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Experiences of awake surgery in non-tumoural epilepsy in eloquent localizations

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ABSTRACT

Background: Whilst modern awake intraoperative mapping has been widely accepted and implemented in the last decades in neuro-oncology, sparse reports have been published on the safety and efficiency of this approach in epilepsy surgery.
Method: This article reports four cases with different locations of epileptogenic zones as examples of possible safe and efficient resections.
Result: The results of the resections on seizure control were Engel 1 (no disabling seizures) in all cases and no patient experienced significant neurological deficits.
Discussion: The discussion focuses on aspects of the future of epilepsy surgery in a hodotopical paradigm.

1. Background

Resective surgery for epilepsy, often divided in temporal and extra-temporal, is a well-established treatment. The main aims of the epilepsy surgery evaluation are to identify the epileptogenic zone and to assess the risk of removing it. Every case is processed in a thorough team-based work-up of possible risks vs. potential benefits of the prospective resection [1].

In neuro-oncology, the method of performing surgery while monitoring the patient awake, is a well-established concept. Historically this method has also been used in epilepsy surgery during the 20th century by such prominent neurosurgeons as Foerster, Penfield and Ojemann. Publications by Penfield greatly contributed to the early understanding of function localization [2–5], although the present view of brain function has developed into a deeper understanding of functions as networks rather than localizations referred to as hodotopy, or connectomics, rather that topography. This philosophy of brain function has had broad implications in intraoperative mapping in surgery for low grade gliomas [6,7].

There are different techniques for non-invasive preoperative mapping in brain surgery. The aim is to localize eloquent areas, especially motor, sensory and language function. Functional MRI (fMRI) can localize motor cortex and cortical language areas but not subcortical function. Navigated transcranial magnetic stimulation can localize motor cortex and cortical language function areas. Magnetoencephalography (MEG) can also localize functions in cortex. DTI (diffusion tensor imaging) tractography may visualize tracts important for language for instance the arcuate fasciculus, the corticospinal tract and the optic radiation. These methods do however not always identify eloquent areas or important tracts with precision. These methods provide important information to plan surgery and together with intraoperative neuronavigation help to preserve important functions.

During surgery direct cortical and subcortical stimulation with a handheld probe is regarded as the golden standard to map eloquent areas in the cortex and important tracts. The accuracy is greater than with the non-invasive methods mentioned above. With stimulation of motor cortex and the corticospinal tract it is easy to see the response by recording EMG or look for muscle twitches. Monitoring of motor function can be done in asleep patients with continuous or intermittent cortical stimulation and recording of EMG. In awake patients this can be

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done in the same way but also by clinical testing of motor function during surgery. For mapping of cortical language areas and tracts important for speech function electrical stimulation is delivered by a handheld probe during simultaneous testing of language, most often picture naming. During surgery even spontaneous talk is working as monitoring language. Language and cognitive function are not possible to monitor in asleep patients. Visual function can in some instances be monitored by VEP (visual evoked potentials) in asleep patients, but it is not validated to monitor the visual tract (optic radiation). In awake patients it is possible to map the visual tract by direct subcortical stimulation with a handheld probe. A computer screen with figures or pictures in four quadrants is presented to the patient during electrical stimulation. If the optic radiation is stimulated the patient will experience flashes or blurring of the pictures. Awake surgery may sometimes allow a larger resection, but if this leads to better seizure outcome is not thoroughly studied.

In the 21st century, several publications with epilepsy surgery performed on awake patients can be found [8–11]. For example, several works of importance of understanding memory function has been published based on patients undergoing awake surgery for epilepsy [12]. Most studies on awake surgery in epilepsy have, however, included tumour patients. One small case series, Wang et al., concludes that awake craniotomies benefit long-term seizure control in patients with epileptic gliomas [13]. Additionally, there are publications on anesthesiological aspects of awake surgery in epilepsy [14–16]. A few cases have been published [17–19] with a technical description of awake surgery of epileptogenic lesions in eloquent areas. Few cases, though, focus on both safety and efficiency, i.e. seizure control. In one case, cortical – but not subcortical – mapping of visual fields was performed and seizure control after 12 months was reported as Engel 1. In another case, discrepancies between preoperative and intraoperative mapping were described, and seizures were reported as declined post-operatively. Although unpublished, the latter patient is reported to be seizure free ten years after surgery. Sitnikov and coworkers [19] have published a series of awake craniotomies among which the majority had lesional epilepsy. Most of the 41 patients had tumors though, but a few patients with cavernomas and malformations of cortical development were also included in this material. This group describe Engel 1 among 80 %, but only a minority of the patients were included in the follow up. A more homogenous material from South Korea describe 55 patients with non-lesional neocortical epilepsy (mainly cortical dysplasia) who underwent awake resective surgery [20]. The seizure outcome was lower with 49, 1% reaching Engel 1, but the awake surgery resections with intraoperative mapping were regarded as safe with the exception of resections close to Broca's area. As the aims of epilepsy surgery are efficiency and safety, both aspects must be considered when introducing and evaluating new methods and procedures. This should be done in the form of ethically approved research.

Awake craniotomy is an alternative when the epilepsy focus is adjacent to eloquent cortex controlling speech, motor function, vision, sensory function or memory. We present four illustrative cases in which modern awake functional mapping have made safe and efficient epilepsy surgery possible despite close relation to different localizations traditionally regarded as eloquent.

2. Aim

The aim of this publication is to demonstrate the safety and efficiency of awake craniotomy in patients that have previously been excluded from epilepsy surgery.

3. Method

All patients underwent thorough epilepsy surgery team evaluation including most of the following: 3 T MRI, functional MRI, tractography, electroencephalography-videometry (video-EEG, scalp and/or intracranial electrodes), neuropsychological assessment, EEG source imaging, transcranial magnetic stimulation, SPECT and ophthalmological examination. A team conference decision was made regarding the epileptogenic zone as surgical target vs the risk profile.

Local anesthetics were applied in the planned incision site and as regional scalp block. Patients were under general anesthesia with a laryngeal mask during the first part when skin and scull were opened. The dura was soaked in local anesthetic and the patient was awakened [21,22]. During the awake part of the surgery, functional mapping of language, motor function and/or visual fields was performed using direct cortical and subcortical monopolar subcortical stimulation. In cases 2–4, cortical stimulation and recording of MEP (motor evoked potentials) to monitor function in the corticospinal pathways were performed intermittently throughout the surgery. Electrocorticography was used to detect seizure activity and assist in limiting the resection. The anesthesiological, neurophysiological and surgical methods applied, have been described in detail in our previous publication [23].

The patients were pre-treated with 500 mg FE of intravenously administered fos-phenytoin with an estimated peak concentration at the second, awake, part of the surgery.

Ethics: the project has been assessed and approved by the Regional Ethics Committee, dnr 2017/515-31.

4. Cases

All surgeries were performed by PV.

4.1. Female with Sturge-Weber malformation in the right occipital lobe

A 25 year old female with a history of seizures since the age of 6. Previously evaluated for epilepsy surgery but found inoperable. In childhood focal seizures with visual phenomena and hypertropia but without impairment of consciousness were described. In adulthood the patient experienced 1–2 focal seizures a month, starting with a visual phenomena with colors and hypertropia, followed by automatisms (lip smacking), head turning to the left and impaired consciousness. Urinary incontinence occurred sporadically at night, but no bilateral convulsive seizures were reported. At the time of the evaluation the patient was taking lamotrigine, levetiracetam and lacosamide and limited to work approximately 25 % due to the risk of seizures. Radiological findings were consistent with the Sturge Weber syndrome. Video-EEG confirmed epileptogenic zone in the lesion. Visual field perimetry examination (*Humphreys*) detected homonymous central defects in the superior left quadrant. Visual evoked potentials (VEP) were normal (Fig. 1).

The first resection of the lesion was performed under general anesthesia using intra-operative EEG monitoring and VEP monitoring. Resection was limited by the potentials detected by VEP monitoring. The patient was only seizure free one month. Visual field perimetry showed a slightly enlarged visual defect.

After consultation with professor Hugues Duffau a second surgery was performed under awake conditions. DTI (diffusion tensor imaging) tractography of the optic radiation was not judged as a safe method [24] to avoid damage to the visual fields during surgery in asleep patient. Intraoperative VEP monitoring is not well validated to preserve the visual fields. Awake surgery with mapping of the optic radiation was regarded as the safest procedure. Intraoperative cortical and subcortical mapping of the visual pathways guided the resection, a method previously described by Gras-Combe et al. [7] This is a different approach than that of a recently published case in which only cortical mapping was performed [18]. The patient experienced flashes in visual field quadrants on a computer screen, in cortical as well as subcortical pathway stimulation, which was used to identify the functional borders of the resection. Resection was macroscopically and radiologically radical in regard to pre- and intraoperative structural pathology. Intra-operative EEG monitoring did not detect any remaining epileptiform activity. Pathology was consistent with Sturge-Weber

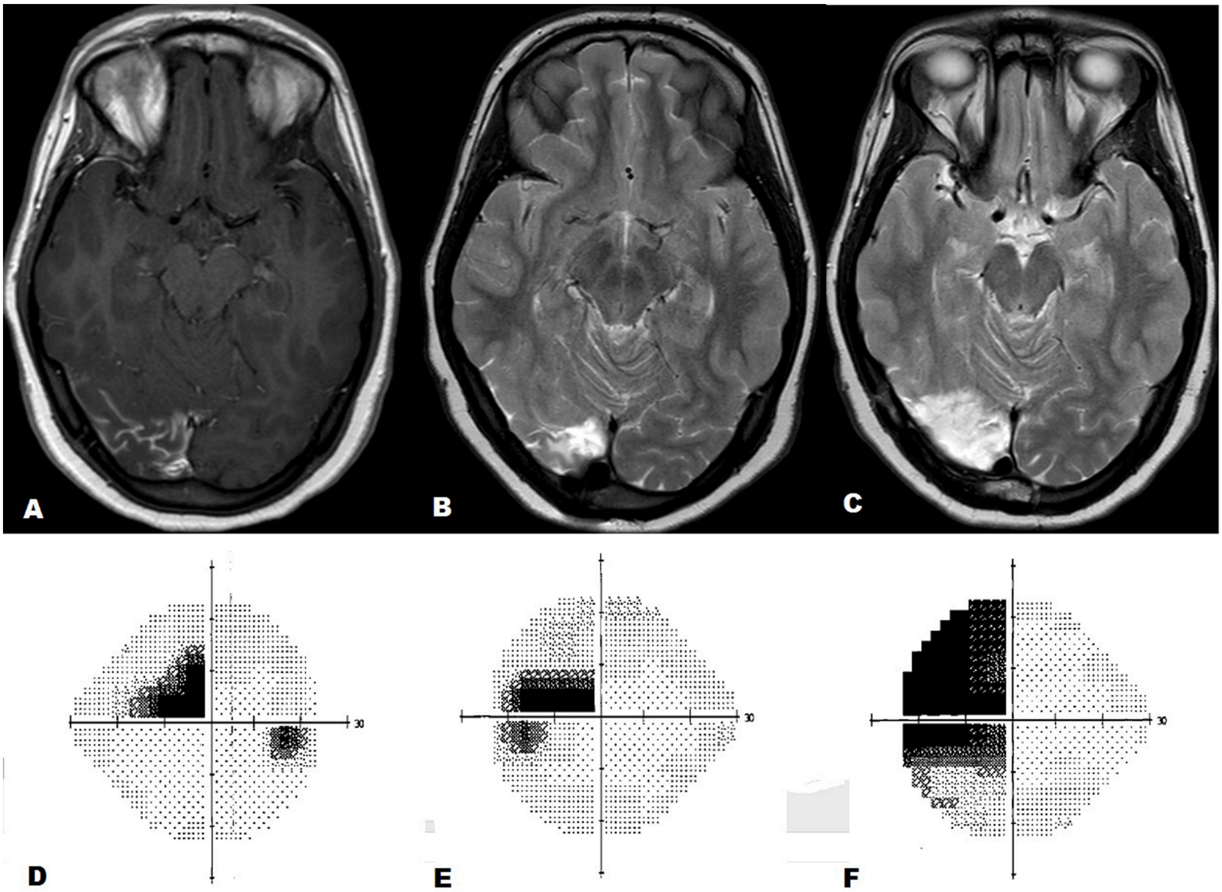

Fig. 1. MRI findings before surgery with T1 contrast enhancement in the right occipital lobe consistent with Sturge-Weber malformation (A),T2 weighted MRI after first (B) and second (C) surgery. Humphrey perimetry before surgery (D) showing partial upper quadrant homonymous anopia, after first, VEP-guided surgery (E) and after awake surgery with cortical and subcortical mapping (F).

malformation.

Visual field perimetry 3 months after the awake surgery showed an expected left superior homonymous quadrantanopia, while the inferior left quadrant only was slightly and incongruently affected (VFI right 58 %, VFI left 63 %). The patient did not experience the visual field to be additionally impaired following the resection. The patient was in full time employment after 7 months. All antiseizure drugs (ASM:s) were finished after one year. At three years months follow-up, the patient was still totally seizure free and in full time employment.

4.2. Female with left temporal transmantle cortical dysplasia

A 35-year old female with seizures since the age of 24. Focal seizures with impaired consciousness occurred approximately 3–4 times a week while the patient was on 4 different ASM:s(lamotrigine, levetiracetam, lacosamide and topiramate). The semiology of the seizures started with a deja-vu phenomenon, followed by aphasia and thereafter often impaired consciousness, sometimes evolving to a bilateral convulsive seizure.

Radiological findings were consistent with a transmantle cortical dysplasia and subcortical heterotopia in the majority of the left temporal lobe. EEG-evaluation using subdural electrodes and an intracerebral depth electrode, indicated that the epileptogenic zone was found in the anterior part of the lesion. Functional MRI and transcranial magnetic stimulation indicated that language function was localized in the vicinity of the epileptogenic zone. The visual field was intact on a visual field perimetry examination. In this location there is a high risk of speech disturbance after surgery if it is done asleep. There is also a risk to damage Meyer’s loop with quadrant anopsia. Therefore awake surgery with mapping of cortical speech areas and subcortical tracts was recommended as the safest procedure (Fig. 2)

Resection of the left temporal lobe was performed under awake conditions. Intraoperative mapping of language and motor function as well as visual field monitoring guided the resection. At the end of the resection an extensive left temporal lobe resection including the anterior lesion had been accomplished. There was no impairment of speech function, motor function or visual fields intraoperatively, however, some semantic difficulties were observed during stimulation in the posterior part of inferior temporal gyrus. During the direct postoperative period, perseverations were observed while motor function and visual fields remained intact. Pathology showed cortical dysplasia.

At 12 months follow up the patient had not experienced any epileptic seizures. There was an impairment of object naming but other, more complex, verbal functions, were preserved, as all other tested functions. The husband described a situation of restored freedom for the patient as she could go for walks and go shopping independently, he experienced no verbal impairment in the patient. The patient described a decline of short-time memory, not detected in neuropsychological assessment. This was attributed to improved awareness of the pre-surgical impairment, due to lack of seizures. Hence, a rehabilitation strategy directed towards coping strategies was introduced. A few months into the program, the patient reports improved reading capacity and a subjectively improved general cognitive situation. At follow up three years after surgery she is still seizure free.

4.3. Female with left frontal schizencephaly

A 37-year old nurse – working with interventional cardiology – with

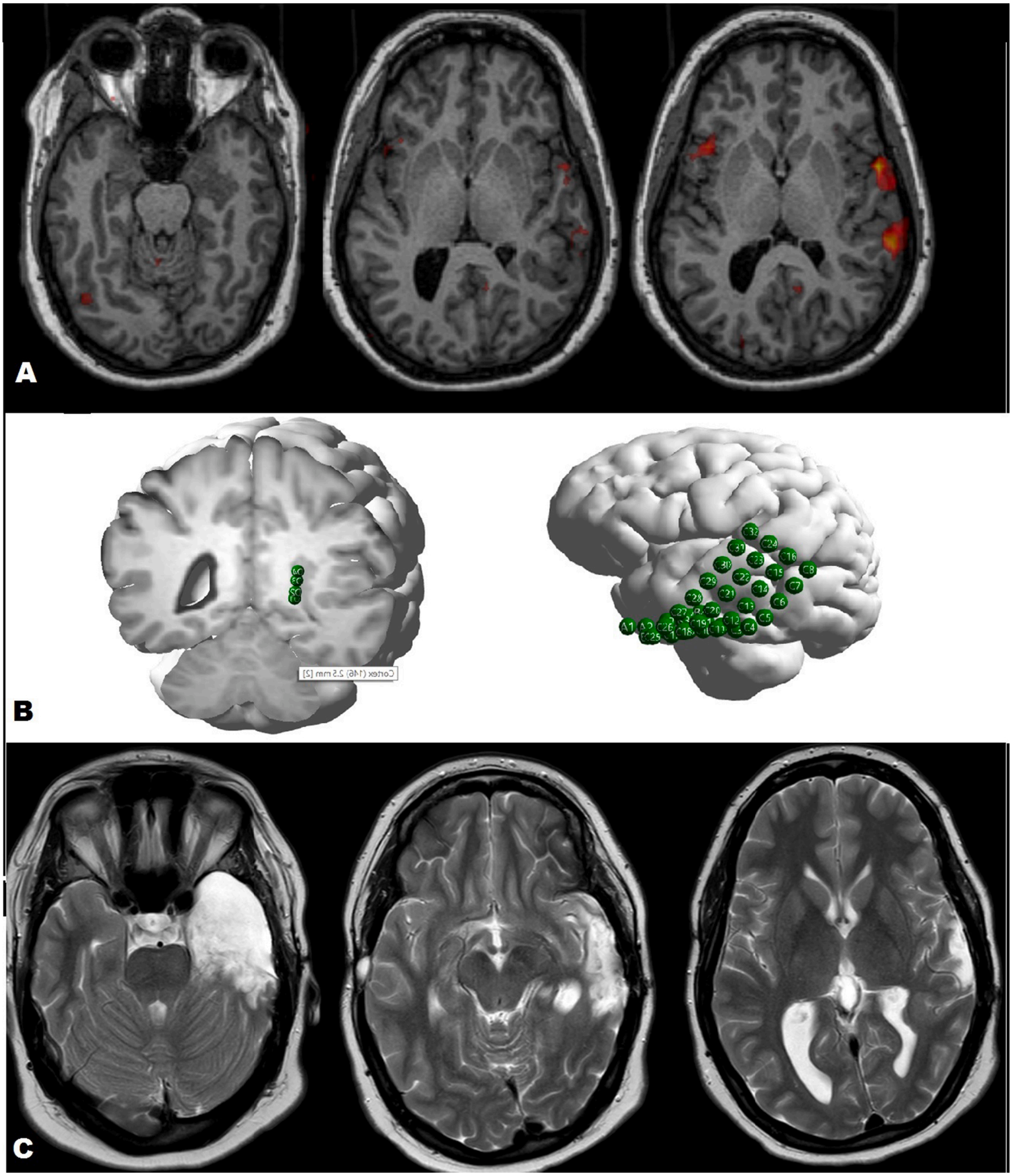

Fig. 2. Functional MRI before surgery showing a transmantle focal cortical dysplasia and activation patterns in the sentence completion test (A), placement of depth electrode in a cortical heterotopia lateral to the left ventriclar trigonum and grid (B), and post-operative radiology showing a large left temporal lobe resection(C).

epilepsy since the age of 17 was previously evaluated for epilepsy surgery at another centre but discarded as inoperable. Work capacity was declining due to increased seizure frequency and decreasing subjective cognitive and emotional function, i.e. irritability. Seizures started with anxiety and a sensory phenomenon in the right hand without impaired consciousness. At few occasions she had bilateral convulsive seizures. Radiology showed a closed lip schizencephaly from the cortex to the anterior part of the left sella media. fMRI showed a close relationship to language activated areas and tractography showed a tight relationship to the corticospinal tracts. Seizure initiation was confirmed in the posterior part of the schizencephaly using depth electrode and subdural strips (Fig. 3).

Neuropsychological evaluation showed verbal function above average, except for a below-average verbal working memory. According to the pre-surgical functional evaluation there was a risk to damage speech areas and the corticospinal tract during surgery if the patient was operated asleep.

Surgery was performed under awake conditions. The resection was limited by subcortical stimulation of the corticospinal tract with activation at 1 mA. Speech function was identified cortically but not subcortically. No post-operative motor or speech impairment was identified. MRI showed radical resection of the lesion. Pathology

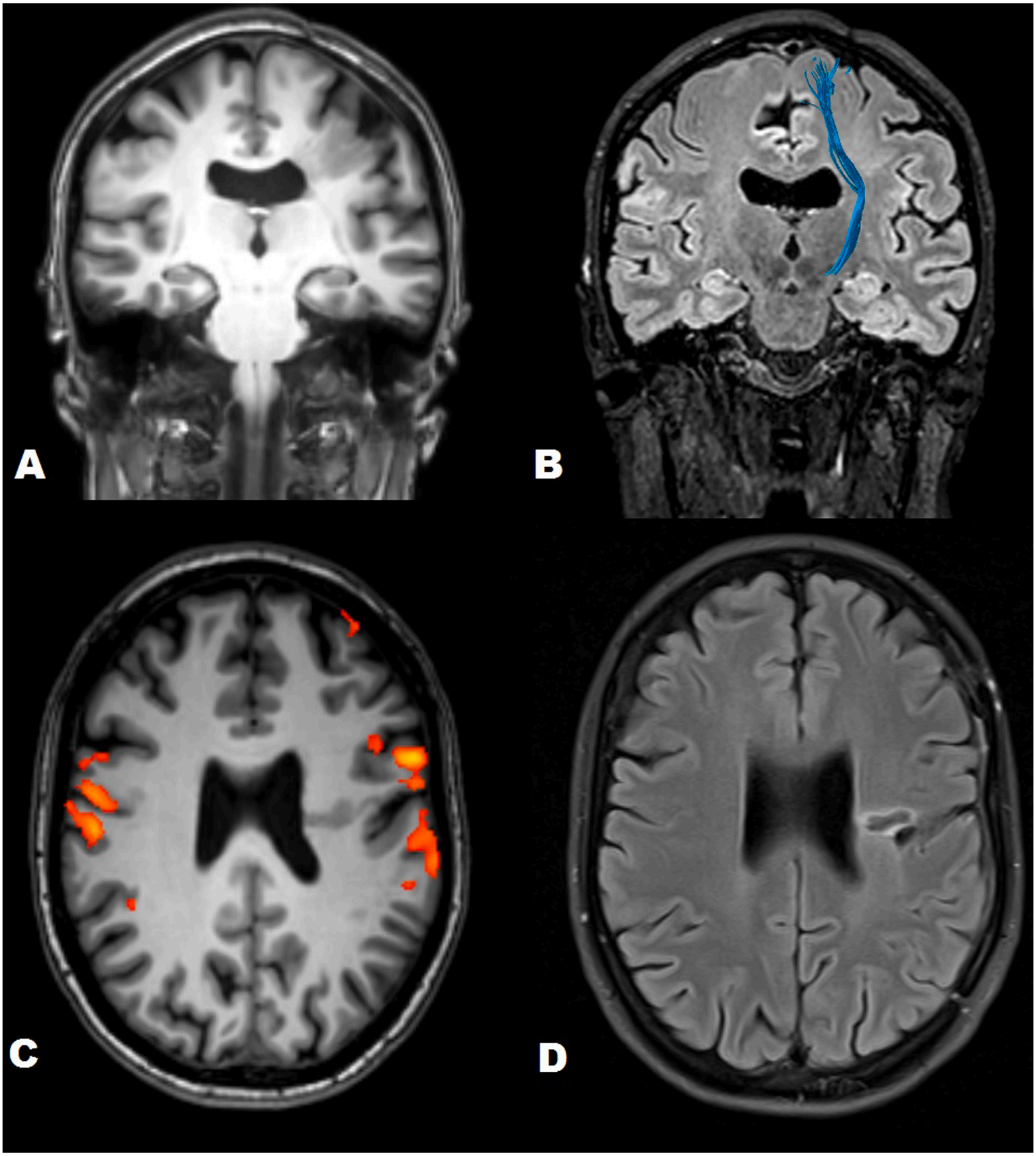

Fig. 3. Pre- operative MRI findings showing a closed lip schizencephly in the left frontal lobe (A). Diffusion tensor imaging tractography of cortocispinal tract (B) and functional MRI activation in the word generation test (C) in close vicinity to the lesion and a post-operative MRI.

showed cortical heterotopia, in accordance with schizencephaly.

The patient was back in working half time as a nurse after two months, though planning to change into a less complex environment than interventional cardiology.

At 1-year follow-up, the patient had no un-provoked seizures and had been able to reduce medication, although a short period of a more extensive reduction resulted in a few episodes of prodromal symptoms, resolving when medication was increased, though with lower dosage than pre-surgically. At three years follow-up, the patient experienced sparse focal seizures without impaired consciousness.

4.4. *Female with MRI negative right temporal epilepsy*

The patient was refereed to our center at the age of 34, with epilepsy since the age of 20. She was studying nursing but quit because of increasing seizure frequency and subjectively increasing memory disturbances. At presentation she had generalized tonic-clonic seizures, but at referral these had not occurred for several years. Present semiology was epigastric rising followed by aphasia and visual phenomena with changes of shapes of objects, sometimes followed by impaired consciousness, but without automatisms. The patient was treated with several ASM:s.

MRI showed no pathology – a discrete incomplete hippocampal inversion was interpreted as non-significant – and fMRI showed left lateralized language function. EEG source imaging and subdural strips showed seizure initiation in the medial right temporal lobe with no contralateral seizure activity. Neuropsychological assessment showed normal verbal memory but impaired visuospatial memory.

Due to the aphasia component of the seizures, we decided to perform awake right temporal lobe resection.

Accordingly, severe reproducible semantic impairment was found during cortical stimulation in the lateral temporal lobe, just 3.5 cm from the temporal tip. The resection was limited by this finding and a medial-anterior temporal lobe resection was performed. Pathology was "discrete gliosis". During three postoperative weeks, the patient had severe headache, but no sign of infection, and this resolved completely (Fig. 4)

After the resection the patient was seizure-free for eight months but later suffered three convulsive seizures, which were provoked by lack of compliance or infections. One more ASM was added and at three- years follow- up she had been seizure- free for 16 months. She suffers from fatigue and memory problems, but neuropsychological follow showed similar results as pre-operatively.

5. Discussion

Several earlier publications include patients undergoing awake epilepsy surgery with intraoperative mapping. However, epilepsy surgery has the primary aim of seizure control and the efficiency of this aspect, after awake surgery, has only been sparsely mentioned in previous case reports. In surgery for infiltrating low grade gliomas, there is an acceptance for radiologically residual tumor, as a subtotal major resection still adds prognostic value to the treatment, as compared to no or a more limited resection. There is also the aspect of a more correct diagnosis with a larger resection, than a biopsy, making tailored oncological treatment possible.

In epilepsy, however, a resection that does not lead to better seizure control or – more adequately – higher quality of life is not motivated. Thus, only considering safety aspects of resections in eloquent localizations, is not enough to describe the potential usefulness of intraoperative awake mapping in epilepsy surgery. If awake intraoperative mapping only allowed making resection possible, but not effective, it would have no place in epilepsy surgery. Our cases are therefore important, implying that resections in direct vicinity to eloquent structures – in several different conditions and localizations – can be effective in seizure control. Neurocognitive testing is the most effective method to preserve critical functions and awake craniotomy may therefore lead to more extensive resections and consequently more effective seizure control. Larger series are of obvious importance, also comparing efficiency and safety between patients operated with, and without, awake intraoperative mapping.

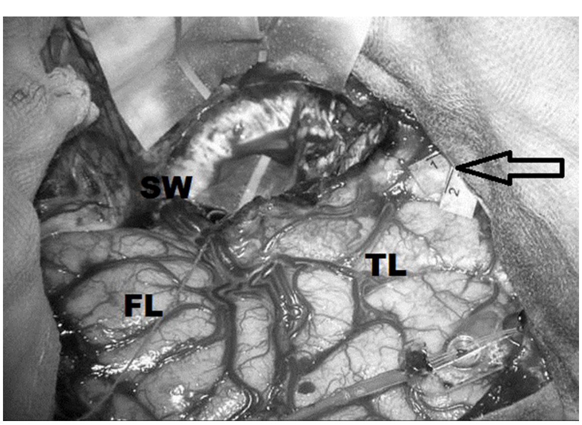

Fig. 4. Intra-operative photography of the frontal lobe (FL), temporal lobe (TL), greater sphenoid wing (SW) and location of semantic problems at cortical stimulation (arrow) at 3.5 cm from the tip of the temporal lobe.

Important tracts in the brain can be anatomically visualized with preoperative tractography, for example the corticospinal tract, the optic radiation, the arcuate fasciculus and association pathways. This can be of value during the preoperative planning and can be used together with neuronavigation during surgery. However, this cannot replace intraoperative mapping because tractography is not the same as function. During surgery it is important to test the function of the subcortical tissue with electrical stimulation and appropriate testing before resection. The corticospinal tract is possible to map during surgery in asleep patients but other important functions such as language, visual field and cognitive functions depends on cooperating with the patient. For language the most frequently used test is picture naming with simultaneous electrical stimulation. For monitoring language also spontaneous speech is useful.

The concept of eloquence should be questioned, as there is function located in the entire brain, and focus should thus be on preserving networks with enough connections to compensate for the damage that every surgery does. The importance of subcortical mapping must be stressed. It also makes experienced neuropsychological involvement important: in planning, during surgery and in follow-up. One earlier case report focused on intraoperative surface perimetry. Applying the experiences from tumor surgery, though, focus must also be made on subcortical pathways as in case 1 above. In tumor surgery, subcortical pathways are well-described [6,7,18,25,26]. In epilepsy, however, subcortical mapping is not so well-described, making it possible that the predictability of the pathways in different malformations is low with the present level of knowledge [27]. In case 2, the intraoperative semantic problems could be attributed to affection of the inferior fronto-occipital fascicle, although it anatomically was found more temporal than what would be expected in a normal brain. The post-operative naming difficulties might be due to partial damage to the inferior longitudinal fasciculus, although there were no such detectable difficulties during stimulation [25,28]. A hypothesis proposed by the post-operative test profile is that it is rather a decline in semantic organization appearing as object naming impairment, rather than a direct expressive deficit. Further studies are needed on the development of subcortical networks in epileptogenic malformations.

Furthermore, case 2 and 4 exemplifies that rehabilitation should be planned for patients undergoing epilepsy surgery. Although substantially improved seizure control and preserved neuro-psychological function, there is a risk that already existing cognitive deficits becomes more apparent to the patient when being able to face the normal challenges in life, earlier limited by the epilepsy. This is sometimes referred to as the "burden of normality" [29–32].

The concept of neuroplasticity is a related important possible difference between epilepsy surgery and glioma surgery. Whereas neuroplasticity is a well-described phenomenon in infiltrating gliomas, the situation might be different in epilepsy as the lesion itself is cortical, albeit heterotopic. Long-time seizures also seem to decrease cortical plasticity. On the other hand, learning the properties and variants of the underlying connectome in epileptogenic lesions, may make limitation of the resections optimized for the combination of safety and efficiency [26,27,33].

Considering the entire brain "eloquent", the high frequency of clinically significant memory impairment, and visual fields defects, in surgery for temporal lobe epilepsy must be addressed. With frequencies at 30–50 % for either complication in the literature, there are few other surgical procedures that would accept such high complication risk. In relation to this, there is a long since ongoing discussion on efficiency vs safety of the two most common methods in temporal lobe epilepsy: selective amygdalahippocampectomy and temporal lobe resection [34]. With validated methods of testing memory networks intraoperatively, this could be a non-question, as resections could be guided by individualized balance between the aim of seizure control and mapping and avoidance of memory networks. Memory though, is a complex concept and there is no validated method for testing intraoperatively with the aim of avoiding post-operative impairment, although there are methods of exploring memory intraoperatively described in several publication [35]. For visual field mapping, there are applicable methods as described above.

There were no problems in these cases with intraoperative seizures, although case 2 experienced semantic difficulties. They were not specifically induced by stimulation. We did not interpret these as seizures as there was no seizure activity on electrocorticography and similar difficulties were found consistently in the pre-operative assessment, although somewhat stress-related.

Case 1 and 3 had been assessed as non-operable under general anesthesia in previous epilepsy surgery evaluations. Case 2 was the subject of a consultation of another center, regarding the patient as non-operable. Case 4 might have been operated under general anesthesia with the consequence of severe lingual complications, not considering that previous dogmas on lateralization have been significantly questioned following studies on patients during awake surgery for gliomas [26]. The successful surgery of these cases could imply that intraoperative mapping in awake patients can increase indications of epilepsy surgery, as it has in glioma surgery. Further controlled studies are needed to evaluate seizure control in relation to risk of post-operative deficits [26].

6. Conclusion

The successful surgery of these cases could imply that intraoperative mapping in awake patients can increase indications of epilepsy surgery, as it has in glioma surgery. Further controlled studies are needed to evaluate seizure control in relation to risk of post-operative deficits. These should specifically focus on more complex cognitive functions, such as memory and executive function. Furthermore, these cases illustrate the need for predictive methods in regard to the risk of "burden of normality".

Credit authorship contribution statement

Patrick Vigren: Conceptualization, aquisition, formal analysis, methodology, investigation writing original draft, writing-review and editing. Martin Eriksson: interpretation, writing original draft. Hugues Duffau: Conceptualization, formal analysis. Anna Wretman: acquisition, investigation. Hans Lindehammar: aquisition, investigation, Writing review and editing. Peter Milos: aquisition, formal analysis. Johan Richter: aquisition, formal analysis. Thomas Karlsson: formal analysis. Helena Gauffin: conceptualization, aquisition, formal analysis, investigation, writing review abd editing.

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