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Evaluating resective surgery targets in epilepsy patients: A comparison of quantitative EEG methods

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ABSTRACT

Background: Quantitative analysis of intracranial EEG is a promising tool to assist clinicians in the planning of resective brain surgery in patients suffering from pharmacoresistant epilepsies. Quantifying the accuracy of such tools, however, is nontrivial as a ground truth to verify predictions about hypothetical resections is missing.

New method: As one possibility to address this, we use customized hypotheses tests to examine the agreement of the methods on a common set of patients. One method uses machine learning techniques to enable the predictive modeling of EEG time series. The other estimates nonlinear interrelation between EEG channels. Both methods were independently shown to distinguish patients with excellent post-surgical outcome (Engel class I) from those without improvement (Engel class IV) when assessing the electrodes associated with the tissue that was actually resected during brain surgery. Using the AND and OR conjunction of both methods we evaluate the performance gain that can be expected when combining them.

Results: Both methods' assessments correlate strongly positively with the similarity between a hypothetical resection and the corresponding actual resection in class I patients. Moreover, the Spearman rank correlation between the methods' patient rankings is significantly positive.

Comparison with existing method(s): To our best knowledge, this is the first study comparing surgery target assessments from fundamentally differing techniques.

Conclusions: Although conceptually completely independent, there is a relation between the predictions obtained from both methods. Their broad consensus supports their application in clinical practice to provide physicians additional information in the process of presurgical evaluation.

1. Introduction

Epilepsy is one of the most prevalent neurological disorders and affects at least 50 million people worldwide (World Health Organization, 2001). In approximately one third of all patients seizure freedom is not achieved by pharmaceutical therapies and in these cases surgical treatment should then be considered. The goal of epilepsy surgery is to selectively resect brain tissue with the aim that this procedure renders the patient seizure free. However, there is currently no diagnostic method to unequivocally delineate the neuroanatomical areas that are necessary and sufficient to generate epileptic seizures, the

epileptogenic zone (EZ) (Rosenow and Lüders, 2001; Lüders et al., 2006). Instead, the area showing first ictal epileptiform EEG signals (the seizure onset zone, SOZ) is often used in clinical practice as a proxy for the EZ, since the SOZ is thought to overlap with the EZ (Rosenow and Lüders, 2001). However, the exact boundaries of the SOZ and the actual extent of overlap with the EZ for any given patient remain unknown. Moreover, a recent study found that to attain seizure freedom, complete resection of the SOZ was necessary in only one out of eight pediatric patients (Huang et al., 2012). Together with evidence that long-term seizure freedom is only achieved in up to 2/3 of patients who undergo surgery (Wiebe et al., 2001; Téllez-Zenteno et al., 2005; de Tisi et al.,

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2011; Engel et al., 2012), doubt can be cast regarding whether the SOZ is the best approximation to the EZ, or whether alternative methods to identify which regions of tissue to resect could be beneficial. An additional challenge to the use of the SOZ is that it is determined predominantly by visual analysis of EEG recordings, which is not only time consuming but also prone to inter-rater variability.

To address these shortcomings, a variety of quantitative intracranial EEG (iEEG) analysis methods have been developed to aid identification of candidate tissue for surgical resection. Many different approaches are used to assign estimates about epileptogenicity of brain tissues associated with specific channels of intracranial electrodes (see e.g. Pereda et al., 2005; Lehnertz et al., 2009; Wendling et al., 2010; van Mierlo et al., 2014). Some studies examined the relation of quantitatively determined channels with the channels determined visually as the site of seizure onset (see e.g. Urrestarazu et al., 2007; Worrell et al., 2008; Jacobs et al., 2009; Gnatkovsky et al., 2011, 2014; Boido et al., 2014; Geier et al., 2015). Others explicitly verified the potential of quantitative measures to act as biomarkers of the epileptogenic zone by its relation with the actually resected brain tissue or the post-surgical seizure control. Some by capturing high-frequency oscillations (see e.g. Jacobs et al., 2010; Wu et al., 2010; Modur et al., 2011; Park et al., 2012; Roehri et al., 2017), others using graph theory to determine nodes' values of connectivity, centrality or similar (see e.g. Jung et al., 2011; Zubler et al., 2015; Wilke et al., 2011; van Mierlo et al., 2013) and also different techniques (see e.g. Bartolomei et al., 2008; Kim et al., 2014, 2010). Many of these methods have shown to provide useful information in the preoperative process. Rummel et al. recently investigated how post-operative seizure control is associated with different qEEG measures representative for four different classes of signal analysis methods (Rummel et al., 2015). They calculated four different measures and salient channels were selected by a data-driven manner for each measure. For three of these measures, the overlap between salient channels and actually resected channels was significantly larger for class I patients compared to class IV patients. A measure derived from a nonlinear interrelation matrix could best differentiate between actual resections with favorable and unfavorable outcome by identifying their overlap with the channels associated with the resected brain tissue.

Computational models capable of drawing inferences about specific hypothetical resections under modifiable input conditions have been developed rather recently. Hutchings et al. used diffusion tensor imaging data and showed their model to successfully identify regions known to be involved in temporal lobe epilepsy (TLE), however, it was not validated with actual patient outcomes (Hutchings et al., 2015). Sinha et al. used interictal electrographic recordings to generate their model, which then in simulated resections showed agreement with the clinical outcome for five of six patients (Sinha et al., 2014). These two models allow to make predictions on the ictogenicity of individual nodes of a derived network. Sinha et al. recently extended their approach to make predictions about the overall efficacy of a surgical resection by averaging the seizure likelihood of all nodes under a resection and comparing it to the average obtained from random resections (Sinha et al., 2016). When simulating the actual resections the predicted outcomes coincided with the actual outcomes in 13 of 16 patients. Goodfellow et al. introduced a model that is able to quantify local and global ictogenicity of a network under perturbations of specific nodes (Goodfellow et al., 2016). They found that the overlap between resected tissue and the nodes having the biggest ictogenicities is significantly larger in patients with good response to surgery than in class IV patients. Furthermore, the model predicts a greater reduction in network ictogenicity when simulating actual resections of class I patients than for class IV patients. Based on the global network ictogenicity they classified correctly 14 out of 16 patients (AUC = 0.87). Steimer et al. presented a distributional, soft clustering model for the predictive modeling of multivariate, peri-ictal iEEG time series (Steimer et al., 2017). This model permits patient-specific predictions about seizure propensity under arbitrary simulated resections of brain tissue.

Whereas the simulated resection of the brain areas that were actually surgically removed reduces the model's seizure probability in most Engel class I patients, for most Engel class IV patients the model confirms the inefficiency of the actual resection to impede an imminent seizure. Moreover, successful actual resections are significantly separated from unsuccessful ones and from equally-sized random resections while unsuccessful actual resections cannot be separated from random resections.

The availability of many alternative methods to predict which tissue should be resected raises the issue of selecting an appropriate method for a given patient. Unfortunately, because the true effect of all possible resections except those actually carried out cannot be known, determining accuracies of such methods is always restricted to very few data points and thus remains vague. A starting point to address this is to explicitly compare predictions arising from different methods and quantify, in the first instance, to what extent predictions differ, if at all. Providing a framework to answer this question would significantly advance the clinical usefulness of quantitative methods in epilepsy surgery and other treatments for neurological and neuropsychiatric disorders more generally.

For this cross-method verification of two fundamentally differing methods we focus on comparing two methods that have recently been developed and tested at our institute and have shown convincing performances by quantitative comparison with the actual resection and outcome in patients undergoing surgery. That is, we directly compare the assessments of hypothetical resections by the nonlinear interrelation measure examined by Rummel et al. (2015) with the resections' seizure suppressing efficiencies as estimated by the model of Steimer et al. (2017). Both methods have shown promise in the prediction of tissue resection in epilepsy surgery. However, it remains unclear if their predictions are coherent beyond the common feature that successful actual resections are recognized as effective and thus get high performances. To investigate the extent to which predictions from these methods are in agreement, we compare in a first part the individual performances of the two methods for a common set of patients. In addition, we examined the performance gain that can be expected when combining the methods' binary classifiers. In a second part we present the results of the investigation looking for a link between these methods' classification of arbitrary resections. Finally, we discuss the obtained results and address issues of possible future work aiming to derive objective markers of target tissue or to assess such approaches.

2. Methods

2.1. Patients & data

In this study we included the peri-ictal intracranial EEG recordings of 20 patients of the epilepsy surgery program of the Inselspital Bern (15 female, 5 male; median age 31 years, IQR 16 year, range 10–66 years). A precondition for the selection of patients was the availability of the information about the resected brain tissue (incl. the associated electrodes) and their outcome according to the Engel classification scheme (Engel et al., 1993). We included patients who were post-surgically free of disabling seizures and auras for at least one year (Engel class I) or who showed no worthwhile improvement following resection (Engel class IV). All patients are listed with further details in Table 1.

All recordings were visually inspected by an experienced epileptologist/electroencephalographer (K.S.) to remove channels exhibiting permanent artifacts (< 5% of channels) and to determine the clinical seizure onset (the time of earliest EEG change associated with seizures) and its corresponding zone (SOZ). Furthermore, pre- and post-operative MR images and post-implantation CT images were coregistered to identify the resected brain tissue and the position of the electrodes and thereby the channels recording from the subsequently resected tissue. These channels constitute the actual resection. A more detailed description of this procedure can be found in Rummel et al.

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