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RESEARCH ARTICLE

Novel Features to Capture Temporal Variations of Rhythmic Limb Movement to Distinguish Convulsive Epileptic and Psychogenic Non-epileptic Seizures

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SUMMARY AND KEY WORDS

Objective: Investigate the characteristics of motor manifestation during convulsive epileptic and psychogenic non-epileptic seizures (PNES), captured using a wrist-worn accelerometer (ACM) device. The main goal was to find quantitative ACM features that can differentiate between convulsive epileptic and convulsive PNES.

Methods: In this study, motor data was recorded using wrist-worn ACM-based devices. A total of 83 clinical events were recorded: 39 generalized tonic-clonic seizures (GTCS) from 12 patients with epilepsy, and 44 convulsive PNES from 7 patients (1 patient had both GTCS and PNES). The temporal variations in the ACM traces corresponding to 39 GTCS and 44 convulsive PNES events were extracted using Poincaré maps. Two new indices: tonic index (*TI*) and dispersion decay index (*DDI*) were used to quantify the Poincaré-derived temporal variations for every GTCS and convulsive PNES event.

Results: The *TI* and *DDI* of Poincaré-derived temporal variations for GTCS events were higher in comparison to convulsive PNES events ($p < 0.001$). The onset and the subsiding patterns captured by *TI* and *DDI* differentiated between epileptic and convulsive non-epileptic seizures. An automated classifier built This article is protected by copyright. All rights reserved

using *TI* and *DDI* of Poincaré-derived temporal variations could correctly differentiate 42 (sensitivity: 95.45%) of 44 convulsive PNES events and 37 (specificity: 94.87%) of 39 GTCS events. A blinded review of the Poincaré-derived temporal variations in GTCS and convulsive PNES by epileptologists differentiated 26 (sensitivity: 70.27%) of 44 PNES events and 33 (specificity: 86.84%) of 39 GTCS events correctly.

Significance: In addition to quantifying the motor manifestation mechanism of GTCS and convulsive PNES, the proposed approach also has a diagnostic significance. The new ACM features incorporate clinical characteristics of GTCS and PNES thus, providing an accurate, low-cost and practical alternative for differential diagnosis of PNES.

Key Words: Accelerometer (ACM), Convulsive seizures, Psychogenic non-epileptic seizures, Differential diagnosis, ACM features.

INTRODUCTION

Psychogenic non-epileptic seizures (PNES) are sporadic paroxysmal events that are accompanied by an apparent change in state of consciousness or behaviour without any epileptiform activity in the brain, where the aetiology is believed to be primarily psychological¹. There is no accepted pathophysiologically defined mechanism for PNES however, PNES events are found to have an association with sporadic attacks resulting from autonomic malfunction linked to major psychosocial distress². PNES are involuntary, and can be associated with random movements, sensory, and mental manifestations resembling generalized epileptic tonic-clonic seizures (GTCS)³, and are often misdiagnosed as such⁴.

Although a number of clinical features such as: postictal serum prolactin, postictal confusion, eye-widening, and seizure duration among others have been proposed to assist with diagnostically distinguishing PNES from epileptic GTCS, the sensitivity and specificity of these features is insufficient to establish a definitive diagnosis in many cases^{5,6}. Moreover, patients with PNES are often diagnosed with concurrent epileptic seizures, which indicates that out-patient diagnosis of PNES is difficult^{7,8}. Mismanagement and delayed diagnosis of PNES increases the risk of morbidity and mortality due to intubation from prolonged seizures^{9,10}.

Definitive diagnosis of PNES currently requires long-term video-electroencephalography monitoring (VEM). However, VEM is a highly resource intensive procedure incurring significant healthcare cost¹¹. In addition, VEM can be susceptible to artifacts in electroencephalography (EEG) recording that can render the study nondiagnostic⁷. Despite the limitations, VEM remains the gold standard and a cost-effective approach for diagnosing PNES as individuals with timely intervention

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and correct diagnosis of PNES are shown to have a better treatment outcome¹². A mean delay of 5.2 years was reported until the correct diagnosis of PNES¹, indicating the short-comings and unsatisfactory nature of current diagnostic procedures.

Accelerometers (ACM) have been shown as an effective tool for detection of convulsive seizures especially, GTCS¹³. In our previous work¹⁴, we showed that ACM can be reliably used for detection of convulsive PNES events. However, differentiation of convulsive PNES and GTCS requires identification of unique features that can distinguish epileptic and non-epileptic motor activity. Previously, approaches based on time-frequency mapping of the rhythmic motor activity have been employed to differentiate GTCS from convulsive PNES^{15,16}. The classical frequency and time-frequency based analysis are suitable for capturing variability, the existence of periodicity and the frequency foot-print of a time-varying signal; however, to discover complex patterns such as quasi-periodic or chaotic motion, more sophisticated signal processing techniques are required¹⁷. Poincaré map is a technique to capture complex patterns in time-varying signals¹⁸. It has been extensively used in the analysis of cardiac signals and is central to the field of heart rate variability analysis^{19,20}. In addition, it can also describe non-linear dynamics of short length signals¹⁴. Therefore, we hypothesize that use of Poincaré maps will provide better insight about the motor manifestation characteristics of different seizure events (GTCS and PNES).

In this study, we propose new quantitative ACM features based on Poincaré-derived temporal variations in rhythmic limb movement during seizures. To our best knowledge, no study on quantification of temporal dynamics of limb movements during GTCS and convulsive PNES has been published. This study investigates: (1) quantitative ACM features that can differentiate GTCS and convulsive PNES; and (2) the relevance and clinical utility of a wearable ACM-based device in differential diagnosis of convulsive PNES.

METHODS

A. Participants and Data Acquisition

In a study spanned over 2012 – 2015 a total of 79 patients undergoing VEM at the Comprehensive Epilepsy Unit of the Royal Melbourne Hospital were recruited in the study. Patients were assessed based on the history and description of the seizures. Inclusion criteria was the patient having a history of seizures that mimics generalized seizures, or are characterized by the presence of bilateral convulsions. Patients having intracranial monitoring or suffering from psychiatric disorder such that it prevents informed consent were excluded. The study was performed in accordance with the Declaration of Helsinki and was approved by the Melbourne Health, Human Research Ethics Committee (HREC Project 300:259). The patients were recruited for the

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complete duration of VEM, which lasted at least 3 days. A wireless device with a built-in microelectromechanical systems (MEMS)²¹ ACM sensor was strapped on the wrists of the recruited patients. The data packets were sampled at a rate of 50Hz. Movement data recorded in three axes with a time stamp was saved on the flash memory of the device and was later extracted for offline processing.

B. Diagnosis of PNES versus GTCS

The diagnosis of PNES or epileptic GTCS for all recorded convulsive events was determined at a consensus meeting of 2 – 6 epileptologists where a decision was made based on the clinical history, neurosychiatric evaluation, neuroimaging studies, video-EEG and observed seizure semiology as previously reported¹. A convulsive movement was defined by simultaneous clonic or other rhythmic motor manifestation of limb(s) that lasted at least 10 s. Low amplitude tremors, intermittent jerking (e.g. behavioral sleep movements), and events with only mild to moderate movements were classified as non-convulsive. This consensus classification of the seizures by epileptologists was considered as the “gold standard”. This classification was made blinded to the accelerometer traces.

C. Extraction of Temporal Variations in Limb Movement Patterns

Time stamped ACM traces corresponding to seizure events were used to extract the resultant ACM signal r ($r = \sqrt{a_x^2 + a_y^2 + a_z^2}$). The resultant signal was then filtered to remove the effect of static gravity and frequencies above 25Hz. The cut-off frequency is chosen empirically, based on the analysis of rhythmic artifacts as seen on EEG. The temporal variations are then extracted from the resultant ACM signal.

The Poincaré map is a geometrical representation of the time series data, obtained by plotting each sequence in a series against the following interval^{18,19,20}. It can be used to extract rhythmic and chaotic patterns as well as temporal variations of a time series data¹⁸. A Poincaré map can be quantified using standard descriptors like $SD1$ and $SD2$ (equations (1) and (2)). $SD1$ captures the short-term variability or high frequency changes in a time-varying signal. By contrast, $SD2$ captures long-term variations or low frequency changes.

$$SD1^2 = \frac{1}{2}Var(r(n) - r(n + 1)) \quad (1)$$

$$SD2^2 = \frac{1}{2}Var(r(n) + r(n + 1) - 2\bar{r}) \quad (2)$$

Where, Var is the variance, $r(n)$ denotes the resultant ACM time series $n \in [1 \dots N]$, $r(n + 1)$ represents the sequence at $lag = 1$, and $\bar{r} = E[r(n)]$. For a discrete time signal, $lag = 1$ represents a time delay of $1/F_s$ (s) where, F_s is the sampling frequency.

In addition, multiple parameters can be extracted from a Poincaré map. Parameters like ratio ($\frac{SD1}{SD2}$) and area ($4 * \pi * SD1 * SD2$) obtained using the standard Poincaré descriptors capture the non-linear dynamics of a non-stationary time sequence¹⁹. The Poincaré-derived temporal variations can be estimated by analyzing the progression of different Poincaré descriptors over the course of an event. As events can have varied durations, the temporal progression of the Poincaré descriptors can only be compared across events if they have a uniform duration on the time axis. Therefore, all the events were re-sampled using cubic splines to a uniform length of 60 s. The events re-sampling does not alter the frequency content of the signal and the temporal patterns in the ACM signal are restored.

The resultant ACM signal corresponding to the re-sampled event was analyzed in time epochs of 2.56 s with 50% overlap resulting in a total of 45 epochs (Figure 1 A and B). Poincaré maps were obtained for every epoch resulting in a graphical representation of every sequence as a function of the previous one (Figure 1 C and Figure 1 D). Descriptors capturing both linear (SD1 and SD2) and non-linear dynamics (ratio and area) were computed from each Poincaré map (Figure 1 E, F, G, and H).

Figure 1: Protocol for analysis of temporal variations: column one shows a GTCS and column two shows a PNES event; In each column (A) is raw signal, (B) shows the signal after re-sampling to 60 s. The re-sampled signal is analyzed in 2.56 s epochs with 50% overlap, and a total of 45 epochs are obtained by this windowing procedure. The epochs are shown by colored blocks of 2.56 s; (C) shows 2.56 s accelerometer epochs (resultant signal) during start (1.28 – 3.78 s), during (30.72 – 33.22 s), and at the end of an event (56.32 – 58.82 s); (D) shows the Poincaré maps corresponding to each 2.56 s epoch; (E), (F), (G), and (H) shows temporal evolution of extracted Poincaré features in windows of 2.56 s over the course of an event, and (I) shows the division of an event into quartiles where, the first quartile division (block in red) represents the temporal variations during onset while, the last quartile division (block in purple) represents the subsiding behavior, and the region (block in green) between first and third quartile represents the transition from onset to subsiding period.

D. Protocol for Analysis of Temporal Variations

Events with uniform length of 60 s were segmented into quartiles. This allowed us to study the temporal variability in Poincaré descriptors across the different phases (onset, transition, and subsiding) of an event.

E. Quantification of Temporal Variability

To quantify the tonic-phase in an event we introduce a new parameter in this work, which is

termed as tonic index (TI) of an event. Whereas, to capture the subsiding nature of an event we introduce another parameter that is termed as dispersion decay index (DDI). Both, the indices are described herewith:

- a. TI: The TI can be described as the ratio of the coefficient of variation (CoV) of the descriptors in first quartile (onset) to CoV of the descriptor over rest of the signal.

The onset of a GTCS event involves increased muscle tone, represented by stiffening limb movements that manifest as long-term variations, resulting in high SD2 and low SD1. However, as the muscle tone decreases, high-frequency clonic jerking begins, which involves more short-term changes, resulting in low SD2 and high SD1. Therefore, the quotient of the covariance of the computed features captures the variations during the onset relative to rest of the seizure. The TI can be explained as shown in (3).

$$TI_D = \frac{CoV(\{D_{k1}\})}{CoV(\{D_{k2}\})} \quad (3)$$

where, $CoV = \left(\frac{\text{standard deviation}[SD]}{\text{mean}} \right) * 100$, $\{D\}$ represents a discrete time series for D^{th} descriptor (SD1, SD2, ratio, and area), $\lfloor 1 \leq k1 \leq N/4 \rfloor$, $\lfloor N/4+1 \leq k2 \leq N \rfloor$ and $N=45$ is the total number of 2.56 s windows (50% overlap) for an event of duration 60 s.

- b. DDI: The DDI measures the relative change in dispersion or randomness as an event subsides. DDI captures the variance or randomness of an event in first three quartiles relative to the last quartile.

The high frequency clonic jerks in a GTCS event can be characterized by an increased dispersion of the ACM traces. However, the frequency of the jerks subsides as the event progresses towards termination, which results in a lower dispersion in the last quartile. A high variance of the computed features represents increased dispersion and a chaotic motion. Therefore, the quotient of the variance of the two intervals captures the change in dispersion as an event subsides.

The DDI can be described as shown in (4)

$$DDI_D = \frac{Var(\{D_{k1}\})}{Var(\{D_{k2}\})} \quad (4)$$

where, $\{D\}$ represents a discrete time series for D^{th} descriptor (SD1, SD2, ratio, and area), $\lfloor 1 \leq k1 \leq 3*N/4 \rfloor$, $\lfloor 3*N/4+1 \leq k2 \leq N \rfloor$ and $N=45$ is the total number of 2.56 s windows (50% overlap) for an event of duration 60 s.

F. Statistical Analysis

The statistical analysis includes the two-sided non-parametric Mann-Whitney U test to compare the mean TI and DDI values for GTCS and convulsive PNES events. Statistical significance was considered for $p < 0.001$, and the area under the receiver operating characteristic (ROC) curve

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(AUC) was used to evaluate the classification performance²². All statistical analysis was performed using Matlab2015b (MathWorks, Natick, MA, U.S.A.).

G. Statistical Machine Learning: Development of automated classifiers

The next step was to build an automated classifier using the new ACM features. A Support Vector Machine (SVM)²³ classifier was trained using the TI and DDI of all Poincaré descriptors. We performed a leave-one-patient-out validation, where SVM was trained using data from N-1 patients (N = 18), and the learned classification model was then used to classify the events of the left-out patient. The classification performance was measured in terms of PNES detection sensitivity, specificity, positive predictive value (PPV), classification accuracy, and Fscore. For full description of the classification algorithm refer to Data S1.

H. Blinded Review

To validate the clinical usefulness and potential of the proposed ACM features, a blinded review was conducted by presenting the temporal evolution of the extracted Poincaré descriptors (Figure 1 E, F, G, and H) to two certified clinical neurologists (Co-authors B. Yan and T.J O'Brien). The neurologists were required to label the events as either GTCS or convulsive PNES, or term the event as non-diagnostic (the consensus decision was registered). During the whole exercise, the neurologists were blinded to the ground truth (VEM diagnosis) and all other neurophysiologic data.

RESULTS

A. Seizure Data Collected with ACM Device

Out of the 79 recruited patients, 35 (44.3%) had seizures among which 20 (25.3%) patients had convulsive seizures and 15 (18.9%) patients had non-convulsive seizures. Out of 20 patients with convulsive seizures 11 (55%) had GTCS events, 6 (30%) had PNES events, 1 had complex partial seizures (CPS), 1 had multiple types of seizures (GTCS+CPS), and 1 patients had comorbid epilepsy (PNES+GTCS). The seizure cohort comprised of 60% females and the mean participant age was 31.6 years (20 – 38.2, median 29). The demographics of the seizure cohort are shown in Table S1. A total of 83 events were recorded during the monitoring period, which included 39 (46.9%) GTCS from 12 (15.2%) patients and 44 (53%) convulsive PNES events from 7 (8.8%) of 79 patients (Table S1).

B. Motor Manifestation of GTCS and Convulsive PNES

A GTCS event has a clearly defined motor symptomatology as seen on VEM: tonic phase followed by a clonic phase (Figure 2); however, seizures are heterogeneous therefore, a clear distinction between phases may always not be possible. Nonetheless, the motor symptomatology of every GTCS event can be defined using a combination of different phases (Figure 2). The motor manifestation of a GTCS event can

be characterized by an onset that involves stiffening movements due to increased muscle tone accompanied with irregular and asymmetric jerking (Figure 3 A), followed by tremulousness that translates into clonic activity before subsiding gradually where the movement activity was interrupted by silent periods (shown by (*) in Figure 3 A). In contrast, 35 (79.5%) of 44 recorded PNES events had overlapping phases (Figure 3 B) while, 9 (20.5%) events had a clonic phase that was separable from the tonic-phase in the ACM recordings (Figure 3 C). The PNES events with separable phases involved quasi-repetitive movements that had multiple silent periods over the course of the event (Figure 3 C). Therefore, the motor manifestation of GTCS and convulsive PNES shows distinct temporal dynamics.

Figure 2: *Clinically defined phases of a GTCS event with progression in the direction of the arrow; any GTCS event can be defined using a combination of these phases. The intensity of motor activity increases in the direction of the arrow; and the first three phases characterize the onset of a GTCS event.*

Figure 3: *ACM traces of a typical: (A) GTCS event with demarcations highlighting onset, tremulousness + clonic, and subsiding behavior. The asterisk (*) shows the silent periods as the event terminates. (B) Convulsive PNES event where the tonic and the clonic phase are not separable. The envelope of the event is continuously waxing and wanning over the course of an event. (C) A convulsive PNES event stereotypical of a clonus activity; note the presence of multiple silent periods over the course of the event. The X, Y, and Z represents the ACM traces across the three Cartesian co-ordinates.*

C. Tonic Index (TI)

The TI of SD1 was significantly higher for GTCS (1.04 - 2.60; median 1.65) as compared to convulsive PNES (0.24 - 1.33; median 0.66) (Figure 4a). The TI of SD1 resulted in an area under the ROC curve (AUC) of 0.95 (Table I). This shows that a good class separation can be achieved using TI of SD1. Similarly, the TI of SD2 was significantly higher for GTCS (0.83 - 3.64; median 1.70) in comparison to convulsive PNES (0.21 - 1.43; median 0.80) (Figure 4a). An AUC value of 0.91 could be achieved using TI of SD2 (Table I). Further, the TI of area was also significantly higher for GTCS (1.04 - 2.99; median 1.68) in comparison to convulsive PNES (0.27 - 1.34; median 0.81) (Figure 4a) and showed an AUC value of 0.94 (Table I). In contrast, the TI of ratio was found to have a much lower AUC value of 0.78 while, having a significant difference between GTCS (0.46 - 2.40; median 1.05) and convulsive PNES (0.29 - 1.29; median 0.69) (Figure 4a). The TI performs well for all the descriptors except ratio, and the

TI of SD1 showed best class separation between GTCS and convulsive PNES with an AUC value of 0.95 (Table I).

Figure 4: (A) The TI, and (B) DDI for descriptors SD1, SD2, ratio, and area shown as box and whisker plots for GTCS and convulsive PNES events.

D. Dispersion Decay Index (DDI)

The DDI of SD1 was significantly different for GTCS (0.87 – 4.57; median 1.56) and convulsive PNES (0.46 – 2.57; median 1.05) (Figure 4b) events with an area under the ROC curve of 0.76. Similarly, the DDI of SD2 was significantly higher for GTCS (0.67 – 3.23; median 1.86) in comparison to convulsive PNES (0.41 – 2.90; median 0.94) (Figure 4b). However, the area under the ROC curve for DDI of SD2 (AUC 0.80) was slightly higher than DDI of SD1 (AUC 0.76) (Table I). Similarly, the difference in DDI of area was also statistically significant for GTCS (0.53 – 7.22; median 1.64) and convulsive PNES (0.33 – 3.22; median 0.98) however, a considerable class overlap was seen using DDI of area (AUC 0.72) (Figure 4b). In contrast, the DDI of ratio showed a better class separation (AUC 0.88) (Table I). The DDI of ratio was significantly higher for GTCS (0.92 – 2.87; median 1.79) in comparison to convulsive PNES (0.64 – 1.53; median 0.92) (Figure 4b). Thus, it can be seen that the DDI of ratio shows the highest class separation between GTCS and convulsive PNES, which suggests that ratio is the most efficient Poincaré' descriptor to capture dispersion or randomness in movement of limbs as an event subsides.

E. Automated Classifier

Using TI and DDI of all descriptors (total 8 features as shown in Table I), a classification model was built using SVM (refer to Data S1 for full description of algorithm). The machine learning model correctly classified seizure like events as PNES in 42 (sensitivity: 95.5%) of 44 PNES events and being as GTCS in 37 (specificity: 94.9%) of 39 GTCS events, while the PPV and Fscore were both 95.5%, respectively (Table II).

F. Blinded Review

Based on the temporal dynamics of GTCS and convulsive PNES the following criterion were defined for differentiating GTCS and PNES: the Poincaré' derived temporal variations (SD1, SD2, ratio, and area) in GTCS events demonstrate a continuously evolving nature. In contrast, the Poincaré' derived temporal variations in PNES events were relatively stable over the course of a convulsive PNES event (right sub-column Figure 1 E, F, G, and H). In the blinded analysis, the epileptologists correctly classified 26 of 37 events as PNES (sensitivity: 70.3%) and 33 of 38 as GTCS (specificity: 86.8%); while 1 GTCS and 7 PNES events were classified as non-diagnostic.

DISCUSSION

Seizures have heterogeneous manifestation and exhibit considerable intra- and inter- patient variability. Given the variability across events, trained personnel with considerable experience are required for a confirmed diagnosis. In this study, we present a novel method for differential diagnosis of convulsive PNES based on the rhythmic limb movement patterns captured using a wrist-worn ACM device. Novel ACM features to quantify the temporal variations in limb movement during seizures were proposed: (1) TI; and (2) DDI.

A. Performance of TI

TI captures the mean normalized variability during onset of an event relative to rest of the event. The onset of a GTCS event has a defined organic pathway and can be captured using a wrist-worn ACM-based device (Figure 3). The Poincaré'-derived temporal variations showed a specific evolution in time throughout the course of a GTCS event: a gradual onset that peaks during the tonic phase (left sub-column Figure 1 E, F, and H). This pattern was not observed during convulsive PNES events (right sub-column Figure 1 E, F, and H). Therefore, the TI of Poincaré'-derived temporal variations for GTCS events were higher in comparison to PNES events (Figure 4 A, $p < 0.001$). Among all the Poincaré'-derived descriptors, TI_{SD1} , TI_{SD2} , and TI_{area} showed a high class separation between GTCS and convulsive PNES (Table I). The descriptors SD1, SD2, and *area* showed a continuously evolving pattern including a prominent onset for GTCS events while, the descriptors were comparatively stable or had less variability over the course of a convulsive PNES event (Figure 1 E, F, and H). Therefore, the TI of descriptors (SD1, SD2, and *area*) showed the best discriminative ability for GTCS and convulsive PNES. On the other hand, both GTCS and convulsive PNES events showed a continuously evolving pattern for *ratio* (Figure 1 G); therefore, the TI of *ratio* showed the least discriminative ability.

B. Performance of DDI

While TI captures the temporal variations during the onset, the DDI captures the subsiding pattern of an event. DDI measures the variance in two-third of the signal relative to the last quartile. GTCS events involve a clonic phase that follows the tonic phase. The clonic phase can be characterized by high frequency jerking movements of the limbs. The frequency of these clonic jerks decreases as the event terminates (the silent periods shown by (*) in Figure 3 A), leading to a lower variance in the last quartile relative to rest of the signal ($p < 0.001$). However, no such pattern was observed in convulsive PNES events with distinct tonic- and clonic-phases. All these cases of PNES involved quasi-periodic movements; the clonus activity continued after the silent periods (Figure 3 C). Therefore, DDI of Poincaré'-derived temporal variations for GTCS events were higher in comparison to PNES events (Figure 4 B, $p < 0.001$). Among DDI's of all the Poincaré'-derived descriptors, the DDI_{ratio} showed the highest AUC for differentiating GTCS and convulsive PNES (Table I). *ratio* is a measure of randomness

or dispersion in a time-varying; therefore, the DDI of *ratio* (DDI_{ratio}) has the highest AUC in comparison to rest of the descriptors (Table I, and Figure 4 B).

Among TI and DDI, the TI of Poincaré'-derived descriptors showed a higher class separation (Figure 4, and Table I). The reason for the better performance of TI can be attributed to the distinct onset phase in GTCS than convulsive PNES. These findings indicate that convulsive PNES events have a characteristic non-evolving pattern on the time-scale over the course of an event. By contrast, GTCS events have distinct phases and thus exhibit a continuously evolving pattern on the time scale. As the proposed approach is based on a time-scale analysis, the validity of this approach further reinforces the findings of the preliminary study by Vinton et al.²⁴, who showed that convulsive PNES events displays a characteristic pattern of rhythmic EEG artefact with a stable non-evolving frequency footprint that differs from the evolving pattern during an epileptic seizure.

C. Performance of Automated Classifier versus Blinded Review

The TI and DDI of Poincaré'-derived temporal variations was found to be a reliable and objective marker for differentiating between GTCS and convulsive PNES, with GTCS events demonstrating significantly higher values of TI and DDI (Table I). The automated classifier achieved a PNES detection sensitivity of 95.5% (95% confidence interval [CI]: 90 – 96%), and a specificity of 94.87% (95% [CI]: 87 – 99%) (Table II). 2 PNES and 2 GTCS events were misclassified by the automated approach resulting in diagnostic accuracy that was superior to the blinded review of Poincaré'-derived temporal variations by epileptologists (Table II). In addition, 7 of 8 events labelled as non-diagnostic during the blinded review belonged to a single patient (P₁₇; Table S1). The automated classifier correctly differentiated all the 7 PNES events of P₁₇ that were labelled as non-diagnostic (PNES cases without rhythmic clonic movements) (Table S2). Therefore, the results suggest that the new quantitative features (TI and DDI) are performing better than the qualitative assessment of features by experts. However, the blinded analysis of the Poincaré'-derived temporal variations was of utmost importance as it ensured removal of any bias that the automated classifier might have had towards the gold standard VEM diagnosis.

Further, it is important to be recognized that a patient can experience both types of seizures (GTCS and PNES). In a study by Jones et. al.¹ it was found that 8.1 – 17.9% of the patients admitted to our VEM unit had comorbid epilepsy along with PNES. In this study we had one patient who experienced both seizure types (patient P₅ Table S1) and the automated classifier was able to differentiate all GTCS and PNES events correctly. Thus, illustrating the importance of long-term longitudinal recordings that can capture a greater number of patient's typical seizures and present the entire diagnostic picture – this is possible by outpatient monitoring where ACM-based devices can be a feasible solution. Therefore, the new ACM features (TI and DDI) shows the potential to have a significant positive impact on the clinical management and prognosis of patients with PNES.

D. Comparison with Existing Studies

As a first comparison we compare the results of the proposed approach to our previously published method¹⁵. In our previous study¹⁵, we showed that a 32% cut-off on CoV of limb movement frequency differentiated between convulsive epileptic seizures and PNES. In contrast to the previous approach based on a stringent CoV threshold (AUC 0.78), the proposed automated classifier (AUC 0.96) resulted in better performance (Δ AUC 0.18, $p=0.002$). The better performance of the proposed approach can be attributed to the multiple Poincaré'-derived parameters (Table I) in comparison to a single frequency-based index proposed earlier.

Although non-EEG-based differential diagnosis of PNES is seldom discussed, a few research groups have investigated different modalities for diagnosing non-epileptic seizures^{16,25}. ECG-derived ictal HRV parameters differentiated 88% of GTCS and 73% of PNES correctly²⁵. However, heart rate changes may vary with the vigilance state of the person therefore, ECG based systems are not specific²⁶. Beniczky et al.¹⁶ investigated sEMG signals recorded from the deltoid muscles for differentiating GTCS and convulsive PNES. They showed that the HF/LF ratio (HF: high-frequency 64-256 Hz; LF: low-frequency 2-8 Hz) and RMS of the sEMG signal could differentiate all GTCS from convulsive PNES (sensitivity 100%). However, the proposed approach has several advantages over a sEMG-based system: continuous use of sEMG electrodes can be uncomfortable and has the potential for detaching²⁷. In contrast, the proposed system is an electrodeless system, thus is more comfortable and less encumbering to the patient. Moreover, the proposed approach is based on a time-domain analysis, which is computationally efficient and confers the opportunity for real-time analysis²⁸.

E. Clinical Utility of The Proposed Approach

Considerable experience is required for analysis of a patient's neurophysiologic and VEM data to make a definitive prognosis²⁹. The proposed quantitative method yields a non-linear projection of the 3D rhythmic limb movement into a numerical score, thus allowing reliable distinction between GTCS and convulsive PNES with less experience. In addition, wearable ACM-based devices can be reliably used for long-term continuous monitoring of patients¹⁴; therefore, in future the clinical utility of the proposed approach can be further enhanced by the incorporation of automated algorithm for detection and differentiation of GTCS and convulsive PNES into a wearable device.

At this stage, an analysis of other convulsive epileptic and non-epileptic types was beyond the scope and limitations of the current study. However, it is probable that TI and DDI may also facilitate identification of other seizure types which do not manifest as rhythmic clonic activity as in complex partial seizures¹⁴. Nonetheless, the proposed method can help overcome the limitations of the current diagnostic procedures^{7,29}; and shows the potential to be used as a diagnostic tool to assist epileptologists in differentiating GTCS and convulsive PNES.

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DISCLOSURE

None of the authors have any conflict of interest to be disclosed.

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ETHICAL PUBLICATION STATEMENT

We confirm that this report is consistent with the Journal's position on issues involved in ethical publication.

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Table I: Median, inter quartile range, and area under the ROC curve statistics for TI and DDI of Poincare' derived descriptors corresponding to GTCS and convulsive PNES events.				
Index	GTCS (median $\pm$ iqr)	PNES (median $\pm$ iqr)	p-value	AUC*
TI _{SD1}	1.65 $\pm$ 0.69	0.66 $\pm$ 0.22	5.48exp(-13)	0.95
TI _{SD2}	1.70 $\pm$ 1.16	0.80 $\pm$ 0.42	1.29exp(-10)	0.91
TI _{ratio}	1.05 $\pm$ 0.64	0.69 $\pm$ 0.29	7.00exp(-06)	0.78
TI _{area}	1.68 $\pm$ 0.99	0.81 $\pm$ 0.41	1.06exp(-12)	0.94
DDI _{SD1}	1.56 $\pm$ 1.48	1.05 $\pm$ 0.77	3.94exp(-05)	0.76
DDI _{SD2}	1.86 $\pm$ 1.26	0.94 $\pm$ 0.50	2.67exp(-06)	0.80
DDI _{ratio}	1.79 $\pm$ 0.70	0.92 $\pm$ 0.34	2.09exp(-09)	0.88
DDI _{area}	1.64 $\pm$ 1.57	0.98 $\pm$ 0.89	4.21exp(-04)	0.72
* AUC, area under the receiver operating characteristics curve				

Table II. The diagnostic performance of the proposed approach based on the blinded analysis of Poincare' descriptors; and an automated classifier based on TI's and DDI's of GTCS and convulsive PNES events.					
Diagnosis	PNES	PNES	GTCS	GTCS	Non-

Gold Standard		PNES	GTCS	GTCS	PNES	diagnostic					
	n	TP ^a	FP ^b	TN ^c	FN ^d		Acc*	Sens*	Spec*	PPV*	Fscore*
							(%)	(%)	(%)	(%)	(%)
Blinded Review	83	26	5	33	11	8	78.7	70.3	86.8	83.9	76.5
Automated Classifier	83	42	2	37	2	N/A	95.2	95.5	94.9	95.5	95.5

^a TP is the number of PNES events distinguished correctly

^b Type I error: number of false positives, i.e, the number of GTCS events distinguished as PNES

^c TN is the number of GTCS events distinguished correctly

^d Type II error: number of false negatives, i.e, the number of PNES events distinguished as GTCS

* Statistical measures of performance; Overall accuracy: $ACC (\frac{TP+TN}{TP+TN+FP+FN})$, Sens: sensitivity ($\frac{TP}{TP+FN}$), Spec: specificity ($\frac{TN}{TN+FP}$), PPV: positive predictive value ($\frac{TP}{TP+FP}$), and Fscore: $\frac{2*TP}{2*TP+FP+FN}$. All metrics shown are calculated using the optimal threshold of the classifier except, for the blinded review by epileptologists.

KEY POINT BOX

- An alternate approach for differentiation of generalized tonic-clonic seizures (GTCS) and psychogenic non-epileptic seizures (PNES) is developed using a wrist-worn accelerometer (ACM)-based device.
- Two novel indices: Tonic Index (TI) and Dispersion Decay Index (DDI) that incorporate the motor symptomatology of GTCS and PNES are proposed for differentiation of GTCS and convulsive PNES.
- A unimodal automated classifier based on the new ACM features correctly differentiated 42 of 44 PNES (sensitivity: 95.45%) and 37 of 39 GTCS events (specificity: 94.87%).
- An ACM-based approach that has the potential to be used as a diagnostic tool to assist epileptologists in differential diagnosis of convulsive PNES.

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