EDITORIAL

Investigating the Inverse Problem of Epileptogenic Zone Localization

Insights From Simultaneous EEG and SEEG

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Neurosurgery is an underutilized, potentially curative treatment for patients with drug-refractory epilepsy.[1] Patient selection and assessment depend on careful, multidisciplinary presurgical evaluation.[2] Recording habitual seizures with detailed analysis of electroclinical features is an essential step, and these data are integrated with other clinical information including patient history, neuroimaging, neuropsychological testing, etc., to decide on whether a unifocal, spatially constrained and potentially operable zone of seizure onset is likely. If the ensemble of noninvasive data are insufficient for surgical decision-making, then invasive recording may be proposed, with many teams around the world now using stereo-EEG (SEEG), a method developed in France over 50 years ago[3] because of its demonstrated effectiveness and favorable safety profile.[4] SEEG implantation strategy is heavily dependent on optimal interpretation of available noninvasive data by an experienced clinical team to formulate hypotheses about likely cerebral origin of seizure generation.[5] Ictal scalp EEG is essential yet often elusive because many scalp-recorded seizures show patterns whose localizing or lateralizing value is unknown.[6]

In this issue of *Neurology*®, Ferrand et al.[7] report on the largest series to date of simultaneous SEEG and scalp recordings. Their study describes 129 patients undergoing epilepsy presurgical evaluation in a single French center, comprising a variety of temporal and extratemporal localizations of the epileptogenic zone as finally confirmed by SEEG. The practice of simultaneous scalp EEG and SEEG brings various practical technical and safety issues, related to the placement of scalp electrodes (using aseptic technique) between the entry points of depth electrodes, with the head then re-covered in protective bandages, and recording of both scalp EEG and SEEG performed over several days. This was carefully performed in this study without significant complications and with excellent technical results.

The "inverse problem" in science consists of using the results of actual observations to infer the values of the parameters characterizing the system being investigated. Here, the authors apply the inverse problem to investigation of the cerebral organization of seizures: Starting from the description of scalp EEG patterns, what related possible seizure onsets are observed on the more anatomically specific intracerebral recording? This approach was feasible here thanks to a large data set and high-quality SEEG recordings regarding appropriate case selection and adequate sampling strategy across the series, evidenced by the satisfactory yield of SEEG (around 70% of cases proceeding to surgery and Engel class 1 outcomes achieved in 82.4%). This lends weight to the use of SEEG as a "ground truth" in this study because we can assume that the SEEG-defined lobar epileptogenic zone was likely to be correct in most of the cases, given overall good surgical outcomes. After clinicians' visual analysis and classification of scalp seizure onset patterns with good interobserver agreement, hierarchical cluster analysis of scalp seizures was performed, thus allowing classification without any preconceived ideas about the included variables. Both spatial (anatomical distribution) and temporal (frequency) aspects of scalp EEG seizure patterns were taken into account.

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The choice here to study the inverse problem rather than its opposite (i.e., the direct problem, which would start with SEEG seizure patterns and then look at scalp EEG correlates) is of interest because the inverse problem follows the clinician's timeline and logic. This brings knowledge of practical value in the epilepsy presurgical setting. For example, because posterior cortex epilepsies were the only lobar localization in which falsely lateralizing scalp EEG seizures were seen, when patients are suspected of having posterior epilepsy and require intracranial exploration, bilateral implantations of SEEG are likely to be necessary. Overall, no scalp EEG pattern was pathognomonic of any single intracerebral localization; even in those cases with the well-recognized pattern of ipsilateral anterior temporal rhythmic theta or delta discharge on the scalp, 20% were found to have extratemporal onset on SEEG, mainly from frontal lobe. Differences were seen in seizure durations according to lobar localization, the longest being associated with the "temporal discharge" cluster and the shortest SEEG seizures being associated with no visible change on scalp EEG. Most scalp EEG patterns tended to show clear lag between the "true" SEEG seizure onset and the scalp EEG onset, which could be seen up to 13.8 seconds later. Limitations of this study relate to the inevitable sampling bias of any intracranial EEG study, but this is mitigated here by the satisfactory yield of surgery post-SEEG as mentioned above.

The lack of specificity of ictal scalp EEG as an isolated indicator of epilepsy localization is a reminder of the need to evaluate EEG data in the light of clinical (semiologic) seizure features, as well as considering other multimodal investigation findings. We can assume that seizure semiology played an important role shaping the team's decisions on the SEEG implantation strategy. A next step for investigating the inverse problem could be to combine clinical variables with scalp EEG. Because electrical and clinical aspects of seizure expression are inextricably linked,[8] this would be expected to increase the predictive power of scalp video-EEG in localization of the epileptogenic zone. The present observations are highly relevant to thinking about how we weigh up different pieces of evidence from noninvasive data, which can be augmented by source localization methods,[9] when formulating hypotheses of likely cerebral seizure origin during presurgical evaluation. This process of hypothesis formulation is a cornerstone of SEEG methodology because the decision of where to place electrodes will greatly influence the quality of the subsequent anatomical electroclinical correlations that can be made during intracerebral recording (and thus the ability to make optimal surgical decisions for each patient). Refining knowledge of the predictive value of different noninvasive data sources more generally should help to improve patient selection for epilepsy presurgical evaluation, improve SEEG implantation strategies, and potentially allow avoidance of invasive recording in some surgical candidates.[2,8] These issues are particularly pertinent given the accumulating research aimed at identifying critical nodes within dynamic epileptic networks[10] with the aim of applying targeted therapies that halt the onset and propagation of seizures.[11] Further progress in knowledge of noninvasive correlates of cerebral epileptic activity will be essential to optimize much-needed therapeutic choices for patients with refractory epilepsy.

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