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Review

Quantitative analysis of surface electromyography: Biomarkers for convulsive seizures

Sándor Beniczky [a,b,*], Isa Conradsen [a,c], Ronit Pressler [d,e], Peter Wolf [a,f]

[a] Danish Epilepsy Centre, Dianalund, Denmark
[b] Aarhus University, Aarhus, Denmark
[c] IctalCare A/S, Hørsholm, Denmark
[d] Department of Clinical Neurophysiology, Great Ormond Street Hospital, London, UK
[e] Clinical Neuroscience, UCL Institute of Child Health, London, UK
[f] Department of Clinical Medicine, Neurological Service, Federal University of Santa Catarina, Florianópolis, SC, Brazil

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HIGHLIGHTS

- Quantitative surface-EMG features differentiate between epileptic and non-epileptic muscle activation.
- Specific quantitative-EMG features constitute neurophysiological biomarkers, implemented in automated algorithms that can run real-time.
- These algorithms can accurately detect GTCS and can distinguish them from convulsive PNES.

ABSTRACT

Muscle activity during seizures is in electroencephalographical (EEG) praxis often considered an irritating artefact. This article discusses ways by surface electromyography (EMG) to turn it into a valuable tool of epileptology.

Muscles are in direct synaptic contact with motor neurons. Therefore, EMG signals provide direct information about the electric activity in the motor cortex. Qualitative analysis of EMG has traditionally been a part of the long-term video-EEG recordings.

Recent development in quantitative analysis of EMG signals yielded valuable information on the pathomechanisms of convulsive seizures, demonstrating that it was different from maximal voluntary contraction, and different from convulsive psychogenic non-epileptic seizures. Furthermore, the tonic phase of the generalised tonic–clonic seizures (GTCS) proved to have different quantitative features than tonic seizures. The high temporal resolution of EMG allowed detailed characterisation of temporal dynamics of the GTCS, suggesting that the same inhibitory mechanisms that try to prevent the build-up of the seizure activity, contribute to ending the seizure.

These findings have clinical implications: the quantitative EMG features provided the pathophysiologic substrate for developing neurophysiologic biomarkers that accurately identify GTCS. This proved to be efficient both for seizure detection and for objective, automated distinction between convulsive and non-convulsive epileptic seizures.

* Corresponding author at: Danish Epilepsy Centre, Visby Alle 5, 4293 Dianalund Denmark.
E-mail address: sbz@filadelfia.dk (S. Beniczky).

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Contents

1. Introduction

In spite of the advances in functional neuroimaging methods, we still know little about the pathomechanisms of the convulsive epileptic seizures in humans, and most of the evidence comes from animal models (Fusco et al., 2008; Zifkin and Dravet, 2008). Limited investigation time makes it unlikely that such an event is recorded in the scanner, and artefacts caused by excessive motor activity make it technically extremely challenging (Moeller et al., 2009). EEG and MEG signals are typically distorted by signals from the head muscle, and also by electrode artefacts. Thus, there is a need for a non-invasive method for characterising the activity in the motor system during convulsive epileptic seizures.

Neuromuscular junctions connect motor neurons and muscles. Long-term recording of surface EMG signals is technically easy, yet it provides, at high temporal resolution, direct evidence on the activity of the motor nervous system (Mothersill et al., 2000; Tassinari and Rubboli, 2008). This is different from functional MRI, which has poorer temporal resolution and provides indirect evidence, based on the neurovascular coupling (Lauritzen, 2001). Quantitative analysis of EMG signals in patients with extrapyramidal movement disorders provided valuable information that helped understanding the pathomechanisms of these conditions (Berardelli et al., 1998, 2001; Hallett, 1998, 2000).

Surface EMG has traditionally been part of polygraphic long-term recordings in epilepsy monitoring units (EMU) (Gastaut and Broughton, 1972; Mothersill et al., 2000; Tassinari and Rubboli, 2008). Qualitative analysis (inspection by trained experts) of EMG signals is helpful in characterising the motor phenomena during seizures, excluding artefacts, and in identifying and describing motor seizures (Fusco et al., 2008; Inoue et al., 2008; Mothersill et al., 2000; Tassinari and Rubboli, 2008). EMG channels can help to verify asymmetry of events and thus help with lateralisation; this is particularly important in seizures where lateralisation may be difficult to detect by observation only, such as spasms or tonic seizures. The temporal relation of EMG signal and EEG spike in an electroclinical event gives information on the source of the event (Bisulli et al., 2002). EMG signals during myoclonic seizures constitute trigger-points in time for averaging EEG traces. This method (EMG triggered back-averaging) by improving the signal-to-noise ratio allowed identification of small-amplitude cortical signals which otherwise were hidden by the ongoing EEG background activity (Shibasaki and Hallett, 2005). EMG is also an important tool for several methods of artefact detection and rejection such as normal eye movements, myogenic potentials, head movement causing slow posterior delta activity or sharp occipital theta activity in a seated patient (EMG from cervical muscles).

In spite of advances in signal analysis methods, quantitative analysis of surface EMG signals during convulsive seizures has so far received surprisingly little attention. We addressed this in a series of studies. First, in exploratory studies we investigated whether muscle activation during convulsive epileptic seizures is different from physiological muscle activation and muscle activation during non-epileptic convulsive events. Then we focused on the distinction between different types of convulsive seizures. We attempted to characterise the temporal dynamics of GTCS using quantitative EMG features. Based on the specific features yielded by the explorative studies, we constructed a neurophysiological biomarker for accurate identification of convulsive epileptic seizures. In clinical validation studies, we assessed whether this can be efficient for seizure detection and for automated distinction between epileptic and non-epileptic convulsive seizures. Our findings have been confirmed by other groups, whose studies are included in this review.

2. Surface EMG recordings

It is technically easy recording surface EMG using either conventional electrodes (9 mm, silver/silver chloride surface electrodes) and amplifiers in the EMU or recording devices specifically designed for this purpose, in an out-patient setting. The active electrode is placed on the belly of the muscle, while the reference electrode is placed on the nearby bone ("unipolar recording"). EMG can be recorded from many muscles simultaneously (up to 14 in our setting). Recording from many muscles makes it possible to follow the chronological order and the somatotopic pattern of muscle activation, even by inspection of the signals (Bisulli et al., 2002; Meletti et al., 2003). However, recording from many muscles is a disadvantage when designing devices for ambulatory, outpatient recordings, as the feasibility is lower and the discomfort to the patient considerable. Deltoid and biceps muscles proved to be involved early during generalised convulsive seizures. In most of our studies we analysed signals from the deltoid muscles, on both sides.

We recorded surface EMG from patients with generalised convulsive seizures (tonic seizures and GTCS), healthy controls acting generalised convulsive seizures and in patients with convulsive psychogenic non-epileptic seizures (PNES). These recordings were part of polygraphy during long-term video-EEG monitoring (LTM).

3. Neurophysiology: epileptic versus physiologic muscle activation

Fig. 1A, D and G shows typical surface EMG recordings from convulsive epileptic seizures (tonic seizures and GTCS) and seizures acted by healthy volunteers, instructed to imitate convulsive seizures. Surface EMG was recorded during 63 seizures from 20 patients with epilepsy (10 with tonic and 10 with tonic–clonic seizures). Twenty age- and gender matched healthy volunteer's imitated 100 convulsive seizures, and performed maximal voluntary contraction (MVC).

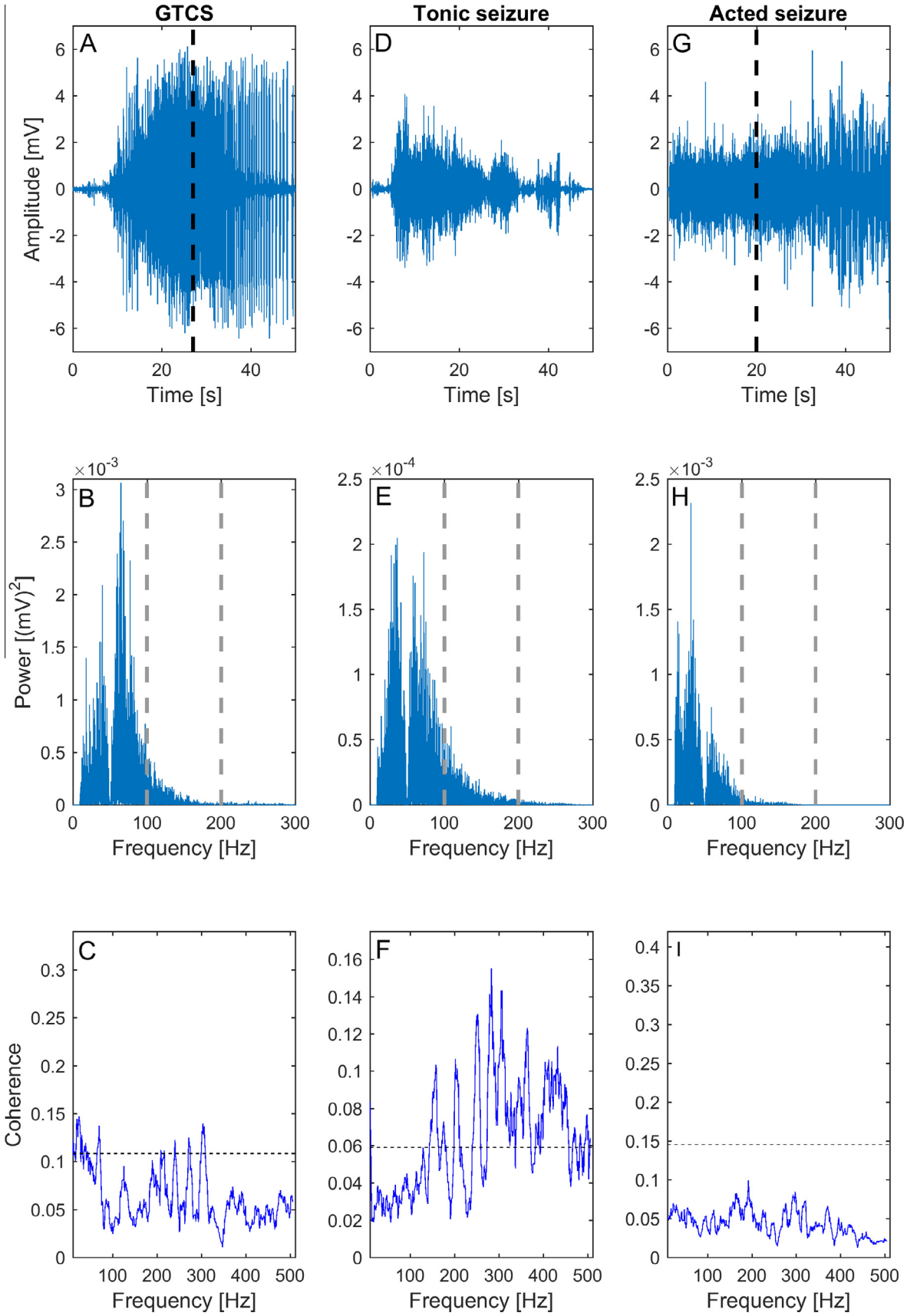

Fig. 1. EMG signals and quantitative EMG parameters from a GTCS (A–C), tonic seizure (D–F) and an acted seizure (G–I). A, D and G show EMG signals. The stippled vertical line in A and G marks the end of the tonic phase. B, E and F show the power spectrum for the three conditions. C, F and I show the musculo-muscular (left–right) coherence; the horizontal line marks the significance level for coherence.

Quantitative EMG parameters were significantly different between epileptic and non-epileptic groups (Conradsen et al., 2011). Tonic seizures had significantly higher frequency values than the acted seizures. This was shown by the mean frequency of the signal calculated for the whole seizure period and by the relative power of frequencies higher than 100 Hz (Fig. 1B, E and H: power spectra for the EMG signals showed in A, D and G). Patients with GTCS had higher amplitudes of the EMG signal (measured as root mean square) than acted seizures (physiologic MVC), while tonic seizures had smaller amplitudes than acted seizures (Fig. 1A, D and G).

The musculo-muscular coherence (reflecting the synchronisation of the muscle activation between the left and right side) was significantly higher for both types of convulsive seizures, as compared with physiologic muscle activation (Fig. 1C, F and I) (Conradsen et al., 2011). This suggests that the motor neurons innervating the left and right sided muscles are more synchronised during convulsive seizures than during physiological activation (MVC).

Our findings have been confirmed by another group, who recorded EMG from the biceps muscle, both during MVC and epileptic seizures (Szabó et al., 2015). They could define thresholds in the quantitative EMG parameters reliably separating MVC from seizure-activity.

4. Neurophysiology: tonic seizures versus GTCS

We compared quantitative EMG parameters measured throughout the tonic phase of GTCS with tonic seizures (Conradsen et al., 2011). We found that, calculated for the whole seizure period, the frequency values (MF, relative power >100 Hz) of tonic seizures were significantly higher than for the tonic phase of GTCS (Fig. 1B and E). This was contrasted by the amplitude, which was significantly higher for the tonic phase of GTCS than for tonic seizures (Fig. 1A and D).

The ILAE definitions do not make a distinction between tonic seizures and the tonic phase of GTCS (Blume et al., 2001). Tonic seizures are defined as sustained increase in muscle contraction lasting from seconds to minutes (Gastaut et al., 1963), whereas tonic–clonic seizures are defined as a sequence consisting of a tonic followed by a clonic phase (Commission on Classification and terminology of the ILAE, 1981). However, our results suggest that the pathomechanisms are different. The marked increase in frequency throughout the whole seizure period of tonic seizures suggests recruitment of more motor neurons, including high-threshold ones (Riley et al., 2008; Wakeling, 2009). The tonic phase of GTCS had marked increase in amplitude, which emphasises the role of synchronisation of activation among motor units.

5. Neurophysiology: temporal dynamics of GTCS

The quantitative parameters described above were calculated for the whole period of tonic seizures and for the whole tonic phase of the GTCS. However, the quantitative characteristics of muscle activation throughout these seizures are not constant in time. The high temporal resolution of surface EMG signals seemed to be ideal for investigating the temporal dynamics of muscle activity during convulsive seizures. We recorded surface EMG during 26 GTCS from 13 patients and compared it with 50 GTCS-like events acted by 10 control subjects (Conradsen et al., 2013). We found that GTCS had a characteristic evolution in time, which was remarkably similar for different seizures and different patients, regardless of their aetiology (Fig. 2A–E) (Conradsen et al., 2013). This common pattern starts with a gradual increase in amplitude and in frequency of muscle activity. The onset phase is followed by a period characterised by marked increase in frequency: the tonic-maintenance phase. Then the frequency decreases and tonic muscle activity is interrupted by longer and longer periods with suppressed muscle activity, leading to the clonic phase. These features could not be reproduced by voluntary muscle activation imitating seizures (Fig. 2F and J).

Wavelet analysis showed that two frequency domains characterised these phases (Conradsen et al., 2013). A high-frequency (64–265 Hz) component dominated the tonic-maintenance phase. A low-frequency component (2–8 Hz) had peaks during the onset phase and during the clonic phase (especially at the transition between tonic and clonic phases) and it was completely suppressed during the tonic maintenance phase. The low-frequency component corresponded to the interruption of tonic bursts, indicating that it reflected an inhibitory phenomenon. Thus, the high frequency component reflects the recruitment of more motor neurons, including high-threshold ones, while the low-frequency is the manifestation of an inhibitory phenomenon. The typical dynamics of high and low frequency components allowed an automated segmentation of seizure duration, based on the ratio between high and low-frequency components (Fig. 2C–E).

Our recordings showed that all GTCS started with a gradual build-up of tonic muscle activity. This is consistent with intracranial recordings with microelectrodes, showing that the synchronisation between neurons is achieved not at the beginning but later during the seizure (Bower et al., 2012; Truccolo et al., 2011). Our findings contradict the ILAE definition of GTCS which states that these seizures start with a "sudden sharp tonic contraction of the muscles" (Commission on Classification and terminology of the ILAE, 1981). This is clearly not the case for GTCS.

The inhibitory low-frequency components peaked not only when the clonic phase emerged, but also during the onset phase, suggesting that inhibitory mechanisms attempted to prevent the build-up of seizure activity. Furthermore, there was a significant, inverse correlation between the duration of the onset and the clonic phases, suggesting that the inhibitory mechanisms counteracting the development of a seizure are related to those that in the end stop it: a weak inhibition at seizure-onset causes a short onset (quick build-up) and at seizure termination, a prolonged clonic phase (slow stop). The opposite happens when inhibition is strong (long build-up and short clonic phase). Patients with EMG signs of weak inhibition (short build-up and long clonic phase) had higher seizure frequency than those with a strong inhibition (long build-up and short clonic phase).

The duration of the tonic phase, and the duration of EMG-bursts during the clonic phase were remarkably constant, suggesting that differences between seizures are primarily due to differences in inhibitory mechanisms (Conradsen et al., 2013). During the clonic phase, EMG bursts were interrupted by longer and longer "silent periods" (SP) with suppressed EMG activity (Fig. 3A). The increase in the duration of the SPs corresponded to an exponential function (Fig. 3B). The dynamics of the clonic phase could not be reproduced by healthy volunteers acting GTCS (Conradsen et al., 2013).

Contrary to GTCS, the evolution in time of tonic seizures showed significant intra- and inter-individual variability, although all tonic seizures shared a common EMG feature (high frequency activity). In most of the patients the seizures had a long, gradual increment and also a long decrement phase. However, some seizures started with a rapid increase in the amplitude and frequency (Larsen et al., 2014).

All but one patient in our series had secondarily generalised TCS. Thus, from a statistical point of view, the results are mainly given by secondarily generalised TCS. Nevertheless, the results described above were even most pronounced in the patient with Idiopathic Generalised Epilepsy (with primary GTCS).

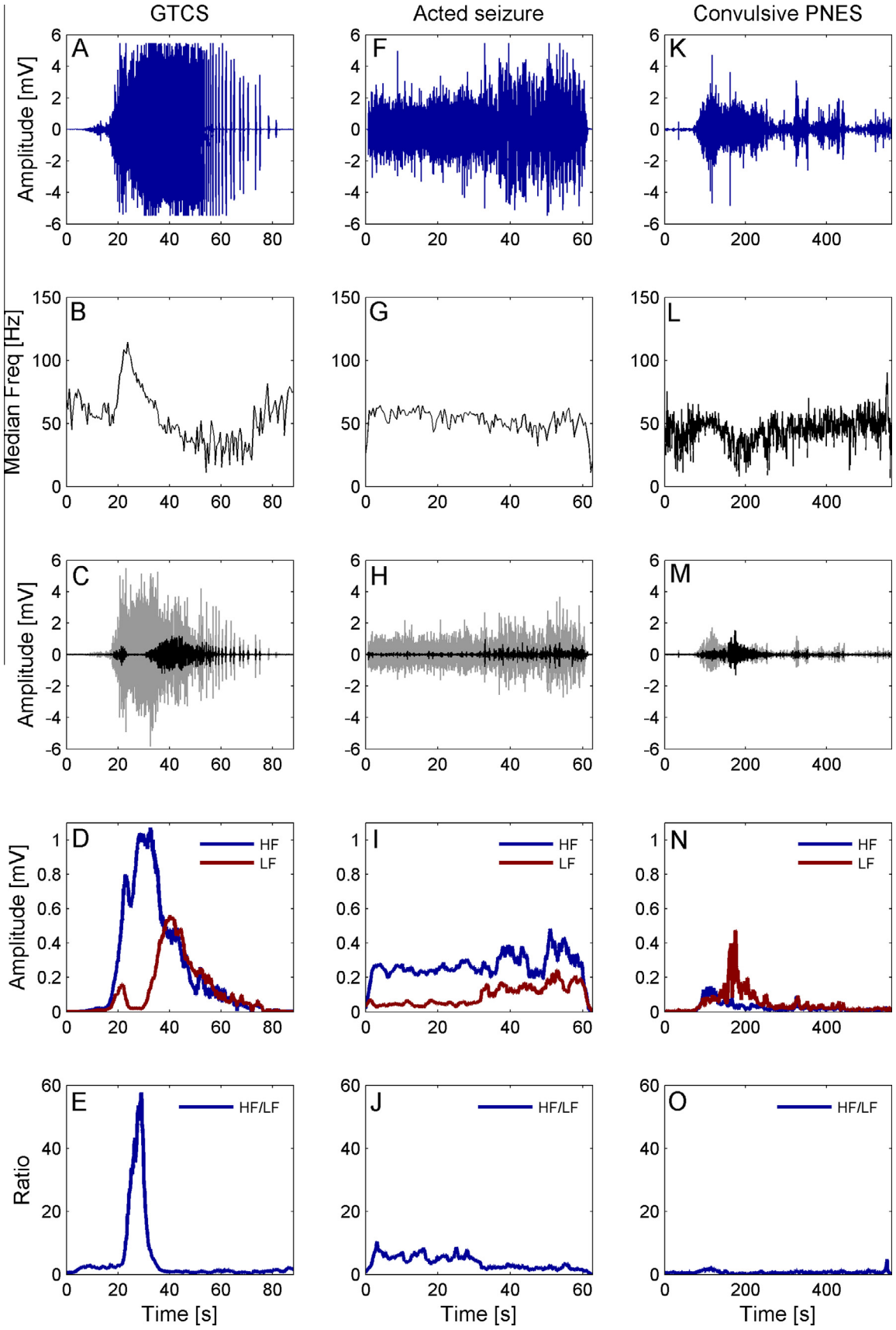

Fig. 2. EMG signals from GTCS (A–E), acted seizure (F–J) and convulsive PNES (K–O). A, F and K shows the EMG signals. B, G and L show the evolution of the median frequency throughout the three conditions. C, H and M show the signals corresponding to the low-frequency component (in black) and the high frequency component (in grey). D, I and N show the normalised amplitudes corresponding to the low-frequency (red) and high-frequency (blue) components. E, J and O show the evolution of the HF/LF ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

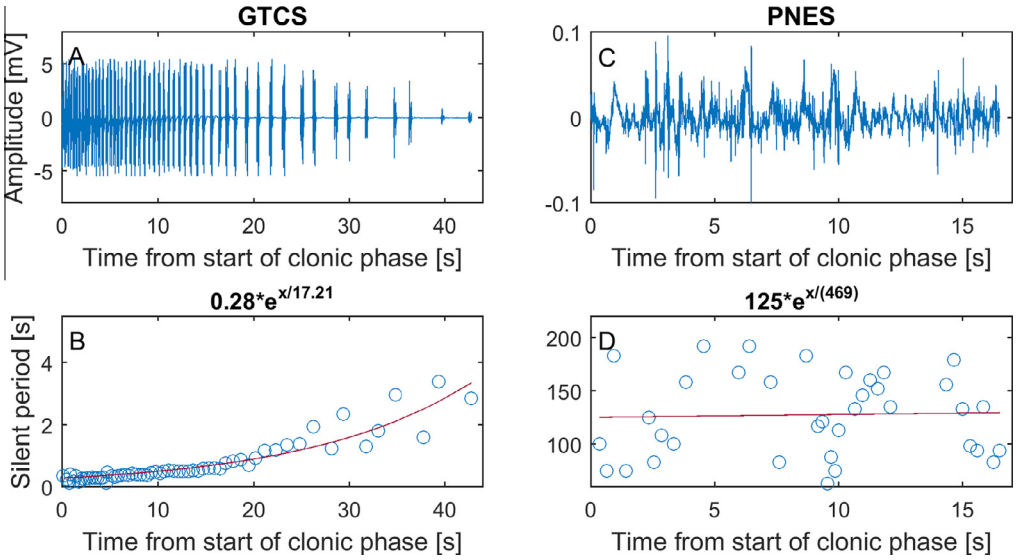

Fig. 3. Dynamics of the clonic phase: GTCS (A and B) and convulsive PNES (C and D) A and C show the EMG signals. C and D show the temporal evolution of the silent-period duration (*y*-axis) throughout the clonic phase (*x*-axis).

6. Differential diagnosis: epileptic versus non-epileptic convulsive seizures

We compared quantitative EMG features and temporal dynamics of GTCS with convulsive psychogenic non-epileptic seizures (PNES) and convulsive syncope (Beniczky et al., 2014). Surface EMG was recorded from 25 patients and 21 healthy volunteers. Forty-six clinical episodes were recorded: 28 GTCS from 14 patients with epilepsy, and 18 convulsive PNES from 12 patients (one patient had both GTCS and PNES). The healthy volunteers were acting GTCS. Several quantitative EMG parameters distinguished between epileptic and non-epileptic convulsive events, also at individual level (Figs. 2K–O; 3C–D). The amplitude of the EMG signal was smaller than the range of GTCS for all but one PNES. The dynamics of high and low frequency components clearly distinguished between epileptic and non-epileptic convulsive episodes, and a combination between amplitude and the ratio between high and low frequency components completely separated the two groups. Only 39% of PNES had a clonic phase clearly distinguishable from the tonic phase. In all other PNES the jerks were superimposed on the tonic muscle activation. In the PNES-cases where a clonic phase was identifiable, the periods between cloni had constant duration, causing rhythmic contractions, as opposed to the clonic phase of GTCS, which had SP with an exponential evolution in time (Fig. 3B and D) (Beniczky et al., 2014).

The rhythmic contractions recorded during convulsive PNES can also be accurately identified by accelerometers (Bayly et al., 2013). However, in our series less than half of PNES showed this feature, indicating that measuring only this feature could not help in evaluating all convulsive episodes.

A blinded review by trained experts of the EMG features distinguished correctly between epileptic and non-epileptic convulsive episodes in all cases (Beniczky et al., 2014).

Prolonged duration is considered to be one of the most reliable indicators of PNES (Avbersek and Sisodiya, 2010). In our cases duration of the PNES was significantly longer than the GTCS. However, more than one third of the PNES cases had duration of episodes within the range of GTCS, thus duration could not distinguish at individual level between epileptic and psychogenic episodes. This emphasises the need for more sophisticated, quantitative parameters.

Another relevant finding in this study was the quantitative difference between PNES and acted seizures performed by healthy subjects instructed to imitate convulsive seizures: PNES had smaller amplitudes and a smaller ratio between the high and low frequency components. These results confirm that PNES are not generated voluntarily (Beniczky et al., 2014).

7. Management: neurophysiological biomarker for GTCS

Our goal was to develop a neurophysiological biomarker for GTCS, based on surface EMG signals. The biomarker had to be specific for GTCS, identifying seizures with a high sensitivity, yet simple enough to run real-time in a portable device. Such a biomarker would have important clinical applications: it could detect seizures even in an ambulatory setting, and it could help physicians in distinguishing between epileptic and non-epileptic episodes. GTCS are associated with an increased risk of injuries, and for sudden unexpected death in epilepsy (SUDEP), especially when patients are unattended (Hesdorffer et al., 2011, 2012; Lhatoo et al., 2010; Tomson et al., 2004). A portable device that accurately and with short latency detects GTCS could trigger an alarm calling for help. Many nocturnal seizures remain unnoticed and, automatic seizure detection could help with an objective monitoring of seizure frequency in these patients.

We developed an algorithm targeting the quantitative EMG features specific for GTCS, as described above (Conradsen et al., 2012a, b). To focus on the high frequency components that are increased during the tonic-maintenance phase, we filter the EMG signals with a high-pass filter of 150 Hz. Then, the algorithm calculates the number of zero-crossings (ZC). This quantitative feature reflects the frequency of the signal, yet the computation is easy, so that it can run real-time. As the amplitude increases significantly during GTCS, we imposed a hysteresis of ±50 μV. The time-windows for calculating ZC was 1 s with 75% overlap. Based on the data from the explorative studies, we hypothesised that GTCS will have high values of ZC in successive time-windows, and that this feature will be specific for GTCS.

8. Management: seizure detection

We used receiver operating characteristic analysis to optimise the value of the threshold of ZCs and the number of successive

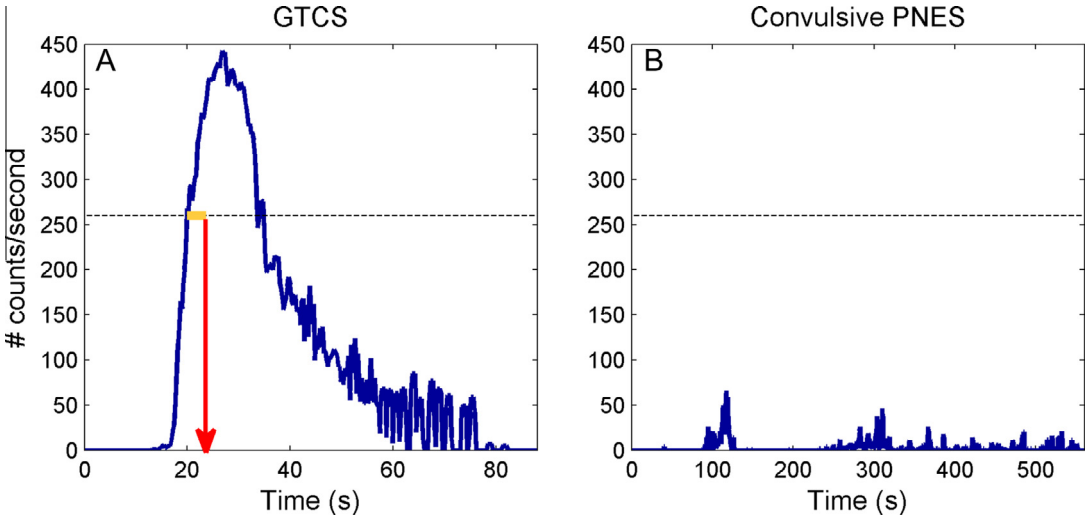

Fig. 4. Evolution of the number of zero counts (*y*-axis) throughout a GTCS (A) and a convulsive PNES (B). The stippled horizontal line marks the threshold for identifying an epileptic seizure. The yellow horizontal line depicts the minimum number of time-windows with ZC exceeding the threshold, necessary for seizure identification. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

time-windows with ZC exceeding the threshold for identifying a GTCS (Fig. 4A), in order to achieve the highest possible sensitivity, the lowest possible rate of false-detections and the shortest possible detection latency, based on surface EMG data from 22 GTCS, recorded from 11 consecutive patients. The algorithm was generic (i.e. not patient-tailored).

Using a threshold of 241 ZC/s in 19 consecutive time-windows allowed detection of all GTCS (100% sensitivity) with a very low rate of false detections (0.03/24-h) and a short detection latency (mean = 13.9 s) (Conradsen et al., 2012a). This algorithm can run real-time and we implemented it in a portable device that can record and analyse surface EMG in an outpatient setting (Fig. 5).

Two other groups confirmed that algorithms based on surface EMG signals, either alone or in combination with accelerometers, could accurately detect GTCS (Cavazos et al., 2015; Milosevic et al., 2015; Szabó et al., 2015). Szabó et al. recorded surface EMG from biceps muscle in 33 adult patients with epilepsy (Szabó et al., 2015). Their seizure-detection algorithm utilised Hotelling's *T*-squared power analysis of compound muscle action potentials, and it was patient-tailored: MVC was measured in each patient to establish the baseline physiologic muscle threshold. The algorithm was tested offline (retrospectively). It detected 20 out of the 21 GTCS, in 11 patients (sensitivity: 95%). The average detection-latency was 20 s. Only one false positive detection was reported (Szabó et al., 2015). The preliminary results of a Phase-III trial implementing this algorithm showed promising results: all 24 GTCS were detected, and the rate of false alarms was 1.44/24-h (Cavazos et al., 2015).

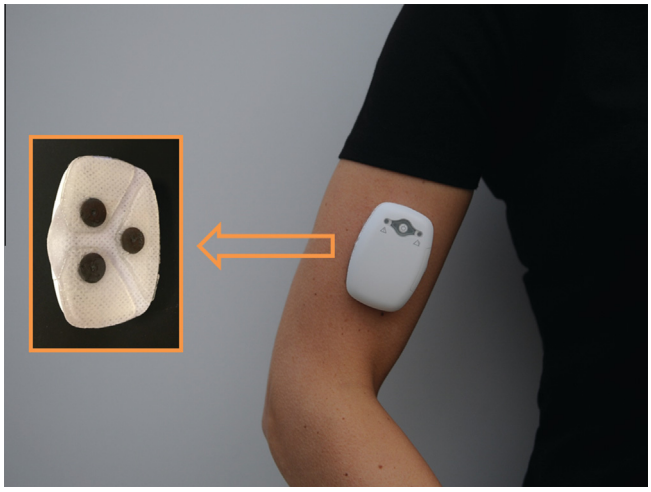

Fig. 5. Portable device for recording and analysis of surface EMG, running real-time the seizures detection algorithm. The figure in the orange box shows the self-adhesive patch and the three electrodes (active, reference and ground). The device is in this case recording from the biceps muscle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Combining several modalities into a seizure-detection algorithm can theoretically improve its accuracy. In a pilot study using signals from EMG, acceleration (ACC) and angular velocity (ANG) we obtained better results than with the unimodal approach (Conradsen et al., 2010). This was later confirmed by another group, who used a multimodal seizure detection system comprising surface EMG and accelerometers (Milosevic et al., 2015). Their approach was based on machine learning techniques, including feature selection and least-squares support vector machine classification. The algorithms were evaluated on nocturnal recordings in 56 paediatric patients, of which 7 had 22 tonic–clonic seizures. The multimodal approach gave a more robust detection of short and non-stereotypical seizures (91%).

We also attempted to develop an algorithm specifically for tonic seizures. However, due to the significant variability of tonic seizures, a generic algorithm could not be achieved for these (Larsen et al., 2014). Using patient-specific algorithms we achieved complete seizure detection also for tonic seizures, yet with a much higher rate of false detections (between 0.08 and 7.9). The special challenge with tonic seizures is the low amplitude, which makes them similar to the patterns given by high-frequency noise (induction artefacts). The other challenge we encountered for detection of tonic seizures was physiologic muscle activation at smaller intensity than the maximal voluntary contraction. It turned out that occasionally sub-maximal muscle activations had higher frequency content than maximal voluntary contraction, bringing them closer to the features of tonic seizures.

9. Management: automated distinction between epileptic and non-epileptic convulsive seizures

Besides seizure detection, the other important clinical application of an algorithm constituting a neurophysiological biomarker

for GTCS would be the automated differentiation between GTCS and convulsive PNES. A portable device running the automated algorithm would be a useful adjunctive measure for objective differentiation between these conditions. It could provide decisive help to physicians in the emergency room, with the difficult distinction of status epilepticus and psychogenic non-epileptic status. In an outpatient setting it could help differentiating between GTCS and convulsive PNES, especially when a caregiver could provide a description of the event and identify it as the patientś habitual seizure.

In a blinded trial, 44 consecutive episodes with convulsive events were automatically analysed with the algorithm: 25 generalised GTCSs from 11 patients, and 19 episodes of convulsive PNES from 13 patients (Beniczky et al., 2015). The gold standard was interpretation of video-EEG recordings by experts blinded to the EMG results. The algorithm described above distinguished GTCS from convulsive PNES with an overall accuracy of 95% (Fig. 4B) (Beniczky et al., 2015).

In the study on seizure detection by Szabó et al. four nonepileptic spells occurred. None of them was detected by their seizure-detection algorithm, confirming the specificity of surface EMG-based algorithms for the characteristic muscle activation during epileptic, convulsive seizures (Szabó et al., 2015).

10. Conclusions

Quantitative analysis of surface EMG provides further insight into the pathophysiology of convulsive seizures. The quantitative features of muscle activation differentiate between epileptic seizures and convulsive PNES as well as acted seizures (physiologic maximal voluntary contraction). The specific quantitative EMG features constitute neurophysiologic biomarkers, implemented as automated algorithms that can run real-time. The algorithm can accurately detect GTCS and distinguish them from convulsive PNES. Portable devices with this algorithm implemented could have a considerable clinical impact.

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Conflict of interest: Dr. Conradsen is currently employed by IctalCare A/S, Hørsholm, Denmark. The remaining authors have no conflicts of interest.

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