Stereoelectroencephalography Versus Subdural Electrodes for Localization of the Epileptogenic Zone: What Is the Evidence?

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Abstract

Accurate and safe localization of epileptic foci is the crux of surgical therapy for focal epilepsy. As an initial evaluation, patients with drug-resistant epilepsy often undergo evaluation by noninvasive methods to identify the epileptic focus (i.e., the epileptogenic zone (EZ)). When there is incongruence of noninvasive neuroimaging, electroencephalographic, and clinical data, direct intracranial recordings of the brain are often necessary to delineate the EZ and determine the best course of treatment. Stereoelectroencephalography (SEEG) and subdural electrodes (SDEs) are the 2 most common methods for recording directly from the cortex to delineate the EZ. For the past several decades, SEEG and SDEs have been used almost exclusively in specific geographic regions (i.e., France and Italy for stereo-EEG and elsewhere for SDEs) for virtually the same indications. In the last decade, however, stereo-EEG has started to spread from select centers in Europe to many locations worldwide. Nevertheless, it is still not the preferred method for invasive localization of the EZ at many centers that continue to employ SDEs exclusively. Despite the increased dissemination of the SEEG method throughout the globe, important questions remain unanswered. Which method (SEEG or SDEs) is superior for identification of the EZ and does it depend on the etiology of epilepsy? Which technique is safer and does this hold for all patient populations? Should these 2 methods have equivalent indications or be used selectively for different focal epilepsies? In this review, we seek to address these questions using current invasive monitoring literature. Available meta-analyses of observational data suggest that SEEG is safer than SDEs, but it is less clear from available data which method is more accurate at delineating the EZ.

Key Words Epilepsy · seizures · neuroimaging · neurosurgery · focal cortical dysplasia · tumor · stereotaxy

Introduction and Background

Epilepsy affects 39 to 50 million individuals worldwide, approximately 3 to 10 people per 1000, and seizures fail to respond to antiepileptic drug therapies in 30% to 40% [1, 2]. Patients with drug-resistant epilepsy are at increased risk of poor long-term intellectual and psychosocial outcomes as well as a decreased health-related quality of life [3]. A recent

randomized single-center pediatric trial showed 77% of patients to be seizure free following resective surgery compared to only 7% seizure freedom following medical therapy alone [3]. Therefore, accurate and safe delineation of the epileptogenic zone (EZ) is essential for safe and effective resective surgery for focal epilepsy [4, 5]. Up to 70% of patients can have their EZ localized on the basis of noninvasive clinical, neuroimaging, and electrophysiological data [2]. However, when this noninvasive data is incongruent and leaves unanswered questions or specific yet untested hypotheses about the localization of the EZ, the implantation of electrodes for direct cortical recordings is necessary to identify the EZ [6]. Though there is a range of neurosurgical techniques for implanting electrodes to localize the EZ, stereo-electroencephalography (SEEG) [7] or craniotomy with implantation of subdural electrodes (SDEs) [8] has been the most common approach for many years. Some centers also place SDE strips through burr holes (without craniotomy), but this can be topographically imprecise and is becoming less common given the increasing

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availability of SEEG [9–11]. Historically, SEEG has been the predominate approach in France, Italy, and some Canadian epilepsy centers [12, 13], while SDE has been used throughout the Americas, Asia, and some European centers [14]. Recent reviews of the technical aspects and diagnostic utility of various invasive EEG modalities seem to suggest that these techniques may have distinct indications or diagnostic advantages or disadvantages [6, 15], but it is important to note that these techniques have primarily been used for the same indications at different centers on the basis of each center's preference regardless of the specific indication. Despite the fact that SEEG and SDE have been used for invasive localization of the EZ for many years, albeit at different centers, it remains unknown if either method is superior for identification of the EZ and which technique is safer.

Interestingly, the last decade has seen a significant increase in the use of SEEG throughout North America and the rest of the world [16, 17]. It is thought that the increased use of SEEG outside of traditional SEEG centers is the result of advances in neuroimaging, robotics, and stereotactic techniques along with an emphasis on minimally invasive techniques [17]. However, the exact reasons are a matter of debate. Although the use of SEEG has spread considerably, the relative merits of SEEG *versus* SDE remain a matter of debate. Unfortunately, the complexity of invasive monitoring and the heterogeneity of this patient population make it difficult to perform prospective clinical trials comparing SEEG and SDE. However, the plethora of literature from observational studies on the safety and efficacy of SEEG and SDE can help guide our understanding of these 2 techniques. Furthermore, new technology in neuroimaging and robotics has led to the evolution of intracranial recording methods that may contribute to an increased capability to safely and effectively treat the EZ.

The aim of this manuscript is to review the findings of the multiple observational studies, and meta-analyses, that have examined the safety and efficacy of SEEG and SDE to determine the relative merit of these 2 techniques in the clinical setting. Further, we will examine the relative benefits of SEEG and SDE for various epilepsy etiologies (e.g., periventricular nodular heterotopia) and epilepsy patient populations (e.g., pediatrics).

SEEG and SDE Methodology

Regardless of the method applied (i.e., SEEG or SDE), invasive monitoring has the same indication: to identify the EZ, to determine whether it can be safely resected, to develop a surgical plan for resection of the EZ, and sometimes, to identify the eloquent cortex. Though practice patterns are varied with regard to the indications for invasive recordings, invasive recordings are necessary in approximately 25% to 50% of patients with focal epilepsy who are candidates for resective

epilepsy surgery [7, 18, 19]. Despite the equivalent indications for SEEG and SDE, there are important conceptual and technical differences that are important for understanding these 2 invasive recording methods [20, 21]. Though both SEEG and SDE involve direct cortical recordings to define the EZ, centers employing these 2 techniques have traditionally held separate ideas about the definition of the EZ. Many North American centers, for example, define the EZ as the “minimal area of cortex that must be resected to produce seizure-freedom” [4]. In contrast, some European epilepsy centers have held a different view developed by Talairach and Bancaud that the EZ is defined as the “site of the beginning and of the primary organization of the epileptic seizures” [5]. It is important to note that these 2 definitions of the EZ are not mutually exclusive, as North American centers often consider the SOZ as part of the EZ and European centers often consider the distribution of interictal discharges (i.e., the *irritative zone*) when planning resections. However, these views of the EZ have had some influence on invasive recording implantation strategies and thus are important for understanding differences in traditional SEEG and SDE implantation methods.

SEEG implantation strategies are aimed to elucidate the EZ as defined as the site of the onset and primary organization (and spread) of the epileptic seizure [5, 12]. Thus, the traditional SEEG implantation strategy is based on the development of anatomico-electro-clinical (AEC) hypotheses to test for the onset and spread of the seizure [17, 22, 23]. The development of AEC hypotheses is based on the detailed analysis of ictal semiology, scalp EEG, and neuroimaging. SEEG electrodes are then implanted to simultaneously record from brain structures whose anatomical site and functional role implicate them in the onset and spread of the seizure [5]. Given that direct cortical recordings are relatively sparse (whether using SEEG or SDE), it is crucial that SEEG electrodes be implanted accurately within the network of regions involved in the seizure. As noted by Kahane and colleagues [5] writing about the SEEG implantation strategy, “It is clear, when looking at this method, that if the pre-SEEG hypotheses are wrong, the placement of intracerebral electrodes will be inadequate, the interpretation of SEEG findings is likely to be erroneous, and surgical results will probably be poor.” Thus, the successful use of SEEG absolutely depends on the formulation of a well-conceived AEC hypothesis to guide the electrode implantation strategy.

SEEG and SDE Technique

Many variations in SEEG and SDE technique have evolved over the years, and we review only the basic characterizing features of SEEG and SDE implantations here, which are summarized in Table 1.

Table 1 Technical considerations and characterizing features between SEEG and SDE

	SEEG	SDE
Age	> 2 years old	All ages
Cortical coverage		
Superficial	Sparse	Dense
Sulci	Good	Only if DE
Deep	Good	Only if DE
Mapping	More difficult—needs extensive pre-op planning	Easily accessible
Craniotomy		
Can perform limited craniotomy for resection	No	Yes
Bilateral	Yes, easily completed	Possible, but requires additional craniotomy

DE = depth electrode

SEEG involves the implantation of intracerebral electrodes to stereotactically targeted gray matter sites hypothesized to be involved in the onset, organization, and symptoms of a seizure [17, 24]. In the pre-implantation phase, high-resolution 3D MR and cerebral angiographic imaging are often merged to plan avascular electrode trajectories [25, 26]. Electrodes are then inserted using either a Talairach frame [27], a Leksell frame [28, 29], or a frameless stereotactic robot-assisted technique [30–32]. Using 1 of these stereotactic guidance systems, holes are then drilled and guidance bolts are placed and subsequently anchored to the skull. Electrodes are then inserted through these guidance bolts to each target. In contrast to depth electrodes implanted with SDEs, traditional SEEG electrodes target gray matter specifically and thus are, by definition, intracerebral electrodes.

SDEs are implanted most commonly through a craniotomy [33], though they can also be implanted through burr holes when implanting strip electrodes. An advantage of SDEs is that grid electrodes can be placed onto the cortical surface under direct visualization. Additionally, image guidance can be used to place depth electrodes into lesions or other selected targets [34]. When cortical areas to be sampled are not directly visible, strip or grid SDEs can be gently guided over the brain curvature to cover brain structures that are not exposed [35–38]. For example, a dense coverage of the temporal pole can be achieved without direct exposure of the temporal pole in its entirety by passing subdural electrode arrays over the curvature of the temporopolar cortex [36, 37]. Similarly, the anteromedial temporal cortex can be covered with the use of an anteromedial strip electrode, or interhemispherically placed subdural electrodes can be utilized to monitor paramedian regions [38, 39].

A reported disadvantage of SEEG compared to SDEs is a relatively limited coverage of the gyral surface [6]. This often cited disadvantage of SEEG coverage may be overstated given that 2 thirds of the cortical gray matter is embedded in sulci, which cannot be recorded from by SDEs (in the absence of depth electrodes). While it is true that SEEG is likely associated with less coverage of the gyral gray matter, SDE is certainly associated with less coverage of the sulcal gray matter,

which makes up a greater proportion of the overall cortical gray matter. Thus, both recording methodologies result in sparse coverage of the cortical gray matter.

When the laterality of the EZ has not been determined, bilateral electrode recordings are likely easier with SEEG electrodes given that they can be implanted bilaterally without repositioning or performing a bilateral craniotomy. SEEG has been used with success for the characterization of the EZ in patients with bitemporal epilepsy [40–42], obviating the need for bilateral craniotomies or burr holes that would be required with SDEs. At centers using SDEs, bilateral craniotomies can be avoided by using bilateral burr holes with implantation of strip electrodes, bilaterally. This is likely a less morbid approach than bilateral craniotomies; however SEEG electrodes can be placed bilaterally with greater precision.

Another technical distinction is that SEEG cannot be utilized in young children (age 2 or younger) given the thickness of bone at this age [43]. This is because the use of SEEG anchor bolts requires a skull thickness of > 3 mm [27]. Thus, even if SEEG is the preferred technique at a given center, if that center is involved in the care of young pediatric patients (< 2 years of age), it may sometimes be necessary to implant SDEs [44].

Relative Safety of SEEG and SDE

The relative safety of SEEG and SDE techniques has been a matter of intense debate for many years [45, 46]. The perception that unfamiliar techniques (either SEEG or SDE) are less safe is 1 possible explanation for this debate and a possible reason why SEEG was not used outside of select centers for many years. This debate continues today despite numerous observational studies [7, 27, 47–51] reporting on the safety of either SEEG or SDE. To date, there is a paucity of clinical studies providing direct comparisons of the safety of SEEG and SDE, possibly due to the fact that most centers use predominantly SEEG or SDE, depending on their preferences. However, a review of the available observational data comparing the safety of SEEG and SDE shows that both have low

complication rates and provides insight into the relative safety of these 2 techniques.

Two recent meta-analyses independently analyzed complication rates related to SEEG [45] and SDE [46] implantation. The findings of these 2 meta-analyses are summarized in Table 2 and described here.

Complications of SDE

In 2013, Arya and colleagues [46] described adverse events related to extraoperative localization of the EZ with SDE. This meta-analysis reviewed results from 21 observational studies that included SDE implantations in 2542 patients. In this meta-analysis, neurologic infections (i.e., meningitis, cerebral abscess, subdural empyema) had a pooled prevalence of 2.3%. Superficial infections (i.e., skin infections) had a pooled prevalence of 3.0%. Bone flap osteomyelitis had a pooled prevalence of 1.8%, which often required treatment with bone flap removal and subsequent cranioplasty. CSF leak was 1 of the most common adverse events related to SDE placement with a pooled prevalence of 12.1%. During SDE placement, sutures are often placed around electrode exit sites to prevent CSF leak, and when CSF leak occurs, some have applied collodion to electrode exit sites to stop the leak [52].

Arya and colleagues [46] also analyzed hemorrhagic complications of SDE. Intracranial hemorrhage had a pooled prevalence of 4.0%. Of intracranial hemorrhages reported, subdural hematoma was most common ($n = 41$), followed by epidural hematoma (EDH) ($n = 11$) and intracerebral hemorrhage (ICH) ($n = 11$). Of note, 34 of the patients with reported intracranial hemorrhages were symptomatic or required surgical intervention. Additionally, symptomatic raised intracranial pressure was reported in 26 patients (pooled prevalence of 2.4%) and often required hastened surgery. It is our experience that early intracranial pressure elevations can be associated with EEG slowing that diminish the usefulness of direct cortical recordings and, when the EZ has not been localized, can require craniectomy with subsequent SDE recordings to better localize the EZ. Interestingly, 2 clinical studies [53, 54] reported that almost all patients with SDE implantation exhibit some degree of extra-axial fluid collection postoperatively with

varying degrees of mass effect and clinical symptoms. Both of these groups note that it is difficult to characterize extra-axial fluid collections after SDE implantation due to artifact caused by the electrodes themselves. These 2 studies suggest that the rate of extra-axial fluid collections associated with SDE grid placement is very high but does not always lead to symptoms or additional surgery.

The meta-analysis by Arya and colleagues [46] reported a 4.6% pooled prevalence of neurologic deficit; however, most were not permanent. As noted by Arya and colleagues [46], inferring a causative association between permanent neurologic deficits and SDE recordings is inherently difficult as many SDE recordings are associated with additional surgery for resection of the EZ. Of the 2542 patients included in this meta-analysis, there were five reported deaths (0.19%). Ten hardware-related complications were reported in this SDE meta-analysis, but it is not reported if any of these complications led to additional surgery. As reported by Arya and colleagues [46], the overall rate of complications resulting from SDE placement that goes on to require additional surgical intervention is up to 3.5%.

Complications of SEEG

In 2016, Mullin and colleagues [45] published a meta-analysis of observational data describing rates of SEEG complications. This meta-analysis included 30 articles describing complications of SEEG implantation in 2624 patients. In this meta-analysis, the overall pooled prevalence of infection was 0.8%, with cerebral abscess being the most common type of infection encountered. A total of 11 abscesses were reported, 4 of which were severe enough to require craniotomy for treatment. Post-implantation meningitis had a pooled prevalence of 0.6%.

Mullin and colleagues [45, 52] reported hemorrhagic complications being the most common complication type after SEEG implantation. The pooled prevalence of a hemorrhagic complication (i.e., subdural hematoma, epidural hematoma, or intracerebral hematoma) was 1.0%. ICH was the most common type of hemorrhage (pooled prevalence, 0.7%) and was associated with surgical evacuation in 7 patients and death in 2

Table 2 Comparisons of 2 meta-analyses of SEEG *versus* SDE safety

	SEEG (Mullins et al. [45])	SDE/depths (Arya et al. [46])
Sample size	2624 patients (30 studies)	2542 patients (21 studies)
Overall complication rate	1.3%	3.5% required additional surgery due to complications
Hemorrhagic occurrence	1.0%	2.4%
Infection	0.8%	2.3% neurologic 3.0% superficial
Mortality	5 patients in series (0.3%)	5 patients in series (0.3%)

patients in this meta-analysis. SDH and EDH were less common than ICH with a pooled prevalence of 0.4% and 0.3%, respectively. One of the reported EDHs in this meta-analysis required surgical intervention. Unlike the SDE meta-analysis by Arya and colleagues [46], Mullin and colleagues [45, 52] did not specifically report ICP-related events, potentially because they are extremely unusual after SEEG implantation.

In this meta-analysis, Mullin and colleagues [45, 52] reported a 0.6% pooled prevalence of transient neurologic deficit and a 0.6% pooled prevalence of permanent neurologic deficit but noted that the cause of permanent neurologic deficit in these cases may not be directly attributable to SEEG implantation. Of the 2624 patients included in the study, there were 5 reported deaths: 2 from ICH, 2 from pre-implantation ventriculography (which is no longer performed at most centers), and 1 from severe cerebral edema thought to be from an underlying metabolic derangement. This meta-analysis reported a total of 11 hardware complications (pooled prevalence, 0.4%), including 1 that required additional craniotomy for removal of a retained electrode.

Comparison of SEEG and SDE Safety Profiles

A comparison of the results of the meta-analyses by Arya and colleagues [46] and Mullin and colleagues [45] suggest several important points about the safety of SEEG and SDE, which are summarized in Table 2. Overall, Mullin et al. [45, 52] show an overall complication rate of 1.3% for SEEG implantation, whereas Arya et al. [46] report an overall rate of 3.5% for patients who *require additional surgery* for complications related to SDE implantation. According to these meta-analyses, the rate of hemorrhagic complications is lower with SEEG implantation compared to SDE implantation (1.0% vs 2.4%). Additionally, the rate of infectious complications is lower with SEEG implantation when compared to SDE implantation (0.8% for overall infection complications with SEEG vs 2.3% rate of neurologic infection for SDE). The rate of neurologic deficit for SEEG also seems to be more favorable with a pooled prevalence of 4.6% with SDE implantation and 0.6% with SEEG implantation.

The rate of hardware complications and mortality related to SEEG and SDE implantations reported in these 2 meta-analyses is similar. However, given the difference in rates of infection, hemorrhage, and neurologic deficit, SEEG seems to have an overall favorable safety profile with regard to invasive monitoring for localization of the EZ.

Comparison of these 2 meta-analyses is limited for several reasons. First, a majority of the studies included were published by highly experienced SEEG groups in France and Italy and it is possible that the relatively low SEEG complication rates published reflect long-term experience with the technique and may not be replicable by centers that are less experienced with SEEG. However, this does not seem to be the

case, as a retrospective series of SEEG published by groups that have traditionally used SDE reported complication rates [47, 48] similar to those of experienced SEEG groups [7, 24]. Second, these meta-analyses are based on observational data and, as such, may not be completely comparable to each other. Most of the studies in these meta-analyses are from centers that use SEEG and SDE for predominantly the same indications, which make the reported results comparable to some degree. Finally, different SDE methods likely have different complication profiles. For example, burr holes for the placement of strip electrodes without a craniotomy is likely to be less morbid than craniotomy for placement of grid electrodes. These differences are not adequately accounted for in the comparison of complication rates that we present here.

Regardless of the method used (SEEG vs SDE), the risks of invasive monitoring must be weighed against the potential benefit of seizure freedom and improved quality of life after ultimate resective epilepsy surgery. Thus, understanding the efficacy of these methods with regard to localizing the EZ is also crucial.

SEEG and SDE for Localization of the EZ and Seizure Freedom

In addition to the debate regarding the relative safety of SEEG and SDE, there is also significant debate about which of these modalities is superior for identification of the EZ. To date, there has not been published head-to-head series directly comparing SEEG and SDE for enhanced identification of the EZ; furthermore, there has been no direct comparison with regard to post-implantation and post-resection seizure freedom rates. SEEG has been reported to be beneficial in cases of lesional epilepsy associated with periventricular nodular heterotopia [9]. In cases of periventricular nodular heterotopia, SEEG can help to define the relationship between the lesion and to establish the limits of the surgical resection of the EZ if beyond the borders of the actual lesion [9]. This is particularly beneficial as periventricular nodular heterotopia can involve both deep (periventricular) and superficial cortical sites at seizure onset [55]. In addition, others have advocated for SEEG in epilepsy associated with multiple lesions when phase 1 data strongly suggest multiple or unique EZs as the epileptogenic region may not be limited to a lesional *focus*, but formed from larger networks of epileptogenicity extending outside the lesion [9, 56, 57]. Craniotomy and SDE placement have been advocated for extensive neocortical continuous coverage of surface gyri, especially when lateral frontotemporal cortical coverage is desired [11]. This can be important in cases of epileptic spasms, for example, when extensive coverage of the neocortical surface can aid in localization of the EZ [58]. Additionally, in cases of EZ localization in neocortical regions involving or adjacent to the eloquent cortex, craniotomy and

Table 3 Recent large cohort studies comparing SEEG *versus* SDE and seizure freedom

Name (year)	Patients	SEEG/ SDE	% resection	% seizure freedom
Cossu (2005)	211	SEEG	82	56
Serletis (2014)	200	SEEG	87	68
SEEG total	<i>411</i>			
Yang (2014)	137	SDE	97	49
Van Gompel (2008)	189	SDE	69	47
Vale (2013)	91	SDE	77	34
Mullin (2016)	102	SDE	82	70
Bekelis (2012)	100	SDE	84	68
Fountas (2007)	185	SDE	81	68
SED total	<i>804</i>			

Italic numbers found in the table were Number of Patients

grid placement have been the preferred approach by some authors [11]. This method has allowed continuous coverage over a large area of cortical surface and permits mapping of the eloquent cortex, while in the epilepsy monitoring unit [11]. It is important to mention that although there seems to be technical advantages for SEEG or SDE in the previously mentioned epilepsies, there have been no studies directly comparing SEEG and SDE for these conditions.

Numerous observational studies have published seizure freedom rates following resective epilepsy surgery guided by SEEG or SDE [19, 27, 59–62]. Table 3 describes many recently published large cohort studies evaluating seizure freedom with the use of SEEG or SDE [45, 49, 52, 60, 63, 64–68]. Three of the largest studies utilizing SEEG in 411 patients showed seizure freedom/Engel class I in 56% to 68% of patients [66–68], compared with 6 of the largest studies utilizing SDE in 804 patients showing seizure freedom/Engel class I in 30% to 70% of patients [49, 52, 60, 62, 64, 65]. Based on these studies, there is no definitive superiority in seizure freedom from 1 approach *versus* the other. It has been hypothesized that SEEG has an increased ability to sample and record from deep cortical structures with greater accuracy and sample bihemispherically without bilateral craniotomy, and has the capability to better map the 3D epileptic network [66, 68]. Ultimately, however, further studies directly comparing SEEG to SDE are necessary to determine which technique has superiority in specific clinical situations.

Added benefits of SEEG include decreased perioperative pain and shorter recovery time than with SDE [11]. Reoperation requiring implants has been noted to be safer with SEEG compared with SDE [69–71]. Additionally, there is increased convenience of SEEG in timing for definitive surgical treatment as it is not influenced or dictated by the need to return to the operating room for grid explantation [11]. SEEG removal is a minor procedure without the need for craniotomy [11]. Additionally, the use of robotic assistance has been shown to decrease operative time and optimize or enhance surgical results [72, 73].

Furthermore, given the variety of epileptic etiologies described in observational studies of invasive monitoring (e.g.,

ranging from temporal lobe epilepsy [37, 74] to periventricular nodular heterotopia [75, 76]), the seizure freedom rates reported by these studies are difficult to compare. In the future, studies directly comparing SEEG *versus* SDE may shed light onto which the technique may be enhanced in confirming the epileptogenic foci and seizure freedom in specific etiologies.

Conclusions

To better understand optimal methods and techniques for localizing the EZ and providing seizure freedom, there is a great need for meta-analyses and, ideally, clinical trials that directly compare the safety and efficacy of SEEG and SDE. A careful review of meta-analyses of the safety of SEEG and SDE demonstrates that SEEG is likely a safer technique, though both approaches exhibit similar mortality rates. The overall efficacy of SEEG and SDE with regard to ultimate seizure freedom is more difficult to determine based on the available literature, though it can be reasoned that SEEG and SDE are at least equivalent for almost all indications. SEEG may be better tolerated by the patient and, with the use of robotic methods, may be safer and more time-efficient for the neurosurgeon.

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