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Invited review

Seizure prediction for therapeutic devices: A review

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ABSTRACT

Research in seizure prediction has come a long way since its debut almost 4 decades ago. Early studies suffered methodological caveats leading to overoptimistic results and lack of statistical significance. The publication of guidelines addressing mainly the question of performance evaluation and statistical validation in seizure prediction helped revising the status of the field. While many studies failed to prove that above chance prediction is possible by applying these guidelines, other studies were successful. Methods based on EEG analysis using linear and nonlinear measures were reportedly successful in detecting preictal changes and using them to predict seizures above chance. In this review, we present a selection of studies in seizure prediction published in the last decade. The studies were selected based on the validity of the methods and the statistical significance of performance results. These results varied between studies and many showed acceptable levels of sensitivity and specificity that could be appealing for therapeutic devices. The relatively large prediction horizon and early preictal changes reported in most studies suggest that seizure prediction may work better in closed loop seizure control devices rather than as seizure advisory devices. The emergence of a large database of annotated long-term EEG recordings should help prospective assessment of prediction methods. Some questions remain to be addressed before large clinical trials involving seizure prediction can be carried out.

Contents

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1. Introduction

For decades, treatment options for epilepsy remained mainly pharmacological and to lesser extent surgical. Antiepileptic drugs have limitations (Deckers et al., 2003) and fail to control seizures in roughly 20–30% of patients. Advances in neuroimaging, electrode technologies and computerized surgical planning helped in better management of intractable seizures by reducing their severity and frequency, and in some cases by attaining seizure freedom. Patients who do not respond to medication and who are not candidates for surgery are in need of new treatment options. Recently, new lines of therapeutic treatment have emerged. Devices based on electrical stimulation (or neuromodulation) (Fisher, 2012), drug-delivery (Bennewitz and Saltzman, 2009; Fisher and Ho, 2002; Stein et al., 2000) and focal-cooling (Fujii et al., 2010; Rothman, 2009) have proven levels of efficacy in controlling seizures. Stimulation devices in particular have been thoroughly investigated. While their mechanisms of therapeutic action remain generally unexplained, evidence of their antiepileptic effects is supported by series of large controlled clinical trials (DeGiorgio et al., 2013; Fisher et al., 2010; Fregni et al., 2006; Heck et al., 2014; Morrell, 2011; Rong et al., 2014). Most of these devices administer continuous stimulation. The responsive neurostimulator system (RNS®) by NeuroPace, Inc. (Mountain View, CA, USA) delivers stimulation only when a seizure activity is detected from chronic EEG recordings. This type of intervention, known as closed-loop stimulation, has arguably an advantage over the continuous stimulation, mainly because less stimulation is used, which improves the power efficiency of the device and reduces side effects of long term stimulation (Springer et al., 2006).

Stimulation is thought to be more effective in abating seizures when it is administered earlier than later, before the onset of a seizure (Motamedi et al., 2002; Murro et al., 2003), but an optimum time at which stimulation is most effective has yet to be identified. This is true for most of the therapeutic modalities and it is mostly due to the lack of a full understanding of ictogenesis mechanisms. Electrical stimulation based on early seizure detection techniques has shown promising results in stopping seizures a few seconds after the electrographic onset (Fountas et al., 2005; Kossoff et al., 2004; Osorio et al., 2005). Closed-loop interventions from seconds to hours before the electrographic or clinical seizure onset are investigational. Such a therapeutic approach relies in principle on a sensitive and specific prediction of seizure occurrences to achieve seizure control and to minimize side effects from unnecessary interventions. The possibility of seizure prediction was explored for over 25 years, typically from EEG analysis. In most of the early studies, the main question was whether changes in the EEG preceding seizure onset could be identified. Measures derived from linear and non-linear analysis were reportedly successful in detecting changes minutes to hours before seizure onset (Lehnertz, 2001). The optimistic results of these studies were regarded as a proof-of-concept of the existence of a preictal state. The question of seizure predictability remained open though as the specificity of the preictal changes was not assessed. The first studies to evaluate specificity on controlled data were retrospective. Many showed methodological flaws largely related to optimization problems (in-sample data used in optimization and testing) and lack of statistical validation (superiority to random prediction) rendering the prediction power of many measures questionable.

The requirements for an acceptable range of sensitivity and specificity are not standard and depend on the clinical application. Nearly all published methods of seizure prediction are not tailored towards specific interventional devices. Their performance could not be assessed independently from a clinical context. In an attempt to define a maximum rate for false predictions, the patient's seizure frequency under epilepsy monitoring settings was used as a reference (Aschenbrenner-Scheibe et al., 2003; Winterhalder et al., 2003). Since an average of 3.6 seizures per day (equivalently 0.15 seizures per hour) are recorded during epilepsy monitoring (Haut et al., 2002), false prediction rates above 0.15/h are deemed questionable, at least outside of closed-loop intervention systems.

To assure methodological quality and practical assessment of seizure prediction methods, guidelines and statistical frameworks have been proposed (Andrzejak et al., 2003, 2009; Kreuz et al., 2004; Mormann et al., 2005, 2007; Snyder et al., 2008; Winterhalder et al., 2003; Wong et al., 2007). A number of studies proposing new seizure prediction methods have been carried out on the basis of these recommendations aiming for reliable prediction and clinically useful performance. In this review we present studies on seizure prediction published in the last decade (between January 1st 2004 and December 31st 2014) in peer-reviewed journals and listed in PubMed (Only PubMed search engine was used for retrieval of clinically relevant studies. Key term "seizure prediction" was used in the search). We further restricted the review to studies based on intracranial EEG recordings that attempted to demonstrate statistical significance of the reported performance results using recommended statistical validation procedures. Studies that were previously reviewed in Mormann et al. (2007) are not discussed. Levels of sensitivity and specificity varied between studies. Their usefulness depends on the clinical application. Studies based on scalp EEG analysis are arguably less applicable to chronic interventional devices and are not presented in this review.

2. Requirements of a practical seizure prediction method

The guidelines proposed by Mormann et al. (2007) tackled two major methodological issues in seizure prediction: whether the claimed prediction power of a seizure prediction method could