Epilepsy Research 130 (2017) 27–36

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

# Seizure detection and neuromodulation: A summary of data presented at the XIII conference on new antiepileptic drug and devices (EILAT XIII)

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ARTICLE INFO

*Article history:*
Received 18 October 2016
Accepted 8 January 2017
Available online 16 January 2017

*Keywords:*
EEG
ECG
Seizure detection
Vagal nerve stimulation
Deep brain stimulation

ABSTRACT

The Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII) took place in Madrid, Spain from June 26th to 29th 2016. For the first time, the last day of the conference focused solely on new medical devices and neuromodulation. The current article summarises the presentations of that day, focusing first on EEG- and ECG based methods and devices for seizure detection. These methodologies form the basis for novel cardiac-based methods of vagal nerve and responsive deep brain stimulation that rely on the prediction or early detection of seizures and that are also included in this article.



**Contents**



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http://dx.doi.org/10.1016/j.eplepsyres.2017.01.004
0920-1211/

## 1. Introduction

Despite advances in antiepileptic drug (AED) development with currently over 20 available AEDs and many more in development (see EILAT XIII report, Bialer et al., 2017), about one third of patients continue to have seizures. The use of neuromodulation has grown considerably in those medically refractory patients who are not candidates for resective surgery. The development of closed-loop systems is generally considered the "holy grail" for neurostimulation in drug-resistant epilepsy. In order for such systems to work and a device to function independently, reliable seizure detection methods are required. In closed-loop stimulation, the first half of the loop is seizure detection, and the second half of the loop is the resulting stimulation. Accordingly, the first part of this manuscript provides an overview of EEG and ECG-based seizure detection methods, which is followed by a review of studies using novel cardiac-based vagal nerve stimulation and deep brain stimulation in response to early seizure detection.

## 2. EEG-based seizure detection systems

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Automatic seizure detection developed with the advent of long-term video and EEG monitoring in the 1970s. Until then, the usual 30 min to 2 h EEG recording sessions only captured seizures accidentally. Many methods have been published since the 1980′s, relying on a variety of features extracted from the EEG. No specific feature has proven overwhelmingly dominant. Whereas earlier methods tended to be validated with datasets that were not very extensive, recent methods have been validated on dozens of patients, sometimes more than a hundred, hundreds of seizures and thousands of hours of recording. The performance is usually in the range of 80–90% sensitivity and one false detection every 3–6 h, making such methods useful in the epilepsy monitoring process.

One of the main purposes of long-term monitoring is to capture seizures but it became quickly apparent that this was not an easy task. The level of patient observation by qualified staff varies greatly from hospital to hospital and it is obvious that even close observation cannot be 100% observation. Furthermore, there are seizures with no apparent or very minimal clinical signs and these can be missed unless the EEG is observed continuously, a further level of observation that is rarely undertaken in epilepsy monitoring units. In this context, automatic seizure detection should be conceived as an aid in capturing seizures.

Automatic seizure detection can also be placed in a context other than that of this hospital diagnostic setting. In patients who are not aware of the onset of their seizures, a device that could be carried by the patient providing an alarm as soon as a seizure started which might be useful for the patient or caregivers to take precautionary measures and avoid that the patient gets hurt. A few systems have also been developed as seizure warning devices, giving a signal when a seizure has just started. Such systems are tuned to the particular seizure pattern of a patient and can give a warning 10–12 s after EEG onset (see below section on seizure detection and warning).

It would be even better if the device could predict that a seizure was likely to occur in the near future. One can then go a step further: if a seizure can be detected or predicted, is it possible to devise a method that will prevent the seizure from occurring? It might be possible to achieve this through electrical stimulation or a rapid pharmacological intervention.

Automatic seizure detection has therefore many potential applications. But how does one go about detecting or even predicting a seizure? The most common approach is with the EEG, in which many seizures have prominent manifestations. We will not discuss here other approaches relying on the detection of some of the movements specific to seizures, on the EMG signature of seizures or on ECG changes that occur in many seizures, which is the subject of the next section. We will also not discuss the specific problem of seizures recorded in the Intensive Care Unit, where the definition of a seizure can be quite ambiguous.

### 2.1. Challenges of EEG-based seizure detection

One of the important challenges of seizure detection is that there is no universal definition of a seizure, and thus, the performance of a detector will depend on the definition used in its validation (Gotman, 2011). For our purpose three major aspects must be remembered:

- If the detection is performed from the EEG, then only the seizures that have a clear manifestation on the EEG can be detected: whether one uses scalp or intracranial EEG, there can always be some seizures that have no clear manifestations in the recorded channels and these *cannot* be detected.
- The EEG does not know if there are concomitant clinical manifestations and it is therefore *impossible* for an EEG-based detector to selectively detect seizures with clinical manifestations.
- The definition of a seizure has varied in different validation studies. The consensus of multiple readers is sometimes used as a gold

standard. Many seizures are obvious to all readers but in some situations (EEG discharges lasting a few seconds, rhythmic sharp activity seen in comatose patients) there can be great divergence and this renders the development and the validation of a detector very difficult.

### 2.2. General purpose seizure detection

An early general-purpose EEG-based seizure detector is that of Gotman (1982). It relied on detecting events in the EEG that were *paroxysmal* (standing out from a constantly updated 1 min background), *rhythmic* (with waves of regular amplitude and duration), and *sustained* (lasting several seconds and with an EEG that, even if it was not rhythmic anymore, did not return immediately to baseline). These characteristics try to represent the distinguishing features of a seizure but they are not perfect: some seizures do not have a rhythmic discharge in the sense used here (e.g. spike and wave bursts, generalized seizures starting with an EEG flattening and followed by large amplitude EMG artefact). This exemplifies the difficulty of capturing all aspects of a seizure discharge. Furthermore, some normal EEG patterns have all three characteristics: the onset of alpha activity is paroxysmal, rhythmic and sustained. Such events, and others, are bound to result in false detections. This method is not discussed for its particular merits, but to explain the difficulties encountered when trying to encode in an algorithm the essence of "seizure".

### 2.3. Seizure detection for review of long-term monitoring data

The performance of a seizure detection method is usually measured with two parameters: the *sensitivity* representing the percentage of seizures that can be detected, and the *false alarm rate* representing the number of false detections per hour of EEG analyzed. A delicate balance between the two is necessary: it is important to detect as many seizures as possible, but effectiveness may be compromised if false detections are too frequent and increased sensitivity always results in increased false detections. The level of acceptability will depend on the application. When assessing the performance of a method, it is critical to know how it was measured. It is particularly important that the data on which the performance was evaluated was independent of the data used to develop and tune the method ("out of sample" testing). This "test data set" must be extensive and representative, including a large number of seizures from many patients and preferably hundreds of hours of *unselected* interictal recording. Testing that makes use of an equal number of seizure segments and non-seizure segments, as is often done in the pattern recognition literature, is inappropriate as it cannot encompass the extensive variability of interictal recordings. Results given with *specificity* rather than *false detection rate* can also be misleading: a 98% specificity may appear as excellent performance but it translates as 2.4 false detection per hour (assuming 30 s epochs), a very poor performance.

There is a very vast literature on seizure detection, with several new publications every year and it would be impossible to make an exhaustive review here. A recent review of all types of detection approaches (not limited to EEG) can be found in Ramgopal et al. (2014). Following a recent publication of a method validated on a very large EEG data set (Hopfengartner et al., 2014), *Clinical Neurophysiology* published an editorial (Jin and Nakasato, 2014) summarising the performance of several of the major studies from the last 20 years (Pauri et al. (1992); Gabor (1998); Wilson et al. (2004); Saab and Gotman (2005); Meier et al. (2008); Kelly et al. (2010); Hartmann et al. (2011); Zandi et al. (2012); Hopfengartner et al. (2014)). Sensitivity varies from 76 to 96% with several of the recent methods showing around 80–90%. The false detection rate was quite high in early methods but appears to settle around 0.2 or 0.3 per hour, or one false detection every 3–5 h. A large recent study (Furbass et al., 2015) with 205 consecutive patients from three epilepsy centers yielded a sensitivity of 81% and a false detection rate of 0.29, or a little more than one false detection every 3 h. This is probably a realistic assessment of the performance that is possible on current methods. The inclusion of multicenter data is important as it reduces the possible bias of a method developed in one center and tested in the same center, even if it is on new data.

The above methods are for scalp EEG and are largely designed for epilepsy monitoring units. A few methods have taken aim specifically at intracerebral EEGs, where the conditions are quite different: there is usually no movement artefact, EMG artefact is minimal, but there are larger variations in background amplitude than in scalp EEG, resulting in more frequent paroxysmal rhythmic activity; also there are more often short discharges at the limit between ictal and interictal activity. For these reasons the performance of these methods is in same range as that of scalp EEG, although it is usually noted that the seizures that are missed are brief. Examples are the methods of Grewal and Gotman (2005) and Zhou et al. (2013).

### 2.4. Patient-specific seizure detection and warning

The purpose of most of the methods described above is to mark sections of EEG where seizures are likely, to facilitate the review of long-term monitoring data. Most methods therefore do not attempt to detect a seizure as soon as it starts, but rather detect it any time during its occurrence. Such methods are therefore not useful as *warning systems* that could warn the patient or an observer that a seizure has just started. To act as a warning system, a detection method must have two characteristics, in addition to high sensitivity: its false alarm rate must be particularly low (frequent false alarms will demotivate the user) and its alarm must occur shortly after seizure onset. These requirements make the problem significantly more complex. One possible solution is to tailor the algorithm to the particular seizure pattern of each patient: if, rather than trying to detect all types of seizure patterns, the system aims to detect only one pattern, it can have much fewer false alarms and make detections early while retaining sufficient sensitivity. The first system using this approach is that of Qu and Gotman (1995), who achieved 100% sensitivity with one false detection every 5 h and an average detection delay of 9.5 s after onset. This method was incorporated in a commercial device. A recent patient-specific detection method using intracerebral EEG (Zheng et al., 2015) shows a sensitivity of 92%, a false alarm rate of 0.17/h (once per 6 h) and a detection delay of 12 s. A critical issue in such patient-specific methods is how much of the patient-specific data has to be learned by the method to reach the stated performance. The more data is available (several seizures, hours of interictal data) the more accurate the detection will be, but also the more burdensome is the implementation of the method.

Early seizure detection can also be considered in the context of responsive stimulation, where a device delivers a stimulus aimed at aborting a seizure. In this context it is critical to detect a seizure very early (within 1 or 2 s if possible). To obtain such a performance, it is necessary to tailor the algorithm to the patient, but it is also necessary to accept a high rate of false detection. Unlike when the algorithm is used to warn the patient, a high false detection rate for a responsive stimulator is acceptable because it only results in a non-necessary, but presumably harmless, stimulus.

### 2.5. Seizure prediction

The next logical step after an early seizure detection system is a seizure prediction system. Much effort has gone into the prediction of seizures. After early encouraging results (Lehnertz and Elger 1998; Martinerie et al., 1998), it became clear that the prob-

lem is more complex than originally thought and in particular its statistical validation requires large amounts of data and careful procedures. It appears that seizures can be predicted in some patients with statistical significance. It is not clear yet if this can have an impact on patients' lives. Reliable seizure prediction could lead to the development of devices based on stimulation or local drug injection that could prevent seizure occurrence. The problem is however a lot more complex because, unlike for seizures themselves, there is no known EEG pattern that occurs systematically *prior* to seizures. Because seizure prediction seems like it could be so useful, considerable effort has gone in the development of seizure prediction methods. Optimism in the late 1990′s and early 2000′s gave way to a more rational and statistically sound approach to the problem, and the realization of its difficulty (Mormann et al., 2007). It is clear today that there is no known well-defined preictal pattern that can allow seizure prediction in a high proportion of patients. It appears that there are minimal changes that are relatively patient-specific, require complex analysis methods and are statistically successful in 50–60% of patients (Gadhoumi et al., 2016). "Statistically successful" means that they can predict seizures better than a random predictor. An important issue that has not been solved is that of the *prediction horizon:* how much time before a seizure is it useful to predict a seizure: should a system tell a patient "you are likely to have a seizure in the upcoming five minutes"? Or should it try to give a warning with a two-hour horizon e.g., ("you are likely to have a seizure sometimes in the next two hours")? These issues have not been settled. One seizure prediction device was actually tested in real life and shown to have significant predictive value (Cook et al., 2013), but this may not have been sufficiently effective and the company that developed it did not continue its operations.

### 2.6. Conclusions and outlook

Seizure detection methods do not teach us much about epilepsy. They only become useful if they are incorporated in a commercial device and used broadly. Even though the first EEG-based seizure detection systems were published more than 30 years ago, there are still many challenges. In the context of the epilepsy monitoring unit, seizure detection algorithms are available on commercial equipment. They perform with approximately 80% sensitivity and a manageable number of false detections and they are useful in some patients. Better general-purpose methods have been published but have not found their way to commercial equipment, which is where they can make a difference in patient evaluations. A patient-specific early seizure detection device has been available on commercial equipment. There has not been any commercial development in the area of wearable EEG-based devices that can detect the onset of seizures and warn patients. A responsive stimulator has been developed, but its seizure detection algorithm is thought to have low specificity. Finally a seizure prediction device was developed and evaluated but has not been commercialized.

## 3. Heart rate-based seizure detection systems

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The majority of seizures are not accurately reported by patients or relatives because of various epilepsy- and seizure-related factors or for other reasons (Hoppe et al., 2007; Blachut et al., 2015). Long term EEG-recordings with or without simultaneous video are the technical gold standard to diagnose epileptic seizures. Automated seizure-detection based on scalp EEG yields a sensitivity of about 90% with variable false positive rates (Previous section; Frangos et al., 2015). Some types of frontal lobe seizures or auras, however, may be missed with scalp EEG, especially those that are associated with ictal activity within deeper brain structures. Furthermore, chronic ambulatory EEG-recordings (e.g. with a limited number of scalp electrodes) may be feasible in a subgroup of patients, but appear intolerable for most of the patients.

Epileptic seizures commonly go along with many different signs including motor symptoms as well as alterations of autonomic cardiorespiratory function. Wearable devices that record such extracerebral signals may thus be an appropriate technology for automated seizure counting. For instance, seizure-related motor signs can be measured with accelerometry or electromyography, whereas ictal sweating can be determined with the help of skin electrodes assessing the electro-dermal activity. Due to the exclusive recording of a selected body signal, the performance of non-EEG based detection devices particularly depend on the seizure semiology and the sensor that is used. A number of ambulatory non-EEG based seizure detection techniques have previously been tested in people with epilepsy with mixed results (van Andel et al., 2015). Importantly, most of the previous studies have used devices and sensors to detect seizures with predominant motor symptoms. Auras and seizures with minor motor signs such as typical temporal lobe seizures are likely to be missed with such devices. Changes in heart rate (HR) were described in many different seizure types, suggesting that HR-measurements may be better suited for automated seizure detection. In this section, we provide an overview on factors that influence seizure-related HR, shortly describe available recording technologies and summarize the performance of HR-based techniques for automated seizure-detection.

### 3.1. Seizure-related HR modulation and its determining factors

Cardiac activity is controlled by cortical and subcortical regions that are part of the central autonomic nervous system including the cingulate gyrus, insula, amygdala, hippocampus, thalamus and hypothalamus. As these areas are often involved in the generation or propagation of epileptic seizures, it is not surprising that a large proportion of epilepsy patients display significant increases of HR in association with seizures. Seizure-related HR increases were reported in 40–100% of the patients and 35–100% of their seizures (Eggleston et al., 2014). This high variability is due to differences in study population and related factors that have an impact on seizure-related HR modulation. In fact, the velocity, magnitude and duration of HR-changes largely depend on a number of physiological and seizure-related conditions. For instance, the relative HR-increase of seizures arising during sleep are greater than of those arising from wakefulness, because the sleep-related predominant activity of the parasympathetic system typically lowers the interictal and pre-ictal HR. Apart from the state of vigilance, the type of epilepsy (e.g. frontal or temporal lobe epilepsy), the localization of seizure-onset as well as the seizure type (e.g. focal seizure with or without impaired consciousness, bilateral convulsive seizures with tonic-clonic elements) have an impact on seizure-related HR modulation. Temporal lobe seizures appear to lead more frequently to increases in HR and to greater and longer lasting HR-changes as compared to seizures arising outside of the temporal lobes (Eggleston et al., 2014). Furthermore, bilateral convulsive seizures with tonic-clonic elements usually lead to greater and longer lasting HR-increase than focal seizures with impaired consciousness (Surges et al., 2010). There are conflicting data on the role of the hemispheric lateralization of seizure-onset, but increasing evidence suggests that e.g. temporal lobe seizures with right-sided onset induce more rapidly HR-changes than temporal lobe-seizures arising from the left hemisphere (Hirsch et al., 2015). In addition, spread of ictal activity to other brain regions rather than seizure-duration is associated with greater increases in HR (Surges

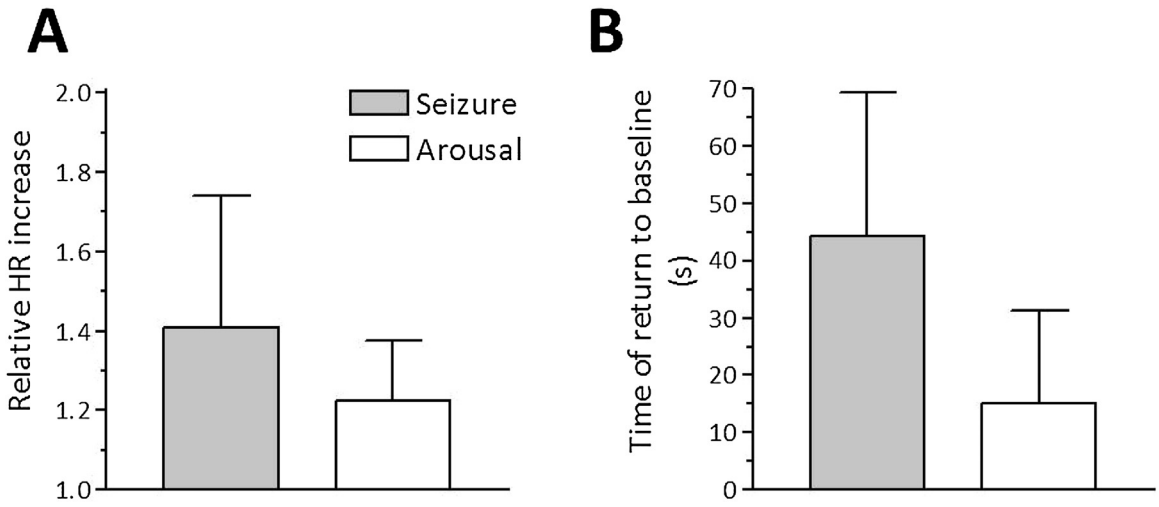


**Fig 1.** Relative HR-changes (A) and time of return to baseline (B) in epileptic seizures versus nocturnal arousals with motor activity. These preliminary data were extracted from 25 seizures (7 focal seizures without and 18 focal seizures with impaired consciousness in 17 patients mostly with temporal lobe epilepsy) and 78 arousal events in 4 patients. Data are given as mean ± SD.

et al., 2013). Importantly, a *decrease* of HR facilitated by seizure-spread to the contralateral hemisphere can occur in up to 1% of the patients (Duplyakov et al., 2014).

Given these modulatory factors, one has also to take into account that seizure-related HR may not be stereotypical in a given patient, but vary from seizure to seizure. Furthermore, transitory HR changes are not specific to epileptic seizures, but occur in many activities of the everyday life such as sports, stair climbing and during sleep. The latter may be particularly important, as nocturnal arousals are frequent and commonly associated with HR-increases that are similar those alterations that are related to nocturnal frontal lobe seizures. Some features, however, may help to distinguish HR-changes due to epileptic seizures from those related to nocturnal arousals with motor activity.

Preliminary results of a study performed at our department suggest that epileptic seizures go along with greater and longer lasting HR-changes than nocturnal arousals with motor activity (Fig. 1), allowing the development of algorithms that can discriminate between seizures and arousals.

### 3.2. ECG-based seizure detection

Studies on ECG-based seizure detection algorithms are scarce. In one study comprising data of 10 patients with severe epilepsy, HR-changes were found in 50 of the 104 seizures with predominant motor signs (van Elmpt et al., 2006). One detection algorithm was tested in 3 of 10 patients with a high inter-individual variability of its performance. The best performance in one patient yielded a sensitivity >90% and a positive predictive value >50%. Another study tested an ECG-based algorithm in 81 seizures of unknown semiology of 241 patients and achieved sensitivities between 86 and 98% with false positive rates between 1.1 and 9.5 per hour (Osorio, 2014).

### 3.3. HR monitoring using photopletysmography

Another widely used technique to monitor HR is the so-called photopletysmography (PPG). This method determines HR by measuring the light absorption by the local tissue (Alian and Shelley, 2014). Photopletysmography sensors contain a light source and a light detector and are usually attached to a finger. As the volume of the local tissue changes with the in- and outflow of blood, the HR can be extracted from the information on light absorption over time. A recent study has tested in 7 patients with epilepsy whether HR can reliably be measured by using a sport-watch equipped with green light PPG (van Andel et al., 2015). Importantly, HR as determined by PPG was not different from that determined by simultaneous ECG. Limits of agreement were greater during wakefulness and during the two seizures that were recorded during the study period, possibly due to motion-artifacts on the ECG traces. These preliminary data suggest that PPG sensors integrated in sport- or smartwatches may be used for HR-based seizure detection, but larger controlled clinical studies are required for further development and validation.

### 3.4. Conclusions and outlook

HR is significantly accelerated in the majority of epileptic seizures. A number of physiological and seizure-related factors have an impact on ictal HR, but greater spread of ictal activity and the seizure type appear to be the most influential ones. An advantage of HR-recordings as compared to detection of other body features (such as movement) is that seizures without predominant motor symptoms can be recognized. However, the major disadvantage of this approach is that HR accelerations are unspecific and do also occur during many everyday life activities. Therefore, more complex algorithms and maybe multimodal detection devices are needed.

HR can be measured by ECG and PPG, but information on HR can also be extracted from videos by analyzing changes of the skin color over time. This particular technique has not been reported in people with epilepsy yet and its usefulness remains to be elucidated in the context of epilepsy.

Importantly, although some of these technologies are already used in commercially available wearables such as fitness trackers, smartwatches and smartphones, their performance with regard to seizure-detection and their clinical utility need to be tested and validated in people with epilepsy.

## 4. Cardiac-based vagus nerve stimulation

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Vagus Nerve Stimulation Therapy (VNS Therapy®; Livanova PLC., London, UK) is the most widely used neurostimulation treatment for drug-resistant epilepsy with well-established improvements in seizure control and quality of life (Morris et al., 2013; Elliott et al., 2011). To further enhance the proven therapeutic effects of traditional VNS a new feature (AutoStim Mode) was developed that leverages the association between HR changes and seizures. Previous studies of patients with concurrently monitored EEG and ECG have shown that increased HR accompanies seizure onset in about 82% of patients with epilepsy, and that, on average, 64% of generalized and 71% of focal onset seizures are accompanied by significant HR increases (Eggleston et al., 2014).

### 4.1. Characteristics of the device

AspireSR® (Model 106; Livanova PLC.) utilizes a proprietary algorithm that delivers stimulation upon detection of pre-specified patterns of HR increases. The AutoStim feature utilizes HR as an input to the detection algorithm. The AspireSR generator and the negative electrode of the bipolar lead act as ECG electrodes for sensing electrical signals produced by the heart. The generator then amplifies and filters these signals, identifies the cardiac R-waves, and calculates the intervals between beats to determine HR. AutoStim mode offers 6 different threshold settings that enable the physician to customize the feature for individual patients (based on degree of ictal HR changes); when a patient's HR increases above the programmed threshold for at least 1 s, stimulation is delivered. The 6 programmable threshold settings are ≥70% above a time-averaged, 5 min baseline HR (least sensitive setting), ≥60%, ≥50%, ≥40%, ≥30%, and ≥20% (most sensitive setting).

### 4.2. Study design

Two prospective studies (E-36 and E-37) were conducted to evaluate the long-term efficacy and safety of the AspireSR® Vagus Nerve Stimulation (VNS) Therapy System featuring Automatic Stimulation Mode (AutoStim) that provides responsive stimulation to HR increases that may be associated with seizure onset.

The E-36 and E-37 trials were prospective, unblinded, multicenter studies, conducted to characterize the safety, performance, and clinical outcomes of the AspireSR VNS Therapy System. The E-36 trial was conducted at 13 sites in the European Union (Boon et al., 2015). The E-37 study was conducted at 10 sites in the United States (Fisher et al., 2015a,b). Both study protocols were approved by applicable regulatory authorities and institutional review boards, and all patients provided informed consent prior to enrollment. ClinicalTrials.gov Identifier: NCT01325623 and NCT01846741, respectively, provide further details. VNS candidates with a history of ictal tachycardia, defined as an increase in HR during a seizure, specifically from a baseline HR to a rate that is greater than 100 bpm and is at least a 55% increase or 35 bpm increase from baseline were included.

Following implant each patient underwent 3–5 days of monitoring in an EMU during which continuous observational video EEG (vEEG) and ECG were recorded. For seizures that were recorded in the EMU, the clinical investigators annotated the seizure type, the onset time, and location of onset (lobe and hemisphere). After discharge from the EMU, Normal Mode and Magnet Mode were activated in combination with AutoStim Mode and patients were evaluated in an outpatient setting for 12 months.

The following objectives and endpoints were evaluated in both the E-36 and E-37 studies: detection algorithm sensitivity, potential false positive rate, latency of seizure detection (i.e., time between seizure onset and detection), seizure duration, and change from baseline in clinical efficacy endpoints, including seizure severity (using the National Hospital Seizure Severity Scale [NHS3] and the Seizure Severity Questionnaire [SSQ]), quality of life (using the Quality of Life in Epilepsy questionnaire, patient-weighted version [QOLIE-31-P]), and seizure frequency.

As of this report date, 50 patients (98%) completed 12 months of follow-up; one patient withdrew prior to completing the 12-month follow-up visit due to an adverse event (AE) of diarrhea and vomiting that was possibly related to VNS Therapy. The patient recovered from the AE, but VNS was permanently programmed 'OFF'.

### 4.3. Statistical analysis

Statistical significance testing and confidence intervals were performed at the 0.05 level with a 2-tailed hypothesis tests. For continuous data, analysis of variance (ANOVA) models and F-tests using PROC GLM were applied for hypothesis testing. For categorical data, the chi-square test evaluated the difference in proportions. All statistical analyses were done using SAS Version 9.3 (SAS Institute, Inc.; Cary, North Carolina).

### 4.4. EMU performance evaluation: sensitivity, potential false positive rates, and latency of detection

Clinical investigators annotated 170 seizures with concurrent vEEG and ECG from 34 patients (67%) during the EMU evaluations. Of these, 28 seizures (17%) met the protocol definition of ictal tachycardia; 69 seizures (41%) were associated with a HR > 100 bpm; and 82 seizures (48%) were associated with a HR ≥ 20% above baseline (representing the lowest threshold of the AspireSR detection capability) (Table 1).

The median latency of detection for all annotated seizures ranged from 5 s after seizure onset to 26 s after seizure onset (at ≥70% and ≥20% thresholds). As expected, increasing the sensitivity of the algorithm generally resulted in earlier detections.

### 4.5. Clinical outcome evaluation: seizure duration, seizure severity, quality of life and responder rates

During the EMU 46 seizures were treated with Automatic Stimulation (i.e. stimulation overlapped seizure duration). Of these, 60.9% (28/46) ended during stimulation, including 87.5% (14/16) focal seizures without impaired awareness, and 47.8% (11/23) focal seizures with impaired awareness. For seizures that ended during stimulation (n = 28 seizures from 14 patients), the closer stimulation was to seizure onset, the shorter the seizure duration. (Fig. 2, R = 0.69), the median time from stimulation onset to seizure end was 20 s. Negative latencies indicate that a pre-ictal rise in HR was detected that was followed by seizure onset as measured from scalp electrodes.

Based on the NHS3 assessment, statistically significant reductions in severity scores for focal seizures with impaired awareness were reported at the end of the EMU (median score reduction: −1.00, $p < 0.001$) up to 12 months of follow-up (median score reduction: −1.33, $p < 0.001$). Improvement in severity scores for focal seizures with impaired awareness was reported in 64.3% (n = 18/28) of patients based on NHS3 (score reduction > 0) during the EMU when only AutoStim Mode was being used, demonstrating the independent contribution of this feature. Similar improvements sustained through 12 months of follow-up with 57.9% (n = 22/38) of patients with focal seizures with impaired awareness exhibiting reduced severity compared to baseline.

Consistent with the reduced severity noted by clinicians using the NHS3, patients reported clinically meaningful improvement across all 6 domains of the SSQ at the 3, 6, and 12

**Table 1**
Modeled Sensitivity, Potential False Positive Rate and Latency, by Magnitude of Tachycardia and Threshold for AutoStim Setting.

| Heart Rate increase from Baseline | Number of Seizures | Threshold for AutoStim Setting | | | | | |
|---|---|---|---|---|---|---|---|
| | | ≥70% | ≥60% | ≥50% | ≥40% | ≥30% | ≥20% |
| ≥70% | 13 | 92.3% | 100% | 100% | 100% | 100% | 100% |
| ≥60% | 18 | | 94.4% | 94.4% | 94.4% | 100% | 100% |
| ≥50% | 30 | | | 90.0% | 96.7% | 100% | 100% |
| ≥40% | 41 | | | | 95.1% | 100% | 100% |
| ≥30% | 63 | | | | | 95.2% | 98.4% |
| ≥20% | 82 | | | | | | 98.8% |
| Potential False Positive Rate (95% CI) [a] [stimulations/hr] | | 0.4 (0.28–0.51) | 0.6 (0.45–0.75) | 1.0 (0.79–1.26) | 1.9 (1.53–2.33) | 3.8 (3.15–4.47) | 7.6 (6.61–8.82) |
| Median Latency of Detection [seconds] | | 26 | 21 | 20.5 | 16 | 11 | 5 |

Table 1 presents the detection sensitivity by magnitude of HR increase using surface ECG recordings from the EMU stay that were processed using a validated software tool. The main diagonal (bolded) shows results for seizure with estimated HR increases that meet or exceed the device threshold HR setting. These sensitivities all exceed 90%. AutoStim settings that are below the threshold expected for seizure detection are shaded gray (e.g. for a ≥50% detection threshold, the HR magnitude categories of ≥40%, ≥30%, and ≥20% are grayed out). Potential false positive rates ranged from 0.4 to 7.6 depending on the AutoStim setting.
*Note*: Gray shading indicates threshold settings that correspond to sub-threshold increases in HR.
[b]Bootstrap confidence intervals using 3000 bootstrap samples.
[a] Potential false positive rate per hour utilized 4516.18 h of monitoring time at each SDA setting.

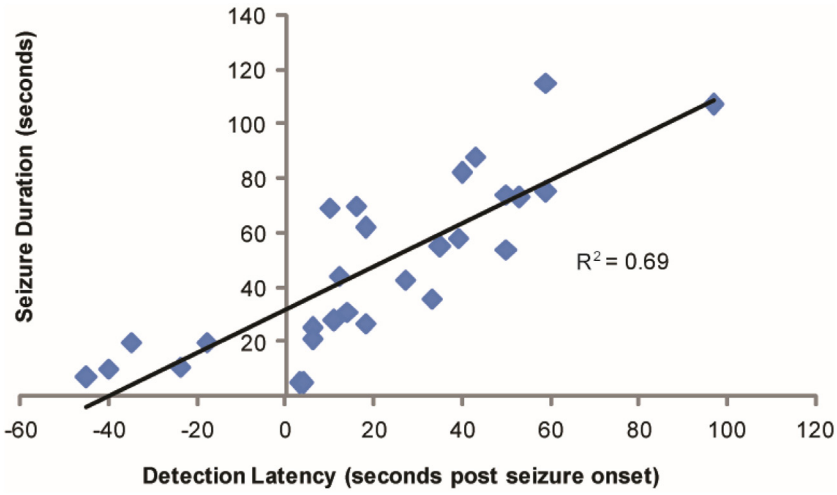


**Fig. 2.** Relationship between Seizure Detection Latency and Seizure Duration, n = 28 seizures.
For seizures that ended during stimulation (28/46 EMU seizures from 14 patients), those stimulated near the annotated onset were correlated with shorter seizure duration.

month follow-up visits. At the 12 month follow-up visit, 51.1% (n = 24/47) of patients showed improvement in the overall QOL final score.

Responder rate was computed and summarized as the proportion of patients who achieved ≥50% reduction in number of seizures compared with baseline. The overall response rate for the ITT population at 3, 6, and 12 months was 22% (n = 11/49; CI: 12%–37%), 26% (n = 13/50; CI: 15%–40%), and 38% (n = 18/47; CI: 25%–54%), respectively.

Interpretation of the above data should take into account the limitations of the study, which include evaluation of a limited sample of patients (n = 51) in an observational setting with no control group.

### 4.6. Safety

Overall, device implant and long term treatment using the AspireSR VNS Therapy generator (including the Automatic Stimulation Mode feature) were well-tolerated, did not produce any unanticipated adverse device effects, and no deaths were reported in either study.

### 4.7. Comparison with previous studies

Overall, these results compare favorably with those reported in the literature, and most notably with the E-04 study (Morris, 2003) in which 23.3% of seizures were reported as having ceased upon Magnet Mode use. Fisher et al. (2015a,b) report that 7 studies indicate 28.5% of patients are able to benefit from terminating seizures using Magnet Mode stimulation. In the E-36 and E-37 studies, 70% of patients (14 of 20 patients) who had seizures treated with AutoStim during the EMU stay had seizure cessation during stimulation, which is a higher proportion compared to the proportion reported in the literature.

In the present study, improvement in severity scores for focal seizures with impaired awareness was reported in 64.3% (n = 18/28) of patients based on NHS3 (score reduction > 0) during the EMU when only AutoStim Mode was being used, with similar improvements through 12 months of follow up (57.9%; n = 22/38).

Patients enrolled in the E-36 and E-37 trial showed improvements that were more pronounced (mean change from baseline in overall quality of life: 14.2) than for the currently approved VNS Therapy. Improvements in overall quality of life reported in our

study were, however, consistent with results reported following surgical therapy for drug-resistant temporal lobe epilepsy reported in two separate trials (mean change from baseline in overall quality of life (QOLIE-89) (Engel et al., 2012).

With respect to safety, the results of these studies indicate that the AspireSR with the AutoStim feature has a similar safety profile to the earlier model VNS Therapy Systems. The most commonly reported AEs occurred at rates consistent with previous reports.

### 4.8. Conclusions

The ability to intervene rapidly and repeatedly at the onset of a seizure may provide a clinically meaningful benefit, which is unique to a device-based approach which responds to ictal biomarkers. Delivering stimulation automatically at the time of seizure onset may have a positive influence on seizure severity and/or seizure duration. Automatically delivering stimulation upon detection of increases in HR that may be associated with seizure onset offers a potential solution for patients who are unable to use the magnet effectively (Dionisio and Tatum, 2010).

### 4.9. Acknowledgements

The authors gratefully acknowledge the E-36 and E-37 study group. This study was sponsored by Livanova, Inc.

## 5. Responsive deep brain stimulation

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### 5.1. Introduction and rationale for development

Since the US FDA approval in 1997 for the treatment of essential and Parkinsonian tremor, deep brain stimulation has become a promising therapeutic alternative for patients with various other neurological disorders, epilepsy (Morrell, 2011), and chronic pain (Kumar et al., 2008). It is also being investigated for several other disorders.

The stimulation paradigms currently used in patients with epilepsy are either continuous (or intermittent, such as in VNS) or responsive (as with responsive neurostimulation devices). The optimal paradigm for the latter methods requires the anticipation of when a seizure may appear, in order to stimulate before the paroxysm materializes so that the stimulation perturbs the transition to the seizure.

Support for the possible success of electrical perturbations in preventing seizures is based on the assumption that if the dynamics of the abnormal synchrony that characterizes paroxysms is perturbed by stimulations so that the ictal phase may not appear, or will be forced to stop if already initiated.

Contrary to the current deep brain or VNS stimulation paradigms that use intermittent (continuous) stimulation, we sought to stimulate when a paroxysm is about to occur, using an on-demand feedback stimulation paradigm based on real-time analysis of brain signals that detects a precursor of paroxysms, and implements a brief (5 s) stimulation to stop transition to the ictal event.

Our work is built on past studies that have indicated that precisely timed low-frequency electrical pulses (0.5 Hz) can stop transition to paroxysms in vitro (Khosravani et al., 2003), as well as observations of reduction of paroxysms by low-frequency stimulation in vivo in rodents (1 Hz, 5 Hz) and in patients (0.5 Hz, 1 Hz, 5 Hz (Tergau et al., 1999; Child et al., 2014; Koubeissi et al., 2013)). We chose to briefly (5 s) stimulate in the time window preceding a possible paroxysm with low frequency (5 Hz) periodic pulses employing rat models of seizures considered to reproduce features of human intractable temporal lobe epilepsy.

The stimulation current was chosen according to safety considerations, which was three times lower than the maximum deliverable charge per phase (Shannon, 1992). This report summarises key findings previously reported by us (Salam et al., 2015) and expands on the mechanisms of action of the proposed neurostimulation therapy based on early seizure detection.

### 5.2. Mechanisms of action

Regarding possible mechanisms of the decrease in synchrony before ictal events and of the stimulation success preventing seizure generation, we offer two perspectives.

From a neurophysiological view, localized populations of cells start to become synchronous heralding the large and widespread synchrony that represents the ictal event; because each local neighborhood cells' activity become synchronous at different frequencies, then when recording from two distant areas a desynchronization between these two sites will be detected. Stimulation right at the moment when the entrainment is occurring perturbs the transition to the widespread synchrony, and therefore this is a reason why there is a need for a feedback, or closed-loop, stimulation protocol.

From a theoretical perspective, the seizure is considered to represent a dynamic bifurcation (Perez Velazquez et al., 2003). At the critical point when bifurcation is about to occur, the system is more sensitive to perturbations, which is perhaps the reason why our relatively "weak" stimulation perturbs the dynamics and prevent the transition towards the new dynamic status manifesting as a seizure.

### 5.3. Animals and seizure models

Fifty-eight male Wistar rats (275–400 g) were included in the study but, of these, 39 could not be used for the stimulation experiments because six died during induction of status epilepticus; 12 lost their electrode head-caps; 19 did not show spontaneous seizures in the hours or weeks after kainic acid (KA) or 4-aminopyridine (4-AP) injection; and two had the equivalent of sudden unexpected death in epilepsy (SUDEP). Manipulations of the rats were performed according to the protocols approved (protocol no. 1000008867) by the Animal Care Committee of the Hospital for Sick Children (Toronto, Canada) according to the Canadian Guidelines for Animal Care. Two well-characterized rodent seizure models were used to reproduce some features of human temporal lobe epilepsy. The seizure induction procedures of the two models are described below.

Chronic condition: KA (13 mg/kg dissolved in saline) was injected intraperitoneally in 46 rats to induce temporal lobe paroxysms. One month to 2 months after the injection, recurrent spontaneous convulsive and nonconvulsive paroxysms developed in 11 rats, which were used for the chronic condition experiments.

Acute condition: 4-AP (300–500 nmol, dissolved in????) was injected in 12 rats through an implanted cannula into the right hippocampus. Following the injection, eight rats had spontaneous recurrent electrographic seizures for at least 2 h and were used in the experiments.

### 5.4. Intracerebral recordings and signal processing

All convulsive motor seizures (475) were recorded behaviorally with video monitoring, whereas 84% (399 of 475) of the convulsive and all nonconvulsive seizures (199) were recorded electrographically using commercial and/or custom-made low-noise amplifiers.

The intracerebral bipolar recordings from both hippocampi were recorded by the feedback stimulator and sent to a computer

for real-time phase synchrony analysis using a MATLAB-based custom-made algorithm. Initially, the recordings were band-pass filtered with cutoff frequencies of F ± 2 Hz, where F is a central frequency. The phase synchrony was investigated at central frequency of 8 Hz and the averaged phase synchrony index values throughout a 1 s time window. The phase synchrony index is defined as $R = |\langle e^{i\Delta\theta} \rangle|$, where $\Delta\theta$ is the phase difference between the two hippocampal recordings (Perez Velazquez et al., 2011).

Our feedback stimulator is a custom-made device, which has 256 recording channels, 64 stimulation channels, and a build-in signal processor (Bagheri et al., 2013). The amplifier in each recording channel has a mid-band gain programmable from 54 dB to 72 dB, programmable bandwidth of 0.1 Hz–5 kHz with 7.99 $\mu V_{rms}$ input-referred noise.

All rats with seizures were divided randomly into two groups: (1) non-stimulation group and (2) stimulation group. In the non-stimulation group (five rats in the chronic experiment and four in the acute experiment), seizures were monitored and marked, and the seizure frequency per hour was determined. The stimulation group went through four experimental phases for the evaluation of the efficacy of the feedback stimulation:

- In phase I, seizures were monitored and marked;
- in phase-II, the feedback stimulator was turned on to trigger the electrical stimulation upon an electrographic seizure precursor detection. The number of feedback stimulations per day in the stimulation group was quantified and used in phase IV.
- in phase III, the feedback stimulation was turned off.
- in phase IV, an open-loop stimulation paradigm was implemented using the same average number of stimulations per day as in phase II, but in a periodic manner (equal intervals), thus not associated with the detection of the seizure precursor. This phase served as a control for the specificity of the feedback stimulation.

During these four phases, all paroxysms were monitored, classified, and the frequency per day determined.

### 5.5. Results

A total of 598 paroxysms were recorded electrographically in 19 rats. Our strategy was to implement the feedback stimulation upon a seizure precursor detection based on changes in synchrony between the two hippocampal signals; therefore, the phase synchrony index (R) was initially assessed to determine the detection performance.

Our experiments show that the R index fluctuates between 0.2 and 0.7 during the interictal period. However, it drops below 0.1 during the preictal period, and gradually increases subsequently above 0.8 during the paroxysm. The phase desynchronization ($R < 0.1$) was observed before the paroxysm onset in all rats ($n = 19$) in both the chronic and acute conditions. For this reason, we refer to this drop in synchrony as the seizure precursor in the rest of the text. The paroxysm detection threshold was consistent for all animals; therefore, no optimization was required. This threshold was used in the feedback system to trigger a stimulation.

In the chronic condition, the paroxysm detection performance was evaluated online and offline (reevaluated) in the non-stimulation group and during the no-stimulation phases of the stimulation group. The phase synchronization analysis detected 95% (351 of 369) of the convulsive paroxysms and 66% (83 of 125) of the non-convulsive paroxysms, with 0.67 ± 0.59 false alarms per day. The overall sensitivity and specificity of the detection were 88% and 86%, respectively. The average early paroxysm detection time was 53.64 ± 13.64 s.

In the acute condition, the paroxysm detection performance was similarly evaluated online and offline in the non-stimulation group. The phase synchronization analysis detected 90% (27 of 30) of the convulsive paroxysms and 79% (59 of 74) of nonconvulsive paroxysms. The overall sensitivity and specificity of the detection were 84% and 94%, respectively; with 0.47 ± 0.20 false alarms per hour. The average early paroxysm detection time was 21.50 ± 11.50 s.

In the chronic condition, the seizure frequency in the stimulation group was 5.39 paroxysms per day in phase I (no-stimulation baseline). In phase II, the feedback stimulation delivered to the hippocampus after the detection of the precursor, resulted in five of the six rats in the stimulation group becoming convulsive paroxysm free, and a 93% reduction of seizure frequency in the sixth rat. Following the feedback stimulation phase, the rats underwent a no-stimulation phase III, which resulted in the average seizure rate going back to that of phase I. In phase IV, an open-loop stimulation was delivered. The open loop stimulation reduced the paroxysm frequencies found in phase I and phase III by 32% and 19%, respectively. Thus, we conclude that our feedback stimulation significantly reduced paroxysmal activity due to the precise timing of stimulation triggered by the seizure precursor detector.

In the acute condition, the average number of paroxysms in the non-stimulation group was quantified in 30 min periods. The stimulation group, which received the feedback stimulation right after the detection of the seizure precursor, had a reduced 81% paroxysm frequency compared to the non-stimulation group ($p < 0.05$).

### 5.6. Planned studies

For the next generation of our feedback neurostimulator device, we have integrated the signal processing block into the hardware (Kassiri et al., 2016). This results in significant improvement in seizure detection latency without sacrificing the accuracy. The device will be tested in an acute in-vivo experiment on rats with temporal lobe epilepsy, and our plan ultimately is to test its efficacy in patients with epilepsy.

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