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CRITICAL REVIEW AND INVITED COMMENTARY

Temporal patterns and mechanisms of epilepsy surgery failure

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Summary

Epilepsy surgery is an accepted treatment option in patients with medically refractory focal epilepsy. Despite various advances in recording and localization noninvasive and invasive techniques (including electroencephalography (EEG), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), subdural grids, depth electrodes, and so on), the seizure outcome following surgical resection remains suboptimal in a significant number of patients. The availability of long-term outcome data on an increasing number of patients suggests two major temporal patterns of seizure recurrence (early vs. late) that implicate the following two different mechanisms for seizure recurrence: (1) a failure to either define/resect the epileptogenic zone, and (2) the nonstatic nature of epilepsy as a disease through the persistence of proepileptic cortical pathology. We describe the temporal patterns of epilepsy surgery failures and discuss their potential clinical, histopathologic, genetic, and molecular mechanisms. In addition, we review predictors of successful surgical interventions and analyze the natural history of epilepsy following surgical intervention. We hypothesize that the acute/early postoperative failures are due to errors in localizing and/or resecting the epileptic focus, whereas late recurrences are likely due to development/maturation of a new and active epileptic focus (de novo epileptogenesis).

KEY WORDS: Epilepsy surgery, Seizure outcome, Early recurrence, Late recurrence, Clinical and basic mechanisms.

Modern surgical treatment epilepsy dates back to the late nineteenth century when Sir Victor Horsley pioneered epilepsy surgery and published reports of successful cortical resections that resulted in a significant reduction in epileptic seizures in three patients. Since then, epilepsy surgery has slowly evolved to become a multidisciplinary specialty with the main purpose of identifying and localizing the epileptic focus, mapping its spatial relationships with functional cortical area(s), and ultimately resecting the epileptic focus to achieve seizure freedom.

Modern epilepsy surgery has become an acceptable and highly beneficial option for the treatment of patients with medically intractable (pharmacoresistant) focal epilepsies (Salanova et al., 1999; Jeha et al., 2006, 2007; Kral et al., 2007; Jehi et al., 2009). The use of surgical approach that aims to completely control seizures is based upon two major underlying assumptions: (1) that the epilepsy is "focal" and its focality can be well defined and delineated based on snapshots of electrical recordings and static images and, more importantly, (2) that a clearly defined, "fixed focus" is the only reason for the expression of epilepsy as a disease in these patients.

For these reasons, most studies reporting on the accuracy of various techniques and technologies—and therefore on the success rate of epilepsy surgery—have previously relied on short-term outcomes (3–12 months) as final end points. More recently, long-term follow-up studies started to show that the early success with epilepsy surgery is not sustainable in a sizable number of patients. Long-term success of epilepsy surgery in achieving complete and sustained seizure control is only close to one half (49%) of patients at last follow-up (Salanova et al., 1999; Burneo et al., 2006; Jeha et al., 2006, 2007; Kral et al., 2007; Jehi et al., 2009, 2010; De Tisi et al., 2011; Fong et al., 2011; Bulacio et al., 2012) and may be considerably lower, depending on the clinical scenario (McIntosh et al., 2012). Moreover, the dynamics of seizure recurrences following epilepsy surgery suggest that the epileptogenic tissue is not "static" and may be influenced following surgical interference with brain networks encompassing epileptic regions. Some patients with late seizure recurrences may be seizure free for months to years before long-lasting recurrences, whereas others who ultimately achieve long-term remission may exhibit some seizures in the first postoperative months (De Tisi et al.,

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2011). As such, a clear understanding of the clinical and basic mechanisms governing basic mechanisms of epilepsy as a lifelong disease and seizure recurrence at various postoperative periods remains lacking.

From a psychosocial point of view, patients and physicians share the hope that correctly indicated surgical procedures will control epileptic seizures (Shorvon & Tomson, 2011). Because procedures fall short of achieving this goal in a sizable number of cases, we decided to critically and comprehensively review predictors of successful surgical interventions and analyze the natural history of epilepsy following surgical intervention. We hypothesize that the acute/early postoperative failures are likely due to errors in characterizing and/or resecting the epileptic focus, whereas late recurrences are likely due to development/maturation of a new epileptic focus (epileptogenesis). This distinction is important, as it carries implications for the success of further surgery with regard to seizure outcome. We discuss the clinical and basic science data in support of these hypotheses.

Outcomes of Epilepsy Surgery

"Early" versus "late" seizure outcomes

Seizure-freedom rates have varied from 44% to 80% (Loring et al., 1994; Manno et al., 1994; Jeong et al., 1999; Jutila et al., 2002; Salanova 1994) after temporal lobe epilepsy (TLE) surgery, and from 15% to 65% (Salanova et al., 1992; Salanova et al., 1995a,b; Aykut-Bingol et al., 1998; Mosewich et al., 2000; Zaatreh et al., 2002; Dalmagro et al., 2005) after surgery for extratemporal lobe epilepsy (ETLE) in various but limited cross-sectional outcome series. The more recent application of longitudinal outcome analyses methods clarified that some of these apparent discrepancies may be explained by varying follow-up durations among the distinct study cohorts, consistently demonstrating that although the majority of patients (up to 80%) are seizure-free within the first 6–12 postoperative months, sustained seizure freedom remains a reality for only half the patients following TLE or posterior quadrant surgery and one-third or even less of the cases after frontal lobe epilepsy (FLE) resections and ETLE surgeries (Yoon et al., 2003; McIntosh et al., 2004; Paglioli et al., 2004; Jeha et al., 2006, 2007; Jehi et al., 2009; de Tisi et al., 2011; McIntosh et al., 2012). In fact, more insight into the mechanisms of seizure recurrence can be found by reviewing the "path taken" to achieve this "long-term outcome," rather than the eventual rate of seizure freedom per se. A detailed analysis of the longitudinal seizure outcomes reveals that, regardless of the type of surgery, half of all patients with recurrent postoperative seizures experience their initial seizure recurrence within the 2–6 months immediately following surgery, whereas the remaining half of the failures occur during the next 10–15 years (Jeha et al., 2006, 2007; Jehi et al., 2009). After TLE surgery, there is an initial phase of steep recurrence, followed by a relapse rate of 2–5% per year for 5 years with subsequent more stable seizure freedom (Yoon et al., 2003; McIntosh et al., 2004; Jeha et al., 2006). The same is seen after FLE and posterior quadrant epilepsy surgery (Jeha et al., 2007; Elsharkawy et al., 2008a,b; Jehi et al., 2009). This consistent observation of two distinct "early" and "late" phases of seizure recurrence suggests two distinct mechanisms of seizure recurrence with a rough cut-off of about 6–12 postoperative months separating them. The following section reviews the clinical evidence supporting the existence of these two recurrence mechanisms.

Early recurrences

A careful analysis of the characteristics of postoperative seizures shows that those starting "early" are more likely to become drug-resistant (or less drug responsive). Having multiple seizures within the first postoperative year has been associated with worse long-term outcome in many studies of recurrence following temporal lobectomy (Garcia et al., 1991; Janszky et al., 2005). In one series, seizures starting within the first six postoperative months were four times more likely to be intractable compared to those starting later (Jehi et al., 2010). Similarly, a better prognosis has been suggested with late as opposed to early recurrences following frontal lobe surgery (Jeha et al., 2007). This suggests that early recurrences, specifically those occurring within the first six postoperative months continue to be "medically intractable."

Investigating the relationship between timing of recurrence and localization of the focus of recurrence provides useful information. An analysis of failed TLE surgery reveals that a distant focus of recurrence was 12 times more likely in surgical failures manifesting within the first six postoperative months, and 28 times more likely in patients who required invasive electroencephalography (EEG) in their initial surgical workup, whereas all patients in whom treatment failure occurred >6 months postoperatively and who never had prior invasive EEG evaluations had recurrent seizures from the temporal tissue immediately adjacent to the surgical bed (Jehi et al., 2010). This inverse correlation between early recurrence and proximity to initial surgical bed supports the notion that intractable seizures that continue unabated after epilepsy surgery may simply represent ongoing manifestations of the original epileptic focus.

In another study analyzing early versus late recurrences independently, predictors of early recurrences included markers of diffuse and poorly localized epilepsy such as bilateral abnormalities on brain magnetic resonance imaging (MRI), the need to obtain ictal and functional mapping through invasive EEG recordings, and presence of interictal epileptiform abnormalities on postoperative EEG (Jeha et al., 2006). The common theme of all these outcome predictors is their reflection of poorly localized epilepsy. Such an inference is intuitively acceptable when considering the poor prognostic correlate of obvious bilateral hippocampal

imaging abnormalities or the electrical signature of persistent or developing epileptogenicity through postoperative EEG spiking (Jeha et al., 2006; Radhakrishnan et al., 1998; Tuunainen et al., 1994). The use of invasive EEG is a subtler predictor for the development of early surgical failures. In a study evaluating outcomes of selective amygdalohippocampectomy, surgical failures that initially required invasive EEG recording had more evidence of extratemporal MR lesions and did not benefit from extension of the original resection (Abosch et al., 2002), as opposed to the situations in which equivalent outcomes were achieved with selective amygdalohippocampectomy and anterior temporal lobectomy (ATL) when epileptogenicity seemed to be restricted to the mesial temporal structures (Wieser et al., 2003; Sadler, 2006). An extratemporal or "temporal plus" epilepsy involving the insula or other components of the limbic network has already been proposed as an important reason for treatment failure in patients with suspected TLE but normal MR imaging requiring invasive EEG (Aghakhani et al., 2004; Ryvlin & Kahane, 2005). This correlation between the use of invasive EEG and early surgical failures provides additional evidence in support of the inaccurate localization of the epileptic focus or its incomplete resection as a recurrence mechanism in these instances. In addition, it also implies that invasive EEG does not help to clarify the situation in these patients.

Late recurrences

Conversely, "late" postoperative seizure recurrences manifesting for the first time several years after surgery are usually milder, less frequent, easier to control with antiepileptic drug adjustment and are most often seen in patients with no clear pathologic substrate of the resected tissue (Jeha et al., 2006; Jehi et al., 2010). More specifically, the "running-down phenomenon" where postoperative seizures arise but eventually disappear occurs twice as often if seizure recurrences start beyond the initial six postoperative months (Hennessy et al., 2000; Jehi et al., 2010). In another study, the only predictor of late recurrence following TLE surgery was the lack of any specific finding on pathologic examination (Jeha et al., 2006). Recently, we analyzed predictors of late failures in patients with the diagnosis of medically intractable epilepsy due to focal cortical dysplasia that required an invasive evaluation. The only predictor of late failure was the pathology consistent with FCD type 1 (Buoni et al., 2008; Krsek et al., 2009; Liava et al., 2012; McIntosh et al., 2012; Pinheiro-Martins AP, Bulacio J, Jehi L, Prayson RA, Bingaman W, Gonzalez-Martinez J, Najm IM, unpublished manuscript). These findings are in line with the TLE late failure predictor (lack of pathologic changes) as the presence of type 1 focal cortical dysplasia (FCD) could mean either "normal" cortex (due to the significant intrarater variability in making the diagnosis of type 1 FCD) or assuming that the diagnosis of FCD type 1 stands, the fact that FCD type 1 is a negative late outcome predictor, may mean that late recurrences in this FCD subtype are due to an activation of a more widespread dormant proepileptic tissue (FCD) and its slow transformation to an epileptic tissue (epileptogenesis). In other words, although "early recurrences" clinically behave much like the "current" intractable epilepsy focus, "late" seizure recurrences clinically behave much like new-onset epilepsy, a dynamic disease that is more easily controlled with medications and that evolves to pharmacoresistance only in a subgroup of patients. It is this group of patients that may represent true epileptogenesis. In a recently published work, we showed that the use of levetiracetam (LEV), an antiepileptic drug (AED) with strong animal model and basic science data on antiepileptogenic effects, may reduce the risk of postoperative seizure recurrence following TLE surgery, with 47% of patients on LEV being completely seizure-free >5 years after surgery as opposed to only 28% of patients who remain seizure free when other AEDs or no AEDs have been used during the postoperative period (Jehi et al., 2012). These results are in concordance with a previously published report that showed a long-lasting antiepileptogenic effect of LEV in the spontaneously epileptic rat (SER) model as compared to other antiepileptic medications that include phenytoin, phenobarbital, valproic acid, and carbamazepine (Ji-qun et al., 2005).

Introducing this framework of two distinct phases and mechanisms of surgical failures (Fig. 1) represents a drastic change from the traditional paradigms to studying surgical outcomes and developing methodologies to improve the results of epilepsy surgery. Historically, efforts at improving surgical outcomes have been focused exclusively on improving imaging and electrophysiologic technology aimed at localizing the epileptic focus. As discussed above and summarized in Table 1, the data highlight the potential of modifying medical therapy postoperatively to alter

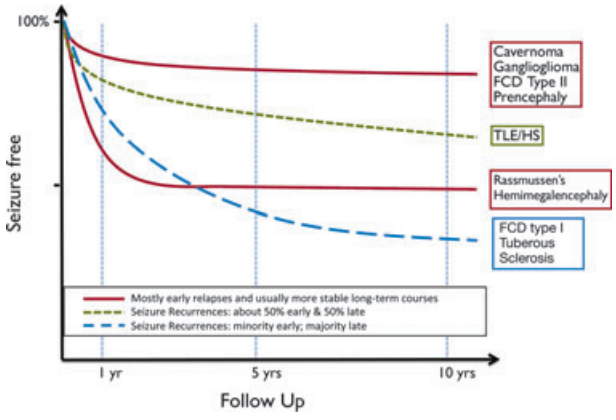

Figure 1.
Patterns of seizure outcomes following epilepsy surgery: effect of pathology of the epileptic lesion(s). Modified from Bulacio et al. (2012).
Epilepsia © ILAE

Table 1. Clinical differences between patients with early and late postoperative seizure recurrences

	Clinical characteristic	Early recurrences	Late recurrences
Preoperative	EEG: Poorly localized	+	–
	MRI: Bilateral/multifocal lesions	+	
Postoperative	Postoperative seizures	Severe, frequent, pharmacoresistant	Mild, rare, pharmacoresponsive
	Running down phenomenon	No	Yes
	Early postoperative EEG	Abnormal	
	Location of recurrence	Distant focus or contiguous to the resection bed	Contiguous to the resection bed
	Possible medication-modifying effect	None	Levetiracetam

epileptogenesis and reduce the risk of subsequent seizure recurrence.

In the following sections of this review we discuss the potential basic mechanisms that argue in support of this distinction and in favor of more focused efforts on preventing late recurrences through medical interventions.

Clinical and Basic Mechanisms of Seizure Recurrences Following Focal Cortical Resections

The outcome data discussed above suggest two clearly distinct temporal patterns for the postoperative failures following surgical resections for the treatment of medically intractable focal epilepsies. These patterns are present in all types of epilepsy surgeries and are rather independent from the type, location, and pathology of the epilepsy (Schramm et al., 2012). Although present in all, this early versus late failure perspective has some interesting variations in relation to the underlying etiology, as illustrated in Figure 1. In some epilepsy-related pathologies, recurrences cluster early, in the first 6–12 months, and occur much more seldom later. Of interest, this pattern is seen either in well-circumscribed MRI-identified lesions (such as FCD type II, cavernomas, and gangliogliomas) (Rowland et al., 2012; Tassi et al., 2012) or in progressive (postnatally developed) hemispheric pathologies (Rasmussen's syndrome) or static (congenital) hemimegalencephaly, although the frequency of early recurrence is much greater in the latter (Hemb et al., 2010; Schramm et al., 2012; Vadera et al., 2012). The recurrence in following hemispherectomy in patients with hemimegalencephaly may be attributable to the presence of contralateral dysplastic pathology (Hallbook et al., 2010; Kometani et al., 2010; Shiroishi et al., 2010). In other entities, the opposite is seen, with most recurrences occurring late, such as in FCD type I (visible or invisible) and tuberous sclerosis (Hemb et al., 2010; McIntosh et al., 2012). Finally, in the common syndrome of TLE due to hippocampal sclerosis (TLE/HS), both patterns operate, suggesting multiple mechanisms for recurrence (Paglioli et al., 2004; Jeha et al., 2006).

The exact reason(s) and mechanisms that underlie these distinct patterns of postoperative surgical failures are not well known. In this section, we discuss the available clinical and basic science data from the perspective of the paradigm-shifting approach to recurrences proposed here, that is, that early recurrences are due to incomplete resections and that late recurrences are due to variable degrees of "de novo" epileptogenesis—or, at least, "de novo" refractory epileptogenicity (Fig. 2).

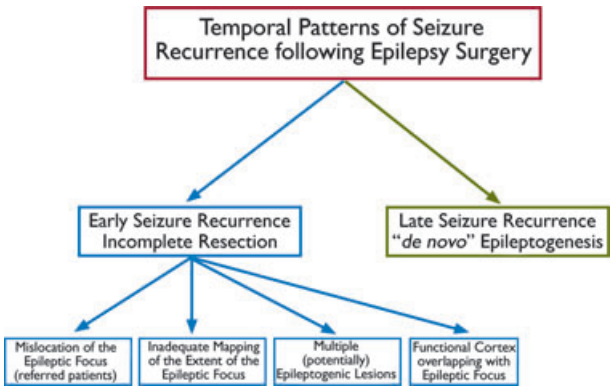

Figure 2.
Temporal patterns of seizure recurrences following epilepsy surgery: mechanisms.
Epilepsia © ILAE

Early Failures and the Reasons for Incomplete Resections

When the epileptic focus is mislocalized, completely or partially

These recurrences may be best illustrated in cases of non-lesional epilepsies, the clinical and EEG findings of which suggest a localized onset, but the exact boundaries of the epileptic region are not clear. Another commonly encountered scenario includes cases of multiple pathologic substrates, whereas the epilepsy is multifocal or originates from one of the lesions that is (are) not resected.

Mislocalization due to "referred" epileptic and clinical patterns

This is the realm of the MRI-negative or unilateral MRI-diffuse refractory epilepsies. As discussed above, the poorest long-term outcomes following surgical resections were

mainly observed to be frontal lobe resections (31% seizure-free at 10 years), as opposed to all other surgery types (57% seizure-free at 10 years after temporal lobe or posterior quadrant surgery) (Jeha et al., 2006, 2007; Jehi et al., 2009). Within the frontal lobe resection group, the least favorable results are evident in those patients with nonlesional MRI studies (Jeha et al., 2006). A further examination of the seizure outcome curves in patients with nonlesional frontal lobe resections reveals a particularly increased incidence of early failures. Although the failure of resective frontal lobe surgery in controlling seizures may be attributed to an inability to entirely remove an epileptic, yet functional, cortex (Sarkis et al., 2010) (discussed below), epilepsy surgery may, however, fail after complete (or apparently complete) resection of the putative "epileptic focus," even when the epileptogenic zone is identified and delineated by direct cortical recordings (intraoperative or extraoperative) (Schwartz & Spencer, 2001; Sarkis et al., 2010). This early failure of epilepsy surgery in these cases may be due to some EEG patterns and/or clinical features that are misinterpreted as arising from the frontal lobe; however, these recorded and mapped epileptic patterns may represent "referred" EEG patterns from other areas of the brain—mainly, the parietal and temporal lobes (Ristić et al., 2012). The parietal lobe comprises large areas of association cortex extensively connected to other lobes. Previous reports showed that the tendency toward multiple EEG spread patterns (in particular to the temporal and frontal lobes), although not an exclusive propensity, is characteristic of seizures originating in the parietal lobe (Williamson et al., 1992; Foldvary et al., 2001; Ristić et al., 2012). We recently reported that the mislocalization of parietal lobe seizures—especially in patients with nonlesional focal epilepsies—to either the temporal or frontal lobes may be responsible for some of these statistical differences (Ristić et al., 2012). Such preoperative misidentification is likely to lead to a more focused localizing electroclinical hypothesis that would result in an invasive evaluation focusing on the "referred" lobe and not on the area(s) of potential epileptic onset. These evaluations would likely result in the identification of the referred focus followed by its "complete" resection with persistence (or early recurrence) of seizures postoperatively. We recently showed that interictal and ictal EEG findings are more variable in their anatomic distribution and/or are more nonlocalizable in patients with parietal lobe epilepsy (PLE) as compared to frontal or temporal lobe epilepsy cases (Ristić et al., 2012). These findings underscore the possibility of mislocalization of the epileptic focus to other lobes (e.g., temporal or frontal) in patients with PLE, particularly in those with nonlesional PLE. The rather elaborate connectivity of the parietal lobe to various distant regions of the brain presents the most probable reason for extraparietal localization of the ictal and interictal EEG patterns in these patients. These anatomic, electroencephalographic, and functional connectivity characteristics may account for mislocalization of nonlesional epilepsies and suggest that a more comprehensive invasive EEG evaluation (that includes sampling of functional networks) in some patients with EEG and/or clinical features of frontal (and to a lesser extent temporal) lobe epilepsy—particularly in the context of normal ("nonlesional") high resolution MRI studies—may lead to better identification of the epileptic focus and therefore could result in a decrease in the incidence of early postoperative failures.

The epileptic boundaries: inadequate mapping of the extent of the epileptic focus

The extent of the epileptic focus is difficult to map noninvasively in the majority of cases, but it is considerably more problematic in nonlesional epilepsies and in focal epilepsies adjacent to eloquent cortex. Even with the use of invasive evaluation techniques such as subdural grids, the task of defining the exact extent of the epileptic focus is not usually straightforward, as there is no agreed upon definition of what is required electrically to determine the extent of the relevant epileptogenic tissue. We conventionally use the strict definition of the epileptic focus as consisting of the site of the earliest ictal EEG changes (Rosenow & Lüders, 2001), although at times these early ictal sites fall short of encompassing the totality of the relevant epileptogenic brain tissue and resections strictly based upon this construct may fail (Bautista et al., 1999; Widdess-Walsh et al., 2007).

The definition of the ictal-onset zone using stereo electroencephalography (SEEG) electrodes is even less clear as it may consist of focal or even nonadjacent regions where EEG ictal patterns progressively build up, but also of areas of "early" spread. It is usually unclear what is meant by "early" spread, although recent efforts to further define it led to the concept of an "epileptogenicity index" (EI) based on both spectral (appearance of high-frequency oscillations replacing the background activity) and temporal (delay of appearance with respect to seizure onset) properties of intracerebral EEG signals (Bartolomei et al., 2008).

Early seizure recurrence due to inadequate identification of the epileptic lesion(s) in the setting of multiple lesions (two or more lesions)

The approach to patients with two or more (e.g., tuberous sclerosis) lesions that can be equally potentially epileptogenic is always challenging. Previous studies reported on the outcome of epilepsy surgery on patients with presurgically identifiable two (potentially) epileptogenic lesions (dual pathologies). In patients with dual pathology (hippocampal sclerosis in addition to a cavernoma, for instance), lesionectomy plus hippocampectomy had a better outcome than single lesionectomy (Hammen et al., 2007). In cases where the resection of the two lesions is possible, previous studies showed the

surgical outcome is as favorable as in cases with single epileptic pathologies (Li et al., 1999; Okujava et al., 2002; Srikijvilaikul et al., 2003; Kim et al., 2010). These observations suggest that in the presence of dual pathology in the setting of medically intractable epilepsy (especially an abnormality involving the hippocampus), an invasive evaluation may be needed unless the hippocampus is directly involved or close to the second pathology—when both lesions can usually be resected during a single procedure, following noninvasive evaluation. The purpose of intracranial evaluation in the context of dual pathology is to sample the potentially epileptogenic lesions, in particular those that are ipsilateral to the electroclinical manifestations and/or those that are part of functionally and anatomically connected networks (e.g., limbic system). The type of invasive evaluation would depend on the location of the lesions and their laterality: subdural grids may be used in patients with lesions that can be directly covered by the surface cortical electrodes and are anatomically contiguous (e.g., lateral frontotemporal, temporoparietal, parietooccipital, or frontoparietal convexities that may be in proximity to eloquent/functional regions), whereas SEEG electrodes may be indicated in patients with lesions that are deeply seated, mesial, and/or anatomically noncontiguous or bilateral. Less commonly, a combination of subdural grids and depth electrodes may be used in patients with suspected hippocampal pathology in the setting of a lateral temporoparietal convexity focal pathology.

When the full resection of the epileptic focus is constrained for functional or technical reasons

At times, the surgeon is unable to perform a complete resection of the epileptic focus because of functional concerns and/or surgical/technical difficulties. An incomplete resection may not only result in early seizure recurrence but rather there may be instances of significant seizure worsening immediately following the resection. We recently reported on a series of eight patients with rolandic epilepsy due to type IIB focal cortical dysplasia (Sarkis et al., 2010). Three of the eight patients exhibited focal status epilepticus in the immediate postoperative period that was controlled only after a reoperation for the removal of a dysplastic (non balloon cell FCD), functional (all three patients had postoperative functional deficits), and intrinsically epileptogenic cortex in the sensorimotor cortex (documented by direct cortical recordings). Palmini previously reported a worsening of seizures during the immediate postoperative period in 20% of the patients who underwent focal resection of the balloon cell–rich regions in the rolandic cortex (Palmini, 2000). A similar phenomenon is also present in lesions of the parietooccipital cortex (Jehi et al., 2009), where failed parietal resections had worsening postoperative seizures.

These observations are in concordance with those of previous reports on the differential expression of epileptogenicity and function in various subtypes of FCDs: the center of balloon cell–containing lesion is less intrinsically epileptic and not functional in itself (upon direct electrical stimulation studies), but it is rather the transitional (but still dysplastic) cortex (surrounding the center of the balloon cell–rich lesion) that is more epileptogenic and is functional (Marusic et al., 2002; Boonyapisit et al., 2003). Previous in vitro studies showed that the balloon cells do not generate any voltage or ligand-gated currents (Cepeda et al., 2003), but slices of tissue removed from areas of non balloon–cell FCDs exhibit significant increase in firing as evidenced by the repetitive bursts of field potentials under zero magnesium conditions (Möddel et al., 2005). In addition, Cepeda et al. (2005), showed that cytomegalic (dysplastic nonballoon cells) neurons are epileptic. In addition, we reported that the increased firing in these slices is dependent on a differential expression of the NR2B subunit of the *N*-methyl-D-aspartate (NMDA) receptor (Ying et al., 1999, 2004; Najm et al., 2000; Möddel et al., 2005). In addition, in situ molecular studies in non balloon cell regions show increased synaptic densities (Ying et al., 2005; Ying Z, Nemes A, Alexopoulos A, Najm IM, unpublished data) and the NR2B subunits of the NMDA receptor are expressed in dysmorphic neurons (Najm et al., 2000; Crino et al., 2001; Najm et al., 2004). More recently we reported on a possible role of balloon cells in clearance of the excitatory glutamate neurotransmitter as these balloon cells exhibit high concentrations of the ATP-dependent glial glutamate transporter (GLT1/EAAT2) and glutamine synthase (an enzyme responsible for the metabolism of glutamate to glutamine prior to its re-uptake in the presynaptic terminals) (González-Martínez et al., 2011). These intriguing clinical observations suggest a possible "inhibitory" role of balloon cells in the setting of FCD. Based on these observations, we hypothesize that the in situ removal of the balloon cell–rich areas without the resection of the surrounding dysplastic and intrinsically epileptic cortex (that is for the most part devoid of balloon cells) may result in a "release" of the excitatory environment in the remaining dysplastic and epileptic cortex, thereby leading to a significant and acute increase in the epileptic firing during the acute postoperative period.

These laboratory observations suggest that a surgical approach aimed at resecting the balloon cell–rich FCD lesion alone (with the most prominent signal abnormality on fluid-attenuated inversion recovery [FLAIR] MRI sequence) without direct electrocorticographic confirmation of the exact location and extent of surrounding epileptogenicity may not achieve seizure freedom (Palmini et al., 1995), and in some instances may lead to significant seizure worsening immediately after surgery. We suggest that an aggressive surgical approach (with complete resection of

the epileptogenic FCD) is warranted in patients with type IIB/balloon cell–containing FCD as the failure to do so may be associated with a high risk of acute postoperative seizure worsening.

Late Recurrences: Variable Degrees of De Novo Epileptogenesis

As illustrated in Figure 1, long-term follow-up of patients who underwent surgical resection and achieved early seizure control show that a number relapse >6–12 months later. There are no clearly established mechanisms to explain this phenomenon; therefore, we resort to available clinical observations as correlated with histopathologic and molecular changes observed in tissue resected from some patients. In addition, we discuss some knowledge acquired from animal models of epilepsy.

Clinical observations

Clinical observations suggest that the late failures after an early successful surgical resection may be due to an incomplete/or no resection of a "proepileptic" focus following a complete removal of the dominant, active focus, which we propose to call the "current epileptic focus" (Awad et al., 1991; Edwards et al., 2000; Bauman et al., 2008; Phi et al., 2009; Bulacio et al., 2012).

Case illustration

A 6-year-old boy with nonlesional left frontal lobe epilepsy had failed to respond to six antiepileptic medications when he was evaluated with subdural grids, followed by anterior and inferior frontal lobe resection. The pathology of the resected tissue revealed the presence of type 1A FCD. The patient remained seizure free postoperatively for 20 months, when his family weaned him off his antiepileptic medications and seizures recurred. He was reevaluated with subdural grid electrodes, and tissue resected at reoperation revealed the same FCD type 1A pathology. Subsequently, the patient achieved seizure freedom and remained seizure free after the reintroduction of levetiracetam as monotherapy.

Recent immunocytochemical examination and characterization of the synaptic changes in the resected tissue after the first and the second surgeries revealed the differential expression of new synapse markers (GAP 43 proteins) (Ying Z, Nemes A, Alexopoulos A, Najm IM, unpublished data). These observations suggest that a leftover proepileptic tissue is nonstatic from the epileptogenicity standpoint, as it retains the ability for the later development of synaptic changes that may transform it into an active epileptic focus. The triggers of the transformation remain unknown at this stage.

Animal data

What can we learn from animal experiments regarding the transformation of a proepileptic lesion into an active epileptic focus?

The rat model of in utero radiation

Rats with cortical dysplasia have lower threshold for spontaneous and pentylenetetrazole (PTZ)–induced seizures; however, despite the diffuse dysplastic lesions, only a very small number of these animals exhibit spontaneous seizures (Kondo et al., 2001; Oghlakian et al., 2009). However, following PTZ- related generalized, prolonged, and repetitive seizures, more than two thirds of the irradiated rats exhibit interictal epileptiform discharges and recurrent seizures. The acute status epilepticus is thus followed by spontaneous seizures in the majority of these animals (Oghlakian et al., 2009). These observations mirror the natural history of epilepsy in some patients with FCD (thought to be due to prenatal/congenital or perinatal insults) in whom the epileptic phenotype does not develop until an otherwise nonepileptic stressors such as trauma, acute infection, metabolic, or even emotional abnormalities come into play.

The molecular and cellular mechanisms underlying this transformation remain unknown, but our previous data point to a propensity of dysplastic neurons and regions (proepileptic lesions) to respond differently to "second hits," as compared to normal cortex. The second hit causes the initial acute (provoked) severe seizures and the later development of chronic spontaneous seizures and epilepsy in rats with proepileptic lesions. The propensity to develop severe and long-lasting seizures after "minor" (typically nonepileptogenic) hits in those animals with proepileptic lesions has been attributed previously to an increased in vitro excitability in slices of rat brain with cortical dysplasia (Roper et al., 1997).

Studies on in utero radiated animal models have also shown an increased susceptibility to, as well as severity of, acute seizures in neocortical slices after injection of bicuculline as compared to slices from normal animals (Roper et al., 1997). Other reports also showed a decrease in spontaneous inhibitory postsynaptic currents (IPSCs) from in vitro neocortical slices resected from radiation-induced cortical dysplasia rats (Zhu & Roper, 2000). In the same line of observations, there was a decrease in the density of inhibitory interneurons in dysplastic cortical tissues resected from human patients (Calcagnotto et al., 2005).

We recently studied the synaptic changes in radiated rats following a single injection of PTZ. Our results showed a significant increase in the expression of GAP43 (a marker of newly formed synapses) proteins in cortical and hippocampal regions of the dysplastic rat brains. In addition, a single injection of PTZ in radiated dysplastic rats, but not in normal animals, leads to a long-lasting up-regulation of the NR2B subunit protein expression (Oghlakian et al., 2009). These changes are similar to those observed in some

patients with epileptic FCDs (after first and second resections) (Ying et al., 1999; Najm et al., 2000, 2004; Möddel et al., 2005).

To better understand the genetic mechanisms that may underlie the nonstatic nature of "proepileptic" lesions, we recently performed a gene expression analysis of dysplastic rat brains (Hiremath et al., 2009). RNA gene expression in cortical and hippocampal regions in normal and dysplastic rat brains was studied using an oligonucleotide microarray platform and real -time, quantitative polymerase chain reaction (RT-qPCR). Six genes seemed relevant to the pathogenesis of FCD: two genes that promoted cell survival (connective tissue growth factor and peroxiredoxin) were upregulated. Two genes involved in glutamate (protein kinase C-α) and 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptor recycling neuron-enriched

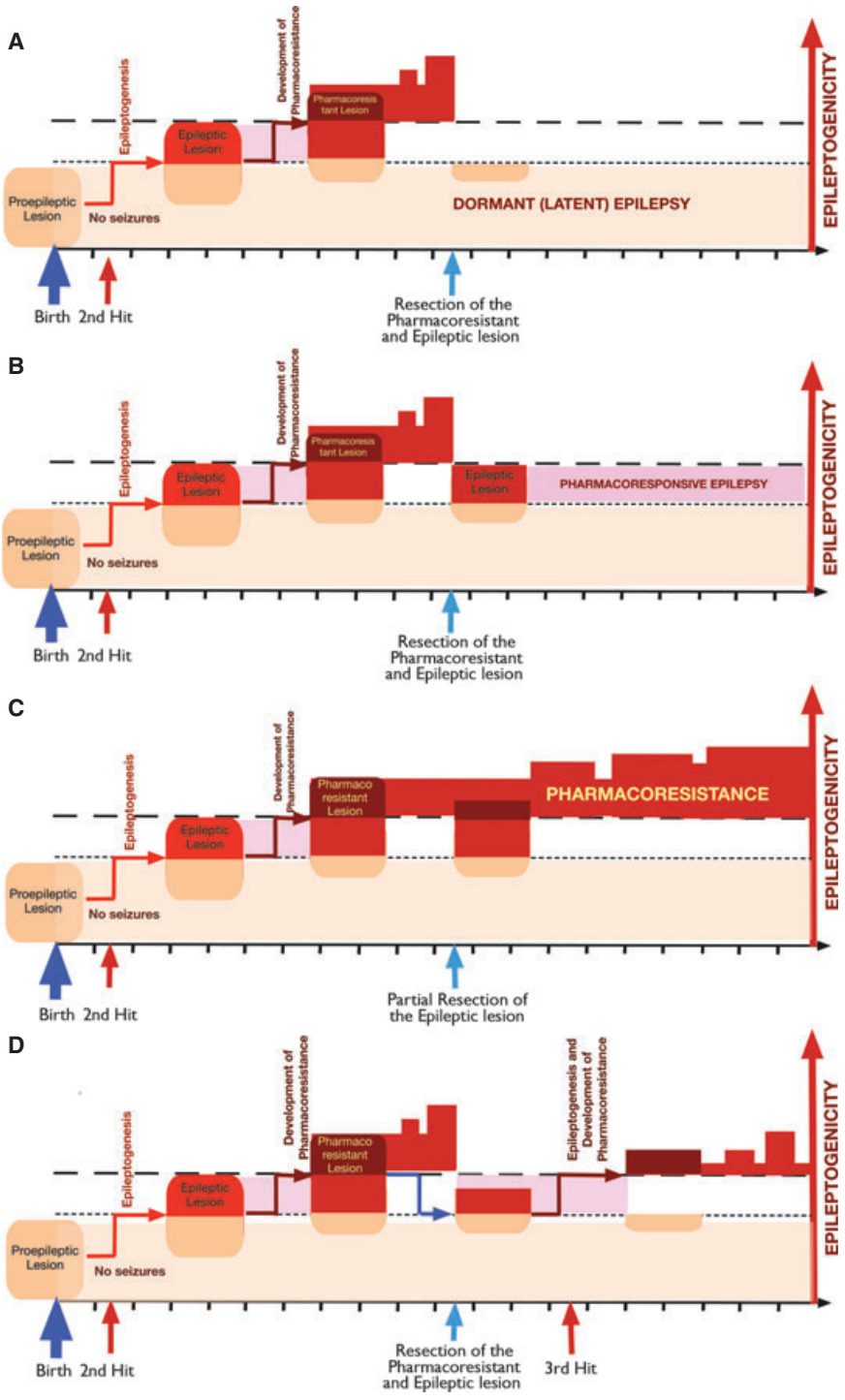

Figure 3.
Schematic representations of the possible outcomes and their determinants following epilepsy surgery: (**A**) Seizure freedom following complete resection of both the pharmacoresistant and pharmacoresponsive "current" (active) epileptic lesions. Patients undergoing this type of resection are likely to achieve long-term seizure freedom, but may be at risk of seizure recurrence following another "hit," leading to the transformation of the remaining "proepileptic" lesion into an active epileptic focus. (**B**) Seizure freedom following complete resection of only the pharmacoresistant "current" (active) epileptic lesion. These patients would likely achieve long-term seizure freedom while they remain on antiepileptic medications (pharmacoresponsive). (**C**) Early postoperative seizure recurrence following the partial or no resection of the "current" epileptic lesion. These patients would exhibit early postoperative seizures due an incomplete resection of the active pharmacoresistant focus. (**D**) Late seizure resection following the resection of the current epileptic lesion, but not of the proepileptic and/or pharmacoresponsive lesion(s). In these patients, a third "hit" would lead to the development of pharmacoresistant epilepsy.

endosomal protein of 21 kD (NEEP-21) and one gene (Shank-1) involved in the control of dendritic maturation were downregulated.

These gene expression results may explain some of the potential mechanisms by which FCD lesions may be highly epileptogenic: disinhibition of aberrant dendritic branching, downregulation of genes involved in glutamate and AMPA receptor recycling, and upregulation of genes promoting cell survival, potentially leading to the perpetuation of the epileptic phenotype in situ over time.

The preexistence of in utero radiation-induced cortical dysplasia is a potentially proepileptic lesion that amplifies the response to a single injection of PTZ through the induction of multiple cellular and receptor changes that are seen only after multiple injections (~20) in normal rats. This second hit theory is suspected to lead to the development of seizures in at least a subgroup of patients with epilepsy who may have had predisposing lesions such as congenital tumors (e.g., gangliogliomas and dysembryoplastic neuroepithelial tumors), vascular malformations (e.g., cavernous angiomas), hippocampal sclerosis, and FCDs.

These animal data suggest that the mere presence of a proepileptic lesion (e.g., FCD), contributes to increased susceptibility for severe seizure induction, and the later development of epileptogenicity (i.e., epileptogenesis).

In conclusion, the clinical observations and animal experiments suggest that the presence of (a) "proepileptic" lesion (s) may not always be associated with a spontaneous epileptic phenotype but may predispose to the development of chronic epilepsy in the presence of triggering factors such as fever, trauma, or infections (at times in the setting of AED withdrawal.

Conclusions and Future Directions

Despite the success of epilepsy surgery in controlling seizures in significant numbers of patients with medically intractable epilepsy, clinical and basic science data strongly suggest that "focal" epilepsy is not necessarily focal and its causative pathology (histologic, molecular, or genetic) is not static (Fig. 3). Therefore, its treatment should not be reduced/simplified to a mere removal of an epileptic focus. The epilepsy community is faced with the following challenges: (1) accurate localization and mapping of the epileptogenic zone, (2) the identification of the proepileptic lesions, and (3) the prevention of epileptogenesis through the use of effective medical treatment modalities, especially in those patients who undergo successful mapping and resection of active epileptic lesions. As illustrated in Fig. 2, the success of presurgical evaluation and epilepsy surgery in the identification of a "current" epileptic focus and its complete removal is a necessary but not the final step in the transformation of some focal epilepsies from medical intractability to medical responsiveness. A successful epilepsy surgery in stopping the recurrent seizures presents a golden opportunity for the institution of a yet to be defined "treatment regimen" that is not necessarily an anti-*epileptic* treatment but an epilepsy *modifying* therapy. This intervention should be aimed toward a change in the natural history of the disease and a prevention of the possibility of epileptogenesis [due to genetic factors or the presence of a more diffuse/larger proepileptic lesion(s)].

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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