEG recordings provide insufficient information to proceed with resective surgery, an MRI may be helpful to make a hypothesis about the optimal site for intracranial electrode implantation [79].

2.3.4 Functional magnetic resonance imaging (fMRI)

Functional MRI (fMRI) can detect regional hemodynamic increases in response to simple, complex, or imagined finger movements, visual stimuli, and a variety of auditory stimuli, as well as language tasks. It can also provide preoperative localization information on the essential functional cortex [22]. Thus, fMRI is also one of the methods available for cortical or functional mapping (attributing a location to some particular functionally significant site in the cortex). It also continues to be studied as a non-invasive alternative to the Wada test for language lateralization [98].

The most important difference between the Wada test and fMRI is that fMRI is an activating test while the Wada test is a deactivating test; fMRI allows examination of patients without any time limitations and repeatedly, if necessary [46]. One drawback of fMRI for epilepsy surgery is the fact that it detects involved language cortex instead of essential language cortex [106]. Consequently, the cortical language areas visualized in fMRI are broader than those defined with direct cortical stimulation. This makes the resection of nearby epileptogenic cortex problematical, if intra-operative orientation is based only on this investigation.

2.3.5 Positron Emission Tomography (PET)

PET provides images of local blood flow, metabolism, and brain transmitter systems in vivo, using short-lived radioisotopes as markers. An epileptic focus appears interictally as low glucose metabolism. It is mainly used to diagnose extra-temporal

focal epilepsy, especially in children with equivocal findings [46]. [^{18}F] FDG-PET can visualize hypometabolic area that correlates with the focus in 80% of patients with focal temporal lobe epilepsy (TLE) [52]. Here surgery can achieve good results also in patients without MR-documented lesions. Indeed a distinct, surgically remediable syndrome of "MRI-negative, PET-positive TLE" has been proposed [15]. The underlying pathophysiological mechanisms are still unclear [19].

2.3.6 Single Photon Emission Computed Tomography (SPECT)

SPECT is based on radioactive isotopes that emit gamma radiation with a much longer half-time than isotopes used in PET scanning. SPECT can be used to measure ictal cerebral blood flow in the focal epileptogenic zone and identify regions of acute ictal hyperperfusion within the temporal lobe. These regions are a surrogate of the epileptic zone, whose excision correlates with satisfactory seizure control. However, the spatial resolution of SPECT alone is considered insufficient, especially when considering limited resections [45], [108].

2.3.7 Neuropsychological testing

Neuropsychological testing can provide information about the patient's preoperative cognitive functions (it tests intelligence, attention, visual and verbal memory, language, higher verbal and visual reasoning). This is helpful for counselling on the possible risks of cognitive deficits after surgery and for planning post-surgical rehabilitation. Epilepsy surgery must always be weighed against the attendant risks of cognitive deficits.

An IQ below 70 in adults is considered a poor prognostic factor for resective epilepsy surgery, since it usually indicates diffuse brain damage often associated with a wide-spread epileptogenic zone [75].

One part of a neuropsychological evaluation is the Wada test, used for lateralization of speech and memory. This test is actually an invasive investigation: a barbiturate (125 – 175 mg sodium amobarbital) is injected by means of a catheter placed in the carotid arteries. The purpose of the investigation is to suppress the ipsilateral functional capacity for a few minutes, enabling the testing of speech and memory in

one hemisphere at a time [117]. Assessment of memory function in the Wada test is based on the hypothesis that pharmacologic inactivation of a single temporal lobe will not create global amnesia if the awake temporal lobe is healthy [71]. Assessment of language function is based on the hypothesis that pharmacologic inactivation of a dominant temporal lobe will create global aphasia. The indications for the Wada test differ from one center to the next; at some centers it is used systematically, however, at others very rarely [116].

This test may not be needed if only mesial temporal lobe resection (amygdalo-hippocampectomy) is done, since these operations require no language mapping and the test may not reliably lateralize the hemisphere that supports memory. However, further investigations are needed to determine the role of the Wada test in pre-surgical investigations for epilepsy patients [91]. Today the test has been replaced in many cases by non-invasive fMRI. It is applied mainly in selected patients to determine language dominance, particularly in hemispherectomy and callosotomy candidates and in patients with epileptic foci close to or overlapping with putative language areas [29], [35], [56].

2.4 Invasive investigations

If non-invasive investigational techniques cannot provide a sufficient amount of information to proceed with surgery, the collected information is too heterogeneous, or the suspected epileptogenic zone is located very close to functionally significant cortex, invasive investigation methods must be considered [40].

Today invasive investigations are required in temporal lobe epilepsy, i.e., in about 20% of all cases. This value differs among the different epilepsy surgery centers. Immonen and colleagues reported that about 45% of all their temporal epilepsy patients underwent invasive investigations [46]. The need for invasive investigations is more frequent in extra-temporal epilepsy than in temporal lobe epilepsy.

In contrast to non-invasive methods, invasive methods carry an increased risk of patient morbidity. They are limited by the size of the investigational region and the time required. One must first propose a strong hypothesis about the seizure origin zone before turning to invasive investigations. The strength of the hypothesis is based on the results of the non-invasive evaluation, which is a key to successful use of

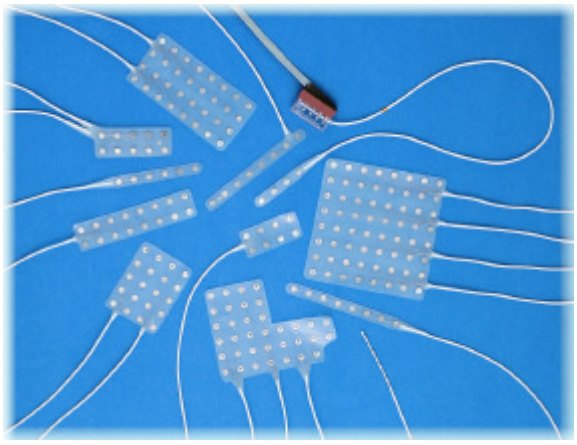
invasive techniques. The clearer the question is for testing, the greater is the chance of success with the invasive evaluation [9].

The questions to be answered by invasive methods include determination of the epileptogenic zone, the functionally significant cortex, the brain lesions, and their interactions.

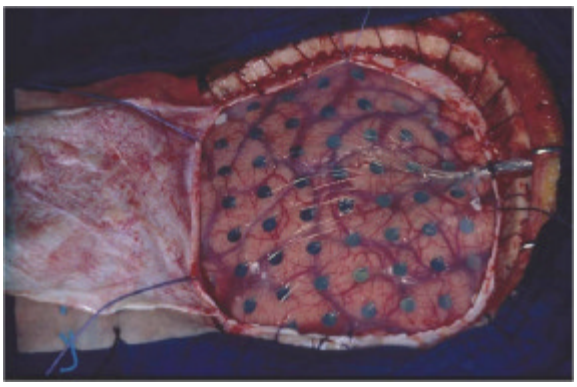
2.4.1 Determination of the epileptogenic zone by invasive electroencephalography and video-EEG monitoring

To perform an invasive electroencephalography, subdural electrodes are placed during a neurosurgical operation (craniotomy) on the brain surface, under the dura mater.

Subdural electrodes are made of biologically inert, flexible (Silastic, Teflon, etc.) material and contain platinum or stainless steel electrode contacts (See Photo No. 1a,b). Electrode contacts are produced with diameters of 2 to 5 mm with center-to-center distances of 1 to 2 cm between electrodes [57].



a



b

Photo No. 1

a – Different subdural electrodes;

b – Large grid electrode placed over cerebral cortex

There are two types of subdural electrodes – strip and grid electrodes. They differ in the number of encompassed electrode lines. Strip electrodes contain only one line of electrodes, from 5 to maximally 16 cm long. Grid electrodes contain up to 10 lines of electrodes of different lengths, thus allowing coverage of broader cortical areas. The decision to use one or the other is based on the pre-operative hypothesis (for example, the width of the cortical area to be explored).

Accordingly, there are also differences in terms of the extent of surgery needed for electrode placement. Strip electrodes can be placed through a simple burr hole, whereas grid electrodes require a vaster craniotomy.

Depending on the extent of surgery, there are also limitations inherent in the unilateral or bilateral placement of subdural electrodes. Strip electrodes can be placed intracranially within a smaller area of surgery, thus carrying less risk for the patient. Therefore these electrodes can be placed bilaterally, if needed. Subdural grid electrode placement, in contrast, requires a broader craniotomy, carries more risks for the patient, and can be performed only unilaterally. Therefore, grid electrode placement necessitates an even stronger hypothesis of the epileptic zone location.

The main indications for invasive video-EEG monitoring can be divided into three overlapping groups: to define (1) the extent and distribution of the epileptogenic zone, (2) the epileptogenic zone versus structural lesion, if present, and (3) epileptogenic zone versus eloquent cortex [40].

The main limitation for precisely defining the epileptic zone with invasive electrodes is the fact that they can only cover a very limited portion of the brain [62].

The following are more detailed examples of instances that may require invasive intracranial EEG monitoring:

- Seizures are lateralized but not localized (e.g., a left-sided, widespread frontal-temporal onset);
- Seizures are localized but not lateralized (e.g., ictal EEG patterns that appear maximally over both temporal lobes);
- Seizures are neither localized nor lateralized (e.g., stereotyped complex partial seizures with diffuse ictal changes or initial changes obscured by artifacts);

- Seizure localization disagrees with other data (e.g., EEG ictal scalp data different with neuroimaging [MRI, PET, SPECT] or neuropsychological data);
- The relation of seizure onset to functional tissue must be determined (e.g., seizures with early involvement of language or motor function);
- The relation of seizure onset to lesion must be determined (e.g., dual pathology or multiple intracranial lesions);
- Seizures are clinically suspected, but video-EEG is inadequate to define them (e.g., simple partial seizures with no detectable scalp EEG ictal discharge or suspected epileptic seizures with unusual semiology that suggests psychogenic seizures [pseudo-pseudo seizures]) [19], [40], [104], [122].

2.4.2 Determination of functionally significant cortex by cortical stimulation

If after completion of EEG registration, the results indicate a possibly resectable epilepsy focus in the cortical region covered and we suppose functionally significant zones to be located in close proximity, we can proceed to direct electrical stimulation of the cortex in order to state the correct localization of the latter areas [66].

Direct intraoperative electrical stimulation is a safe, precise, and reliable method for detecting functional cortical areas and white matter pathways [83], [85], [102]. It has been the gold standard for mapping brain function in preparation for surgical resection since the 1930s [83], [92]. This is mainly due to fact that false negative results are intrinsically impossible. Indeed, each eloquent structure, whatever its actual role in brain function, will be in essence electrically disturbed by direct electrical stimulation, which thus induces an obligatory functional consequence [28], [68]. However, it is of utmost importance to use certain physical parameters (see below) in cortical stimulation, since the slightest technical approximation can result in false negatives [59], [111].

In cortical stimulation a small electrical current is passed through individual electrodes, and any symptoms of interference with the cortical function are closely observed [66], [82]. Stimulation is either by electrodes placed in subdural or intracerebral space (extra-operative stimulation), or during the operation (intra-operative stimulation). The cortical stimulation process is supposed to define

functionally significant cortical regions that should be preserved in epilepsy surgery. On the basis of the results of cortical stimulation we can draw a map of cortical representations of different functionally more and less significant areas. This is called “cortical mapping”. According to such a cortical map of representations of functionally significant cortex and earlier estimated epileptogenic zone, we can plan the actual epilepsy surgery – if it is possible at all (to what extent), without damaging significant cortical areas.

Since cortical stimulation mapping (either extra-operative or intra-operative) plays an essential role in epilepsy surgery around language areas, we give here a short history of cortical stimulation mapping, and also describe the physics on which it is based.

2.4.2.1 History of general nerve cell stimulation

There is little agreement between the data and opinions appearing in the literature, as to who first discovered nerve cell excitability and who first actually performed brain stimulation. However, according to reliable data, the first scientists to discover nerve cell excitability were Luigi Galvani (See photo No. 2) and Alessandro Volta (See photo No. 3) in the 18th century [44].

Photo No. 2 Luigi Galvani

Photo No. 3 Alessandro Volta

Galvani showed that the muscle could be made to contract if a zinc electrode attached to the muscle and a copper electrode attached to the nerve were brought in

contact with each other. Galvani incorrectly concluded that the contractions were the result of "animal electricity" released from storage in the muscle, only to return via the closed zinc and copper path through the nerve. In 1793, one year after Galvani's initial publication on "animal electricity", the Italian physicist Alessandro Volta proposed that the electrical stimulus responsible for the contraction was due to dissimilar electrical properties at the metal-tissue saline interfaces. It was not until 1800 that Volta conclusively proved that the stimulus was of electrical origin: the voltage difference due to the unbalanced half-cell potentials of the zinc-saline and copper-saline interfaces excited the neuromuscular preparation. The early work of Galvani and Volta provided physiologists with a basic understanding of the mechanisms of neural and muscular excitation. While the mechanistic details would be filled in nearly 150 years later, it was clear that neural and muscular signals could be generated and transported by electrical means [44].

Data on the first brain stimulation mention an Italian scientist Felice Fontana (See photo No. 4), who worked in the beginning of the 19th century and was influenced by Galvani and Volta.

Using a series of voltaic cells, Fontana carried out the first known human brain stimulation experiments on cadavers, invoking facial spasms in the recently deceased by applying the voltaic cell to specific brain regions. When public concern over his experiments led to a law forbidding such work, Fontana responded by continuing his work on living volunteers [44].

Photo No. 4

Soon thereafter several groups of scientists started experiments on animal brain stimulation. One of the first scientists to describe electrical stimulation of an animal’s

brain were Gustav T. Fritsch and Eduard Hitzig (See photo No. 5) in the year 1870. Their work was entitled “Über die elektrische Erregbarkeit des Grosshirns”.

Photo No. 5 Fritsch and Hitzig

The predecessors of Fritsch and Hitzig did not resolve the critical question of whether the cerebral cortex could be electrically excited. Their demonstration that it was electrically excitable is considered one of their major contributions. Perhaps the greatest importance of their research, however, was its contribution to the theory that functions are localized in the brain [113].

One of the clearest and most detailed early account of human brain stimulation was published in 1874 by the American physician Roberts Bartholow (See photo No. 6), who stimulated the cortex of the 30-year-old patient Mary Rafferty.

Photo No. 6 Roberts Bartholow

She was said to be of good health until an ulcer appeared on her scalp a little more than a year before she was admitted to the hospital. Mary's ulcer was attributed to the "friction of a piece of whalebone in her wig and the skull is eroded and has disappeared over a space of two inches in diameter, where the pulsations of the brain are plainly seen". Bartholow reported on a series of six observations, during which needle electrodes caused a mechanical stimulation. Stimulation was performed in varying depths and current strengths. The results varied from no response to

distinct muscular contractions, very evident pain, great distress, and finally – to loss of consciousness and violent convulsions. Later the publication of his observations resulted in Bartholow's being forced to leave Cincinnati [113].

2.4.2.2 History of intraoperative cortical stimulation

One of the first to perform an intraoperative cortical stimulation is the founder of epilepsy surgery, Sir Victor Horsley (See photo No. 7).

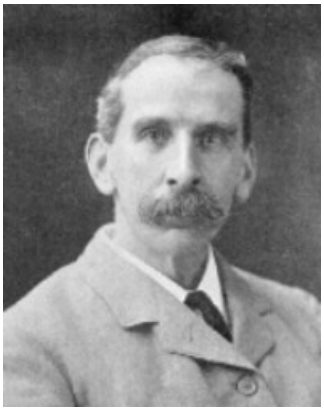


Photo No. 7 Sir Victor Horsley

He published a report of successful cortical resections already in 1886. Working together with H.J. Jackson (epileptologist) and D. Ferrier (neurophysiologist), they identified the region to be resected by locating either a structural lesion and/or the area of cortex which when stimulated, reproduced the initial symptoms of the clinical seizure.

As it was afterwards noted by J.H. Jackson, they hoped that surgery could “cut out the discharging lesion”, which, to their mind, was “the very local cause of the fits” [62].

It was Feodor Krause (See photo No. 8) from Berlin together with his co-worker Schum, who in 1932 published a 900-page volume on epilepsy. Here they stated for the first time that the only worthwhile epilepsy surgery is the excision of the epileptic focus.

The earliest stimulation Krause performed took place on 16 November 1893. The patient was a 15-year-old girl, who suffered from Jacksonian seizures and Jacksonian status starting at age 3. It was due to a postencephalitic cyst following meningitis at the age of 2. After removal of the cyst, the patient remained seizure free for the rest of her life and also markedly improved in her mental performance.

Photo No. 8 Feodor Krause

Thus, together with Sir Horsley, Krause seems to have been the first one to systematically stimulate the human motor cortex during epilepsy surgery. In his work Krause included a detailed functional map of the motor strip, which was based on stimulation results from 142 operations. He also advocated monopolar faradic stimulation and described the method in detail, because he felt it induced less severe seizures than galvanic stimulation, which was more favored by O. Foerster (See photo No. 9), another very prominent personality in the history of epilepsy surgery.

Photo No. 9 Otfrid Foerster

Photo No. 10 Wilder Penfield

It was Otfrid Foerster, together with Wilder Penfield (See photo No. 10), who in 1930 produced a less detailed, but much more extensive cortical map than that of Krause [125]. He also had a much keener and more detailed interest in the semiology of seizures and its localizing significance. This provided important information for epilepsy surgery in the time before the development of EEG and the electrocorticogram [126]. While Foerster initially used cortical mapping to identify motor and sensory cortex, Penfield and colleagues subsequently applied the technique to identify language cortex, with the goal of sparing these functional areas from resection.

2.4.2.3 History of extraoperative cortical stimulation

The first brain electrode implantation took place in the early 1940s, followed in 1946 by the introduction of the first stereotactic instrument for use in humans by Spiegel and Wycis [41]. Large subdural grids were introduced and systematically produced beginning in the 1980s. They have had a major impact on identifying patients who are eligible for surgery [1], [66].

2.4.2.4 First steps of epilepsy surgery close to speech areas

In the early years of focal epilepsy surgery, patients with seizures that arose from the left hemisphere were refused surgical treatment, unless it was certain that the lesion was located in the anterior of the frontal lobe or in the posterior of the occipital lobe. Any other area in the left hemisphere was considered “forbidden territory” for fear of producing postoperative aphasia [93]. The clinical use of cortical stimulation mapping for language began with Wilder Penfield and colleagues in the 1940s. Due to Penfield’s innovative technique of cortical language mapping, surgical treatment became a viable treatment option for numerous patients who had not been helped by pharmacological treatment of epilepsy. Thus, the implementation of cortical stimulation was the starting point for epilepsy surgery close to speech areas.

2.4.2.5 The physics of cortical stimulation

As mentioned before, the use of certain physical parameters in direct cortical stimulation is of utmost importance, because the slightest technical approximation can result in false negatives. As noted by Taylor and co-workers, if the intensity of stimulation is too low, if the duration is too short, or if a stimulation is performed during a transient post-epileptic refractory phase, an erroneous "negative mapping" may result [111].

2.4.2.5.1 Current spread and tissue excitability

There are two very important physical properties that play an important role in electrical stimulation of brain tissue. These are *current spread* and *tissue excitability*. Both of these issues have been investigated by several methods (single-cell recording, behavioral methods, and neuroimaging) [112].

2.4.2.5.2 Current spread

It is commonly accepted that the initial segment and the nodes of Ranvier are the sites at which a neuron can be directly activated by electrical microstimulation [36], [76], [77], [99]. These zones contain the highest concentrations of sodium chanels, thus making them the most excitable segments of a neuron [18], [76], [77].

The amount of current injected through a microelectrode to directly activate a neuron (cell body or axon) is proportional to the square of the distance between the neuron and the electrode tip.

This is expressed as:

$$\mathbf{I = Kr^2}$$

I – the current level (μA)
r – distance (mm)
K – excitability constant ($\mu A/mm^2$)

This relationship is derived from studies of cortical and corticospinal neurons of rats, cats, and primates [4], [69], [78].

The effective current spread from an electrode tip can be expressed as the square root of the current divided by the square root of the excitability constant $(I/K)^{1/2}$. This relationship is illustrated in Fig. 1.

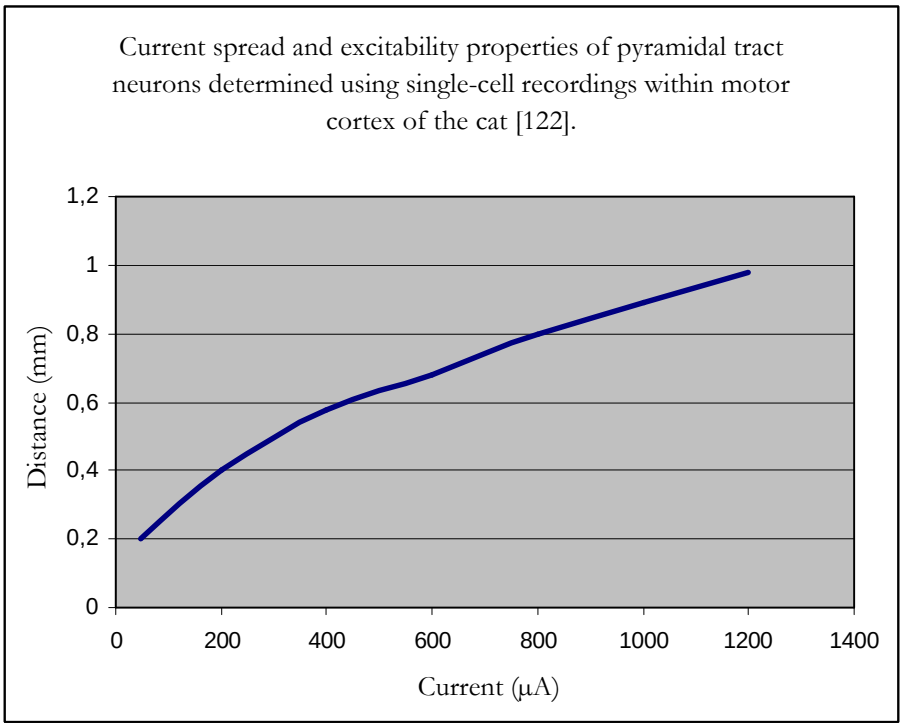


Fig. 1: Radial distance (in millimeters) of a direct activation of pyramidal tract neurons using the equation radial distance = $(K/I)^{1/2}$. The curve represents the amount of current required for the antidromic elicitation of an action potential 50% of the time using a single cathodal pulse of 0.2 ms duration. The average K value was 1,292 μA/mm^2 for12-cell studies.

Fig.1 shows that the higher the current used, the larger is the current spread.

Another important factor influencing current spread is the conduction velocity of axonal elements. The conduction velocities of myelinated pyramidal tract neurons range from 3 to 80 m/s, with the largest of these neurons exhibiting the highest velocities [13], [23], [67]. The conduction velocities of small unmyelinated cortical fibers are <1 m/s [78]. Thus, the excitability constant (the constant reflecting the excitability of a neural element 1 mm away from the electrode tip) derived with a 0.2 ms pulse can be as low as 300 μA/mm^2 for the largest myelinated cortical neurons and as high as 27,000 μA/mm^2 for the smallest unmyelinated cortical neurons [78], [109].

This explains why large myelinated cortical neurons are easier to excite than small unmyelinated cortical neurons.

The current spread characteristics have always been a subject of debate – to what extent current spreads through directly activated neurons subcortically and to what extent through transynaptic or lateral connections. The most precise responses are achieved through direct cortical – subcortical activation, but at the moment of stimulation there is also an indirect current spread laterally, which can involve more distant cortical areas and give some false-positive responses. To assess the functional localizing value of cortical stimulation, we have to know the extent of the direct and indirect neuronal activations.

Several factors let us assume that current spreads mainly in a direct (cortical - subcortical) way. First, there is the scientifically based fact that lateral connections within the cortex are often unmyelinated and therefore much less excitable [78], [110]. Second, microstimulation activates the most excitable elements in the cortex, that is, by and large the fibers of the pyramidal cells, which project subcortically rather than laterally [112], [78], [13], [23]. Third, microstimulation of the neocortex evokes precise responses because directly activated neurons make more significant contribution to the evoked response. This is due to fact that these neurons are more synchronously activated in contrast to neurons further away from the electrode tip which are activated transynaptically in the cortex [114].

Using a modern diagnostic tool, like functional MRI, scientists recently recorded higher current lateral spread, which is contradictory to data published earlier. An obvious reason for these differences is the appreciably larger currents and longer train durations used in the fMRI study [114].

2.4.2.5.3 Estimates of excitability and strength – duration functions

To deduce the excitability of stimulated neurons, current can be traded-off against pulse duration to elicit some response [3], [4], [5]. Normalized strength – duration functions for pyramidal tract neurons are illustrated in Fig.2.

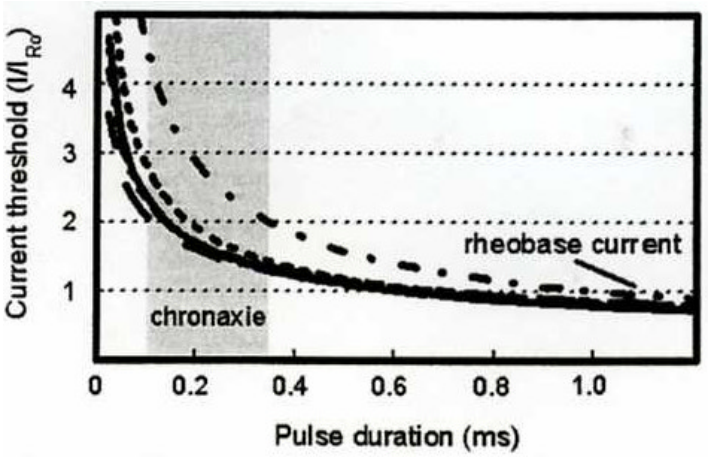


Fig. 2: Normalized strength – duration functions of pyramidal tract neurons [4], [109].

As the pulse duration is increased, the amount of current needed to evoke an action potential 50% of the time diminishes to an asymptotic level; this level is called the **rheobase current**.

The excitability or **chronaxie** of a stimulated element is expressed as the pulse duration at twice the rheobase current. The shorter the chronaxie, the more excitable is a directly stimulated neural element (shorter pulse duration is necessary for their activation). Chronaxie depends on the characteristics of the tissue being stimulated, specifically on its impedance. The few studies in this area have produced resistance values of 250 Ohms for gray matter, 500 Ohms for white matter, and 65 Ohms for cerebrospinal fluid [72]. Axons have shorter chronaxies than their cell bodies (axons: 0.03 – 7 ms; cell bodies: 7 – 31 ms [76]), and large, myelinated axons have shorter chronaxies than small, nonmyelinated axons (large: 0.03 – 7 ms; small: >1.0 ms [60],[97], [119]). Moreover, impedances can be modified in patients in an awake or anesthetized state. Also any pathological process, whether lesional (tumor) or non-lesional (epilepsy, post-ictal status), can interfere directly with the tissue's excitability [48]. Research on current spread and excitability investigations is still continuing.

2.4.2.6 Stimulation parameters

Cortical stimulation produces clinical effects only when very special stimulation parameters are used. The four following essential factors must be considered [63]:

- stimulus intensity;
- duration of each individual stimulus;
- stimulation frequency;
- duration of the stimulus train.

2.4.2.6.1 Stimulus intensity (voltage or amperage)

Ideally the stimulation intensity should be strong enough to produce significant depolarization (or hyperpolarization) of all the neurons underlying the stimulating electrode but without affecting surrounding brain tissue or producing brain damage. A stimulation of 15 mA seems to accomplish this. There are various reasons why the "ideal" stimulation intensity of 15 mA can frequently not be used. The main reason is that afterdischarges and painful or unpleasant sensations are produced by electrical stimulation [66].

Afterdischarge per definition is "the portion of the response to stimulation in a nerve which persists after the stimulus has ceased and consists of rhythmic, high-voltage, high-frequency spikes, sharp waves, or spike-wave complexes which occur at the region stimulated and are distantly different from background activity" [17].

Afterdischarges can be triggered only in certain circumstances, for example, if electrical stimulation is at sufficient intensity, has a repetitive rate, and is of certain duration. Initially they tend to be limited to the stimulating electrode, but they often spread to adjacent electrodes, activating extensive cortical areas. The symptomatology elicited when afterdischarges are triggered is not only an expression of the area directly stimulated electrically but also of the whole region activated by the afterdischarges. Therefore, in such cases we cannot be sure if the response at the electrode site, where the afterdischarges are elicited, is due to the stimulation or if it is produced by the afterdischarge. Consequently only those symptoms and signs elicited by stimuli that do not produce afterdischarges are counted.

In some cortical sites even quite low intensities (for example, 2 mA) produce striking positive effects, such as muscle twitches. Clinical trials warn that too high a stimulus intensity could cause tissue damage due to excessive heat, produced especially by hydrolysis; or "leaking" of the intracellular current, which goes from the anode to the cathode through the cytoplasm, posing a risk of lesion to the mitochondriae and the endoplasmic reticulum; or even alter the homeostasis if neurons are activated in a manner that is too repetitive and synchronous [127]. Usually the initial stimulus intensity is very low. It is gradually increased until a positive response, afterdischarges, or the maximum intensity is reached.

2.4.2.6.2 Duration of each individual stimulus

The duration of each individual stimulus in cortical stimulation varies from 0.1 to 0.3 ms [106]. Usually it is 0.2 ms.

2.4.2.6.3 Stimulation frequency

Single stimuli produce functional effects only at very high intensity. Repetitive stimulation, most probably due to temporal facilitation, produces functional alterations at a much lower intensity [100]. The ideal stimulus frequency (stimulus frequency producing clinical effects at the lowest effective stimulus intensity) is approximately 15 to 50 Hz.

2.4.2.6.4 Duration of the stimulus train

Repetitive electrical stimulation and relatively low stimulus intensities frequently trigger clinical symptoms after a variable delay of 1 to 3 seconds. The temporal summation of stimuli of the human cortex is an essential factor in the generation of clinical symptoms. It is necessary to note that with longer stimulation durations, the effect of the stimulation on both positive or negative symptoms not infrequently tends to diminish after 5 to 10 sec of stimulation (due to alternative pathways [58] or cortical adaptation) [66]. Usually the cortex is stimulated either until there is a positive effect or the maximal timing (15 seconds) is reached [63].

2.4.2.7 Characteristics of a stimulus

Normally a biphasic stimulus is used for cortical stimulation. It is not as effective as a monophasic (sinusoidal) stimulus, but it is safer for the brain, since the second stimulus phase inverses the effects of the first.

If sinusoidal impulses were used for stimulation, they would increase the threshold needed to be reached in order to generate the impulse (because the neural structures are kept in a state of infraliminar depolarization). This phenomenon is known as “accommodation”. “Accomodation” carries the risk of inducing a cerebral lesion due

to the accumulation of negative charge at the level of the cathode or the production of metal ions at the level of the anode. Therefore, rectangular (biphasic) impulses are recommended [2], [66], [68].

2.4.2.8 Physiological concerns of cortical stimulation

Electrical stimulation of the human cortex is the best experimental model of the effect of activation of the cortex by an epileptiform discharge [64].

Contrary to mapping of the rolandic cortex, language cortex mapping depends on the electrical blockade of cortical function rather than on eliciting function [83].

Electrical stimulation generates membrane excitability (membrane potential (MP) of the neuron at rest varies between -60 mV and -100 mV) via an initial phase of passive modification of local MP at the level of the cathode (the negative electrode). Before this happens, the inner side of the membrane becomes progressively less negative than the outer side (the membrane becomes inversely hyperpolarized with regard to the anode). The intensity of this phenomenon depends on the parameters of the stimulations and of the characteristics of the membrane (as mentioned before, the membrane can be more easily stimulated at the level of the initial segment of the axon, at the level of fibers that are myelinized and of larger diameter) [50], [55], [61], [96]. If the MP reaches the laminar depolarization threshold, a second phase occurs that begins with the opening of voltage-dependent ionic channels, which allow entry of Na+ ions, and which therefore invert the MP between +20 mV and +30 mV. A secondary output of K+ ions, associated with an inhibition of the entering flux of Na+ ions, brings the MP back to its resting state. Once generated, this rapid sequence of MP fluctuation – the action potential – is still the same, no matter what the stimulation parameters are (law of “all or nothing”) [68].

The effect of stimulation is more or less strictly limited to the area of brain beneath the two electrodes being stimulated. The current flow only reaches sufficiently high current density to stimulate the brain at the two poles (electrodes) and their immediate vicinity. (These considerations apply, however, only when no afterdischarges are triggered by the stimulus.) [95]

It is important to point out that cortical stimulation, even in the primary afferent/efferent cortical areas, has a highly non-physiological effect. This explains why most effects of stimulation in cortical areas are non-physiological (paresthesias,

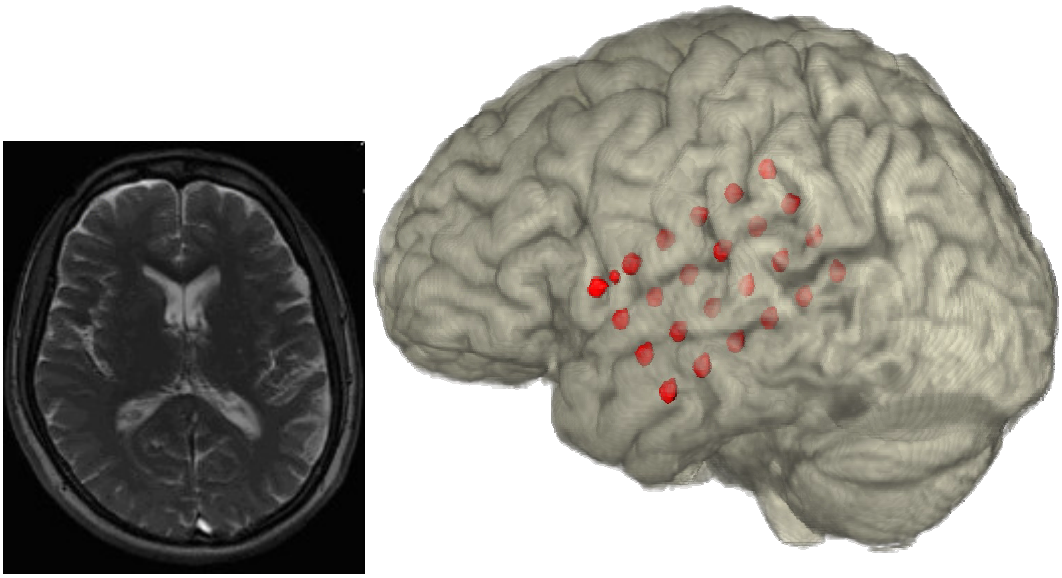
unusual motor movements, etc.). Also in associative cortical areas, the massive synchronized activation or deactivation of neurons by the electrical stimulus is extremely un-physiological [95]. The full details of the physiological basis of nerve-cell activation by electrical stimulation, however, remain unclear.

2.4.2.9 Procedure of extra-operative EEG recording and cortical mapping

Grid electrodes in our clinic are mainly used for both - extra-operative EEG recording and cortical stimulation, whereas strip electrodes are mainly used for EEG recording alone - often in situations, when seizure lateralization is necessary and electrodes must be implanted bilaterally.

Consecutive, extra-operative cortical mapping is indicated in cases when localization of the detected epileptogenic zone is close to or overlaps with eloquent areas [19], [40], [104].

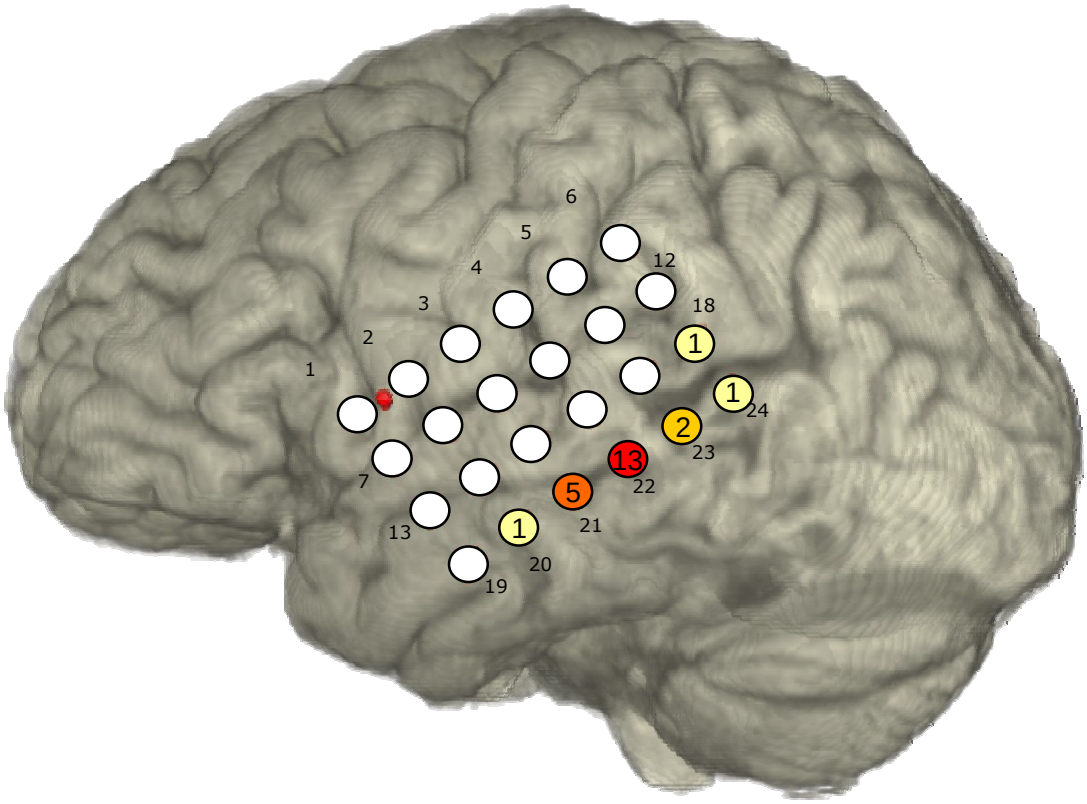
The type, number, and position of the electrodes are determined by the location of the suspected epileptogenic zone in each patient, according to data gathered from all non-invasive investigations (pre-investigational hypothesis). After implantation of subdural electrodes by means of surgery and possibly after monitoring in the intensive care unit (depending on the extent of surgery), the patient is brought for further observation, recording of EEG, and cortical stimulation to the epilepsy intensive station. Meanwhile a CT scan has also been made to locate the subdural electrodes. This scan is merged with pre-operative MRI images to yield a three-dimensional picture of the precise electrode locations over the cerebral sulci [124] (See Picture No. 1).



Picture No.1: This 53-year-old epilepsy patient had seizures due to cerebral trauma at the age of 17. Magnetic resonance revealed a broad contusion in the left temporo-parietal region (Left). The merged pre-operative MRI and post-operative CT picture (Right) indicates the precise localization of the subdural electrodes.

After antiepileptic medication is gradually reduced, the patient is monitored 24 hours a day for epileptic seizures in the epilepsy intensive ward. The monitoring is videoed and checked by an epileptologist and/or a specialized nurse. When the epileptologist feels that a sufficient number of seizures have been recorded to judge the localization of the epileptogenic zone, a summary of the epileptogenic activity is made (See Picture No. 2). At this point the volume of the epileptogenic zone, its relation to the cerebral cortex, and initial impressions of the possibility of resection of a pathological cortical region can be considered.

Summary of Seizure Origin



Picture No. 2: Summary of seizure origins (overall 17 seizures were recorded in this case) in the same 53-year-old epilepsy patient after invasive EEG registration by subdural electrode.

The next stage is the localization of functionally significant cortex - cortical stimulation/ mapping. The physical parameters of stimulation are shown in Tab.1.

	Physical parameters	**Unit**
Stimulus intensity	1 – 15	mA
Duration of each individual stimulus	0.2	ms
Stimulation frequency	50	Hz
Duration of the stimulus train	5 – 15	sec

Tab. 1: Physical parameters used in extra-operative cortical mapping.

At the beginning, each pair of electrodes on the grid are stimulated and the reaction is observed. In this way the “reference electrode”, where no function has been triggered, is found. Later all the other electrodes are stimulated with reference to this one electrode.

Initially the cortical stimulation begins at a minimal current strength and duration (for example 1 mA for 5 sec.) and continues until some response, afterdischarges, or maximal current strength – 15 mA is reached. During the stimulation the patient has to perform certain tasks, depending on the stimulated zone (expected) and the observed response. The main tasks include motor activities (moving arms and fingers); also neuropsychological tests (naming several objects presented, counting numbers or months of the year; reading aloud from a book or journal, sorting different objects by their colour, shape, etc.). If any changes in these actions are observed or the patient reports any uncustomary feelings, more detailed tasks to clarify this response

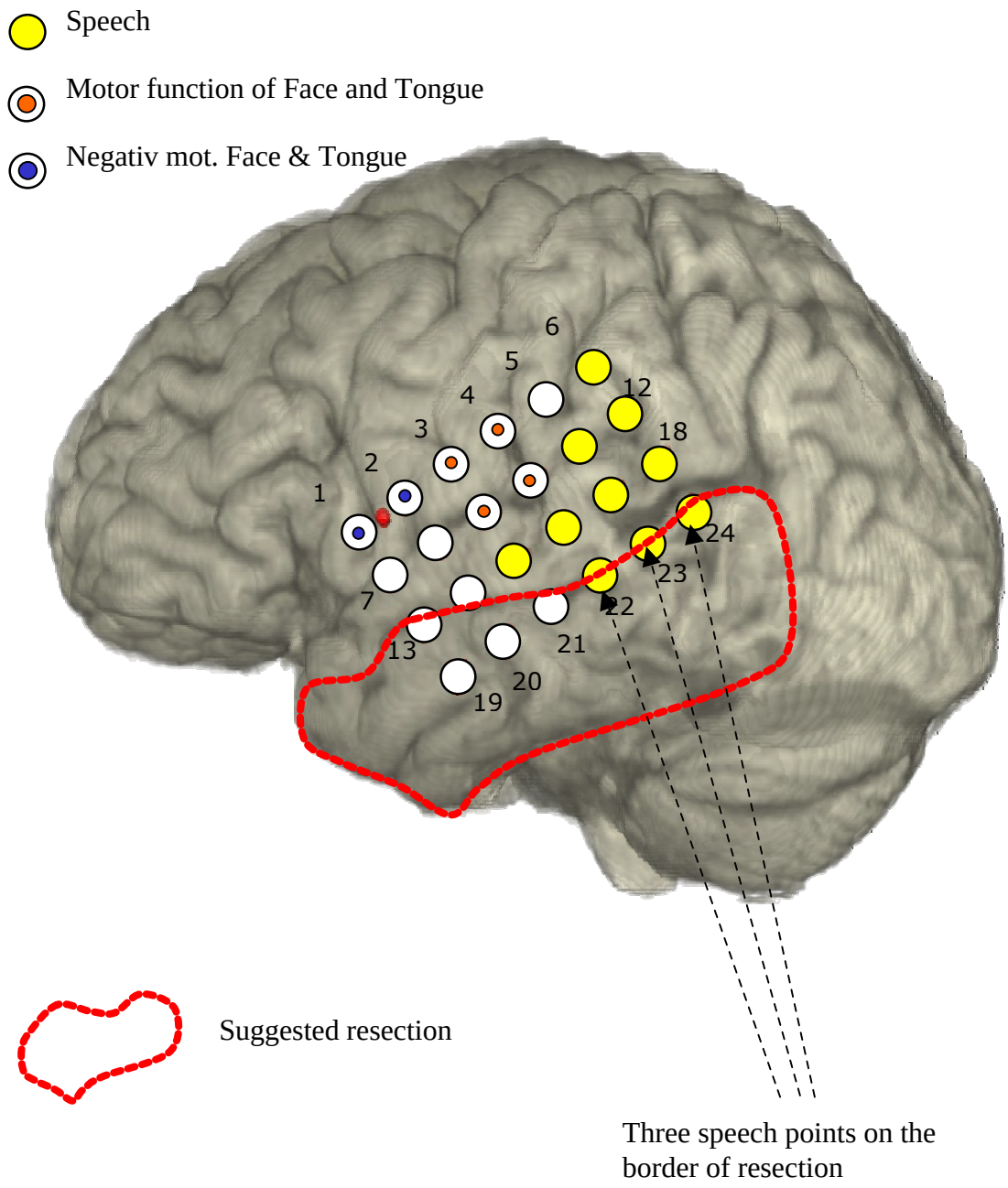
are required. Symptoms during stimulation may include positive motor phenomena (tonic or clonic contraction of muscle groups), negative motor phenomena (inhibition of voluntary movements of the tongue, fingers, or toes), somatosensory phenomena (tingling, tightness, or numbness of a part of the body), or language impairment (speech hesitation or arrest, anomia, or repetitive difficulties) [9]. Sites where stimulation produces consistent speech arrest or anomia (*anomia - impaired recall of words with no impairment of comprehension or the capacity to repeat the words*) are considered essential to language function [106].

A significant response is considered to be any response during stimulation which is observed or which is noted by the patient during at least three consecutive stimulations at the same cortical site.

The duration of invasive monitoring greatly depends on the seizure frequency, the success of any planned stimulation, and patient compliance [41].

By combining acquired stimulation results with the previous localization of the epileptogenic zone on the 3-dimensional cortical picture, we obtain a reflection of the relation between the epileptogenic zone and functionally significant cortex in the investigated cortical region. On the basis of these data, we make the final decision about resective surgery and estimate the resection borders (See Picture No. 3).

Summary of extra-operative language mapping and suggested resection



Picture No. 3: Summary of extra-operative investigation by subdural electrodes in the same 53-year-old epilepsy patient. Extra-operative language mapping revealed 3 language points located on the border of epileptogenic zone. An intra-operative language mapping was performed to validate the border of maximal cortical resection.

2.4.2.10 Procedure of intra-operative cortical mapping

As indicated by the name, this cortical stimulation method is performed during the neurosurgical operation, directly before the resection.

This method can successfully be used in cases when there is no need for additional recording of electroencephalography (cases with well known/ defineable borderline of the epileptogene zone). It can, however, be joined with the use of corticography – direct intra-operative recording of electric activity of cortex. It is also used for better intra-operative orientation and direct anatomical specification of resection borders in situations, in which previous extra-operative stimulation has shown a very close relation (or direct overlapping) to both cortical areas. We have often used this tactic in epilepsy surgery near speech areas and will treat it in more detail later in this work.

	Physical parameters	**Unit**
Stimulus intensity	4 – 12	mA
Duration of each individual stimulus	0.2	ms
Stimulation frequency	50	Hz
Duration of the stimulus train	4	sec

Tab. 2 Physical parameters used in intra-operative cortical mapping

There are differences in the intra-operative mapping of sensory, motor, or language cortex. In the following we focus on intra-operative stimulation mapping of the language cortex.

The most significant feature of intra-operative language mapping is that craniotomy is performed while the patient is awake (local intracutaneous anaesthesia) – the patient must stay awake during surgery in order to be able to undergo neuropsychological testing of language function localization just before cortical resection. To achieve this and ensure the patient's cooperation, which is essential for a successful cortical mapping procedure, the patient must be prepared before the operation, must understand the need and goals of this procedure, as well as go through the neuropsychological language tests used intra-operatively.

The procedure is as follows: after craniotomy and the opening of the dura, the investigational cortex is marked with numbers (sterile paper numbers are placed on the cortex). Each number is placed approximately 0.7 to 10 mm from the previous one (See photo No. 11).

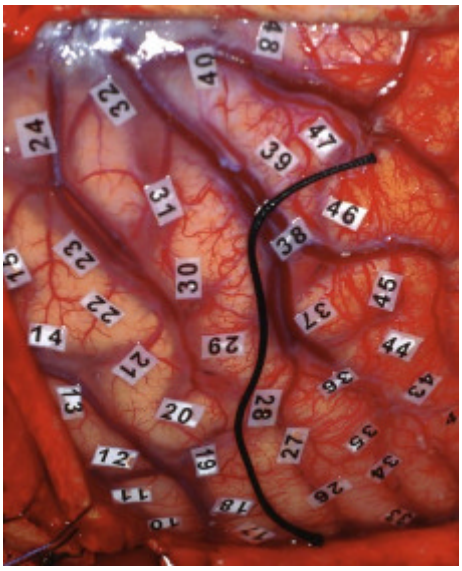


Photo No. 11: Cerebral cortex marked with numbers for intra-operative cortical stimulation. The black thread indicates already stated resection border.

If an extra-operative cortical stimulation was performed previously and there is need for additional intra-operative cortical language mapping, the numbers of the stimulation sites are placed in the exact order and location as they appeared on the extra-operative electrode (See photo No. 12.)

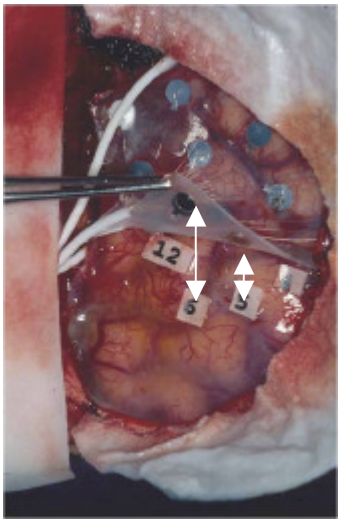


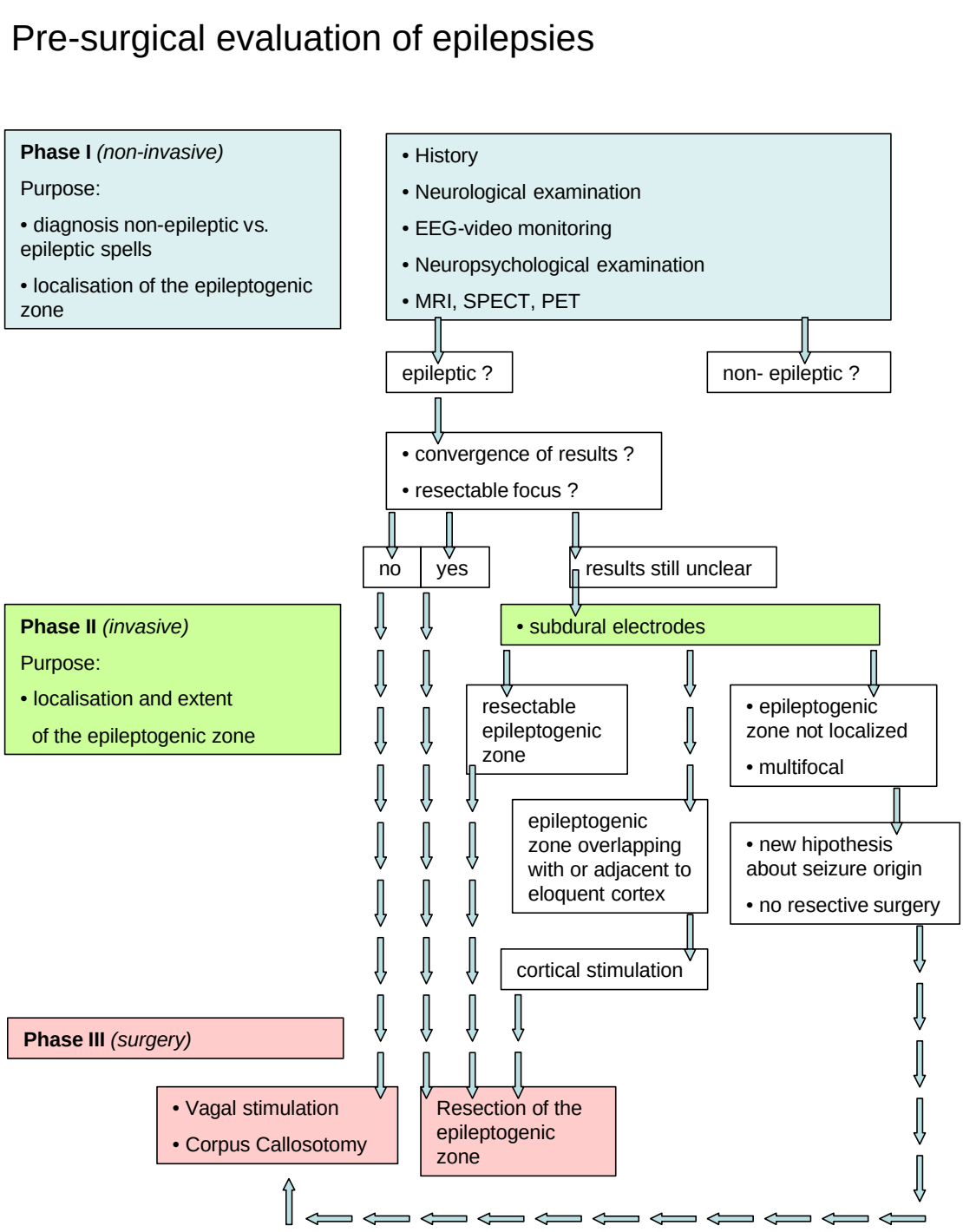
Photo No. 12 shows the cortical sites where intra-operative stimulation must be repeated. Note that each number on the cortex corresponds to the same number on the sub-dural electrode plate (white arrows), ensuring that intra-operative stimulation is performed exactly in the same locations as pre-operative stimulation.

Then a direct cortical stimulation is performed with bipolar stimulation tweezers at each of these points. Simultaneously, the patient is asked to name different objects (visual naming test, indicating visual naming sites) presented on the computer screen in front of him. The patient has to say a full sentence, for example “This is a dog”; “This is a house”. In order to maximize the validity of the stimulation results, the patient has undergone identical visual naming tests pre-operatively. Later intra-operatively only those visual stimuli are used, for which there was no pre-operative failure in naming.

Parallel to the stimulation, the patient’s verbal response is observed by the neurophysiologist. Similarily as in extra-operative language mapping, sites where stimulation produces consistent speech arrest or anomia are considered essential to language function [106].

Stimulation is at first done sequentially at all points and then is repeated twice, increasing the current strength each time, since some points give positive response at only higher current strengths. The upper limit of current strength is 15 mA. For patients in whom speech has already been extra-operatively mapped and additional intra-operative language mapping is now indicated, the latter is normally performed only in the region where there is a close relation between the epileptogenic zone and language sites or where overlapping of both areas has been seen. Thus, the exact borders of the language cortex can also be directly determined intra-operatively. In cases where no speech was found extra-operatively and repeated intra-operative stimulation is indicated to approve this, stimulation normally includes a broader area of the cortex (all the cortex accessible in craniotomy) as in extra-operative language mapping. This way of mapping language is also used in cases, in which only intra-operative language mapping is performed. Only those cortical sites, where language disturbances are found in all three consecutive stimulations, are considered essential for language and are preserved during resection.

All essential language sites are registered, and the final summary of results provides a direct anatomical image of the cortical representation of language sites, as well as the resection border. The resection is then performed, while keeping a distance of 10 mm from the essential cortical locations.



Drawing Nr 1: Algorithm of epilepsy surgery

3 The Operation – Cortical Resection

After detailed and in-depth pre-surgical investigation, a decision is made as to whether it is possible to resect an epileptogenic zone and to what extent. Once a cortical resection operation is considered justified, the operation is performed.

Operations around the language cortex typically include a resection of neocortex in which the epileptogenic zone is found. A resection margin of 1 cm away from the essential language site is currently considered satisfactory for functionally safe (regarding language) surgery [12].

To better illustrate the implementation of the above-mentioned measures in epilepsy surgery around speech areas and to present its complexity and results, as well as to analyze the best tactic of language mapping in this surgery group, we have summarized our 10 years of experience with this subgroup of epilepsy patients.

4 Hypothesis of the study:

Since the surgical tactics in this epilepsy surgery subgroup are mostly shaped by the data gathered in language mapping, the accuracy of invasive language mapping is of utmost importance. We have used two different tactics for language mapping, our decision based on the significance of conflict between epileptogenic and language areas. Habitually the language was mapped by extra-operative method alone. In those cases, where very close relationships (less than 10 mm) between epileptogenic zone and speech cortex or overlapping of both areas was seen in extra-operative mapping, additional intra-operative language mapping was used.

We hypothesize that additional intra-operative language mapping is beneficial for a better postoperative language and seizure frequency outcome in cases in which a close relation between epileptogenic and language areas had been detected in previous extra-operative language mapping.

5 Apart from confirming our hypothesis, we also sought answers to several other questions:

1. What is the common investigational characteristic of epilepsy surgery patients whose epileptogenic zone is close to neocortical language areas?
2. How are cortical mapping techniques typically used in this group of epilepsy surgery patients?
3. What results as regards post-operative language outcome are seen in the whole group of patients with epileptogenic zone around speech cortex and what results are seen in both language mapping subgroups (extra-operative and combined extra- plus intra-operative cortical mapping)?
4. What results as regards seizure outcome are seen in the whole group and two different language mapping subgroups? Does the combined language mapping technique influence post-operative results as regards seizure control?

6 Therefore the following goals of the study were stated:

1. To summarize 10 years of experience in epilepsy surgery around speech areas in the Neurosurgery Clinic of Munich University Hospital, Grosshadern;
2. To analyze the use of pre-surgical investigation methods in this group of patients;
3. To compare the use of two invasive language mapping techniques in two different groups of patients (extra-operative versus combined extra-intra operative);
4. To compare the results of both language mapping methods per se;
5. To analyze the post-operative results as regards language function in the whole group of patients and compare them in both invasive mapping groups;
6. To appraise our indications for using extra-operative or combined extra- and intra-operative language mapping tactics (these indications are stated in the following section “Investigation of language function and cortical language mapping”);
7. To analyze the post-operative results as regards seizure control in this group of patients and both subgroups of cortical stimulation;

8. To estimate the percentage of situations in which the epileptogenic zone could not be fully resected due to overlapping or close relationships with language cortex;
9. To discuss our results and possible measures for their improvement.

7 METHODS

7.1 Patients

Between September 1997 and June 2007, a total of 22 medically refractory epilepsy patients whose epileptogenic zone was close to the speech areas underwent operations. In all cases the primary reason for neurosurgical treatment was medically refractory epilepsy that significantly influenced the patient's quality of life. However, in one case a low-grade astrocytoma had been diagnosed pre-operatively, in another case a low-grade astrocytoma had been diagnosed post-operatively, and in one other case operation for a dysembryoplastic neuroepithelial tumor (DNET) had been repeated. Four patients underwent repeated operations for epilepsy.

All patients, except one, were examined with both non-invasive and invasive methods described earlier. In one case only non-invasive investigations were used. In this case speech mapping had been done by functional magnetic resonance imaging (f-MRI) for an insular cavernoma, diagnosed as the cause of the epileptic seizures. It was well confined and safely (with regard to language function) accessible by neuronavigation, when combined with f-MRI data. There was thus no need for additional invasive investigations.

We included in our study only those cases in which

- positive speech points were found during direct language mapping;
- these speech points were located close to the epileptogenic zone (in the majority of cases detected by direct subdural EEG recording).

Five patients had an epileptogenic zone located close to frequently described language sites (posterior portion of Gy Frontalis superior, Gy angularis), but we did

not manage to find any positive speech point by direct cortical stimulation here. In two of these cases only extra-operative cortical stimulation was used, and in three cases a combination of extra- and intra-operative stimulation was used. Due to the negative language mapping results (apparently no speech sites were located close to the epileptogenic zone), these patients were not included in our study. None of these patients had a post-operative language deficit.

Three patients who had needed invasive investigations, which proved unsuccessful, were also excluded from the study. In one case the reason was a personal wish of the patient to have the invasive electrodes removed after 12 days of invasive monitoring when no seizures were registered. In another case subdural electrodes could not be placed due to severe adhesions between the dura mater and the cerebral cortex. In the third case the patient had a subdural hematoma following placement of the subdural electrodes as a result of sudden drug-induced coagulation disorders. For reasons of patient safety it was decided to remove the electrodes and not perform resective surgery.

Three patients who underwent left hemisphere neocortical epilepsy surgery and in whom language was localized on the right hemisphere (detected by the Wada test) were also excluded from our study.

7.2 Investigation of language function and cortical language mapping

Language testing before and after the operation was performed by a neuropsychologist, a neurosurgeon, and a neurologist. The neuropsychologist used the Token test (part of Aachen Aphasia Test) to evaluate language. The neurologist and neurosurgeon assessed language through everyday observations. This pre-operative language assessment was done several days to weeks before the surgery.

Post-operative assessment of language was done during the hospitalization period after surgery and in the following visits to the neurosurgeon (the same surgeon who examined patient before and performed the operation) or the neurologist (first visit normally 4 to 6 months after surgery or earlier if needed, next visit after every 4 to 6 months on average or earlier if needed). The patient was sent for repeated neuropsychological evaluation (Token test) post-operatively if any kind of language disturbance was detected by the neurologist or neurosurgeon or was reported by the

patient. If a patient still had disturbed language function 6 months after the last resective surgery, it was classified as a permanent deficit.

The following language deficits were classified: *anomia* – patient cannot name objects, but is able to repeat sentences and speaks fluently; *expressive aphasia* – patient's expression in speech or writing is impaired; *receptive aphasia* – patient's speech is fluent, but meaningless, the ability to understand spoken or written words is also impaired.

All cases patients had left-sided language dominance.

The localization of cortical language areas was done invasively, except in one patient (well-demarcated insular cavernoma, mapped by f-MRI).

In one case (pre-operatively known low-grade astrocytoma) only intra-operative language mapping was used. Here non-invasive EEG investigations credibly indicated tumor as an epileptogenic zone, and no further invasive EEG investigation was necessary. The remaining 20 patients with an epileptogenic zone close to the cortical speech areas can be divided into two groups. In one group only extra-operative language mapping was used, in the other group a combination of extra- and intra-operative cortical mapping was used.

Our indications for the use of either only the extra-operative or the combined extra- and intra-operative cortical language mapping method are as follows:

1. Only extra-operative language mapping (Ex-M) was used in situations in which language mapping (measured in 3-dimensional cortical maps) indicated a distance of at least 10 mm between cortical language points and the epileptogenic zone. In such situations this distance was assumed to be safe to perform a resection with a diminished possibility of resection-caused damage to language areas and subsequent permanent post-operative language deterioration.

   (It was also used for one patient, in whom part of the speech cortex overlapped with the epileptogenic zone. Since the overlapping part of the language cortex was identified as the basal temporal language cortex, it was considered as safe for resection and no intra-operative mapping was performed. The case is more profoundly presented later in the discussion chapter.)

2. Combined extra- and intra-operative language mapping (Co-M) was used in situations, when language cortex found extra-operatively overlapped with the epileptogenic zone, or the distance between these cortical regions was less than 10 mm. Here there was an increased risk for resection-caused damage to the language areas. Additional intra-operative language mapping was applied in order to achieve the most precise resections, while at the same time preserving a safe amount of language cortex. The next step was the precise, maximal resection of the epileptogenic zone, keeping a distance of 10 mm from the language cortex. Additional intra-operative cortical stimulation was also used in a few cases, in which the results of extra-operative language mapping appeared to contradict the data in the literature or our previous experience. Thus, the repeated intra-operative stimulation was used here partly to confirm the extra-operative language mapping data and partly as an additional investigation to obtain more in-depth information.

In one case in which additional intra-operative language mapping was indicated, this could not be done due to the youth (10 years) and psychological problems of the patient.

The procedures of intra- or extra-operative stimulation, physical parameters, and materials used are described in the corresponding above sections.

7.3 Neurological examinations and post-operative seizure outcome

Pre-operative neurological examination was done by both the neurosurgeon and the neurologist; the pre-surgical seizure frequency was documented by the neurologist. Post-operative follow-up was done by the neurosurgeon, neurologist, or both on a regular basis (every 4 to 6 months or more frequently if needed). The post-operative seizure frequency data were summarized, starting from 2 years after last resective surgery, and were assessed using the Engel post-surgical seizure outcome scale [30] in four classes: Class Ia – seizure free, Ib – only auras; Class II – rare seizures (not more than 2 per year); Class III – worthwhile improvement (reduction of seizures by 85% or more); Class IVa – significant reduction, IVb – unchanged seizure frequency.

In most cases (19; 86.3%) data were gathered retrospectively from in-patient documents and out-patient letters. Some (3) prospective patients were assessed post-operatively only as regards language function, since the post-operative control period occurred after at least 6 months, but less than 2 years at the endpoint of this study (12/2007).

7.4 Statistical analysis

The statistical analysis was done using Windows Excel program and Fischer's Exact Test. The "p" value was considered significant, if $p < 0.05$.

8 RESULTS

8.1 Characteristics of patients

The study included 11 men (50%) and 11 women (50%) with a mean age of 31.9 years (range 10 to 53 years). The mean duration of epilepsy was 16.3 years (range 6 months to 38 years). All 22 patients had medically refractory epilepsy and underwent neurosurgical operation for resection of an epileptogenic cortex. In all of these patients the language cortex was located near the epileptogenic cortex or directly overlapped with it.

Four epilepsy patients (18.1%) underwent repeated operations for epilepsy. One of them had undergone an operation for frontal arterio-venous malformation (AVM) and needed additional frontal resection. Another had first undergone a neurosurgical operation for left frontal cerebral abscess, and another operation later on for epilepsy but had needed an additional frontal resection for seizure freedom. Two others had had a previous resection of the temporo-mesial structures and in one case additional temporal neocortical resection was necessary; the other required an additional frontal neocortical resection.

8.2 Non-invasive pre-operative investigations

All the patients were examined neurologically by both the neurosurgeon and the neurologist. Testing for speech function showed that one patient (4.5%) had an

insignificant, preoperative light dysphasia and one patient (4.5 %) light expressive aphasia. Eight patients (36.3%) had short post-ictal aphasia, seen as a lateralizing sign for language function.

All patients were examined by magnetic resonance imaging with the following results: unspecified lesion (including changes after previous resective operation) – 8 (36.4 %), post-contusional cortical changes – 3 (13.7%), no visible pathology – 3 (13.7%), cortical dysplasia – 4 (18.2%), low-grade tumor 2 (9.0%), cavernoma – 1 (4.5%).

Non-invasive EEG-video recording was also used for all 22 patients.

Positron emission tomography (PET) was needed in 19 cases (86%). It was not used in situations, when we had a strong pre-operative hypothesis of the epileptogenic cortex location after non-invasive EEG-video investigation. In one case the patient had insular cavernoma, another patient had had previous AVM resection, and one patient was suspected to have an astrocytoma.

Single proton emission computer tomography (SPECT) was used for 10 patients (45.4 %) when the previous search results for the epileptogenic zone were still not persuasive.

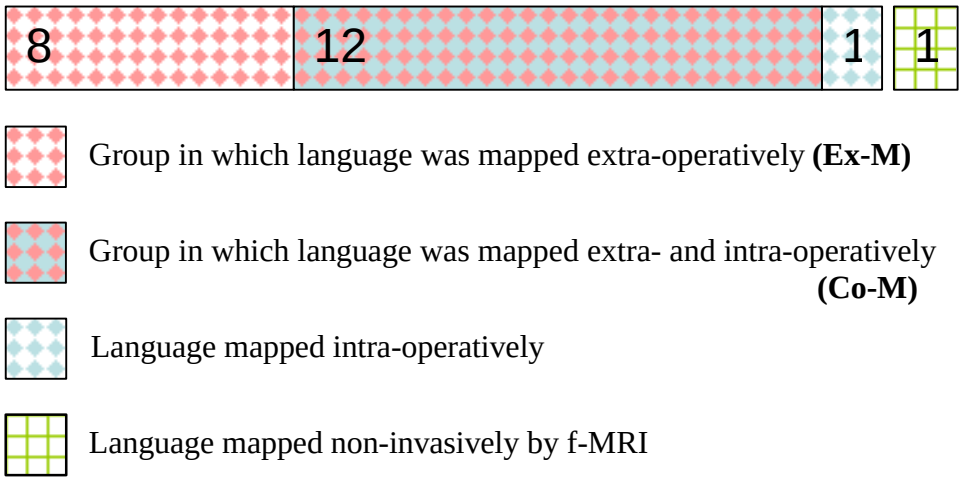
As described before, a functional magnetic resonance imaging (fMRI) was used for language mapping in one case, when insular cavernoma was the reason for the epileptogenic seizures.

The Wada test for language lateralization and memory assessment was used for 8 patients (36.3%). The use of this invasive test has greatly declined in the last 7 years due to its invasive nature and relatively high complication risk, as well as the possibility of now using fMRI for language lateralization. We used the Wada test for patients, in whom there was a strong possibility of speech dislocation due to long persisting lesion and brain plasticity.

8.3 Invasive language mapping

Invasive investigations to locate language cortex were performed in 21 out of 22 patients (95.4%) (in one case language was mapped non-invasively by functional magnetic resonance). (See drawing No. 2)

In one patient (4.5%) only intra-operative stimulation was done (a case of pre-operatively known low-grade astrocytoma). In eight cases (36.4%) only extra-operative language mapping was used. Both stimulation methods were combined for 12 patients (54.5%).



Drawing No. 2
The frequency of different language mapping methods used in our work.

If we consider the applicability of both language mapping methods separately, the following results are seen: extra-operative stimulation was used in 20 cases; intra-operative stimulation in 13 cases. In all 20 extra-operatively examined patients, positive speech points were found in 18 cases (90%). In all intra-operatively examined patients positive speech points were found in 12 cases (92.3%). The statistical value of differences in language finding by both methods was p=1.0 (insignificant).

8.4 Correspondence of extra- and intra-operative stimulation results (in the Co-M group):

The results of both mapping methods corresponded in 9 cases (75%) out of 12. (If we also add to this number those 3 patients, who had both language mappings and no speech was found in either mapping (not included in our study), the results corresponded in 12 cases (80%) out of 15.)

Three cases out of 12 had discordant results: in 2 cases (16.7%), no language cortex was found extra-operatively. However, intra-operative language mapping showed positive language points. In one case (8.3 %) (See Picture No. 3), some positive

language points found extra-operatively were stimulated also intra-operatively, but no language function could be confirmed in these locations.

SUMMARY OF RESULTS:	
Variable	**Value**
Men	11 (50-%)
Women	11 (50~~0~~-%)
Mean age	30.3 y
- Age range	10 – 53
Duration of Epilepsy	16.3 y
- Range	0.5 – 40 y
Significant language ~~deficite~~ deficits pre-operatively	
- Light expressive ~~aphasie~~ aphasia	1 (4.5-%)
Magnetic resonance	22 (100%)
- Unspecified lesion (including changes after previous resective operation)	8 (36.4 -%)
- Post-contusional changes	3 (13.7-%)
- No visible pathology	3 (13.7 -%)
- Cortical ~~Dysplasie~~ Dysplasia	4 (18,2-%)
- Low grade tumor	2 (9.0-%)
- Cavernoma	1 (4.5-%)
- Hippocampus sclerosis	1 (4.5-%)
Non-invasive 24 h video – EEG	22 (100-%)
PET	19 (86-%)
SPECT	10 (45.4-%)
f-MRI	1 (4.5-%)
~~WADA~~ Wada test	8 (36.3-%)
Invasive EEG rec./ language mapping	21 (95.4-%)
- Only i/op mapping	1 (4.5-%)

SUMMARY OF RESULTS:	
Variable	**Value**
Resective operation	22 (100-%)
- Frontal	8 (36.4-%)
- Fronto-Parietal	2 (9.2 -%)
- Fronto-Temporal	1 (4.,5-%)
- Temporal	8 (36.4-%)
- Temporo-Occipital	1 (4.5-%)
- Temporo-Occipito-Parietal	1 (4.5-%)
- Parietal	1 (4.5-%)
Pathology (n=20)	
- Sclerosis/ Gliosis	10 (50-%)
- ~~Dysplasie~~ Dysplasia (Cortical, Glioneural)	7 (35-%)
- ~~Tumour~~ Tumor (Astroc WHO II; DNET)	2 (10-%)
- Cavernous angioma	1 (5-%)
Post-operative complications	3 (13.5-%)
- Meningitis	1 (4.5-%)
- Subdural hematoma	1 (4.5-%)
- Epidural hematoma	1 (4.5-%)
~~Post~~ Post-operative language ~~deficite~~ deficits	10 (45.4-%)
- new permanent ~~deficite~~ deficits	1 (4.5-%)
Post-surgical outcome regarding seizure control *	(n-18)
- Engel I	9 (50-%)
- Engel II	0
- Engel III	2 (11.1-%)
- Engel IV	7 (38.9-%)

8.5 Resective operations

All 22 patients underwent a resective operation. It included the following cerebral lobes: frontal 8 (36.4%), fronto-parietal 2 (9.2%), fronto-temporal 1 (4.5%), temporal 8 (36.4%); temporo-occipital 1 (4.7%); temporo-occipito-parietal 1 (4.5%), parietal 1 (4.5%).

In 6 (54.5%) out of 11 temporal lobe resections, mesial temporal structures were also removed. This was done in cases, in which invasive EEG investigations showed some mesial epileptogenic activity.

Four patients (18.2%) underwent repeated operations for epilepsy.

In four cases (18.2%) of the total group, after repeated intra-operative stimulation of language sites (all cases in Co-M group) there was clear overlapping of language cortex with the epileptogenic zone. In these cases our inability to resect the whole epileptogenic cortex had been clear before the actual resection.

In one young epilepsy patient, an additional intra-operative language mapping was also indicated (language sites were very close to the epileptogenic zone). An operation could not be performed due to the patient's youth and psychological instability. Therefore we had also assumed pre-operatively that we would not be able to resect a full epileptogenic zone while preserving the language cortex intact. In another case, no full resection of the epileptogenic zone (low-grade astrocytoma) was possible due to the patient's complaints of short eyesight disturbances and our observation of horizontal nystagmus, while removing the rest of posterio-mesial temporal tumor in awake brain surgery. Thus, in six cases (27.2 %) out of all, we knew that we had not resected the complete epileptogenic zone at the endpoint of resective surgery. In all the other cases we assumed that we had resected the compete epileptogenic zone.

Pathologically following diagnosis were made: Sclerosis/ Gliosis (50 %); Cortical / Glioneural Dysplasia (35 %), Tumor (Astrocytoma WHO grade II, DNET) (10 %), Cavernous angioma (5 %).

8.6 Post-operative results as regards language function

Overall, postoperative speech deterioration was noted in 10 cases (45.4 %) out of 22 (anomia – 5, expressive aphasia – 3, receptive aphasia – 1, combination of expressive aphasia and anomia – 1 case). In all of these cases speech disturbances regressed soon after surgery; however, only in 8 out of 10 patients did speech return to its pre-operative performance either already during the hospitalization period or by the time of the first check-up (4 to 6 months after surgery). In the remaining two cases a complete regression of speech disturbances was not seen even after 6 months of observation; these speech deficits were considered permanent. In one of these two cases, language disturbance (light expressive aphasia) was noted already before the resective operation; therefore, new permanent language deficit occurred in one case (4.5%) of the whole group.

If we compare the post-operative language deterioration between the two groups (Ex-M and Co-M), the results are as follows. Post-operative speech deterioration was seen in 6 (75%) out of 8 patients in the Ex-M group (See Fig. No. 3) and in 4 (33.3%) out of 12 patients in the Co-M group (See Fig No. 4). The statistical significance of difference in post-operative language deterioration in both groups was $p = 0.169$ (insignificant).

A comparison of new, permanent language deterioration in both groups revealed one case (12.5%) in the Ex-M group. One patient of the Co-M group had had permanent language deterioration already pre-operatively. The statistical significance of difference between the two groups as regards new, permanent post-operative language deficit was $p=0.4$ (insignificant).

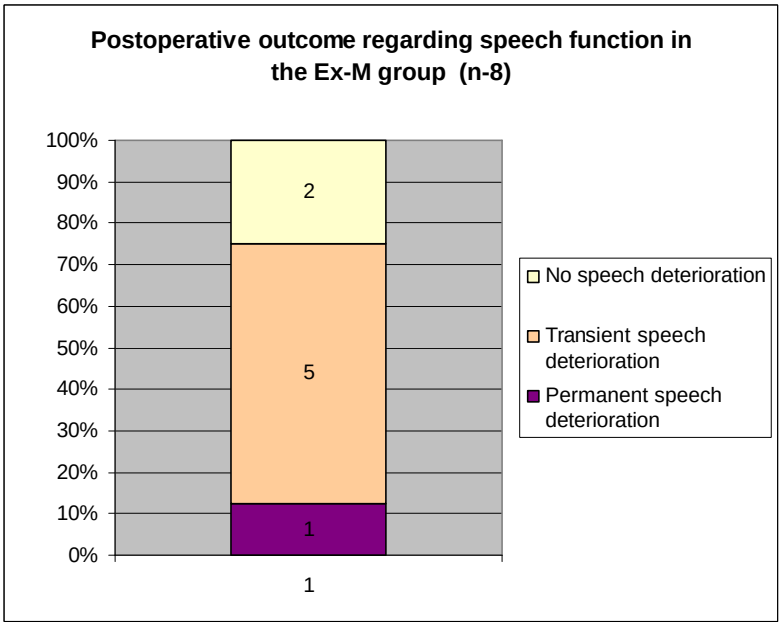


Fig. No. 3

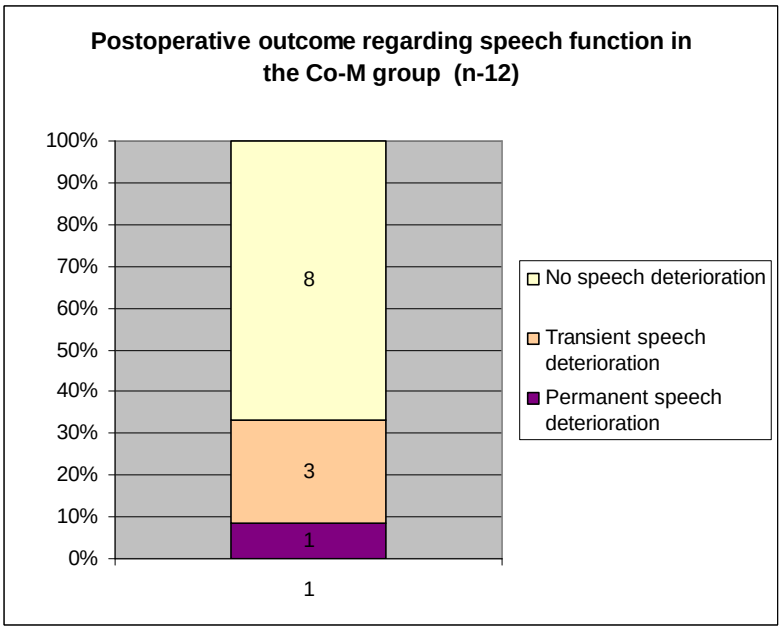


Fig. No. 4

8.7 Post-surgical outcome as regards seizure control

Post-surgical seizure outcome of 2 or more years after last resective epilepsy surgery (mean follow-up period 46.6 months, range 24 to 96 months) was determined for 18 (81.8%) out of 22 patients. These were all only retrospectively analysed cases. Four patients were not included in this summary of post-operative results. In one case the seizure frequency had not declined since resective surgery, and a vagal nerve

stimulator had been implanted 1 year later. The remaining three patients hade not had a sufficient follow-up period post-operatively by the endpoint of this study (12/2007).

The Engel classification data for 18 patients who underwent operations for epilepsy close to speech areas are as follows (See Fig No. 5):
Engel I – 9 patients (50%) (Ia – 8 cases, Ib – 1 case); Engel III – 2 patients (11.1 %), Engel IV – 7 patients (38.9 %) (IVa – 3 cases, IV b – 4 cases).

In six cases (27.2 %) we were not able to resect the complete epileptogenic zone and stated it already during the resective surgery. Half of these cases were in the IVb group, two cases in the IVa group (all together 5 cases). In one case the follow-up period was too short (8 months) by the endpoint of our study (12/2007), this patient was not included in the evaluation of seizure outcome.

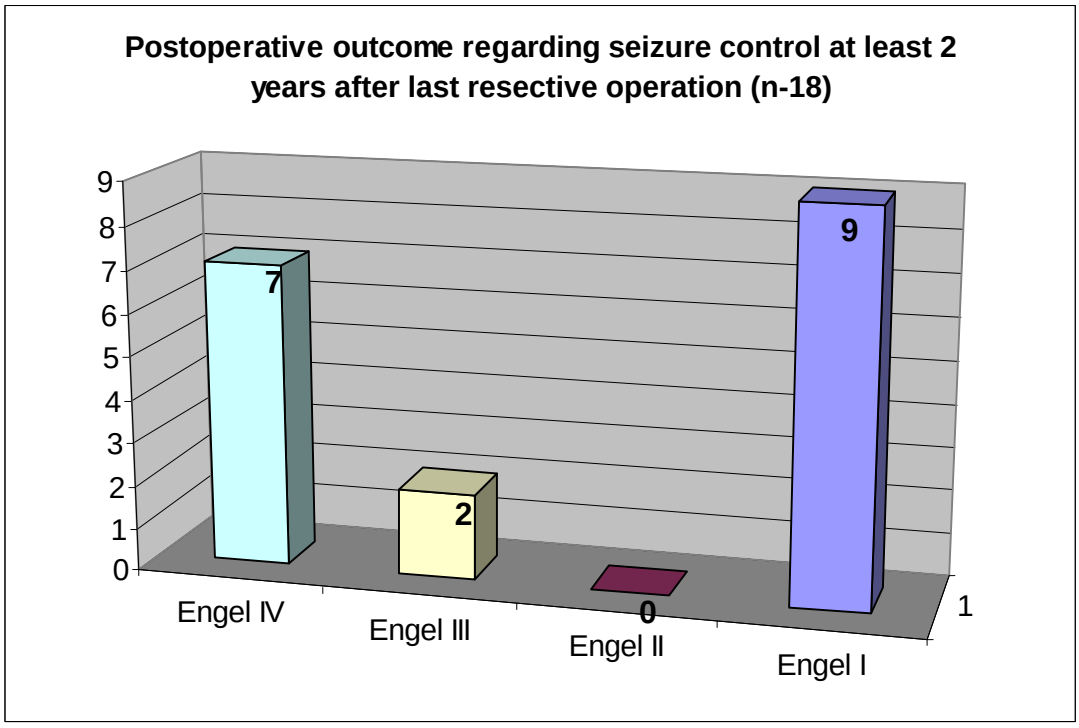


Fig. No. 5

If we compare the post-operative outcome for seizure control in both groups of different language mapping methods (extra-operative and combined language mapping group), the results are as follows. In the Co-M group, data were compiled for nine patients. Engel class I outcome was seen in three cases (33.3 %), Engel class II –

none, Engel class III – one case (11.1 %), Engel class IV – five cases (55.6 %). (See Figure No. 6)

In the Ex-M group, data were compiled on seven patients. Engel class I outcome was seen in four cases (57.1%), Engel class II – none, Engel class III – 1 (14.2%); Engel class IV – two (28.7%). (See Figure No. 7)

The statistical significance of differences between Ex-M and Co-M groups, as regards Engel class I outcome, was p=0.63 (insignificant).

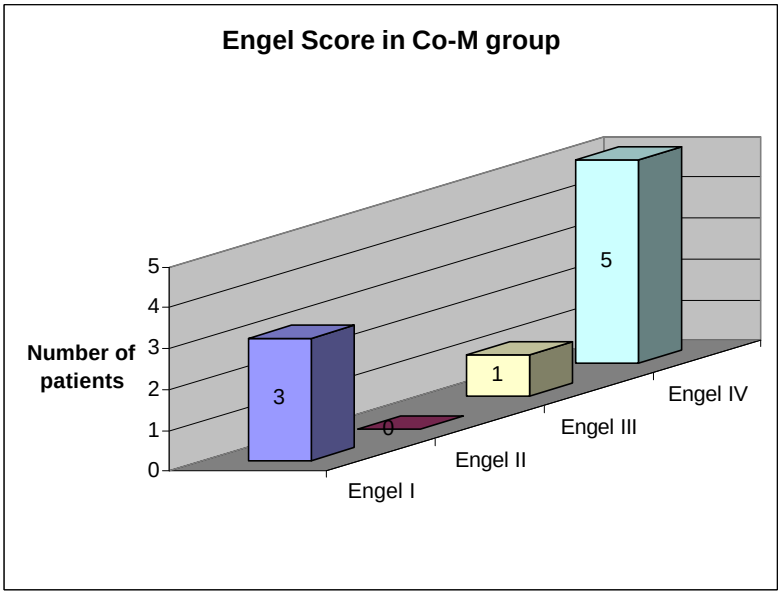


Fig. No. 6: Post-operative outcome for seizure control (Engel Score) in combined language mapping group.

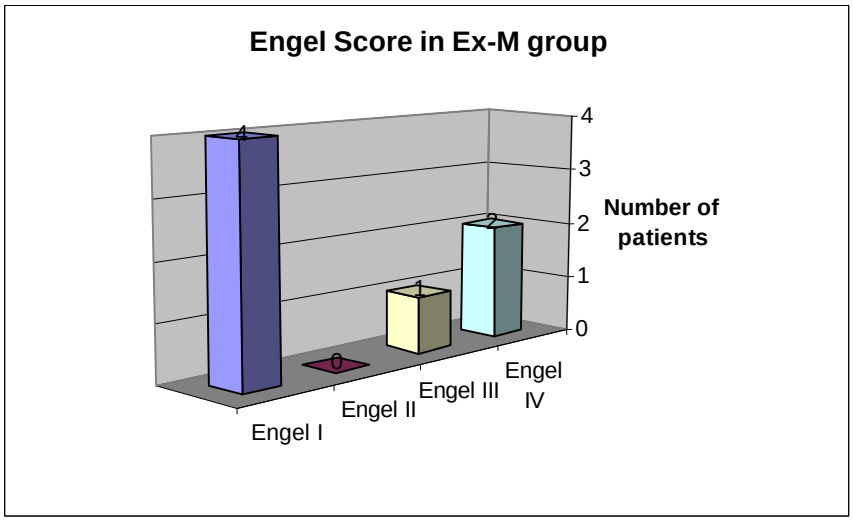


Fig. No. 7: Post-operative outcome regarding seizure control (Engel Score) for extra-operative language mapping group.

8.8 Post-operative complications

The following post-operative complications were diagnosed: meningitis (4.5%), subdural hematoma (4.5%), epidural hematoma (4.5%). All complications occurred in cases in which large craniotomies with insertion of subdural electrodes had been performed. All patients recovered well after the operations, and no permanent neurological deficits were apparent.

8.9 The summary of statistical analysis data

The significance of differences between extra-operative (Ex-M) and combined (Co-M) language mapping groups as regards postoperative language and seizure outcome:

Comparing difference as regards	**p value**	**Difference estimated as**
Immediate post-operative language deterioration	0.169	insignificant
New, persistent language deterioration	0.4	insignificant
Engel class I outcome	0.63	insignificant

The significance of differences between extra-operative and intra-operative language mapping technique as regards the identification of language sites:

Comparing difference as regards	**p value**	**Difference estimated as**
Identification of language sites	1.0	insignificant

9 DISCUSSION

9.1 Patients and non-invasive investigations

Our study demonstrates that epilepsy surgery around speech areas is a very complex subgroup of epilepsy surgery. This complexity is reflected in the diversity of patient characteristics and investigation results (significant age range, varying duration of epileptic seizures, localization of epileptogenic zone, localization of speech cortex, various pathological data, etc.). A significant variability in patient characteristics, in their turn, makes difficult any decisions on the site and amount of resection as well as prediction of post-surgical seizure control outcome.

The preservation of intact language areas and postoperative language function has always been of primary importance in our work, even superior to the full resection of the epileptogenic zone.

The suspicion that language cortex is located close to the epileptogenic zone must be considered a serious, difficult condition for surgery, in which both good post-operative seizure control and the simultaneous preservation of language function are expected. Such proximity almost always necessitates vast pre-surgical investigations, often including the most recent and expensive investigational methods available in neurosurgery. This, of course, restricts the investigational process of epilepsy surgery to only a few neurosurgical clinics.

One of the first serious factors that necessitates more detailed investigations is the difficulty of determining the precise borders of lesions in magnetic resonance imaging. Although it was possible to identify a certain lesion in 86% of our cases, in most of these situations the lesion was rather diffuse, and we had to resort to additional investigation methods to specify the exact borders of the epileptogenic zone.

Non-invasive EEG also provided insufficient information about the topography of the seizure focus. This investigation is considered too insensitive to be used for determining exact borders of the epileptogenic zone [40], [108]. It also has a spatial limitation - it can only record brain electrical activity in an area of about 6 cm^2 [62].

In 80% of adult temporal lobe epilepsy cases (in mesial temporal lobe epilepsy, the frequency rises to 90%), magnetic resonance and ictal non-invasive EEG recording alone provide sufficient information for localizing the seizure origin and making a decision about surgery. In contrast, epilepsy surgery around speech areas normally requires the implementation of several additional investigational techniques to achieve the same goal [33], [46]. Only in one case (4.5%) were we able to proceed with surgery on the basis of MRI and EEG alone: the patient had a well-confined insular cavernoma. In this case we were certain that the pathology corresponded to the epileptogenic zone and the danger of damaging functionally significant language areas was stated here as low. In the remaining 21 patients (95.5%) several additional non-invasive (PET) and (SPECT) as well as invasive investigations were necessary to more precisely delimit the epileptogenic zone. The danger of damage to the functionally significant language cortex during the resective surgery was variable in these cases.

An invasive Wada test was used in situations, in which non-typical speech lateralization was suspected. Due to its invasive nature, we have increasingly restricted the use of this investigation in our work over the last 7 years only to cases in which the presence of epileptogenic lesion and epileptic seizures had been seen or had been expected for a considerable time (especially since childhood). This strategy is based on findings that early onset of left hemisphere seizure foci is associated with altered language lateralization and increased incidence of right hemisphere dominance [10], [47]. However, in our epilepsy surgery practice only three (2,9%) out of all 103 left hemisphere epilepsy surgery patients had a right-sided language representation. In only one of these (epidermoid tumor, epileptic seizures since the age of 16, lasting for 15 years) could a reorganization of language cortex be validly suspected due to the early pathology and long duration of the seizures. The second case involved a young patient with left-sided hippocampal sclerosis. Seizures had first occurred at the age of 15 and lasted for 3 years. In this case it was hard to say if 3 years of epileptic seizure history were sufficient for language function dislocation. We also do not have information about the duration of the “silent period” – time interval between first pathological changes in the hippocampus and their clinical manifestation. Therefore it is not clear if the patient had had these pathological changes already for a longer time and if this factor played a significant role in the displacement of language. The third

patient was 56 years old, had a left temporal lesion, histologically diagnosed as dysplasia, and a 10-year history of epilepsy. These three patients, of course, were not included in our study; their cases simply illustrate the complexity of deciding whether to give the Wada test for language lateralization. With such few data we cannot conclude that early development of an epileptic lesion and/or seizures is directly connected with language dislocation to the opposite hemisphere. Duchowny and colleagues also confirmed this, reporting that the language cortex tended to remain in the left hemisphere, in proximity to, or even overlapping developmental lesions (e.g., dysplasia) and the epileptogenic cortex in patients with early seizure onset (age <5 years). Only very large early lesions acquired before age five and which destroyed language cortex were associated with right hemisphere language [27].

In summary, we cannot infallibly prove that a long history of seizures and epileptogenic lesion is a definite indication for the use of the Wada test in this group of patients. The use of this test largely depends on the experience made with it in each individual neurosurgery clinic.

A good alternative to the Wada test for language lateralization is functional magnetic resonance imaging (f-MRI) [24]. In our study, however, it was not used for language lateralization, but instead for non-invasive language mapping in one patient with insular cavernoma as an epileptogenic lesion. Although Roux and co-workers found that f-MRI cannot be used for making surgical decisions in the absence of direct (invasive) brain mapping [102], we performed a resective operation without direct cortical language mapping in this one case due to the fact that good intra-operative orientation and preservation of the speech cortex were possible by combining of neuronavigation and f-MRI data. No post-operative speech deficits were seen in this case.

9.2 Invasive language mapping and post-operative language function

For the remaining 21 patients (95.5%) in our group, language was mapped invasively by direct cortical stimulation. In one case epileptic seizures were caused by a low-grade tumor. On the basis of previous non-invasive investigations, we were quite sure that the epileptogenic zone corresponded with the tumor, and we saw no

indications for inserting subdural electrodes to record additional invasive EEG data. Nevertheless, language mapping was needed and it was done intra-operatively during awake brain surgery.

For the remaining 20 patients (91%), no well-confined cortical lesions (in 13.7% no lesions at all) were seen, nor did other successive non-invasive investigations assure us of precise epileptogenic zone boundaries. We did not consider it safe to proceed directly with resective surgery with only intra-operative language mapping; therefore, subdural electrodes were used to better specify the epileptogenic zone as well as for successive language mapping.

Poor EEG localization of interictal spikes, seizure onset, the presence of a broad, often ill-defined epileptogenic area, as well as the extension of the proposed area of resection into brain areas of high functionality have also been mentioned as significant problems in several other studies [90], [94], [123]. However, these studies involved only extra-temporal epilepsy cases. In contrast, our study included also temporal neocortical epilepsy cases that required additional invasive pre-surgical investigations.

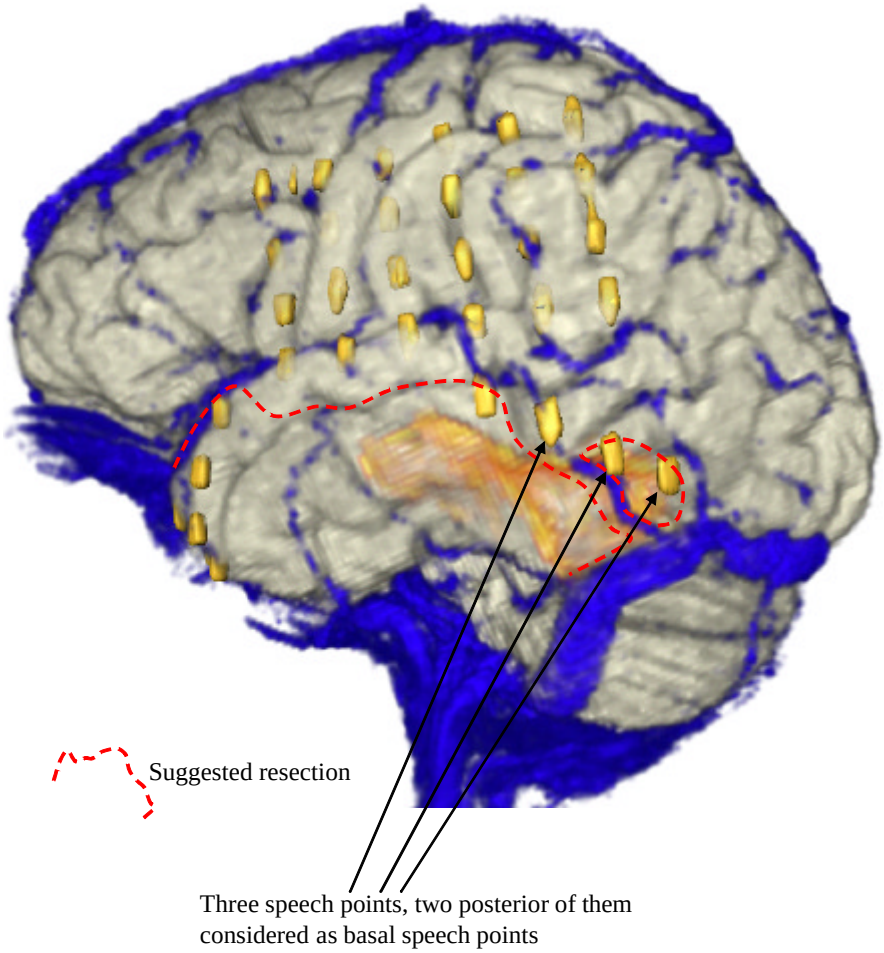
Thus, the majority of epilepsy surgery patients with an epileptogenic zone located close to speech areas required apart from the usual resective operation, a complex invasive investigation, including craniotomy, insertion of subdural electrodes, and 8 to 12 days of continued monitoring in the epilepsy intensive care unit.

The use of extra-operative or combined extra-intra-operative language mapping techniques was in almost all cases based on the measure of overlap between epileptogenic and language zones. The few exceptions will be discussed later.

Our assumption that epileptogenic areas, located at least 10-mm away from language areas, are at a rather safe distance from each other and thus the maximal amount of epileptogenic zone can be resected without significant fear of post-operative language disturbances was based on data published by Haglund and colleagues. They reported that a resection margin of >1 cm from the language area results in significantly less permanent language deficits [37]. According to Silbergeld, any injury to essential language areas will lead to permanent difficulties [106]. Thus, the strategy of leaving

a 10-mm resection margin from the language areas is also followed in centers with considerable experience in neurosurgery around speech areas [12].

In the first group of patients (only extra-operative language mapping group (**Ex-M**)) we also included one patient in whom the basal temporal language area directly overlapped with the epileptogenic zone (Picture No. 4). There was no need for additional intra-operative specification of language cortex borders in this case. We based our decision on data firstly published by Krauss GL et al,, who reported that resection of basal temporal language areas does not cause permanent decrease in naming in most cases and therefore might be an acceptable risk, when the goal is treatment of severe partial epilepsy [53]. This particular patient directly developed post-operative deterioration of the language function, but these changes were of a regressive nature and at the time of first post-operative visit to the neurosurgeon (4 months after surgery) no more speech disturbances were observed.



Picture No 4 A 37-year-old patient with epileptic seizures due to cerebral contusion defect (trauma 10 years previously). Speech was detected at three temporo-occipito-basal points, two of which were located in the area of the planned resection. Due to the basal localization of these points and insignificant functional value, it was decided to perform resection without repeated intra-operative language mapping. Initially language disturbances were observed post-operatively, but speech returned to its pre-operative state 4 months after surgery.

It was necessary in the second group of patients (combined cortical mapping group (**Co-M**)) to repeat intra-operative language mapping. We assumed that there was a significant trade-off between maximal resection of the epileptogenic zone and preservation of the language cortex (preservation of a margin of at least 10 mm from the language cortex) due to the close relation between the two cortical areas. In our opinion, intra-operative orientation and resection of the epileptogenic cortex could not be performed here only on the basis of extra-operative invasive investigation data (summarized in report with 3-dimensional image as seen in Picture No.3).

Interestingly, the initial post-operative data showed more frequent decreases of immediate post-operative language performance (in 75% of the cases) in the Ex-M group, although pre-operatively a rather in-significant trade-off between epileptogenic and language cortex had been supposed. In contrast, the immediate post-operative language performance in the Co-M group showed a decrease in only 33.3% of the cases. In the majority of these cases, however, language deterioration was of a regressive nature. Permanent language deterioration was seen in only one patient (12.5%) in the Ex-M group and in one patient (8.3%) in the Co-M group (in this one case deterioration was seen before the resective operation).

Even if these differences are considered statistically insignificant (due to the often similar performance of both language mapping techniques and the small number of study patients), they illustrate quite well the impact of larger resections on post-operative language function in cases in which the epileptogenic zone is located close to speech areas. In the Ex-M group, where a less significant trade-off between both cortical areas was supposed, resection could be performed in a somewhat freer manner and include broader cortical areas. This slightly freer manner and larger resection could account for more frequent temporary post-operative language deterioration.

An explanation for more frequent temporary speech deterioration and for one case of new, permanent language deterioration in the Ex-M group could be that the resection caused damage to the language association (supplementary) cortex (in one case permanent deficit – damage to the essential language cortex). If at least some of the supplementary language cortex had been missed in extra-operative language mapping, we could have also included some part of it or part of the subcortical language tracts in the resection. This may indicate the need for better detection of different speech zones (essential and supplementary).

An additional factor is the difficult intra-operative anatomical orientation, based on 3-dimensional extra-operative language mapping images, not on actual anatomical representation of language sites that were more precisely detected by intra-operative mapping. Thus, it may be that a safe distance of at least 10 mm from language sites was not maintained at all sites.

Among some in the literature expressed views, Hamberger and colleagues suggest that a resection of auditory naming (AN) sites, undetected during mapping based on

the sole use of visual naming tests (in our work also only visual naming tests were used for intra-operative language mapping), possibly contributes to such decline of post-operative language function [38]. They also mention the possibility that stimulation produces more limited localized response, whereas resection results in more extensive damage to neuronal/ cognitive processes underlying word retrieval. Another reason for transitory speech disturbances could be a post-surgical edema at the resection site.

The reasons for transient speech deterioration in the Co-M group could include the presence of post-operative edema or damage to the language association cortex, auditory naming sites (also here exclusive use of visual naming tests during neuropsychological investigation) or subcortical language tracts. The reason for the fewer temporary post-operative language deficits in this group is most probably somewhat more cautious surgery in combination with better intra-operative orientation by intra-operative language mapping. However, we were not able to ascertain the location of associative language cortex in these patients, and we did not perform a subcortical language mapping or auditory naming tests. Thus, this remains only a presumption of the cause of post-operative transitory language deterioration.

Bello and colleagues report that even if cortical structures are preserved, permanent morbidity may depend on surgical damage to the subcortical pathways. They have advocated an additional use of subcortical intra-operative language mapping [7].

Regarding resection caused damage to the supplementary language cortex (also called “sites of partial naming errors” by Ojemann [89]) was reported in one small study of 10 patients. The authors noted that removal of these sites is not associated with persistent language decline, whereas encroachment on essential sites (where function disturbance was found in 100% by cortical mapping) is related to postoperative (at 3 months) decline of language function [89]. In their study two patients out of ten had their supplementary language sites removed but postoperatively did not have any permanent language disturbance. However, further and larger scale studies are needed to clarify this question.

Another observation has been made on the post-operative consequences after resection of the supplementary motor area. Although its stimulation can induce motor and even language problems, it is described as possible to remove this area with only a transient “supplementary motor area syndrome” followed by a complete recovery

[28]. These experiences of only transient disturbances, combined with observations after resection of basal speech sites, recommends considering the resection of suspected associative language cortex in situations when it hinders full resection of the epileptogenic zone. The only problem is the precise localization of the associative language cortex.

Our current knowledge and investigative methods are insufficient for clearly distinguishing between essential and associative language areas as well as for defining the actual neurophysiological defect after resection of the latter. The complex organization and significant individual variability of the language cortex still remain a topic for many further studies [83], [103].

On the basis of our current knowledge and these study data, both extra- and combined extra-intra operative language mapping techniques are good and reliable for use in epilepsy surgery close to speech areas. There are no statistically significant differences between post-operative language outcomes in either group; however, a combination of both methods is associated with less frequent temporary postopertive language deterioration and should be considered at least in cases in which there is a very close relation between the epileptogenic and the language cortex. Large-scale studies are needed to better evaluate each language mapping tactic used as well as to determine the organization of the language cortex, the role of associative language cortex in language function, and the best diagnostic measures for defining associative and essential language cortex.

A comparison of the results of both stimulation methods in the Co-M group reveals the congruence of language mapping data in 9 (75%) out of 12 cases (if we also add the 3 excluded cases in which both cortical mapping methods consistently showed no presence of speech cortex close to the epileptogenic zone, both mapping methods correspond in 12 (80%) out of 15 cases). This proves that they are highly reliable methods for language mapping.

In three cases the two language mapping methods yielded incongruent results. In two of these cases no speech could be found extra-operatively, but only intra-operatively. The subdural electrodes were placed over the classic Wernicke (Gy Angularis) and Broca areas (posterior portion of Gy Frontalis Inferior). By additional intra-operative

language mapping we wanted to verify here the negative extra-operative language mapping results. In one case, stimulation indicated language sites in the same location, where subdural electrodes had previously been located. It is not clear why the two mapping techniques yielded different results in this case. There might have been poor contact between the subdural electrodes and the cerebral cortex, although no problems were noted during direct EEG recording at these sites. It might have been due to the very small size of the speech site, localized close to (in between) the subdural electrodes, but not overlapping them. Earlier observations indicated that unique and reliable responses occur at sites within only a few millimeters of each other [87], [88]. However, this is an extraordinary case and should not be seen as a typical difficulty of subdural mapping.

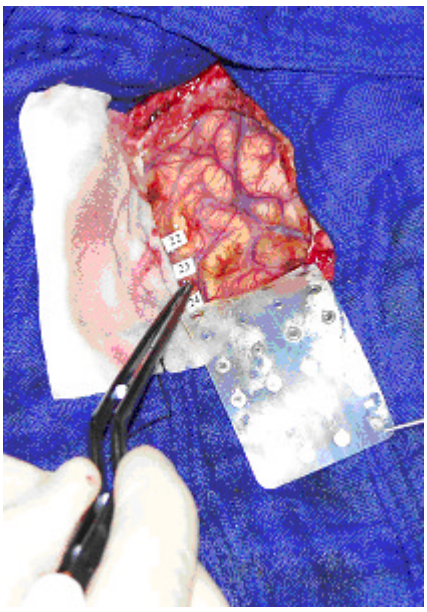
In the other discrepant case, a broader cortical area was stimulated intra-operatively, and language sites were found close to the area covered by subdural electrodes. Perhaps the choice of subdural electrode size was inappropriate, and the distribution of the language areas was atypical due to the early onset of epilepsy [26]. (This patient had had seizures for 38 years, ever since the age of 14.) However, we cannot clearly attribute the dislocation of speech areas in this patient to the long duration of epileptic seizures. Also Ojemann G. and co-workers could not prove that dislocation of language areas was due to abnormal early development in their study of 117 left language-dominant frontal or frontotemporoparietal craniotomies [83]. However, a study published by Bell and colleagues reported reorganization of the language function within the left hemisphere as a result of an early precipitating injury and/or early onset left temporal lobe epilepsy [6]. In their study, the mean onset age for early-onset temporal lobe epilepsy group was 4.2 years, which is significantly earlier than in our patients.

These results prove the importance of the investigational hypothesis for placement of subdural electrodes and its complexity, as well as the need for a critical weighing of the investigational data.

In the third case of incongruent language mapping results, three extra-operatively found language sites overlapped with the epileptogenic zone (See Picture. No. 3).

Repeated intra-operative stimulation at these three points (See Photo No. 13) found no language function, apparently indicating their associative nature. In view of

the intra-operatively assumed associative function of these points and severe epileptic seizures of this patient, we chose to resect the complete epileptogenic zone, including all three extra-operatively found language sites. This particular patient had light expressive aphasia preoperatively. Immediately after the resective operation the aphasic disturbances increased, but they returned to their pre-operative level at the end of the first month after surgery. This experience seems to support the earlier presumed non-significant role of particular (in this case, presumably associative) speech areas in language function. This also exemplifies a possible strategy in situations in which the suspected associative language cortex overlaps with the epileptogenic zone, arguing in favor of the resection of associative language areas without fear of permanent language deterioration postoperatively.



However, as mentioned earlier, the best method for defining an associative cortex remains unclear. We cannot prove here that intra-operative language mapping is the best means for differentiating between essential and associative language cortex. This, as well as the consequences of associative language area resection, must be investigated in a specific large-scale study.

Photo No. 13 Intra-operative stimulation of 3 overlapping language points

The use of two different language mapping techniques in this study allowed us to additionally evaluate the general performance of both methods individually. The two methods yielded quite similar results: extra-operative language mapping identified positive language points in 90% of cases, intra-operative language mapping, in 92.3%. Also statistically the difference between the two language mapping methods was insignificant. However, these data do not agree with other published data comparing the stimulation methods. This might be due to the fact that we did not measure the number of positive responses in each language mapping method, but only whether

speech was found or not. Noachtar reported that more positive responses were detected by extra-operative stimulation in a case in which both stimulation methods were used to localize the motor cortex [74].

Analysis of the post-operative results regarding language function in the whole group of patients with epileptogenic cortex close to speech areas revealed that permanent language deficits were found in only two cases (9.0%), whereas the deficit was new in only one case (4.5%). Comparison of these data with that of the post-operative language function in a recently published study of 250 glioma patients who underwent resective operations close to the speech cortex showed there was a permanent language deterioration 6 months after surgery in four cases (1.6%) [103]. The increased percentage of permanent speech deteriorations in our study might be due to the small number of cases.

9.3 Post-operative seizure control

Analysis of the seizure outcome at least 2 years post-operatively (18 patients) revealed almost only diametrically opposite results – the best possible outcome (Engel I) in nine cases (50%) versus the worse possible outcome (Engel class IV) in seven cases (38.9%). For easier further evaluation the results of Engel class III and IV (9 patients) were combined in one group. This group can be called the unfavorable seizure frequency outcome group.

In the majority of cases in this unfavorable outcome group (five cases, all Engel IV), no full resection of the epileptogenic zone was possible. This was known already during the surgery. In four of these patients, full resection of the epileptogenic zone was not possible due to its close relation to the language cortex. In the fifth case a full resection of the epileptogenic zone (low-grade astrocytoma) was not possible due to intraoperative complications - patient's complaints (during awake brain surgery) of eyesight disturbances and intra-operatively observed transient horizontal nystagmus.

In the remaining 13 cases (out of 18 cases with 2 years postoperative follow-up period), we initially supposed that the complete epileptogenic zone had been resected. During the follow-up period, four more cases had repeated seizures; apparently

no complete resection of the epileptogenic zone had been achieved by the resective surgery. In two of these cases the seizure frequency was reduced by about 85%, compared with the pre-operative results (Engel class III); two other cases corresponded to Engel class IV outcome.

Analyzing retrospectively the reasons for poor seizure control in these four patients, we reached the following conclusions:

- In two cases a significant trade-off between complete resection of the epileptogenic cortex and preservation of the language cortex was seen pre-operatively. In both cases an additional intra-operative language mapping was used with subsequent careful resection around language areas. This more restricted mode of surgery could be the cause for unsatisfactory seizure outcome.
- In all 4 cases there were difficulties with determination of the epileptogene zone. In two cases rather diffuse lesions (cortical dysplasia and cortical contusion in combination with hippocampus sclerosis) were identified in the MRI. In two other cases no lesions at all could be found in the MRI (non-lesional cases). Also despite vast invasive investigations, no complete detection and/or resection of the epileptogene zone was achieved.

Here we can state the main reasons for unfavorable seizure frequency outcome in the whole group:

- conflict between full resection of the epileptogenic zone and simultaneous preservation of safe distance to language cortex together with
- difficult localization of the epileptogenic zone.

The latter reason is specific for general neocortical epilepsy surgery, and has been described in several studies of extra-temporal epilepsy surgery [90], [94], [123].

Analysis of the post-operative seizure freedom in both language mapping groups, assuming equal results in the definition of the epileptogenic zone, revealed better results in the Ex-M group, where the trade-off between the epileptogenic zone and the language cortex was suspected to be less significant preoperatively. Thus, more of the epileptogenic cortex could be resected in a freer manner and more completely. And

exactly this increased extent of surgery might account for the more complete resection of the epileptogenic zone and better post-operative seizure outcome.

Although the difference in seizure outcome in both groups was found to be statistically insignificant, the less positive seizure control in the Co-M group seems indicative of the complexity of epilepsy surgery close to speech areas. It once more highlights the significance of the trade-off between full resection of the epileptogenic zone and preservation of the language cortex in this epilepsy surgery group. It was not that the combined mapping technique was the reason for worse post-operative seizure outcome, but rather the above-mentioned trade-off and our inclination to less aggressive surgery around speech cortex, fearing to cause significant post-operative neuropsychological deficits.

However, despite the complex pathology of these patients - often unequivocal noninvasive findings, including wide-spread neocortical lesions or non-lesional cases, the complicated definition of the epileptogenic zone and language cortex, their close interactions or even overlapping as well as cases in which complete resection of the epileptogenic focus was not possible, 50% of the cases had complete seizure freedom and satisfactory results.

Described post-operative complications indicate the high risks of invasive investigation. All of these complications occurred in patients in whom an extensive investigation with subdural electrodes was performed. This once more stresses the importance of strong indications for invasive extra-operative language mapping.

10 Drawbacks of the study

One of the main drawbacks of this study is the small number of cases. This is directly connected with the relatively small number of epilepsy surgery patients in neurosurgery and the even smaller number of patients with the epileptogenic zone close to the language cortex. The second drawback of this study is the mainly retrospective mode of analysis.

11 Final remarks

This work illustrates the complicated nature of epilepsy surgery close to speech areas. Apart from the complicated localization of the epileptogenic zone, which is not unusual for neocortical epilepsy cases, its close location to or overlapping with the language cortex makes a complete resection of the epileptogenic zone and subsequent full post-operative seizure control difficult or sometimes even impossible. The success of surgical treatment can be promoted by accurate and extensive pre-surgical investigation. Its quality greatly depends on the experience of the individual epilepsy surgery team.

These few study data do not permit us to statistically, prima facie, prove that additional intra-operative language mapping is beneficial for better postoperative language and seizure frequency outcome in cases in which previous extra-operative language mapping detected the close relation of epileptogenic and language areas. Thus, we also cannot statistically confirm our initial hypothesis. Nonetheless, better postoperative language function is associated with the additional use of such methods. The combined method is especially advisable in cases in which a full resection of the epileptogenic zone would significantly endanger the preservation of language areas. Better postoperative seizure outcome is seen in cases in which there is a less significant tradeoff between the two cortical areas and thus larger resections are possible.

The use of invasive methods for language mapping is well-founded due to still many uncertainties towards the performance of different non-invasive language mapping techniques and despite the many unknowns about the organization and function of

language. In some individual cases of severe epilepsy, resection of the basal temporal or associative language areas may be considered for better seizure control without fear of permanent post-operative language deterioration. Nevertheless, which methods are best for distinguishing between essential and associative language cortex remain unclear.

Large-scale studies are needed to study the organization of the language cortex, to define the supplementary and essential language areas, to determine their role in language function, as well as to recommend the best methods/ tactics for language mapping and resective surgery close to speech areas.

12 CONCLUSIONS

1. Epileptogenic cortex located close to or overlapping with speech areas is a very complex pathology. The complexity is based on the diversity of patient characteristics, localization of the epileptogenic zone and language sites.
2. Parallel to the common burdensome factor for full resection of the epileptogenic zone in neocortical epilepsy surgery – its adequate localization, a significant additional, specific factor in this sub-group is seen. This is a close localization or overlapping of language cortex with the epileptogenic zone.
3. Therefore in the majority of cases in our clinic, pre-surgical investigations in this subgroup of epilepsy surgery patients include a wide range of specific and high-cost procedures.
4. The use of the Wada test for language lateralization in this group of patients depends largely on the experience of each epilepsy surgery center. Successful language lateralization can also be done with non-invasive functional magnetic resonance.
5. In the majority of cases a vast neocortical extension of the epileptogenic zone necessitates insertion of subdural electrodes; the close and individually different location of language areas requires successive language mapping.
6. The main factor that influences the extensiveness of resective surgery is the need to avoid any new permanent neuropsychological morbidity, especially in connection with language function.
7. The overall post-operative language outcome is satisfactory and thus justifies the use of invasive language mapping as currently the best language localization method.
8. The patient groups that underwent extra-operative and extra-intra operative language mapping showed no statistically significant difference post-operatively as regards language function. This can be attributed to the small number of study cases and the quite similar performance of both language mapping techniques.
9. Both invasive language mapping tactics can be successfully used in epilepsy surgery close to speech areas. However, the use of combined extra-intra operative language mapping is associated with better post-operative language outcome. Thus, combined language mapping is strongly indicated at least in

cases in which the tradeoff between epileptogenic and language areas is significant. It can be seen as significant, if the distance between both cortical areas is less than 10 mm.

10. Post-operative seizure control in the whole group of epilepsy surgery close to speech areas can be considered satisfactory, in view of the complex pathology of these patients. Complete seizure freedom is seen in 50% of these cases.
11. Better post-operative seizure outcome is seen in those cases, in which there is less significant tradeoff between the two cortical areas and thus more aggressive resections of the epileptogenic zone are possible.
12. The choice of language mapping technique did not statistically influence the level of postoperative seizure control.
13. The main reasons for unfavourable seizure outcome in this epilepsy surgery subgroup are inability to perform complete resection of the epileptogenic zone due to its direct overlapping or close relationships with the language cortex and/or difficult location of the epileptogenic zone.
14. Better post-operative seizure freedom might be possible in situations in which the epileptogenic cortex overlaps with the supplementary language cortex. In individual cases of severe epilepsy a resection of the supplementary areas might be reasonably considered. However, the best methods for precisely distinguishing between essential and supplementary/associative language cortex are unclear and remain a subject for further study. The precise impact of the resection of associative language sites must also be investigated in large-scale studies.
15. The impact of the disperse location of the epileptogenic zone in neocortical epilepsy can be minimized by patient examination in experienced epilepsy surgery centers and the use of the most advanced investigational techniques.
16. Larger scale studies are needed for more profound evaluation of both language mapping tactics in epilepsy surgery.

13 Possibilities for further improvement in epilepsy surgery around speech areas

Subcortical intra-operative language tract mapping should be seen as a useful addition to the usual cortical stimulation for epilepsy surgery close to speech areas, when the epileptogenic lesion involves both cortical and subcortical tissues. Bello and colleagues advocate its use in their study of patients with gliomas that involved language pathways [7]. Even when preserving cortical structures, permanent morbidity may depend on the surgical damage to the subcortical pathways. Bello and co-workers describe the use of the same current threshold for subcortical stimulation, as used in stimulation of the cortex. Subcortical stimulation was alternated with surgical removal and used when the resection came close to the subcortical structures located near the cortical language sites, all around the surgical cavity, and at its boundaries. They recommend subcortical stimulation as a reliable tool for guiding surgical resection and, at the same time, for predicting the likelihood of postoperative language deficits in cases of tumors involving speech areas.

Henry and colleagues advocate the **combination of diffusion tensor MRI fiber tracking with intraoperative mapping** for better detection of the subcortical pathways in surgery close to eloquent regions [43].

In another study, Bello and co-workers recommend the use of cortical and subcortical **language mapping for all the languages in which a patient is fluent** [8]. Bilingual patients are known to have the same, but also different, cortical areas for the various languages they speak; these are located in both the temporo-parietal and the frontal areas [83], [101],[102], [118], but moreso in the temporo-parietal area. Due to the various representations of different languages in the cerebral cortex, Roux and colleagues also recommend the **use of different language tasks for** better language mapping in their study of language organization in **bilingual patients** [103]. We do not have any data on different languages spoken by our epilepsy surgery patients. All were evaluated only in one language (German), however, all did not have German as their first language. Therefore, we should consider the use of different language mapping tasks for mapping different languages in the future. The importance of the language tasks chosen for language mapping accuracy has also been noted by Ojemann and co-workers [81].

Hermann and colleagues reported that the exclusive use of only visual naming tasks in language mapping and the consecutive sparing of only visual naming (VN) sites from resection does not appear to consistently protect left temporal lobe epilepsy patients from post-operative naming decline [42]. They suggest the additional use of auditory-based naming tasks (test includes questions like “What a king wears on his head”) instead of using only VN tests that detect VN sites [38], [39]. They found that patients who had auditory naming (AN) sites removed tended to exhibit worse objective naming postoperatively, whereas patients who did not have AN sites included in their resection tended to perform as before the operation or in some cases, even improved in naming tasks. Despite the sparing of VN sites in all patients of this study, those who had AN sites removed were worse not only in AN tasks, but in VN tasks as well.

Therefore we consider the **implementation of an auditory naming test in language mapping** as a reasonable addition to achieve better post-operative language function; however, it has not yet been definitely determined whether sparing AN sites influences seizure outcome.

For better intra-operative localization of language cortex borders, Silbergeld recommends **having the patient continue naming objects during that part of the resection that is close to the identified language site** (within 2 cm of the identified language area) [106]. The resection can then be halted if naming errors occur.

14 Summary in English

Background. Both epilepsy surgery and surgery close to functionally significant cortical areas have challenged neurosurgeons in the last two decades.

With this work we wanted to illustrate the current status of epilepsy surgery close to language cortex in our clinic (Neurosurgery Clinic, University of Munich) and to evaluate our tactic of repeated intra-operative language mapping after initial extra-operative language mapping in cases, where language areas lie very close to or overlaps with the epileptogenic zone.

First part of this work describes the process of decision making in epilepsy surgery – patient admission criteria, gradual investigational process from non-invasive to invasive.

The main emphasis is put to the analysis of invasive language mapping (extra- and intra-operative) as this is the current gold standard of language localization in neurosurgery. Here the historical development of language mapping, together with its physical and physiological concerns is discussed.

The next part of this work is devoted to the analysis of two different invasive language mapping tactics – extra-operative versus combined extra- and intra-operative mapping.

Methods. Group of retrospective (19) and prospective (3) patients, operated in our clinic in time period from 1997 to 2007, was gathered. Among these 22 patients were 11 male and 11 women with a mean age of 31,9 years and mean epilepsy duration of 16,3 years. Only those patients, by whom either by extra-, intra-operative or both stimulation methods a language cortex close to or overlapping with epileptogenic zone was found, were included in our study.

The patients were divided in 2 groups, basing on the language mapping tactic, used during the investigation. Only extra-operative language mapping was used in cases, where rather safe distance (more than 10 mm) between language sites and epileptogenic zone was seen (Ex-M group). The necessity for additional intra-operative language mapping was seen in cases, where rather small (less than 10 mm) distance between language sites and epileptogene cortex or overlapping of both zones was seen (Co-M group).

Results. Only extra-operative language mapping was used for 8 patients and the combination of both language mapping techniques was used in 12 cases. In 1 case language was mapped by functional magnetic resonance and in 1 case – only intra-operatively.

All patients underwent resective operations.

Immediate post-operative language deterioration was seen only in 10 (45,4 %) cases (6 (75%) cases in Ex-M sub-group and 4 (33,3%) in Co-M sub-group) out of the whole group. In 2 cases (1 in each group) the language deterioration was permanent (detectable also 6 months after surgery). The patient in the Co-M sub-group had permanent language deterioration already pre-operatively. Thus the only new permanent post-operative language deterioration was seen in 1 case of Ex-M sub-group, where rather safe distance between language and epileptogenic zone was thought pre-operatively.

Regarding seizure outcome, patients were evaluated for at least 2 years (mean follow up 46,6 months). The results were gathered from 18 patients (only retrospective patients) and were as follows: Engel I – 9 cases (50%), Engel II – none, Engel III – 2 (11,1%) cases, Engel IV – 7 (38,9%) cases.

In 9 unfavourable seizure outcome cases (combination of Engel class III and IV cases) apparently no full resection of the epileptogene zone was achieved. In 5 cases this was known already intra-operatively, in the remaining 4 cases it was noted during the follow up period. In 8 of these cases the reason for incomplete resection of the epileptogene zone was its close relationship or overlapping with speech cortex and/or difficult localization of the epileptogenic zone. In 1 case complete resection could not be done due to intra-operative complications.

In the Co-M sub-group (n=9) the results were following: Engel I – 3 (33,3%) cases, Engel II – none, Engel III – 1 (11,1,%) case and Engel IV – 5 (55,6%) cases. In the Ex-M sub-group (n=7), the results were following: Engel I – 4 (57,1%), Engel II-none, Engel III – 1 (14,2%), Engel IV – 2 (28,7%) cases.

No statistically significant differences were observed between both groups regarding immediate post-operative language deterioration, new persistent language deterioration and Engel class I outcome.

Conclusions. Apart from casual neocortical epilepsy surgery, neocortical surgery close to speech areas identifies the need for language mapping in order to state safe resection borders. The long term post-operative results regarding language outcome in our study are satisfying and justify the use of invasive language mapping as the best language localization method.

As no statistically significant differences regarding language outcome are seen in comparison of both groups, we can conclude that both invasive language mapping tactics can be successfully used in epilepsy surgery. However, the use of combined extra-intra operative language mapping is associated with better post-operative language outcome. Here we can appraise our indications for combined language mapping to be considerable at least for cases where significant tradeoff (distance of less than 10 mm) between epileptogenic and language areas is seen.

Also seizure outcome is found not to be significantly influenced by use of one or another language mapping technique. Better post-operative results are seen in cases, where less significant conflict between both cortical areas is seen and thus somewhat more aggressive resections of the epileptogenic zone are possible. The post-operative results regarding seizure control in the whole group of epilepsy surgery close to speech areas can be seen as satisfactory, taking into account the complex pathology of these patients. A complete seizure freedom is seen in 50% of cases. The main reasons for unfavourable seizure outcome were significant conflict between full resection of the epileptogene zone and preservation of safe distance from speech cortex together with difficult localization of the epileptogene zone.

Finally, we can conclude that epilepsy surgery close to speech cortex is a very complex treatment method. The complexity is based on the diversity of patient characteristics, localization of the epileptogenic zone and language sites. However, with the use of vast investigational techniques and gathered experience, it is possible to achieve good post-surgical results.

We would also like to advocate a need for similar study with larger number of patients. This could provide more significant analysis of both language mapping tactics in epilepsy surgery close to speech areas.

15 Summary in German / Zusammenfassung

Einleitung: Neurochirurgie in der Nähe von funktionell bedeutsamen Cortexarealen im Allgemeinen und Epilepsiechirurgie im besonderem stellen in den letzten zwei Jahrzehnten eine grosse Harausforderung dar. Epileptogene Foci und zu entfernendes Hiranareal bei der Focusresektion befinden sich manchmal in enger Nähe von oder überlappen mit sprachtragenden Cortexarealen.

Mit der vorliegenden Arbeit sollte der aktuelle Stand der Epilepsiechirurgie in der Nähe von Sprachareale an der Neurochirurgischen Klinik der Ludwig Maximilians-Universität München dargestellt und der Einsatz eines zusätzlichen intraoperativen Sprachmonitorings nach initialem extraoperativen Sprachmapping in besonders gelagerten Fällen überprüft werden. Es geht dabei primär um Patienten, bei denen sich eine enge Nachbarschaft zwischen Sprachareal und epileptogener Zone bzw. eine Überlappung beider Regionen zeigt.

Die Arbeit beschreibt im ersten Teil den Prozess der Entscheidungsfindung in der Epilepsiechirurgie, die Kriterien der Aufnahme der Patienten in des Epilepsiechirurgie-Protokoll und das stufenweise Vorgehen und Anwendung der nicht invasiven und invasiven diagnostischen und therapeutischen Techniken.

Es folgt dann eine Beschreibung der verschiedenen invasiven Methoden der Sprachlokalisation. Bei der extraoperativen Sprachlokalisation oder Sprachmapping erfolgt die Zuordnung der sprachrelaventen Areale über die Stimulation von in den Subduralraum implantierten Gitterelektroden, bei der intraoperativen Cortexstimulation wird am ebenfalls wachen Patienten beim sogenannten Sprachmonitoring eine Benennungsschleife durch Stimulation unterbrochen und daraus eine individuelle Landkarte für die Sprachfunktion erstellt. Beide Methoden sind derzeit als der Goldstandard in der Lokalisierung von Sprachareale anzusehen.

Die extraoperative Stimulation nach subduraler Gitterelektrodenimplanatation fand für die prächirurgische Diagnostik der Patienten auf der Video-EEG-Monitoring-Station der Neurologischen Klinik statt, während die intraoperative Stimulation bei der anschliessenden epilepsiechirurgischen Fokusresektion im Operationssaal durchgeführt wurde.

Methoden: 22 Patienten mit epileptogenen Foci in unmittelbarer Nähe zu sprachrelevanten Regionen wurden in der Zeit von 1997 bis 2007 operiert und in diese Studie aufgenommen. Dabei wurden die Daten von 19 Patienten retrospektiv und von 3 Patienten prospektiv ausgewertet. Die Gruppe bestand aus 11 männlichen und 11 weiblichen Patienten. Beide Gruppen hatten ein mittleres Alter von 31,9 Jahre und eine mittlere Epilepsiedauer von 16,3 Jahren.

Bei diesen Patienten wurde entweder mit der extra- oder intraoperativen bzw. einer Kombination beider Stimulationsmethoden die Entfernung des Sprachkortex von der epileptogenen Zone oder die Überlappung des Sprachkortex mit derselben bestimmt.

Auf Grund der im Einzelfall angewandten Methode des Sprachmappings wurden die Patienten in 2 Gruppen unterteilt:

In der Gruppe, in der sich eine sichere Distanz (mehr als 10 mm) zwischen den Sprachareale und der epileptogene Zone ergab, wurde ausschließlich das extraoperative Mapping verwendet (Ex-M Gruppe).

In den Fällen, in denen das extraoperative Sprachmapping eine geringe Distanz zwischen den Sprachareale und dem epileptogenem Kortex zeigte (weniger als 10 mm), wurde zusätzlich ein intraoperatives Mapping für notwendig erachtet (Co-M Gruppe).

Ergebnisse: Alle 22 in die Studie eingeschlossenen Patienten haben die Resektionsoperation gut toleriert. Die Mortalität war 0%.

8 Patienten wurden einem alleinigem extraoperativen Mapping unterzogen, während die Kombination aus extra- und intra-operativem Sprachmonitoring bei 12 Patienten eingesetzt wurde. In einem Fall haben wir die Sprache mittels funktioneller Kernspintomographie untersucht, bei einem weiteren Patienten kam ausschließlich das intraoperative Sprachmonitoring zur Anwendung.

Eine sofort nach der Operation aufgetretene Sprachstörung wurde bei 10 (45,4 %) von 22 Patienten beobachtet (6 (75%) der Ex-M Gruppe, 4 (33,3 %) der Co-M Gruppe). Diese Störung war in den meisten Fällen vorübergehend. Nur in 2 Fällen (jeweils ein Patient aus jeder Gruppe) war die Sprachstörung permanent, d.h. auch 6 Monate nach der operativen Resektion noch vorhanden. Dabei war die Sprachstörung bei einem der Patienten aus der Co-M Gruppe bereits vor der Operation nachweisbar. Somit wurde nur in einem Fall, bei dem präoperativ eher eine gefahrlose Distanz

zwischen Sprachregion und epileptogener Zone vermutet worden war, eine neuaufgetretene permanente Sprachstörung beobachtet.

Bezüglich des postoperativen epileptischen Anfallsleidens haben wir die Patienten über mindestens 2 Jahre verfolgt. Die mittlere Beobachtungszeit betrug 46,6 Monate. Bei 18 Patienten - die Auswertung betraf nur die retrospektive Gruppe - ergab sich folgendes: Engel I – 9 (50%), Engel II – keine, Engel III – 2 (11,1%), Engel IV – 7 Fälle (38,9%). Bei 9 Patienten mit einem ungünstigen postoperativen Verlauf des Anfallsleidens (Klasse Engel III und IV) wurde demnach keine vollständige Resektion der epileptogenen Zone erreicht. Bei 5 der Patienten wurde dieses bereits intraoperativ erkannt, bei den übrigen 4 Fällen wurde dieses erst während der postoperativen Periode offensichtlich. Bei 8 Fällen lag die Ursache für eine inkomplette Resektion der epileptogenen Zone in ihrer engen Beziehung zum Sprachkortex und/oder in der ungünstigen Lokalisation der neokortikalen epileptogenen Zone. In einem Fall einer zusätzlichen temporomesialen Resektion musste diese aufgrund des Auftretens von störendem Nystagmus und Doppelbildern in Hirnstammnähe vorzeitig beendet werden. In keinem Fall tragen intraoperative Komplikationen auf.

In der Co-M Gruppe (n=9) wurden folgende Resultate erzielt: Engel I – 3 (33,3%), Engel II – keine, Engel III – 1 (11,1%) und Engel IV – 5 Fälle (55,6%).

In der Ex-M Gruppe (n=7) erzielten wir folgende Ergebnisse: Engel I – 4 (57,1%), Engel II – keine, Engel III – 1 (14,3%) und Engel IV – 2 Fälle (28,6%).

Wir haben keinen statistisch relevanten Unterschied zwischen den Gruppen

Ex-M und Co-M in Bezug auf die Häufigkeit einer transienten bzw. permanenten postoperativen Sprachstörung und in Bezug auf das Operationsergebnis, repräsentiert durch die Zuordnung zu Engel Klasse I gesehen. Dieses Fehlen deutet daraufhin, das unsere beiden Methoden des Sprachmappings eine ähnliche Wertigkeit haben, es aber einer größeren Patientenzahl bedarf, um eine statistische Signifikanz zu zeigen.

Diskussion: Zusammenfassend stellten wir fest, daß Epilepsiechirurgie in der Nähe von Sprachareale eine sehr komplexe Behandlungsmethode darstellt. Die Komplexität beruht auf der Inhomogenität der Patientencharakteristika, der Lokalisation der epileptogenen Zone und ihrer Beziehung zu den Sprachareale.

Für die Mehrzahl der Patienten mit einem epileptogenen Fokus in der Nähe des Sprachkortex ist die Einlage einer subduralen Gitterelektrode und ein anschließendes

Sprachmapping erforderlich. Deshalb ist diese Behandlung nur in speziell dafür eingerichteten neurochirurgischen Zentren möglich.

Alle postoperativen Resultate bezüglich der Sprachstörung sind sehr befriedigend und bestätigen den Einsatz eines invasiven Sprachmapping als beste Methode zur Lokalisation der sprachrelevanten Areale. Beide invasiven Methoden des Sprachmappings können in der Epilepsiechirurgie für Focusresektionen in der Nähe von Sprachareale erfolgreich angewandt werden. Allerdings ist die kombinierte Anwendung des extra- und intraoperativen Sprachmappings mit einem befriedigenderen Ergebnis in Bezug auf das postoperative Sprachvermögen verbunden. Hier konnten wir zeigen, daß unsere Indikation für ein kombiniertes Sprachmapping vor allem für jene Patienten entscheidend sein kann, bei denen durch die Nähe der prospektiven Resektionszone zum Sprachkortex Komplikationen zu erwarten sind.

Auch die Ergebnisse im Hinblick auf das postoperative Ergebnis bezogen auf die Anfallsfrequenz sind erfreulich, vor allem wenn man die komplexe Pathologie dieser Patienten in Betracht zieht. Eine komplette Anfallsfreiheit wurde bei 50% der Fälle erreicht.

Neben den allgemeinen Risiken, die bereits die komplette Resektion der epileptogenen Zone einer neokortikalen Epilepsie mit sich bringt liegt bei der in der vorliegenden Studie beschriebenen Patientengruppe in der Lokalisation der Foci in unmittelbarer Nähe zur Sprachregion ein zusätzlicher bedeutsamer Risikofaktor. Er beruht auf der engen lokalisatorischen Nachbarschaft zwischen Sprachareal und dem geplanten Resektionsareal bzw. in extremis auf der Überlappung von beiden. Bessere postoperative Ergebnisse in Bezug auf das Anfallsgeschehen sind dort zu erwarten, wo ein grösserer Abstand zwischen beiden Kortexarealen vorliegt und somit eine ausgedehnte Resektion möglich ist.

Die enge Nachbarschaft und in extremis Überlappung von sprachrelevanten Corterxarealen einerseits und epileptogener Zone sowie prospektivem Resektionesareal andererseits bleibt ein kritischer und erschwerender Faktor in Bezug auf eine positive Beeinflussung des Anfallsleidens für diese Subpopulation von Patienten in der Epilepsiechirurgie.

16 References

1 Adelson PD, Black PM, Madsen JR, et al. (1995) Use of subdural grids and strip electrodes to identify a seizure focus in children, Pediatr Neurosurg 22:174 – 180.

2 Agnew WF, McCreery DB (1987) Considerations for safety in the use of extracranial stimulation for motor evoked potentials, Neurosurgery, 20:143 – 147

3 Armstrong DM, Harvey RJ, Schild RF (1973) Cerebello-cerebellar responses mediated via climbing fibres, Exp Brain Res 18:19 – 39

4 Asanuma H, Arnold A, Zarzecki P (1976) Further study on the execution of pyramidal tract cells by intracortical microstimulation, Exp Brain Res 26:443 – 461

5 Bartlett JR, DeYoe EA, Doty RW, Lee BB, Lewine JD, Negrao N, Overman WH Jr (2005) Psychophysics of electrical stimulation of striate cortex in macaques, J Neurophysiol 94:3430 – 3442

6 Bell B, Hermann B, Seidenberg M, Davies K, Cariski D, Rosenbek J, Woodard A, Rutecki P, Bishop M (2002) Ipsilateral reorganization of language in early-onset left temporal lobe epilepsy, Epilepsy & Behavior 3, 158 - 164

7 Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, Baratta P, Songa V, Conte V, Branca V, Stochetti N, Papagano C, Gaini SM (2007) Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas, Neurosurgery 60:6 – 82

8 Bello L, Acerbi F, Giussani C, Baratta P, Taccone P, Songa V, Fava M, Stochetti N, Papagano C, Gaini SM (2006) Intraoperative language localisation in multilingual patients with gliomas, Neurosurgery 59:115 – 125

9 Benbadis S, Wyllie E, Bingman WE (2001) Intracranial Electroencephalography and Localisation Studies, The treatment of Epilepsy, 3rd edition, edited by E. Wyllie, Lippincott Williams & Wilkins.

10 Benton AL, Hamsher KDS, Varney NO., Spreen O (1983) Contributions to neuropsychological assessment. New York: Oxford University Press

11 Berger H (1929) Über das Elektrenkephalogramm des Menschen, Arch Psychiat Nervenkr 87:527 – 570

12 Berger MS (2008) Introduction, Language localisation in the dominant hemisphere, J Neurosurg 108:410

13 Calvin WH, Sypert GW (1976) Fast and slow pyramidal tract neurons: an intracellular analysis of their contrasting repetitive firing properties in the cat, J Neurophysiol 39:420 – 434

14 Carreno M, Lüders HO (2001) General principles of presurgical evaluation, Epilepsy surgery 20:185 – 199

15 Carne RP, O'Brien TJ, Kilpatrick CJ, MacGregor LR, Hicks RJ, Murphy MA, Bodwen SC, Kaye AH, Cook MJ (2004) MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain; 127:2276 – 2285

16 Cascino GD, Kelly PJ, Sharbrough RW, Hulihan JF, Hirschon KA, Trenerry MR (1992) Long – term follow – up of stereotactic

lesionectomy in partial epilepsy: Predictive factors and electrencephalographic results, Epilepsia 33:639 – 644

17 Cataltepe O, Comair YG (2000) Intrasurgical Cortical Electrical Stimulation, Epileptic Seizures Pathophysiology and Clinical Semiology, Edited by Lüders HO, Noachtar S, 10:172 – 186

18 Catterall WA (1981) Localisation of sodium chanells in cultured neuronal cells, J Neurosci 1:777 - 783

19 Clusmann H, Kral T, Schramm J (2006) Present Practice and Perspective of Evaluation and Surgery for Temporal Lobe Epilepsy, Zentralblatt für Neurochirurgie; 67:165 – 182

20 Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, Haun D, Elger CE (2002) Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. J Neurosurg 97:1131 – 1141

21 Cockerell OC, Sander JW, Shorvon SD (1995) Remission of epilepsy. The NGPS. National General Practice Study of Epilepsy. Lancet 346:1228

22 Cross SA, Smith JL (1982) Crossed-quadrant homonymous hemianopsia. The “checkboard” field defect, J Clin Neuroophtalmol 2:149 – 158

23 Deschenes M, Labelle A, Landry P (1979) Morphological characteristics of slow and fast pyramidal cells in the cat, Brain Res 178:251 – 274

24 Desmond JE, Sum JM, Wagner AD, Demb JB, Shear PK, Glover GH, Gabrieli JDE, Morell MJ (1995) Functional MRI measurement of language lateralisation in Wada-tested patients, Brain, 118: 1411 – 1419

25 Devinsky O, Pacia S (1993) Epilepsy surgery, Neurol Clin, 11:951 – 971

26 Devinsky O, Perrine K, Llinas R, Luciano DJ, Dogali M (1993) Anterior temporal language areas in patients with early onset of temporal lobe epilepsy, Ann Neurol, 34:727 – 732

27 Duchowny M, Jayakar P, Harvey AS, Resnick T, Alvarez L, Dean P, et al (1996) Language cortex representation: Effects of developmental versus acquired pathology, Annals of Neurology, 40, 31 - 38

28 Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L (2005) New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations, Brain Apr; 128 (Pt 4): 797 – 810

29 Elger CE, Grunwald T, Lehnertz K, Kutas M, Helmstaedter C, Brockhaus A, Van Roost D, Heinze HJ (1997) Human temporal lobe potentials in verbal learning and memory processes, Neuropsychologia 35:657 – 667

30 Engel J Jr (1993) Outcome with respect to epileptic seizures. In: Surgical treatment of the epilepsies. Raven Press, New York: 609 – 621

31 Engel J Jr (1993) Update on surgical treatment of the epilepsies. Summary of the Second International Palm Desert Conference on Surgical Treatment of the Epilepsies (1992). Neurology 43:1612 – 1617

32 European Federation of Neurological Societies Task Force (2000)

33 Foldvary N (2001) Recognition of Potential Surgical Candidates and Video-Electroencephalography Evaluation, The Treatment of Epilepsy, 3rd edition, edited by Wyllie E, Lippincott Williams & Wilkins, 73: 1019 – 1030

34 Foldvary N, Klem G, Hammel J, Bingman W, Najm I, Lüders H (2001) The localizing value of ictal EEG in focal epilepsy. Neurology 57:2022 – 2028

35 Grunwaldt T, Elger CE, Lehnertz K, Van Roost D, Heinze HJ (1995) Alterations of intrahippocampal cognitive potentials in temporal lobe epilepsy, Electroencephalogr Clin Neurophysiol, 95:53 – 62

36 Gustaffson B, Jankowska E (1976) Direct and indirect activation of nerve cells by electrical pulses applied extracellularly, J Physiol 258:33 – 61

37 Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA (1994) Cortical localisation of temporal lobe language sites in patients with gliomas, Neurosurgery, 34(4): 567 – 76

38 Hamberger MJ, Seidel WT, Mckhann II GM, Perrine K, Goodman RR (2005) Brain stimulation reveals critical auditory naming cortex, Brain; 128:2742 – 2749

39 Hamberger MJ, Tamny TR (1999) Auditory naming and temporal lobe epilepsy, Epilepsy Research, 35:229 – 243

40 Hamer HM, Morris HH (2001) Indications for invasive video-electroencephalographic monitoring. In: LüdersHO, Comair YG (eds) Epilepsy surgery. Lippincott Williams & Wilkins, Philadelphia, pp 559 – 566

41 Harkness WFJ, McEvoy A (2005) Methods of epilepsy surgery, http://www.e-epilepsy.org.uk/pages/articles/text.cfm?id=63

42 Hermann BP, Perrine K, Chelune GJ, Barr W, Loring DW, Strauss E, Trennery MR, Westerveld M (1999) Visual confrontation naming following left anterior temporal lobectomy: a comparison of surgical approaches, Neuropsychology; 13:3 – 9

43 HeNo.y RG, Berman JI, Nagarjan SS, Mukherjee P, Berger MS (2004) Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping, Neuroimage, Feb; 21(2):616 – 622

44 History of Brain Stimulation http://www.bidmc.harvard.edu/display.asp?node_id=4638

45 Ho SS, Berkovic SF, Berlangieri SU, Newton MR, Egan GF, Tochon-Danguy HJ, McKay WJ (1995) Comparison of ictal SPECT and interictal PET in the presurgical evaluation of temporal lobe epilepsy. Ann Neurol; 37:738 – 745

46 Immonen A, Jutila L, Kälviäinen R, Mervaala E, Partanen K, Partanen J, Vanninen R, Ylinen A, Alafuzoff I, Paljärvi L, Hurskainen H, Rinne J, Puranen M, Vapalahti M, (2004) Preoperative Clinical Evaluation, Outline of Surgical Technique and Outcome in Temporal Lobe Epilepsy. Advances and Technical Standards in Neurosurgery, 29: 88 – 132

47 Jastak S, Wilkinson GS (1984) Wide range achievement test-revised. Wilmington, DE: Jastak Associates Inc

48 Jayakar P (1993) Physiological principles of electrical stimulation, In: Devinsky O, Beric A and Dogali M, eds. Electrical and Magnetic Stimulation of the Brain and Spinal cord, Raven press, Ltd., New York

49 Jones-Gotman M, Hardanek MC, Kubu CS (2000) Neuropsychological assessment for temporal lobe surgery, Can J Neurol Sci; 27 (Suppl1):39 – 43

50 Jayakar P (1993) Physiological principles of electrical stimulation, In: Devinsky O, Beric A and Dogali M, eds. Electrical and Magnetic Stimulation of the Brain and Spinal cord, Raven press, Ltd., New York

51 Kim H, Yi S, Son El, Kim J (2004) Lateralisation of epileptic foci by neuropsychological testing in mesial temporal lobe epilepsy, Neuropsychology; 18:141 – 151

52 Knowlton RC, Laxer KD, Klein G, Sawrie S, Ende G, hawkins RA, Aasar OS, Soohoo K, Wong S, Barbaro N (2001) In vivo hippocampal glucose metabolism in mesial temporal lobe epilepsy, Neurology 57:1184 – 1190

53 Krauss GL, Fisher R, Plate C, Hart J, Uematsu S, Gordon B, Lesser RP (1996) Cognitive effects of resecting basal temporal language areas, Epilepsia, 37(5): 476 - 483

54 Krämer G, Schweizerische Epilepsie-Zentrum Zürich (2007) http://www.swissepi.ch/web/swe.nsf/swehomepage?OpenPage

55 Krnjevic K, Randic M, Strnoghan DW (1966) An inhibitory process in the cerebral cortex, J Physiol (lond) 184:16 – 48

56 Kurthen M, Linke DB, Elger CE, Schramm J (1992) Linguistic perseveration in dominant-side intracarotid amobarbital tests, Cortex, 28:209 – 219

57 Lesser RP, Gordon B, Fisher R, Hart J, Uemats S (1991) Subdural Grid Electrodes in Surgery of Epilepsy, Epilepsy Surgery, Raven Press, New York, 46:399 – 408

58 Lesser RP, Lüders H, Morris HH, Dinner DS, Kleim G, Hahn J, Harrison M (1986) Electrical stimulation of Wernicke's area interferes with comprehension, Neurology, 36:658 – 663

59 Leuthardt EC, Miller K, Anderson NO., Schalk G, Dowling J, Miller J, Moran DW, Ojemann JG (2007) Electrocorticographic frequency alteration mapping: a clinical technique for mapping the motor cortex, Neurosurgery 60 [ONS Suppl 2]:ONS-260-ONS-271

60 Li CL, Bak A (1976) Excitability characteristics of the A- and C- fibres in peripheral nerve, Exp Neurol 50: 67 – 79

61 Li CL, Chou SN (1962) Cortical intracellular synaptic potentials and direct cortical stimulation, J Cell Comp Physiol, 60:1 – 66

62 Lüders HO, Najm I, Nair D, Widdess-Walsh P, Bingman W (2006) The epileptogenic zone: general principles, Epileptic Disord, 8 (Suppl.2):51 – 59

63 Lüders HO (2000) Symptomatogenic Areas and Electrical Cortical Stimulation, Epileptic Seizures Pathophysiology and Clinical Semiology, Edited by Lüders HO, Noachtar S, 6:131 – 140

64 Lüders H, Noachtar S (1995) Atlas und Video epileptischer Anfälle und Syndrome, Wehr, Germany

65 Lüders HO, Awad I (1991) Conceptual Considerations, Epilepsy Surgery, New York, Raven Press, 7:51 – 62

66 Lüders H, Lesser RP, Dinner D, Morris HH, Hahn JF, Friedman L, Skipper G, Wyllie E, Friedman D (1987) Commentary: Chronic Intracranial Recording and Stimulation with Subdural Electrodes, Surgical Treatment of the Epilepsies, edited by Engel J, Jr, Raven Press, 297 – 321 New York

67 Machperson J, Wiesendanger M, Marangoz C, Miles TS (1982) Corticospinal neurons of the supplementary motor area of monkeys: a single unit study, Exp Brain Res, 48:81 – 88

68 Mandonnet E, Winkler PA, Duffau H (2007) Electrical stimulation : an input gate to brain functional networks – publication in progress

69 Marcus S, Zarzecki P, Asanuma H (1979) An estimate of effective current spread of stimulation current (Appendix), Exp Brain Res 34:68 – 72

70 Morris HH, Lüders H (1985) Electrodes, Long-term monitoring in epilepsy, Amsterdam, Elsevier Science Publishers Biomedical Division, 3 – 25

71 Milner B (1997) Amobarbital memory testing: some personal reflections, Brain Cogn 33:14 – 17

72 Nathan SS, Lesser RP, Gordon B, Thakor NV (1993) Electrical stimulation of the human cerebral cortex. Theoretical approach. In: Devinsky O, Beric A and Dogali M, eds. Electrical and Magnetic Stimulation of the Brain and Spinal cord, Raven press, Ltd., New York

73 The National Society for Epilepsy (United Kingdom) (2007) www.epilepsynse.org.uk

74 Noachtar S (2003): Subdural electrodes in focal cortical dysplasia, Epileptic Disord; 5 (Suppl 2):S91 – S94

75 Noachtar S, Winkler P, Lüders HO (2003) Surgical Therapy of Epilepsy, Neurological Disorders: Course and Treatment, Second Edition, Elsevier Science

76 Nowak LG, Bullier J (1998) Axons, but not cell bodies , are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements, Exp Brain Res 118: 477 – 488

77 Nowak LG, Bullier J (1998) Axons, but not cell bodies , are activated by electrical stimulation in cortical gray matter. I. Evidence from selective inactivation of cell bodies and axon initial segments, Exp Brain Res 118: 489 – 500

78 Nowak LG, Bullier J (1996) Spread of stimulating current in the cortical grey matter of rat visual cortex studied on a new in vitro slice preparation, J Neurosci Methods 67:237 – 247

79 von Oertzen J, Urbach H, Jungbluth S, Kurthen M, Reuber M, Fernandez G, Elger CE (2002) Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy, J Neurol Neurosurg Psychiatry; 73: 643 – 647

80 von Oertzen J, Urbach H, Blumcke I, Reuber M, Traber F, Peveling T, Menzel C, Elger CE (2002) Time – efficient T_2 relaxometry of the entire hippocampus is feasible in temporal lobe epilepsy.
Neurology; 58:257 – 264

81 Ojemann JG, Ojemann GA, Lettich E (1997) Cortical stimulation mapping of language cortex by using a verb generation task: effects of learning and comparison to mapping based on object naming;
J Neurosurg 97:33 – 38

82 Ojemann GA, Sutherling WW, Lesser RP, et al. (1993) Cortical stimulation, Surgical treatment of the Epilepsies, 2nd Ed, edited by Engel J Jr, New York, Raven Press, 399 – 414

83 Ojemann GA, Ojemann JG, Lettich E et al. (1989): Cortical language localisation in left dominant hemisphere: an electrical stimulation mapping investigation in 117 patients, Jneurosurg 71:316 – 326

84 Ojemann GA, Dodrill CB (1985) Verbal memory after left temporal lobectomy for epilepsy: mechanism and intraoperative prediction,
J Neurosurg; 62:101 – 107

85 Ojemann GA (1983) Brain organisation for language from the perspective of electrical stimulation mapping. Behav Brain Sci; 6:189 – 206

86 Ojemann GA (1982) Interrelationships in the localisation of language, memory, and motor mechanisms in human cortex and thalamus.
In: Thompson RA, Green JR, eds. New perspectives in cerebral localisation. New York: Raven Press, 1982:157 – 175

87 Ojemann GA (1982) Intrahemispheric localisation of language and visuospatial function: Evidence from stimulation mapping during

craniotomies fro epilepsy. Advances in Epileptology: XIIIth Epilepsy International Symposium 373 – 378

88 Ojemann GA, Whitaker HA (1978) Language localisation and variability. Brain Lang; 6:239 – 260

89 Ojemann GA (1979) Individual variability in cortical localisation of language, J Neurosurg; 50: 164 – 169

90 Olivier A, Awad I (1993) Extratemporal resections. In: Engel J, ed. Surgical treatment of epilepsies, New York: Raven Press, 489 – 500

91 Ozdemir A, Black PM (2005) Mapping of Human Visual Cortex, Neurosurg Q, Vol 15, Numb 2:65 – 71

92 Penfield W (1937) The cerebral cortex and consciousness, in *The Harvey Lectures*, Baltimore, Williams & Wilkins Co., pp 35 – 69

93 Penfield W, Roberts L (1959) Evidence from cortical mapping. In L.R.W. Penfield (Ed.), Speech and brain mechanisms (pp. 119 – 137), Princeton, NJ: Princeton University Press.

94 Quesney LF (1992) Extra-temporal epilepsy: clinical presentation, preoperative EEG localisation and outcome, Acta Neurol Scand Suppl; 140:81 – 94

95 Racine RJ (1972) Modification of seizure activity by electrical stimulation. I. Afterdischarge treshold, Electroencephalogr Clin Neurophisiol 32: 269 – 279

96 Ranck JB (1981) Extracellular stimulation, Petterson MM, Kesner RP, eds. Electrical stimulation research methods, New York: Academic press, 2 – 36

97 Ranck JB Jr (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review, Brain Res 98:417 – 440

98 Rausch R (2002) Epilepsy surgery within the temporal lobe and its short-term and long-term effects on memory, Curr Opin Neurol 15:185 – 189

99 Rattay F (1999) The basic mechanism for the electrical stimulation of the nervous system, Neuroscience 89:335 – 346

100 Rosenthal J, Walter HJ, Amassion VE (1967) An analysis of the activation of motor cortical necrosis by surface stimulation, J Neurophysiol, 30:844 – 858

101 Roux FE, Treumolet M (2002) Organisation of language areas in bilingual patients: a cortical stimulation study, J Neurosurg 97(4):867 – 864

102 Roux FE, Boulanouar K, Lottiere JA, Nejdoubi M, LeSage JP, Berry I (2003) Language functional magnetic resonance imaging in preoperative assessment of language areas: Correlation with direct cortical stimulation. Neurosurgery; 52:1335 – 1347

103 Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection, N Eng J Med, 358: 18 – 27

104 Schramm J, Kral T, Grunwald T, Blümcke I (2001) Surgical treatment for neocortical temporal lobe epilepsy: clinical and surgical aspects and seizure outcome, J Neurosurg 94:33 – 42

105 Seidenberg M, Hermann B, Wyler AR, Davies K, Dohan Jr FC, Leveroni C (1998) Neuropsychological outcome following anterior temporal lobectomy in patients with and without the syndrome of mesial temopral lobe epilepsy, Neuropsychology; 12:303 – 316

106 Silbergeld DL (2001), Cortical mapping, Epilepsy Surgery, edited by Lüders HO, Comair YG, Second edition, Lippincott Williams & Wilkins, 633 – 635

107 Smith SJM (2005) EEG in the diagnosis, classification, and management of patients with epilepsy, J Neurol Neurosurg Psychiatry; 76 (Suppl 2): 112 – 117

108 Spencer SS (1994) The relative contributions of MRI, SPECT, and PET imaging in epilepsy. Epilepsia; 35:72 – 89

109 Stoney SD Jr, Thompson WD, Asanuma H (1968) Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulation current, J Neurophysiol 31:659 – 669

110 Swadlow HA, (1985) Physiological properties of individual cerebral axons studied in vivo for as long as one year. J Neurophysiol 54: 1346 – 1362

111 Taylor MD, Bernstein M (1999) Awake craniotomy with brain mapping as a routine surgical approach to treating patients with supratentorial intraaxial tumors: a prospective trial of 200 cases, J Neurosurg; 90:35 – 41

112 Tehovnik EJ, Tolias AS, Sultan F, Slocum WM, Lagothetis NK (2006) Direct and indirect activation of cortical neurons by electrical microstimulation, J Neurophysiol 96:512 – 521

113 Thomas RK, Donaldson Young C (1993)
Journal of General Psychology
http://findarticles.com/p/articles/mi_m2405/is_n1_v120/ai_14174315

114 Tolias AS, Sultan F, Augath M, Oeltermann A, Tehovnik EJ, Schiller PH, Logothetis NK (2005) Mapping cortical activity elicited by electrical microstimulation using fMRI in the macaque, Neuron 48: 901 – 911

115 Urbach H, Hattingen J, von Oertzen J, Luyken C, Clusmann H, Kral T, Kurthen M, Schramm J, Blumcke I, Schild HH, (2004) MR imaging in the presurgical workup of patients with drug-resistant epilepsy, Am J Neuroradiol 25:919 – 926

116 Valton L, Mascott CR (2004) What is the current role of a Wada test in the pre-surgical work-up of pharmacologically intractable epilepsy in adults? Rev Neurol (Paris);160 Spec No 1:5S164-9. Review. French

117 Wada J, Rasmussen T (1960) Intracarotid injection of sodium Amytal for the lateralization of cerebral speech dominance: Experimental and clinical observations, J Neurosurg 17:226 – 282

118 Walker JA, Quinones-Hinojosa A, Berger MS (2004) Intraoperative speech mapping in 17 bilingual patients undergoing resection of a mass lesion, Neurosurgery 54:113 – 118

119 West DC, Wolstencroft JH (1983) Strength – duration characteristics of myelinated and non-myelinated bulbospinal axons in the cat spinal cord, J Physiol 337:37 – 50

120 Whitaker H, Ojemann GA (1977) Graded localisation of naming from electrical stimulation mapping of left cerebral cortex,

Nature; 270: 50 – 51

121 Wilensky A (1993) A history of focal epilepsy and criteria for medical intractability, Neurosurg Clin North Am, 4:193 – 198

122 Wilkus RJ, Thompson PM, Vossler DG (1990) Bizarre ictal automatisms: frontal lobe epileptic or psychogenic seizures? J Epilepsy ; 3: 207-13

123 Williamson PD, Spencer SS (1986) Clinical and EEG features of complex partial seizures of extratemporal origin, Epilepsia; 27 (suppl 2):S46-63

124 Winkler PA, Vollmar C, Krishnan KG, Pfluger T, Brückmann H, Noachtar S (2000) Usefulness of 3-D reconstructed images of the human cerebral cortex for localization of subdural electrodes in epilepsy surgery Epilepsy Res; 41: 169-178

125 Winkler PA, Piotrowska N (2007) Otfrid Foerster: (1873 -1941) – the great neurologist and neurosurgeon from Wroclaw (Breslau) in his time - his traces in todays Wroclaw. Journal Neurosurg, 107: 451-456

126 Wolf P (1991) The History of Surgical Treatment of Epilepsy in Europe. Epilepsy Surgery, Raven Press, New York, 2:9 – 16

127 Yeomans JS (1990) Principles of brain stimulation, New York, Oxford University Press

17 CURRICULUM VITAE

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January 2004	Clinical elective period, The National Hospital for Neurology and Neurosurgery, Queen Square, London University College
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