Review article

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Frontal lobe epilepsy

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ABSTRACT – Frontal lobe epilepsy accounts for only 10-20% of the patients in surgical series, but the incidence in non-surgical patient cohorts seems to be much higher. The typical clinical presentation of the seizures includes contralateral clonic movements, uni- or bilateral tonic motor activity as well as complex automatism. The yield of surface EEG may be limited due to the difficulty in detection of mesial or basal foci, and the patient may be misdiagnosed as having non-epileptic events. In addition, in patients with mesial frontal foci the epileptiform discharges may be mislateralized ("paradoxical lateralization"). Therefore, epilepsy surgery has been commonly considered as less promising in patients with frontal lobe epilepsy. However, the advent of sophisticated neuroimaging techniques, particularly MRI with epilepsy-specific sequences, has made it possible to delineate the epileptogenic lesion and detect a specific etiology, in an increasing number of patients. Thus, the success rate of epilepsy surgery in frontal lobe epilepsy is currently comparable to temporal lobe epilepsy, if the candidates are carefully selected. Patients with frontal lobe epilepsy who do not respond to anticonvulsive medication, and who are not eligible for epilepsy surgery may benefit from alternative approaches such as electrical brain stimulation.

KEY WORDS: frontal epilepsy, epilepsy surgery, seizure semiology, SMA, orbitofrontal

Patients with temporal lobe epilepsy, particularly when associated with hippocampal sclerosis, have been investigated extensively [1, 2]. On the other hand, patients with frontal lobe epilepsy have only rarely been studied. In surgical series, patients with frontal lobe epilepsy account only for 10-20% of the cases [3, 4]), even when the prevalence of frontal lobe epilepsy is much larger in the general population [5]. Unfortunately, it is difficult to define the general characteristics of frontal lobe epilepsy because surgical series usually consist of highly selected patients, whereas studies performed in patients with less severe epilepsy are hampered by the difficulties of correctly assessing the location of the epileptic focus. We know, for example, that seizure types considered as "typical" for frontal lobe origin may actually arise from different brain regions, and *vice versa*. Thus, a review of epilepsies of the frontal lobe requires some theoretical considerations about the concepts of defining the area of epileptogenicity.

In the evaluation of patients with epilepsy, it has been found to be essential to identify the epileptogenic zone [6]. The epileptogenic zone includes not only the area that is generating the patient's habitual seizures, but also the brain regions that are still capable of generating seizures once the original seizure onset zone has been resected. Thus, the epileptogenic zone is a theoretical concept, and its location and extent cannot be determined precisely with the current diagnostic techniques, but only inferred indirectly. The most reliable evidence for the location and extent of the epileptogenic zone is seizure-freedom after epilepsy surgery. Therefore, patients who are

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seizure-free after frontal lobe resections form the most reliable cohort of frontal lobe epilepsy patients. However, only a minority of patients with frontal lobe epilepsy undergo surgery. In addition, in some patients who have had extensive presurgical evaluation, surgery is either not possible or the extent of the resection has to be limited because of the need to preserve eloquent cortex. In these cases, the location of the epileptogenic zone can be inferred by defining the location and extent of the following five cortical zones [6]: the symptomatogenic zone (i.e. the cortical area whose activation produces the ictal symptoms), the irritative zone (i.e. the cortical area that generates interictal EEG spikes), the seizure onset zone (i.e. the cortical area from which clinical seizures are actually generated), the lesion zone (i.e. the cortical area where a presumed epileptogenic lesion is visible on imaging), and the functional deficit zone (i.e. the cortical area that is functionally abnormal interictally). The degree of concordance of these five areas determines the reliability of the localization of the epileptogenic zone. In general, a lesion, which on MRI is concordant with seizure semiology, EEG, or functional imaging findings seems to be the best evidence for the location of the epileptogenic zone if no surgical outcome is available. Therefore, the precise description of the patient cohort is essential in order to assess the reliability of any observation ascribed to frontal lobe epilepsy.

Anatomy of the frontal lobe cortex

The frontal lobe cortex is defined by its surface anatomy landmarks: it is limited posteriorly by the central sulcus, medially by the intrahemispheric fissure, and inferiorly by the sylvian fissure. The lateral convexity contains the precentral gyrus as well as the superior, middle and inferior frontal gyrus. The medial view includes the cingulate gyrus ventrally to the medial rim of the superior frontal gyrus, and posteriorly the paracentral lobule. The basal surface can be divided into the gyrus rectus, the medial and the lateral orbital gyrus.

Functional anatomy

Traditionally, the frontal cortex has been divided into the precentral, and prefrontal (or premotor) cortex, with the precentral area consisting mainly of the primary and secondary motor areas, and the prefrontal cortex anterior to it. However, this does not take into account the complex and reciprocal connections of a given region with other cortical and subcortical areas [7]. The combination of different modalities of investigation (e.g. connectivity studies and receptor radiography) may lead to different views of cortical organization [8]. However, for practical purposes in epileptology, the main functional areas, as defined by stimulation studies in humans and other primates, are still crucial and will be described further *(figure 1)*.

Precentral/primary motor area

This area includes the whole precentral gyrus as well as posterior parts of the superior, middle and inferior frontal gyri *(figure 1)*. It receives input not only from other sensorimotor regions, but also from a wide variety of visual, acoustic, thalamic, reticular or cortico-cortical afferents [7]. The main efferents are corticospinal, but are also

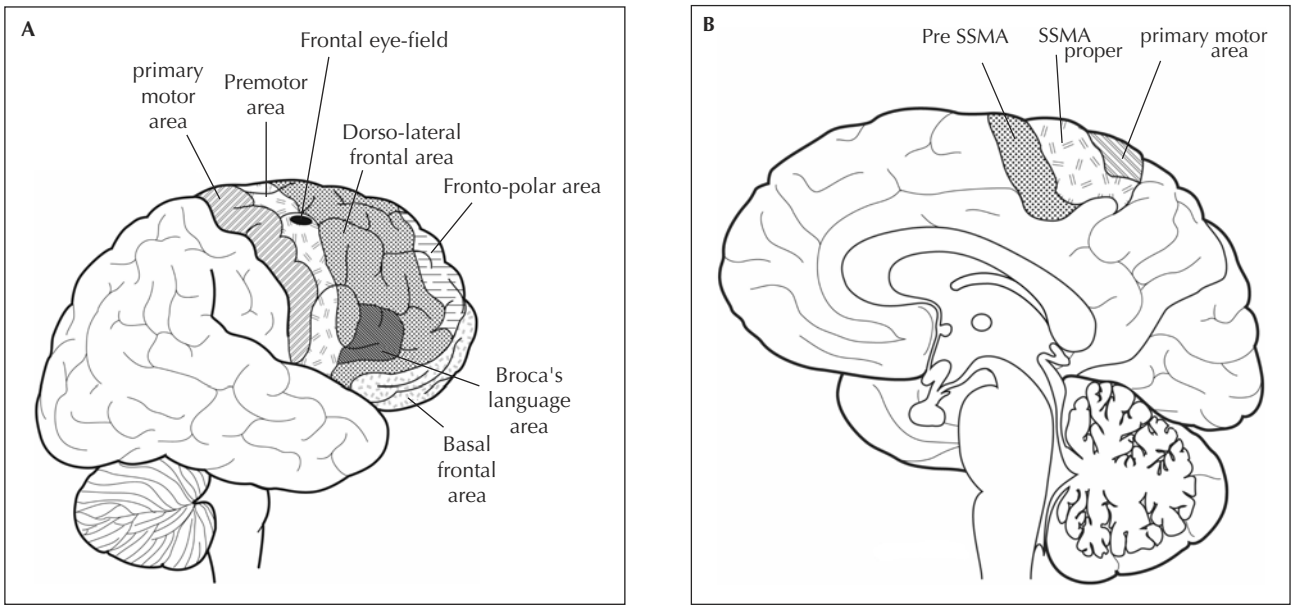

Figure 1. *Simplified surface anatomy of the human brain with location of important eloquent areas of the frontal lobe (dominant hemisphere): A) lateral view, B) mesial view*

directed to several other cortical and subcortical areas. Electrical stimulation studies in humans and monkeys resulted in clonic or tonic muscle contraction of the contralateral limb, predominantly distal, and organized in the well known homunculus according to Penfield and Rasmussen [9]. However, stimulation of the primary motor area also elicited sensory or negative motor responses, and simple motor responses were seen with stimulation of postcentral areas. Moreover, the somatotopic organization varies greatly inter-individually, particularly in patients with lesions in that region [10].

Supplementary sensorimotor area (SSMA)

The SSMA (sometimes also referred to as the secondary motor area) is located in the mesial aspect of the posterior part of the superior frontal gyrus and in the paracentral lobule, bordering to the primary motor area mediating leg and perineal movement (Figure 1). There is increasing evidence that the area commonly referred to as SSMA actually consists of two independent and functionally different fields: the SSMA proper, located more caudally, bordering to the primary leg motor area, and the pre-SSMA rostrally [11]. Both areas receive their main input from the thalamus, the premotor and the postcentral cortex, but afferents from the primary motor area, as well as corticospinal projections exist only in the SSMA proper [11, 12]. The SSMA proper has executive motor properties, whereas the pre-SSMA plays an important role in planning and initiation of movements [11]. Electrical stimulation of the SSMA proper elicited predominantly tonic and proximal motor responses ipsi-, contra- or bilaterally [13], but also bilateral or contralateral sensory symptoms, and contralateral eye deviation similar to the movements seen after stimulation of the lateral frontal eye field [14]. However, SSMA-typical motor responses were also seen after stimulation of the lateral aspect of the superior frontal gyrus [13]. Stimulation of the pre-SSMA resulted in inhibition of intentional movements (see 'negative motor areas')

Frontal eye field

The frontal eye field is located in the posterior part of the middle frontal gyrus, immediately bordering the primary motor cortex *(figure 1)* [15]. It receives afferents mainly from the occipital cortex as well as the dorsal thalamus. Efferent projections end mainly in the preoccipital cortex and the superior colliculus. Electrical stimulation elicits mainly saccadic, contralateral, conjugate eye-movement, frequently followed by head version [15].

Frontal language area (Broca's area)

The frontal language area is located in the pars operculare and triangulare of the inferior frontal gyrus of the dominant hemisphere *(figure 1)* [16]. It has extensive connections with the primary motor area controlling tongue and larynx, as well as the (receptive) language area in the posterior temporal lobe. Electrical stimulation interferes with speech output function (speech arrest, slowing of speech, paraphasia, alexia or agraphia) [16, 17], but also with speech comprehension [18].

Negative motor areas

Negative motor areas are found in the posterior inferior frontal gyrus, immediately in front of the primary motor face area, and in the posterior mesial superior frontal gyrus, immediately in front of the SSMA proper *(figure 1)* [19]. In contrast to the primary motor areas, its main cortical afferents arise from the prefrontal areas which have no direct connections with the spinal cord or the primary motor region [7], suggesting primary involvement in planning as opposed to execution of movement of these areas [14]. Electrical stimulation causes inhibition of predominantly distal voluntary fine movements without interference in truncal tone. Interference with tongue and pharyngeal movement also may cause speech arrest [19], and in the dominant hemisphere, Broca's language area is frequently a subset of the negative motor area [20]. Therefore, it is essential to test language comprehension/processing and tongue movement inhibition separately.

Prefrontal cortex

Based on connectivity studies and functional imaging studies, the prefrontal cortex can broadly be divided into three subregions: dorsolateral (superior to the inferior frontal lobe), ventrolateral (below the dorsolateral region), and anterior frontal or frontopolar [21]. The best investigated function of the prefrontal region is most likely its executive role in maintenance and storage of information [22]. This function is frequently referred to as 'working memory' [23].

Orbitofrontal and anterior medial areas

The function of the orbitofrontal areas has been underrecognized for some time. However, recent studies have been able to elucidate the structure and networks. The orbitofrontal and anterior medial structures seem to form two different but interacting networks: the orbital network, receiving processed sensory input of all modalities and serving mainly as a system for sensory integration, and the medial network with prominent projections to several hypothalamic fields as a visceromotor system [24]. Both networks seem to work together closely, and play an important role not only in visceromotor control, but also in emotional and behavior guidance [24, 25].

Seizure semiology

The symptomatogenic zone, i.e. the cortical area which, when activated, produces the ictal symptoms, has been

used as a reference to determine the location of the epileptogenic zone since the time of Hughlings Jackson [26]. In the last 20 years, the advent of videography has allowed recording and therefore careful analysis of ictal events. Double blind studies by different epileptologists, unaware of other related clinical findings, allowed assessment of the relationship of the symptomatogenic zone with the location of the epileptogenic zone or the etiology of epilepsy, or both. In addition, cortical stimulation with subdural or intracerebral electrodes permits further delineation of the location of symptomatogenic zones by reproducing epileptic activation in a controlled setting. The symptomatogenic zone and the epileptogenic zone do not necessarily overlap. Epileptic symptoms are frequently the product of the spreading of the epileptic activity from the epileptogenic zone into the symptomatogenic zone. In addition, large cortical areas do not elicit symptoms when stimulated ("silent cortex"), suggesting that epileptiform discharges, generated in a silent epileptogenic zone, will not produce symptoms unless there is spread to eloquent areas. Thus, epileptiform discharges involving eloquent brain areas may or may not produce symptoms. Although analysis of clinical seizure semiology is an important tool in localizing the epileptogenic zone, one has to be careful not to overlook signs implying seizure onset in a different lobe or even hemisphere.

In studies involving seizure semiology, the inclusion criteria are crucial. In studies in which the assessment of the location of the epileptogenic zone is based only on EEG and/or imaging, it is most likely that such studies also include patients in which the true epileptogenic zone was outside the frontal lobe. On the other hand, studies including only patients after successful surgery (seizure-free post-surgery) are also not truly representative of frontal lobe epilepsy because a considerable number of patients with frontal lobe epilepsy are not good surgical candidates or surgery is never considered because they are well controlled.

Studies with a more inclusive definition of frontal lobe epilepsy

Wieser was the first one to use cluster analysis methodology to distinguish 'psychomotor seizures' (i.e. seizures with semipurposeful behavior and automatisms) arising from different locations. His findings are included in the International Classification of Epilepsies of 1989 [27]. Similar techniques were used in our institution to investigate seizure symptomatology of temporal lobe seizures [28] and also frontal lobe seizures [29, 30]. According to these findings, frontal lobe seizures can be subdivided into the following larger groups: focal clonic seizures, bilateral asymmetric tonic seizures, complex motor seizures.

Focal clonic seizures

Spread of epileptic activity into the primary motor cortex usually leads to focal clonic motor activity in the contralateral body [31]. This activity tends to start with a continuous increase in muscle tone associated with repetitive fast spiking over the precentral gyrus, followed by a regular pattern of synchronous, short contraction of agonistic and antagonistic muscles alternating with muscle relaxation [32]. The motor activity may be preceded by a somatosensory or nonspecific aura in 20-30 of the cases [30, 33]. The most frequent sequence consists of clonic activity starting unilaterally in the face, then spreading to the arm of the same side, followed by speech arrest, and eye blinking [30]. One of the main characteristics of this seizure type is the preservation of consciousness [30].

Bilateral asymmetric tonic seizures

Classically, seizures elicited in the SSMA area are short (10-40 seconds) and consist of bilateral asymmetric tonic posturing with abduction/elevation of the arms and flexion at the elbows and preserved consciousness [34]. Frequently, the patients experience a somatosensory aura of tingling, numbness or tension [30, 34, 35]. The tonic phase of the seizure may start with tonic vocalization [30, 34]. The patient may speak during the seizure, but speech arrest is more frequent [35, 36]. The head usually turns contralaterally [37], but can also turn ipsilaterally, and is not a reliable lateralizing sign if the seizure does not evolve into a generalized tonic-clonic seizure. Toward the end of the tonic seizure, a few clonic movements may occur [34]. Postictal confusion is very rare. The seizures frequently occur nocturnally, often in clusters [34].Although the symptomatogenic zone of this seizure is the SSMA, the epileptogenic zone may also be found in the mesial frontal, basal frontal or mesial parietal region [38].

Complex motor seizures

Complex motor seizures are defined as seizures with organized and semi-purposeful movements. If they predominantly affect proximal limb portions, they are classified as "hypermotor seizures" [39]. This seizure type, whose signs have also been described as "complex gestural automatisms", "gestural motor disorders" or "repetitive motor activity", is considered to be characteristic of frontal lobe epilepsy [27].

Motor activity includes thrashing of the extremities, body rocking, bicycling leg movements, laughing and shouting [4, 30, 40-42]. The majority (50-90) of the patients have auras [4, 41, 42], which may consist of feelings of tightness or tingling of certain body parts [4, 41], vague experiential feelings [42], or fear [41]. Usually, the complex motor activity is not the only ictal symptom. In the majority of the cases, the motor automatisms are preceded or followed by tonic muscle activity of different limbs [41]. However, the motor activity of the hypermotor phase may be so striking that other clinical signs may be overlooked. The seizures tend to last less than a minute [41], and occur more often during sleep than during wakefulness [4, 43]. According to

Bancaud and Talairach [40], there are five different frontal regions from which this seizure type usually arises: anterior cingulate gyrus, frontopolar, orbitofrontal, opercular-insular, and medial-intermediate region.

Other types of seizures associated with frontal lobe epilepsy or activation of frontal areas include versive seizures, dialeptic seizures, akinetic seizures and aphasic seizures. Versive seizures are defined by forced, sustained and unnatural head turning, frequently with conjugate, saccadic eye movement to the same side [44]. If arising from the frontal lobe, they are most likely elicited by discharges in the frontal eye field [15]. However, they may be associated with seizures from any cortical region without clear predominance of a particular lobe [45, 46]. Seizures consisting of a brief lapse of consciousness ('absence seizures' or 'dialeptic seizures') also occur in frontal lobe epilepsy and seem to be associated with mesial frontal or orbitofrontal seizure onset [40]. Associated symptoms with this type of seizure include behavioral arrest, conjugate eye and head deviation, and immediate recovery of consciousness [47].

The inability to initiate or maintain movements (akinetic seizure) may be associated with activation of frontal negative motor areas. This type of seizure has been reported rarely [48]. Evidence from the case reports as well as from cortical stimulation studies suggests that akinetic seizures are produced by activation of the frontal negative motor areas. However, akinetic seizures may also occur in generalized epilepsy [48]. Aphasic seizures are defined as seizures with aphasia as a prominent feature as opposed to ictal aphasia defined as some degree of aphasia in seizures with other leading symptoms [49]. Although aphasic seizures may be generated by activation of the frontal language area, most published reports involve patients with temporal lobe epilepsy [49].

Seizure types in patients seizure-free after frontal lobe resection

There are only a small number of studies mentioning semiological features of seizures of a cohort of consecutive patients who became seizure-free after frontal lobe resections [36, 50, 51]. An aura was found in 60% of the patients, predominantly somatosensory, cephalic or autonomic [36, 51]. Automatisms were found in 25-30%, and secondary generalization in 90% of the patients. In addition to these studies, one study focuses exclusively on seizure semiology in this patient group, but it excluded patients with focal clonic and bilateral asymmetric tonic seizures, or frontotemporal and frontocentral lesions [29]. In the remaining 14 patients with complex motor seizures, a wide variety of seizure symptoms, including epigastric auras, alimentary automatisms and autonomic signs were found. The most frequent features, however, were an aura of indescribable, whole body sensations, behavioral arrest and staring, repetitive and flailing proximal leg and arm movements, and vocalizations. Loss of consciousness was reported in more than three quarters of the seizures and usually occurred in the first third of the seizure. Secondary generalization occurred infrequently (5).

Electroencephalography in frontal lobe epilepsy

Since surface EEG is not invasive, and current technology allows for digital processing and storage of large amounts of EEG data, long-term monitoring has become the gold standard of epilepsy diagnosis. However, because of its inherent limitations (low sensitivity for small or deep foci, sampling error of intracranial electrodes), findings of surface and invasive EEG should be congruent, and must be confirmed by other diagnostic modalities to provide reliable information for epilepsy surgery.

Interictal EEG

There are studies reporting that up to 40% of the patients with frontal lobe epilepsy do not have any interictal epileptiform discharges [52-54]. However, visual inspection of continuous long-term EEG recordings may have a significantly higher yield. The field of the discharges frequently is widespread. Quesney *et al*. [55] found lobar and multilobar spikes more frequent than spikes of a more restricted field, and bilateral spikes were the most common single finding. The spikes may even have the same distribution as in generalized epilepsy [56]. Focal interictal epileptiform discharges seem to be more common in lateral frontal foci [53, 57] and may be found in almost half of the patients [54]. If the epileptogenic zone is medial, focal spikes may occur in the midline electrodes [58]. Electrodes closely spaced over the regions of interest may help to distinguish between temporal and frontal, or left and right hemispheric origin [59]. However, the lateralization may be misleading [58]. The morphology of interictal patterns includes paroxysmal fast activity, single and multiple spikes, and spike-wave complexes [3] *(figure 2)*.

The significance of interictal epileptiform discharges on subdural or intracerebral areas is still controversial, and there are only a few data regarding interictal findings of invasive recordings. In patients with frontal lobe epilepsy, interictal discharges are usually widespread, involving multiple electrodes, close as well as distant to the scalp findings, even if the scalp EEG findings are more localized [52].

Ictal EEG

In frontal lobe seizures, motor activity is frequently seen during the initial stages of the seizure. Thus, EEG activity during the seizure is obscured by artifact in approximately 20 of cases [55, 60]. Since muscle artifacts are prevalent in least the midline electrodes, transverse montages may be

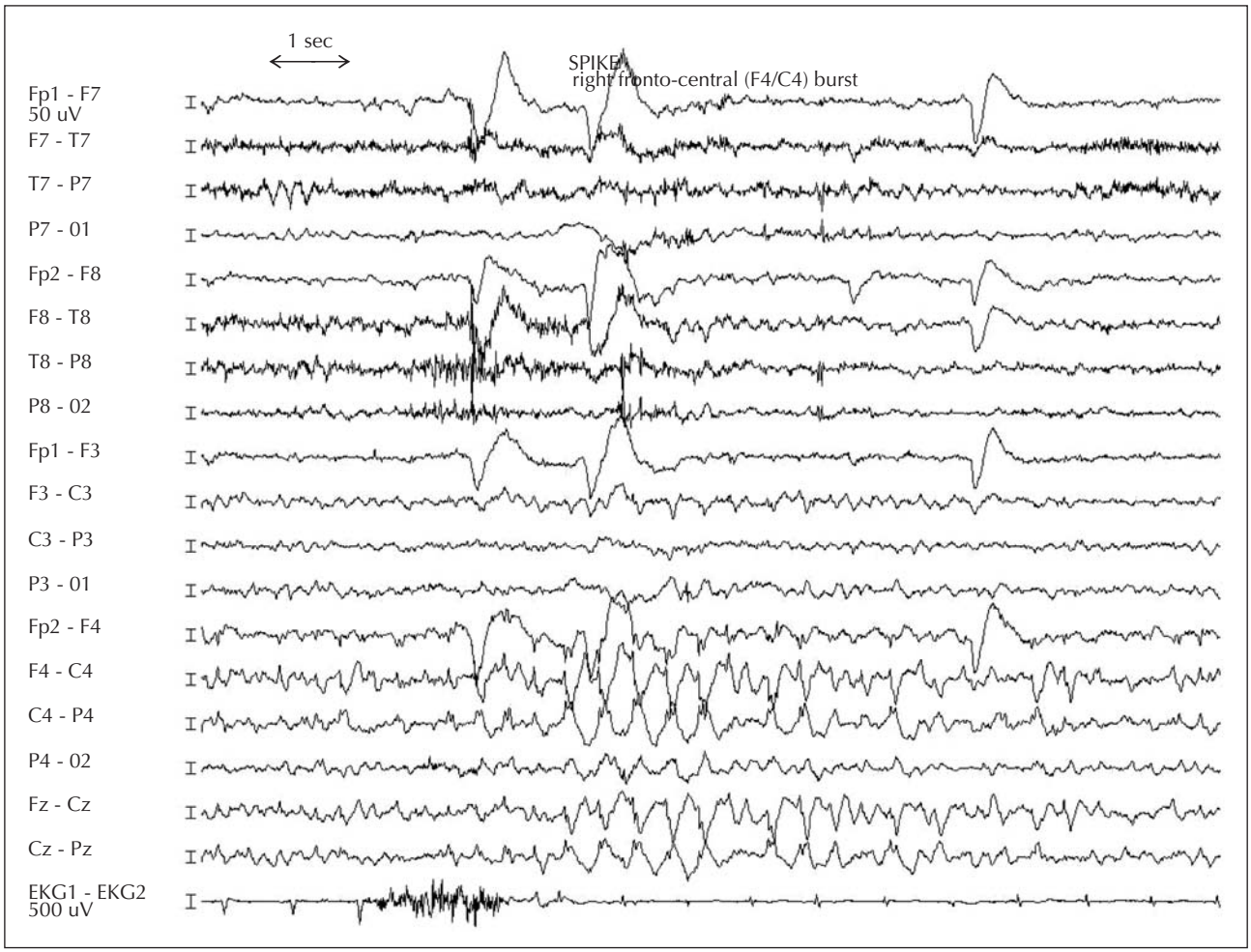

Figure 2. *Interictal epileptiform discharges in a patient with frontal lobe epilepsy: bursts of spikes and slow waves right fronto-central*

helpful [61]. Generalized or bilateral, approximately symmetrical patterns have been reported in 20-67% of the seizures [54, 55, 60]. Localizable EEG seizure onsets were found in only 30-40% of the cases [52, 54, 60]. Typical ictal patterns on scalp EEG associated with lateral frontal seizures include rhythmic fast activity frequently preceding clinical onset [53], localized repetitive spiking or rhythmic delta activity [62]. Mesial frontal lobe seizures characteristically start with a high-amplitude, sharp transient followed by bilateral frontocentral low-voltage fast or electrodecrement evolving into fast and rhythmic activity [34, 63] *(figure 3)*.

Even if the EEG onset on scalp electrodes is widespread, subdural electrodes may show circumscript seizure onset in 50-80% of the cases [52, 64, 65]. Initial seizure propagation was contiguous spread in more than 80% of the seizures in one study, with the mesial frontal area propagating faster than orbital or dorsolateral areas [65]. Ictal onset patterns seem to consist predominantly of low amplitude fast activity, but high amplitude spike and polyspike discharges were also found [64]. However, fast spread from and into frontal regions, especially the mesial frontal region, has been frequently reported [65-68]. In cases where no focal onset is obvious, special recordings (direct current (DC)-shifts, fast sampling rate, high amplitude range) may be helpful [69, 70].

Electrocorticography and cortical stimulation

Intraoperative electrocorticography (ECoG) has been used for defining the resection borders in epilepsy surgery and as an indicator for postsurgical outcome for decades. Epileptiform activity on post-resection ECoG has been reported as indicating favorable outcome in some reports [71], while other studies did not find a significant correlation between post-resection ECoG and outcome [72]. In a large series of frontal lobe epilepsy patients, spatial limited epileptiform activity on pre-resection ECoG, and absence of epileptiform on post-resection ECoG strongly correlated with favorable surgical outcome [73].

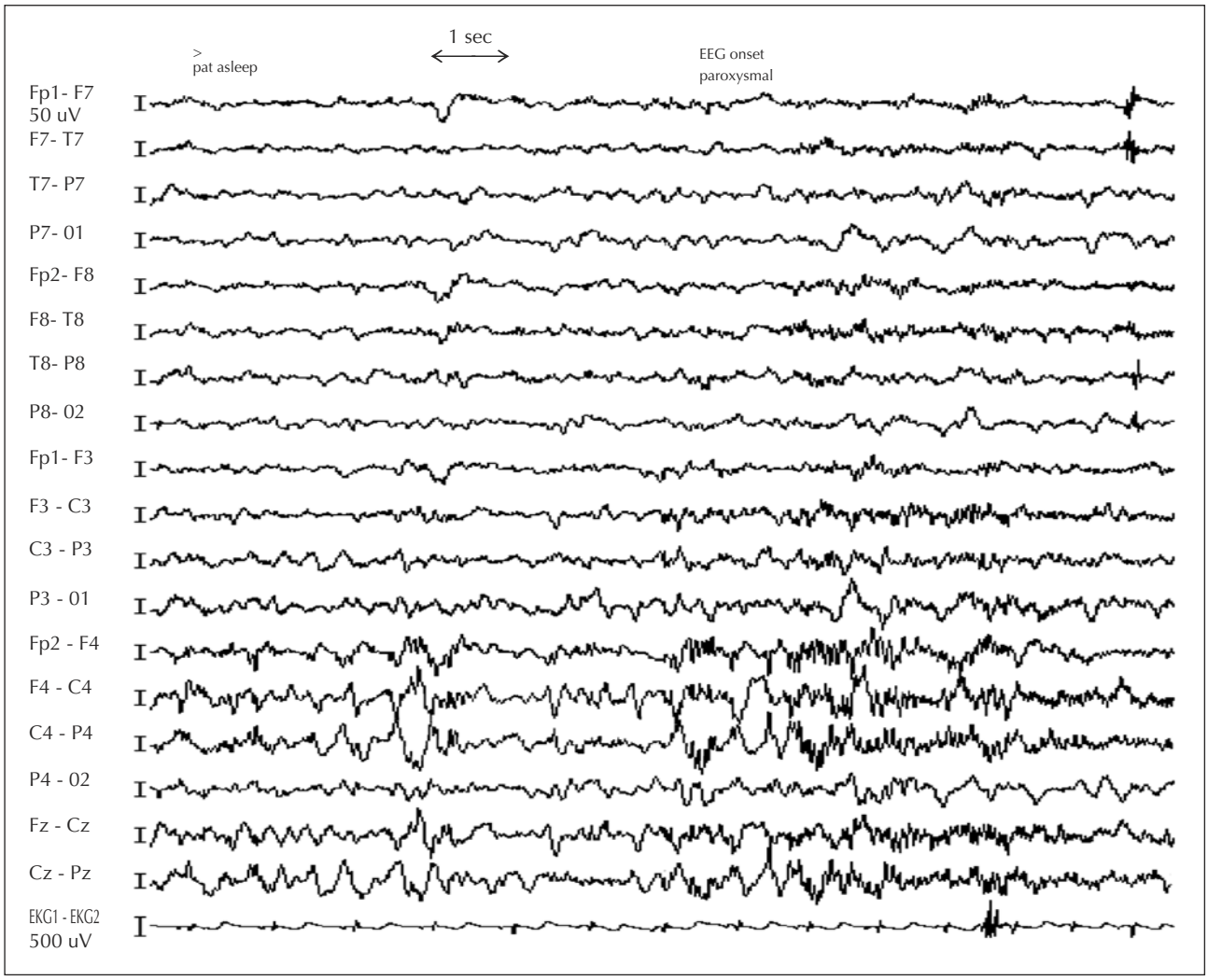

Figure 3. *Ictal pattern in a patient with frontal lobe epilepsy: paroxysmal fast activity arising from the right fronto-central region*

Intra- and extraoperative cortical stimulation can help in identifying the seizure-onset zone by eliciting typical auras [74]. In addition, it can identify eloquent cortical areas and thus help define the resection limits more accurately. Usually, electrical stimuli of increasing strength are applied to the cortex via subdural grid electrodes until a response is elicited, or the upper limit of current amplitude is reached. Cortical stimulation may be of particular value in extratemporal epilepsies with non-localizing imaging findings [75].

Magnetoencephalography (MEG)

MEG detects magnetic fields of epileptiform discharges. Therefore, MEG signals are independent of a reference and are not distorted by dura, skull or scalp. However, similar to EEG, MEG is dependent on the size of and distance from the area of synchronously discharging neurons similar to EEG [76]. MEG is only capable of detecting dipoles horizontal to the surface. Thus, it seems to be more sensitive to generators lining sulci, but less sensitive to discharges from gyral surfaces [77]. In several cases of frontal lobe epilepsy, co-localization of interictal [78, 79] and ictal [78] MEG dipoles with subdural EEG recordings has been reported. In general, it seems that EEG and MEG provide complementary localizing information [80]. Because of its inherent strengths and limitations, it may be more helpful in detecting mesial than lateral frontal foci.

Structural and functional imaging

Structural and functional imaging techniques serve two major goals in epileptology: they have become invaluable tools for the localization of the epileptogenic zone by assessing a tentative lesional zone and functional deficit zone. Moreover, imaging methods are essential in determining the etiology of the epilepsy.

Magnetic resonance imaging (MRI)

MRI has become the method of choice for detecting epileptogenic lesions [6]. The standard T1-, and T2- and proton density sequences are usually modified and adapted to optimize sensitivity and specificity for the lesions typically seen in epileptic patients [61, 81]. In series of patients with frontal lobe epilepsy determined on the basis of clinical and neurophysiological findings, focal MRI lesions were identified in 30-65 of the cases [82-87]. However, these studies were performed before the introduction of fluid-attenuated inversion recovery (FLAIR) sequences and high-resolution volumetric acquisition of T1-sequences that are considered most sensitive for cortical dysplasia [88]. Recently it was shown that interpretation of standard MRI by readers not experienced in epilepsy-specific neuroradiology, had a sensitivity of only 50 compared to 91 in expert reports of epilepsy-specific MRI sequences [89]. In that study, MRI lesions were found in 85% of the patients with a histopathologically confirmed focal lesion. This suggests that with increasing technological progress in MRI, more and more cases of frontal lobe epilepsy, formerly regarded as "idiopathic" or "cryptogenic", may prove to be due to a focal lesion.

Positron emission tomography (PET)

PET has been used to localize epileptogenic foci since the late 1970s [90]. Since then, technological advances regarding the production of the radioactive tracers and signal processing have made it a widely available clinical tool. The tracer 2-[^{18}F] fluoro-2-deoxyglucose (FDG) is used most commonly for imaging cerebral glucose metabolism. In extratemporal lobe epilepsy, normal FDG-PET scans are found more frequently than in mesial temporal lobe epilepsy [91-93] If the MRI is normal, FDG-PET shows abnormalities in only 35-45 of the patients with frontal lobe epilepsy [92, 94]. The area of hypometabolism is usually more widespread than the EEG seizure-onset zone or the structural lesion, and may include regions outside the frontal lobe or even subcortical regions [95, 96], increasing the difficulty of delineating the epileptogenic zone. Thus, in patients with normal MRI, FDG-PET may be of limited value.

The interictal imaging of central benzodiazepine receptor density with [^{11}C]-Flumazenil (FLZ)-PET was suggested as a complementary investigation. In temporal lobe epilepsy, decreased FLZ-binding is seen more circumscribed than corresponding hypometabolism in FDG-PET [96]. The same phenomenon was seen in patients with frontal lobe epilepsy [92, 97]. However, results from an early study suggesting high diagnostic yield of this method in frontal lobe epilepsies [97] could not be reproduced, and even provided false lateralization compared to electroclinical and MRI data in some patients [92]. The role of FLZ-PET in frontal lobe epilepsy is thus still controversial.

[^{11}C]-alpha-methyl-L-tryptophan (AMT)-PET has been used to identify epileptogenic tubers in children with tuberous sclerosis [98], and may also prove useful in non-lesional neocortical epilepsy. In three out of 11 children with MRI-negative refractory epilepsy, there was increased AMT-binding corresponding to the epileptogenic zone, identified by surface and intracranial EEG [99]. AMT showed a higher specificity but lower sensitivity than FDG-PET in that study. AMT-PET has also been used to identify epileptogenic areas in patients who were ineligible for epilepsy surgery [100]. Since only a few small series have been published so far, its value in frontal lobe epilepsy has still to be assessed.

Tracers for the imaging of cerebral blood flow (e.g. 15O-H_2O), opiate receptors (e.g. 11C-carfentanil), and other targets have been used experimentally in neocortical epilepsy, but their role in clinical practice has still to be determined [96].

Single photon emission computed tomography (SPECT)

SPECT imaging of regional blood flow changes has been introduced into epilepsy evaluation as a more affordable alternative to interictal PET studies [6]. However, interictal SPECT studies proved to be less specific and less sensitive than PET (101). Ictal studies, on the other hand, are limited by the necessity of injecting the tracer within at least 45-60 seconds [102], demanding the bedside presence of a trained nurse or technician. Even under optimal conditions, the tracer injection lags behind seizure onset on EEG which itself may already represent a spread pattern. This may be true in particular for frontal lobe seizures arising from the mesial or basal regions. Again, data from early studies suggesting a high diagnostic yield [85] could not be confirmed by larger series using stricter inclusion criteria [103]. A systematic study of the localizing and lateralizing value of ictal SPECT in a larger number of patients with frontal lobe has not yet been performed. Digital subtraction of ictal and interictal studies followed by co-localization of the difference image of with MRI (SISCOM) increases the yield of SPECT studies [102, 104]. It has a better inter-rater reliability, a higher rate of localization, and predicts surgical outcome better than visual inspection of the interictal and ictal studies alone [105] and therefore may be a more suitable tool in frontal lobe epilepsy.

Magnetic resonance spectroscopic imaging (MRSI)

MRSI detects and quantifies specific proton (1H) or phosphorus (31P) containing metabolites of brain tissue *in vivo* and has been used to detect metabolic abnormalities in patients with epilepsy. There are only a few small studies investigating the value of MRSI in patients with extratemporal or frontal lobe epilepsy. In these series, metabolic abnormalities were seen in the hemisphere of the epileptogenic zone in almost all patients with extratemporal

epilepsy [106-109]. However, these changes were found to be much more widespread than the presumed epileptogenic area [107, 109]. Therefore, and due to the inherently low spatial resolution of this method, MRSI may prove more useful for lateralizing rather than localizing the epileptogenic zone.

Etiologies

Although a thorough analysis of all potential factors contributing to frontal lobe epilepsy is outside the scope of this review, it seems that epilepsies do not have a single, but multiple pathogenic factors. In this review, we will focus on the most prominent and easily identifiable etiologic factors in a patient with frontal lobe epilepsy.

Tumors

Recent studies with access to modern neuroimaging found that 20-30% of the patients with frontal lobe epilepsy undergoing epilepsy surgery had neoplastic lesions [110-112] *(figure 4)*. On the other hand, patients with brain tumors develop seizures in 20-70% of cases, depending on the type of tumor. Seizures are more frequent in older patients who have tumors [113-115]. The risk of developing seizures also depends on the location of the lesion, particularly if there is involvement of cortical grey matter [113, 115, 116]. Tumors in the centroparietal region seem to have more epileptogenic potential than in other lobes [117]. The highest prevalence of seizures was found in low-grade astrocytomas (40-70), followed by mixed gliomas and gangliogliomas (30-60), whereas glioblastomas and metastases, as well as meningeomas are less likely to cause seizures [114, 118].

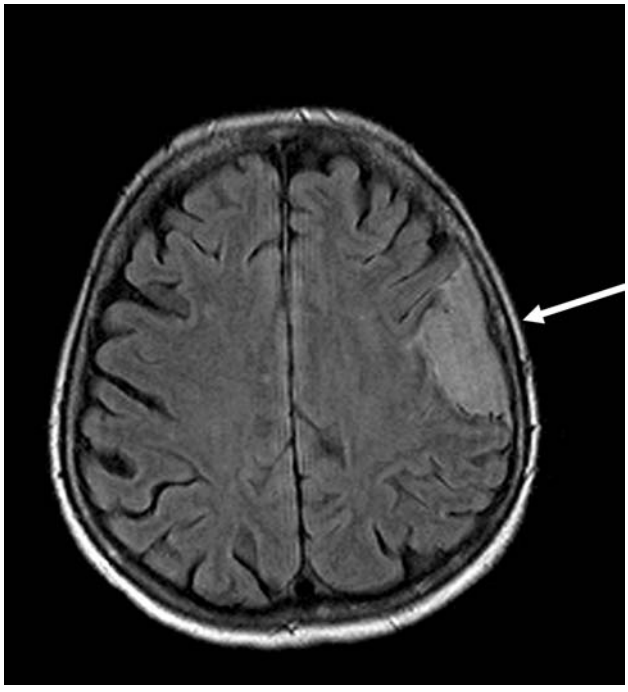

Figure 4. *A patient with a meningeoma in the left lateral frontal lobe (arrow) and seizures arising from this region*

Dysembyoplastic neuroepithelial tumors (DNET) as well as hamartomas have similarities with malformation of cortical developments, but may, not infrequently, mimick astrocytomas or other potentially malignant tumors [119].

Cortical dysplasia

Cortical dysplasia (CD) is the result of malformation of cortical development (MCD). In patients with epilepsy, cortical dysplasia tends to have more intrinsic epileptogenicity than gangliogliomas [120]. The additional intrinsic factors causing epileptogenicity in MCD are not known, but there is evidence of overexpression of the subtype 2B of NMDA receptors in areas of CD that also show frequent spiking in subdural grid electrode recordings [121].

Focal MCD is frequently seen in the frontal lobe [122]. In one series of patients with frontal lobe epilepsy undergoing epilepsy surgery, 58% of the patients were diagnosed with MCD based on postoperative histology [50]. In patients with MCD, one of the most important factor for good seizure outcome after surgery seems to be the completeness of lesion resection [123]. Complete resection of MCD is frequently difficult because epileptogenicity may extend beyond the borders of the MRI-visible MCD [124], or because the epileptogenic zone borders to or includes eloquent cortex areas.

Vascular malformations

Cerebral vascular malformations are developmental, abnormal vascular structures in the CNS. They are detected in 2.3 patients/100.000 per year [125], but in approximately 5% of the patients with epilepsy [57]. Cerebral vascular malformations can be divided into arteriovenous malformations (AVM), cavernous angiomas (CA), venous malformations (VM) and teleangiectasias (TA) [126]. AVM are the most common vascular malformations. They present with epilepsy in 20-30% of patients [127, 128]. They seem to be more common and more frequently epileptogenic in the temporal lobe [128]. In frontal lobe epilepsy patients undergoing surgery, they were found in 6-14% [129, 130]. After resection of the lesion and surrounding tissue, postoperative seizure control can be achieved in 80-90% [117].

Cavernous angiomas are present with seizures in up to 60% of the supratentorial cases [131]. However, of patients with CA presenting with seizures, infratentorial CA were visible on high resolution MRI studies in 6 only [132]. Thus, in some patients with CA, the seizures may be coincidental and not related to the malformation. In patients with frontal lobe epilepsy, CA have been found in 4-7 [129]. VA and TA usually are asymptomatic. They

have been observed in patients with epilepsy, but they are probably almost always coincidental findings [126].

Posttraumatic lesions

In the general epilepsy population, head injury was reported as a risk factor in 2-30% [133-135]. The higher rates are most likely due to inclusion of relatively mild head injuries that had no causal relationship with the epilepsy. In newer series, the proportion of patients with posttraumatic lesions undergoing epilepsy surgery is 20% [130, 136]. Complete resection of the scar tissue together with surrounding gliotic tissue, resulted in a high success rate in one small series of frontal lobe epilepsy patients [137]. However, other series reported less favorable outcome in posttraumatic frontal lobe epilepsy [123, 130].

Genetic etiology

Although epilepsy is caused by the interplay of different etiological factors on several biological levels, in some patients there is evidence for a predominant genetic factor [138]. Most of these patients have an inherited metabolic disease associated with seizures (e.g. myoclonus epilepsies). However, familial clustering with mendelian inheritance of some types of generalized as well as partial epilepsies has also been reported [138]. In families where so-called autosomal dominant (AD) nocturnal frontal lobe epilepsy (NFLE) has been reported [139], several associated mutations and gene products have been identified [140, 141].

Therapy and outcome

Epilepsy therapy primarily consists of treatment with anticonvulsive drugs. In patients who comply with the prescriptions, seizure-freedom can be achieved in over 60% [142]. If medication fails, patients with focal epilepsy may be eligible for epilepsy surgery. In addition, neuromodulation with vagal nerve stimulation has been proven to alleviate the seizure burden [143, 144], and other methods of neuromodulation are currently under investigation.

Drug therapy

In a large group of patients with focal and generalized epilepsy, almost 50% became seizure-free for at least one year with the first drug, and an additional 13% with the second drug [142]. With the exception of ethosuximide and mesuximide, virtually all drugs licensed for epilepsy therapy have proven effectiveness in focal epilepsy [145]. However, virtually no large drug study distinguishes between focal epilepsies arising from different brain regions. Therefore, drug equivalence for frontal, temporal, occipital or other types of focal epilepsies can only be assumed. Only one, small, open-label, non-randomized study found that the combination therapy of lamotrigine and valproate led to seizure-freedom for one year in 10 out of 21 patients with frontal lobe epilepsy who previously failed to improve with at least three other drugs [146]. However, because of severe methodological constraints regarding the identification of the epileptogenic zone, the results have to be regarded with caution.

Neuropsychological aspects of non-surgically treated frontal lobe epilepsy

There have been several studies about neuropsychological and behavioral abnormalities in non-surgical patients with frontal lobe epilepsy. When compared with temporal lobe epilepsy patients, frontal lobe epilepsy was associated with impairment of motor skills and response inhibition [147]. These deficits may be expressed as other personal and clinical conditions such as hyperactivity, obsession and addiction. Since seizure control affects neuropsychological variables, behavioral and neuropsychological problems may not be constant but state-dependent [148]. However, larger series with longer follow-up periods are needed to fully understand the contribution of other factors to the deficits observed.

Epilepsy surgery

Epilepsy surgery has been shown to be a relatively safe procedure, providing freedom from seizures that impact on quality of life in 58% of the patients compared with 8% on optimal medical treatment for temporal lobe epilepsy [149]. A similar controlled, randomized trial has not yet been performed in patients with frontal lobe epilepsy. However, there is a long history of epilepsy surgery of the frontal lobe, starting with the first successful frontal lobe resection for the treatment of seizures in 1886 [150]. In the first large cohort of patients with non-tumoral frontal lobe cortical resections, 24 (13%) out of 184 patients eventually became seizure-free [51]. Later series also found comparatively low rates of postoperative seizure control [151-153]. Because the quality of neuroimaging is crucial for the localization of the focus, these studies have to be interpreted in the light of the availability of CT, MRI, and epilepsy-specific sequences of MRI (e.g. FLAIR) are not necessarily representative of modern series that have access to the latest diagnostic tools. *Table 1* shows the results of consecutive series with patient recruitment largely after 1990, when MRI became increasingly available. According to these data, the rate of patients maintaining seizure-freedom for at least one year after surgery, is 70-80%, and is thus comparable to patients undergoing surgery for temporal lobe epilepsy [154].

Univariate analysis showed that good surgical outcome was associated with a potentially epileptogenic lesion in neuroimaging [129, 155-157], the absence of febrile seizures [156], generalized or bilateral epileptiform activity on surface EEG [50, 129, 152, 158], widespread epilepti-

Table 1. Epilepsy surgery limited to the frontal lobe and presurgical evaluation including MRI

Study	Institution	Performed from ... to	Number of patients	Number of patients with MRI	Etiologies	Follow-up	Outcome
Munari *et al.* 2001	Grenoble, (F) /Milan, (I)	1990-1998	33	All	Tumor: 3 CD: 10 VM: 2 TS: 4 other: 4 no lesion:10	> 1year	Engel Ia: 25 (70%) Engel II: 1 (4%) Engel III: 3 (9%) Engel IV: 4 (16%)
Zaatreh *et al.* 2002	Yale, (USA)	1985-1999	37	All	Neoplasm: all	> 1 year	Engel Ia/b: 13 (35%) Engel II: 12 (32%) Engel III: 7 (19%) Engel IV: 5 (14%)
Kral *et al.* 2001	Bonn, (D)	1989-2000	32 (children only)	All	Neoplasm: 7 other: 22 no lesion: 3	> 1 year	Engel I/II: 21 (66%) Engel III/IV: 11(34%)
Swartz *et al.* 1998	Los Angeles, (USA)	1986-1995	15	All	n/a	> 6 months	Seizure-free: 9 (60%) > 90% reduction: 3 (20%) > 75% reduction: 3 (20%)
Laskowitz *et al.* 1995	Philadelphia, (USA)	1986-1993	14	All	Neoplasm: 6 gliosis: 6 no lesion: 2	> 1 year	Engel Ia/b: 10 (71%) Engel II: 1 (7%) > 80% reduction: 3 (21%)
Mosewich *et al.* 2000	Rochester, MN, (USA)	1987-1994	68	66 (97%)	EM: 17 neoplasm 10 CD:5 VM: 5 other:2 no lesion: 29	n/a	Seizure-free or rare non-disabling simple partial/ nocturnal seizures only: 40 (59%)
Schramm *et al.* 2002	Bonn, (D)	1989-1999	68 (adults only)	All	Neoplasm: 24 CD: 18 VM: 10 gliosis: 14 no lesion: 2	1-108 months (mean 28.4 ± 23.3)	Seizure- free/auras only: 37 (54%) 1-2 seizures/year: 13 (19%) > 75% reduction: 10 (15%) < 75% reduction: 8 (12%)

CD = cortical dysplasia, VM = vascular malformation, EM = encephalomalacia, n/a = no data available

form activity in ECoG [73], or neoplasm as etiology [155, 159]. Residual epileptogenic tissue as assessed by seizures/frequent spikes ECoG or MRI was a strong predictor for poor outcome [50, 129, 158, 160].

Immediate postoperative complications include intracranial or scalp/skull infections, hemorrhage, edema, neurological deficits and seizures in up to 40-50% of the patients, resulting in a second surgery in 10-15% of the patients, and permanent neurological deficits in 2-3% of the patients [129, 157, 161]. Other series report much lower overall complication rates of 20-25%, but approximately the same rate of permanent neurological deficits [130, 162].

Both success rate and complications are dependent on the location and type of surgery. Resections of cortex in or near eloquent areas bear a greater risk of permanent or transient neurological deficits than frontal lobe surgery. Destruction of the primary hand motor area usually results in permanent loss of fine motor function in that limb. Resection of the SSMA area leads to a profound weakness of the contralateral, sometimes even ipsilateral extremities and aphasia (if the surgery is in the dominant hemisphere), in most of the patients. This deficit usually resolves within months [163-165], but a permanent deficit may remain if the whole SSMA (including the SSMA proper in the paracentral lobe rostral and ventral to M1). Neuropsychological sequelae of epilepsy surgery of the frontal lobe include deficits in speed/attention, motor coordination, short-term memory, and aphasic symptoms. The number and quality of deficits are directly related to the resected area. Resections of the premotor and SSMA areas, as well as lobectomies, carry a high risk of immediate postoperative neurological and neuropsychological deficits [163], particularly if the resection involved the language-dominant hemisphere. Although most of these symptoms may be transient, they may be seen at least three months after surgery

[163]. In children, postoperative improvement of attention, memory and manual coordination was seen regardless of postoperative seizure outcome [166]. As in temporal lobe epilepsy [167], cognitive outcome proved to be inversely correlated to preoperative functional status. i.e., high functioning predicted relatively worse outcome after surgery [163].

Electrical brain stimulation

Vagal nerve stimulation as treatment for epilepsy was developed 15 years ago. Its effectiveness is similar to that reported for new anticonvulsants [143, 144]. In clinical practice, it is used predominantly as a palliative device in patients who are not eligible for resective epilepsy surgery. No study has been performed differentiating the effect of VNS on patients with different epileptogenic zones (generalized versus focal versus different focal locations).

Since the early experiments of Moruzzi and Magoun in the 1930s, numerous experiments have been performed to investigate the effect of electrical stimulation of several different brain structures on epilepsy [168]. In spite of reports of success in several small case series, none of the approaches has been proven effective in a randomized, controlled, double-blind trial. None of the series has focused on patients with frontal lobe epilepsy. However, some of the approaches, particularly STN stimulation, focal cortical stimulation and rTMS, may be useful in frontal lobe epilepsy, particularly in patients where the epileptogenic zone extends into important eloquent cortical areas and thus precludes resective surgery.

Summary

Frontal lobe epilepsy is not a disease entity, but rather a heterogenous group of disorders with seizures of frontal origin as the predominant symptom. Seizure semiology is determined by the location of the epileptogenic zone as well as the individual characteristics of the patient's brain, particularly the etiology. The diagnostic and therapeutic approach for frontal lobe epilepsy is very similar to those used in focal epilepsies of other regions. Surgical therapy may be as successful as in temporal lobe epilepsy if all available diagnostic tools are used effectively. Other therapies are being developed for patients who do not become seizure-free with medication and who are not eligible for epilepsy surgery. □

References

1. French JA, Williamson PD, Thadani VM *et al*. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 1993; 34: 774-780.

2. Williamson PD, French JA, Thadani VM *et al*. Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. *Ann Neurol* 1993; 34: 781-787.

3. Rasmussen T. Surgery of frontal lobe epilepsy. *Adv Neurol* 1975; 8: 197-205.

4. Williamson PD, Spencer DD, Spencer SS *et al*. Complex partial seizures of frontal lobe origin. *Ann Neurol* 1985; 18: 497-504.

5. Manford M, Hart YM, Sander JW *et al*. The National General Practice Study of Epilepsy. The syndromic classification of the International League Against Epilepsy applied to epilepsy in a general population. *Arch Neurol* 1992; 49: 801-808.

6. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. *Brain* 2001; 124: 1683-1700.

7. Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 1998; 106: 283-296.

8. Kötter R, Stephan KE, Palomero-Gallagher N *et al*. Multimodal characterisation of cortical areas by multivariate analyses of receptor binding and connectivity data. *Anat Embryol (Berl)* 2001; 204: 333-350.

9. Penfield W, Rasmussen T. *The cerebral cortex of man*. New York: MacMillan, 1950.

10. Nii Y, Uematsu S, Lesser RP *et al*. Does the central sulcus divide motor and sensory functions ? Cortical mapping of human hand areas as revealed by electrical stimulation through subdural grid electrodes. *Neurology* 1996; 46: 360-367.

11. Rizzolatti G, Luppino G, Matelli M. The classic supplementary motor area is formed by two independent areas. *Adv Neurol* 1996; 70: 45-56.

12. Luppino G, Matelli M, Camarda R *et al*. Corticospinal projections from mesial frontal and cingulate areas in the monkey. *Neuroreport* 1994; 5: 2545-2548.

13. Lim SH, Dinner DS, Pillay PK *et al*. Functional anatomy of the human supplementary sensorimotor area: results of extraoperative electrical stimulation. *Electroencephalogr Clin Neurophysiol* 1994; 91: 179-193.

14. Dinner DS, Lüders HO, Lim SH. Electrical stimulation of the supplementary sensorimotor area. In: Lüders HO, Noachtar S. *Epileptic seizures - Pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 192-198.

15. Godoy J, Lüders H, Dinner DS *et al*. Versive eye movements elicited by cortical stimulation of the human brain. *Neurology* 1990; 40: 296-299.

16. Penfield W, Roberts L. *Speech and brain-mechanisms*. Princeton: Princeton University Press, 1959.

17. Lesser RP, Lueders H, Dinner DS *et al*. The location of speech and writing functions in the frontal language area. Results of extraoperative cortical stimulation. *Brain* 1984; 107 (Pt 1): 275-291.

18. Schaffler L, Lüders HO, Dinner DS *et al*. Comprehension deficits elicited by electrical stimulation of Broca's area. *Brain* 1993; 116 (Pt 3): 695-715.

19. Lüders H, Lesser RP, Dinner DS *et al*. Localization of cortical function: new information from extraoperative monitoring of patients with epilepsy. *Epilepsia* 1988; 29 Suppl 2: S56-S65.

20. Lüders HO, Dinner DS, Morris HH *et al*. Electrical stimulation of negative motor areas. In: Lüders HO, Noachtar S. *Epileptic seizures - pathophysiology and clinical semiology*. New York: Churchill Livinstone, 2000: 199-210.

21. Fletcher PC, Henson RN. Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 2001; 124: 849-881.

22. Goethals I, Audenaert K, Van de WC *et al*. The prefrontal cortex: insights from functional neuroimaging using cognitive activation tasks. *Eur J Nucl Med Mol Imaging* 2004; 31: 408-416.

23. Baddeley A. Working memory. *Science* 1992; 255: 556-559.

24. Öngür D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex* 2000; 10: 206-219.

25. Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav Brain Res* 1990; 41: 81-94.

26. Jackson HH. Convulsive spasms of the right hand and arm preceding epileptic seizures. *Med Times Gazette* 1863; 1: 110-111.

27. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; 30: 389-399.

28. Kotagal P, Lüders HO, Williams G *et al*. Psychomotor seizures of temporal lobe onset: analysis of symptom clusters and sequences. *Epilepsy Res* 1995; 20: 49-67.

29. Kotagal P, Arunkumar GS, Hammel J *et al*. Complex partial seizures of frontal lobe onset statistical analysis of ictal semiology. *Seizure* 2003; 12: 268-281.

30. Salanova V, Morris HH, Van Ness P *et al*. Frontal lobe seizures: electroclinical syndromes. *Epilepsia* 1995; 36: 16-16.

31. Ikeda A, Nagamine T, Kunieda T *et al*. Clonic convulsion caused by epileptic discharges arising from the human supplementary motor area as studied by subdural recording. *Epileptic Disord* 1999; 1: 21-26.

32. Hamer HM, Lüders HO, Knake S *et al*. Electrophysiology of focal clonic seizures in humans: a study using subdural and depth electrodes. *Brain* 2003; 126: 547-555.

33. Bonelli SB, Baumgartner C. [Frontal lobe epilepsy--clinical seizure seminology]. *Wien Klin Wochenschr* 2002; 114: 334-334.

34. Morris HH, III, Dinner DS, Lüders H *et al*. Supplementary motor seizures: clinical and electroencephalographic findings. *Neurology* 1988; 38: 1075-1082.

35. Connolly MB, Langill L, Wong PK *et al*. Seizures involving the supplementary sensorimotor area in children: a video-EEG analysis. *Epilepsia* 1995; 36: 1025-1032.

36. Quesney LF, Constain M, Fish DR et al. The clinical differentiation of seizures arising in the parasagittal and anterolaterodorsal frontal convexities. *Arch Neurol* 1990; 47: 677-679.

37. Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain*. Boston: Little, Brown, 1954.

38. Ikeda A, Sato T, Ohara S *et al*. "Supplementary motor area (SMA) seizure" rather than "SMA epilepsy" in optimal surgical candidates: a document of subdural mapping. *J Neurol Sci* 2002; 202: 43-52.

39. Lüders H, Acharya J, Baumgartner C *et al*. A new epileptic seizure classification based exclusively on ictal semiology. *Acta Neurol Scand* 1999; 99: 137-141.

40. Bancaud J, Talairach J. Clinical semiology of frontal lobe seizures. *Adv Neurol* 1992; 57: 3-58.

41. Holthausen H, Hoppe M. Hypermotor seizures. In: Lüders HO, Noachtar S. *Epileptic seizures - pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 439-448.

42. Manford M, Fish DR, Shorvon SD. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. *Brain* 1996; 119 (Pt 1): 17-40.

43. Waterman K, Purves SJ, Kosaka B *et al*. An epileptic syndrome caused by mesial frontal lobe seizure foci. *Neurology* 1987; 37: 577-582.

44. Chee MW. Versive seizures. In: Lüders HO, Noachtar S. *Epilepic seizures. Pathophysiology and clinical semiology*. New York: Churchill Livingstone, 1, 2000: 433-438.

45. Bleasel A, Kotagal P, Kankirawatana P *et al*. Lateralizing value and semiology of ictal limb posturing and version in temporal lobe and extratemporal epilepsy. *Epilepsia* 1997; 38: 168-174.

46. Jayakar P, Duchowny M, Resnick T *et a*l. Ictal head deviation: lateralizing significance of the pattern of head movement. *Neurology* 1992; 42: 1989-1992.

47. Noachtar S, Desudchit T, Lüders HO. Dialeptic seizure. In: Lüders HO, Noachtar S. *Epileptic seizures. Pathophysiology and clinical semiology*. New York: Churchill Livinstone, 2000: 361-376.

48. Noachtar S, Lüders HO. Akinetic seizures. In: Lüders HO, Noachtar S. *Epileptic seizures - Pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 489-500.

49. Benbadis S. Aphasic seizures. In: Lüders HO, Noachtar S. *Epileptic seizures - Pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 501-506.

50. Janszky J, Fogarasi A, Jokeit H et al. Lateralizing value of unilateral motor and somatosensory manifestations. *Epilepsy Res* 2001; 43: 125-125.

51. Rasmussen T. Characteristics of a pure culture of frontal lobe epilepsy. *Epilepsia* 1983; 24: 482-482.

52. Salanova V, Morris HH, III, Van Ness PC *et al*. Comparison of scalp electroencephalogram with subdural electrocorticogram recordings and functional mapping in frontal lobe epilepsy. *Arch Neurol* 1993; 50: 294-299.

53. Bautista RE, Spencer DD, Spencer SS. EEG findings in frontal lobe epilepsies. *Neurology* 1998; 50: 1765-1765.

54. Swartz BE, Walsh GO, Delgado-Escueta AV *et al*. Surface ictal electroencephalographic patterns in frontal vs temporal lobe epilepsy. *Can J Neurol Sci* 1991; 18: 649-662.

55. Quesney LF. Preoperative electroencephalographic investigation in frontal lobe epilepsy: electroencephalographic and electrocorticographic recordings. *Can J Neurol Sci* 1991; 18: 559-563.

56. Ralston B. Cingulate epilepsy and secondary bilateral synchrony. *Electroencephalogr Clin Neurophysiol* 1961; 13: 591-598.

57. Quesney LF, Constain M, Rasmussen T *et al*. How large are frontal lobe epileptogenic zones ? EEG, ECoG, and SEEG evidence. *Adv Neurol* 1992; 57: 311-323.

58. Blume WT, Oliver LM. Noninvasive electroencephalography in supplementary sensorimotor area epilepsy. *Adv Neurol* 1996; 70: 309-317.

59. Morris HH, III, Lüders H, Lesser RP *et al*. The value of closely spaced scalp electrodes in the localization of epileptiform foci: a study of 26 patients with complex partial seizures. *Electroencephalogr Clin Neurophysiol* 1986; 63: 107-111.

60. Laskowitz DT, Sperling MR, French JA *et al*. The syndrome of frontal lobe epilepsy: characteristics and surgical management. *Neurology* 1995; 45: 780-780.

61. Bleasel A. Mesial frontal lobe epilepsy. In: Lüders HO, Comair Y. *Epilepsy surgery.* Philadelphia: Lippincott, Williams, Wilkins, 2, 2001:

62. Foldvary N. Noninvasive electroencephalographic and magnetoencephalographic evaluation. In: Lüders HO, Comair Y. *Epilepsy surgery.* Philadelphia: Lippincott, Williams, Wilkins, 2, 2000: 431-439.

63. Pedley TA, Tharp BR, Herman K. Clinical and electroencephalographic characteristics of midline parasagittal foci. *Ann Neurol* 1981; 9: 142-149.

64. Toczek MT, Morrell MJ, Risinger MW *et al*. Intracranial ictal recordings in mesial frontal lobe epilepsy. *J Clin Neurophysiol* 1997; 14: 499-499.

65. Blume WT, Ociepa D, Kander V. Frontal lobe seizure propagation: scalp and subdural EEG studies. *Epilepsia* 2001; 42: 491-491.

66. Baumgartner C, Flint R, Tuxhorn I *et al*. Supplementary motor area seizures: propagation pathways as studied with invasive recordings. *Neurology* 1996; 46: 508-514.

67. Cukiert A, Forster C, Buratini JA *et al*. Secondary bilateral synchrony due to fronto-mesial lesions. An invasive recording study. *Arq Neuropsiquiatr* 1999; 57: 636-636.

68. Ikeda A, Matsumoto R, Ohara S *et al*. Asymmetric tonic seizures with bilateral parietal lesions resembling frontal lobe epilepsy. *Epileptic Disord* 2001; 3: 17-22.

69. Allen PJ, Fish DR, Smith SJ. Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1992; 82: 155-155.

70. Ikeda A, Terada K, Mikuni N *et al*. Subdural recording of ictal DC shifts in neocortical seizures in humans. *Epilepsia* 1996; 37: 662-674.

71. Salanova V, Quesney LF, Rasmussen T *et al*. Reevaluation of surgical failures and the role of reoperation in 39 patients with frontal lobe epilepsy. *Epilepsia* 1994; 35: 70-80.

72. Wyllie E, Lüders H, Morris HH, III *et al*. Clinical outcome after complete or partial cortical resection for intractable epilepsy. *Neurology* 1987; 37: 1634-1641.

73. Wennberg R, Quesney F, Olivier A *et al*. Electrocorticography and outcome in frontal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1998; 106: 357-357.

74. Schulz R, Lüders HO, Tuxhorn I *et al*. Localization of epileptic auras induced on stimulation by subdural electrodes. *Epilepsia* 1997; 38: 1321-1329.

75. Cukiert A, Buratini JA, Machado E *et al*. Results of surgery in patients with refractory extratemporal epilepsy with normal or nonlocalizing magnetic resonance findings investigated with subdural grids. *Epilepsia* 2001; 42: 889-894.

76. Ebersole JS. EEG and MEG dipole source modeling. In: Engel J, Pedley TA. *Epilepsy: a comprehensive textbook.* 1998: 919-935.

77. Hari R, Kaukoranta E. Neuromagnetic studies of somatosensory system: principles and examples. *Prog Neurobiol* 1985; 24: 233-256.

78. Ishibashi H, Morioka T, Shigeto H *et al*. Three-dimensional localization of subclinical ictal activity by magnetoencephalography: correlation with invasive monitoring. *Surg Neurol* 1998; 50: 157-163.

79. Ossenblok P, Fuchs M, Velis DN *et al*. Source analysis of lesional frontal-lobe epilepsy. *IEEE Eng Med Biol Mag* 1999; 18: 67-67.

80. Wheless JW, Willmore LJ, Breier JI *et al*. A comparison of magnetoencephalography, MRI, and V-EEG in patients evaluated for epilepsy surgery. *Epilepsia* 1999; 40: 931-941.

81. Ruggieri PM, Najm IM. MRI techniques in the evaluation for epilepsy surgery. In: Wyllie E. *Treatment of epilepsy: principles and practice.* Philadelphia: Lippincott, Williams, Wilkins, 3, 2001: 1031-1041.

82. Cascino GD, Jack CR, Jr., Parisi JE *et al*. MRI in the presurgical evaluation of patients with frontal lobe. *Epilepsy Res* 1992; 11: 51-51.

83. Fish DR. Magnetic resonance imaging and supplementary motor area epilepsy. *Adv Neurol* 1996; 70: 341-351.

84. Lorenzo NY, Parisi JE, Cascino GD *et al*. Intractable frontal lobe epilepsy: pathological and MRI features. *Epilepsy Res* 1995; 20: 171-171.

85. Spencer SS. The relative contributions of MRI, SPECT, and PET imaging in epilepsy. *Epilepsia* 1994; 35 Suppl 6: S72-S89.

86. Swartz BE, Halgren E, Delgado-Escueta AV *et al*. Neuroimaging in patients with seizures of probable frontal lobe origin. *Epilepsia* 1989; 30: 547-558.

87. Swartz BW, Khonsari A, Vrown C *et al*. Improved sensitivity of 18FDG-positron emission tomography scans in frontal and "frontal plus" epilepsy. *Epilepsia* 1995; 36: 388-395.

88. Usui N, Matsuda K, Mihara T *et al*. MRI of cortical dysplasia--correlation with pathological findings. *Neuroradiology* 2001; 43: 830-837.

89. Von Oertzen J, Urbach H, Jungbluth S *et al*. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *J Neurol Neurosurg Psychiatry* 2002; 73: 643-647.

90. Kuhl DE, Engel J, Jr., Phelps ME *et al*. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of 18FDG and 13NH3. *Ann Neurol* 1980; 8: 348-360.

91. Henry TR, Sutherling WW, Engel J, Jr. *et al*. Interictal cerebral metabolism in partial epilepsies of neocortical origin. *Epilepsy Res* 1991; 10: 174-182.

92. Ryvlin P, Bouvard S, Le Bars D et al. Clinical utility of flumazenil-PET versus [18F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. *Brain* 1998; 121 (Pt 11): 2067-2081.

93. Swartz BE, Halgren E, Simpkins F *et al*. Primary or working memory in frontal lobe epilepsy: An 18FDG-PET study. *Neurology* 1996; 46: 737-737.

94. Kim YK, Lee DS, Lee SK *et al*. (18)F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. *J Nucl Med* 2002; 43: 1167-1174.

95. da Silva EA, Chugani DC, Muzik O *et al*. Identification of frontal lobe epileptic foci in children using positron emission tomography. *Epilepsia* 1997; 38: 1198-1208.

96. Henry TR. Positron emission tomography in epilepsy surgery evaluation. In: Lüders HO, Comair Y. *Epilepsy surgery.* Philadelphia: Lippincott, Williams, Wilkins, 2, 2000: 257-276.

97. Savic I, Thorell JO, Roland P. [11C]flumazenil positron emission tomography visualizes frontal epileptogenic regions. *Epilepsia* 1995; 36: 1225-1232.

98. Chugani DC, Chugani HT, Muzik O *et al*. Imaging epileptogenic tubers in children with tuberous sclerosis complex using alpha-[11C]methyl-L-tryptophan positron emission tomography. *Ann Neurol* 1998; 44: 858-866.

99. Fedi M, Reutens D, Okazawa H *et al*. Localizing value of alpha-methyl-L-tryptophan PET in intractable epilepsy of neocortical origin. *Neurology* 2001; 57: 1629-1636.

100. Juhasz C, Chugani DC, Padhye UN *et al*. Evaluation with alpha-[11C]methyl-L-tryptophan positron emission tomography for reoperation after failed epilepsy surgery. *Epilepsia* 2004; 45: 124-130.

101. Stefan H, Pawlik G, Bocher-Schwarz HG *et al*. Functional and morphological abnormalities in temporal lobe epilepsy: a comparison of interictal and ictal EEG, CT, MRI, SPECT and PET. *J Neurol* 1987; 234: 377-384.

102. O'Brien TJ, So EL, Mullan BP *et al*. Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. *Neurology* 1998; 50: 445-454.

103. Weil S, Noachtar S, Arnold S *et al*. Ictal ECD-SPECT differentiates between temporal and extratemporal epilepsy: confirmation by excellent postoperative seizure control. *Nucl Med Commun* 2001; 22: 233-237.

104. Kaiboriboon K, Lowe VJ, Chantarujikapong SI *et al*. The usefulness of subtraction ictal SPECT coregistered to MRI in single- and dual-headed SPECT cameras in partial epilepsy. *Epilepsia* 2002; 43: 408-414.

105. Cascino GD. Surgical Treatment for Extratemporal Epilepsy. *Curr Treat Options Neurol* 2004; 6: 257-262.

106. Garcia PA, Laxer KD, van der GJ *et al*. Proton magnetic resonance spectroscopic imaging in patients with frontal lobe epilepsy. *Ann Neurol* 1995; 37: 279-279.

107. Li LM, Cendes F, Andermann F *et al*. Spatial extent of neuronal metabolic dysfunction measured by proton MR spectroscopic imaging in patients with localization-related epilepsy. *Epilepsia* 2000; 41: 666-674.

108. Lundbom N, Gaily E, Vuori K *et al*. Proton spectroscopic imaging shows abnormalities in glial and neuronal cell pools in frontal lobe epilepsy. *Epilepsia* 2001; 42: 1507-1507.

109. Stanley JA, Cendes F, Dubeau F *et al*. Proton magnetic resonance spectroscopic imaging in patients with extratemporal epilepsy. *Epilepsia* 1998; 39: 267-273.

110. Frater JL, Prayson RA, Morris III HH *et al*. Surgical pathologic findings of extratemporal-based intractable epilepsy: a study of 133 consecutive resections. *Arch Pathol Lab Med* 2000; 124: 545-549.

111. Morris HH. Neoplastic lesions in epilepsy - overview. In: 1, 1999: 297-300.

112. Wolf HK, Zentner J, Hufnagel A *et al*. Surgical pathology of chronic epileptic seizure disorders: experience with 63 specimens from extratemporal corticectomies, lobectomies and functional hemispherectomies. *Acta Neuropathol (Berl)* 1993; 86: 466-472.

113. Gilles FH, Sobel E, Leviton A *et al*. Epidemiology of seizures in children with brain tumors. The Childhood Brain Tumor Consortium. *J Neurooncol* 1992; 12: 53-68.

114. Liigant A, Haldre S, Oun A *et al*. Seizure disorders in patients with brain tumors. *Eur Neurol* 2001; 45: 46-51.

115. Cascino GD. Epilepsy and brain tumors: implications for treatment. *Epilepsia* 1990; 31 Suppl 3: S37-S44.

116. Penfield W, Erickson TC, Tarlov I. Relation of intracranial tumors in symptomatic epilepsy. *Arch Neurol Psychiatry* 1940; 44: 300-315.

117. Wetjen NM, Cohen-Gadol AA, Maher CO *et al*. Frontal lobe epilepsy: diagnosis and surgical treatment. *Neurosurg Rev* 2002; 25: 119-119.

118. Oda M, Arai N, Maehara T *et al*. Brain tumors in surgical neuropathology of intractable epilepsies, with special reference to cerebral dysplasias. *Brain Tumor Pathol* 1998; 15: 41-51.

119. Degen R, Ebner A, Lahl R *et al*. Various findings in surgically treated epilepsy patients with dysembryoplastic neuroepithelial tumors in comparison with those of patients with other low-grade brain tumors and other neuronal migration disorders. *Epilepsia* 2002; 43: 1379-1384.

120. Rosenow F, Lüders HO, Dinner DS *et al*. Histopathological correlates of epileptogenicity as expressed by electrocorticographic spiking and seizure frequency. *Epilepsia* 1998; 39: 850-856.

121. Najm IM, Ying Z, Babb T *et al*. Epileptogenicity correlated with increased N-methyl-D-aspartate receptor subunit NR2A/B in human focal cortical dysplasia. *Epilepsia* 2000; 41: 971-976.

122. Marusic P, Najm IM, Ying Z *et al*. Focal cortical dysplasias in eloquent cortex: functional characteristics and correlation with MRI and histopathologic changes. *Epilepsia* 2002; 43: 27-27.

123. Ferrier CH, Alarcon G, Engelsman J *et al*. Relevance of residual histologic and electrocorticographic abnormalities for surgical outcome in frontal lobe epilepsy. *Epilepsia* 2001; 42: 363-371.

124. Palmini A, Lüders HO. Classification issues in malformations caused by abnormalities of cortical development. *Neurosurg Clin N Am* 2002; 13: 1-16, vii.

125. Al Shahi R, Bhattacharya JJ, Currie DG *et al*. Prospective, Population-Based Detection of Intracranial Vascular Malformations in Adults: The Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke* 2003; 34: 1163-1169.

126. Vives KP, Awad IA. Vascular causes of epilepsy - overview. In: Kotagal P, Lüders HO. *The epilepsies. Etiologies and prevention.* San Diego: Academic Press, 1, 1999: 371-376.

127. Crawford PM, West CR, Shaw MD *et al*. Cerebral arteriovenous malformations and epilepsy: factors in the development of epilepsy. *Epilepsia* 1986; 27: 270-275.

128. Hoh BL, Chapman PH, Loeffler JS *et al*. Results of multimodality treatment for 141 patients with brain arteriovenous malformations and seizures: factors associated with seizure incidence and seizure outcomes. *Neurosurgery* 2002; 51: 303-309.

129. Ferrier CH, Engelsman J, Alarcon G *et al*. Prognostic factors in presurgical assessment of frontal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 1999; 66: 350-350.

130. Schramm J, Kral T, Kurthen M *et al*. Surgery to treat focal frontal lobe epilepsy in adults. *Neurosurgery* 2002; 51: 644-644.

131. Cappabianca P, Alfieri A, Maiuri F *et al*. Supratentorial cavernous malformations and epilepsy: seizure outcome after lesionectomy on a series of 35 patients. *Clin Neurol Neurosurg* 1997; 99: 179-183.

132. Requena I, Arias M, Lopez-Ibor L *et al*. Cavernomas of the central nervous system: clinical and neuroimaging manifestations in 47 patients. *J Neurol Neurosurg Psychiatry* 1991; 54: 590-594.

133. Jallon P, Loiseau P, Loiseau J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Coordination Active du Reseau Observatoire Longitudinal de l' Epilepsie. *Epilepsia* 2001; 42: 464-475.

134. Murthy JM, Yangala R, Srinivas M. The syndromic classification of the International League Against Epilepsy: a hospital-based study from South India. *Epilepsia* 1998; 39: 48-54.

135. Osservatorio Regionale per L'Epilessia (OREp) L. ILAE classification of epilepsies: its applicability and practical value of different diagnostic categories. *Epilepsia* 1996; 37: 1051-1059.

136. Kotagal P, Arunkumar GS. Lateral frontal lobe seizures. *Epilepsia* 1998; 39 Suppl 4: S62-S62.

137. Cukiert A, Olivier A, Andermann F. Post-traumatic frontal lobe epilepsy with structural changes: excellent results after cortical resection. *Can J Neurol Sci* 1996; 23: 114-117.

138. Kaneko S, Okada M, Iwasa H *et al*. Genetics of epilepsy: current status and perspectives. *Neurosci Res* 2002; 44: 11-30.

139. Scheffer IE, Bhatia KP, Lopes-Cendes I *et al*. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. *Lancet* 1994; 343: 515-517.

140. Phillips HA, Favre I, Kirkpatrick M *et al*. CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. *Am J Hum Genet* 2001; 68: 225-231.

141. Rozycka A, Trzeciak WH. Genetic basis of autosomal dominant nocturnal frontal lobe epilepsy. *J Appl Genet* 2003; 44: 197-207.

142. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-319.

143. Handforth A, DeGiorgio CM, Schachter SC *et al*. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology* 1998; 51: 48-55.

144. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* 1995; 45: 224-230.

145. Camfield CS, Camfield PR. Initiating drug therapy. In: Wyllie E. *The treatment of epilepsy. Principles and practice.* Philadelphia: Lippincott, Williams, Wilkins, 3, 2001: 759-767.

146. McCabe PH, McNew CD, Michel NC. Effect of divalproex-lamotrigine combination therapy in frontal lobe seizures. *Arch Neurol* 2001; 58: 1264-1268.

147. Helmstaedter C, Kemper B, Elger CE. Neuropsychological aspects of frontal lobe epilepsy. *Neuropsychologia* 1996; 34: 399-406.

148. Helmstaedter C. Behavioral Aspects of Frontal Lobe Epilepsy. 2001; 2: 384-384.

149. Wiebe S, Blume WT, Girvin JP *et al*. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; 345: 311-318.

150. Olivier A. Surgery of frontal lobe epilepsy. *Adv Neurol* 1995; 66: 321-321.

151. Commission on Neurosurgery of Epilepsy of the International League Against Epilepsy. A global survey on epilepsy surgery, 1980-1990: a report by the Commission on Neurosurgery of Epilepsy. *Epilepsia* 1997; 38: 249-255.

152. Turmel A, Giard N, Bouvier G *et al*. Frontal lobe seizures and epilepsy. Indications for cortectomies or callosotomies. *Adv Neurol* 1992; 57: 689-705.

153. Wieser HG, Hajek M. Frontal lobe epilepsy. Compartmentalization, presurgical evaluation, and operative results. *Adv Neurol* 1995; 66: 297-318.

154. Munari C, Tassi L, Cardinale F *et al*. Surgical treatment for frontal lobe epilepsy. In: Lüders HO, Comair Y. *Epilepsy surgery.* Philadelphia: Lippincott, Williams, Wilkins, 2nd, 2001: 689-698.

155. Kral T, Kuczaty S, Blumcke I *et al*. Postsurgical outcome of children and adolescents with medically refractory frontal lobe epilepsies. *Childs Nerv Syst* 2001; 17: 595-601.

156. Mosewich RK, So EL, O'Brien TJ *et al*. Factors predictive of the outcome of frontal lobe epilepsy surgery. *Epilepsia* 2000; 41: 843-849.

157. Swartz BE, Delgado-Escueta AV, Walsh GO *et al*. Surgical outcomes in pure frontal lobe epilepsy and foci that mimic them. *Epilepsy Res* 1998; 29: 97-108.

158. Kazemi NJ, So EL, Mosewich RK *et al*. Resection of frontal encephalomalacias for intractable epilepsy: outcome and prognostic factors. *Epilepsia* 1997; 38: 670-677.

159. Zaatreh MM, Spencer DD, Thompson JL *et al*. Frontal lobe tumoral epilepsy: clinical, neurophysiologic features and predictors of surgical outcome. *Epilepsia* 2002; 43: 727-733.

160. Lawson JA, Cook MJ, Vogrin S *et al*. Clinical, EEG, and quantitative MRI differences in pediatric frontal and temporal lobe epilepsy. *Neurology* 2002; 58: 723-729.

161. Cascino GD, Sharbrough FW, Trenerry MR *et al*. Extratemporal cortical resections and lesionectomies for partial epilepsy: complications of surgical treatment. *Epilepsia* 1994; 35: 1085-1090.

162. Smith JR, Lee MR, King DW *et al*. Results of lesional vs. nonlesional frontal lobe epilepsy surgery. *Stereotact Funct Neurosurg* 1997; 69: 202-202.

163. Helmstaedter C, Gleissner U, Zentner J *et al*. Neuropsychological consequences of epilepsy surgery in frontal lobe. *Neuropsychologia* 1998; 36: 681-681.

164. Smith JR, King DW. Surgical strategies for patients with supplementary sensorimotor area epilepsy. The Medical College of Georgia experience. *Adv Neurol* 1996; 70: 415-427.

165. Spencer DD, Schumacher J. Surgical management of patients with intractable supplementary motor area seizures. The Yale experience. *Adv Neurol* 1996; 70: 445-450.

166. Lendt M, Gleissner U, Helmstaedter C *et al*. Neuropsychological Outcome in Children after Frontal Lobe Epilepsy. 2002; 3: 51-51.

167. Chelune GJ, Naugle RI, Lüders H *et al*. Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. *Neurology* 1991; 41: 399-404.

168. Kellinghaus C, Loddenkemper T, Möddel G *et al*. [Electric brain stimulation for epilepsy therapy]. *Nervenarzt* 2003; 74: 664-676.