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FULL-LENGTH ORIGINAL RESEARCH

Time frequency mapping of the rhythmic limb movements distinguishes convulsive epileptic from psychogenic nonepileptic seizures

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Summary

Purpose: **A definite diagnosis of psychogenic nonepileptic seizures (PNES) usually requires in-patient video–electroencephalography (EEG) monitoring. Previous research has shown that convulsive psychogenic nonepileptic seizures (PNES) demonstrate a characteristic pattern of rhythmic movement artifact on the EEG. Herein we sought to examine the potential for time-frequency mapping of data from a movement-recording device (accelerometer) worn on the wrist as a diagnostic tool to differentiate between convulsive epileptic seizures and PNES.**

Methods: **Time-frequency mapping was performed on accelerometer traces obtained during 56 convulsive seizure-like events from 35 patients recorded during in-patient video-EEG monitoring. Twenty-six patients had PNES, eight had epileptic seizures, and one had both seizure types. The time-frequency maps were derived from fast Fourier transformations to determine the dominant frequency for sequential 2.56-s blocks for the course of each event.**

Key Findings: **The coefficient of variation (CoV) of limb movement frequency for the PNES events was less than for the epileptic seizure events (median, 17.18% vs. 52.23%; $p < 0.001$). A blinded review of the time frequency maps by an epileptologist was accurate in differentiating between the event types, that is, 38 (92.7%) of 41 and 6 (75%) of 8 nonepileptic and epileptic seizures, respectively, were diagnosed correctly, with seven events classified as "nondiagnostic." Using a CoV cut-off score of 32% resulted in similar classification accuracy, with 42 (93%) of 45 PNES and 10 (91%) of 11 epileptic seizure events correctly diagnosed.**

Significance: **Time-frequency analysis of data from a wrist-band movement monitor could be utilized as a diagnostic tool to differentiate between epileptic and nonepileptic convulsive seizure-like events.**

KEY WORDS: **Psychogenic nonepileptic seizures, Epileptic seizures, Time-frequency mapping, Limb movements.**

Psychogenic nonepileptic seizures (PNES) are paroxysmal events that behaviorally resemble epileptic seizures, as they may involve episodes of altered movement, emotion, and experiences similar to seizures due to epilepsy (Lesser, 1996; Jones et al., 2010). However, such events are not caused by epileptiform electrical discharges in the brain (Reuber, 2008). PNES are generally considered to be physical symptoms of an underlying psychological disturbance. They are believed to be involuntary, and may be triggered by stress-related or emotional events (Reuber, 2008).

As with epileptic seizures, several types of PNES can be differentiated; the most common of these events involve excessive limb, trunk, and head movement paired with loss of consciousness, resembling a generalized tonic–clonic seizure (Jones et al., 2010). Motor, sensory, or experiential events analogous to partial epileptic seizures, in the absence of ictal electrical discharges, are also commonly seen in patients with PNES.

The definitive diagnosis of PNES usually requires in-patient video–electroencephalography (EEG) monitoring (VEM) with approximately 20–30% of patients admitted for VEM found to be experiencing PNES (Ghougassian et al., 2004). Moreover, in the general population, the prevalence rate is 2–33 per 100,000, making PNES nearly as prevalent as multiple sclerosis (Benbadis & Hauser, 2000). Outpatient diagnosis of PNES on the basis of the clinical history is often difficult and frequently inaccurate (Ghougassian et al., 2004). Previous research has found that >75% of patients who are diagnosed as having PNES on VEM had been referred with a presumed diagnosis of

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epilepsy by their treating neurologist (Martin et al., 1998; Ghougassian et al., 2004). Conversely, there is an important group of patients who are presumed to have PNES who are found to be in fact having epileptic seizures on VEM (Ghougassian et al., 2004; Jones et al., 2010). It has been found that patients experiencing PNES are not correctly diagnosed until an average 7.2 years after the manifestation of the seizures (Reuber et al., 2002). This long delay in the correct diagnosis of PNES clearly demonstrates the unsatisfactory nature of current procedures for evaluating this important group of patients (Martin et al., 1998; Ghougassian et al., 2004). Accurate diagnosis of PNES is extremely important. Misdiagnosis of epilepsy in patients with PNES usually results in treatment with antiepileptic drugs (AEDs), which are of no benefit and may expose the patients unnecessarily to the risk of serious adverse side effects or teratogenicity. It has been reported that, on average, there is an 84% reduction in AED use 6 months following the diagnosis of PNES. Inaccurate diagnosis may also result in delayed psychological treatment for the issues underlying the attacks and social stigma associated with epilepsy.

The differentiation of convulsive epileptic seizures from PNES is often challenging. Many features have been associated more so with PNES than with epileptic seizures, such as stable ictal heart rate, pelvic thrusting, closed eyes, longer duration of events, and events induced by suggestion (Benbadis et al., 2000; Opherk & Hirsch, 2002). VEM is currently the gold standard in the diagnosis of epilepsy; however, it is expensive, inconvenient for patients, and of limited availability in many health systems. In addition, inpatient VEM has a limited sampling timeframe, and takes the patient away from their usual environment and the circumstances in which they have their typical events. As a result it is common for no typical events to be recorded during the monitoring period, thereby rendering the study nondiagnostic. Clearly there is a pressing need for accurate and practical out-patient diagnostic tests for PNES.

Our previous research suggests that the pattern of evolution of the frequency of rhythmic movement artifact on EEG during PNES differs from that during epileptic seizures (Vinton et al., 2004). It was observed that convulsive PNES display a characteristic pattern of rhythmic movement artifact that remains stable over time, whereas the EEG activity during convulsive epileptic seizures tends to evolve over time (Vinton et al., 2004). This current study sought to apply these observations to examine the utility of using time-frequency mapping of data from a movement-recording device (accelerometer) worn on the wrist as a diagnostic tool to differentiate between PNES and epileptic seizures. If this approach demonstrated appropriate sensitivity and specificity it would have the potential to be utilized as an outpatient ambulatory diagnostic device.

Method

Participants

Patients who underwent VEM at the Royal Melbourne Hospital for the diagnosis of the nature of convulsive seizure-like events were offered participation in the study. From 2007 to 2009, 99 patients were enrolled and had the accelerometer device fitted to their wrist during the video-EEG monitoring. Of these patients, 35 experienced convulsive seizures from which rhythmic data were captured by the accelerometer and were included in the analysis. Convulsive seizures were defined as seizure-like events where, on the review of the video-EEG, there was apparently rhythmic movements affecting at least one limb and lasting >10 s. Bilateral asymmetric convulsive events were allowed. Seizures that started and stopped were considered one event if the interval between the periods of movement was <60 s. Loss of consciousness during the seizure was not required. The classification for an event being included in the study was done prior to the time-frequency analysis of the limb movements being performed.

Diagnosis of PNES versus epileptic seizures

Convulsive PNES were defined as paroxysmal episodes of jerky limb movement in the absence of ictal electrical discharges in the brain (Reuber, 2008). All patients included in the study experienced rhythmic limb movements or "convulsions." The gold standard diagnosis of whether these events were epileptic or PNES was determined at a consensus meeting of epileptologists after review of the clinical history, EEG recording, seizure semiology as observed on video recording, and neuropsychiatry and neurology evaluation. This evaluation was done blinded to the results of the accelerometer recording. If a patient experienced both epileptic and PNES convulsive seizures, both seizure types were included in the analysis.

Acquisition of accelerometer recordings

Movement was measured at the wrist with a light weight accelerometer held firmly on the wrist with an elastic sweat band to prevent nonbiologic movements. The accelerometer used was an ADXL330 low power, three-axis accelerometer (Analog Devices, Norwood, MA, U.S.A.). The accelerometer had a full scale of ±3 g and was sampled at 100 Hz via an embedded electronic data logging board, Logomatic V1.0 (SparkFun Electronics, Boulder, CO, U.S.A.). The movement frequency could be assessed from 0 to 20 Hz. The data logger was assembled into a mobile, battery-operated unit worn at the waist and connected to the wrist worn accelerometer by ultraflexible shielded minicable. The movement data were stored on an SD Memory card from which it was later transferred to an off-line computer for analysis. Examples of the raw accelerometer data of the three axes during event is shown in Fig. 1. The overall acceleration combining X, Y, and Z

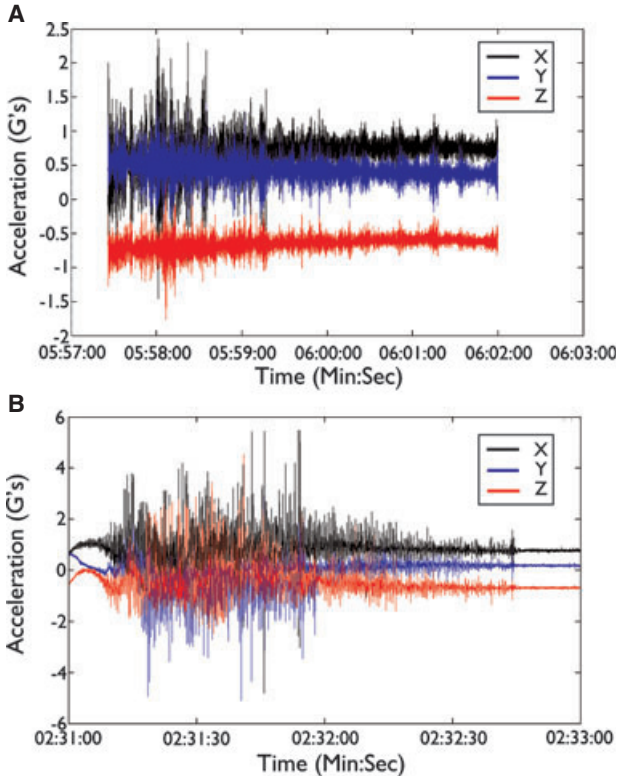

Figure 1.
Raw recordings along X (black), Y (blue), and Z axes (red from accelerometer traces were identified and "blocked"— nonepileptic (**A**) and epileptic (**B**).
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axes was calculated and used for further analysis (Fig. 2 – top rows of A and B).

Time- frequency mapping of accelerometer recordings during events

Time-frequency mapping of the accelerometer tracings during the captured events was performed using MATLAB and Neuroscan software (Compumedics, Melbourne, Australia). The events on the recordings were identified, "blocked" (Fig. 2 – middle rows of A and B), and divided into 2.56 s time epochs for analysis. Fast Fourier transformations (FFTs) were performed for each epoch resulting in a frequency-amplitude presentation (Fig. 2 – bottom rows of A and B). From this, the dominant frequency of each 2.56-s epoch was determined and plotted against time for the course of the event (Fig. 3; i.e., time-frequency mapping). The pattern of movement displayed by the time-frequency maps of the events in the patients with PNES (Fig. 3A) were compared with those of the seizures in the patients with epileptic seizures (Fig. 3B) in terms of frequency evolution throughout the duration of the seizure. This comparison was done in two ways: (i) by visual inspection of the time-frequency maps by an epileptologist (TOB) blinded to the clinical details and nature of the seizures, and (ii) by analysis of the coefficient of variation (CoV) of the frequency of the events during the seizures using a cut-off of 32% (i.e., CoV <32% categorized as PNES and $\geq$32% categorized as an epileptic seizure), which was predetermined based on our previous study (Vinton et al., 2004).

Both the visual inspection of the time-frequency maps, and adopting a CoV cut-off of 32% to discriminate between PNES and epileptic events, were evaluated for their diagnostic sensitivity, specificity, and positive and negative predictive values.

Blinded analysis of the time-frequency maps

The time-frequency maps were randomly presented on a computer screen to an epileptologist (TOB) who was blinded to the results. The epileptologist was asked to classify the seizures as epileptic, PNES, or nondiagnostic (Table 2). This classification was compared to the gold standard diagnosis as determined by the consensus Comprehensive Epilepsy Program meeting.

Quantification of the CoV of the time-frequency mapping of epileptic seizures versus PNES

A quantitative statistical analysis of the variability in the dominant frequency for the multiple time points throughout each seizure was calculated by the CoV. These values were compared between the two types of events. The CoV is calculated using the following formula:

$$\text{Coefficient of variation(CoV)} = (\text{standard deviation[SD]}/\text{mean}) \times 100$$

The CoV provides a normalized measure of variability of a probability distribution, that is, it ensures that the standard deviation of movement frequency is viewed in the context of the mean frequency. For example, a seizure that demonstrates an evolving range of limb movement frequency will have a low CoV value. On the other hand, a seizure that demonstrates a stable limb movement frequency will have a high CoV value. The median CoV for the PNES events was compared with that for the epileptic seizures. In addition, events were classified as epileptic seizures or PNES on the basis of whether the CoV was $\geq$32% or <32%, respectively.

Statistical methods

Statistical analysis was performed using SAS (SAS Institute Inc., Cary, NC, U.S.A.). The nonparametric Mann-Whitney U test (two-tailed) was used to compare the median CoVs for the PNES versus epileptic seizures.

Results

Captured and analyzed events

Thirty-five (35.4%) of the 99 patients enrolled in the study had a convulsive "seizure-like" event during the

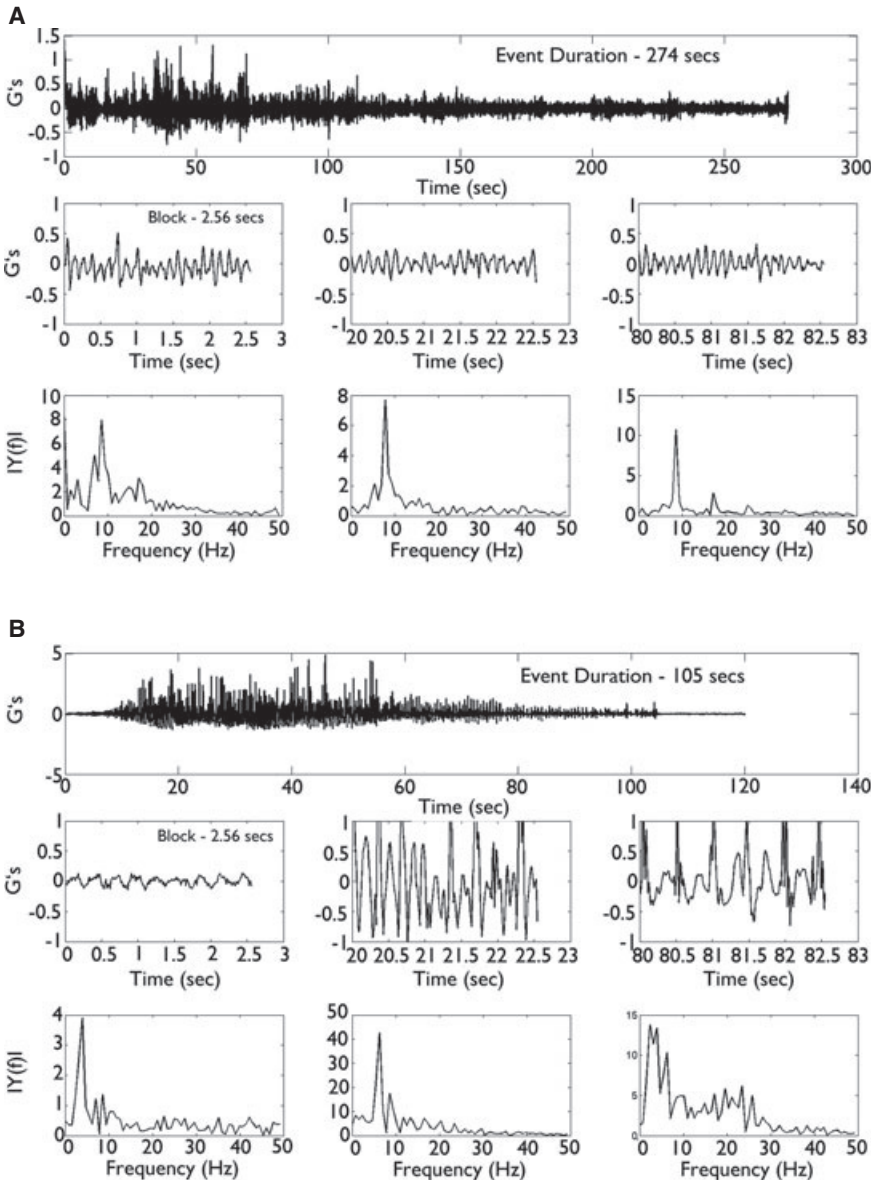

Figure 2.
Frequency response during the course of the events—nonepileptic (**A**) and epileptic (**B**) events: top row, acceleration during the whole event; middle row, 2.56-s epoch during start (0–2.56 s), during (20–22.56 s), and at the end of the event; bottom row, Fast Fourier Transformations (FFTs) of the 2.56-s epochs shown in the middle row, resulting in a frequency-amplitude presentation.
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period they were wearing the accelerometer. Of these 35 patients, 27 patients (77.14%) experienced PNES and 9 (25.71%) experienced epileptic seizures; one patient experienced both epileptic and nonepileptic seizures. A total of 45 PNES events (range, 1–3 per patient) and 11 epileptic seizures (range, 1–2 per patient) were captured and analyzed. The mean duration of the PNES events was 151.0 ± 27.2 s and for the epileptic seizures was 80.8 ± 10.3 s ($p = 0.22$, Student *t*-test).

Of the remaining 64 patients, 33 had no events during the video-EEG monitoring admission, 11 had only nonconvulsive events, and 20 had their events only when they were not wearing their accelerometer or the device was not recording. The clinical characteristics of the 35 patients who experienced a seizure-like event are presented in Table 1.

Time-frequency maps

During the PNES events, the dominant frequency of movement generally remained stable throughout each of the recorded events (Fig. 3A). On the other hand, epileptic seizures demonstrated more variable frequencies over the course of the events, which evolved over time (Fig. 3B).

Compared to the gold standard, the blinded analysis of the time-frequency maps by an epileptologist correctly diagnosed the seizure-like events as being PNES in 38 of 41 (sensitivity 92.7%) and as being epileptic in 6 of 8 (specificity 75.0%) (Table 2), with 7 of 56 events (12.5%) classified as nondiagnostic. These events were considered nondiagnostic because the reviewer felt that the pattern was not clearly one of either a stable dominant frequency throughout the recorded events or an evolving frequency. The positive predictive

Table 1. Demographic and video-EEG monitoring characteristics of the patient cohorts

	PNES[a]	Epileptic seizures[a]
Number of patients	26	8
Median years of age (range)	38 (19–83)	33 (20–69)
Male:Female	7:19	4:4
Interictal EEG		
Normal (%)	19 (73.1%)	0
Ictal EEG		
PNES only	26 (100%)	0
Generalized onset seizure	0	3 (37.5%)
Focal onset, secondary generalized seizure	0	5 (62.5%)

[a]Not including one patient whom recorded both PNES and epileptic seizure events.

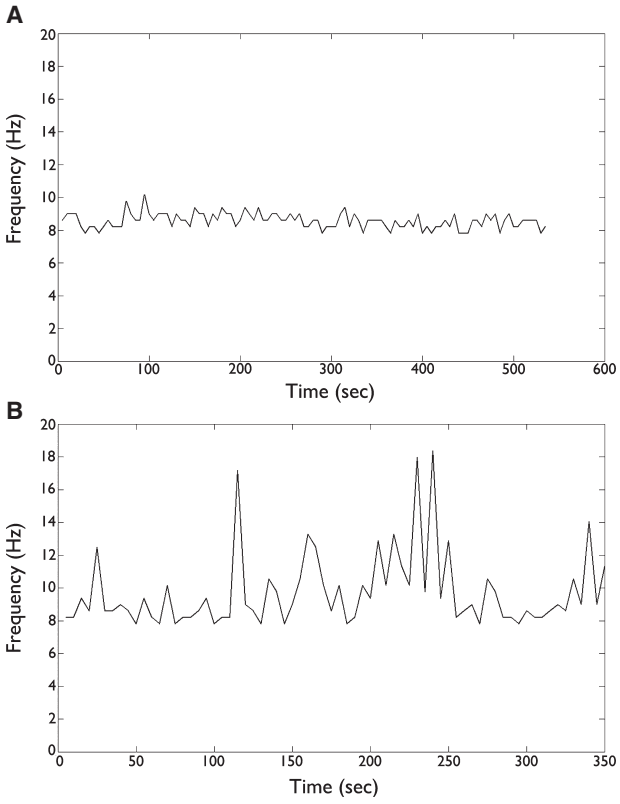

Figure 3.
Time-frequency mapping of the dominant frequencies from each 2.56-s time epoch were plotted against time for the course of the event in two different patients—one with PNES (**A**) and one with epileptic seizures (**B**).
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value (PPV) and negative predictive value (NPV) for predicting PNES events were 95.0% and 66.7%, respectively.

CoV of time-frequency maps

The CoV value was significantly greater in patients experiencing epileptic seizure events (Fig. 4). Using a CoV cut-off point of 32%, the CoV value correctly diagnosed the seizure-like events as being PNES in 42 of 45 (sensitivity 93%) events and as being epileptic in 10 of 11 (specificity 91%) epileptic seizure events (Table 2). The PPV and NPV for predicting PNES events were 98.0% and 77.0%, respectively.

The individual who experienced both PNES and epileptic seizure events obtained CoV values of 7% and 8% for the two PNES events and 51.97% for the single epileptic seizure event.

Discussion

This study demonstrates that PNES displayed a stable dominant frequency of movements during the course of a seizure, whereas epileptic seizures showed more variable, evolving dominant frequency of the rhythmic limb movement, and that the time-frequency maps of the movement patterns has potential to be used as a diagnostic tool. This is consistent with the findings of a previous study from our center based on the analysis of the rhythmic movement artifact on EEG recordings during seizures (Vinton et al., 2004). This is also consistent with observations from other groups that during convulsive PNES, limb movements go through phases of vigorous and less vigorous motor activity with muscle twitching varying in terms of amplitude but not frequency (Reuber, 2008). There have also been clear frequency dynamics reported during epileptic seizures to localize muscle activity at approximately 8 Hz, which then either increases or decreases as the seizure progresses and usually decreases as the seizure comes to an end (Quian Quiroga et al., 1997).

The CoV values for the dominant frequency on the time-frequency maps during the events was found to be a reliable, objective, differentiator between PNES and epileptic seizures, with epileptic seizures demonstrating higher CoV values. Using a CoV cut-off point of 32% to distinguish between the groups resulted in only one of 11 epileptic seizures and three of 48 PNES events misclassified, a diagnostic accuracy that was superior to that of the blinded visual review by an epileptologist of the time-frequency maps (Table 2).

The accurate and early diagnosis of PNES has great potential to reduce the risks and expenses of inappropriate treatment for epilepsy. Misdiagnosis of epilepsy in patients with PNES usually results in treatment with AEDs that are of no benefit and that may expose the patients unnecessarily to the risk of serious adverse side effects and teratogenicity. It has been suggested that patients may experience an 84% average reduction in seizure-related medical expenses over a period of 8 months following correct diagnosis of PNES, including significant reductions in medication expenses, outpatient clinic visits, and emergency room visits (Martin et al., 1998). Inaccurate diagnosis may also result in delayed psychological

Table 2. The diagnostic performance of differentiating PNES events from epileptic seizure events based on the blinded analysis of time-frequency maps; and a CoV cut-off value of 32%

Diagnosis Gold Standard	n	PNES PNES TP[a]	PNES Epileptic FP[b]	Epileptic Epileptic TN[c]	Epileptic PNES FN[d]	Nondiagnostic	Sens*	Spec*	PPV*	NPV*
Blinded analysis	56	38	2	6	3	7	92.7%	75.0%	95.0%	66.7%
CoV 32% cut-off	56	42	1	10	3	N/A	93.3%	90.9%	97.7%	76.9%

[a]TP, number of true positives: PNES correctly classified as PNES.
[b]FP, (type I error) number of false positives: epileptic seizures incorrectly classified as PNES.
[c]TN, number of true negatives: epileptic seizures correctly classified as epileptic seizures.
[d]FN, (type II error) number of false negatives: PNES incorrectly classified as epileptic seizures; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

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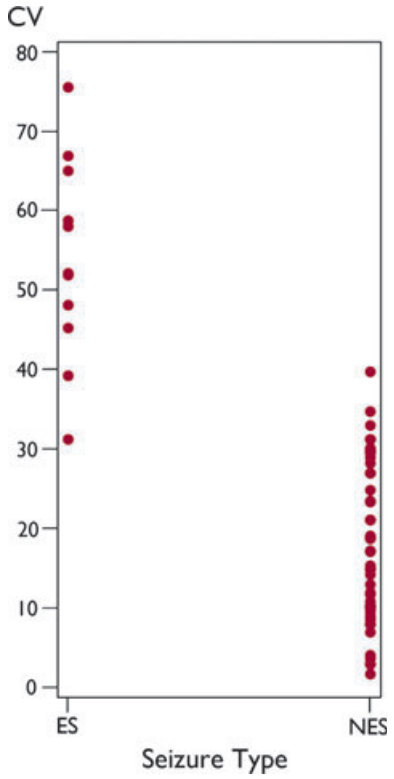

Figure 4.
Box plot demonstrating the coefficient of variation (CoV) of the frequency of dominant rhythmic limb movement during seizures. The median for nonepileptic seizures was 17.18%, ranging from 1.8% to 39.8%, whereas the median CoV for epileptic seizures was 52.23%, ranging from 31.3% to 75.6%. The CoV of the epileptic seizures was significantly greater than that of nonepileptic seizures ($p < 0.001$, Mann-Whitney *U* test).
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treatment for the issues underlying the attacks and social stigma associated with epilepsy. A delay in diagnosis can also adversely affect the impact of PNES on patients' lives. For example, one study found that 69% of patients with PNES were employed at the time the events started; however, by the time they eventually underwent diagnostic VEM, only 20% were still employed (Reuber et al., 2002; Reuber, 2008). Early diagnosis of PNES and the institution of appropriate psychological intervention may also improve the prognosis for cessation of the events (Meierkord et al., 1991; Reuber & Elger, 2003).

When considering application of the diagnostic approach tested in this study to clinical practice it is important to recognize that a proportion of patients will have both PNES and epileptic seizures—8.1–17.9% of patients with PNES in a previous study from our in-patient VEM population (Jones et al., 2010). In this current study there was one patient who had both epileptic and PNES recorded, and the analysis of the time-frequency maps could correctly diagnose both types of events in the patient. This illustrates the importance in clinical practice of recording several of the patient's typical seizure types to get a complete diagnostic picture—and this is potentially easier to achieve in an outpatient setting where longer sampling periods are possible.

The results of this study indicates that time-frequency analysis of data from a wrist-band movement monitor has the potential to be utilized as a diagnostic tool to differentiate between epileptic and PNES. This may be suitable to incorporate into a device for outpatient monitoring of ambulatory patients. The future clinical utility of this approach could be further enhanced by the incorporation of automatic event-detection algorithms based on the characteristic time-frequency mapping patterns of PNES and epileptic seizures demonstrated in this study.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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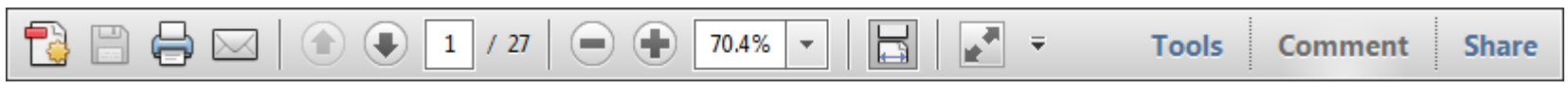

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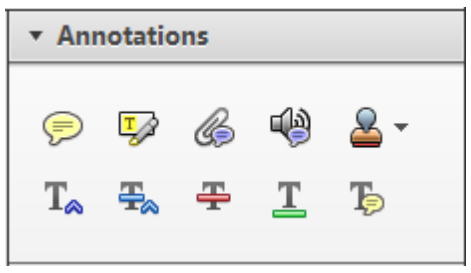

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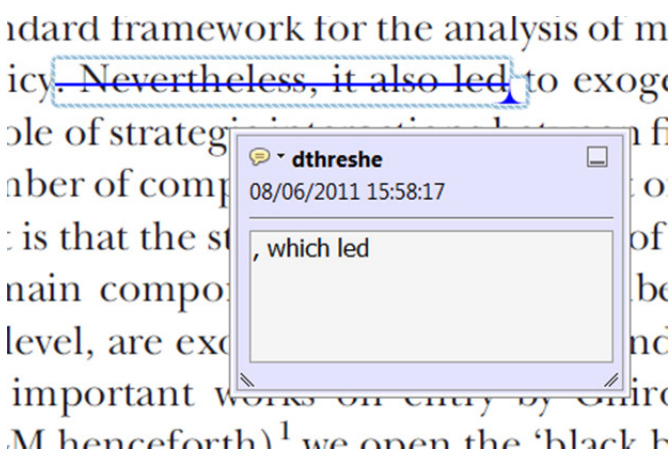

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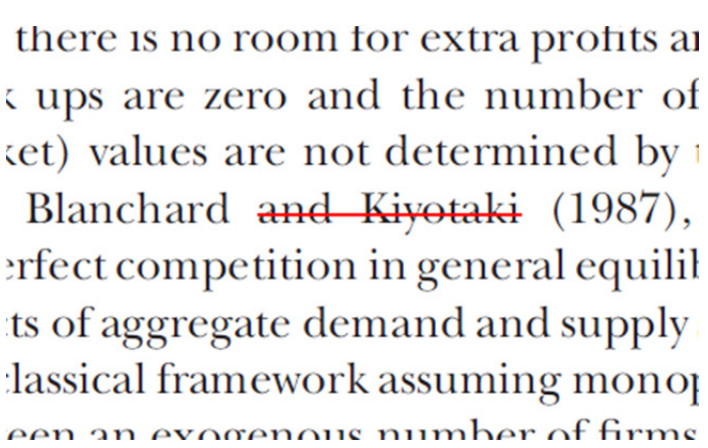

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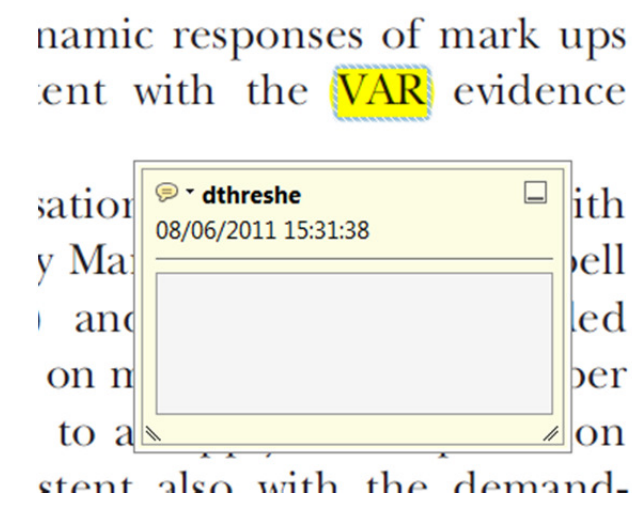

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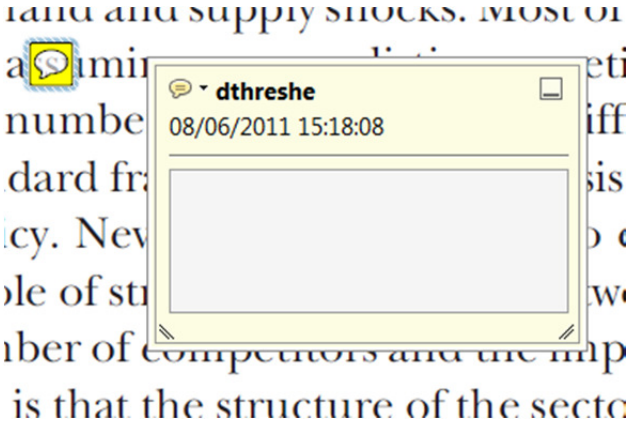

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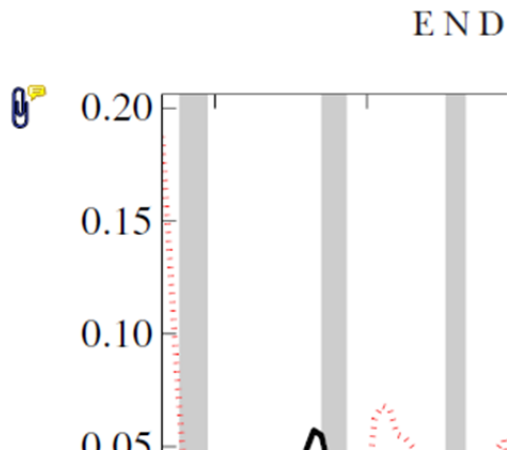
5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

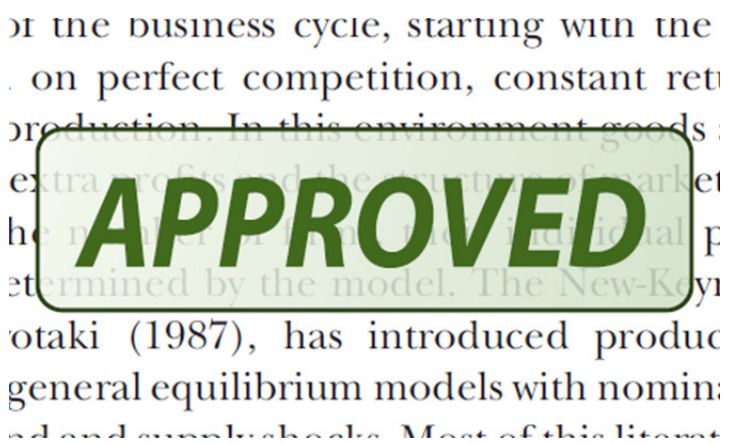


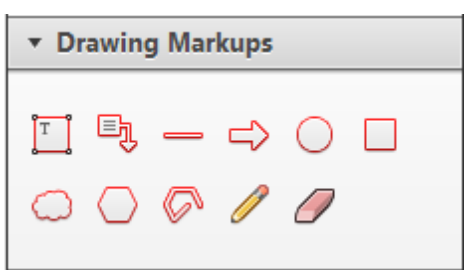
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).



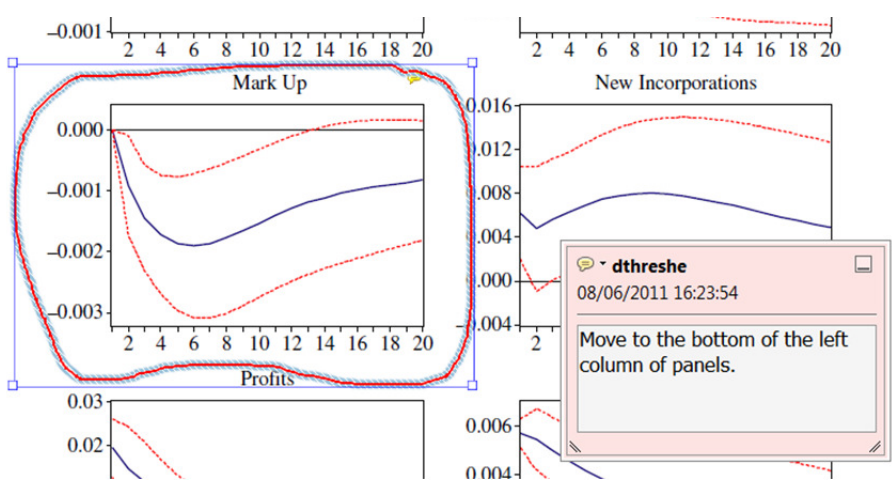


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: