Self-prediction of seizures in drug resistance epilepsy using digital phenotyping: a concept study

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ABSTRACT

Drug-resistance is a prevalent condition in children and adult patients with epilepsy. The quality of life of these patients is profoundly affected by the unpredictability of seizure occurrence. Some of these patients are capable of reporting self-prediction of their seizures by observing their affectivity. Some patients report no signs of feeling premonitory symptoms, prodromes, or aura. In this paper, we propose a concept study that will provide objective information to self-predict seizures for both the patient groups. We will develop a model using digital phenotyping which takes both ecological momentary assessment and data from sensor technology into consideration. This method will be able to provide a feedback of their premonitory symptoms so that a pre-emptive therapy can be associated to reduce seizure frequency or eliminate seizure occurrence.

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1 INTRODUCTION

Epilepsy is the most common neurological disorder characterized by unprovoked and unexpected electrical bursts in the brain, which results in seizures. More than 50 million people worldwide are affected by epilepsy [1]. Initially, most epilepsy treatments depend on anti-epileptic drugs (AEDs). Nevertheless, 30% of these patients posses drug-resistant epilepsy. According to the International League Against Epilepsy (ILAE), drug-resistant, also named intractable epilepsy or refractory epilepsy is defined as the failure of two tolerated, appropriately chosen administered AEDs (whether as mono-therapy alternatively, in combination) to achieve seizure freedom [12]. The predictability of seizure can be better understood by exploring the pre-ictal, ictal, and inter-ictal state of the brain. While most epilepsy research focuses on the inter-ictal state of the brain, which is the baseline state, limited research is found when it comes to predicting seizure before seizure onset or the transition to the brain's pre-ictal state. Understanding this will eventually improve the burden of unpredictability from the patients with epilepsy (PWE), further increasing the quality of life (QoL). The QoL of these patients highly depends on other comorbidities such as cognitive impairment, depression, medication side effects, sleep quality, restricted independence, and privacy, embarrassing situations, stigmatization, and, importantly, the unpredictability of seizure occurrence. Apart from QoL, sometimes the severity of the seizure can lead to Sudden Unexpected Death in Epilepsy (SUDEP).

Many PWE have subjective feelings of an upcoming seizure and reports to self-control seizures by non-pharmacological strategies [11]. These feelings are highly specific to individuals. For some patients, it comes a few seconds to a few minutes preceding a seizure known as *auras*. Aura happens in the ictal state of the brain and is seen as objective abnormalities in the Electroencephalography (EEG) recordings. Depending on the localization of the brain, these auras can be different, i.e., sudden overwhelming emotion, such as joy, sadness, fear or anger, a tingling or burning sensation, déjà vu and others. On the other hand, *prodromes* are subjective feelings occurring in the pre-ictal state of the brain and are not accompanied by EEG changes. Prodromes happen between 5 minutes to 48 hours before the clinical seizures [11]. Approximately 6.9% to 39% of PWE reports prodromes, which includes behavioral changes, cognitive disorders, mood changes, fatigue, sleep disorders, headaches, gastrointestinal symptoms, changes in appetite, and altered voice [19].

Additionally, the *precipitant factors* occurring in the inter-ictal phase can have alert symptoms from several days to 24 hours before. A previous study mentions that 90% of the patients with epilepsy report at least one precipitant as a measurable trigger factor to identify pre-ictal state [20]. Among these factors, stress is the most frequently reported precipitant factor by the PWE [16]. Furthermore, a recent demographic study reports that approximately 30% of the PWE reports seizure triggers which by frequency were: stress (37%), missing sleep (18%), menses (12%), overexertion (11%), diet (9%), missed medications (7%), and fever/infection (6%) [4]. Additionally, alcohol consumption or withdrawal, infection, fasting leading into hypoglycemia, caffeine: mainly if it interrupts normal sleep patterns, pain killers, or antibiotics, can also supplement as seizure triggers. The data of seizure triggers was collected from a mobile application (App), which is reported by the PWE. Nevertheless, this is only applicable for people who experience an aura before and have time to open up the App on the watch.

To identify the variables of the pre-ictal phase using clinical data, a prospective study is performed which analyzes a self-reported paper-diary of the patients with a mean specificity of 83.2% and a

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sensitivity of 31.9% [7]. This study found a strong correlation between seizure occurrence and less sleep, whereas almost no significant correlation between seizure occurrence and stress and anxiety. Since this study is limited by a paper-diary format and collects the mood state's data once in a day, analysis on the psychological and biological mechanisms related to stress and anxiety needs further investigation. Further research replaces the paper-diary with an electronic diary (e-diary) for better identification of the pre-ictal states [6]. Using a Personal Digital Assistant (PDAs) with objective time tracking, this study demonstrates that both change in mood and other premonitory features (blurred vision, light sensitivity, dizziness, and more) contributes to the prediction of seizures. These results contradict another research in the parallel time [13], which uses both PDA and e-diary but found no significant reliable results on preceding seizures by prodromal symptoms. However, the latter is limited to choose a small cohort who are already convinced that they could predict seizures, which could eventually lead to a biased decision. Moreover, a later study by the same author in [6] showed no correlation with depression, anxiety, and self-efficacy scores with seizure outcome [8]. On the other hand, it also suggested that applying stress reduction interventions will reduce seizure frequency in drug-resistant epilepsy patients. The possible reason for the inconsistent results could be the exclusion of participants with more advanced anxiety/depression or the applied intervention, which might not reduce anxiety enough.

The most recent study by the authors who have published the most extensive series of studies examining clinical seizure prediction concludes that self-prediction is strongly associated with an increased risk of seizures [17]. Also analyzing the association of mood, premonitory symptoms, stress, and circadian influences on seizure self-prediction, this study shows that mood factors as well as premonitory features do not directly influence seizure occurrence but it contributes to positive self-prediction linked to seizure occurrence. They also found a circadian pattern in seizure occurrence. Though the sensitivity and positive predictive value (PPV) is quite low in this study, the achievement of high specificity and negative predictive value (NPV) is of great statistical significance in seizure predictions.

Conclusively, the literature shows that the complex relationship between affective states preceding seizures led to contradictory results to date. Firstly, patients are reporting stress as the most frequent trigger in several pieces of researches [16][4], but another study found no correlation between stress and seizure occurrence [7]. Secondly, both the studies in [13] and [6] showed different results of prodromes preceding seizures. Thirdly, the study in [8] shows depression/anxiety does not affect seizure occurrence whereas the study in [17] mentions the indirect influence of premonitory symptoms preceding seizures. The possible reason could be that the patient-reported mood may also misguide the self-prediction of seizures, for example, problems like predicting seizures during an aura remain, which will eventually mislead the ictal phase as a pre-ictal one. Moreover, diary studies, in general, have always been questioned on the accuracy and the reliability of the data. An investigation of a more comprehensive array of possible triggers, along with examining the biological patterns of the patients, will help to improve the existing seizure prediction models. Importantly, these findings of the statistical correlation between mood changes as premonitory features of seizure occurrence have potential clinical and physiological implications once more object methodology can be introduced. Hence, incorporating the physiological measures into a seizure prediction model would improve the measurement of patient-reported mood and self-prediction of seizures and provide a robust multi-modal seizure prediction with unobtrusive and non-invasive recordings. Therefore, we aim at twofold outcomes from this research, to eradicate contradictions on possible prodromes and triggers and to incorporate physiological measures of the premonitory symptoms.

2 OBJECTIVES AND RESEARCH QUESTIONS

Within this research framework, the main objective is to quantify prodromes and premonitory symptoms in the pre-ictal and the inter-ictal state of the brain consecutively, which leads to the following research questions:

- Which affective states are responsible for preceding seizures in the pre-ictal and inter-ictal phase? Is it possible to extract more reliable and conclusive outcomes on affective states preceding seizures compared to the state-of-art discussed?
- Is it possible to demonstrate the patient-reported feelings of prodromes or premonitory symptoms of seizure self-prediction by physiological measures?
- To improve the QoL, is it possible to provide objective information of prodromes or premonitory symptoms from physiological measures to PWE who can not self-predict seizure?
- Sensitivity: what percentage of seizures which are preceded by prodromes or premonitory symptoms can be detected using the proposed system? What are the correct PPV and correct NPV of seizures? Does it comprehend the state of the art findings?
- False prediction rate: what percentage of specificity can be achieved?

3 SEIZURE RELATED BIOMARKERS

To use digital phenotyping with sensor technology for seizure prediction it is important to know the reliable bio-markers for premonitory symptoms. In the following sections, we will discuss some of the major seizure triggers and the bio-signals responsible behind.

Affective states: From the circumplex model of affect [18], stress is the most reported seizure trigger. The epileptic electrical brain activity affects the same parts of the brain that regulates the autonomic nervous system (ANS) tones activated by physiological stress. Possible correlation between epileptic seizures and stress was measured by analyzing heart rate variability (HRV) patterns since HRV analysis can detect the changes in sympathetic nervous systems (SNS) and parasympathetic nervous systems (PNS) of the ANS tones [9]. This study also provides evidence that EEG analysis detects a PNS suppression 10 seconds before seizure onset. A similar study was provided with 30 seconds prior information on seizure onset [15]. Other patient-reported emotional states of a person affect brain activity, which can be detected by EEG measurement. Additionally, the skin conductance increases when the body sweats under stress or emotional arousal [2]. Therefore, looking into Electrodermal Activities (EDA) also known as Galvanic

Skin Response (GSR) signals will help to differentiate between the emotional states. The Skin Temperature (ST) can also be changed. Moreover, the change in muscle activity due to different affective states can also be measured by facial Electromyography (EMG), voice recorder or cameras.

Sleep is also one of the seizure triggers and studies have already confirmed that sleep deprivation causes to increase EEG epileptiform activity, cortical excitability, and seizure occurrence [3]. And also sleep deprivation promotes inter-ictal epileptiform discharges [14]. Therefore, an EEG measurement for sleep analysis has widely been used in the literature. Chin EMG also provides valuable information on sleep [14].

4 RESEARCH METHODOLOGY

4.1 Subject recruitment

In this paper, we propose a multi-center study on patients who are diagnosed with drug-resistant focal or generalized epilepsy. Suitable patients will be identified in the outpatient clinics of the participating epilepsy centers (to be confirmed). Adult patients (at least 18 years old) with drug-resistant focal or generalized epilepsy since 2 years and at least one seizure during the last 6 months who are planned for subsequent inpatient diagnostic assessment and treatment will be given the opportunity to participate in this study. Changes in AEDs are allowed to achieve best medical treatment. We expect to recruit about 20 patients per participating center within 12 months, i.e. 60 patients in 3 comprehensive epilepsy care centers within 12 months. Patients with any learning disability, any history of neurosurgery or cardiovascular disease, any psychiatric history, diabetes, or any chronic illness will be excluded from this study.

4.2 Study design

At the beginning of our study, we will choose a set of patients according to the criterion mentioned above and monitor them for two weeks as a baseline study. As depicted in figure 1, the PWE will be divided into two groups: group 1: who are capable of reporting premonitory symptoms and/or prodromes and group 2: who do not report of premonitory symptoms and/or prodromes. Both the groups will answer questions from the Beck Depression Inventory-II (BDI), Generalized Anxiety Disorder–7 (GAD), State-Trait Anxiety Inventory (STAI), Self-Efficacy Scale, and Positive and Negative Affect Schedule (PANAS) screening tools. The scores from these screening tools will be essential to do the psychometric evaluation of depression, anxiety, stress, and affectivity, which will be used as ground truth for PWE. Along with that, each PWE will be given a smartphone with E-diary App developed in [8]. In this App, they will log their seizures, premonitory symptoms, sleep hours, medication adherence, menstrual cycle, current illness once in a day at a randomly prompted time. The PWE also has to complete multiple mood items adapted from the circumplex models of affect using a visual analog scale. The PWE will be prompted to fill in this mood model and will be asked by the application to mention their contextual information at randomly sampled intervals daily. To measure the physiological signals such as HRV, EDA, unobtrusively, the PWE will be asked to wear smart wearable devices containing multiple sensors. These physiological signals will provide objective information about their affectivity. For group 1, we will try to recognize patient-reported premonitory symptoms preceding seizures with the physiological signals measured. For group 2, we will try to find abnormalities in the physiological signals that might have led to a seizure.

	2020		2021	
	July-Aug	Sep-Dec	Jan-June	July-Dec
Literature review, Concept study design				
Pilot study with healthy cohort				
Ethics proposal approval				
Patient recruitment				
Data collection, analysis				

Table 1: Research timeline

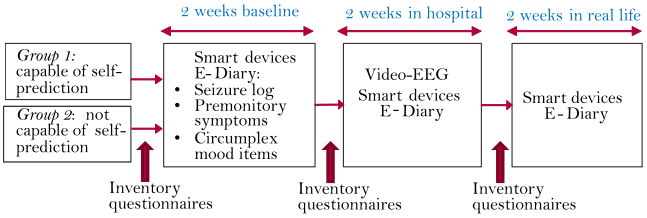

Figure 1: Study design

In the next two weeks, we would monitor the PWE in the hospital and observe them with video-EEG. These patients will have minimum movement restrictions to make the data more realistic to real life. To compare the emotional intensity with the previous baseline study for each patient, the emotional regulations will be evaluated by presenting five films inducing emotional responses discussed in [10]. The skin conductance will be monitored while performing the attention task and suppression task. Apart from that, the PWE will be asked to perform simple cognitive task by solving arithmetic problems with the App used in [5]. The physiological signals will be monitored for the whole period of study. Before leaving the hospital, the PWE will be asked to fill up the set of questions in the inventory mentioned earlier.

After this hospital settings, the patients will be monitored for two more weeks in an uncontrolled environment. At that time, the physiological signals, the questionnaires from the inventory and E-diary will be monitored again. This data will be used for a comparison study with the baseline and the hospital study. The processing of the collected data will be used to set up a model explained in the next section and the timeline of the research is summarized in table 1.

4.3 Methodology

From the two-week baseline study, we will derive the baseline depression, stress, anxiety detector [5]. As a pre-processing step of this baseline study, the physiological signals will be denoised individually with an adaptive filter [21], as depicted in figure 2(a). The signals from the Accelerometer (ACC) sensor will be another input of the filter to perform context-aware monitoring of the data. This filtering is essential since sensor data is often affected by the motion artifacts produced due to the unintentional movements

of the patients. ACC will be used as an external input, and the filter will be able to detect unanticipated physiological abnormality dynamically. For better predictive performance, the parameters inside the filter will also be updated based on the measured signal. The denoised signal will then be used to a typical machine learning

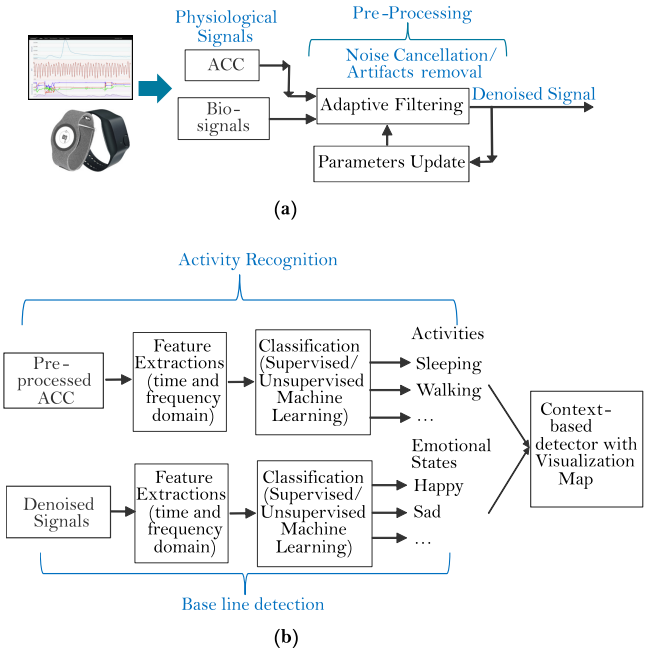

Figure 2: (a) Data pre-processing, (b) Context based detector

pipeline for creating a baseline classifier [5]. As depicted in figure 2(b), the features will be extracted from the denoised signal. The quality of the extracted featured is highly dependant on the quality of the denoised signal. Therefore, in the real-life scenario, the choice of features might be different. These features can be extracted and labeled from the questionnaire and the e-diary used in the classification algorithm. For example, for stress, we will classify the signal as stress and no stress.

After baseline detection, we will use the ACC data for activity recognition shown in figure 2(b). This will be performed in hospital settings and real-life study also. The context-based stress detector has achieved 92% accuracy [2]. Therefore, we will perform activity recognition to get context-based information. The most relevant features to be extracted from the raw data from a three-axis ACC are mean, standard deviation, energy, and correlation. Later on, the classification will be performed with the available classifiers. Finally, we will train a context-based stress detector depicted in figure 2(b) with an experimentally chosen machine learning algorithm with the features of the base detector and the average activity level.

5 CONCLUSION

In this paper, we propose a system which will provide an objective self-prediction of seizures for patients with drug-resistant epilepsy. Once the model is designed successfully, it will bring a new dimension of epilepsy treatment with a significantly improved quality of life of the patients.

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