Tampere University

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Machine Learning in Video-Based Monitoring of Epilepsy Patients

Feasibility in seizure detection, classification and documentation

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ACADEMIC DISSERTATION
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ABSTRACT

Background: Seizure diaries have traditionally been used in follow-up and management of epilepsy. According to previous research, seizure diaries are prone to inaccuracies due to the inability to observe seizures and inter-observer discrepancy. Due to the increased risk of mortality and morbidity caused by unobserved seizures especially during the nighttime, improved seizure documentation is indicated. Video-based monitoring devices hold potential to increase accuracy of seizure documentation and classification, which may improve patient care and treatment efficacy. Automatic seizure detection, especially video-based detection devices, have been studied increasingly during the last decade.

Aims of the study: The main objective of this research was to examine automatic detection and classification of seizures by utilizing machine learning in the analysis of motion signals extracted from the video data. Other objectives were to assess the feasibility of video monitoring in drug intervention by comparing the video-based seizure documentation with patient-provided seizure diaries, and to examine changes in algorithmically-evaluated movement intensity over time.

Materials and methods: This research consisted of four studies. Overall 46 patients with drug resistant epilepsy participated in one or multiple studies. All patients underwent a four or eight-week nighttime home video monitoring. In all studies, feature extraction was used for the video data recorded from patients to obtain three different biosignals - sudden motion, oscillation, and changes in sound volume - to characterize seizure activity. In studies III and IV, the brivaracetam intervention was examined. In the first study, the method was applied to detect seizures of one patient from a 4-week home monitoring. In the second study, accuracy of automatic seizure classification was evaluated by utilizing motion features from the motion feature collection (catch22) to create time series for clustering and visualization (hyperkinetic, tonic, and tonic-clonic seizures were included). The training dataset included 130 seizures from 10 patients, and the testing dataset included 98 seizures from 17 patients. In the third study, the seizure documentation of seizure diaries and automatic video-based seizure monitoring was compared and the effect of documentation method on the interpretation of treatment outcomes was evaluated. The study sample included 13 patients. The study

also evaluated qualitative changes in movement intensity before and after the intervention by utilizing feature analysis. In the fourth study, the characteristics of signal profiles were explored to evaluate the generalizability and variability in a single patient setting and between patients. Video data of the fourth study consisted of 13 hyperkinetic seizures, 65 tonic seizures, 13 tonic-clonic seizures and 138 motor seizures from 11 patients.

Results: In the first study, with optimal parameters and thresholding that were set to 90% sensitivity, the model reached false discovery rate of 0.38/h and 1.02/h for seizures with a clonic component and seizures with a tonic component, respectively. Motion, oscillation and sound signals formed distinguishable signal profiles characteristic for different seizure types. In the second study, temporal motion features achieved the best results in clustering analysis, and the system differentiated hyperkinetic, tonic, and tonic-clonic seizures with an accuracy of 91%, 88%, and 45% after 100 cross-validation runs, respectively. F1-scores were 93%, 90% and 37%, respectively, and overall accuracy and f1-score were both 74%. In the third study, during the follow-up phase of intervention, three patients reached >50% decrease in seizure frequency, four patients did not respond to intervention, and seizure frequency increased in two patients according to the results from the video monitoring. Five out of nine patients documented 40 to 70% of their seizures to their seizure diaries compared to video monitoring system. Signal feature analysis showed significant changes in movement intensity in three patients, and statistically significant differences in features were found in 8 out of 9 patients. In the fourth study, tonic component formed a distinguishable seizure signature in motion signal, but hyperkinetic and motor seizures have overlapping signal profile characteristics which might hamper their differentiation. Visually recognizable changes were observed in the signal profiles of two patients after the initiation of brivaracetam. Motion signals might be useful in the assessment of movement intensity changes and to evaluate the treatment effect.

Conclusions: Automatic video-based seizure monitoring was able to automatically detect motor seizures and differentiate tonic, clonic, and tonic-clonic seizures by using sudden motion, oscillation and sound features extracted from the video data. Signal profiles of different motor seizure types might be useful in seizure classification and further development of this system. Video monitoring increased sensitivity of seizure detection in compared to seizure diaries which improved the treatment outcome evaluation. The video-based system also enabled feature analysis and visualization of signal profiles in movement intensity evaluation after the initiation of brivaracetam.

TIIVISTELMÄ

Tausta: Kohtauspäiväkirjat ovat olleet keskeisessä osassa epilepsian seurannassa ja hoidon suunnittelussa. Aiempien tutkimusten mukaan kohtauspäiväkirjat ovat alttiita epätarkkuuksille kohtausten vajavaisen havaitsemisen sekä kohtausten tulkinnanvaraisuuden vuoksi. Havaitsemattomat kohtaukset nostavat kuolleisuutta ja sairastavuutta, joten kohtausten dokumentoinnin parantaminen on tärkeää, erityisesti yöaikaisten kohtausten kohdalla. Videoon perustuvilla kohtausten tunnistamisjärjestelmillä on potentiaalia parantaa kohtausten dokumentoinnin ja luokittelun tarkkuutta, mikä voisi parantaa ja tehostaa potilaiden hoitoa. Automaattista kohtausten tunnistamista ja etenkin videokuvaan perustuvia laitteita on tutkittu yhä enemmän viimeisen vuosikymmenen aikana.

Tavoitteet: Tutkimuksen ensisijainen tavoite oli tutkia kohtausten tunnistamista ja luokittelua automaattisesti hyödyntämällä tekoälyä, joka analysoi videokuvasta erotettuja liikesignaaleja. Lisäksi arvioitiin videomonitoroinnin soveltuvuutta lääkeinterventioon vertailemalla sen antamia dokumentointituloksia kohtauspäiväkirjamerkintöihin, sekä liikeintensiteetin muutoksen arviointia lääkeintervention jälkeen tutkimalla liikkeen ominaisuuksia (motion feature) ja liikesignaaleja.

Materiaalit ja metodit: Tämä väitöstutkimus koostui neljästä osatutkimuksesta. Yhteensä 46 lääkeresistenttiä epilepsiaa sairastavaa potilasta osallistui yhteen tai useampaan osatutkimukseen. Jokaista potilasta kuvattiin kotonaan neljästä kahdeksaan viikkoa yöaikaan. Kaikissa tutkimuksissa hyödynnettiin feature extraction -menetelmää, jolla erotettiin videoista kolme biosignaalia: liike, oskillaatio ja ääni. 3. ja 4. tutkimuksessa tutkittiin brivarasetaami-intervention vaikutusta. Ensimmäisessä tutkimuksessa metodilla tunnistettiin automaattisesti yhden potilaan kohtaukset neljän viikon monitoroinnista. Toisessa tutkimuksessa automaattisen kohtausluokittelun tarkkuutta tutkittiin hyödyntämällä liikefeaturekokoelmaa (catch22). Sen avulla luotiin signaalidata klusterianalyysiin ja tulosten visualisointiin. Tutkimuksessa analysoitiin hyperkineettisiä, toonisia ja tooniskloonisia kohtauksia. Tekoälyn harjoittamiseen käytetty potilasdata sisälsi 130 kohtausta 10 potilaalta, ja sen testaamiseen käytetty data sisälsi 98 kohtausta 17 potilaalta. Kolmannessa tutkimuksessa verrattiin kohtauspäiväkirjojen ja videomonitoroinnin

kohtausdokumentointia ja arvioitiin dokumentointimenetelmän vaikutus hoidon tulosten tulkintaan yhteensä 13 potilaan otannalla. Lisäksi tutkimuksessa arvioitiin kvalitatiivisia muutoksia liikeintensiteetissä ennen ja jälkeen intervention hyödyntämällä algoritmipohjaista featureanalyysiä. Neljännessä tutkimuksessa tutkittiin liikesignaalien muodostamien signaaliprofiilien piirteitä eri kohtaustyypeissä ja arvioitiin signaaliprofiilien yleistettävyyttä ja vaihtelua yksittäisellä potilaalla ja potilaiden välillä. Videodata sisälsi 13 hyperkineettistä kohtausta, 65 toonista kohtausta, 13 toonisklooniista kohtausta ja 138 motorista kohtausta 11 potilaalta.

Tulokset: Ensimmäisessä tutkimuksessa säädettiin parametrit ja kynnysarvot 90 % sensitiivisyydelle, joilla saavutettiin väärien löydösten määräksi 0.38/h kloonista liikettä sisältäville kohtauksille ja 1.02/h toonista liikettä sisältäville kohtauksille. Liike, oskillaatio ja äänen signaalit muodostivat erilaisia signaaliprofiileja eri kohtaustyypeille. Toisessa tutkimuksessa ajalliset liikeominaisuudet (temporal motion features) suoriutuivat parhaiten klusterianalyysissä, ja järjestelmä luokitteli automaattisesti hyperkineettiset kohtaukset 91 %:n, tooniset kohtaukset 88 %:n ja toonisklooniset 45 %:n tarkkuudella 100 ristiinvalidoinnin jälkeen. F1-score oli 93 %, 90 % ja 37 % näille kohtaustyypeille. Kolmannessa tutkimuksessa kolme potilasta koki 50 %:n kohtaustiheyden laskun intervention jälkeen, neljä potilasta ei reagoinut hoidolle ja kahdella potilaalla kohtaustiheys kasvoi videomonitoroinnin tulosten perusteella. Viisi potilasta yhdeksästä dokumentoi 40-70 % kohtauksista päiväkirjoihin verrattuna videomonitorointiin. Featureanalyysi osoitti merkittäviä muutoksia kohtausten liikeintensiteetissä kolmella potilaalla, ja tilastollisesti merkittäviä eroja featureissa kahdeksalla potilaalla. Neljännessä tutkimuksessa havaittiin, että tooninen kohtauskomponentti muodosti tunnistettavan muodon liikesignaaleihin. Hyperkineettisten ja motoristen kohtausten signaaliprofiileissa on yhteneväisiä piirteitä, mikä voi hankaloittaa kyseisten kohtausten erottamista. Visuaalisesti havaittavia muutoksia signaaliprofiileissa esiintyi kahdella potilaalla brivarasetaamin aloittamisen jälkeen.

Johtopäätökset: Automaattinen kohtausten videomonitorointi kykeni havaitsemaan automaattisesti motorisia kohtauksia ja erottamaan tooniset, klooniset ja toonisklooniset kohtaukset hyödyntämällä liikkeen, oskillaation ja äänen signaaleja. Eri motoristen kohtaustyyppien signaaliprofiilit saattavat olla hyödyllisiä kohtausten luokittelussa ja järjestelmän kehittämisessä. Videomonitorointi paransi kohtausten havaitsemisen herkkyyttä ja hoitovasteen arviointia päiväkirjoihin verrattuna. Videokuvaan perustuva järjestelmä mahdollisti myös featureanalyysin ja signaaliprofiilien visualisoinnin liikeintensiteetin arvioimiseksi brivarasetaamin aloituksen jälkeen.

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ABBREVIATIONS

ACM	Accelerometry
ASM	Anti-seizure medication
BRV	Brivaracetam
CNN	Convolutional neural networks
DBS	Deep brain stimulation
DRE	Drug resistant epilepsy
ECG	Electrocardiography
EDA	Electrodermal activity
EEG	Electroencephalography
EMG	Electromyography
EMU	Epilepsy monitoring unit
FDR	False detection rate
FLE	Frontal lobe epilepsy
fNIRS	Functional infrared spectroscopy
FTBTC	Focal to bilateral tonic-clonic
GTCS	Generalized tonic-clonic seizure
ILAE	International League Against Epilepsy

KDE	Kernel density estimation
LSTM	Long-short-term memory
MLSTM-FCN	Multivariate long short-term memory with fully connected layers
MRI	Magnetic resonance imaging
OLE	Occipital lobe epilepsy
PCA	Principal component analysis
PLE	Parietal lobe epilepsy
PPV	Positive predictive value
QoL	Quality of life
SUDEP	Sudden unexpected death in epilepsy
TLE	Temporal lobe epilepsy
Video-EEG	Video-electroencephalography
VEM	Video-EEG monitoring
VNS	Vagus nerve stimulation

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text as Roman numerals I-IV:

I Ojanen P, Knight A, Hakala A, Bondarchik J, Noachtar S, Peltola J, Kaufmann E. An integrative method to quantitatively detect nocturnal motor seizures. Epilepsy Res. 2021 Jan;169:106486.

II Ojanen P, Kertész C, Morales E, Rai P, Annala K, Knight A, Peltola J. Automatic classification of hyperkinetic, tonic, and tonic-clonic seizures using unsupervised clustering of video signals. Front Neurol. 2023 Nov 2;14:1270482.

III Ojanen P, Zabihi M, Knight A, Roivainen R, Lamusuo S, Peltola J. Feasibility of video/audio monitoring in the analysis of motion and treatment effects on night-time seizures - Interventional study. Epilepsy Res. 2022 Aug;184:106949.

IV Ojanen P, Kertész C, Peltola J. Characteristics of motion signal profiles of tonic-clonic, tonic, hyperkinetic and motor seizures. Submitted.

AUTHOR'S CONTRIBUTION

In study I, author annotated seizure data which was then semiologically classified by Soheyl Noachtar and Elisabeth Kaufmann. Andrew Knight and Anna Hakala analyzed seizure data and provided signal profiles and detection performance results. All authors participated in interpretation of results and revision of the manuscript.

In study II, author annotated seizures included in the study with contribution of Jukka Peltola. Author trimmed all seizure video data for analysis. Csaba Kertész analyzed video data and provided seizure cluster plots and performance analysis with contribution of Elisabeth Morales and Andrew Knight. Author coordinated the writing process of the manuscript. All authors participated in interpretation of results and revision of the manuscript.

In study III, author annotated video data and reviewed seizure diary entries. Morteza Zabihi analyzed seizure video data and provided feature analysis results and kernel density estimations. Author coordinated the writing process of the manuscript. All authors participated in interpretation of results and revision of the manuscript.

In study IV, author annotated seizures included in the study with contribution of Jukka Peltola. Author cropped all seizure video data for analysis. Csaba Kertész analyzed video data and provided seizure signal profiles. Author coordinated the writing process of the manuscript. All authors participated in interpretation of results and revision of the manuscript.

1 INTRODUCTION

Epilepsy is a common neurological disease which manifests as epileptic seizures caused by abnormal neuronal activity. According to previous studies, even 30% of epilepsy patients do not reach seizure freedom despite adequate treatment with anti-seizure medication (ASM) (Kwan et al., 2010). Drug-resistant epilepsy (DRE) significantly increases a risk of mortality and morbidity (Laxer et al., 2014), and sudden unexplained death in epilepsy (SUDEP) (Massey et al., 2014).

Seizure diaries have been used in seizure documentation due to low costs and usability of the method. However, previous research has shown inaccuracies of seizure diaries which reflects to the follow-up and treatment evaluation of patients (Elger & Hoppe, 2018). Improved documentation could help to evaluate therapy outcomes and it could also enable analysis of lateralizing and localizing information to determine epileptogenic zone which is useful in diagnosing epilepsy or epileptic syndrome.

To address this issue, several different seizure detection methods have been developed, as well as applications to improve seizure diaries. EEG-based methods have been developed for hospital use, and despite high sensitivity and specificity, they are useful in a short-term monitoring. Other methods, such as devices measuring acceleration, pressure, autonomic changes or heart rate, have been used especially for motor seizures (Conradsen et al., 2012). Video-based methods detect movements by utilizing computer vision techniques to detect movements from video data, and seizures with major motor manifestations have been detected automatically with high sensitivity and specificity (Garção et al., 2023; Geertsema et al., 2018). Previous studies claim that video-based systems yield lower sensitivities for seizures with small motor manifestations, even though recent research has shown improvements also for these seizures (Hou et al., 2022). Despite broad research and development of seizure detection systems, monitoring in a home setting may be challenging, and more research are indicated to improve performance and generalizability of these methods in a larger patient population. Also, detection accuracies of seizure diaries and video monitoring as well as the effect of

documentation method on treatment outcome interpretation has not been studied before.

In addition to seizure detection, video-based analysis of semiological features and automatic seizure classification have been examined recently. Machine learning has been utilized in the analysis of movement of face and body (Ahmedt-Aristizabal et al., 2018), as well as movement trajectories (L. Chen et al., 2009). Temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) have been differentiated with promising results (Karácsony et al., 2022). However, only few studies have assessed utilization of machine learning in automatic classification of multiple motor seizure types.

Given the problems related to use of seizure diaries, automatic seizure detection devices have several applications of use. Especially video-based methods hold a significant potential for development to improve automatic documentation and classification of seizures. The purpose of this study is to present a video-based detection method and examine its performance in automatic detection and classification of seizures. Also, clinical feasibility of video monitoring in drug intervention was evaluated by assessing the effect of documentation method on treatment outcome interpretation.

2 REVIEW OF LITERATURE

2.1 Definitions of epileptic seizures and epilepsy

An epileptic seizure is a diverse sequence of signs and symptoms related to cognitive and motor functions which take place due to abnormal excessive or synchronous activity of neurons in the brain. People may experience seizures because of various reasons. Common toxic-metabolic etiology causing a provoked immediate seizure are alcohol or benzodiazepine intoxication or withdrawal, hyponatremia, hypocalcemia, hypo- and hyperglycemia, epileptogenic drugs (antibiotics, antipsychotics, antidepressants, pain medications, amphetamines, hallucinogens), and abuse of other drugs (e.g., clozapine, tramadol, bupropion, cocaine) (Foster et al., 2019; Gavvala & Schuele, 2016). A provoked or acute symptomatic seizure with aforementioned etiology may not confirm the diagnosis of epilepsy. However, if a patient experiences an unprovoked seizure (a seizure without an inciting stimulus) or a seizure associated with epileptic syndrome, epilepsy diagnosis should be considered (Fisher et al., 2014). After a first seizure without ongoing risk factors, the risk of a second seizure is 30% at 5 years, and it is higher among patients with symptomatic etiology, and if epileptiform discharges are present in EEG after a seizure (Hauser et al., 1982). Patients with positive family background, previous febrile seizures, partial seizures, or Todd paralysis have a higher risk for epilepsy (Rizvi et al., 2017).

Epilepsy on the other hand causes a permanent tendency to generate seizures, and it has several neurobiological, cognitive, and psychological effects. According to the International League Against Epilepsy (ILAE) official report (Fisher et al., 2014), epilepsy is defined by at least one of the following conditions: (1) two or more unprovoked seizures occurring >24 h apart, (2) one unprovoked seizure and the same probability of following seizures as general recurrence risk after 2 unprovoked seizures, or (3) diagnosis of an epilepsy syndrome. In addition to clinical manifestations of seizures, diagnosis of epilepsy is often accompanied with electroencephalography (EEG) or video-EEG, and neuroimaging (MRI) to determine the etiology and epilepsy type (Guerrini et al., 2015; Rüber et al., 2018).

It is estimated that even 10% of all population experience a single seizure during their lifetime. However, prevalence of epilepsy is only 1% (Falco-Walter, 2020), and

lifetime risk of developing epilepsy is 2-3% (Hauser & Beghi, 2008). Annual incidence of epilepsy is 61 per 100,000, with infants and the elderly being at highest risk for developing epilepsy; the increased incidence in the elderly is suggested to associate with aging-related changes in the brain (Beghi & Giussani, 2018). Patients with epilepsy has often comorbidities such as psychiatric disorders, somatic conditions (fractures, asthma, migraine), and Parkinson's disease and neurodegenerative diseases among the elderly (Gaitatzis et al., 2004). Epilepsy is regarded as resolved either if a patient has an age-dependent epilepsy but a patient has passed the suitable age, or a patient has been seizure-free for the last decade and without anti-seizure medication (ASM) for the last 5 years (Fisher et al., 2014).

Seizure frequency varies greatly among epilepsy patients. Epilepsy is often stigmatized, and patients might not get diagnosis or treatment, especially in middle- and low-income countries (Fiest et al., 2014; Thijs et al., 2019). Epileptic seizures reduce the quality of life (QoL) of epilepsy patients (Tomson & Forsgren, 2005). Patients with epilepsy have reduced life expectancy in compared to the general population and the risk of suicide, accidents, and traumas is increased. Also, the psychosocial aspects affect the quality of life: epilepsy patients were reported less likely to get married and employed (Jacoby & Baker, 2008). SUDEP is the most common reason for death among the epilepsy patients. It includes sudden and unexpected death not related to trauma or drowning, which might be related to a recent seizure. Annual incidence of SUDEP varies from 0.09-1.2 per 1000 in the general epilepsy population, and it is higher among patients with drug-resistant epilepsy (DRE) and lower among pediatric patients (Friedman et al., 2014). The risk for SUDEP is especially high in nocturnal seizures (Lamberts et al., 2012).

2.2 Classification of epileptic seizures

2.2.1 ILAE classification of seizures

The classification of seizures is significant for many reasons. The classification improves the communication of clinicians, enables the categorization of patients to receive appropriate therapies based on the seizure type, and helps diagnosing epilepsy.

The most recent classification guidelines were published by ILAE in 2017. As the knowledge related to onset of seizures increases, the need for updated terminology increases to improve the accuracy of seizure classification. Some seizure types can

have either focal or generalized onset, and if the onset is unclear, the onset is unclassified. To determine the onset of seizures, the knowledge of clinical manifestations of seizures, and possibly EEG, is required (Fisher, Cross, French, et al., 2017). In compared to the 1981 ILAE classification ("Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy.," 1981), the terminology has been updated, awareness is a classifier, and some seizure types are in many categories (Fisher, Cross, D'Souza, et al., 2017).

According to ILAE 2017 seizure classification (Fisher, Cross, D'Souza, et al., 2017), the seizures are first classified based on the onset. Seizures with focal onset occur in the networks limited to one hemisphere (Berg et al., 2010) but the localization of these seizures may be discrete or widely distributed. Generalized onset seizures originate within bilaterally distributed neural connections, then they rapidly spread to both hemispheres. The onset is not known in unknown-onset seizures, but these seizures may be classified to focal or generalized category after further investigation. The next classification level is level of awareness which is defined as knowledge of self and environment during the seizure, and it can be assessed by evaluating responsiveness and memory (Blumenfeld, 2012). If the awareness is not intact during any phase of the seizure, the seizure is classified as impaired awareness seizure. Classification of focal and generalized seizures includes both motor and nonmotor characteristics. Focal onset seizures include focal motor features such as atonic (loss of muscle tone), tonic (sustained muscle stiffening), clonic (rhythmic muscle jerking), myoclonic (irregular, brief twitch), hyperkinetic (complex movements, e.g. pedaling, thrashing), epileptic spasms (flexion or extension of arms and flexion of trunk) and automatisms (purposeless, repetitive motor activity, e.g. smacking) (Fisher, Cross, French, et al., 2017). Nonmotor features include behavior arrest (cessation of activity), autonomic features (e.g. flushing), cognitive, emotional, and sensations (Fisher, Cross, French, et al., 2017). Generalized seizures have motor characteristics such as tonic-clonic (stiffening followed by jerking), clonic, tonic, myoclonic, atonic, and epileptic spasms, as well as nonmotor characteristics such as various absence seizures: typical and atypical absence seizures, myoclonic absence seizures, and eyelid myoclonia (Fisher, Cross, French, et al., 2017). Absence seizures typically have a sudden start and end, and patients suffering from them are usually young but, however, atypical absence seizures may have slow onset or termination (Fisher, Cross, D'Souza, et al., 2017). ILAE classification of seizures is presented in Figure 1.

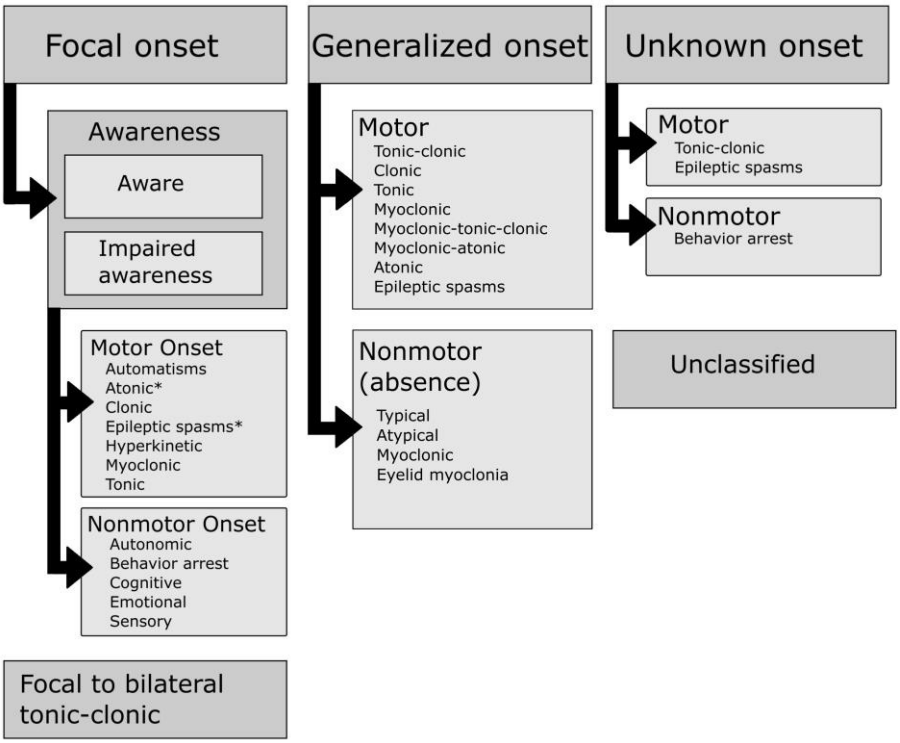

Figure 1. ILAE 2017 seizure classification. * Degree of awareness usually not specified. Modified from Fisher, Cross, French, et al., 2017.

2.2.2 Semiological classification of seizures

In compared to the ILAE seizure classification, which approaches the classification by the onset zones of seizures, semiological classification of seizures is based on both observable ictal seizure semiological findings reported by witnessers or recognized in video monitoring and subjective symptoms. EEG is not needed in this classification even though it helps to determine the epileptogenic zone in the deeper parts of the brain (Martinez-Lizana et al., 2022; Turek & Skjei, 2022). Semiological classification concentrates on ictal seizure features, enables identification of ictal semiological features independent of other tests, and underlines the importance to observe clinical semiological manifestations. It has been used in the evaluation prior to surgical treatment (Kim et al., 2002).

In semiological classification, seizure manifestations can be caused by epileptic activity in sensory, consciousness, autonomic, or motor domains (Lüders et al., 1998). If a suspected seizure event is not considered epileptic, it is classified as

paroxysmal event. Epileptic activity in sensory domain causes auras which are brief subjective symptoms occurring in the beginning of the seizure that includes features such as somatosensory, visual (hallucinations), auditory (auditory hallucinations), olfactory (perception of smell), gustatory (perception of taste), autonomic (abdominal sensations) or psychic features (complex hallucinations, déjà vu) (Beniczky et al., 2022; Lüders et al., 1998). Seizures with interference in consciousness domain is classified as dialeptic seizure (Beniczky et al., 2022; Lüders et al., 1998). Autonomic seizures manifest as episodic changes in autonomic functions such as sensations (hot flashes, palpitations) (Bautista & Lüders, 2000; Beniczky et al., 2022). Motor domain contains simple and complex motor seizures, where simple and complex refers to the complexity of movement. Simple motor seizures include epileptic spasms, myoclonic, tonic, clonic, tonic-clonic and versive seizures (movement of eyes, head, half or whole body to one side) (Beniczky et al., 2022; Lüders et al., 1998). Complex motor seizures include hyperkinetic seizures, automotor seizures (seizures consisted of automatisms), and gelastic seizures (laughing as a main manifestation) (Beniczky et al., 2022; Lüders et al., 1998). If a seizure does not fit to any of the aforementioned domains, it is classified as special seizure which includes inhibitory motor seizures, such as atonic seizures, astatic seizures, hypomotor seizures, akinetic seizures, negative myoclonic seizures and aphasic seizures (Kim et al., 2002; Tufenkjian & Lüders, 2012).

In order to improve the characterization of seizures, the somatotropic modifiers can be used in the description of a seizure, such as somatotropic side of symptoms (left or right), somatotropic area (hand, arm, foot, etc.), laterality (bilateral, asymmetric, axial, generalized), and hemisphere of origin (right or left) (Beniczky et al., 2022). Also sequence of seizures can be described as components in the chronological order of appearance (Hirfanoglu et al., 2007; Lüders et al., 1998). Semiological seizure classification features have been presented in Table 1.

Table 1. Semiological seizure classification modified from Beniczky et al., 2022; Lüders et al., 1998. [1]Left/right/axial/generalized/bilateral/asymmetric [2]Left hemisphere/right hemisphere

Epileptic seizure	Aura	Somatosensory[1]	
		Auditory[1]	
		Olfactory	
		Abdominal	
		Visual[1]	
		Autonomic[1]	
		Psychic	
	Autonomic seizure[1]		
	Dialeptic seizure[2]		
	Motor seizure	Simple motor seizure[1]	Myoclonic seizure[1]
			Epileptic spasm[1]
			Tonic seizure[1]
			Clonic seizure[1]
			Tonic-clonic seizure[1]
			Versive seizure[1]
		Complex motor seizure[2]	Hyperkinetic seizure[2]
			Automotor seizure[2]
			Gelastic seizure
	Special seizure	Atonic seizure[1]	
		Astatic seizure	
		Akinetic seizure[1]	
		Hypomotor seizure[2]	
		Aphasic seizure[2]	
		Negative myoclonic seizure[1]	
Paroxysmal event			

2.3 Classification of epilepsies

Epilepsy classification is a significant tool to assess seizures and disease of an epilepsy patient, and to choose the most appropriate treatment. Classification allows to understand the seizure types, other seizure types that are likely to occur, the

potential factors that triggers seizures, and even the prognosis. The most recent classification guidelines were presented in 2017 (Fisher, 2017; Scheffer et al., 2017).

The ILAE 2017 classification of the epilepsies is a multilevel classification, which categorizes the epilepsy in seizure type, epilepsy type, and epilepsy syndrome levels (Zuberi et al., 2022). Seizure onset is the first level of classification, which include focal, generalized, and unknown onset by using EEG, video, or imaging studies. The second level of classification, epilepsy types, includes focal, generalized, unknown, and combined generalized and focal epilepsy. Generalized epilepsies show generalized spike-wave activity on EEG on both hemispheres, and they may include various seizure types such as absence, myoclonic, atonic, tonic, and tonic-clonic seizures. Category of focal epilepsies contain disorders involving one hemisphere, with focal or multifocal onset. Combined generalized and focal epilepsies include patients who suffer from both generalized and focal seizures. Unknown epilepsy is used if it is undetermined whether the patient has focal or generalized epilepsy. Third level of classification is diagnosis of epilepsy syndrome, which refers to a cluster of characteristics including age at onset, seizure types, seizure triggers, EEG, and imaging features, and they may have related prognostic and treatment implications (Scheffer et al., 2017). Classification of epilepsies is demonstrated in Figure 2.

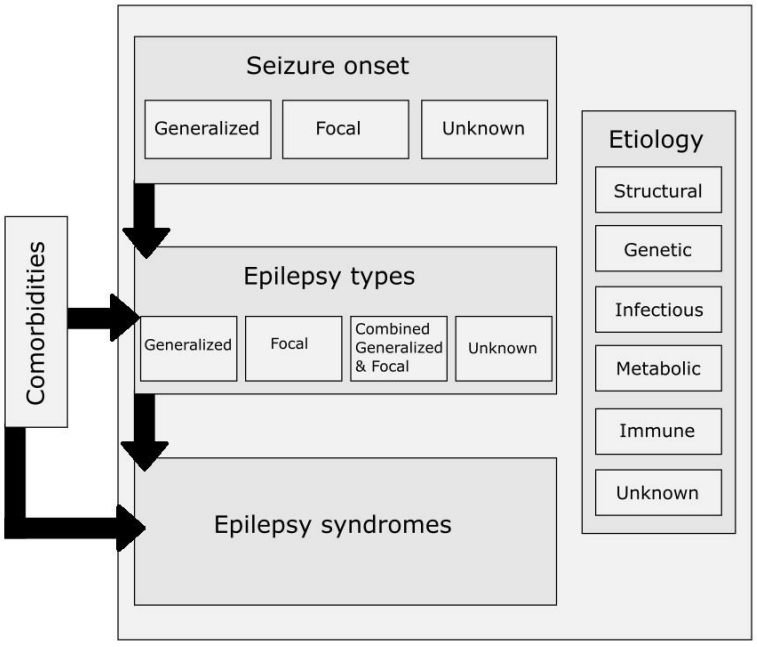

Figure 2. Classification of epilepsies. According to ILAE classification of epilepsies. Modified from Scheffer et al, 2017.

Characteristics of focal epilepsies with different seizure onset zone

Approximately 60% of all epilepsies have focal origin (McIntosh & Das, 2023; Téllez-Zenteno & Hernández-Ronquillo, 2012). Focal epilepsies have various clinical characteristics according to the zone of seizure onset. Based on which lobe the onset focus is located, epilepsies are divided to temporal lobe epilepsy, frontal lobe epilepsy, parietal lobe epilepsy and occipital lobe epilepsy. On the following section, characteristics of each lobular epilepsy type are described. Different characteristics can help to recognize and diagnose epilepsy type based on the documented seizures.

Temporal lobe epilepsy (TLE)

Temporal lobe epilepsy includes a variety of disorders in which the common factor is origin from temporal lobe. TLE is the most common form of focal epilepsy (Radaelli et al., 2021), and it is the cause for 30-35% of all epilepsies (Yang et al, 2020). One third of patients in general TLE population develop DRE but the prevalence is twice as high in patients with mesial temporal sclerosis (Bjørke et al, 2018). It causes damage in the temporal lobe and thus it adversely affects cognitive functions, immediate story recall, working memory, delayed memory tasks, and visuospatial memory and learning (Tallarita et al., 2019). Early diagnosis in children with TLE may predict drug-refractory characteristic of the disorder (Rzezak et al., 2014). Early surgical operation improves the cognitive prognosis and quality of life of pediatric patients with TLE (Asadi-Pooya et al., 2017; Rzezak et al., 2014).

Frontal lobe epilepsy (FLE)

Frontal lobe epilepsy has an onset zone in the frontal lobe in the brain. FLE includes 20-30% of focal epilepsies and 10-20% of DREs (Giovagnoli et al., 2020). FLE can cause a diverse type of seizures depending on the origin of seizures, such as motor cortex or sensorimotor supplementary area (Lee et al., 2008). According to a recent study, FLE can adversely affect epistemic and affective mental states such as knowledge, motivation, willing, persuasion, deception and lying, causing significant impact on social cognition (Giovagnoli et al., 2020), especially among pediatric patients (Braakman et al., 2013). A significant proportion of patients with FLE is refractory to ASMs, and even though surgical procedures have been done in treatment of FLE, success rate of operational treatment in FLE is lower than in TLE (Lee et al., 2008).

Parietal lobe epilepsy (PLE)

It is estimated that almost 6% of focal seizures is caused by PLE (Salanova, 2018). It can cause a variety of clinical manifestations, but it is typically characterized by the presenting auras such as paresthesia, numbness, and tingling sensations (Salanova, 2018). However, most patients with PLE have misleading symptoms or no symptoms at all. Localization of epileptic zone may be difficult due to the indistinct symptoms which may result inefficacy in operational treatment (Siegel & Williamson, 2000). However, EEG and neuroimaging features may improve the localization of PLE(Kurşun et al., 2016). Patients with posterior epilepsies (OLE and PLE) have reported impaired visuoconstruction (e.g., spatial movements and drawing), verbal activities (e.g., picture naming), and executive functions (Traianou et al., 2019).

Occipital lobe epilepsy (OLE)

Occipital lobe epilepsies cause mainly visual and oculomotor ictal manifestations, such as simple visual hallucinations, ictal amaurosis, eye movement sensations, forced blinking of eyes, as well as postictal headache (Adcock & Panayiotopoulos, 2012). Patients may also experience ictal nausea, vomiting or autonomic symptoms, such as sweating, cardiac and breathing symptoms (Williamson et al., 1992). ASMs are often effective in OLE, but some patients may need operational treatment (Yilmaz & Karatoprak, 2015).

2.4 Drug-resistant epilepsy

DRE is defined as a failure to reach seizure freedom despite the appropriate use of two tolerated ASMs (Kwan et al, 2010). Patient must have used appropriate medication which has been proven to be effective for patient's epilepsy and seizure types including the proper use of ASMs, which means the use of adequate dosage for a sufficient length of time (Kwan et al., 2010). It is estimated that 30% of epilepsy patients suffer from DRE. Several clinical factors are associated with DRE, such as age at onset, symptomatic epilepsy, abnormal neuroimaging, abnormal EEG, mental retardation, neuropsychiatric disorders, and status epilepticus (SE) (Xue-Ping et al., 2019). However, variety of clinical course and seizure frequency among patients, and the inconsistency in defining DRE impede the estimation of epidemiology (Kalilani et al., 2018). Mechanistic hypotheses are largely unknown, but they can be divided into three groups: disease-related mechanisms, drug-related mechanisms, and genetic mechanisms. However, DRE is most likely caused by multiple mechanisms (Lerche, 2020). Patients with DRE are at higher risk for sudden death, injuries, psychosocial

dysfunction, and decreased QoL (Löscher et al., 2020). In these patients, the health-related QoL is related to incomplete seizure control, seizure severity, anxiety, depression, and other comorbidities (Conway et al., 2016). Furthermore, possible intolerable side-effects of ASMs can decrease QoL despite improved seizure control (Szaflarski et al., 2006).

2.5 Epileptogenesis

Epileptogenesis is a process where formerly normal function of neuronal networks of the brain has changed towards increased probability of triggering seizures (Russo & Citraro, 2021). Typically, epileptogenesis initiates when the brain confronts an epileptogenic risk factor (e.g., injury or stroke), and it has been suggested to end in the appearance of first spontaneous epileptic seizure. However, studies have proven that epileptogenesis continues to increase the seizure frequency and maintain the progression after the first spontaneous seizure (Terrone et al., 2016). Epileptogenesis has also a counter component, antiepileptogenesis, which opposes the effects of epileptogenesis (Pitkänen et al., 2015). Epileptogenesis is regarded as a dynamic process which changes the excitability of neurons, generates critical connections between neurons, and possibly causes the structural alterations in the brain such as generation and degeneration of neurons, gliosis, axonal damage, inflammatory reaction in brain tissue, and reorganization of extracellular and intraneuronal structure (Pitkänen et al., 2015; Terrone et al., 2016). ASMs do not seem to prevent acquired epileptogenesis, though they prevent epileptic seizures. In fact, proconvulsant drugs, such as atipamezole or rimonabant, may improve antiepileptogenesis after epileptogenic insults (Pitkänen & Lukasiuk, 2011). Beneficial effects have been reported by using immunosuppressants, gene therapy, antibodies, and pharmacological neurostimulation (Pitkänen & Lukasiuk, 2011).

The role of molecular, histologic, radiographic, and physiologic biomarkers has been investigated in epileptogenesis to develop a method to prevent epilepsy (Pawlik et al., 2021). However, despite extensive research of epileptogenesis and biomarkers related to it, no treatment has been managed to develop to prevent the establishment of epilepsy. According to recent studies, genetic, molecular, imaging, and EEG biomarkers have shown potential as a biomarker for epileptogenesis. A few genetic biomarkers have been linked to increased risk of structural epileptogenesis, and two molecular biomarkers are promising in the evaluation of epileptogenesis (Engel & Pitkänen, 2020). Imaging technology such as MRI can be used to explore structural abnormalities, whereas PET and SPECT can be utilized in the evaluation of ictal

activation of brain tissue. They are highly specific and accurate in evaluation and determination of the epileptogenic changes in the brain, and the development of MRI can increase the specificity even further in the future. However, a key flaw of the imaging biomarkers is the ambiguity whether the changes in the structure of the brain is caused by epileptogenesis or the epileptogenic insult (Reddy et al., 2019). It is suggested that EEG signal dimension decreases during epileptogenesis indicating a potential biomarker but most of these studies have been executed with animal models, and the potential of biomarker needs to be confirmed also in human studies (Rizzi et al., 2019).

2.6 Etiology of seizures and epilepsy

According to earlier guidelines (Berg et al., 2010), etiology of epilepsy can be divided into three categories: genetic, structural/metabolic, and unknown cause. Due to the clinical need for more specific categorization, the classification was later reformed, and the number of categories increased to classify the etiology into more diverse categories. According to ILAE 2017 guidelines, etiology of epilepsy has been divided into structural, genetic, infectious, metabolic, immune, and unknown etiology, and epilepsy can also be classified into more than one of these categories (Zuberi et al., 2022).

Etiology is structural if abnormalities in the brain are visible in neuroimaging, and based on the findings from imaging it is likely that the abnormalities cause seizures (Gaillard et al., 2009). Structural etiology may be induced by stroke, trauma, infection, or malformation of cortical development. Structural etiology, such as malformations, may have developed due to genetic mutation (Scheffer et al., 2017). Genetic etiology is related to a known or assumed genetic mutation which causes seizures or epilepsy syndromes (Dibbens et al., 2009). However, epilepsies in which the genetic etiology has been considered are varying and the underlying genes are usually not yet known (Scheffer et al., 2017). Some of the genetic mutations might increase the risk of epilepsy without causing it, and genetic tendency may not necessarily be inherited (Carvill et al., 2013). Infectious etiology is the most common etiology globally, and it is a consequence of an infection such as meningitis, encephalitis, tuberculosis, HIV, or cerebral malaria (Egesa et al., 2022; Scheffer et al., 2017). Acute seizures and generation of epilepsy after central nervous infection is likely related to arteritis, ischemia, and infarction triggering defense mechanisms, and this etiology also includes the postinfectious development of epilepsy when immune reaction is triggered after the infection such as autoimmune encephalitis

(Vezzani et al., 2016). Metabolic etiology is a result of a metabolic disorder which causes biochemical changes in the body, such as porphyria, uremia, aminoacidopathies, or pyridoxine-dependent seizures (Scheffer et al., 2017). Unknown etiology is defined if the diagnosis can't be accurately determined based on electroclinical findings or further investigations are not available. Identification of etiology is significant to recognize comorbidities and the possible disease that causes epilepsy, and to treat patients adequately and efficiently (Scheffer et al., 2017).

2.7 Treatment of epilepsy

2.7.1 Drug treatment

The main objective in treatment of epilepsy is to reach seizure-freedom with as few adverse effects as possible. Most appropriate option is usually monotherapy (use of only one anti-seizure medication (ASM)), but many ASMs are licensed, and often used, as an adjunctive therapy in combination (polytherapy). The aim in polytherapy is to select ASMs with different mechanisms of action to achieve the most optimal treatment effect. There are a great number of ASMs available which can make it challenging to select the most appropriate option to treat a patient. Several factors should be acknowledged when choosing the ASM, such as seizure type, possible epilepsy syndrome, other medications, comorbidities, age, and gender (G. Liu et al., 2017). ASMs can be divided into three classes based on their therapeutic efficacy: broad spectrum drugs that can be used both in focal and generalized epilepsy, narrow spectrum drugs mainly used in focal and focal-to-bilateral seizures, and narrow spectrum drugs mainly used in generalized absence seizures (Hakami, 2021). However, there are differences between studies and treatment recommendations which ASMs are considered first-line treatment and which ones are considered second-line ASMs.

Carbamazepine and oxcarbazepine are generally regarded as a first-line drug for monotherapy in adults with focal epilepsy (Lattanzi et al., 2019; Schmidt & Sachdeo, 2000). Second and third generation ASMs have been studied and compared to carbamazepine as a first-line treatment for newly diagnosed epilepsy. According to an evidence review, levetiracetam and zonisamide have been suggested as initial monotherapy in treatment of focal epilepsy in addition to carbamazepine and oxcarbazepine (Glauser et al., 2013; Kanner & Bicchi, 2022; G. Liu et al., 2017). Second-line drugs are considered lamotrigine, topiramate, valproate, and also

phenobarbital for neonatal seizures (Hakami, 2021). Brivaracetam is one of the most recent ASMs that have been used as monotherapy and adjunctive therapy for patients with focal epilepsy. In a phase 3 study, adjunctive brivaracetam significantly reduced seizure frequency compared to a placebo (Klein et al., 2015).

In patients with generalized epilepsy, valproate, lamotrigine and levetiracetam are considered the most effective alternatives for treatment (Nevitt et al., 2017) but choosing medication should be based on type of epilepsy syndrome, sex, age, and psychiatric history of the patient (Kanner & Bicchi, 2022). For generalized and unclassifiable epilepsies, valproate is recommended as the first-line drug but due to the severe adverse effects on fetus it is not recommended for women with potential of pregnancy (A. Marson et al., 2021). Therefore, lamotrigine and levetiracetam are especially recommended for women with potential of pregnancy, as these ASMs do not have similar effects on fetus, and they are considered as effective as valproate (A. Marson et al., 2021; A. G. Marson et al., 2007). Other ASM monotherapy options for generalized tonic-clonic seizures (GTCS) are brivaracetam, topiramate, clobazam and zonisamide (Hakami, 2021). Some studies also suggest that carbamazepine, oxcarbazepine, phenobarbital, and phenytoin have level C evidence on their efficacy as monotherapy (Glauser et al., 2013; G. Liu et al., 2017).

According to Finnish treatment guidelines for epilepsy, if first and second ASM does not gain seizure control as a monotherapy, monotherapy is considered ineffective and polytherapy is recommended (Epilepsy: Finnish Current Care guidelines, 2020). At present, there's no polytherapy guidelines. The best combination of ASMs has been examined but only few effective drug combinations have been explored in human trials. Among patients with DRE, combination of lamotrigine and valproate has been considered the most recommended treatment (Verrotti, Tambucci, et al., 2020), but also valproate and levetiracetam is considered effective (Pipek et al., 2022). During pregnancy, lamotrigine and levetiracetam seemed to offer the best treatment outcomes (Pipek et al., 2022; Vajda et al., 2018).

Generalized epilepsy usually responds to medical treatment more effectively than focal epilepsy; 64-82% of patients with generalized epilepsy and 25-70% of those with focal epilepsy become seizure free (Seneviratne et al., 2012). Despite the development of new drugs, a great number of patients don't achieve seizure freedom. About 50% of patients reach seizure-freedom by using the initial monotherapy, and the rest of the patients are usually treated with polytherapy (Verrotti, Lattanzi, et al., 2020). According to studies, the probability of seizure freedom decreases if the first ASM treatment fails. Among the patients who reached seizure-freedom, half of patients reached seizure freedom with the first ASM, one

third of patients with the second one, and only 24% and 15% of patients with third and fourth ASM, respectively (Brodie et al., 2012; Z. Chen et al., 2018). Thus, the ASM combinations should be limited to two drugs. It is also notable that combinations of ASMs can greatly increase a variety of adverse effects such as anorexia, increased risk of kidney stones, increased bodyweight, anxiety, depression, emotional lability, and psychosis (Verrotti, Lattanzi, et al., 2020).

2.7.2 Epilepsy surgery

If ASMs fail to reach seizure freedom, epilepsy surgery can be considered as a treatment option. Surgical treatment can be implemented by resection, destruction, or disconnection of brain tissue (Moshé et al., 2015). It is important to identify candidates for surgery, and several requirements must be notified prior to surgery, such as seizure semiology, EEG, and neuroimaging findings. In order to fulfill the requirements, seizure control has not been achieved with 2 ASMs, seizures must have focal semiology, most candidates have interictal EEG abnormalities which may provide localization value in temporal epilepsies, and neuroimaging methods such as MRI usually recognize structural abnormality which is usually cause of seizure disorder and can be surgically removed (Ryvlin & Rheims, 2008). If MRI is normal, imaging methods such as PET and SPECT imaging can be utilized to localize epileptic origin, or intracranial EEG could detect abnormal neural activity and provide localization value (Ryvlin & Rheims, 2008). Also, transcranial magnetic stimulation (TMS) can be used to localize motor and language areas in the brain prior to surgery which could help to evaluate risk-benefit ratio, especially in pediatric patients (Narayana et al, 2021). Normal MRI finding is considered with decreased surgical treatment outcome (Téllez-Zenteno et al., 2010). Brain lesions suitable for surgical treatment are usually caused by genetic mutations, and genetic testing is recommended to assist the selection of patients who are suitable for operational treatment (Stevelink et al., 2018).

The aim of epilepsy surgery is to reach seizure control without cognitive, psychiatric, or neurological deficits after treatment, but usually compromises between seizure control and post-surgical dysfunctions are required (Rugg-Gunn et al., 2019). Surgery seems to provide better treatment outcome than ASM treatment for patients who are candidates for surgery, as 58% of patients reached seizure freedom after surgery in comparison to 8% of patients who continued ASM treatment (West et al., 2019). After 5 and 10 years from surgery, 47% and 38% of patients who underwent operational treatment remained seizure free, respectively,

and 74% and 70% of patients experienced >50% seizure reduction (Mohan et al., 2018). Even though surgery seems to improve treatment outcomes and reduce adverse effects of ASMs, it may still not be completely utilized (Cascino & Brinkmann, 2021); patients who undergo surgery may suffer from delay of 15-20 years between onset of epilepsy and surgical treatment (Rugg-Gunn et al., 2019).

2.7.3 Neurostimulation

Neurostimulation is a treatment option for patients with DRE who are not candidates for operational treatment. The mechanism of action of neurostimulation is to stimulate neurons activated during seizures to decrease the epileptic activity in the brain, as well as seizure frequency and severity. Stimulation of neurons is carried out by a lead wire coiled around the left vagus nerve attached to a pulse generator (vagus nerve stimulation, VNS), or by utilizing intracranial electrodes placed in the brain tissue in a surgery (deep brain stimulation, DBS).

Vagus nerve stimulation (VNS)

Specific mechanism of action of VNS is not completely understood but according to animal studies, VNS treats DRE by activating nucleus tractus solitarius and surrounding brain regions, controlling GABAergic activities, and decreasing hypersynchronized cortical activity and neuroinflammation (Xue et al., 2022). VNS is suitable for a variety of DRE patients without age or seizure type restrictions which explains the status as the most used neurostimulation method (Moshé et al., 2015; Wheless et al., 2018). Age, sex, seizure type, etiology or seizure frequency do not predict the treatment outcome of VNS (Wheless et al., 2018). Candidates for VNS are patients who suffer from DRE with nonepileptic events excluded, and patient are not eligible for epilepsy surgery (Wheless et al., 2018). Contraindications of VNS are prior resection of the left vagus nerve or high risk of complication, psychiatric disorders such as personality disorders and psychosis, alcohol or drug use, heart diseases, history of vasovagal syncope, vagotomy, or respiratory disorders such as asthma (Toffa et al., 2020).

In randomized controlled trials, VNS caused >50% seizure decrease in 26-40% of patients (Klinkenberg et al, 2012; Pérez-Carbonell et al, 2020). Efficacy of VNS on seizures seems to increase over time: >50% seizure reduction is achieved by 45-65% of patients during a several years of follow-up (Elliott et al., 2011; Toffa et al., 2020). Despite the significant effect on seizure frequency, only few patients achieve seizure freedom after implantation of VNS (Toffa et al., 2020; Wheless et al., 2018).

That's why the role of VNS has been considered more palliative in treatment of epilepsy. Complications of VNS implantation include infections and vocal cord paresis, and adverse effects of VNS include hoarseness, voice change and cough (González et al., 2019).

Deep brain stimulation (DBS)

DBS is mostly used to treat severe DREs (Moshé et al., 2015). Target areas of DBS in the brain include anterior nucleus of thalamus (ANT), centromedian nucleus of thalamus (CMT), and hippocampus (HC). Recent studies have been examined DBS targeting cerebellum (CB-DBS) and subthalamic nucleus (STN-DBS) but the lack of uncontrolled studies decreases their clinical use (Xue et al., 2022).

Criteria for DBS and VNS candidates are similar. In a recent randomized controlled study, median reduction in seizure frequency was 33% at 2 years and 55% at 5 years with responder rates of 32% and 53%, respectively (Peltola et al, 2023). Other studies have reported median seizure reduction of 43, 56, 69, and 74% after 1, 2, 5, and 7 years from the initiation of ANT DBS, respectively (Ryvlin et al., 2021; Zhou et al., 2018). ANT-DBS has been suggested to be the most effective for focal and FBTC seizures (Vetkas et al., 2022). CMT has connections to ascending reticular system, insula and basal ganglia, and it potentially control seizures via these brain connections (M. C. H. Li & Cook, 2018). CMT-DBS may be effective against generalized epilepsy such as Lennox-Gastaut syndrome (Dalic et al., 2022). The initiation of CMT DBS caused seizure reduction from 65 to 95% at 1 and 2 years of follow-up (Valentín et al., 2013; Zhou et al., 2018).

Studies have shown effect of HC-DBS in treatment of refractory TLE, but further studies may be needed to examine clinical feasibility (Xue et al, 2022). By using HC DBS, the mean seizure reduction varied from 58 to 78% but some patients with initial unilateral stimulation converted to bilateral stimulation experienced improvement in seizure frequency from 40 to 70% (Han et al., 2014; Zhou et al., 2018).

Similarly as VNS, DBS mainly affects the seizure frequency, and only few patients reach complete seizure freedom (Ryvlin et al., 2021). Responder rates of ANT, CMT and HCP varies 44-100%, 50-100% and 60-100% (Zhou et al., 2018). Treatment outcomes of DBS and VNS were similar when they were compared (Kulju et al., 2018). However, it is notable that effect of DBS varies greatly between patients, and it seems that connectivity between brain regions via neuronal circuits greatly affects the efficacy of DBS (Järvenpää et al., 2018; Torres Diaz et al., 2021). Most common

adverse effects related to DBS were infections and hemorrhages (Zhou et al., 2018) but also depression and memory decline have been reported (Ryvlin et al., 2021).

2.8 Seizure detection

2.8.1 Seizure diaries in seizure detection

Seizure detection generally relies on traditional patient-kept seizure diaries in which patients or their caregivers document seizures. There are several applications to document seizures along with traditional diaries, and low costs explain the wide use of this method. However, according to previous studies, there are several problems related to use of seizure diaries. Even 50% of motor seizures are missed by patients, and the accuracy of documentation varies greatly depending on time of day (Aghaei-Lasboo & Fisher, 2016; Blachut et al., 2015; Elger & Hoppe, 2018; Kerling et al., 2006). Sensitivity of seizure diaries varied greatly between seizure types; 26.8% in focal impaired awareness seizures, 73.8% in focal seizures with intact awareness, and 58.3% in secondarily generalized tonic-clonic seizures (Hoppe et al., 2007). Nocturnal seizures especially underline the inaccuracy of seizure diaries; even 85% of them are failed to be documented (Hoppe et al., 2007). Seizure diaries are not only prone to underestimation but also overestimation of seizure counts (Chiang et al., 2018; Goldstein et al., 2021). Tendency of seizure diaries to underestimate seizure counts is identified, and patients seems to know that they under-report seizures (Blachut et al., 2015). However, despite their inaccuracies, seizure diaries are still significant in seizure documentation due to cost-effectiveness especially in long-term management (Egenasi et al., 2022).

Accurate documentation when using seizure diaries requires prioritization and an orderly approach which makes them prone to inaccuracies. Seizure diaries are unreliable especially due to postictal amnesia of patient, and the inability of patient or caregiver to observe and document seizures which may be contributed by the incomplete supervision, lack of clinical features, or the delayed documentation after the occurrence of seizure (Elger & Hoppe, 2018). Accuracy of seizure diaries also depends on seizure types; inaccurate documentation is more common with impaired awareness focal seizures, absence seizures, infantile spasms while GTCS are rarely missed (Akman et al., 2009). In addition to ictal or postictal amnesia and level of consciousness during seizures, poor baseline memory function itself may also impede the ability of documentation (Detyniecki & Blumenfeld, 2014).

Consciousness, in turn, may be altered by seizure type, localization by hemisphere and lobe, and preictal vigilance state at seizure onset. Seizures originating in temporal lobe and left hemisphere are more likely missed (Detyniecki & Blumenfeld, 2014). Interpretation of seizure diaries may cause difficulties if the patient does not understand the instructions to use and maintain diary, the patient loses the diary before meeting with clinician or records adverse events or false positives in the diaries (Fisher et al., 2012).

Inaccurate seizure detection has various effects on patients and their treatment. If seizure count is inaccurate and seizure frequency has been underestimated, a sufficient treatment response might be assumed which can lead to complicated or prolonged seizures, even SUDEP (Detyniecki et al., 2018; Walczak et al., 2001). Inaccurate documentation hampers the evaluation of therapeutic outcomes of drug interventions both in clinical practice and within drug trials (Dalrymple & Appleby, 2000; Elger & Hoppe, 2018). According to Blachut et al, (2017), and the inaccuracy of seizure diaries is present both among the non-participants and participants of clinical drug trials which causes inaccuracies in the results of clinical trials. Inaccurate documentation also adversely affects the everyday life; uncontrolled epilepsy precludes the patient from getting a driving license or applying to certain occupations and the diagnosis could be concealed due to these reasons (Dalrymple & Appleby, 2000). Consequently, improved seizure documentation could help clinicians to choose the most appropriate drug treatment based on seizure type and provide more accurate and reliable information of treatment effect for drug trials.

New applications have been developed to improve the usability and sensitivity of seizure diaries. Electronic diaries have several advantages in compared to the traditional one: it is more accessible as smartphones are common, data is not easily lost, date- and timestamped diary notes are allowed, and reminder functions (medication, seizure documentation, visits) improves treatment adherence even though disadvantages, including privacy issues, needs to be solved (Fisher et al., 2012; Gray et al., 2022). Mobile applications can help patients in self-management of their epilepsy and help them to record seizures (which is not possible with traditional paper diaries), provide knowledge about epilepsy, and they are easy to use which confirmed the patients' satisfaction of the application (Choi et al., 2021; Yoo et al., 2020). However, these applications did not seem to increase sensitivity when compared to video-EEG monitoring, and limitations such as small study populations, short duration of use, and lower adherence among adolescent patients affect the reliability of the results (Choi et al., 2021; Escoffery et al., 2018; Yoo et al., 2020). Despite the increasing amount of epilepsy self-management applications, only

a minority of epilepsy patients are using them even though they could increase adherence to treatment could improve seizure control, which is also one of the main objectives in treatment of epilepsy (Alzamanan et al., 2021).

2.8.2 EEG in seizure detection

Epileptic events can cause various manifestations in EEG, such as desynchronization, decrease of amplitude, appearance of high amplitude activity, and irregular paroxysmal activity (Fisher et al., 2014; Haueisen et al., 2012). By using EEG, epilepsy diagnosis, seizure and epilepsy syndrome classification, surgical candidates can be determined. Video-EEG has been considered as a golden standard for seizure detection.

Several methods have been developed to improve the efficacy without loss of reliability, such as automated EEG analysis software by creating algorithms to identify seizure patterns in the EEG. Automatic analysis of EEG can be done during or after the recording (Ahmad et al., 2022; Martin et al., 2022; Wang et al., 2022). It can improve patient safety, but high number of false positives may limit its use in EMUs. For example, automated EEG analysis algorithm, EpiScan, detected electrographic seizure with a sensitivity of 81-83% and FDR of 0.29/h (Elezi et al., 2022; Fürbass et al., 2015; Hartmann et al., 2011). Another software, Persyst 13, reached a sensitivity of 76-81% of electrographic seizures and 87% of focal impaired awareness and focal to bilateral tonic-clonic seizures with a FDR of 0.14-0.9/h (Ganguly et al., 2022; Kamitaki et al., 2019; Koren et al., 2021).

Convolutional neural networks (CNN) deep learning method utilized in EEG analysis achieved accuracy of 96-99%, sensitivity of 96-98% and specificity of 96-98% (Cimr et al., 2023; C. Li et al., 2022; Tanveer et al., 2021). Binary classification algorithm in combination with deep learning methods has reached 90-97% sensitivity and specificity with a true alarm rate of 95% on scalp EEG recordings (H. Liu et al., 2021; Ruiz Marín et al., 2021; Zhang et al., 2020). However, these methods have poor generalizability, and the same sensitivity has not been achieved in clinical practice as in research settings. When utilizing Riemannian geometry to form a feature vector from EEG channel data, sensitivity of 99.91%, specificity of 99.82% was reported in an EMU setting, and studies with more robust datasets are needed (Shariat et al., 2021).

There are several limitations related to the use of EEG and video-EEG. Video-EEG requires a lot of time and resources, and the cost-effectiveness may be questioned in the case of infrequent seizure events. Options to video-EEG, such as

routine EEG and continuous EEG, have been used. Continuous EEG has been recommended for epilepsy patients with impaired consciousness in compared to routine EEG (lasting < 30 minutes) (Herman et al., 2015; Rossetti et al., 2020). Even though routine and continuous EEG are less expensive than video-EEG and those methods can monitor patients longer, infrequent seizures are still possibly missed by all these methods. In addition, EEG is considered uncomfortable and even stigmatizing for patients (Schulze-Bonhage et al., 2010; Ulate-Campos et al., 2016).

2.8.3 Automatic seizure detection

Various systems to detect epileptic seizures automatically have been developed. Wearable devices, such as smartwatches and bracelets, were most acceptable, and most concerns were related to discomfort, false negatives (especially with alarm systems) and costs (Herrera-Fortin et al., 2021; Sivathamboo et al., 2022; Van de Vel, Smets, et al., 2016). There are many ways to receive data from ictal events of patients, such us motion and pressure sensors, video or audio data, EEG (discussed above), electrocardiography (ECG), electromyography (EMG), and electrodemal activity (EDA) (Naganur et al., 2022; Ulate-Campos et al., 2016). A detection system may consist of either one method (unimodal system) or multiple methods combined (multimodal system).

Unimodal seizure detection

Changes in heart rate before and during seizures have been widely studied. The change in heart rate is larger in patients with seizures including autonomic and major motor manifestations, especially on GTCS, hyperkinetic and temporal lobe seizures (Jansen et al., 2013). Among the patients with significant ictal change in heart rate (>50 beats/min), ECG detection algorithm reached sensitivity of 83-87% with 0.9 false detections per day (De Cooman et al., 2017; Jeppesen et al., 2020). Another study reported sensitivity of 86-98% with false detection rate (FDR) of 1.1-9.5 /h depending on selected parameters in a dataset of 241 seizures (Osorio, 2014) suggesting high sensitivity in expense of false detections. Sensitivity of ECG in seizure detection varies greatly between seizure types: 96% for tonic-clonic, 72.5% for hyperkinetic, 46.2% for tonic and clonic seizures (De Cooman et al., 2018). However, the algorithm was run offline, not in real time, and the requirement of change in heart rate exclude a great number of patients (De Cooman et al., 2018; Jeppesen et al., 2020). FDR of unimodal ECG analysis varied between 0.7-5.4/h (van Westrhenen et al., 2019).

EMG measures electric signals from muscle activity. Many studies have focused on detection of convulsive seizures which have resulted sensitivity of 93.8-100% and FDR of 0.03-1.4 per day (Arbune et al., 2020; Beniczky et al., 2016; Beniczky, Conradsen, Henning, et al., 2018; Szabó et al., 2015). For tonic seizures, sensitivity varied between 53-63% with FDR of 1.49-4.03 per hour (Larsen et al., 2014). Also, EMG has been reported to be useful in quantification and detection of myoclonic movements (Rissanen et al, 2021). EMG provides a highly sensitive method to detect convulsive seizures, but the performance is mostly limited only to that seizure type (Arbune et al., 2020; Beniczky, Conradsen, & Wolf, 2018) which limits the feasibility of the device for larger patient populations.

EDA sensors measures the activity of sweat glands which is modulated by sympathetic nervous system activated during epileptic seizures (Lanteaume et al., 2007), especially tonic-clonic seizures (Poh et al., 2010). The system detected GTCS with 94% sensitivity and 0.74 false alarms per day, but among patients with no GTCS, the mean FDR was 0.98 per day (Poh et al., 2012). However, due to low number of seizures, more studies are needed to confirm the feasibility to seizure detection (Poh et al., 2012). Also, this system requires autonomic manifestations during seizures which limits the suitable patient population.

Only few studies have been made related to audio-based seizure detection. By using audio algorithms, ictal sounds can be analyzed to detect seizures. Tonic-clonic and GTCS with recognizable sounds can be detected with mean sensitivity of 81%, positive predictive value (PPV) of 40% and FDR of 1.29 per night, but seizures with recognizable sounds were found in only half of their patient population (J. B. Arends et al., 2016). Other study reached a sensitivity of 88,1% with FDR of 0.83/h (Kok et al., 2022). As the system requires significant sounds occurring in the beginning or during the seizures to detect them, the generalizability of this method is limited.

Emfit measures pressure, movement, and rhythmic jerks with sensors placed under the mattress. The system detects convulsive seizures and yields a sensitivity of 70-89% with FDR of 0.55 per night (Narechania et al., 2013; Nouboue et al., 2023; Poppel et al., 2013; Van de Vel et al., 2014). Among patients with various seizure types, such as tonic-clonic, myoclonic, focal impaired awareness seizures, tonic, and focal motor seizures, sensitivity was 30% during daytime and 54% during night-time (Poppel et al., 2013) but also 0% sensitivity for non-convulsive seizures has been reported (Nouboue et al., 2023). However, daytime activities increase the number of false positives and location of the device, weight of patient and thickness of mattress may affect the number of false negatives (Narechania et al., 2013). Despite low

sensitivity of seizures with smaller motor manifestations, the system is useful in detection of nocturnal tonic-clonic seizures (Poppel et al., 2013).

Multimodal seizure detection systems

Multimodal detection devices combine data from more than one modality, which seems to enable increased sensitivity and lower false detection rates in compared to unimodal systems (Baumgartner et al., 2018; Ulate-Campos et al., 2016). Various combinations of different modalities have been studied previously.

VARIA system combines video, accelerometry, and radar-induced activity recording. The camera is placed near to patient's bed, and the radar identifies the speed and direction of accelerometer sensors to recognize normal and seizure-related motion (Amengual-Gual et al., 2019; Van de Vel, Milosevic, et al., 2016). VARIA reached a sensitivity of 56% and FDR of 20 per night (Van de Vel et al., 2014) but in another study, sensitivity was 66.8% and false detections per night was 1.16 (Van de Vel, Milosevic, et al., 2016). The system also managed to detect some seizures missed by caregivers (Van de Vel et al., 2014; Van de Vel, Milosevic, et al., 2016). Non-continuously recorded data, small patient population, and the lack of golden standard (EEG) limit reliability of the results, and inability to detect tonic phase can lead to missing tonic-clonic seizures if the clonic phase is short. VARIA achieved higher sensitivity and lower FDR than caregivers' documentations (Van de Vel, Milosevic, et al., 2016) but more studies are needed to confirm the performance in a larger patient group.

Various wrist and ancle sensors have been examined in multimodal seizure detection. Empatica wrist sensors included electrodermal activity (EDA) and accelerometry (ACM) sensors in patients with tonic-clonic seizures and resulted sensitivity of 92-94% and FDR varied from 1.26 per hour to 0.2 per day (Onorati et al., 2017, 2021). In another study, it detected GTCS with a sensitivity of 100% with FDR of 0.42 in inpatient settings (conducted in EMUs) and 93% sensitivity with 0.58 FDR in outpatient settings (conducted at patient's home and everyday life) (Regalia et al., 2019). Larger, prospective, home-based studies with longer follow-ups are needed in further evaluation. Physical activity in everyday life can rise FDR and affect the results (Onorati et al., 2017). Also, this device was tested in patients with only tonic-clonic seizures which reduces generalizability of the results. Nightwatch wristband, which combined ACM and heart rate, reached median sensitivity of 86%, FDR of 0.23 per night and PPV of 49% when tested in a patient population including tonic-clonic, generalized tonic, hyperkinetic, and myoclonic seizures (J. Arends et al., 2018). Among pediatric patients with motor seizures,

median sensitivity was 75%, PPV 26% and FDR 0.2/h but after adjusting settings it reached 93% median sensitivity, 58% median PPV and FDR 0.08 /h (Lazeron et al., 2022). However, this method was tested in hospital settings and without EEG as a golden standard. These methods are mostly suitable for seizures with motor components.

Multimodal intelligent seizure acquisition (MISA) system combines surface electromyography, accelerometry, and gyroscopes. When all of these modalities were used, the system yielded sensitivity of 100%, 0 FDR and 0.75 s latency. However, the attachment of the motion sensors can hamper getting adequate patient data, and the mentally retarded patients could not tolerate the suit (Conradsen et al., 2012). Despite the promising results, MISA has been examined in only few studies and more studies are needed to evaluate the generalizability of the device.

Another study tested automatic seizure detection device combining EEG, EMG and ECG (Fürbass et al., 2017). Each modality was tested both separately and combined, and with different number of electrodes. When all modalities were combined, overall sensitivity was 74 %, 81 %, and 86 % and the FDR 6.0, 13.5, and 16.5 per day when 7, 8, and 22 electrode montages were used, respectively. The system performed with higher sensitivity in patients with TLE (84-94%) and bilateral tonic-clonic seizures (94-100%) (Fürbass et al., 2017). Validation studies and generalizability have not been examined in larger patient populations.

Functional infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique that forms a picture of cortical hemodynamic conditions by using infrared light (Kassab et al., 2021). It has been used in combination with EEG to examine metabolic and spatial effects of frontal lobe seizures (Nguyen et al., 2013). A multimodal system combining EEG and fNIRS in 40 DRE patients which achieved 89.7% sensitivity and 95.5% specificity with FDR of 5.6% for multimodal data (Sirpal et al., 2019). fNIRS combined with deep learning method (CNN) resulted promising results (95-100% sensitivity, specificity of 98-100%, and PPV of 98-100%) (Rosas-Romero et al., 2019). High computational time, parameter tuning, and small study populations limit the generalizability of the results and further studies are needed (Rosas-Romero et al., 2019; Sirpal et al., 2019). On the other hand, many patients don't have significant ictal changes in neurovascular hemodynamics, which makes the detection inconsistent, and it might also explain why fNIRS is not a very common method in seizure detection (W.-L. Chen et al., 2020).

Summary of unimodal and multimodal automatic seizure detection systems has been gathered in Table 2.

Table 2. Summary of unimodal and multimodal automatic seizure detection systems. *N.A. Not available

Unimodal detection methods							
Detection method	Authors	Data input	Seizures detected	Sensitivity	False detection rate (FDR)	Advantages	Disadvantages
EEG	Kamitaki et al, 2019 Koren et al, 2021 Ganguly et al, 2022 Li et al, 2022	excitatory and inhibitory post-synaptic potential	Motor seizures	76-99.9%	0.14-0.9 /h	Golden standard, high sensitivity	Discomfort during recording, risk for movement artifact
EDA	Poh et al, 2012	activity of sweat glands	GTCS	94%	0.74 /d	Good sensitivity for GTCS, adjunctive tool in multimodal systems	Requires activity of sympathetic nervous system, sensitive mainly to convulsive seizures
ECG	De Cooman et al, 2018 van Westrhenen et al, 2019	Change in heart rate	Tonic-clonic Hyperkinetic Tonic and clonic	96% 72.5% 46.2%	0.7-5.4 /h	Easy to record	Requires significant change in heart rate which limits the suitable seizure types
EMG	Szabó et al, 2015 Beniczky et al, 2016 and 2018 Arbune et al, 2020	Muscle activity	Tonic-clonic Tonic	93.8-100% 53-63%	0.03-1.4 /day 1.49-4.03 /h	High sensitivity for convulsive seizures	Sensitive mainly to convulsive seizures
Audio	Arends et al, 2016 Kok et al, 2022	Change in audio level	Tonic-clonic, tonic Seizures with sounds	81% 88%	1.29 per night 0.83 /h	Good in seizures with sound	Requires significant sound change, low number of studies
Mattress sensor	Poppel et al, 2013 Narechania et al, 2013 Nouboue et al, 2023	Movement	Convulsive seizures Motor seizures	70-89% 30-54%	0.55 per night	Marker-free system, easy for nocturnal detection	Detects mainly major motor seizures, daytime activity increase FDR
Multimodal detection methods							
Detection method	Authors	Data input	Seizures detected	Sensitivity	False detection rate (FDR)	Advantages	Disadvantages
VARIA	Van de Vel et al, 2014	Video, accelerometry,	Tonic-clonic and GTCS	56-66.8%	1.16-20 per night	Ability to recognize the	Non-continuous data recording, lack of

	Van de Vel et al, 2016	radar-induced recording				patient's position in bed	golden standard, inability to detect tonic movement
Empatica wrist sensors	Onorati et al, 2017 Regalia et al, 2019	Accelerometry, EDA	Tonic-clonic	92-100%	0.2 per day – 1.26/h	User friendly, good sensitivity for tonic-clonic seizures	Daily activities may affect FDR, more studies with longer follow-up are required
Nightwatch wrist sensors	Arends et al, 2018 Lazeron et al, 2022	Accelerometry, ECG	Median sensitivity Tonic-clonic Generalized tonic Hyperkinetic Myoclonic	75-93% 96% 89% 73% 84%	0.23 per night – 0.2/h	User friendly, good sensitivity for tonic-clonic and generalized tonic seizures	Tested in hospital settings, no golden standard
MISA	Conradsen et al, 2011	EMG, accelerometry, gyroscopes	Simulated seizures	100%	0	Low FDR and latency	Seizures were simulated; suit does not fit for patients with mental retardation
Multimodal system	Fürbass et al, 2017	EEG, EMG, ECG	FBTCS Focal seizures Motor seizures	94-100% 89% 86%	14.1 16.4 16.5	High sensitivity for FBTC	High false detection rate
Multimodal system	Sirpal et al, 2019	EEG, fNIRS	N.A	89.7%	5.6%	good sensitivity and specificity	Larger studies are required, parameter tuning decreases generalizability, no golden standard
Multimodal system	Rosas-romero et al, 2019	Convolutional Neural Networks (CNN), fNIRS	N.A	95-100%	N.A	High sensitivity, specificity and PPV	Larger studies are required, high computational time, no golden standard

2.8.4 Video-based seizure detection

Seizure monitoring devices

Video based seizure detection methods utilize recorded video data to recognize seizure-like patterns, such as velocity and change of movement, oscillation, and duration, to detect seizures (Cuppens et al., 2010; Geertsema et al., 2018; Kalitzin et al., 2012; Karayiannis, Xiong, et al., 2006), and it is part of the gold standard for seizure detection when combining with EEG (Van de Vel, Cuppens, et al., 2016). Typically, video records movements from whole body, but also use of facial expression analysis in detection of absence seizures has been reported (Pediaditis, Tsiknakis, Koumakis, et al., 2012). Many video-based device use an optical flow method to distinguish moving pixels in each frame to construct a vector field with a motion vector in each pixel, and it may be combined with a background subtraction method which notices the distance of moving pixels when calculating motion signal (Cuppens et al., 2010; Pediaditis, Tsiknakis, & Leitgeb, 2012). Some of the methods also utilize deep learning methods, such as convolutional, quantum and cosine radial basis function neural networks (Karayiannis, Xiong, et al., 2006).

Video-based method can be classified into marker-free and marker-based methods. Marker-based methods include markers, such as infrared markers attached to patient's anatomic landmarks combined with video recording (Rémi et al., 2011), and marker-free methods only includes video recording without markers (Abbasi & Goldenholz, 2019; Pediaditis, Tsiknakis, & Leitgeb, 2012). Patients generally prefer marker-free detection system, as they don't disturb the patient and they are not as stigmatizing as EEG (Ulate-Campos et al., 2016). Also, video-based detection methods are significantly less expensive than EEG and video-EEG which enables longer monitoring periods and better chance of detecting infrequent seizures.

Automatic video analysis combined with depth sensors in infant patients with clonic seizures was examined by analyzing a dataset contained 10 video recordings which durations were 5 minutes. By using only video data, they reached sensitivity of 88% and specificity of 96%, and by combining it with depth sensors resulted 92% sensitivity and 88% specificity (Cattani et al., 2017). Karayannis et al. studied automated detection of videotaped myoclonic and focal clonic seizures in neonatal patients. They involved 240 video events including non-epileptic random movements and 160 seizures. Depending on the neural network used in the study, the system resulted sensitivity of 90-99% and specificity of 89-97% (Karayiannis,

Xiong, et al., 2006) which were both increased above 90% in another study (Karayiannis, Tao, et al., 2006). Among pediatric epilepsy patients, a study reported PPV of 82-100% and sensitivity of 100% with a dataset of less than 2 hours of recorded video and 11 convulsive seizures (Cuppens et al., 2010). Other study with larger dataset of pediatric patients >3 years of age (n=22) with overall 1661 nocturnal seizures reported overall sensitivity of 94% for convulsive seizures and 100% sensitivity for hyperkinetic seizures; overall FDR was 0.05 per night (van Westrhenen et al., 2020). When Gaussian mixture models were employed in background/foreground modeling and extracted displacement and oscillation features to detect motion characteristics of seizures, displacement and oscillation features reached 93.3% sensitivity but 53.3% and 93.3% specificity, respectively (Lu et al., 2013). Dataset of 15 seizures set limits to the generalizability of this method, and patients wore a color pyjamas to improve motion tracking (Lu et al., 2013).

Some studies have explored the use of CNN deep learning in the movement analysis of seizure videos. Yang et al. used a dataset of 76 GTCS videos from 37 patients and analyzed them with CNN+LSTM (long-short-term memory) network method and reached 88% sensitivity and 92% specificity with 22 seconds detection latency (Yang et al., 2021). Another study analyzed 52 seizures recorded in EMUs by using infrared and depth sensors combined with a camera and detected seizures with sensitivity of 87% and specificity of 81% for convulsive seizures but only sensitivity and specificity of 80% and 59% for tonic and automotor seizures, respectively (Achilles et al., 2015).

The sensitivity varies greatly between different seizure types in adult patients. Sensitivity of 75% and PPV over 85% was achieved in patients with myoclonic seizures by utilizing spatio-temporal interest points (STIP) in marker-free seizure detection system (Cuppens et al., 2012). Among patients with clonic seizures, video detection yielded a sensitivity of 95% and FDR of 1 per 24h without assistance of neural network methods (Kalitzin et al., 2012). Another study used video-based detection in combination with neural networks and reached a sensitivity of 100% for convulsive seizures, 60% for hyperkinetic and 66% major motor seizures with FDR of 0.78 per night and detection latency of <10s in 78% of detections (Geertsema et al., 2018). As for the tonic-clonic seizures, even 99% sensitivity and specificity have been reported by utilizing optical flow, principal component analysis and machine learning in a small dataset (21 tonic-clonic seizures) (Garção et al., 2023).

In studies with small dataset, the results may overestimate the performance (risk of overfitting) which can be avoided by dividing the data into training set and validation set (Abbasi & Goldenholz, 2019; van Westrhenen et al., 2020). On the

other hand, bigger datasets may require large computational power for analysis. Also, overestimation of results can be caused by missed seizures if a night was not annotated during monitoring period (van Westrhenen et al., 2020). However, despite the small data size studies still demonstrate the potential of video-based detection and deep learning methods (Abbasi & Goldenholz, 2019). Retrospectively recorded videos may decrease the generalizability of the results when assessing the method as an alarm system, and the privacy issues may concern patients, as retrospective analysis requires video storage (Van de Vel, Cuppens, et al., 2016; van Westrhenen et al., 2020). Many systems have been validated in the hospital setting instead of home, were other persons, pets, background noise and change of illumination can affect the results (van Westrhenen et al., 2020; Yang et al., 2021). Sensitivity of video detection is usually lower in short seizures with small motor manifestation which may hamper the utilization for patients suffering of those seizures (Kalitzin et al., 2012), even though more recent studies have shown accurate detection also for those seizures (Hou et al., 2022). Seizure annotations are limited to symptoms in sight of the camera (Geertsema et al., 2018), and a blanket can impede the movement analysis in the case of nocturnal seizures (Lu et al., 2013). Given the challenges in monitoring in a home setting, and generalizability and accuracy of results in different seizure types, further studies are indicated to develop video detection systems. Beniczky and Ryvlin have previously suggested classification criteria for validation studies of seizure detection devices according to patient count, video recordings and reference standard, similarly as in medical drug trials (Beniczky and Ryvlin, 2018). According to the criteria, most studies about automatic video-based seizure detection are early studies belonging to phase I-II (Beniczky & Ryvlin, 2018) which underlines the importance of further research. Results from studies related to video-based seizure detection have been summarized in Table 3.

In this study, the Nelli® seizure monitoring system was explored. The Nelli® seizure monitoring system is a semi-automatic (hybrid) monitoring platform which utilizes machine learning to analyze videos and to identify kinematic data indicating seizure. The video-based method significantly reduced the review time of video to 14% of the total time and reached sensitivity of 100% for tonic-clonic and clonic seizures and 82% for focal motor seizures (Peltola et al., 2022). Phase II validation of Nelli system regarding sensitivity and FDR is currently being conducted but not published yet. Figure 3 demonstrates the video monitoring system in a home setting.

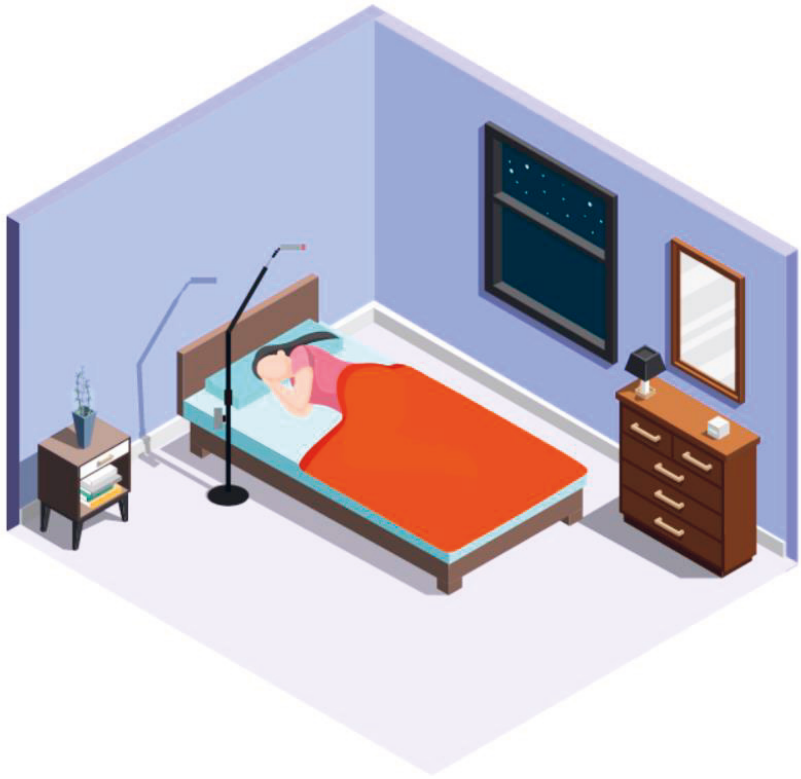

Figure 3. A video-based monitoring system in a home setting. The device has been placed next to the patient's bed to detect nocturnal seizures. Published with permission from Neuro Event Labs Oy, Tampere, Finland.

Applications of seizure monitoring devices

In addition to seizure detection, video monitoring devices can be applied to alarm systems and many of the systems can detect movement and turn on the alarm when suspecting seizure-related behavior (Poppel et al., 2013), and changes in seizure frequency can be used for follow-up (Geertsema et al., 2018). It is important to note that if a monitoring system is used as a detection system it is important to accurately detect the prominent and subtle seizures in the expense of false positives, while high number of false positives could impede the use of the device as an alarm system. Also, as an alarm system, the latency of the seizure detection time is aimed to be low. Parameter threshold settings may depend on purpose of use of the monitoring device.

Video monitoring systems can also be utilized in defining seizure semiology. Video data recorded by monitoring devices has been utilized in quantitative analysis

of seizure semiology with potential results: both sound volume changes (Hartl et al., 2018) and motion analysis can be used to automatically identify semiological features with a localizing value (Ahmedt-Aristizabal et al., 2018; Cunha et al., 2016). Differentiation of semiological features has been utilized in automatic classification of sleep related hypermotor epilepsy (SHE) and disorders of arousal (DOA) which resulted an accuracy of 80% (Moro et al., 2023).

Only few studies have examined automatic seizure classification. Hyperkinetic seizures have been differentiated from non-hyperkinetic seizures with an 80% probability, but non-hyperkinetic seizures yielded a low probability of 0.02% (Rémi et al., 2011). A more recent study evaluated the use of CNN machine learning in movement analysis in differentiation between epileptic seizures of FLE, TLE and non-seizure events. They compared 3 different classification models with a large 3D seizure video dataset. The system managed to differentiate 2 classes (FLE seizures from TLE), and 3 classes (FLE, TLE and non-seizure events from each other) with an f1-score of 0.833 and 0.763, respectively (Karácsony et al., 2022). By using the most optimal classification model, the system managed to properly classify FLE seizures with 87% specificity and 79% sensitivity and TLE seizures with 79% specificity and 87% sensitivity (Karácsony et al., 2022). Automatic near-real time seizure classification was not reported before in the literature, especially with such promising results. Despite improvements in seizure documentation, seizure classification based on video data can be challenging for machine learning methods (Shoeibi et al., 2021), and even for human experts due to the inter-observer discrepancy (McGonigal et al., 2021).

Table 3. Summary of video-based seizure detection systems. *Studies were classified into phases 0-4 according to Beniczky and Ryvlin, 2018.

Study	Study Phase*	Method of video data analysis	Patient population	Seizures	Sensitivity	Other results
Kariyannis et al, 2006	I	Optical flow, neural networks	Infants	myoclonic, focal clonic	90-99%	Specificity 89-97%
Cattani et al, 2017	I	Optical flow, depth sensors, neural networks	Infants	clonic seizures	88-92%	Specificity 88-96%
Cuppens et al, 2010	I	Optical flow	Children	Convulsive seizures	100%	PPV 82-100%
van Westrhenen et al, 2020	II	Optical flow	Children	Convulsive seizures Hyperkinetic seizures	94% 100%	FDR 0.05 per night
Cuppens et al, 2012	I	Optical flow, spatio-temporal interest points (STIP)	Not specified	Myoclonic seizures	75%	PPV 87%
Lu et al, 2013	I	Gaussian mixture model	Children (age 1-15)	Motor/hyperkinetic seizures	Displacement feature: 93% Oscillation feature: 93%	Specificity: Displacement feature: 93%, Oscillation feature: 53%
Kalitzin et al, 2012	II	Optical flow	Not specified	Clonic seizures	95%	FDR 1 per 24h
Geertsema et al, 2018	II	Optical flow, neural networks	Not specified	Convulsive seizures Hyperkinetic and tonic Major motor seizures	100% 57% 66%	FDR 0.78 per night Latency <10s for GTCS
Yang et al, 2021	II	Optical flow, CNN	Not specified	GTCS	88%	Specificity 92% Mean latency 22s
Achilles et al, 2015	I	CNN	Not specified	Convulsive seizures Tonic and automotor seizures	87% 80%	Specificity 81% Specificity 59%
Garção et al, 2023	II	Optical flow, principal component analysis, independent component analysis, machine learning	Not specified	Tonic-clonic seizures	99.06%	Specificity 99.06% Average latency 37.45 s

3 AIMS AND OBJECTIVES

The general purpose of this thesis was to present a video-based seizure detection system and examine its performance in automatic detection and classification of seizures. Also, clinical feasibility of video monitoring was evaluated in drug interventions by assessing the effect of documentation method on treatment effect interpretation.

The specific aims of original research articles were as follows:

1. The aim of study I was to present a proof-of-concept model that measures seizure features quantitatively to detect nocturnal seizures.
2. In study II, the aim was to assess accuracy of a signal algorithm method in automatic classification of tonic-clonic, tonic, and hyperkinetic seizures.
3. The aim of study III was to compare the accuracy of video monitoring and seizure diaries, and to evaluate the change in movement intensity and seizure duration in drug intervention.
4. In study IV, the aim was to establish the utilization of seizure motion signal profiles to provide information of inter- and intra-patient variability of seizures and to explore effect of drug intervention on signal profiles to evaluate movement intensity change during the intervention.

4 MATERIALS AND METHODS

4.1 Study samples

4.1.1 Total study sample

46 patients with DRE were included in the studies of this thesis. Patients participated in one or multiple studies; four patients in study II were included from study III, and six patients from study III participated to study IV. Patients were treated in Tampere University hospital, Turku University hospital, Helsinki University hospital, Vaasa Central hospital. Additionally, some of the testing patients of study III were treated in hospitals in Uppsala, Linköping, and Dianalund. The study protocol and informed consent forms were reviewed and approved by the ethics committee of Tampere University Hospital.

In all studies, only seizures with unequivocal semiology were included. An expert epileptologist classified seizures into seizure types according to ILAE 2017 classification (Fisher, Cross, French, et al., 2017). Semiology was determined in studies II, III and IV according to semiological classification guidelines (Beniczky et al., 2022; Lüders et al., 1998) for each type of seizure using descriptors for the recognizable ictal movement manifestations. To confirm the unequivocal seizure type and semiology, previous video-EEG monitoring (VEM) reports were used for assessment of behavioral characteristics of seizures by comparing movements manifestations in the video and seizure description in the VEM reports. If suspected seizure events were not unequivocally recognized as seizures, they were excluded from the analysis which has been regarded as a feasible reference standard for the phase two study (Beniczky & Ryvlin, 2018). Seizures were regarded as unequivocal to a certain type of seizures only if they were recognized in VEM reports and their behavioral symptoms are similar to the classification criteria.

4.1.2 Study I

The study I included only one patient, aged 18 at the time of publishment of the article. Patient suffered from multifocal DRE causing tonic, clonic, myoclonic, focal

to bilateral tonic-clonic and motor seizures. Patient was treated with vagal nerve stimulator (VNS), and sodium valproate, lamotrigine and clobazam with daily doses of 1200mg, 200mg and 30mg, respectively. The dataset was collected during the 4-week monitoring period, containing 24 focal tonic seizures, 3 focal clonic seizures, 5 focal to bilateral tonic-clonic seizures, 2 focal myoclonic, and 2 focal motor seizures with 7 semiologies. Tonic-clonic and tonic seizure categories were divided based on the presence of guttural sounds in their semiology. Guttural sounds were present in 4 out of 5 focal to bilateral tonic-clonic seizures and in 12 out of 24 focal tonic seizures. Focal to bilateral tonic-clonic seizures with guttural sounds, as well as all tonic seizures, were observed previously in the video-EEG registration, other seizure semiologies were not documented previously.

4.1.3 Study II

27 patients were included in the study. All patients underwent a home monitoring of 4 to 8 weeks, 7-11.5 hours were recorded each night (median 9.25 h, average 9.19 h). Only tonic-clonic, tonic, and hyperkinetic seizures with unequivocal semiology were included in the study. Unequivocal seizures from previous home-monitoring periods were used if enrolled patients did not have unequivocal seizures in the most recent recording session. Four of the training patients were included from the study III, and the rest of the training and testing patients were selected from Nelli® research database. Testing patients were required to have at least 3 unequivocal seizures of the 3 seizure types of interest observed during the video monitoring. Based on the exclusion criteria, 129 seizures from 10 patients were included in the cohort to train the model. The cohort of testing patients included 17 patients with 98 seizures which was used in the assessment of classification accuracy of the model. Patient population and seizures in both phases of the study are presented in Table 4.

Table 4. Patient population and seizure count of each seizure type in the training phase and testing phase.

Training phase			Testing phase	
Seizure type	Subjects	Seizures	Subjects	Seizures
Tonic-clonic	4	12	3	7
Hyperkinetic	5	73	7	41
Tonic	3	44	7	51
Total	10*	129	17	98
*Two subjects contributed seizures of multiple types				

4.1.4 Study III

Study III consisted of two phases: in phase 1, patients were monitored 4 weeks without changes in their medication, and in the phase 2, brivaracetam (BRV) was administered to the medication after the first week of the 4-week monitoring. Thirteen patients with focal DRE were included in the study and participated through phase 1. After the phase 1, two patients did not continue due to the infrequent seizure events, and two patients did not choose to start taking BRV. Nine patients participated both phases. Study patients suffered from hyperkinetic, myoclonic, tonic, tonic-clonic, and motor seizures. All patients used two or more ASMs, and 4 patients were using VNS device.

4.1.5 Study IV

Study IV included patients who had undergone 8-week home monitoring which was divided as a baseline and follow-up phases. BRV was initiated in the beginning of fourth week.

15 patients with focal DRE participated in the home monitoring, and 11 of the patients had seizures with motor manifestations during the monitoring period. 6 patients participated in study II as training patients, and the same video monitoring data was used in this study. The dataset consisted of 138 motor seizures, 13 hyperkinetic seizures, 65 tonic seizures and 13 tonic-clonic seizures.

4.2 Monitoring system

In all studies, video recording was conducted by NEL (Neuro Event Labs, Tampere, Finland) utilizing its Nelli® seizure monitoring device. The system consists of a camera module, a microphone, and a computer which collected the video and audio data. When monitoring a patient, the camera was placed at the foot of the bed or next to the bed. The camera was directed to the bed so that patient is completely visible in the camera in order to maximize the number of "active" pixels in the image.

In studies II and IV, professional epileptologist trimmed the seizure videos from the original data in order to optimize the extraction of seizure signals from the video and to reduce the background noise of the signals during the seizure. Videos were trimmed by comparing ictal movement manifestations and VEM reports, and only the video between assumed beginning and ending of the seizure activity was included in the analysis.

4.3 Methods

4.3.1 Model structure in seizure detection

In study I, our aim was to detect nocturnal motor seizures by utilizing signal biomarkers. As motor seizures are usually identified due to abnormal ictal movement of patients, the system was developed around the feature extraction to distinct manifestations characteristic for motor seizures but absent in physiological movements.

Due to the variety of semiological features in video data, we addressed three biomarkers: sudden motion, sustained oscillatory motion, and sudden audio level growth, related to a tonic component, a clonic component, and ictal vocalization, respectively. Signal processing algorithms were paired for each biomarker, resulting three input signals for analysis of the system. Based on these signals, a multi-layer approach was created to determine whether an event is a seizure and to optimize model parameters. Parameters of these layers were selected so that upper layers intend to identify all possible seizures (indicating high sensitivity) while lower layers intend to remove false positives (indicating high PPV). The model architecture is demonstrated in Figure 4.

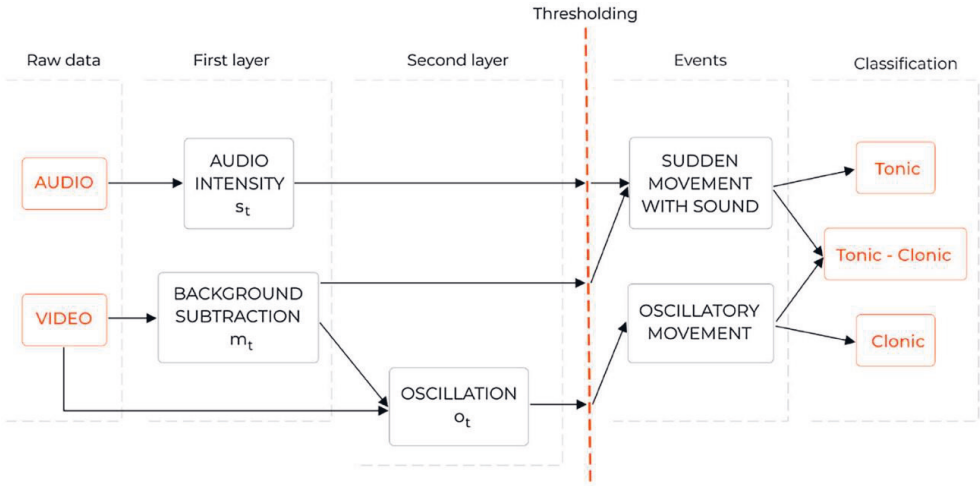

Figure 4. Model Architecture. The multi-layered model extracts biosignals from raw video data and audio which are thresholded to extract events predictive of seizure activity.

Extraction layer

Extraction layer extracts motion and audio features which creates motion and sound biomarkers. It also cuts out signal periods with low amplitude and interest.

Motion of the scene was modeled by combining a background subtraction method (Zivkovic & Van Der Heijden, 2006) and a stereo correspondence filter (Hirschmuller, 2008). Background subtraction formed a binary mask of the moving pixels of the video frames which were normalized by the distance in meters. The average value of "distance-normalized pixel" mask value for each frame formed a one-dimensional signal from video data. Motion signal m_t was formed from the proportion of active pixels (M_t) and total pixels (M_{max}) of each frame by using the binary mask M as follows (1):

$$m_t = \frac{M_t}{M_{max}} \quad (1)$$

To determine the sound volume, a signal S indicated the proportion of the raw sound data by subsampling it to 30 Hz which measures sound intensity signal at specific moment, which has been suggested to have value in seizure localization (Hartl et al., 2018). The sound intensity signal, s_t, was derived by normalizing sound level S against the maximum sound level (S_{max}) as follows (2):

$$s_t = \frac{S_t}{S_{max}} \quad (2)$$

To detect sustained oscillation (ictal clonic component), an optical flow (Horn & Schunck, 1981) based method was utilized to calculate a time-series motion vector area for the video clip of interest. The vector area was utilized to create a sparse path sequence. The paths that were successfully constructed were analyzed for direction reversal, with a requirement of more than 90° change of direction. The signal o_t was determined as the count of non-zero values from the set of successfully constructed paths, *P*, including reversals above the threshold N (3):

$$o_t = \sum\{P \wedge 1 : P \geq N\}_t \quad (3)$$

Based on the experiments, a threshold *N*=5 (or 2.5Hz) was determined to act as a good filter to distinct ictal oscillatory movements.

Thresholding layer

This layer produces events depending on thresholds for amplitude, duration, and sample count from the input signal. By selecting certain parameters, the model can be optimized to improve the chosen assessment variable, such as maximal sensitivity or maximal PPV. Based on each signal and their target evaluation criteria, event types were defined as follows: oscillation events (E_o), sudden movement events (E_m), and sound events (E_s). These event types enabled combination based on their time intersection to create intersected events.

Threshold selection

In study I, our aim was to discover cut-off thresholds which aim is to reach sensitivity of 100% at minimum expense of positive predictive value. To distinguish physiological and ictal events, differences in movement patterns between those events should exist. To find the differences, the value of distribution of each event type was compared with the ground truth dataset. The ground truth data was split into 5 folds to perform cross-validation, and to find cut-off values between seizure and non-seizure events.

For the data of study I, the Euclidean (L2) distance between the maximum and average magnitudes was used. As it favors both maximum and average of magnitudes, kernel density estimation (KDE) was used to assess population density function of the values. As the target was sensitivity of 90%, the most optimal threshold value was chosen to be the 10th percentile of the cumulative distribution

function. For each signal, this was repeated 5 times, and the average of the result values was used in the assessment.

For sudden motion biomarker, the system detected 1525 events, with 24.8 second mean duration (range 3.3-997.8 s). The optimal threshold was 0.0092 ($\sigma = 0.0011$), determined from tonic seizure folds.

For sound level signal, a total of 5681 events were detected, with 1.9 second mean duration (range 0.6-257.5 s). 34 / 36 (94% sensitivity) seizures were detected by one or two sound events according to the hit criteria. This may indicate that non-audible seizures were missed at seizure onset or that signal would need adaptive filtering. As the model targeted the audible seizures, data set with guttural sounds was utilized, and the optimal threshold was 0.025 ($\sigma = 0.013$). The large variance implies that the intensity measure can't differentiate events based on sound feature.

For the events with oscillation biomarker, 25 events were detected, with 8.1 second mean duration (range 3.6 to 25.4 s). Even though the distributions are not significantly different ($p > 0.1$), the distributions seem to be significant when seizures and events that did not hit a clonic seizure were compared ($p < 0.02$). The optimal threshold for oscillation was 0.0037 ($\sigma = 0.0042$). Probability density distributions for sudden motion, sound level and sustained oscillation have been presented in Figure 5.

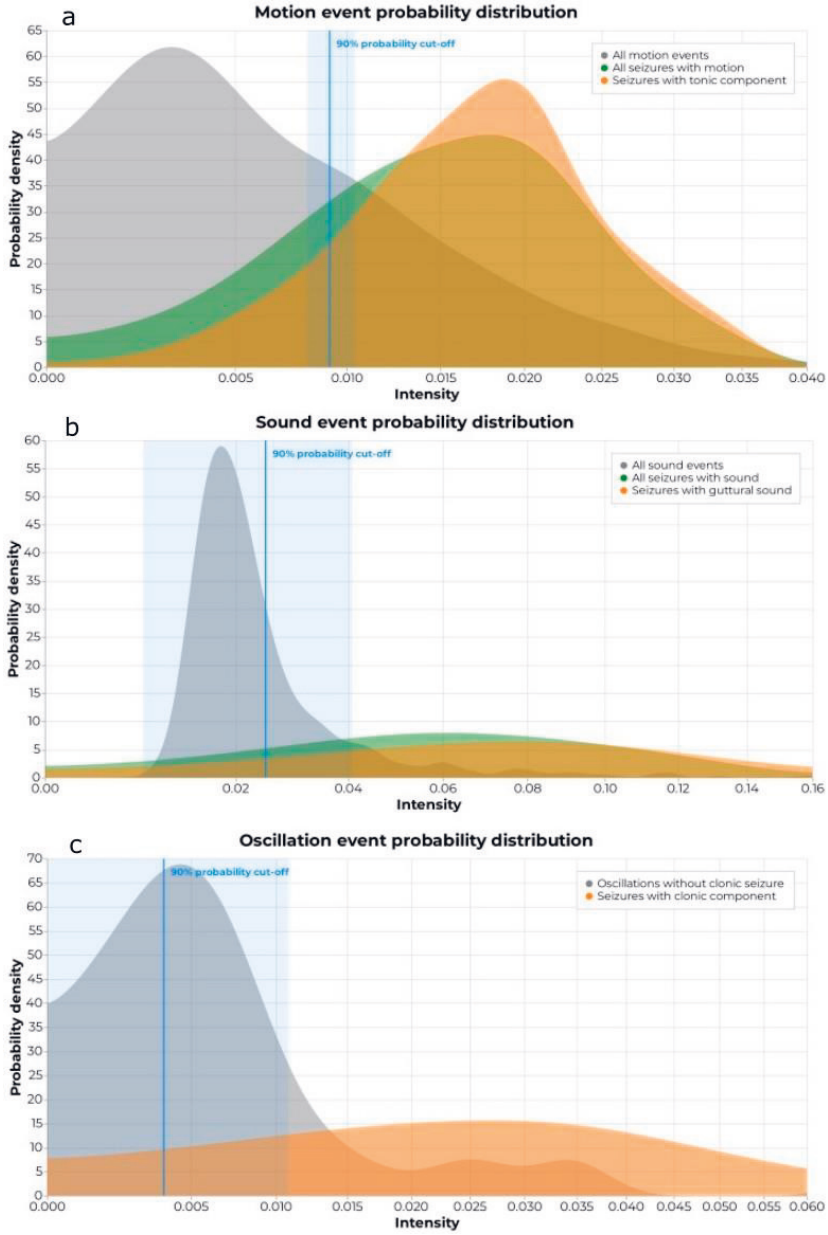

Figure 5. Probability density distribution. Figure 5a shows distribution of all motion events compared to ictal motion events. Figure 5b shows distribution of all sound events compared to ictal sound events. Figure 5c shows distribution of all oscillation events compared to ictal oscillation events. Blue shading indicates variation in 5-fold threshold training. Intensity has been calculated by using L2 distance between mean and maximum magnitudes for the event depicting the amount of sustained motion. Modified and reproduced from original publication I under the terms of Creative Commons Attribution License (CC BY).

4.3.2 Automatic seizure classification

In study II, feature extraction for sudden motion, sustained oscillation and sound level signals was conducted prior to clustering analysis and performance analysis with the same method described in section 4.3.1.

Clustering analysis

Unsupervised data representations were examined to separate tonic-clonic, tonic, and hyperkinetic seizures. To visualize data, cluster diagram was utilized so that a data sample is represented on a 2D diagram which was inspected by an annotator or a clustering algorithm to define clusters. Due to the multidimensionality of data samples, data reduction algorithms were needed for transformation of data samples into 2D chart before creating the diagram. Since the original data was projected into lower dimensions, the diagram axes do not have any specific unit or meaning.

After extracting the features and generating signal data, motion and oscillation time-series were transformed to lower data space by utilizing extraction of statistical features of time series to gain low and fixed data dimensions. As the duration of seizures (and length of time-series) varied, a fixed data dimension was required to conduct a principal component analysis (PCA) to reduce the data dimension into 2D. Motion features from the catch22 time-series feature collection were used to analyze ictal movement characteristics. 22 statistics obtained from the catch22 library (Lubba et al., 2019) were utilized for the training set and fed into PCA. Cluster plots were then created from the finalized 2D data representing the seizures in different colours for visualization of data distribution. The differentiation capability of those 22 statistics were then evaluated on the training cohort, and the original catch22 feature set was decreased to 5 features prior to the PCA phase by visual observation of the cluster diagram after removing unnecessary features.

First, the reduction of dimension was utilized for the training cohort to create a 2D data diagram for visualization and determination of the optimal parameters to separate seizures. After the training phase, the PCA coefficients were used to the testing cohort to project the testing data by the same dimension reduction transformations, and the performance evaluation of the method by visually assessing the data points and classification analysis. After that, agglomerative clustering was utilized to explore clustering on the chart and examine how the unsupervised cluster shows differentiation of seizures.

Classification analysis

To evaluate the performance of supervised learning method, a classification method was also utilized. The discriminative ability of the features can be better assessed by analyzing the data by utilizing various methods because the first technique decreases the dimension of data, and the second technique directly analyses the time-series. It's important to notice that the time-series of pixel statistics have decreased dimensionality compared to the video data. A deep learning network (multivariate long short-term memory with fully connected layers, MLSTM-FCN) specialized for time-series classification (Karim et al., 2019) was constructed based on the training data for differentiation of the hyperkinetic, tonic, and tonic-clonic seizure data points to predict unseen testing data. Tsai library (Oguiza, 2022) was utilized in the implementation of the method. The previous clustering method transformed the time series into 2D data with dimensional reduction techniques (catch22, PCA), and the MLSTM-FCN model worked on the time series directly, processing and classifying a time series into a single seizure category. After the analysis of the testing data, the performance of the method was assessed by computing overall accuracy, as well as the accuracy and f1-score of classification of hyperkinetic, tonic, and tonic-clonic seizures separately. The method used in study II is demonstrated in Figure 6.

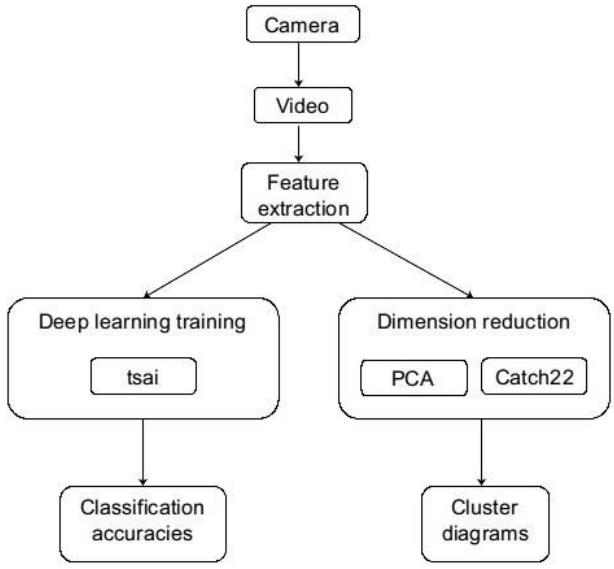

Figure 6. Summary of the method in study II. Reproduced from original publication II under the terms of Creative Commons Attribution License (CC BY).

4.3.3 Assessment of seizure diaries, movement intensity and duration of seizures

Assessment of seizure diaries and effect of intervention

In phase 1 of study III, seizure count and diary entries during the 4-week monitoring period were compared, and the daily average of seizures, diary entries, sensitivity and positive predictive value of seizure diaries were determined. In phase 2, the change of diary entries between the baseline and the last week of follow-up was calculated for each patient. By comparing the difference between baseline and the last week of follow-up based on the seizure average of the video monitoring and seizure diary entries, the accuracy of diaries on treatment outcome evaluation was assessed.

The effect of treatment in phase 2 was evaluated by calculating and comparing seizures per night average for each week based on video monitoring and seizure diary entries.

Analysis of movement intensity and seizure duration

The effect of BRV intervention on the movement intensity and duration of seizures was assessed by investigating 12 visual and 15 sound volume features in each patient and each seizure type. The visual features were calculated from optical flow and background subtraction methods in OpenCV (Open Source Computer Vision Library). Power spectral density was extracted across various frequency values to model sound volume.

The features with significant differences were explored before and after the BRV initiation by utilizing visual analysis and the Wilcoxon rank-sum test. The Wilcoxon rank-sum test was utilized to evaluate the difference in intensity between the distributions before and after the intervention. The duration of features was normalized to avoid the impact of varying duration of seizure. Similarly, the duration of seizures was explored as a separate feature using the Wilcoxon rank-sum test.

4.3.4 Evaluation of signal profiles

Time-series data of sudden motion, sustained oscillation and sound level was extracted similarly as described in study I (see section 4.3.1). Signal profiles were then created to present motion, oscillation and sound signals of each seizure type and each patient in a column.

Variance of signals was then calculated for each seizure semiology. By comparing signal profile figures and variances of each seizure semiology of each patient and between patients, the intra-patient and inter-patient variability of seizures and seizure types could be assessed. To improve the assessment of intra-patient variability of seizures, the most representative seizure for each seizure semiology for each patient was chosen to act as a reference for other seizures of the same type. The most representative seizure was chosen by an expert epileptologist based on the visual analysis of typical and distinct ictal manifestations on the video without significant background noise and artefacts from lighting and blanket. Then, a combination of quartile and median visualizations were then used based on the signals of motion, oscillation and sound to improve readability and visual analysis.

In this study, our secondary objective was to assess the effect of BRV intervention on signal profiles. To visualize the effect of BRV, the combination of quartile and median visualizations were used separately for seizures before and after the intervention for each seizure type. Mean signal values averaged over the seizure duration and their variance were calculated. Based on mean signal values and the visually recognizable changes in motion signals, the effect of intervention could be evaluated.

5 RESULTS

5.1 Seizure detection performance

Based on the data of study I, signals of sudden motion, sustained oscillation and sound level was created to utilize them both separately and as intersected events in seizure detection. As shown in Figure 7, each seizure class manifested a distinguishable signal profile. Seizures with one or multiple clonic periods are visible as an increase in the oscillation signal o_t compared to seizures with bilateral tonic semiology. Bilateral tonic seizures manifested a sudden movement and sound which caused distinctive increase in motion signal (m_t) and sound signal (s_t), and especially guttural sounds increased the amplitude in sound signal. Based on the signal profiles which are different for each seizure semiology, they managed to distinct tonic and clonic phases.

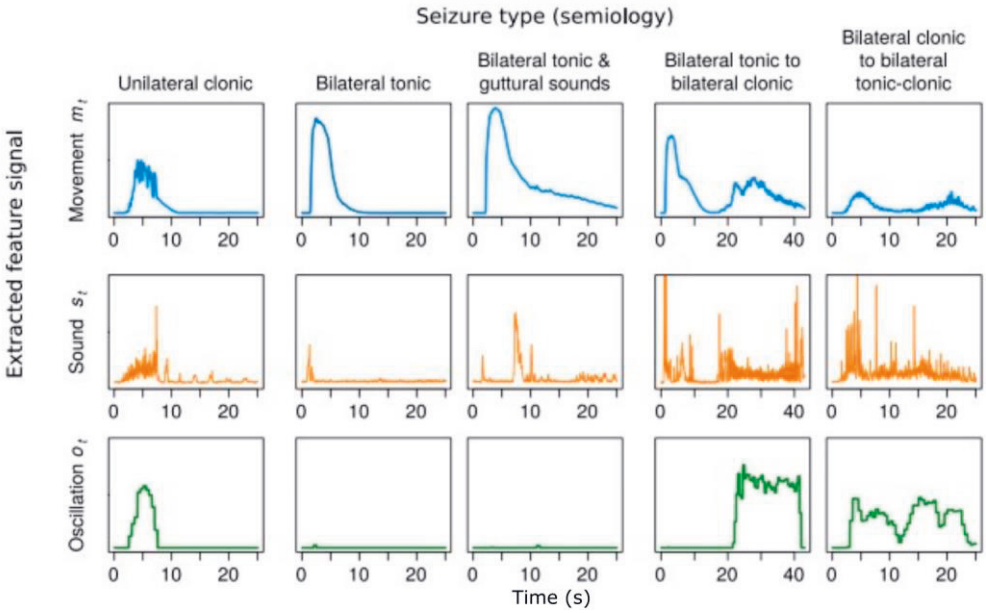

Figure 7. Signal profiles according to different seizure types. With the chosen biomarkers, each seizure type has a unique and descriptive signal profile. Reprinted from original publication I under the terms of Creative Commons Attribution License (CC BY).

For seizures with tonic component, the model E_i (events including sudden motion and sound) achieved the best prediction for tonic seizures. By using only events created by sound signal (E_s) resulted PPV of 2.0% with 1938 false positives, while the events created by sudden motion signal (E_m) achieved a PPV of 3.9% with 661 false positives. Utilization of events of both signals (E_i) increased the PPV to 8.8% and decreased the number of false positives to 268 while reaching 90% sensitivity.

The oscillation signal detected seizures with one or multiple clonic periods. Two seizures manifested a short tonic phase followed by clonic phase which were detected with perfect sensitivity (100%), decent PPV (50%) and low FDR (0.038/hour). The four FTBTCs were recognized with sensitivity and PPV of 100%.

Overall statistics

The detection performance results are presented in Table 5. Besides standard accuracy values, a review time of video has been evaluated to provide an estimate of time to determine whether an event is epileptic. The parameters were set for at least 90% sensitivity for all models. The oscillation model achieved good PPV for seizures with clonic component with less than one false detections per night. The intersected tonic model also gave less than one false detection per hour, which could be acceptable in clinical settings.

Table 5. Resulting statistics and characteristics of the detected events E per model. Oscillation (E_o) and noticeable motion movement (E_m) events are derived from video signals, and the audible sound (E_s) events from audio signals. E_i represents the intersection of motion and sound events ($E_m \cap E_s$). Multiple hits to the same event are marked in parentheses.

	Clonic E_o	Tonic E_i	Tonic E_m	Tonic E_s
ILAE 2017 seizure types containing the targeted events	I.D.01 (5) I.C.05 (2) I.C.03 (3)	I.D.01 (5), I.C.05 (24)		
Targeted events	10	29		
Detections	20	294	688	1977
True positives	10	26	27	28 (+11)
False positives	10	268	661	1938
Sensitivity	100%	90%	93%	97%
PPV	50%	8.8%	3.9%	2.0%
F1 score	0.67	0.16	0.075	0.039
FDR (FP/hour)	0.038	1.0	2.5	7.4
Review time	7 min	98 min	229 min	659 min

5.2 Accuracy of automatic seizure classification

5.2.1 Unsupervised clustering analysis

Two motion feature settings, static and temporal motion features, were examined to compare their feasibility (Figures 8 and 9, respectively). In both figures, tonic-clonic, hyperkinetic, and tonic seizures were marked as green, blue, and orange, respectively, referring to results from training phase, and light green, light blue and light orange, respectively, referring to results from testing phase.

In figure 8A, tonic-clonic and tonic seizures formed a cluster on the left side and hyperkinetic seizure created clusters on the right side of the figure. The tonic-clonic seizures do not form a recognizable cluster on the chart. Figure 8B demonstrates the agglomerative clustering that managed to separate the tonic and hyperkinetic clusters. When utilizing temporal motion features (Figure 9A), sides of the clusters changed: hyperkinetic and tonic clusters were separated, but tonic-clonic seizures were not distinguished in either of the phases. Figure 9B shows the agglomerative clustering that differentiated two clusters, for hyperkinetic and for tonic seizures.

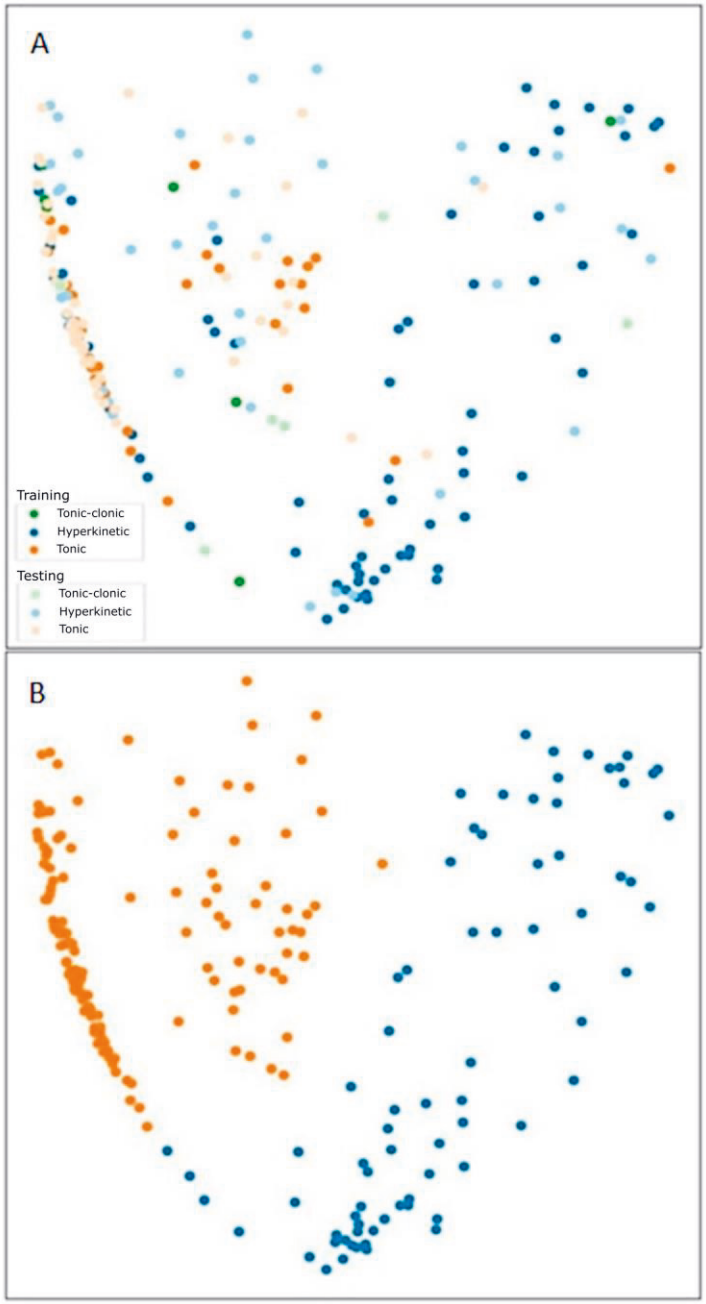

Figure 8. Clustering analysis of tonic-clonic, hyperkinetic, and tonic seizures using static motion features in the training and testing phase (A). Agglomerative clustering results (B). Reproduced from original publication II under the terms of Creative Commons Attribution License (CC BY).

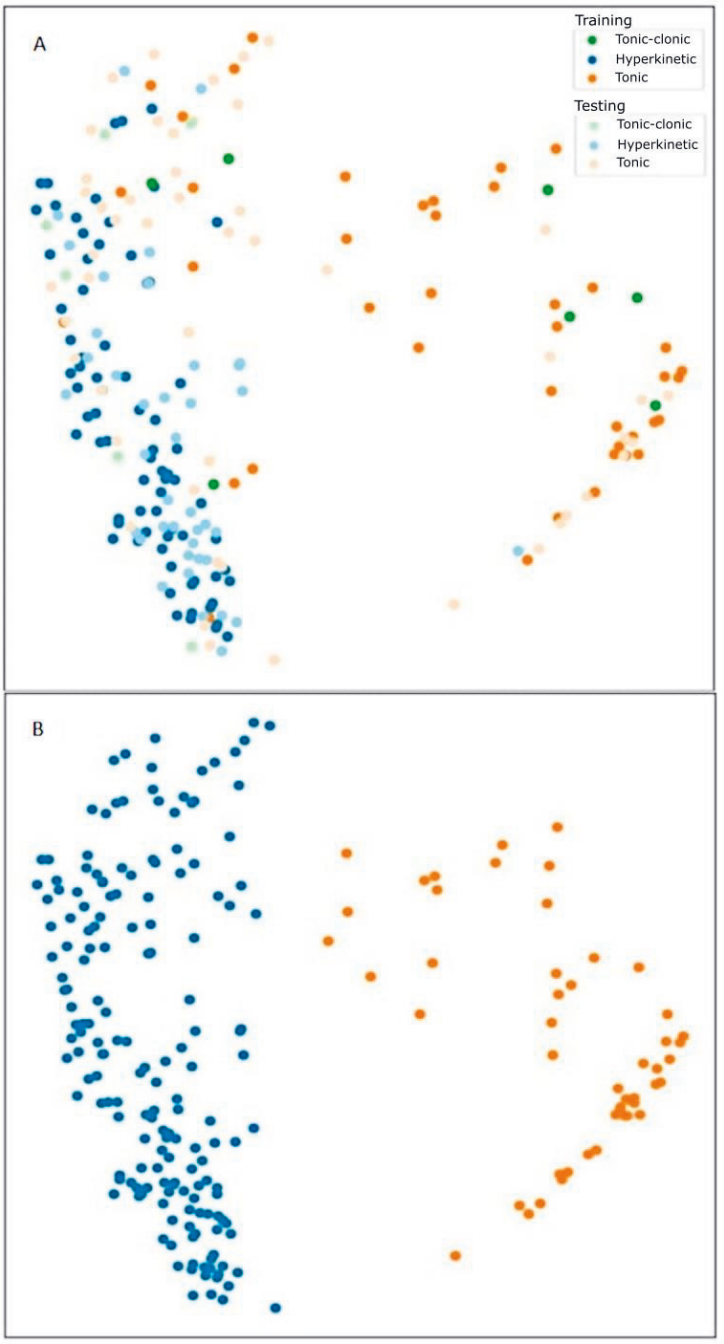

Figure 9. Clustering analysis of tonic-clonic, hyperkinetic and tonic seizures using temporal motion difference features in the training and testing phase (A). Agglomerative clustering results (B). Reproduced from original publication II under the terms of Creative Commons Attribution License (CC BY).

5.2.2 Performance analysis

To assess the accuracy of this classification model, the background subtraction signal was used to train a deep learning network and the results were compared with the human annotations. The leave-one-out cross-validation was run 100 times to evaluate the unbiased accuracy and its confidence interval. Overall accuracy and f1-score was 74.68% and 74.26%, respectively. Mean accuracies were 91.03%, 87.90%, and 45.12% and the mean f1-scores were 92.83%, 89.79% and 37.18% for hyperkinetic, tonic and tonic-clonic seizures, respectively. The confidence intervals (p=0.05) for accuracies were 1.1%, 1.5%, and 4.2% as well as 1%, 1.5% and 4.1% for f1-scores, respectively. Table 6 presents the performance of seizure classification.

Table 6. The accuracies, f1-scores, and confidence intervals for each seizure type.

Unbiased accuracy and confidence intervals after 100 cross-validation runs			
	Hyperkinetic seizures	**Tonic seizures**	**Tonic-clonic seizures**
Mean accuracy	**91.03%**	**87.90%**	**45.12%**
Confidence intervals for accuracy	**±1.1%**	**±1.5%**	**±4.2%**
F1-score	**92.83%**	**89.79%**	**37.18%**
Confidence intervals for f1-score	**±1%**	**±1.5%**	**±4.1%**

5.3 Brivaracetam intervention and seizure diaries

5.3.1 Accuracy of seizure diaries

During phase 1, eight out of eleven patients who experienced nocturnal seizures documented by the video monitoring system were able to mark seizures in their diaries. Seizure diaries detected seizures with 8-84% sensitivity. Four of the patients (patients 2, 3, 7, and 8) reported seizure events not observed in the video; and one patient (8) reported more seizures in the diary than confirmed in the video. PPV of seizure diaries was 50% to 95%. The average of seizure count and diary entries per day was 0-10.3 and 0-3.1, respectively. There was also difference in seizure-free

nights during the monitoring which were 16.6-23.2 and 0-8.7 according to seizure diaries and video monitoring, respectively. Seizure diaries caused underestimation of seizure frequency in 7 patients.

During phase 2, seizure diaries detected seizures in five patients (1, 3, 5, 7, and 8). Sensitivities of seizure diaries were from <40% to 70% compared to the video monitoring. Video monitoring showed 28% and 36% seizure reduction for patients 1 and 8, while seizure diaries reported 37% decrease and 2% increase, respectively. For patients 5 and 7, video monitoring showed 56% and 143% seizure increase while diary entries reported a 15% and 200% increase, respectively. 4 patients unable to document seizures in their diaries experienced 0.4 and 6.4 seizures per day in the last week of monitoring. Table 7 shows summarized results from phases 1 and 2.

5.3.2 Effect of intervention

Patients were classified based on the change of seizure frequency as follows: patients with >50% seizure decrease are responders, patients with <50% change in seizure frequency did not respond to intervention, and patients with >50% increase in seizure frequency experienced decrease of seizure control. According to the results from the video monitoring, three patients (4, 6, and 9) were responders, four patients (1, 2, 3 and 8) did not respond to intervention, and seizure frequency increased in two patients (5 and 7) after the follow-up.

Table 7. Results from phases 1 and 2 of study III.

Phase 1							Phase 2							
ID	Seizures (Daily average)	Diary entries (Daily average) [true positives]	Sensitivity	Positive predictive value (PPV)	Seizure free nights / average of 28 days (According to seizure diary)	Registered nights in phase 1	Seizures baseline week (Average per day)	Seizures, week 1 (Average per day) [change to baseline]	Seizures, week 2 (Average per day) [change to baseline]	Seizures, week 3 (Average per day) [change to baseline]	Diary entries Phase 2 (Daily average) [true positives]	Diary entries baseline week (Average per day)	Diary entries week 3 (Average per day) [change to baseline]	Registered nights in phase 2
1	58 (1.9)	8 (0.3) [8]	14%	100%	3/2.7 (23/21)	31	14 (2)	12 (1,71) [-14,5%]	12 (1,71) [-14,5%]	10 (1,43) [-28,5%]	33 (1,18) [27]	8 (1,14)	5 (0,71) [-37%]	28
2	170 (6.1)	20 (0.7) [13]	8%	65%	0/0 (18/18)	28	51 (7,29)	40 (5,71) [-21,7%]	52 (7,43) [+1,9%]	45 (5,6) [-11,7%]	0 (0) [0]	0	0	29
3	29 (1.0)	10 (0.3) [5]	17%	50%	9/8.7 (24/23.2)	29	7 (1)	3 (0,43) [-57%]	3 (0,43) [-57%]	7 (1) [0%]	6 (0,21) [6]	2 (0,29)	2 (0,29) [0%]	28
4	33 (2.1)	0 (0) [0]	0%	-	0/0 (16/28)	16	22 (3,14)	14 (2) [-36,3%]	13 (1,86) [-40,7%]	9 (1,13) [-64%]	0 (0) [0]	0	0	29
5	169 (5.8)	91 (3.1) [91]	54%	100%	0/0 (0/0)	29	32 (4,57)	37 (5,29) [+15,8%]	52 (7,43) [+62,6%]	50 (7,14) [+56,2%]	161 (5,75) [116]	27 (3,86)	31 (4,43) [+15%]	28
6	288 (10.3)	0 (0)	0%	-	0/0 (28/28)	28	54 (7,71)	36 (5,14) [-33,3%]	56 (8) [+3,8%]	20 (2,86) [-63%]	0 (0) [0]	0	0	28
7	87 (3.2)	22 (0.8) [21]	24%	95%	0/0 (16/16.6)	27	21 (3)	24 (3,43) [+14,3%]	114 (16,29) [+443%]	51 (7,29) [+143%]	33 (1,18) [32]	3 (0,43)	9 (1,29) [+200%]	28
8	57 (1.9)	67 (2.2) [48]	84%	72%	1/0.9 (0/0)	30	12 (1,71)	10 (1,43) [-16,4%]	7 (1) [-41,5%]	11 (1,0) [-41,5%]	44 (1,38) [29]	9 (1,29)	14 (1,27) [-1,5%]	32
9	41 (1.5)	0 (0) [0]	0%	-	8/8 (28/28)	28	7 (1)	1 (0,14) [-86%]	5 (0,71) [-29%]	3 (0,43) [-57%]	0 (0) [0]	0	0	28
10[a]	37 (1,3)	5 (0,17) [5]	14%	100%	7/6,8 (24/23,2)	29	Patients did not participate to phase 2.							
11[a]	119 (4,25)	76 (2,7) [76]	64%	100%	0/0 (0/0)	28								
12[a]	0 (0)	0 (0) [0]	0%	-	28/28 (28/28)	28								
13[a]	0 (0)	0 (0) [0]	0%	-	24/28 (24/28)	24								

5.3.3 Feature analysis in evaluation of movement intensity and duration of seizures

All features with p-value <0.05 have been listed in Table 8. Only features with significant difference before and after the BRV initiation verified by p-value < 0.05 and visual inspection were shown in the graphs in Figures 10 and 11. The left graph shows the feature values of each seizure during the monitoring periods, and the right graph represents KDE which demonstrates the feature value distributions before (blue) and after (red) the intervention. The feature analysis showed minor decrease in movement intensity in all patients despite seizure frequency increase of patients 5 and 7. The number of selected features indicate the significance of the changes in patients 5 and 7. The duration of seizures was not changed based KDE graphs even though the duration was significantly different in 4 patients according to Wilcoxon rank-sum test.

Table 8. List of the features with p < 0.05.

Patient	Seizure type	Feature ID
1	Hyperkinetic	9, 11, 12, 15, 16, 17
2	Myoclonic	2, 3, 4, 6, 7, 8, 10, 13, 15, 16, 17, 18, 21, 22, 23, 26, 27
3	Motor	1, 2, 3, 4, 6, 7, 8, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27
	Convulsive seizure	2, 3, 4, 11, 15, 16, 17
5	Hyperkinetic	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 18, 19, 21, 22, 23, 24 25, 26, 27
6	Motor	11, 12, 20
7	Myoclonic	2, 3, 4, 6, 7, 8
	Clonic	2, 3, 4, 7, 8, 21, 22, 23, 25
	Tonic-clonic	9, 10, 14, 20, 25
	Motor	6, 9, 12
	Tonic	1, 2, 3, 4, 6, 7, 8, 9, 12
8	Motor	13, 18, 19, 20, 21, 22, 23, 24, 26, 27
9	Motor	1, 5, 6, 7, 8, 15, 17

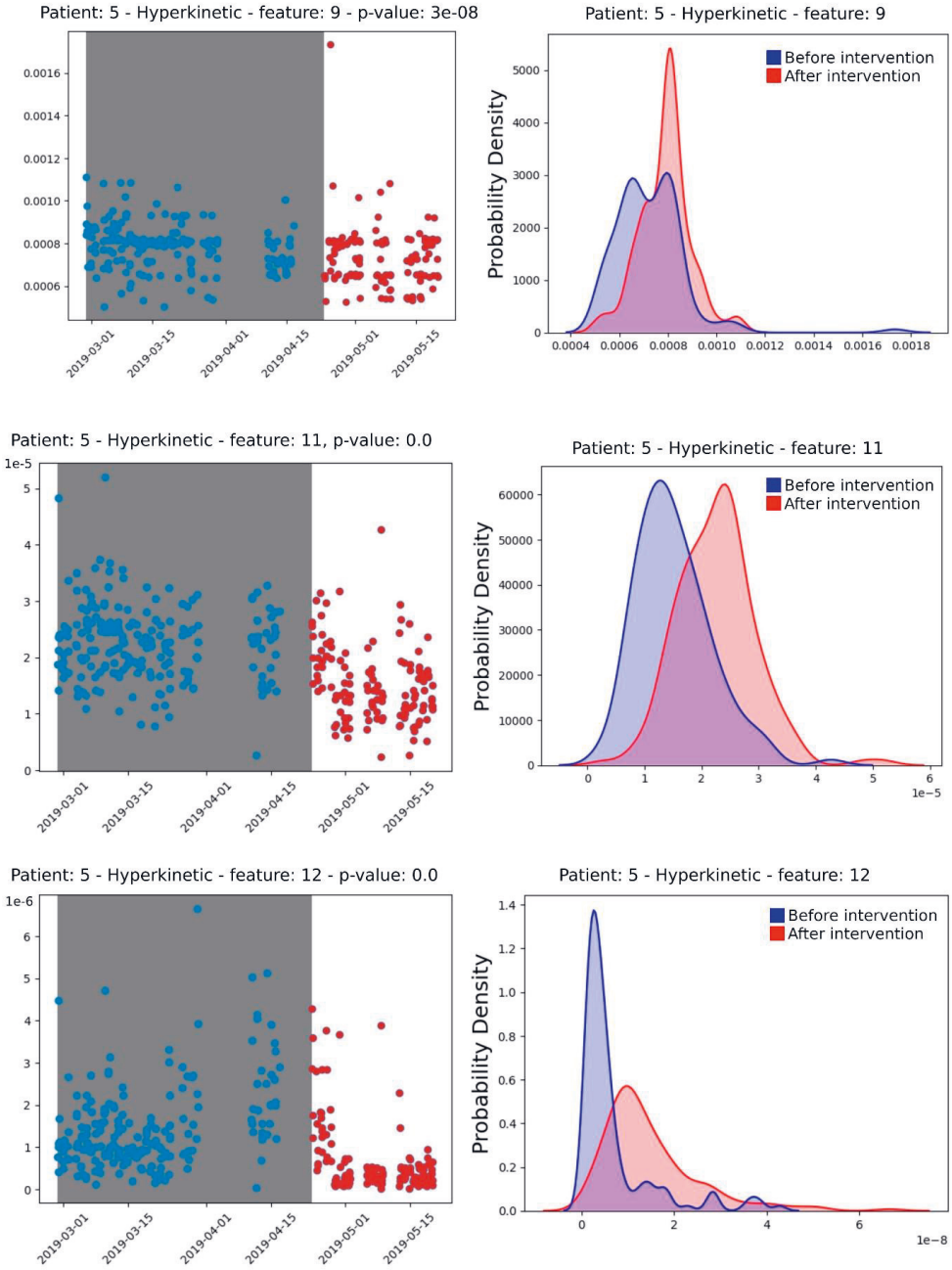

Figure 10. Feature values (left) and KDE (right) from intensity analysis for patient 5. Features 9, 11 and 12 are visual features representing motion characteristics. Reprinted from original publication III under the terms of Creative Commons Attribution License (CC BY).

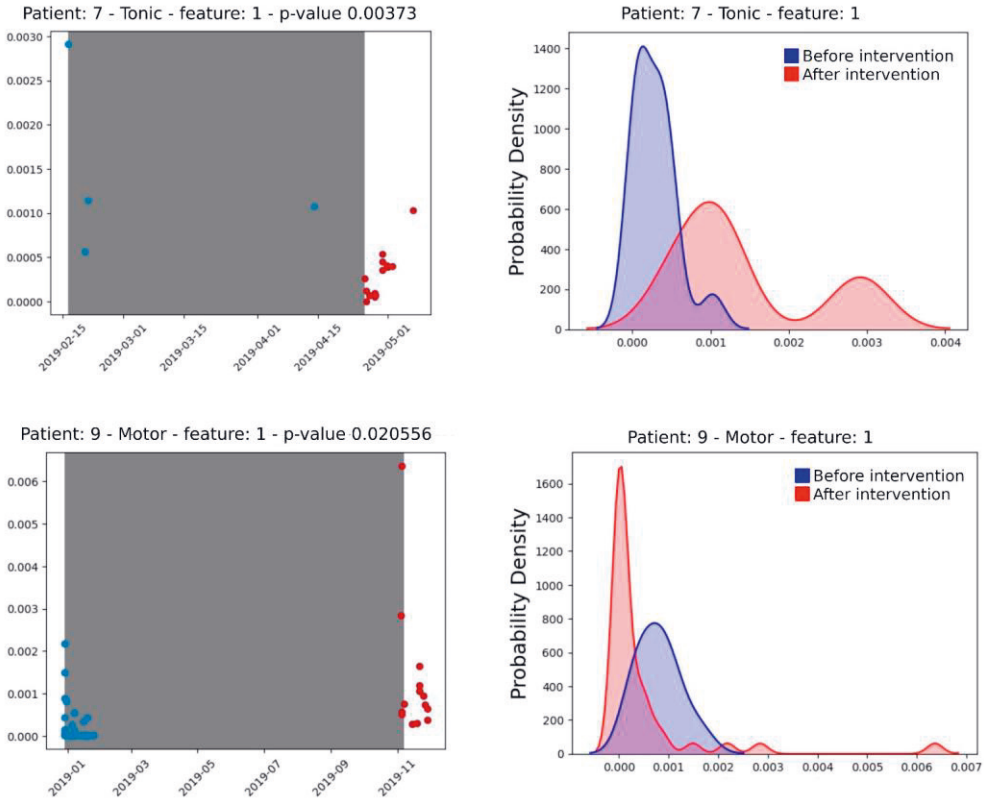

Figure 11. Feature values (left) and KDE (right) from intensity analysis for patients 7 and 9. Feature 1 is a visual feature representing motion characteristics. Reprinted from original publication III under the terms of Creative Commons Attribution License (CC BY).

5.4 Evaluation of signal profiles

During the monitoring period, all patients experienced seizures during the baseline but only 8 patients had seizures during the follow-up. One patient discontinued BRV without experiencing seizures during the follow-up. 6 of the patients had VNS but only one patient (patient 4) was able to activate the device (in 9 out of 10 seizures).

5.4.1 Signal profiles of seizures

For each patient and seizure type, combined median and quartile visualizations were created based on the signals, and they were organized in the same column to represent seizure signal profile. In motion, oscillation and sound signals, the most

representative seizure has been bolded black, and the median of seizures were colored blue. Variance of signals has been colored light blue shading in all figures. Original seizure signals which the median and quartile visualizations were calculated from have been presented in Supplementary Materials of study IV.

Figure 12 shows hyperkinetic seizure signal profiles from 2 patients. Both seizures manifest an abrupt increase in motion signal which was caused by sudden movement in the recorded video. However, after the start of the seizures, there are high spikes in the motion signal which were likely caused by patient's limbs that move close to the camera. These peaks increase the motion signal to significantly higher values than in other seizure types. Patient 2 fell from bed during both seizures and kicked the camera which also affected the motion signal. The oscillation signal remained low during the hyperkinetic phase even though oscillation increased in one seizure of patient 7 which increased the variance while maintaining zero median oscillation. In that case, it might have been caused by a patient's postictal movements. Sound signal activity was caused by kicking and hitting of bed in both patients but also the mattress alarm increased the sound in patient 7. Both patients have similarities in the form of motion signals, such as sudden onset and absence of oscillation.

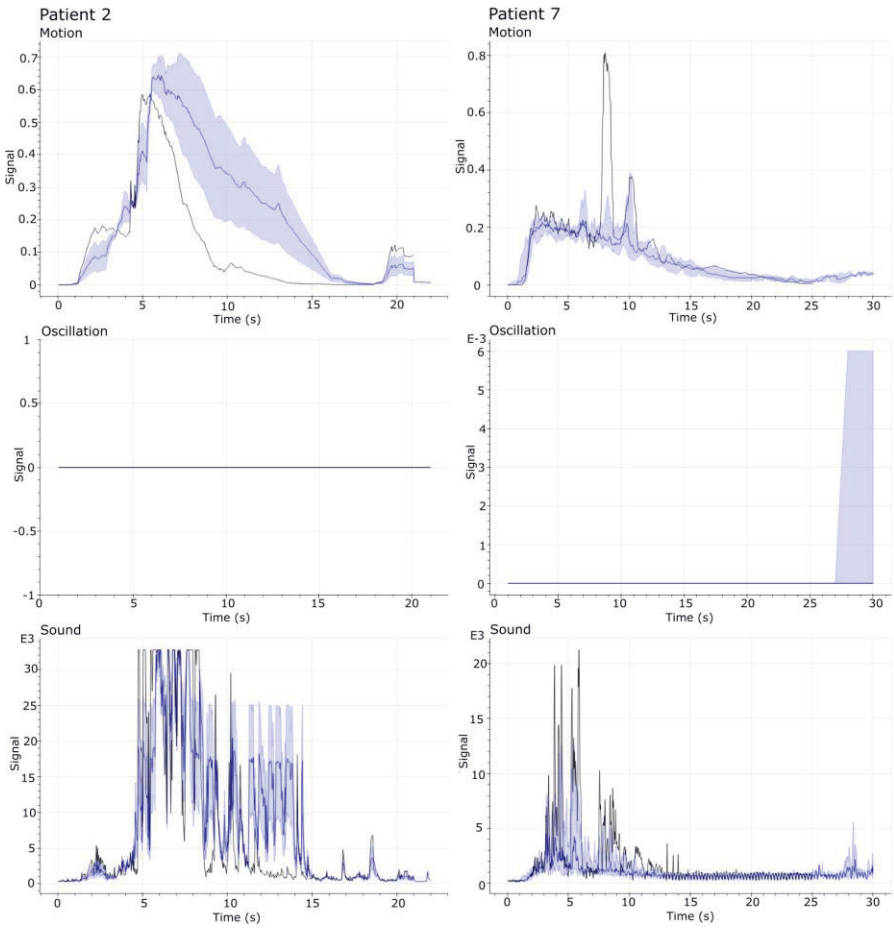

Figure 12. Combined median and quartile visualizations for signal profile figures of hyperkinetic seizures from 2 patients. The most representative seizure has been bolded in all signal figures.

Figure 13 presents tonic-clonic seizure signal profiles from 2 patients on the left, and tonic seizure signal profiles from 4 patients on the right. The sudden increase in motion signal shows a quick onset of tonic activity in both seizure types, and the tonic phase seems to manifest a spike form. Patient 6 had one tonic seizure with individual clonic movements after the tonic phase which caused two spikes in the motion signal. Oscillation does not exist in the tonic seizures of patients 6 and 11. Patient 9 had increased oscillation signal after the motion spike which was caused by a short clonic component after the tonic phase in one seizure. However, the clonic phase was short and thus it was not considered a tonic-clonic seizure. Patient 11 had seizures with a tonic component in 2 different seizure semiologies: tonic seizures

have only a short tonic activity, but motor seizures had a restless motor activity with head turning, kicking and arm movements after the tonic phase which caused oscillation activity. These seizures were marked as "tonic" and "tonic+motor", respectively, in Figure 13.

Regarding the tonic-clonic seizures, patient 8 had a longer motion signal spike during the tonic phase which was caused by individual clonic movements before the start of clonic phase and the movement of caregiver in sight of camera. Clonic phase of tonic-clonic seizures increases the oscillation signal, and the oscillation increases after the tonic spike in motion signal which may indicate the ability to distinguish tonic and clonic phases. In patient 8, oscillation seems to rise at the end of the seizure despite the end of clonic activity even though there was no oscillating movement in sight of the video at a given time point. Tonic-clonic seizures have similar motion and oscillation signal shapes; a sudden motion spike following a flat phase with oscillation activity. On the other hand, the form of motion signals of tonic seizures was very similar in each patient and between patients.

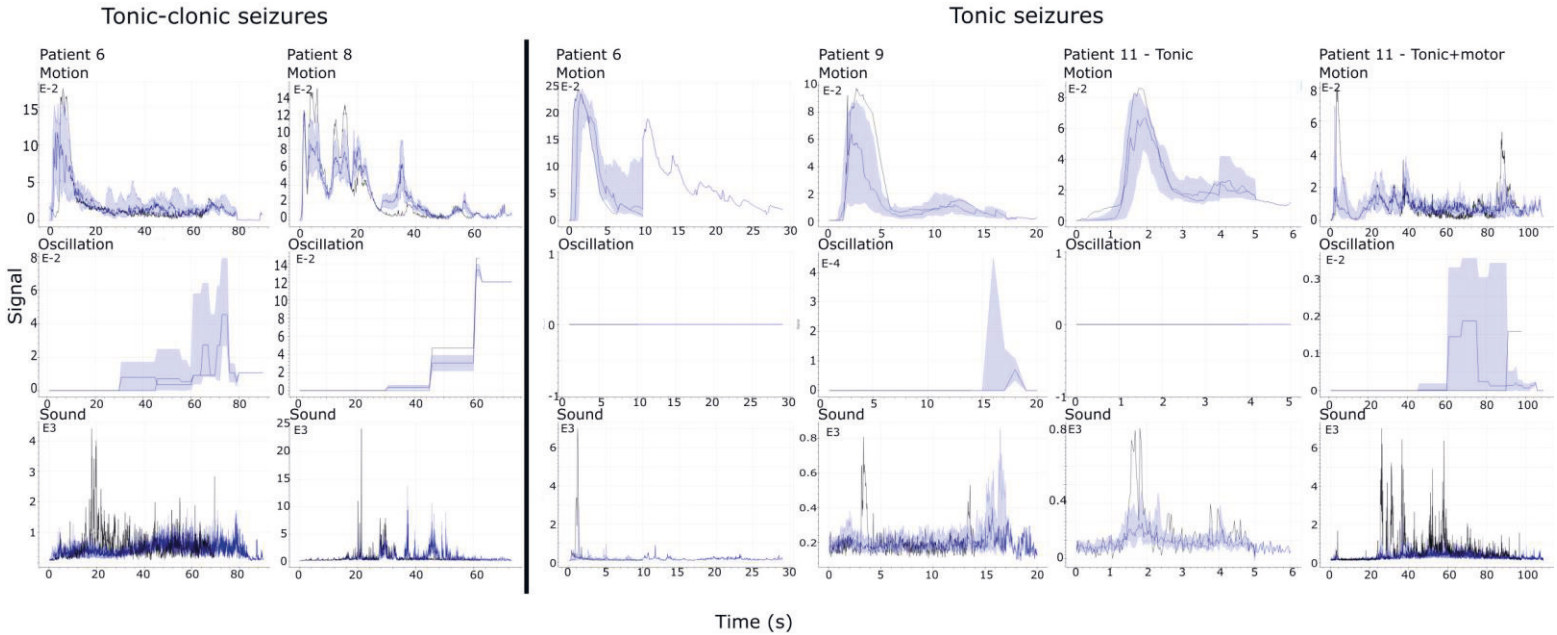

Figure 13. Combined median and quartile visualization for signal profile figures of tonic-clonic seizures from 2 patients and tonic seizures from 4 patients. The most representative seizure of both seizure types has been bolded in all signal figures.

Signal profiles of motor seizures have been presented in Figure 14. As these motor seizures were not further classified, this category included seizures with different manifestations. Variance of motion and oscillation signal was distinguishable in both intra-patient and inter-patient settings. Onset can be rapid or steadily increasing depending on the patient, and the motion signal may have one or multiple spikes during the seizure. Also, the oscillation and sound activity varies a lot between seizures in both intra-patient and inter-patient settings. Unlike in the previous seizure types, motor seizures do not form any generalizable form or other distinctive signal characteristics, as expected. However, some of these signal profiles may mimic signal profiles from other seizure types, as signal profiles from patients 8 and 10 may be falsely interpreted to be tonic-clonic seizures as well as signals of patient 1 could be misclassified as hyperkinetic seizures. On the other hand, according to VEM reports, motor seizures of patient 8 had the same epileptic activity only in the beginning as tonic-clonic seizures without generalization, which may explain the similar signal manifestations of these seizure semiologies.

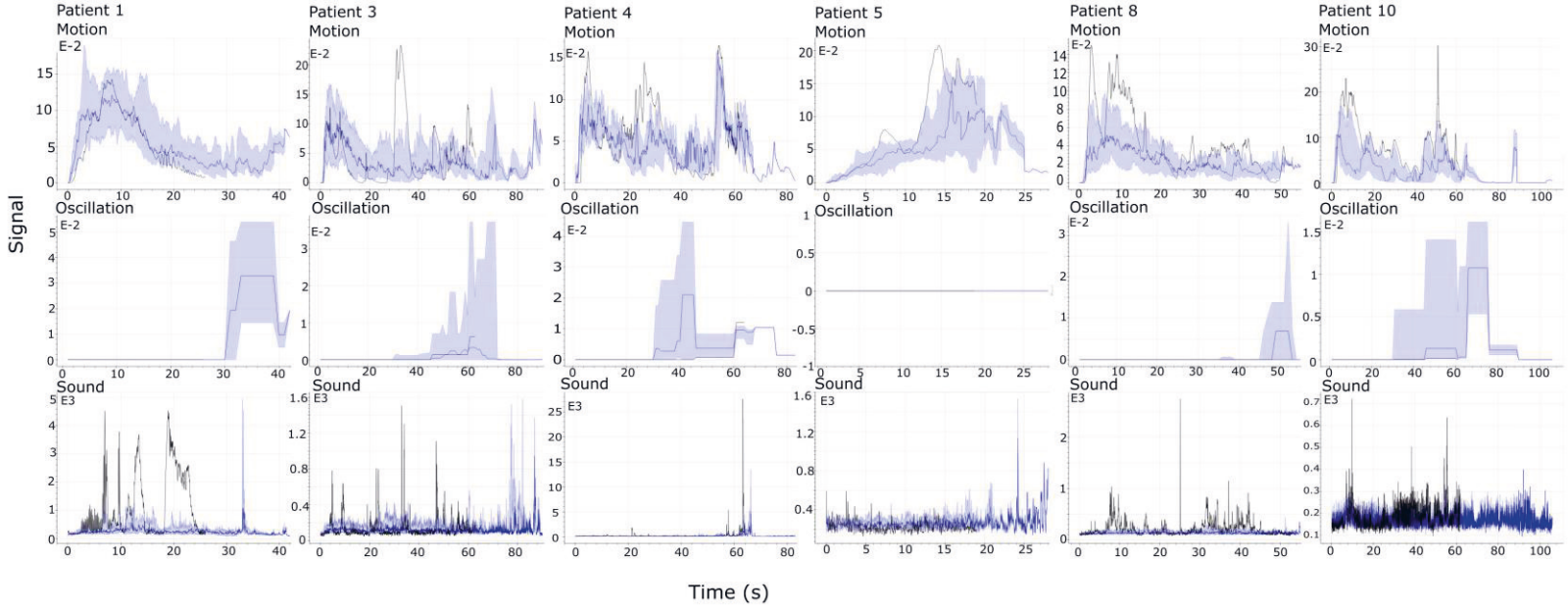

Figure 14. Combined median and quartile visualizations for signal profile figures of motor seizures from 6 patients. The most representative seizure has been bolded in all signal figures.

5.4.2 Effect of intervention on signal profiles

From 11 patients who participated in this study, 10 patients underwent the BRV treatment through follow-up successfully and 8 patients experienced seizures both before and after the intervention. Out of 8 patients, only patients 5 and 9 had visually recognizable changes in their whole signal profiles which have been presented in Figure 15. The changes were confirmed by mean signal values of these patients, as patient 5 experienced 36% and 7% decrease in mean motion and sound values, while patient 9 experienced 61% and 7% increase in those signals, respectively.

Figure 15 presents the median visualization of seizures before and after the intervention. Median and variance of signals before intervention were marked with a blue signal and blue shading, while red signal and red shading indicate median and variance of seizures after the intervention, respectively. As in the previous figures, the most representative seizures were marked with a black signal. As shown in Figure 15, patient 5 has lower motion and oscillation signal values after the treatment, especially after 12 seconds from the onset. Patient 9, however, had increased motion signal values after the treatment, even though the variance of seizures before intervention was high. Thus, patient 5 experienced a decrease and patient 9 experienced increased movement intensity after the initiation of BRV.

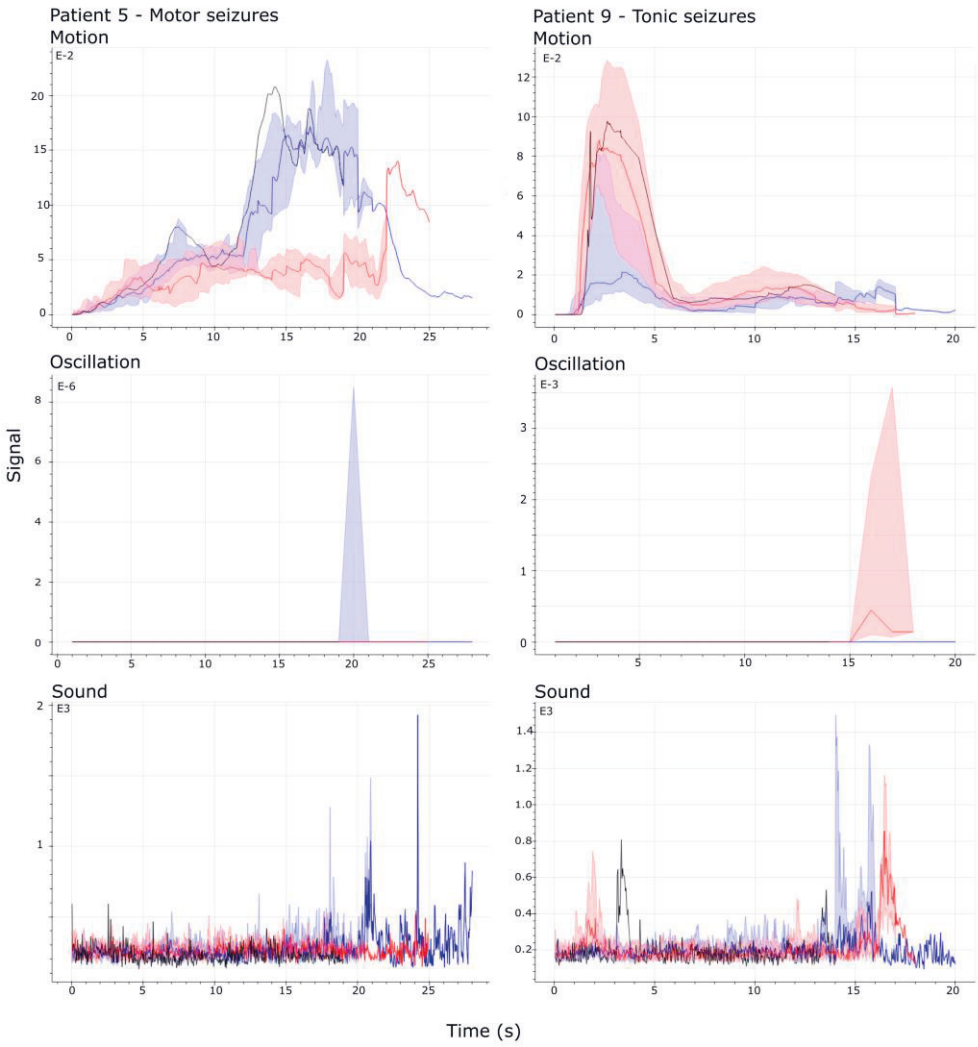

Figure 15. Combined median and quartile visualizations for two patients with significant changes in their signal profiles. Blue and red lines depict median values of signals, and blue and red shadings depict the variance of these signals, before and after the intervention, respectively.

6 DISCUSSION

In study I, the video/audio-based system was examined in a home setting. The automatic system was able to detect nocturnal motor seizures by utilizing three biomarkers which were sudden motion, oscillation, and sound.

In study II, a method using static and temporal motion features in automatic differentiation of tonic, tonic-clonic, and hyperkinetic seizures was presented. The model separated and classified hyperkinetic and tonic seizures with an accuracy of 91 and 88%, and F1-score of 93 and 90%, respectively. However, accuracy and F1-score were only 45% and 37% for tonic-clonic seizures, respectively.

The results from study III demonstrates the fundamental issues related to traditional seizure diaries in the evaluation of both the need for intervention and the therapy outcomes in DRE patients with nighttime seizures, which indicates the feasibility of the video/audio-based seizure monitoring system in drug interventions. Also, the intensity analysis enabled quantification of movement intensity due to intervention.

In study IV, video-based motion signal analysis enabled extraction of motion features characteristic for different signal profiles of tonic, tonic-clonic, hyperkinetic, and motor seizure types. Despite hyperkinetic and motor seizure types may have overlapping signal profiles, separating characteristics were found which indicates the possible utility of signal profiles in future development. Signal profiles might also be useful in the evaluation of change of movement intensity to assess treatment effect.

6.1 Comparison of the documentation methods

As results from study III showed, seizure diaries had significant inaccuracies which had an impact to treatment outcome evaluation in compared to the results of video monitoring. By using seizure diaries, only 8% to 84% of seizures were marked by eight patients during the phase 1, and only <40% to 70% of seizures were marked by five patients during phase 2. This led to underestimation of seizure frequency and inaccurate assessment of therapy outcomes. Some of the patients did not manage to document seizures in their diaries. Video monitoring detected higher seizure counts than diaries in ten patients in phase 1, and in eight patients in phase 2, which led to

underestimated frequency of seizures and overestimated number of seizure free nights. Non-seizure events were marked as epileptic (false positives) by 3 patients during phase 1 which led to overestimated seizure frequency in one patient. Therefore, study III supports the previous results that seizure diaries may underestimate and overestimate seizure frequency (Goldstein et al., 2021; Stokes et al., 2011).

Seizure diaries suggested that only one patient experienced effect on seizure frequency which would have led to a false conclusion that BRV intervention was ineffective in all patients, even though three patients reached >50% seizure decrease according to the information from the video recording. Furthermore, four patients were not able to mark seizures to their diaries, and video monitoring enabled treatment outcome information also for those patients. On the other hand, video monitoring enabled participation to intervention for three patients that were unable to document seizures during phase 1. Thus, the video monitoring system greatly increased the accuracy of therapy outcome evaluation by providing significant findings that the diaries alone were unable to provide.

Improving seizure documentation is important to increase treatment efficacy and to evaluate effect of treatment on multiple seizure types in follow-up of patients and in medical trials. Screening and differential diagnosis between various seizure types are important aspects in seizure detection and treatment implementation (Elger & Hoppe, 2018). In addition, occurrence of the next seizure can't be foreseen if a patient suffers from uncontrolled seizures which may lead to continual fear of seizures and a considerable handicap for patients even though a single or occasional seizure itself does not harm patient directly (Laxer et al., 2014). Uncontrolled seizures or fear of them significantly decrease the ability to live independently, especially in patients with developmental disability (Devinsky et al., 2015).

6.2 Applications of seizure monitoring system

6.2.1 Performance in seizure detection

According to the results of study I, the model utilizing sudden motion, sustained oscillation and sound level biomarkers derived from video data managed to detect seizures automatically. The system reached 8.8 % PPV and 90 % sensitivity for tonic seizures, and 50% PPV and 100 % sensitivity for seizures with clonic phase. Also,

the system enabled analysis of semiological characteristics and evolution of seizures in detail which might enable detection of more subtle motor seizures.

According to previous literature, the performance of automatic seizure detection is varying. Depending on seizure type, sensitivity varies from 75% for myoclonic seizures, 87-100% for convulsive seizures, 93-100% for hyperkinetic seizures, and 80% for tonic and automotor seizures (Achilles et al., 2015; Cuppens et al., 2012; Garção et al., 2023; Geertsema et al., 2018; Lu et al., 2013; van Westrhenen et al., 2020; Yang et al., 2021). However, lower sensitivity values have also been reported, such as 57% for hyperkinetic and tonic seizures (Geertsema et al., 2018). Specificity of 81-99% for tonic-clonic and convulsive seizures has been reported, as well as 59% for tonic seizures and 93% for motor/hyperkinetic seizures (Achilles et al., 2015; Garção et al., 2023; Lu et al., 2013; Yang et al., 2021). In compared to other studies, detection sensitivity of the method in study I is consistent with previous research, while providing further analysis of seizure characteristics. However, low PPV of the method in study I is a significant weakness in compared to state-of-the-art systems (Ahmedt-Aristizabal et al, 2024; Garção et al, 2023).

Furthermore, many of the current devices utilize oscillation as a biomarker to detect tonic-clonic seizures. Even though oscillation is a specific marker, it detects the seizure first during the clonic phase which increases the detection latency and impedes the usability of the technique as an alarm system. On the other hand, by utilizing tonic biomarkers, such as sudden motion and sound, the onset could be detected earlier, and it may support more various seizure types, which was the case in study I. Earlier detection would be beneficial in the implementation of this system as an alarm system. PPV was higher and FDR was lower in seizures with clonic phase while maintaining sensitivity of 90% or higher. However, if this model was developed into an alarm system, optimization of FDR would be more critical than reaching 100% sensitivity.

The performance of the Nelli system has been examined further after study I with larger patient populations. Using the same method as study I, video-based method significantly reduced the review time of video to 14% of the total time and reached sensitivity of 100% for tonic-clonic and clonic seizures and 82% for focal motor seizures (Peltola et al., 2022). In a recent phase 2 study, Nelli system achieved sensitivities of 78-95% with FDR/h of 0.09-4.81 for various motor seizure types with optimal thresholding (Rai et al, 2024).

6.2.2 Performance in seizure classification

Classification of seizures depends on objective criteria of observations made by caregivers or clinicians which makes the observations and differential diagnosis less reliable. Even though motor symptoms can be easily recognizable indicating a certain seizure type, there are no eyewitnesses, especially for nocturnal seizures (Elger & Hoppe, 2018). Classification of seizures can be difficult depending on seizure manifestations, even with the help of videos recorded during seizures due to inter-observer discrepancy which may affect the determination of seizure semiology (McGonigal et al., 2021). Moreover, manual annotation and classification of seizures of each patient may require a lot of time and resources (Reus et al., 2020; Swinnen et al., 2021). Tools that enable automatic video annotation during seizure monitoring could save time and resources, especially if patient experiences multiple types of seizures with high frequency. Automatic seizure classification could enable alarms for different seizure types and thus improve seizure alarm systems which might be beneficial in clinical practice especially in EMUs or institutional settings.

Previously, epileptic seizures and psychogenic non-epileptic events were differentiated automatically by using a multi-stream approach which was tested in seizures-wise cross-validation and leave-one-subject-out analysis, achieving F1-scores of 0.89 and 0.75 and accuracies of 0.87 and 0.72 (Hou et al., 2021). Differentiation of hyperkinetic seizures from non-hyperkinetic seizures and paroxysmal events during sleep achieved probability of 80% (Rémi et al., 2011) and accuracy of 80% (Moro et al., 2023). Another study utilized CNN and recurrent neural network (RNN) combination to automatically differentiate seizures in video data into focal and FTBTC seizures reaching accuracy of 98.9% (Pérez-García et al., 2021). System that automatically classifies seizures with motor manifestations into three seizure categories was not examined before. The performance in classification of hyperkinetic seizures in study II is aligned with the previous research (Moro et al., 2023) but poor classification of tonic-clonic seizures decreases the performance of the model, especially when considering the importance of documentation of tonic-clonic seizures in decreasing the SUDEP risk (Walczak et al., 2001). On the other hand, all tonic-clonic seizures were accurately classified in a large patient population when this video monitoring system was used (Peltola et al., 2022) because of stereotypic and easily distinguishable movements. Since tonic-clonic seizures were not classified when clustering and classification was performed, the applied methods may have not caused this limitation, but the insufficient discriminative power of the extracted time-series descriptor. Catch22 was utilized in the seizure classification with good overall discriminative power, especially for hyperkinetic and tonic seizures

but not for tonic-clonic seizures. The low number of tonic-clonic seizures in compared to hyperkinetic and tonic seizures may explain the low differentiation capability for tonic-clonic seizures.

Catch22 time-series feature collection was used in extraction of statistical descriptors to decrease the dimensionality of the training and testing data. Catch22 proved to be feasible for the task as it included the best features to analyze time series across science fields. In order to choose the suitable statistical features with discriminative capability, the unnecessary steps were deleted from the original set one at a time with simultaneously observing the unaffected clustering charts. After the clustering analysis, examination of the deep learning model verified the discriminative capability. As the tonic-clonic seizure count was lower than other seizure types, it may have caused weaker differentiation for the given seizure type. This is not considered as a cause of catch22 or deep learning method chosen in this study, but a general result when categories are not evenly balanced in the learning task.

6.2.3 Seizure intensity analysis

Quantitative analysis of seizure features allowed to detect changes in severity and propagation of seizures. In study III, the change in movement intensity and duration of seizures before and after BRV initiation was explored by using visual and audio features. The features noticed minor movement intensity changes with statistical significance in 8 patients. Visually recognizable decrease in graphs were noticed in three patients after the BRV initiation, as shown in Figures 10 and 11. As shown in table 8, hyperkinetic, focal motor, clonic and tonic-clonic seizure types were detected with the most diverse statistically significant features which indicates better accuracy and suitability of features in these seizure types with unequivocal and stereotypical motor movement patterns. The change of duration of seizures was not verified in study III.

In study IV, signal profiles were utilized to detect changes in movement intensity. Significant effect of BRV intervention was detected in two patients based on both the visual analysis of signal profiles and mean values of motion signals. In addition, smaller changes in mean signal values were detected in two patients but these changes were not considered clinically significant. Even though quantitative analysis has been applied to seizure semiology analysis (Ahmedt-Aristizabal et al., 2018; Cunha et al., 2016), quantitative analysis of impact of BRV on movement intensity have not been studied before. However, the clinical relevance of even the significant

changes in motion signals have not been validated in the previous research. On the other hand, changes in seizure motion manifestations can affect seizure documentation, especially if seizure diaries are used, which patients and caregivers should be aware of.

6.2.4 Signal profiles

In study IV, our intention was to investigate further the signal profiles in a larger and more diverse patient population. In this patient population, hyperkinetic seizures had a rapid onset in motion signal in both patients, and the absence of oscillation activity may separate them from motor seizures. Tonic-clonic seizures as well as tonic seizures had similarities in their signal profiles of tonic phase, and clonic oscillation can be utilized to separate the two seizure types. Especially hyperkinetic and tonic-clonic seizures had repetitive, stereotypical findings in their motion signals with small variance.

Tonic and tonic-clonic signal profile patterns support the previous findings of study I by showing similar signal profiles for those seizure types in a larger patient population. Also, signal profile characteristics found in study IV may explain the previous findings of study II, as tonic seizures often had similar signal manifestations throughout the dataset which may indicate more accurate recognition of the tonic component. The oscillation of the clonic phase combined with the tonic motion manifestation could be used to recognize tonic-clonic seizures from other seizure types. However, varying semiological characteristics, especially in motor seizures, decreased the generalizability of signal profiles. For example, two seizure types with same onset but different propagation might hamper the separation of these seizure types. Recognition and analysis of specific body parts by utilizing pose estimation might provide solution to this issue, but functional models have not been reported (Pediaditis, Tsiknakis, & Leitgeb, 2012). Also, parameter and threshold adjustment have been used to improve detection performance (Geertsema et al., 2018; Pediaditis, Tsiknakis, & Leitgeb, 2012), and it could be a topic for future research.

In previous literature, multiple studies have reported seizure signal characteristics typical for a seizure type. For example, clonic seizures have been represented by utilizing luminance signals and optical-flow techniques which created a rhythmic signal distinguishable from normal motions (Cattani et al., 2017; Garção et al., 2023; Geertsema et al., 2018). Sound has been utilized in semiology analysis (Hartl et al., 2018), and according to this dataset, the sound signal might help to distinguish tonic-

clonic and hyperkinetic seizures from motor seizures. Inter- or intra-patient motion signal variance of motor seizures has not been reported before.

6.3 Limitations of this research

In any of the studies, video-EEG was not used as a gold standard. However, unequivocal semiology of seizures was determined by comparing seizures with VEM reports which was considered a feasible reference standard, as previously suggested (Beniczky & Ryvlin, 2018). Video-based methods have some general limitations. In order to create motion signals accurately, the patient should stay visible in the camera during seizures and caregivers should avoid it to not disrupt the motion signals. A blanket may hamper detection of small movements of the patient which can cause challenges in the analysis of subtle motor seizures. Maintaining the same recording settings throughout the monitoring period is significant to minimize the impact of patient and environment-related elements on motion signals (Yang et al., 2021). Also, monitoring of patients was conducted during nighttime, and daytime activity might cause challenges for seizure detection due to the increased physical activity of patients. However, nocturnal seizures are more difficult to document, and they correspond to an increased SUDEP risk.

In all studies, the size of study sample limits the reliability and generalizability of the results, and studies with larger patient populations and more seizure types would increase the reliability, especially for seizure detection and classification. More evenly distributed dataset might also improve reliability of automatic seizure classification. Also, only tonic-clonic, tonic, and hyperkinetic seizures were included which typically manifest distinguishable movement symptoms, and seizure type is easily determined. Absence of non-epileptic seizures may also affect the results of study II and IV, even though they have been accurately detected previously (Peltola et al., 2022). Seizures with minor motor manifestations may cause challenges in seizure analysis, even though accurate detection have been reported (Hou et al., 2021).

Effect of intervention was explored in studies III and IV. As statistical significance of features alone does not confirm the reliability of the method, the changes were confirmed by a medical expert from video data in study III. In study IV, generalizability of signal profiles is affected by number of seizures, as well as movements of caregivers. Also, semiology of seizures can cause significant variation of signal profiles, especially in motor seizure category. Varying seizure duration may cause inaccuracies in the end of signals, as the quartile and median visualizations rely on a smaller amount of data. In addition, video-based evaluation of movement

intensity may be inaccurate without confirmation by EEG, as the correlation between motion signal changes and seizure intensity decrease has not been explored. However, the long duration of monitoring period impedes the use of video-EEG to explore the correlation of motion signals and intensity of seizures.

Also, only part of the study population in studies III and IV responded to BRV intervention which decreased the number of changes in feature analysis and signal profiles, which may reduce the generalizability of the intervention effect results. Furthermore, some of the patients who participated the BRV intervention in studies III and IV were not able to record the nights consecutively which led to varying duration of follow-up, and it might have had a small impact on the comparability of the monitoring results between patients in both studies. Follow-up periods of three and five weeks in studies II and IV were relatively short to see visible changes in movement manifestations. Thus, studies with longer follow-up may provide more reliable information about the effect of BRV on movement intensity.

6.4 Future implications

The methodology presented in this dissertation was applied to seizure detection and classification, as well as in movement intensity analysis in drug interventions. The dissertation provided a methodology to detect seizures of different motor seizure types automatically which provided the basis for development to detect more various seizure types. The seizure detection method might require individualization and calibration of parameter settings, and to investigate this hypothesis as well as generalizability of detection performance, studies with larger patient datasets are required. Besides detection of seizures, automatic classification was explored in this dissertation. The methodology reached reasonably high performance for three motor seizure types which forms the background for further research with larger, more varying, and more evenly distributed dataset to better assess the ability of this model to automatically classify seizures. Also, automatic detection and classification of seizures with subtle motor seizures might provide another topic for further research. Effect of BRV was evaluated by utilizing feature extraction which may be beneficial in the assessment of treatment outcomes. However, the relevance of this hypothesis might require validation with larger patient populations in the future by utilizing video-EEG as the gold standard.

The methodology presented in this research have several clinical implications. Automatic detection and classification of seizures may improve documentation of seizures, especially nocturnal seizures and affect treatment of patients, as previously

discussed in this dissertation. It might also reduce work in the video review process and streamline the workflow of clinicians. Infrequent seizures might be documented more likely with video monitoring at home than with video-EEG at EMU due to the longer duration of monitoring period. Thus, video detection systems might potentially achieve cost savings in health care.

7 CONCLUSIONS

Accurate seizure documentation is significant in treatment and management of epilepsy. Due to the inaccuracies related to the use of seizure diaries, video-based seizure detection has been broadly studied to develop automatic detection systems. In this study, a new video-based seizure detection method was presented and its ability to detect and classify seizures automatically was explored.

Video-based home registration utilizing biomarkers of sudden motion, oscillation and sound enabled automatic seizure detection which may imply cost savings and improved patient care. Automated analysis could provide valuable information about seizure frequency and manifestations for epilepsy patients and their caregivers. The methodology presented in study I have achieved promising results also in studies with larger patient populations.

In study II, the quantitative analysis of motion features from video differentiated tonic, tonic-clonic, and hyperkinetic seizures automatically. Based on the results, motion signals may enable differentiation and classification of motor seizures. Even though the accuracy in the classification of tonic-clonic seizures were low, the results could be regarded as a step toward an automatic seizure classification tool for clinical practice.

In study III, video monitoring significantly improved the seizure documentation in compared to seizure diaries which affected the seizure frequency evaluation and interpretation of results of drug intervention. Due to the tendency of seizure diaries to underestimate or overestimate seizure frequency, the results support the feasibility and value of video monitoring to document and confirm seizures.

As observed in study I, video-based motion signal analysis was able to extract signal profile characteristics of different motor seizure types. This observation was further evaluated in study IV, and signal profile characteristics typical for a certain motor seizure type were also found in a larger patient population. These characteristics might be useful in seizure classification and further development of this system. Feature analysis and seizure signal profiles might be useful in the assessment of movement intensity after drug interventions.

In summary, this dissertation demonstrates the potential of video-based seizure detection system to automatically detect and classify seizures with motor

manifestations and implies the significance of detection method on management and follow-up of epilepsy. According to the results, signal biomarkers presented in this research could be utilized in the analysis of epileptic seizures. Even though further research could be useful to improve the reliability of the results in larger study samples, this research provides deeper understanding of the methodology and signal biomarkers which may enable further development of the system. This research contributes the technological advancements in automatic detection and analysis of epileptic seizures which could enable improved treatment of epilepsy and QoL of epilepsy patients in the future.

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PUBLICATION I

An integrative method to quantitatively detect nocturnal motor seizures

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An integrative method to quantitatively detect nocturnal motor seizures

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ABSTRACT

In this proof-of-concept investigation, we demonstrate a marker-free video-based method to detect nocturnal motor seizures across a spectrum of motor seizure types, in a nighttime setting with a single adult female with refractory epilepsy. In doing so, we further explore the intermediate biosignals, visually mapping seizure "fingerprints" to seizure types. The method is designed to be flexible enough to generalize to unseen data, and shows promising performance characteristics for low-cost seizure detection and classification. The dataset contained recordings from 27 recorded nights. Seizure events were observed in 22 of these nights, with 36 unequivocally confirmed seizures. Each seizure was classified by an expert epileptologist according to both the ILAE 2017 standard and the Lüders semiological classification guidelines, yielding 5 of the ILAE-recognized seizure types and 7 distinct seizure semiologies. Evaluation was based on inference of motion, oscillation, and sound signals extracted from the recordings. The model architecture consisted of two feature extraction and event determination layers and one thresholding layer, establishing a simple framework for multimodal seizure analysis. Training of the optimal parameters was done by randomly resampling the event hits for each signal, and choosing a threshold that kept an expected 90 % sensitivity for the sample distribution. With the cut-off values selected, statistical performance was calculated for two target seizure groups: those containing a clonic component, and those containing a tonic component. When tuned to 90 % sensitivity, the system achieved a very low false discovery rate of 0.038/hour when targeting seizures with a clonic component, and a clinically-relevant rate of 1.02/hour when targeting seizures with a tonic component. These results indicate a sensitive method for detecting various nocturnal motor seizure types, and a high potential to differentiate motor seizures based on their video and audio signal characteristics. Paired with the low cost of this technique, both cost savings and improved quality of care might be achieved through further development and commercialization of this method.

1. Introduction

Epilepsy is one of the most common neurological disorders, and is characterized by the occurrence of seizures caused by excessive abnormal brain activity. Accurate seizure documentation is essential in order to assess therapy outcomes and risks, especially of nocturnal seizures which cause remarkable increase in the probability of sudden unexpected death in epilepsy (SUDEP) Lamberts et al. (2012); Baumgartner et al. (2018). However, there is ample data suggesting that even 50 % of motor seizures are missed by patients Elger and Hoppe (2018), and under-reporting is even more frequent for nocturnal seizures or seizures with impaired awareness Hoppe et al. (2007). Seizure diaries are commonly unreliable due to postical amnesia and the inability of caregivers to observe (and accurately describe) all of the patient's seizures Akman et al. (2009). Inaccurate documentation affects the patient's treatment and evaluation of efficacy of treatments Elger and Hoppe (2018). Improved documentation could not only help in assessing therapy outcome and thus facilitate treatment optimization, but could additionally provide information for lateralizing and localizing the epileptogenic zone, which is helpful for classification of seizure syndrome and therapy planning. For these reasons, there is a need for more objective and reliable seizure detection.

Due to the inaccuracies present in traditional diary-based follow-up, new strategies for epilepsy monitoring have been proposed. Non-EEG

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systems can be used for detecting motor seizures Conradsen et al. (2012), but the accuracy and reliability remain problematic for some seizure types. Video-based monitoring systems usually rely on markers attached to the patient – or done purely with computer vision techniques – allowing motor seizures to be detected without physical attachment to a machine. While most of the studies successfully target prominent convulsive seizures, subtle motor seizures tend to yield lower sensitivity and positive predictive values. Even so, video monitoring has been demonstrated as a tool for capturing more subtle seizure types, including those not observed by caretakers or the patient Peciola et al. (2018); van der Lende et al. (2016). Furthermore, seizure audio has been shown as a useful tool for seizure classification De Bruijne et al. (2008); Hartl et al. (2018), and could be combined in a multimodal way to better differentiate video-based detections from false positives.

Given the (1) clinical need for better epilepsy monitoring, the (2) gap in current solutions for a wider spectrum of motor seizures, and the (3) hypothetical power of using a multimodal approach to provide better detection, we propose a framework for a new seizure detection method based on off-the-shelf hardware and open-source software. In this study we present a system that measures seizure features quantitatively, which allows to detect changes in seizure severity or propagation. The parameter selection in this proof-of-concept model is based on a single adult with refractory multifocal epilepsy. Her variety of nocturnal motor seizure types allowed us to explore a spectrum of motor seizures. From a detection method point of view, this study serves as a Phase 1 validation of a new epilepsy monitoring device Beniczky and Ryvlin (2018).

2. Patient and methods

2.1. Clinical history of the patient

The patient is an 18-year-old woman with moderate intellectual disability and refractory epilepsy. The onset of epilepsy was associated with fever and infection at the age of one. She had different seizure types classified according to her pediatric epileptologist, such as myoclonic absences, bilateral tonic seizures, and generalized tonic-clonic seizures. The brain MRI revealed mild cerebellar atrophy and was otherwise normal at the age of five. Genetic testing for Dravet syndrome (SCN1A gene) was negative. The epilepsy was classified as generalized epilepsy with encephalopathy. Despite adequate trials of multiple antiepileptic drugs (AEDs), the patient continued to have frequent seizures.

When the medical care was transferred to the adult neurology unit at the age of 16, a video EEG (VEEG)-monitoring was performed in June 2016 for electroclinical characterization of the seizures and definition of the epilepsy syndrome. The seizures observed in VEEG were similar to those observed during the home monitoring period used in this study; more detailed descriptions are presented below. The VEEG registration demonstrated multifocal from either the left or the right hemisphere with frontal or centro-parietal EEG seizure onset. Based on the unequivocal focal onset of seizures, the epilepsy was reclassified as multifocal epilepsy. Due to the bilateral multifocal onset, resective epilepsy surgery was excluded as a treatment option.

The patient was implanted with a vagal nerve stimulator (VNS) in January 2017. The stimulation was initiated in February 2017 and the primary stimulation target dosing was reached by May 2017 (1.75 mA, 30 Hz, 250 μsec, 30 s ON and 5 min OFF; autostimulation and magnet mode activated). The caregivers (parents) described significant improvement in alertness and decreased seizure severity, but the patient continued to experience the above-mentioned seizure types. The seizures were frequent and mostly nocturnal, and their count, severity and duration were difficult to evaluate based on the seizure diary. In addition to VNS, the patient continues to be treated with a daily dose of 1200 mg sodium valproate, 200 mg lamotrigine, and 30 mg clobazam.

2.2. Semiological classification of the patient's seizures

In order to assess the continuing evolution of the patient's disease, a one-month video-based nighttime home monitoring was performed in May 2018 (the service provider was Neuro Event Labs) at the patient's home. The 35 recorded intervals ranged from 42 min to 11 h 39 min in duration, with a total recorded time of 262 h 8 min, and a mean duration of 7 h 29 min. As the recordings were manually controlled by the patient, variation in the length can be accounted for by natural changes in sleep patterns as well as manual stopping of the recording for privacy reasons. The nocturnal registrations formed the dataset for this case study and was chosen in particular due to the variability and frequency of seizures, as well as the relatively long registration period: seizures were observed in 22 out of 27 recorded nights, with a total of 36 confirmed seizures. All video data was manually reviewed by an annotator. The evaluation was based on suspected seizure events which were detected by the analysis of motion, audio, and oscillation signals recorded during nighttime monitoring. All events were manually evaluated and classified by two experienced epileptologists (E.H., S.N.). This also serves as a reference standard for one study according to Standards for testing and clinical validation of seizure detection devices Beniczky and Ryvlin (2018). Events that were not determined to be unequivocal seizures were divided into two categories: those clearly "not a seizure" and those "unlikely to be a seizure" and excluded from the further analysis. A total of 7 seizure semiologies were indicated, falling under 5 of the ILAE-recognized focal motor seizure types. The seizures are listed in Table 1 along with the ILAE codes Beniczky et al. (2017) in parentheses. Short descriptions of the seizures observed during the home monitoring period, a summary of their quantitative characteristics, and statistics of seizures observed by caregivers are presented below. Also, electrophysiological features of the seizures are summarized if observed in the VEEG registration.

- Focal tonic seizure (I.C.05) (n = 24): started from sleep with sudden stiffening of the body, accompanied by an exhalation sound and typically bilateral raising of arms. In some cases (10/24 seizures) the seizure ended at this stage (bilateral tonic). In the rest of the cases the tonic phase was followed by tonic posturing accompanied by a guttural sound or by a clonic phase (bilateral tonic to bilateral clonic). According to the data from the home monitoring, the duration of these seizures varied from 4 to 42 s. Apart from the seizures with the gutteral sound (12/24 seizures), focal tonic seizures were not witnessed by the caregivers. In the VEEG registration, these seizures were associated with frontal EEG seizure activity.
- Focal clonic seizure (I.C.03) (n = 3): started from sleep with unilateral clonic movement (unilateral clonic). During the home monitoring period, the duration of these seizures varied from 9 to 14 s. Only 1 out of 3 seizures in the dataset was noticed by the caregivers. According to VEEG recordings, the seizure onset was in the right frontal region.
- Focal to bilateral tonic-clonic seizure (I.D.01) (n = 5): started from sleep with sudden stiffening of the body, simultaneously with an exhalation sound, followed by guttural sounds (4/5 seizures). After a bilateral tonic phase of 15–20 seconds, the patient entered a period of bilateral clonic movement. These seizures were noticed by the caregivers, and they lasted from 23 to 45 s. Postictally bilateral flattening in VEEG occurred.
- Focal motor seizure (I.C.01) (n = 2): appeared with awakening. The patient rose and leaned backwards, followed by a clonic movement of the right arm (complex motor, asymmetric clonic) or stiffening of the body (complex motor, bilateral tonic). The duration of these seizures varied from 11 to 26 s. These seizures were not noticed by the caregivers and were not captured during the prior VEEG evaluation.
- Focal myoclonic seizure (I.C.02) (n = 2): consisted of single myoclonic jerks or clusters of myoclonic jerking of arms and legs. The

Table 1
Semiological and ILAE 2017 classification of unequivocal seizures in the dataset; ILAE: international League against epilepsy; VEEG: video-EEG recording.

ILAE 2017 type	Semiologies	Count	Registered during VEEG
Focal to bilateral tonic-clonic (I.D.01)	Bilateral tonic – guttural sound - bilateral clonic	4	Yes
	Bilateral tonic – bilateral clonic	1	No
	Bilateral tonic – guttural sound	12	Yes
Focal tonic (I.C.05)	Bilateral tonic	10	Yes
	Bilateral tonic – bilateral clonic	2	Yes
Focal clonic (I.C.03)	Unilateral clonic left trunk	3	Yes
Focal myoclonic (I.C.02)	Myoclonic jerk	2	No
Focal motor (I.C.01)	Complex motor – bilateral tonic	1	No
	Complex motor – asymmetric clonic	1	No

duration of these seizures was 4–16 seconds. These seizures were not noticed by the caregivers and did not manifest during the VEEG recording.

2.3. Dataset

The original (raw) data from the home registration consisted of the aforementioned 262 h of grayscale 30 frames-per-second (Hz) compressed (VP9-encoded) stereo video at 1280 × 720 ("HD Ready") resolution and accompanying compressed (Vorbis-encoded) 48 kHz stereo audio. Sound was captured using the built-in stereo microphone of an Intel NUC, a low-cost compact PC. This computer was used to perform the collection of the video and audio content.

Video was captured using an Intel Realsense D435 camera module, a low-cost depth sensor containing stereo near-infrared imaging sensors, via a USB connection to the PC. The use of the infrared spectrum allows it to capture clear grayscale images in the dark. This camera's built-in infrared projector is designed for structured light stereoscopy, but this light pattern was coupled with an optical diffuser in order to illuminate the scene in lieu of the structured light pattern. This device has a global shutter, ensuring a fixed frame rate despite changes in lighting conditions. The camera's built-in autoexposure support was enabled to adjust for natural and electrical lighting contributions to the scene's illumination. The camera was placed in a fixed position at the foot of the bed, using a boom arm extending toward the patient. The camera was oriented with the bed to optimize the number of "physiologically active" pixels in the image.

All seizures presented in Table 1 were annotated against this raw data using the UTC timestamp of estimated onset and offset of the ictal period based on observable phenomena.

2.4. Model architecture

As motor seizures are typically recognized by the presence of abnormal movement, we designed the model around the extraction of features typical for motor seizures but absent in normal sleep. It is based on the intuition that any generic measurement of motion or sound (aspects found in motor seizures and detectable by a camera and microphone) might have thresholds or features which are more indicative of seizure behavior than typical behaviors observed during sleep.

Given the distribution of semiological features in the dataset, we focused on three biomarkers: sudden movement (suggesting a tonic component), sustained oscillatory movement (suggesting a clonic component), and sudden increase in audio level (suggesting a vocalization). We paired signal processing algorithms for each of these biomarkers, resulting in three input signals for the model. A basic multilayer approach for event determination and thresholding was then constructed based on these input signals, ordered from most sensitive and inclusive to most specific and exclusive. In the upper layers, the parameters were selected based on the input dataset tuned for sensitivity (to capture all possible seizures), with the lower layers tuned for positive predictive value (to eliminate false positives). The model architecture is presented in Fig. 1.

The sample rate of the extracted signals matches the original video frame rate (30 Hz), and can be described as time (t) dependent functions. The signals are normalized to a range from 0 to 1.

2.4.1. Extraction layer

The computationally inexpensive first layer generates signals closest to the raw data: they filter out periods of time with low salience. This layer includes motion and audio intensity extraction, which form basic

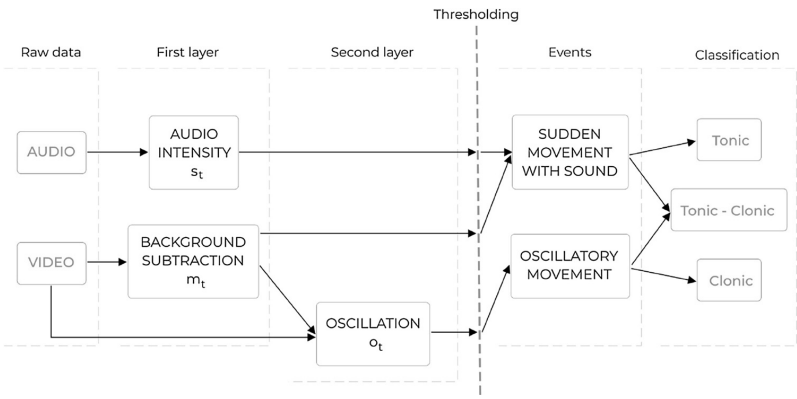

Fig. 1. Model architecture. The multi-layered model extracts biosignals from raw video and audio which are then thresholded to extract events predictive of seizure activity.

physiological biomarkers for movement and sound. To model scene motion, a background subtraction model by Zivkovic and Van Der Heijden (2006) was paired with a stereo correspondence filter by Hirschmuller (2008) based on semi-global matching (both implemented in OpenCV). The background subtraction model provided a binary mask of the moving parts of the image, and each pixel was multiplied by the distance provided by the stereoscopic filter in meters, resulting in lower values for pixels representing points closer to the camera, and larger values for pixels representing objects farther from the camera. Default values from OpenCV were used, as well as following the software manual's guidance for eliminating noise and improving correctness of these models. The mean per-frame value of this mask of" distance-normalized pixels" was recorded as a one-dimensional signal. Denoting this model as M, the ratio of active pixels to total pixels per frame formed the motion signal m_t:

$$m_t = \frac{M_t}{M_{max}}$$

To model the sound level of the scene, a similar approach was used: a signal S was derived from the ratio of the raw audio signal by subsampling it to 30 Hz (down from 48 kHz), taking the maximum value of the subsampled period (in this case 1600 original samples), with the intuition that the general sound intensity ("loudness") could be inferred from this signal. This models only the sound volume at that moment in time, which is consistent with other research showing that vocalization intensity to be a good marker for seizure localization Hartl et al. (2018). In future iterations of the model, more complex audio features such as pitch might improve PPV, as demonstrated by Speck et al. (2018). This sound loudness signal, st, was normalized against the maximum value as follows:

$$s_t = \frac{S_t}{S_{max}}$$

For detecting periods of sustained oscillation (as present in clonic seizures), an optical flow Horn and Schunck (1981) based method, a commonly used approach in video-based seizure detection Geertsema et al. (2018), was applied. Specifically, the "PixFlow" optical flow implementation Facebook (2016) was used to compute a time-series motion vector field for the salient clip. This vector field was used to construct a sparse path history, with paths eliminated from the output where the optical flow algorithm lost confidence in the tracked image feature. The unbroken paths during a sliding window (1 s) were then analyzed for direction reversal, with each change in direction over 90° being considered a reversal. The resulting signal o_t was defined as the count of non-zero values from the set of unbroken paths, P, containing reversals over the threshold N:

$$o_t = \sum \{P \wedge 1 \ : P \geq N\}_t$$

A value of 5 for N (i.e. five reversals, or a 2.5 Hz oscillation frequency) was experimentally found to be a good filter for finding oscillating movements that do not occur during normal sleep.

2.4.2. Thresholding layer

The thresholding layer creates events from the input signal based on thresholds for amplitude, duration, and sample count. In the parameter selection phase of this model (discussed more in the following section), these parameters can be optimized for a given evaluation criterion, e.g. maximal sensitivity. Based on each signal and their target evaluation criteria, a set of events was determined: oscillation events (E_o), noticeable movement events (E_m), and sound events (E_s). This gives a flexible way to combine events based on their time intersection, e.g. finding events with both sudden movement and sound, as observed in many of the tonic seizures within the dataset. This particular case (E_i) can be defined as:

$$E_i = E_m \cap E_s$$

2.5. Threshold selection

For this study, it was desirable to find cut-off thresholds which yielded sensitivity close to 100 %, while maximizing positive predictive value. This is an important distinction with this model architecture, as its purpose is to provide a narrowing view with each added layer: the top model should catch all possible seizures, at the expense of generating many false positives. Each progressive layer filters out positives based on semiological characteristics that can be determined by a biomarker. This section describes a method for optimizing the cut-off values which determine if these events are relevant to the patient's seizures. Further study is required to understand if such thresholds are truly generalizable across patients, how many of a given patient's seizures would needed to be in order to find meaningful thresholds through training, and if these physically-based values can hold well even when the patient and environment are changed.

Under the hypothesis that a characteristic difference exists between seizures and non-seizures within the events detected by this model, a tuning of model's parameters should provide a path to separate the two classes by one or more thresholds. To test this hypothesis, the value distribution for each set of extracted events was compared with the corresponding ground truth dataset to find if any statistically significant effects where at play for the given variable. In order for an event to be considered correspondent to the ground truth, it had to begin within 10 s of the reference standard (before or after), and had to end after the reference standard started (thus eliminating short events which might have started and stopped before the actual seizure). To account for variability, the ground truth (all events containing seizures) was split into 5 folds, each with 80 % of the original hits. This cross-validation of the threshold parameters gives insight into the stability of the cut-off value, and acts as an indicator of how well this model is expected to work on future data from this patient. It also creates a basis for future datasets (from different patients and for different seizure types) to be used to find good parameters given an equivalently-sized" training set" of that patient's seizures.

Given the goal to characterize signal intensity, the possible numerical features which can be extracted from such time-series data is practically limitless. For this study, a simple descriptor was used: the Euclidean (L_2) distance between the maximum and mean magnitudes for the event (both values were scaled by the sample standard deviation before calculation). This descriptor serves as a reasonable marker for intensity, as it favors both events with a sharp peak (maximum magnitude) and those with an overall high energy content (mean magnitude). These values were then used to estimate the population density function using kernel density estimation (KDE). In the interest of retaining at least 90 % sensitivity, the optimal value was selected to be the 10th percentile of the cumulative distribution function of the KDE. As the experiment was performed 5 times for each signal, the mean of the returned values was used in evaluation and the range has been plotted to show variability.

For" noticeable" motion, a total of 1525 events (total duration 630 min) were detected, with a mean duration of 24.8 s and a range from 3.3–997.8 s ($\sigma = 43$ s). All seizures had exactly one match to a corresponding motion (100 % sensitivity). As the distributions appear to be roughly exponentially normal, the x-axis is plotted exponentially and cropped around the central tendency (note that this visually skews the probability distribution, so it must be remembered that the density increases as the x value increases). The seizure samples appear to be from a different distribution than the overall collection ($p < 0.001$ for all seizures, $p < 0.01$ for those with a tonic component), so it is expected that considerable separation power is available with this feature. The optimal threshold was calculated from the tonic seizure folds, and was found to be 0.0092 (range = 0.0081−0.0104, $\sigma = 0.0011$). The small variance in this range suggests that the intensity measure is a good fit to the problem. The density distribution of seizure samples and all motion

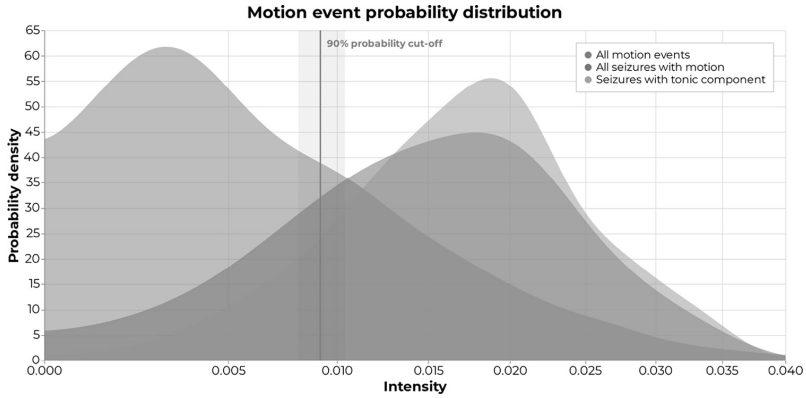

Fig. 2. Probability density distribution of all motion events compared to those during seizure. Blue shading indicates variation in 5-fold threshold training.

events has been presented in figure 2 .

For" audible" sound, a total of 5681 events were detected (total duration 185 min), with a mean duration of 1.9 s and a range from 0.6–257.5 s ($\sigma = 8.5$ s). A total of 48 sound events qualified as seizure detectors, with 34 / 36 (94 % sensitivity) seizures detected by one or two sound events according to the hit criteria. While this implies that the missed seizures did not have audible sound at the beginning of the clinical onset, it may also imply that the signal itself would benefit from adaptive filtering to adjust the noise floor as the ambient sound levels change throughout the recording. The intensity descriptor showed distribution separation between classes, with non-seizure events in gray, all seizures in green, and all" guttural" seizures in orange, as shown in 3 . Visually, it appears that seizures are more likely to contain loud sound samples, which is intuitively expected. The difference in density estimates is statistically significant ($p < 0.001$ for all seizures, $p < 0.01$ for those with guttural sounds). As the most audible seizures were the target of the model, the guttural data set was used; the optimal value occurred at 0.025 (range = 0.0074−0.041, $\sigma = 0.013$). The rather large variance in the range suggests that the intensity measure does not adequately capture the seizure sound feature, or that there is a naturally large variance in such sounds.

Finally, for the richest event type used in this study, E_o, representing" visible oscillation", a mere 25 events were detected (total duration: 3 min 25 s), with mean duration of 8.1 s and a range of 3.6–25.4 seconds ($\sigma = 6.4$ s). As oscillations tend to occur later in the seizure (particularly with FTBTC seizures), the hit criteria was applied to the encapsulating motion event E_m instead of the start of the oscillation. Of the 36 seizure events, 11 had exactly one oscillation event according to the hit criteria (30 % sensitivity), but all 10 seizures with a clonic component were detected (as well as one tonic seizure, apparently due to oscillation of the caregiver patting the patient on the back). The distributions are not significantly different ($p > 0.1$), which is expected given that nearly half of the detections correspond to a seizure. When comparing to events that did not hit a clonic seizure, however, the difference in distributions appears to be significant ($p < 0.02$). All oscillation events without a clonic correspondence are displayed in gray, and hits with a clonic component are shown in orange. The optimal threshold was calculated to be 0.0037 (range = 0.0–0.011, $\sigma = 0.0042$). The variance is somewhat high, suggesting that the chosen intensity measure may not be optimal for the problem. Probability density distribution of oscillation events has been presented in figure 4 .

3. Results

To help illustrate and understand the statistical performance of the model, it is important to document some of the observable

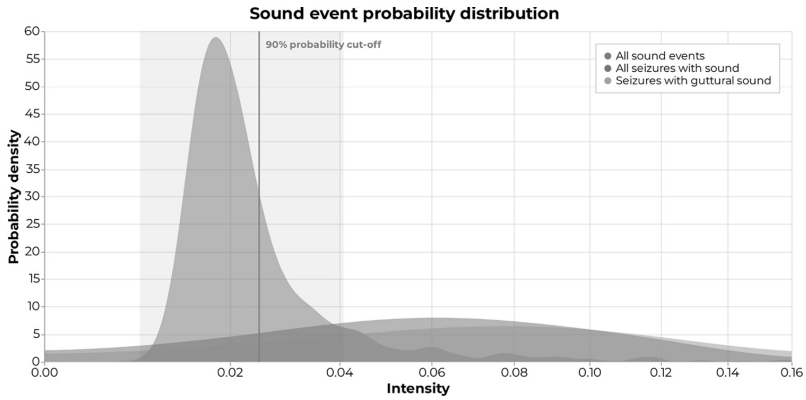

Fig. 3. Probability density distribution of all sound events compared to those during seizure. Blue shading indicates variation in 5-fold threshold training.

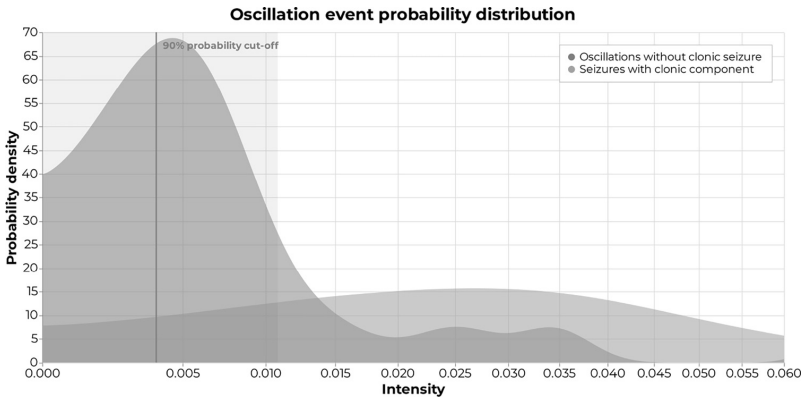

Fig. 4. Probability density distribution of all oscillation events compared to those during seizure. Blue shading indicates variation in 5-fold threshold training.

characteristics of the signal data. Example signal profiles of each biomarker for each seizure semiology are presented in Fig. 5.

3.1. Algorithm-based description of seizures

As Fig. 5 shows, each visually depicted seizure category had a distinctive signal profile. All seizure signal profiles in the dataset are provided in the supplementary material.

Seizures with one or more clonic phases manifested a prominent amount of oscillation o_t compared to the bilateral tonic seizures. The focal clonic seizure on the left in Fig. 5 depicted an oscillating phase without further semiological findings. The observable increase in the sound signal s_t is due to movements of the bed caused by the shaking patient.

Seizures with a bilateral tonic phase revealed a sudden, simultaneous increase in the amount of movement (distinctive spike on m) and sound (distinctive spike on s_t). There was no notable oscillation present in the scene. The two examples of focal tonic seizures in Fig. 5 depict the signal difference caused by the appearance of the guttural sound: movement-related signals were similar, but the bilateral tonic seizure with guttural sounds lead to an altered sound profile. Thereby, guttural sounds increased the variance of the signal after the initial, sudden sound onset.

Generalized convulsive seizures comprised the following features: stiffened arms raised slowly before the patient entered the clonic phase, either without significant vocalization (Fig. 5, bilateral tonic to bilateral clonic) or accompanied by distinct guttural sounds. Furthermore, the patient had one seizure propagating from bilateral clonic to bilateral tonic-clonic, with the tonic stiffening of the body observable as a lack of movement between the two oscillating phases.

The signal profiles were also capable of differentiating between seizure and non-seizure time periods, and this was utilized during the parameter selection phase by optimizing amplitude and duration thresholds for each of the signals separately. The model was derived based on seizures categorized by E.H., S.N. and J.P., and the final parameters quantify the minimum requirements for a signal segment to be counted as a seizure candidate.

3.1.1. Seizures with a tonic component

The most common seizure type in our registration was the focal tonic

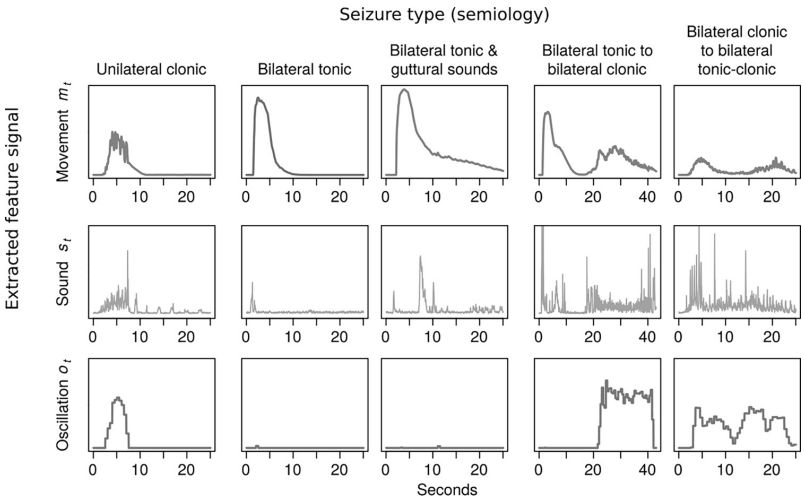

Fig. 5. Signal proles according to dierent seizure types. With the chosen biomakers, each seizure type has a unique and descriptive signal prole.

seizure. Tonic seizures consist of a sustained contraction of one or more muscle groups usually lasting >3 s and leading to "positioning" Noachtar and Peters (2009); Fisher et al. (2017). In our patient, focal tonic seizures manifested in a sudden movement simultaneously with an exhalation sound, which were recognizable both in the movement and sound analysis (Fig. 5) without any change in oscillatory mode. The model E_i (events containing both sudden movement and sound) was the best predictor of this seizure type. This model also detected some seizures which also contained clonic components, and those were considered true positives if they manifested a clear tonic phase. Positive predictive value for events produced by sound signal alone (E_s) was a mere 2.0 %, while the motion model (E_m) yielded a PPV of 3.9 %. The number of false positives detected by the sound feature alone was 1938, whereas the motion model gave 661 false positives. As our system combined the signals (E_i), the results greatly improved: by considering only the time periods where these events intersected, the PPV was boosted to 8.8 % and number of false positives decreased to 268. The sensitivity of this model remained rather high, only missing 3 seizures, for a value of 90 %. Such a model would be good as the basis of further models, or even useful as a clinical aid at only 1 false discovery per hour.

3.1.2. Seizures with a clonic component

The category of focal clonic seizures was the second most common, together with focal to bilateral tonic-clonic seizures. By definition, clonic seizures consist of more or less regular, repeated, short contractions of various muscle groups Noachtar and Peters (2009); Fisher et al. (2017). Seizures with one or more clonic phases were detected using the oscillation signal. Two seizures commenced with a very short tonic activity followed by clonic activity; these seizures were classified as tonic seizures because the tonic phase was considered as the earliest prominent motor feature according to ILAE instructions. In these two cases, sudden total movement was observed before propagation to changes in the oscillation, depicting the oscillation event model (E_o), sensitivity was perfect (100 %) with a reasonably high PPV (50 %) and low false discovery rate (0.038/hour, or about two per week).

The four secondarily generalized seizures – marked as focal-to-bilateral tonic clonic (FTBTC) according to the ILAE definition – were recognized with the motion model (E_m) detecting the sudden seizure onset, whereas the clonic phase was recognized with the oscillation event model (E_o). Using both the motion and oscillation events to detect tonic and clonic phases, both the sensitivity and PPV of FTBTC detection was also 100 % for this seizure type.

3.1.3. Other seizure components

Two complex motor seizures occurred with unspecific motor features, categorized as unclassified motor seizure according to the ILAE specification. These seizures, as well as myoclonic jerks, were not targeted with our system, and were not used in the selection process of the event parameters. However, a single myoclonic jerk was detected using the motion model: despite the small sample size, this anecdotal evidence indicates that such a model may serve as a myoclonic seizure detector as well.

3.2. Overall statistics

The resulting statistics are presented in Table 2 according to the previously established cut-off thresholds. Along with standard accuracy scores, a review time has been provided to give an estimate of amount of effort required to determine the salience of the detections. It is calculated as the total event time, with a minimum duration of 10 s per event (as required by the hit criteria), and a maximum of 20 s per event (suggesting that the reviewer should be able to determine salience within that period).

As expected from the threshold selection, all models gave at least 90 % sensitivity at the selected operating point. The oscillation model exhibited good PPV for clonic seizures, with well under 1 false discovery per night. The tonic model based on motion and sound intersections gave fewer than one false discovery per hour, a performance likely to be acceptable as a clinical aid for closer seizure tracking. While the basic motion and sound models do not perform with high PPV, they clearly demonstrate the filtering power of combining weak estimators to form a stronger one. Furthermore, they act as viable first-pass filters (returning less than 2% of the original recorded material) for later steps in an algorithmic pipeline. While sensitivity appears to be adequate, more can likely be done to find more indicative features of intensity within these biomarkers and to increase PPV.

4. Discussion

In this proof of concept study, we introduce a novel multimodal registration system, based on nocturnal long-term video and audio home monitoring. This system is able to detect nocturnal seizures with prominent motor features through integrating three distinct modes of analysis which are sound, oscillation, and sudden movement. This multimodal approach has potential to discriminate between seizures of tonic, clonic, and tonic-clonic semiologies as well as their evolution. In addition, a further distinction is possible by analyzing the more detailed semiological features and intra-event evolution of the seizures. Thus, it is possible for multimodal system to detect more subtle seizure types such as automatisms, although a naive implementation will likely cause an increase in false positives due to the lower intensity of such signals. However, further development and testing are needed for more reliable detection of subtle seizures and differentiation between seizure types.

According to the previous studies, the sensitivity varies depending on

Table 2
Resulting statistics and characteristics of the detected events E per model. Oscillation (E_o) and noticeable motion movement (E_m) events are derived from video signals, and the audible sound (E_s) events from audio signals. E_i represents the intersection of motion and sound events ($E_m \cap E_s$). Multiple hits to the same event are marked in parentheses.

	Clonic E_o	Tonic E_i	Tonic E_m	Tonic E_s
ILAE 2017 seizure types containing the targeted events	I.D.01 (5) I.C.05 (2) I.C.03 (3)	I.D.01 (5), I.C.05 (24)		
Targeted events	10	29		
Detections	20	294	688	1977
True positives	10	26	27	28 (+11)
False positives	10	268	661	1938
Sensitivity	100 %	90 %	93 %	97 %
PPV	50 %	8.8 %	3.9 %	2.0 %
F1 score	0.67	0.16	0.075	0.039
FDR (FP/hour)	0.038	1.0	2.5	7.4
Review time	7 min	98 min	229 min	659 min

the seizure type: 75 % for myoclonic seizures, 94–100 % for convulsive seizures and 100 % for hyperkinetic seizures Cuppens et al. (2012); Geertsema et al. (2018); van Westrhenen et al. (2020). According to another study, detection of hyperkinetic and tonic seizures is less accurate with a sensitivity of 57 % Geertsema et al. (2018). In this study, we were able to detect tonic seizures with a 8.8 % positive predictive value at 90 % sensitivity and seizures with clonic components with a PPV of 50 % and 100 % sensitivity. While by no means state-of-the-art, these are values are concordant with existing literature, while offering deeper insight into the seizure characteristics through intuitive biomarkers.

Analysis of epileptic seizure semiology relies on qualitative criteria which makes it prone to inter-observer discrepancy Bleasel et al. (1997). Also, capacity for a given detection system to differentiate between seizure types would be helpful but was not reported in previous studies. Our system is capable of measuring the seizure features quantitatively, which allows to detect changes in seizure severity or seizure propagation. Quantitative analysis of movements during video-recorded seizures have been applied to develop objective criteria for the analysis of seizure semiology Cunha et al. (2016), and this might be useful in the presurgical workup or therapy outcome assessment. Currently, devices which detect tonic-clonic seizures use some form of oscillation measurement as a biomarker. While highly specific, this method has the disadvantage that a seizure is first detected during the clonic phase; this higher latency makes the technique less useful as the basis for an alarm. If a multimodal model such as the one described here was to be implemented in an alarm system, the tonic biomarkers (sudden movement and sound) could potentially detect the seizure's onset earlier, as well as support a wider range of seizure types (e.g. seizures with tonic but no clonic activity). As for the detection system, accurate detection of prominent and subtle seizures is the main priority despite the higher number of false positives. In this study, the system was thus tuned to a sensitivity of 90 % or greater for seizures with a either a clonic or tonic component, with much better PPV when clonus was present. If this approach was developed into an alarm, optimizing the false detection rate would naturally be a more important target than achieving perfect sensitivity. Thus the proposed model could be further extrapolated to once provide a seizure classification system, simply by observing the correlation of multiple biomarker models, or by observing specific output ranges within a model. Perhaps most importantly, this model can prove useful as a clinical aid to finding subtle seizures from long recordings, as well as dramatically reducing the amount of material required for manual review in general.

Nevertheless, marker-free video-based methods have some limitations. The camera must be placed so that it observes the patient's body and limbs to detect movement. If patient has a seizure out of the area of interest, seizure recognition is completely based on the sound signal, which causes challenges for detection, and the number of false positives may increase if the parameters were adjusted. Small movements can be difficult to recognize using marker-free systems, especially if part of the patient's body is covered by a blanket. Seizure detection in a home setting usually has changing lighting conditions, and as most commonly available cameras adjust the frame rate based on the lighting, it requires reactions of the algorithm to changing video input. Current challenge for the video detection systems is the recognition of seizures with more subtle motor features, which benefits only part of the patient population Ahmedt-Aristizabal et al. (2018). Reliable detection of subtle seizures might be one of the next steps for development in order to serve a larger portion of epilepsy patients. Because the recordings in our study were mainly captured during sleep, our system extracted only normal motion in addition to movements related to a seizure during the night. Patients move more during daytime, or spend time lying on the bed instead of sleeping, which can cause a challenge for the system to detect daytime seizures with the same accuracy. However, daytime seizures are more easily detected by the parents or their caregivers and correspond to a lower SUDEP risk than nighttime seizures. In addition, the used dataset consists of only one patient and therefore, is individual. Datasets of multiple patients and more diverse seizures could help to better estimate the motor and audio signal PPV due to the inter-individual variability of ictal movements and sounds, which can vary from whispering to screaming and smacking to generalized convulsions. However, decreasing e.g. the audio signal threshold to detect subtle seizures can increase the number of false positives Arends et al. (2016). This reduces the statistic potential of our results and indicates the need for testing a larger patient groups and seizure datasets.

5. Conclusions

In conclusion, this proof-of-concept study introduces a methodological frame-work for deriving biomarkers from a simple video-based home registration system, while demonstrating the use of these biomarkers to model and automatically detect a spectrum of nocturnal epileptic seizures with motor components. Given the non-invasive and relatively low cost (in terms of labor, hardware, and computational power) of this technique, as well as its high sensitivity, it implies a both cost savings and improved quality of care for those suffering from nocturnal seizures. Through the provided automated analysis, the patient (as well as their physician and caregivers) could be kept informed of their seizure frequency and characteristics over the long term. Our intent is to further develop this system, with the goal of improving the models to increase positive predictive value as well as sensitivity to a wider range of seizure types and semiologies. Furthermore, serious investigation is warranted into the amount of individualization and calibration needed when applying this model to unseen data. We are already in the beginning stages of running this method on a larger cohort – 15–20 similarly-monitored patients – allowing us to conduct a phase 2 validation study Beniczky and Ryvlin (2018), in which the models are trained in a generalized manner with separate training and test sets. This will allow us to validate the efficacy (and perhaps the level of individualization needed) of this model over a more diverse population of epilepsy patients.

Declaration of Competing Interest

AK, AH, and JB are employees of Neuro Event Labs, the company that provided the equipment and technology used in the study. PO has provided medical consultation for Neuro Event Labs. JP is a shareholder of Neuro Event Labs. No other authors claim a conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106486.

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PUBLICATION II

Automatic classification of hyperkinetic, tonic, and tonic-clonic seizures using unsupervised clustering of video signals.

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Automatic classification of hyperkinetic, tonic, and tonic-clonic seizures using unsupervised clustering of video signals

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Introduction: This study evaluated the accuracy of motion signals extracted from video monitoring data to differentiate epileptic motor seizures in patients with drug-resistant epilepsy. 3D near-infrared video was recorded by the Nelli® seizure monitoring system (Tampere, Finland).

Methods: 10 patients with 130 seizures were included in the training dataset, and 17 different patients with 98 seizures formed the testing dataset. Only seizures with unequivocal hyperkinetic, tonic, and tonic-clonic semiology were included. Motion features from the catch22 feature collection extracted from video were explored to transform the patients' videos into numerical time series for clustering and visualization.

Results: Changes in feature generation provided incremental discrimination power to differentiate between hyperkinetic, tonic, and tonic-clonic seizures. Temporal motion features showed the best results in the unsupervised clustering analysis. Using these features, the system differentiated hyperkinetic, tonic and tonic-clonic seizures with 91, 88, and 45% accuracy after 100 cross-validation runs, respectively. F1-scores were 93, 90, and 37%, respectively. Overall accuracy and f1-score were 74%.

Conclusion: The selected features of motion distinguished semiological differences within epileptic seizure types, enabling seizure classification to distinct motor seizure types. Further studies are needed with a larger dataset and additional seizure types. These results indicate the potential of video-based hybrid seizure monitoring systems to facilitate seizure classification improving the algorithmic processing and thus streamlining the clinical workflow for human annotators in hybrid (algorithmic-human) seizure monitoring systems.

KEYWORDS

epilepsy, seizure classification, motor seizures, signal analysis, biomarkers

1. Introduction

Overall, 30% of patients diagnosed with epilepsy suffer from uncontrolled seizures despite the adequate use of anti-seizure medications (ASM) (1). Drug-resistant epilepsy (DRE) causes an increased risk of mortality and morbidity (2) and sudden unexplained death in epilepsy (SUDEP) (3). Accurate seizure documentation is essential to optimize the treatment of epilepsy. Previous research studies have demonstrated inaccuracies related to seizure diaries (4, 5), which has given an impetus for the development of various

seizure detection systems, aiming for more objective seizure documentation. Though seizure detection systems have improved seizure documentation, seizure classification based on videos or other data can still be challenging (6–8).

The International League Against Epilepsy (ILAE) has recently published new guidelines for the classification of epileptic seizures (9). ILAE seizure classification categorizes seizures based on their focal or generalized onset, level of awareness, and non-motor and motor manifestations. Seizures can also be classified based on semiology, only highlighting the relevance of the observable ictal motor and other manifestations without electrophysiological information from EEG. In semiological classification, motor manifestations are depicted as simple or complex based on the complexity of the movement (10–12). Laterality (left, right, or bilateral) and chronological order of the symptoms are additional classification features (10, 13).

Video-based methods in the detection of epileptic seizures have been widely studied with high sensitivity and specificity for detection performance (14). Studies have shown promising results in the analysis of semiological features by utilizing convolutional neural networks (CNN) and long short-term memory (LSTM) in facial and body movement analysis (15), deep learning methods (16), and movement trajectories (17) in body movement analysis and ictal sound recordings in seizure semiology analysis (18). However, automatic seizure classification is a less explored topic. Temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) have been differentiated by utilizing movement trajectories (19) or quantitative movement analysis (20). Infrared and depth sensors were used in 3D video data to differentiate between seizures in FLE, TLE, and non-epileptic events reaching a cross-subject f1-score (a metric to assess machine-learning predictive skill) of 0.833 when differentiating between FLE and TLE seizures and of 0.763 when differentiating between FLE, TLE, and non-epileptic events from each other (21). However, only a few studies have evaluated the performance of deep learning in the analysis of multiple distinct motor seizure types.

The Nelli seizure monitoring system is an audio/video-based semi-automated (hybrid) seizure monitoring platform that uses computer vision and machine learning to identify kinematic data (motion, oscillation, and audio) commonly associated with seizures with a positive motor component and human experts to visually assess these epochs (22). Moreover, the utility of the hybrid (algorithm-human) system for reviewing nocturnal video recordings to significantly decrease the workload and to provide accurate classification of major motor seizures (tonic-clonic, clonic, and focal motor seizures) has been demonstrated (23). The potential to differentiate seizure types by utilizing algorithmic signal profiles was first explored in a previous case study (24). Even though Nelli®'s algorithmic performance in seizure detection has been demonstrated in previous validation studies (25), the potential of the algorithmic part of the system to classify seizure types has not been previously explored.

Given the potential of deep-learning methods to differentiate seizure types and the need for a tool to assist in seizure classification, novel methods to classify specific seizure types using video monitoring and deep learning are needed. One recent development on this frontier has been the catch22 feature collection (26). The catch22 project has implemented over 7,700 time-series features from multiple science fields to find the best-performing statistics for time-series classification, finally selecting the top 22 features for their software library to perform feature extraction or dimension reduction for time-series analysis. These features have been applied successfully in a wide range of scientific problems: e.g., tree deformation detection in winds (27), hydroclimatic data processing (28), human breast cancer cell detection (29), commercial sales prediction (30), or cardiometabolic risk detection (31). They have not been previously applied for video-based seizure classification.

The aim of this study was to evaluate the performance of a novel signal algorithm model in classifying tonic, tonic-clonic, and hyperkinetic seizures by utilizing motion and oscillation signal profiles. This study further examines the previously recognized potential of the Nelli system to automatically classify aforementioned seizure types by utilizing signal profiles and deep learning to take a step toward automatic seizure classification.

2. Methods

2.1. Patient population

A total of 27 patients with focal DRE were enrolled in the study. The study protocol and informed consent forms were reviewed and approved by the ethics committee of Tampere University Hospital. Signed informed consent was obtained from each participant. All patients were on two or more ASMs, and some of them were also treated with vagal nerve stimulation (VNS) therapy. Each patient was monitored from 4 to 8 weeks in a home setting for 7–11.5 h per night (average 9.19 h, median 9.25 h). Unequivocal seizures from previous recording sessions of enrolled patients were utilized only if they lacked unequivocal seizures in the latest monitoring period. Training patients were selected partly from a recent interventional study (22) and partly from Nelli® post-market surveillance (PMS) recordings, and testing patients were selected from Nelli® PMS recordings with the requirement that, for each subject, at least three unequivocal seizures of these three seizure types of interest were recorded during Nelli® registration and they had been described in detail in previous video-EEG reports. Due to the exclusion criteria listed above, 130 seizures from 10 patients formed a cohort for the model training, including four patients from the previous study (22). The testing patient cohort consisted of 98 seizures from 17 patients, who were not included in the training phase, to evaluate the performance of the model. Patient demographics and seizure counts are presented in Table 1.

2.2. Video monitoring

Video monitoring was performed by NEL (Neuro Event Labs, Tampere, Finland) using the Nelli® seizure monitoring system consisting of a camera and a microphone installed at the patient's bedside in their home so that the patient stays in sight of the camera during periods of rest. Video data from all patients were manually annotated. The epochs of suspected seizure events were reviewed by expert epilepsy annotators. Previous VEM (video-EEG monitoring) reports obtained before the start of the study

TABLE 1 Patient demographics and clinical characteristics.

Characteristics	Training phase ($n = 10$)		Testing phase ($n = 17$)	
Age range (years)	18–46		18–58	
Mean age (years)	34.5		33.8	
Gender				
Male	5 (50%)		10 (58.8%)	
Female	5 (50%)		7 (41.2%)	
Seizure type	Training phase		Testing phase	
	Patients	Seizures	Patients	Seizures
Tonic-clonic	4	12	3	6
Hyperkinetic	5	73	7	41
Tonic	3	44	7	51
Total	**10***	**129**	**17**	**98**

*Two patients contributed more than one seizure types.

were used for the assessment of behavioral features of seizures that occurred during Nelli monitoring. Seizures were classified by professionals according to the ILAE 2017 classification (9). Suspected seizure events were excluded from further analysis if they were not unequivocally identified as seizures by comparing them to previous VEM reports which were considered a feasible reference standard for the phase two study as previously suggested (32). Seizures were considered unequivocal to a seizure type if they were identified based on VEM reports and they shared similar manifestations as described in classification guidelines. All seizures belonging to the hyperkinetic, tonic, or tonic-clonic seizure type categories were included. These three seizure types were the most common in available recordings, providing a sufficient number of seizures for further analysis. Seizure semiology was defined according to semiological classification guidelines (10, 12) for each seizure type, using additional descriptors for the observable movements during a seizure. Seizure semiologies for each patient have been presented in Supplementary material 1.

To optimize the seizure signal analysis and minimize the effect of the background noise of the video event, seizure video clips were cropped from the raw data by a professional epileptologist. Videos were cropped so that they included the seizure onset and the assumed ending of the seizure activity by comparing the seizure manifestations in recorded video events and VEM reports. The postictal phase was left out of the analysis. For each seizure type and patient, the medians of motion, audio and oscillation signal were calculated using the method described in Section 2.3.

2.3. Signal generation from video data

The model of the system has been described in the previous proof-of-concept study (24) in detail. Similarly, the system relies on motion and oscillation biomarkers.

To create a motion signal, a background subtraction method by Zivkovic and Van Der Hejden (33) was combined with a stereo correspondence filter (34) based on semi-global matching (implemented in OpenCV). The background subtraction model created a binary mask of the moving parts of the image, and the proportion of the moving pixels in an image defined a one-dimensional motion signal for a video.

For movements with an oscillatory component (as present in tonic-clonic seizures), an optical flow-based method was utilized. By using this method, a time-series motion vector field was created. This vector field was utilized to construct a path history, where only the unbroken paths during a period of 1 s were analyzed for direction reversal (a reversal is each change in direction over 90°). An oscillation frequency of 2.5 Hz was previously found to be a good filter for separating ictal oscillation from paroxysmal events (24).

2.4. Clustering analysis

To separate hyperkinetic, tonic, and tonic-clonic seizures, unsupervised data representations were explored. A common technique for data visualization and exploration was used; a cluster diagram where a data sample is represented by a point on a 2D chart that is inspected by a human or a clustering algorithm to find meaningful structures (clusters) to solve a problem. Since the samples are usually multidimensional, they must be transformed by dimensional reduction algorithms into 2D space before drawing the diagram. After the original data are projected into lower dimensions, the diagram axes do not have any particular unit or meaning.

After the complete feature extraction from the patient videos, the time series of motion and oscillation signals were reduced in two dimensions. Each time series was transformed to lower data space by extracting time-series statistical features in order to have low and fixed data dimensions. The seizures had varying duration and variable length time series, but a fixed data dimension for conducting a principal component analysis (PCA) for the data reduction into 2D was used. To analyze ictal motion characteristics in the video data, motion features from the catch22 feature collections were utilized in this study. During

the initial experimentation, 22 statistics were calculated by the catch22 library (26) from the training set and fed into PCA. With the final 2D data, cluster plots were created representing the seizures in different colors to visualize their distribution. The discrimination power of 22 statistics was further analyzed on the training set, and the original catch22 feature set was then reduced to five features before the PCA step by visually observing the relatively unchanging cluster diagram after incrementally removing redundant features.

Data clustering can be especially applied for data visualization, but separate training and testing steps were implemented in this experimentation. The dimension reduction methods were first used for the training patient group to develop an initial visualization and to find the most optimal parameters for seizure differentiation. After the training phase, the computed PCA coefficients were applied to the testing patient data for projecting the testing data points by the same dimension reduction transformations into the 2D data space and assessing the performance of the model by visual evaluation of data points and then by classification analysis discussed below. In the final step, agglomerative clustering was used to discover clusters on the image and observe how the unsupervised cluster represents the different seizure types.

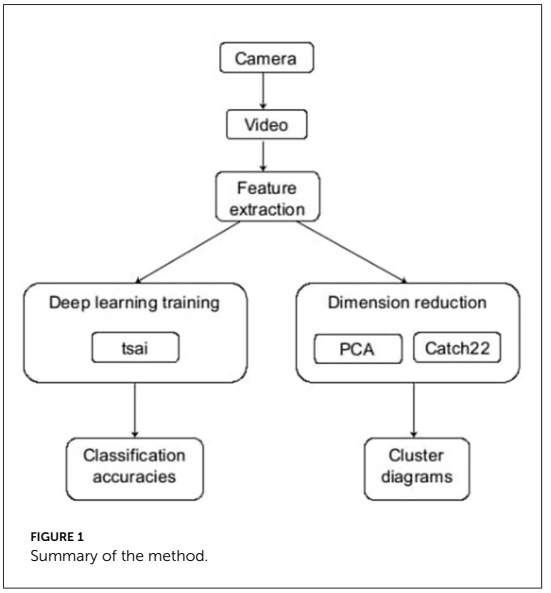

FIGURE 1
Summary of the method.

2.5. Classification analysis

Unlike the unsupervised clustering analysis that is based on dimension reduction and cluster identification on 2D plots, a classification method was also employed in this study to assess the performance of a supervised learning approach. A better insight can be given to the discriminative power of the extracted features by analyzing the same data using these different techniques because the first method reduces the data dimension drastically while the second method works on the time-series directly. Note that the time-series of the pixel statistics are already a heavily reduced data dimension compared to the original video frames. A deep-learning network (multivariate long short-term memory with fully connected layers—MLSTM-FCM) specialized for time-series classification (35) was built on the training set to classify the data points of hyperkinetic, tonic, and tonic-clonic seizures and make predictions for unseen data points of the testing set. The implementation was based on the tsai library (36). The hyperparameters were an RNN layer count of 2, a hidden neuron count of 200, and RNN and FCN dropouts of 0.05. The previous clustering method transformed the time series into 2D data with dimensional reduction techniques (catch22, PCA), and the MLSTM-FCN model worked on the time series directly, processing and classifying a time series into a single seizure category.

After the automatic analysis of the data points of the testing set, we evaluated the performance of the deep-learning network by calculating the accuracy of the classification of hyperkinetic, tonic, and tonic-clonic seizures. Based on the classification, the overall accuracy of the model was determined. The description of the method used in this study is presented in Figure 1.

3. Results

3.1. Unsupervised clustering analysis

Adjunctive changes in the feature generation enabled improved discrimination power to differentiate between tonic-clonic, hyperkinetic, and tonic seizures. Two different motion feature setups, static motion features (Figure 2) and temporal motion features (Figure 3), were used to compare the feasibility of the features. Oscillation tracking was not included in these figures, as it did not improve the seizure cluster formation in clustering analysis (see Supplementary material 2). Although the data points are grouped in different shapes in this case compared to Figure 3, the general considerations do not change, and many tonic-clonic points and a considerable fraction of the clonic points appear in the hyperkinetic cluster.

The static motion features are the original time series extracted from the videos while the temporal features are a delta derivative time series calculated by a lag (a fixed duration, e.g. 1 s), often referred to as time-series lag difference or delta function measuring the change over time. Delta values were calculated with a difference between the current value and a past value (e.g., 1 s before). In all figures, tonic-clonic, hyperkinetic, and tonic seizures were marked as green, blue, and orange, respectively, indicating training phase results, and light green, light blue, and light orange, respectively, indicating testing phase results.

In Figure 2A, a cluster of tonic-clonic and tonic seizures appeared on the left side and hyperkinetic seizure clusters appeared on the right side of the figure. This cluster is visually noticeable in the training phase, while the hyperkinetic cluster spreads to both sides of the figure in the testing phase. Different types of seizures were interspersed in the center of the figure, and hyperkinetic seizures were infused in the left cluster among the tonic-clonic

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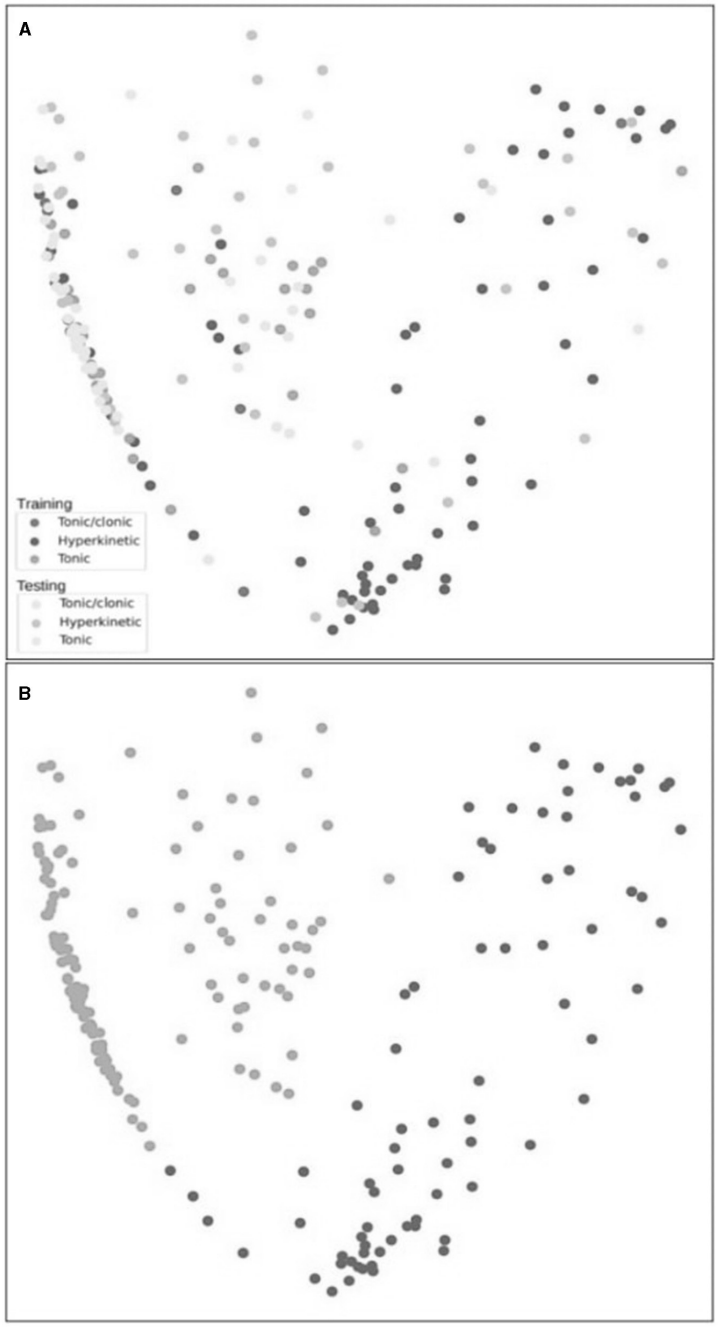

FIGURE 2
Clustering analysis of tonic-clonic, hyperkinetic, and tonic seizures using static motion features in the training and testing phase **(A)**. The second figure shows the agglomerative clustering results **(B)**.

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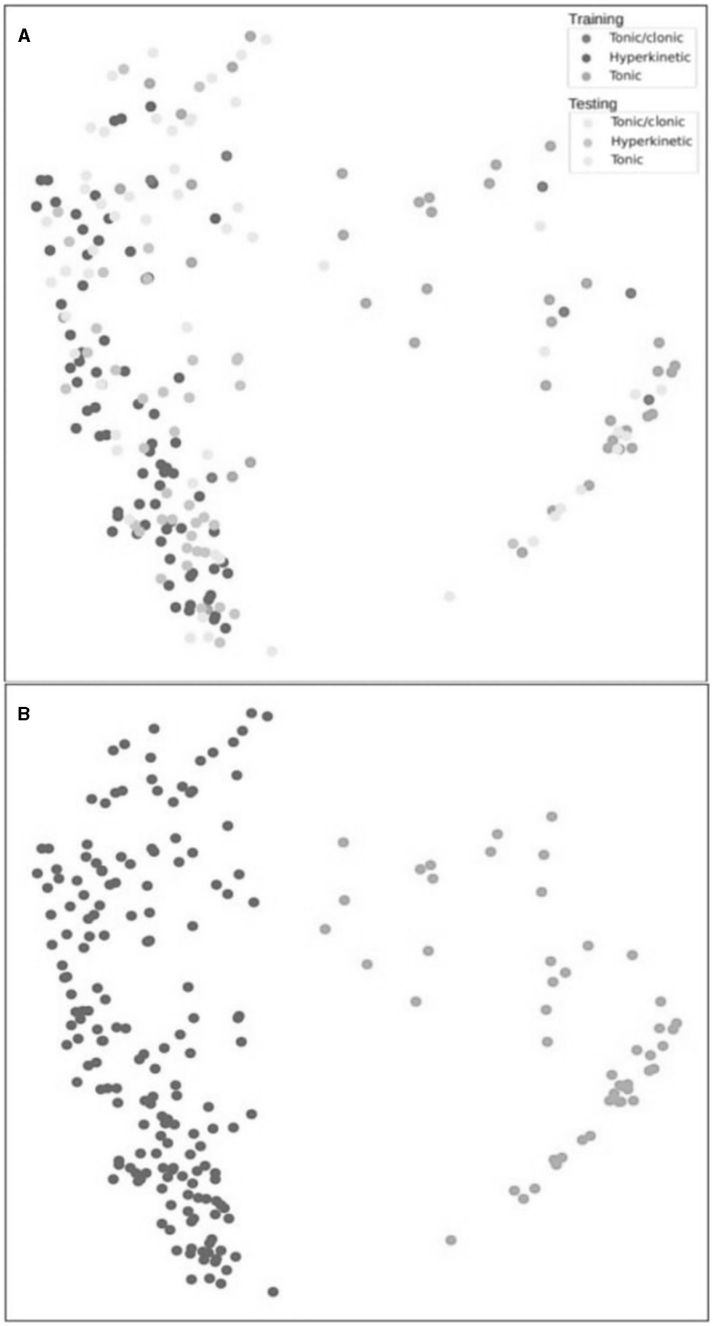

FIGURE 3
Clustering analysis of tonic-clonic, hyperkinetic, and tonic seizures using temporal motion difference features in the training and testing phase **(A)**. The second figure shows the agglomerative clustering results **(B)**.

and tonic seizures. The tonic-clonic seizure does not represent a coherent, separate structure among the data points. Figure 2B shows unsupervised clustering results and the agglomerative clustering isolated the tonic and hyperkinetic clusters successfully on the left and right sides.

In Figure 3A, the clusters switched sides: hyperkinetic and tonic clusters were clearly separate, but the majority of tonic-clonic seizures were part of the hyperkinetic seizure cluster region. The hyperkinetic seizure cluster was plotted clearly on the left side of the figure in both the training and testing phases. The tonic seizure cluster was more dispersed in the testing phase than in the training phase. Tonic-clonic seizures did not separate from hyperkinetic seizures in either of the phases when this motion feature was used. In Figure 3B, the agglomerative clustering discovered two clusters, one for hyperkinetic and one for tonic seizures. The tonic seizures are spread above the hyperkinetic seizures on the left side and the clustering was not able to include this upper part in the tonic cluster.

3.2. Performance analysis

To analyze the performance of the method, incremental analysis was done in addition to unsupervised clustering analysis. By training a deep-learning network based on the background subtraction signal and comparing the results with original annotations, we calculated the accuracy of the seizure classification method. We ran a leave-one-out cross-validation of the deep-learning method. The cross-validation was then repeated 100 times to calculate an estimation of the unbiased accuracy and its confidence interval since the model performance has some variability between each training run because the deep-learning training is not deterministic with the random weight initialization. Our method achieved an overall mean accuracy of 74.68% and an f1-score of 74.26%. The hyperkinetic, tonic, and tonic-clonic seizures had mean accuracies of 91.03, 87.90, and 45.12%, respectively. The mean f1-scores were 92.83, 89.79, and 37.18%, respectively. The hyperkinetic and the tonic seizures had very similar accuracy and f1-score values, while the f1-score of the tonic-clonic seizure was lower by 8%, compared to the accuracy value. The accuracy and f1-scores of hyperkinetic and tonic seizures were high by approximately 90% while the tonic-clonic seizure had only 45.12 and 37.18%, respectively. Regarding the confidence intervals ($p = 0.05$), the hyperkinetic, tonic, and tonic-clonic seizures had 1.1, 1.5, and 4.2% for accuracy and 1, 1.5, and 4.1% for f1-scores, respectively. The confidence intervals were similar for hyperkinetic and tonic seizures, but more than double for tonic-clonic seizures. As the low accuracy and its high confidence interval of tonic-clonic seizures suggest, this seizure type was not recognized on a satisfactory level because of the lack of enough patient data to distinguish this seizure type from the other two types. This result is on pair with our unsupervised clustering results where the hyperkinetic and tonic seizures can be separated quite well, but the tonic-clonic data points are spread around. The accuracy and confidence interval of each seizure type are presented in Table 2.

TABLE 2 The unbiased accuracy, f1-scores, and confidence intervals after 100 cross-validation runs.

Unbiased accuracy, f1-scores, and confidence intervals after 100 cross-validation runs			
	Hyperkinetic seizures	Tonic seizures	Tonic-clonic seizures
Mean accuracy	91.03%	87.90%	45.12%
Confidence intervals for accuracy	±1.1%	±1.5%	±4.2%
F1-score	92.83%	89.79%	37.18%
Confidence intervals for f1-score	±1%	±1.5%	±4.1%

4. Discussion

In this study, we present a novel method for differentiating between tonic-clonic, tonic, and hyperkinetic motor seizures based on the automatic analysis of motion and oscillation signals from previously annotated video data. This algorithmic component of Nelli® hybrid (algorithmic-human) seizure monitoring system has been previously studied for automated seizure detection, but in the present study, it was tested as an automated seizure classification tool by applying adjunctive video and unsupervised clustering analysis for the first time. We intended to develop the differentiation algorithmic ability that would aid clinicians in classifying seizures for Nelli® hybrid seizure monitoring, which is currently used in clinical practice (37). In the present study, our model differentiated and classified hyperkinetic and tonic seizures with a promising accuracy of 91 and 88%, respectively. However, tonic-clonic seizures were classified with only 45% accuracy. The f1-scores for hyperkinetic, tonic, and tonic-clonic seizures were 93, 90, and 37%, respectively.

Screening and differential diagnosis between different seizure types are essential components in the detection of seizures and the correct implementation of treatment (4). Seizure classification relies on objective criteria of ictal observations of caregivers or clinicians. Most motor seizures have distinguishable motor manifestations that indicate a specific seizure type; however, oftentimes, there are no eyewitnesses, especially, for nocturnal seizures (4). However, depending on the motor manifestations of seizures, seizure type classification can be difficult, even with the help of seizures recorded on videos because seizure semiology is often prone to inter-observer discrepancy due to qualitative criteria reliance (observer bias) (38). Moreover, it is very time- and resource-consuming to manually annotate and classify seizures of each patient (39, 40). A system capable of measuring seizure features qualitatively as well as quantitatively would allow the detection of changes in seizure severity or seizure propagation. Also, in case of multiple seizure types and high seizure frequency during the monitoring period, automatic tools could be useful to save time and resources in video annotation during seizure monitoring. Automatic classification could also improve seizure alarm systems by enabling alarms for different seizure

types, which might be useful, especially in epilepsy monitoring units or institutional settings. Furthermore, EEG-based automatic seizure classification methods have already been examined with promising results as a clinical application of the automatic seizure classification tool (41).

In previous studies, automatic classification of epileptic seizures from psychogenic non-epileptic events was conducted by a multi-stream approach, reaching f1-scores and accuracy of 0.89 and 0.87, respectively, in seizure-wise cross-validation and 0.75 and 0.72, respectively, in leave-one-subject-out analysis (42). Hyperkinetic seizures have been automatically differentiated from non-hyperkinetic seizures and sleep-related paroxysmal events with 80% probability (43) and 80% accuracy (44). In another study, CNNs and recurrent neural networks (RNNs) were combined to automatically classify seizure videos into focal onset seizures and focal to bilateral tonic-clonic seizures achieving 98.9% accuracy (45). However, an automatic system that differentiates motor seizures into three types has not been previously reported in the literature. Our study reached a relatively good accuracy in hyperkinetic and tonic seizure classification, and the results from hyperkinetic seizure classification aligned with the previous research study (43). However, tonic-clonic seizures were not differentiated as accurately as the other two seizure types, which weakens the performance, especially when considering the clinical relevance of tonic-clonic seizure documentation in decreasing the risk of SUDEP (46). However, in previous validation studies of the Nelli® seizure monitoring hybrid (algorithmic-human annotation) system, all tonic-clonic seizures were correctly categorized (23) due to stereotypic and easily recognizable motor manifestations. Since the tonic-clonic seizures cannot be separated in both the clustering and the classification methods in this study, it suggests that this limitation is not caused by the applied methods, but the extracted time-series descriptor does not have discriminative power for this task.

Catch22 was utilized to extract statistical descriptors to reduce the data dimensionality of the training and testing sets drastically. This library turned out to be suitable for this task as a collection of the best statistics for time-series analysis across various science fields. To select the statistical features with real discriminative power for the current study, the redundant steps were removed from the initial set one by one after inspecting the unaffected cluster diagrams. The deep-learning experiment after the cluster analysis confirmed the good overall discriminative power. Since there were few tonic-clonic seizures compared to hyperkinetic and tonic seizures, they were not distinguished as well as the other seizures. This is not a by-product of catch22 or deep learning, but a common phenomenon in machine learning when a class is underrepresented in the learning task.

This study has several limitations. Our patient population was quite small, and especially the number of tonic-clonic seizures included in the study was low. The majority (>90%) of seizures included in the study consisted of hyperkinetic and tonic seizures, which may have affected the performance of our model, and a dataset with more evenly represented seizure types might improve the model development in future research. Also, due to availability, we only included tonic, tonic-clonic, and hyperkinetic seizures, which usually have recognizable motor manifestations and are reliably classified by human annotators. Seizures included in this study represented varying semiologies even within a seizure type, as shown in Supplementary material 1, which may have caused challenges in classification. A larger patient group would enable further training of the model and improve the statistical reliability of the results. However, running cross-validation 100 times as done in our study was found as one solution to this issue. The patient dataset consisted of adult patients, which limits the generalizability of the results to pediatric patients. Furthermore, we only tested seizures that were confirmed to be seizures, and we did not have a category for non-epileptic events involved, which may cause an overestimation of the performance. However, previous studies that utilized our system have shown the accuracy of automatic seizure detection in various seizure types (43). The exclusion of non-epileptic events from hyperkinetic seizures has been also reported with relatively high accuracy (42). In addition, seizures with more subtle motor manifestations can be challenging to detect automatically, as previously reported (23), even though studies have shown accurate detection for those seizures (16). However, seizures with minor motor manifestations may be difficult to detect, even for human annotators, which provides a topic for future development. Furthermore, simultaneous analysis of more seizure types might be challenging due to the similar motion and oscillation signal profile such as myoclonic and tonic seizures, as well as tonic-clonic and clonic seizures. There are other general limitations related to video monitoring: a patient should stay in sight of the camera, a caregiver should avoid being in the frame of the camera to not affect the motion signal, and a blanket can impede the movement of the patient. It is important to maintain the same monitoring settings throughout the monitoring period to avoid the effect of patient and environment-related factors on movement detection (47).

5. Conclusion

The quantitative analysis with selected motion features distinguished semiological differences between epileptic motor seizures and enabled differentiation of hyperkinetic and tonic seizure types from video data in patients with DRE. Our results suggest that the motion signal profiles seem to allow motor seizure differentiation and classification. The system achieved a promising accuracy and f1-score of 74% in the testing phase. Tonic and hyperkinetic seizures were classified with 91 and 88% accuracy, respectively, but accuracy for tonic-clonic seizures was only 45%. The f1-scores of hyperkinetic, tonic, and tonic-clonic were 93, 90, and 37%, respectively. Future studies are needed with a larger and more robust dataset, including additional motor seizure types and false positive events. These developments hold the potential to streamline the clinical workflow of video-based seizure monitoring systems by providing a supporting tool for seizure classification. In summary, despite the lack of accuracy in the classification of tonic-clonic seizures, the results from the present study can be considered a step forward toward an automatic seizure classification tool for clinicians.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Tampere University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

PO: Writing—original draft, Writing—review & editing. CK: Writing—original draft, Writing—review & editing, Formal analysis, Software. EM: Formal analysis, Software, Writing—review & editing. PR: Formal analysis, Writing—review & editing. KA: Project administration, Writing—review & editing. AK: Data curation, Formal analysis, Investigation, Methodology, Writing—review & editing. JP: Data curation, Investigation, Supervision, Writing—original draft, Writing—review & editing.

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Conflict of interest

CK, EM, PR, AK, and KA are employees of Neuro Event Labs, the company that provided the equipment and technology used in the study. PO has provided medical consultation for Neuro Event Labs. JP and KA are shareholders of Neuro Event Labs. JP has participated in clinical trials for Eisai, UCB, and Bial; received grants from Eisai, Medtronic, UCB, and Liva-Nova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for Arvelle, Novartis, LivaNova, Eisai, Medtronic, UCB, and Pfizer.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1270482/full#supplementary-material

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PUBLICATION III

Feasibility of video/audio monitoring in the analysis of motion and treatment effects on night-time seizures - Interventional study

Ojanen P, Zabihi M, Knight A, Roivainen R, Lamusuo S, Peltola J

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Feasibility of video/audio monitoring in the analysis of motion and treatment effects on night-time seizures – Interventional study

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ABSTRACT

The aim of the study: This pilot study assessed the ability of a video/audio-based seizure monitoring system to evaluate (I) baseline frequency and severity of nocturnal seizures with motor features in patients with drug-resistant epilepsy (DRE) and (II) the individual effect of brivaracetam (BRV) treatment on number, duration and movement intensity of these seizure types. Algorithmic feature analysis was developed for assessment of qualitative changes in movement intensity measurements within seizure types before and after BRV intervention.
Materials and methods: Night-time motor seizures of recruited patients were recorded in two separate four-week monitoring periods. The first period defined a prescreening phase (n = 13 patients) to establish a baseline, and the second period defined the intervention phase (n = 9 patients), with BRV initiated during the second week of the second monitoring period. All recorded nights were analyzed by an expert video reviewer, and all unequivocal seizures were classified by an epileptologist.
Seizure frequencies using both seizure diaries and video monitoring were compared.
The effect of BRV on both seizure duration and movement intensity was assessed by numerical comparison of visual features calculated from motion characteristics of the video, as well as spectral features from the recorded audio. The statistical significance of changes in seizure duration and intensity before and after the intervention were investigated by Wilcoxon rank-sum test and visual inspection of Kernel density estimation.
Results: 8 patients marked seizures in their seizure diaries during the prescreening phase. During the three-week follow-up, three patients achieved > 50% seizure decrease, four patients did not respond to treatment, and two patients experienced worsening of seizures. Five patients were able to document 40–70% of their seizures compared to the video/audio monitoring system. According to the signal feature analysis the intervention decreased movement intensity with clear clinical significance in three patients, whereas statistically significant differences in features appeared in 8 out of 9 patients.
Conclusions: The novel video/audio monitoring system improved the evaluation of treatment effect compared to the seizure diaries and succeeded in providing a comparative intra-patient assessment of the movement intensity and duration of the recorded seizures.

1. Introduction

A single seizure may occur in 8–10% of the population during a person's lifetime, with 2–3% of individuals developing epilepsy (Gavvala and Schuele, 2016). Approximately one-third of patients have drug resistant epilepsy (DRE) defined as continuation of seizures despite using two or more anti-seizure medications (ASMs) with adequate doses either sequentially or in combination (Kwan et al., 2010). Treatment-resistant epilepsy causes significant mortality and morbidity (Laxer et al., 2014), and the risk of premature death due to epilepsy is 11-fold in comparison to the age-matched general population or siblings unaffected by epilepsy (Fazel et al., 2013). Annually, sudden

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unexplained death in epilepsy (SUDEP) occurs in 1 of 1000 epilepsy patients and in 6 out of 1000 in drug resistant epilepsy patients (Massey et al., 2014).

Outpatient assessment of the type and frequency of seizures is generally based on patient and caregiver reports (seizure diaries) which are used to improve recall of seizure occurrence. However, systematic diary follow-up requires prioritization and a demanding orderly approach, making them prone to inaccuracies. Seizures occurring during sleep or with impaired awareness may go unnoticed, especially in people living alone (Blachut et al., 2017; Geertsema et al., 2018). It is estimated that about half of seizures during wakefulness and up to 90% of nocturnal seizures go unnoticed (Elger and Hoppe, 2018; Hoppe et al., 2007). Complicated or prolonged seizures, or even SUDEP, may occur unexpectedly in situations where a good treatment response has already been assumed (Walczak et al., 2001). Inaccurate documentation of seizure type and frequency makes it challenging to monitor therapeutic outcomes of ASM therapy -both in clinical practice and within drug trials (Elger and Hoppe, 2018; Dalrymple and Appleby, 2000). Improved documentation of seizures could help clinicians to choose the most appropriate treatment based on seizure type and provide more accurate treatment effect data for drug trials.

Several different devices have been developed to detect movement during seizures and these can often be connected to alarm systems (Poppel et al., 2013). Video-based automated analysis of seizure-specific movements can be also used for follow-up of changes in night-time seizure frequency (Geertsema et al., 2018). However, detection of automated computer-assisted methods has been mostly limited to convulsive seizures in previously used devices (Beniczky and Jeppesen, 2019).

The Nelli® seizure monitoring system is an audio/video-based semi-automatic (hybrid) seizure monitoring platform that uses computer vision and machine learning to identify kinematic data (motion, oscillation, and audio) commonly associated with seizures with a positive motor component and human experts to visually assess these epochs (Peciola et al., 2018; Ojanen et al., 2021). In a recent validation study, the Nelli® hybrid system was used in a blinded setting without any prior information on the patients or their seizure types against video-EEG monitoring at a well-established epilepsy center identifying all tonic-clonic and clonic seizures and 82% of focal motor seizures. However, there was low accuracy in identifying seizure types with more discrete or subtle motor phenomena (Peltola et al., 2022). Nelli® has been recommended for clinical use in Finland by a government-appointed committee (the National Coordinating Group for Drug-resistant Epilepsy).

Brivaracetam (BRV) is a selective, high-affinity vesicle protein 2a ligand, which received FDA approval for use as monotherapy and adjunctive therapy for patients with focal epilepsy in 2016. In a phase 3 study, adjunctive BRV (100 and 200 mg/day) significantly reduced frequency of focal seizures compared with a placebo (Klein et al., 2015). BRV is commonly used in Finland as an add-on ASM in patients with DRE.

The aim of the present pilot study was to assess ability of data captured by the video monitoring system to establish (I) the baseline frequency of nocturnal seizures and the sensitivity of seizure diaries during the prescreening phase in patients with DRE scheduled for change of seizure therapy, and (II) the individual effect of ASM BRV treatment on seizure duration and movement intensity. Seizure counts based on subject registrations were compared with conventional seizure diaries in order to evaluate the inaccuracies associated with seizure diaries in the assessment of treatment effect in drug intervention. Additionally algorithmic feature analysis was developed for assessment of qualitative changes in intensity measurements within seizure types before and after BRV intervention. The present study provides proof-of-concept of how computer-assisted video/audio-based detection may aid in documenting individual responses to treatment interventions in patients with DRE.

2. Materials and methods

2.1. Study design

This was an open-label comparison of a computer-vision-assisted seizure monitoring tool and the clinical standard (patient seizure diaries) to observe changes in seizure burden during the initiation of a brivaracetam (BRV). The study consisted of 2 phases. In phase 1 (the prescreening phase), patients underwent a 4-week home monitoring simultaneously as they documented all night-time seizures in their seizure diaries while remaining on stable ASM. No change in medication was done during this phase. Phase 2 (the intervention phase) comprised a 1-week baseline period and a 3-week observational period that began once BRV was administered. Both monitoring tools were used throughout the study. Seizure frequency and semiology captured with each method were compared following each phase.

The study protocol and informed consent forms were reviewed and approved by the Ethics Committee of Tampere University Hospital. Signed informed consent was obtained from each participant. The classification of seizure and epilepsy type and prior knowledge on individual seizure characteristics was available prior to study entry was from VEM recordings obtained as part of routine care.

2.2. Patient population

Thirteen patients with focal DRE were enrolled in the study and participated through phase 1 (Table 1). Two patients did not proceed to the second phase due to infrequent seizure events or unobservable motor components; an additional two patients chose not to initiate BRV treatment. Thus, nine subjects completed both phases of the study.

Seizure types were classified by an expert epileptologist according to ILAE 2017 classification (Fisher et al., 2017) along with the ILAE codes (Beniczky et al., 2017) in parentheses. Semiology was defined according to semiological classification by (Lüders et al., 1998) for each seizure type using additional descriptors for the observable types of movements manifesting during a seizure. All patients were treated with two or more ASMs, and some of the patients (3, 5, 7, and 8) were concomitantly treated with vagal nerve stimulation (VNS) therapy. Patients' clinical information, including age, sex, age at diagnosis, seizure types, seizure semiology, and ASM(s), are presented in Table 1.

2.3. Video monitoring

Video monitoring was conducted by NEL (Neuro Event Labs, Tampere, Finland) using its Nelli video monitoring product. The system includes a camera and microphone, to be installed at the bedside so that the patient is in sight of camera throughout the night. Nelli records epochs of potential seizure activity which is subsequently reviewed by epilepsy technicians and supporting physicians to develop an interactive summary. Information about seizure semiology from VEM reports obtained before the study initiation were used for evaluation of behavioral features of seizures. Behavioral events that were not unequivocally identified as seizures were excluded from assessment. It is important to note that, according to the epilepsy research community, seizures with unequivocal semiology are sufficient to act as a reference standard in this type of phase 2 study and thus video-EEG is not needed as a reference standard (Beniczky and Ryvlin, 2018).

2.4. Accuracy of seizure diaries

In phase 1, we compared each patient's seizure count and seizure diary entries during the 4-week monitoring period. We defined the daily average of seizures, diary entries, sensitivity, and positive predictive value of seizure diaries.

In phase 2, we calculated the percentage change of diary entries between the baseline and the third follow-up week for each patient. By

Table 1
Subject Demographics.

ID	Age	Age when diagnosed	Seizure type (ILAE 2017)	Seizure semiology	ASM (daily dose mg)
1	40	1	**FHS (I.C.08)**	Eyes open – Heavy breathing –Hyperkinetic BL	Valproate (300), Lamotrigine (300 mg), Levetiracetam (3000)[a], Eslicarbazepine (1200), Clonazepam (2)
2	61	56	**FMS (I.C.02)**	Myoclonic R	Zonisamide (200), Lamotrigine (200) VNS
3	17	3	FIAMS (I.B.01)	Change in breathing – Motor BL	Oxcarbazepine (1500), Clobazam (20), Zonisamide (200), VNS
			FBTCS (I.D.01)	Motor BL- Vocalization – Convulsive movement – Heavy breathing	
4	20	4	FIAMS (I.B.01)	Eyes open – Motor BL	Lamotrigine (500), Clobazam (30), Perampanel (4)
			FTS (I.C.05)	Eyes open – Oral automatisms - Tonic BL	
5	46	2	**FHS (I.C.08)**	Eyes open – Hyperkinetic BL – Heavy breathing	Valproate (1000), Lamotrigine (200). VNS
6	36	Childhood	FIAMS (I.B.01)	Vocalization – Oral automatisms – Motor BL	Valproate (1500), Lamotrigine (100), Zonisamide (300)
			FBTCS (I.D.01)	Eyes open – Vocalization – Convulsive movement	
7	28	Infancy	FTS (I.C.05)	Change in breathing – Tonic BL	Lamotrigine (400) Valproate (1600) Rufinamide (2400) Perampanel (8), VNS
			FCS (I.C.03)	Change in breathing – Clonic BL	
			FBTCS (I.D.01)	Change in breathing – Vocalization – Tonic BL – Clonic BL	
			FMS (I.C.02)	Myoclonic BL	
			FIAMS (I.B.01)	Vocalization – Motor BL – Heavy breathing	
8	40	Early Childhood	**FIAMS (I.B.01)**	Crying - Motor BL – Inadequate talk	Lacosamide (500), Clonazepam (6)
9	28	12	**FIAMS (I.B.01)**	Arousal – Motor BL	Eslicarbazepine (1600), Clobazam (25)
10[b]	43	Early Childhood	**FTS (I.C.05)**	Eyes open – Vocalization – Tonic BL	Lamotrigine (200), Carbamazepine (1200), Lacosamide (400), VNS
			FIAMS (I.B.01)	Eyes open - Motor L	
11[b]	43	6	**FHS (I.C.08)**	Eyes open – Hyperkinetic BL - Vocalization	Carbamazepine (1200), Perampanel (4), Pregabalin, (75), Clobazam (20) Acetatzolamide (375), VNS
12[b]	43	21	**FBTCS (I.D.01)**	Head version L – Tonic L – Clonic BL	Lamotrigine (400), Zonisamide, Perampanel (8), Clobazam (20)
			FIAMS (I.B.01)	Arousal – Behavior arrest	
13[b]	37	19	FIAMS	Freezing-aphasia-automatism	Valproate (2000), Oxcarbazepine (1800)

FLE = frontal lobe epilepsy, PLE = parietal lobe epilepsy, MFE = multifocal epilepsy, TLE = temporal lobe epilepsy, FHS = focal hyperkinetic seizure, FMS = focal myoclonic seizure, FIAMS = focal impaired awareness motor seizure, FBTCS = focal to bilateral tonic-clonic seizure, FTS = focal tonic seizure, FCS = focal clonic seizure, ASM = antiseizure medication, BL = bilateral, L= left, R = right, motor = *unspecific motor movement not classifiable to other seizure types*. **According to visual assessment of video recordings, bolded seizure type is considered the most severe seizure type for each patient**.

[a] Levetiracetam was replaced by brivaracetam.

[b] Only in phase 1.

comparing the difference between baseline and the third follow-up week based on the seizure average of the monitoring and seizure diary entries, we could evaluate the accuracy of seizure diary on therapy outcome assessment.

2.5. Effect of intervention

The seizure average per night was calculated for each week based on both video monitoring and seizure diary entries. Changes in overall seizure frequency between follow-up weeks and the baseline week were calculated based on the seizure average per night to avoid bias from additional recorded nights during the monitoring period and to ensure the results of all patients were comparable with each other.

2.6. Movement intensity and duration of seizures

To assess the effect of BRV on the *movement* intensity and duration of seizures before and after the intervention, we investigated 12 visual and 15 audio-based features. The visual features were derived from off-the-shelf optical flow and background subtraction methods in OpenCV. For audio features, power spectral density information was extracted across different frequency bands.

The features in each seizure type and each patient were extracted, and those with significant differences were investigated before and after the intervention using visual inspection and the Wilcoxon rank-sum test. The Wilcoxon rank-sum test was used to assess the difference between the distributions of observations obtained between two separate groups on a dependent variable. The features were normalized based on the length of the features to avoid being biased by the seizure duration. The features are described in Supplementary material 1. The duration of seizures before and after the intervention was also investigated as a separate feature using the Wilcoxon rank-sum test.

3. Results

3.1. Accuracy of seizure diaries

Eleven out of 13 patients during phase 1 had night-time seizures recognizable by the video monitoring system, and eight patients were able to register seizures in their seizure diaries. The sensitivity of seizure diaries varied between 8% and 84%. Overall, four patients *(patients 2, 3, 7, and 8)* marked seizures which were not observable in the video reference (and therefore considered false positives in the diary); one of these patients *(8)* marked more seizure diary entries than confirmed by video altogether. This resulted in a positive predictive value of 50–95% for seizure diaries. The daily average seizure count varied between 0 and 10.3, while the daily average of diary entries was between 0 and 3.1. According to seizure diaries, the average number of seizure-free nights for 28 days ranged from 16.6 to 23.2, but the average number of seizure-free nights measured by the video monitoring system varied from 0 to 8.7. Thus, seizure diaries underestimated the daily average of seizures and overestimated the seizure-free night count in 7 of 8 patients.

In phase 2, five patients *(1, 3, 5, 7, and 8)* recognized and marked seizures in their seizure diaries: two patients *(3 and 7)* with $< 40\%$, one patient *(1)* with 60%, and two patients *(5 and 8)* with 70% of the seizures detected in the video registration marked in the seizure diary

during the baseline week. Only two patients *(5 and 8)* marked > 50% of their seizures during the third week of follow-up. According to the video monitoring, patients 1 and 8 reached 28% and 36% seizure reduction, but their seizure diaries showed a 37% decrease and 2% increase, respectively. Patients 5 and 7 experienced 56% and 143% seizure increase, but their seizure diaries showed a 15% and 200% increase, respectively. According to both video monitoring and the seizure diary, *one patient (3) did not experience a change in seizure frequency*. 4 patients (2, 4, 6, and 9) who did not mark seizures in seizure diaries had a daily seizure average between 0.4 and 6.4 in the third week of follow-up, and three of them reached > 50% seizure reduction. Results from phase 1 and 2 have been summarized in Table 2.

3.2. Effect of intervention

Nocturnal seizure count, seizures per day average, and change to baseline were calculated for every week for all patients, and diary entries, entries per day average, and their change to baseline. Based on the change of seizure frequency, patients were classified as follows: patients who experienced > 50% seizure reduction are responders to the medical treatment, patients with < 50% seizure reduction or < 50% seizure increase did not respond to treatment, and patients with more than 50% seizure increase experienced worsening of seizure frequency.

After three weeks of follow-up, three patients *(4, 6, and 9)* were responders, four patients *(1, 2, 3 and 8)* did not respond to treatment, and two patients (*5 and 7)* experienced worsening of seizure frequency. Seizure counts, seizures per day averages and changes to baseline, diary entries, averages of diary entries, and change to baseline are summarized in Table 2. In addition, the change in total seizure count in all patients has been displayed in Fig. 1.

3.3. Movement intensity and duration of seizures

To present changes in seizure *movement* intensity and duration, two graphs are shown for each patient. One represents the feature values of each seizure over the recording periods, and the other is kernel density estimation which visualizes the distributions of feature values before (red) and after (blue) the intervention. All the features with P-value < 0.05 are listed in Table 3. However, only those significantly different features before and after the intervention using both P-value < 0.05 and visual inspection were presented in the graphs. Fig. 2.

Some differences before and after the intervention are visible in all subjects. The analysis indicates that *movement* intensity decreased after intervention in all subjects, especially in patients 5, 7, and 9, even though the seizure frequency of patients 5 and 7 increased. The number of selected features with a p-value < 0.05 (Table 3) verifies the significance of the changes in patients 5 and 7. However, the results were affected by the changes of external factors in patients 2 and 3. In patient 2, the change in audio features of myoclonic seizures was caused by snoring instead of the change in seizure manifestation. In patient 3, the camera angle and the monitoring setup changed in the second registration, which affected the intensity analysis. The feature values and kernel density estimation graphs from intensity analysis have been gathered in Fig. 3.

Besides the extracted features, the duration of seizures before and after the intervention was studied. According to the Wilcoxon rank-sum test, duration of seizures between before and after intervention in patient 8 (motor seizures), patient 2 (myoclonic seizures), patient 7 (motor and tonic-clonic seizures), and patient 5 (hyperkinetic seizures) is significantly different. However, KDE graphs do not confirm this. Thus, it seems that the intervention does not significantly affect the duration of different seizure types in the nine studied patients. The feature values and kernel density estimation graphs from duration analysis have been gathered in Supplementary material 2.

4. Discussion

The results from the present study reiterate the inherent problems associated with traditional seizure diaries for assessing both the need for intervention as well as for evaluation of the treatment effect in a group of DRE patients with nocturnal seizures. Furthermore, they demonstrate the feasibility and value of a novel video/audio-based hybrid seizure

Table 2
Results from phase 1: seizures, diary entries, daily average (marked in parenthesis), true positives of seizure diaries (marked in square brackets), sensitivity, PPV, seizure-free nights, and overall registered nights. Results from phase 2: seizure counts for baseline and follow-up weeks, diary entries and their daily average during the baseline and third week of follow-up. Daily averages of seizures and diary entries during each week marked in parentheses, and their changes compared to baseline were marked in square brackets. The seizure daily average and its change in follow-up weeks were painted blue to emphasize their comparability.

	Phase 1						Phase 2							
ID	Seizures (Daily average)	Diary entries (Daily average) [true positives]	Sensitivity	Positive predictive value (PPV)	Seizure free nights / average of 28 days (According to seizure diary)	Registered nights in phase 1	Seizures baseline week (Average per day)	Seizures, week 1 (Average per day) [change to baseline]	Seizures, week 2 (Average per day) [change to baseline]	Seizures, week 3 (Average per day) [change to baseline]	Diary entries Phase 2 (Daily average) [true positives]	Diary entries baseline week (Average per day)	Diary entries week 3 (Average per day) [change to baseline]	Registered nights in phase 2
1	58 (1.9)	8 (0.3) [8]	14%	100%	3/2.7 (23/21)	31	14 (2)	12 (1,71) [-14,5%]	12 (1,71) [-14,5%]	10 (1,43) [-28,5%]	33 (1,18) [27]	8 (1,14)	5 (0,71) [-37%]	28
2	170 (6.1)	20 (0.7) [13]	8%	65%	0/0 (18/18)	28	51 (7,29)	40 (5,71) [-21,7%]	52 (7,43) [+1,9%]	45 (5,6) [-11,7%]	0 (0) [0]	0	0	29
3	29 (1.0)	10 (0.3) [5]	17%	50%	9/8.7 (24/23.2)	29	7 (1)	3 (0,43) [-57%]	3 (0,43) [-57%]	7 (1) [0%]	6 (0,21) [6]	2 (0,29)	2 (0,29) [0%]	28
4	33 (2.1)	0 (0) [0]	0%	-	0/0 (16/28)	16	22 (3,14)	14 (2) [-36,3%]	13 (1,86) [-40,7%]	9 (1,13) [-64%]	0 (0) [0]	0	0	29
5	169 (5.8)	91 (3.1) [91]	54%	100%	0/0 (0/0)	29	32 (4,57)	37 (5,29) [+15,8%]	52 (7,43) [+62,6%]	50 (7,14) [+56,2%]	161 (5,75) [116]	27 (3,86)	31 (4,43) [+15%]	28
6	288 (10.3)	0 (0)	0%	-	0/0 (28/28)	28	54 (7,71)	36 (5,14) [-33,3%]	56 (8) [+3,8%]	20 (2,86) [-63%]	0 (0) [0]	0	0	28
7	87 (3.2)	22 (0.8) [21]	24%	95%	0/0 (16/16.6)	27	21 (3)	24 (3,43) [+14,3%]	114 (16,29) [+443%]	51 (7,29) [+143%]	33 (1,18) [32]	3 (0,43)	9 (1,29) [+200%]	28
8	57 (1.9)	67 (2.2) [48]	84%	72%	1/0.9 (0/0)	30	12 (1,71)	10 (1,43) [-16,4%]	7 (1) [-41,5%]	11 (1,0) [-41,5%]	44 (1,38) [29]	9 (1,29)	14 (1,27) [-1,5%]	32
9	41 (1.5)	0 (0) [0]	0%	-	8/8 (28/28)	28	7 (1)	1 (0,14) [-86%]	5 (0,71) [-29%]	3 (0,43) [-57%]	0 (0) [0]	0	0	28
10[a]	37 (1,3)	5 (0,17) [5]	14%	100%	7/6,8 (24/23,2)	29	Patients did not participate to phase 2.							
11[a]	119 (4,25)	76 (2,7) [76]	64%	100%	0/0 (0/0)	28								
12[a]	0 (0)	0 (0) [0]	0%	-	28/28 (28/28)	28								

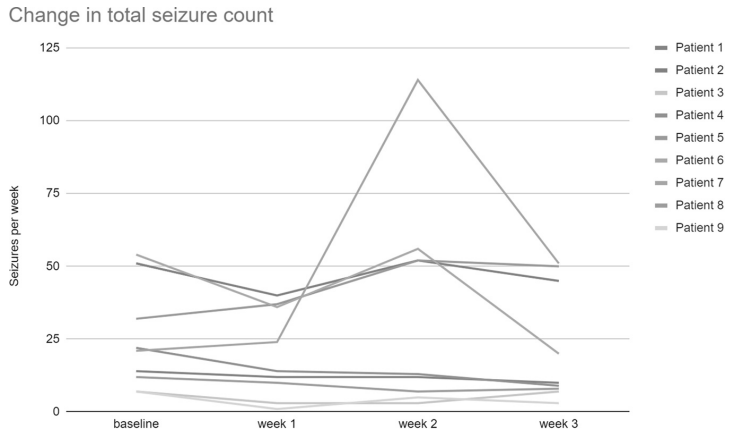

Fig. 1. Change in total seizure count in patients 1–9 during the baseline week and 1, 2, and 3 weeks of follow-up.

Table 3
List of the features with p-value < 0.05.

Patient	Seizure type	Feature ID
1	Hyperkinetic	9, 11, 12, 15, 16, 17
2	Myoclonic	2, 3, 4, 6, 7, 8, 10, 13, 15, 16, 17, 18, 21, 22, 23, 26, 27
3	Motor	1, 2, 3, 4, 6, 7, 8, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27
	Convulsive seizure	2, 3, 4, 11, 15, 16, 17
5	Hyperkinetic	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 18, 19, 21, 22, 23, 24 25, 26, 27
6	Motor	11, 12, 20
7	Myoclonic	2, 3, 4, 6, 7, 8
	Clonic	2, 3, 4, 7, 8, 21, 22, 23, 25
	Tonic-clonic	9, 10, 14, 20, 25
	Motor	6, 9, 12
	Tonic	1, 2, 3, 4, 6, 7, 8, 9, 12
8	Motor	13, 18, 19, 20, 21, 22, 23, 24, 26, 27
9	Motor	1, 5, 6, 7, 8, 15, 17

detection system using human annotation for the confirmation of the algorithmically triggered and classified event. Finally, the intensity analysis presents a novel method to quantify intensity of movements due to treatment. However, further validation would be required before using such analysis in clinical contexts.

Reliable detection of seizures is important to improve patient outcomes and to assess treatment effects on various seizure types both in patient care and in drug development. There is no way to foresee the date or time of the next seizure occurrence in patients with seizures uncontrolled by ASMs. This lack of control may cause constant fear of seizures and is a major handicap for patients even when direct harm is not often caused by a single seizure (Laxer et al., 2014). In patients with developmental disability, uncontrolled seizures or fear of unobserved seizures further reduce the possibility for independent living arrangements (Devinsky et al., 2015).

During the prescreening phase, eight patients *(1, 2, 3, 5, 7, 8, 10, and 11)* documented only from 8% to 84% of seizures in their seizure diaries. During the intervention phase, five patients *(1, 3, 5, 7, and 8)* documented only from $<$ 40–70% of seizures using seizure diary, which caused underestimation of seizure counts and inaccuracies in the evaluation of treatment effect. Some patients were not able to register any of their seizures in their seizure diaries. Seizure counts according to video monitoring were higher than diary entries in ten patients *(1, 2, 3, 4, 5, 6, 7, 9, 10, and 11)* during the screening phase, and in eight patients *(1, 2, 3, 4, 5, 6, 7, and 9)* during the intervention phase, which caused both underestimation of seizure frequency and overestimation of seizure free nights. Three patients *(2, 3, 8)* also marked non-epileptic events as seizures (false positives) in their seizure diaries during prescreening phase, which caused overestimation of seizure frequency in one patient *(8)*. Thus, our study gives further credence to previous findings reporting that seizure diaries are prone especially to underestimation but also to overestimation of the seizure counts (Stokes et al., 2011; Goldstein et al., 2021).

Seizure diaries indicated a significant change in seizure frequency in only one patient (seizure increase in patient 7) and thus BRV treatment would have been considered a failure in all patients. However, 3 patients were responders according to the video monitoring. In addition, video recording provided information about treatment outcome for those four patients who were unable to document any seizures to their diaries. Two patients *(12 and 13)* did not experience any seizures during prescreening phase despite the suspicion of active epilepsy both according to their seizure diaries and video registration confirming the reliability of seizure diaries in these patients. Conversely, Nelli® hybrid system detected seizures that were completely missed by seizure diaries in three patients *(4, 6 and 9)* during prescreening phase, allowing them proceed to the intervention phase. This study indicates that the video monitoring system significantly improved the accuracy of treatment outcome assessment, as it provided additional evidence that the diaries alone could not produce.

Visual and audio features were used to measure the movement intensity and duration of seizures before and after intervention. The features detected change in intensity with statistical significance in 8 out of 9 patients. The intensity of movements decreased most distinguishably in three patients after the intervention, as visualized in Fig. 3. As shown in Table 3, hyperkinetic, focal motor, clonic and tonic-clonic seizure types were detected with the largest variety of statistically significant features, which indicates better accuracy and suitability of features in these seizure types with unequivocal and stereotypical motor movement patterns. The duration of seizures changed in four patients, but the Kernel density estimation did not confirm these results. Keeping the monitoring settings similar in both monitoring periods is significant in movement analysis of video detection system, as it may affect the movement detection (Yang et al., 2021). In this study, the intensity analysis was affected by the change in the monitoring setup and snoring. Even though quantitative analysis has already been used to analyze seizure semiology (Cunha et al., 2016; Hartl et al., 2018; Ahmedt-Aristizabal et al., 2018), previous studies related to quantitative analysis in the effect of BRV on movement intensity and duration have not been reported. Changes in seizure intensity within the same seizure

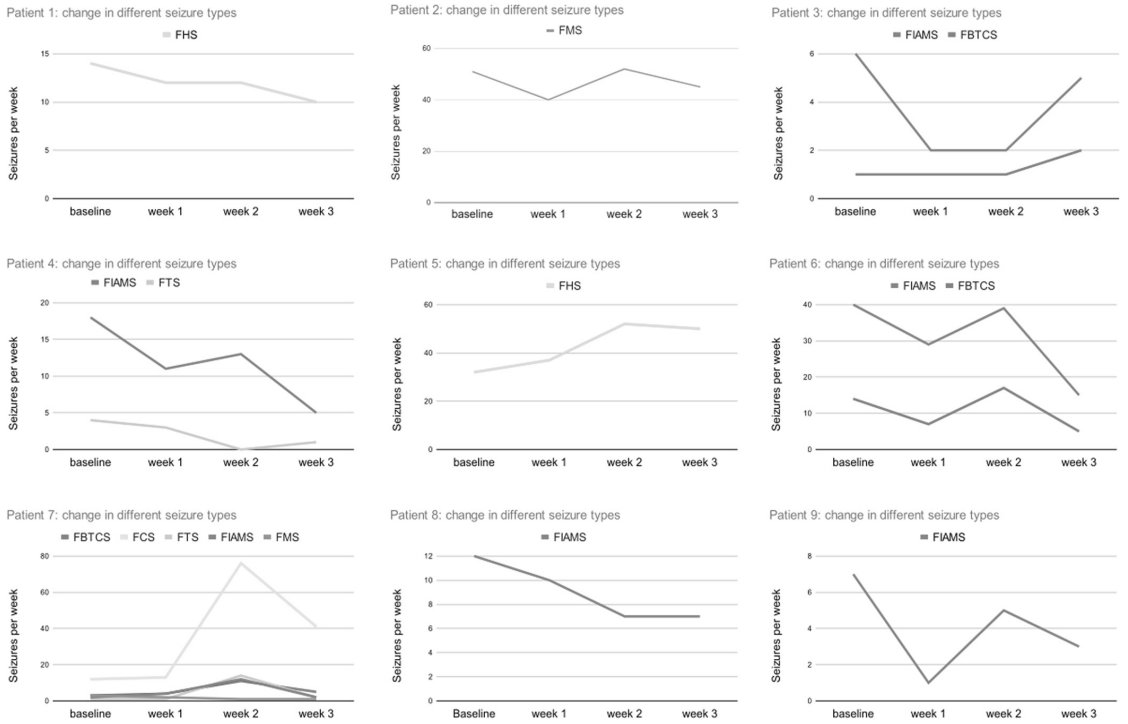

Fig. 2. Change in different seizure types during the baseline and 1, 2, and 3 weeks after the initiation of BRV in patients 1–9. FHS = focal hyperkinetic seizure, FMS = Focal myoclonic seizure, FIAMS = focal impaired awareness motor seizure, FBTCS = focal to bilateral tonic-clonic seizure, FTS = focal tonic seizure, FCS = focal clonic seizure.

type after intervention could be helpful when assessing additional benefits of dose increases of a given ASM, but the relevance of this hypothesis need to be validated in future studies using video-EEG as a gold standard.

There are various methods to quantify the patterns of movement in visual and audio data and utilizing such feature extraction methods highly depends on the application domain. However, the statistical significance before and after the intervention is not reliable enough alone in feature analysis. Therefore, all the changes in features were verified by a medical expert to assure that a selected feature measures the property of interest and were not affected by the environmental noise. For the purpose of clinical validation of the feature analysis a larger patient population is needed to study the efficiency of the proposed features. There are also other limitations of our study. The change of monitoring settings can significantly affect the results based on signal analysis. Seizure detection requires the patient to stay in sight of the camera, a blanket may impede the detection of movements and the device must be turned on. In the Nelli® hybrid system validation study, the performance was good for classifying seizures with clear motor components, but the current challenge for video detection systems was the recognition of seizures with more subtle motor features (Peltola et al., 2022). In the present study, most seizures recorded did indeed have unequivocal motor components. There's a possibility that seizures recorded by patients but not registered by Nelli® hybrid system might represent subtle seizures. However, even though video-EEG could improve identification of subtle motor events, video-EEG is not needed as a reference standard in this phase 2 study according to recent guidelines (Beniczky and Ryvlin, 2018). Furthermore, video-EEG confirmation is not feasible to use for evaluation of treatment effects due to the long duration of the registration required. On the other hand, the assessment of duration and intensity of seizures using video only may be imprecise without confirmation by EEG. In addition, some of the patients were not able to record the nights consecutively. This caused the 3-week follow-up period to vary from 28 to 40 nights causing dissimilarity and hampering comparison of the recording results between patients.

5. Conclusions

The video/audio-based seizure-monitoring system enabled recognition of a significant effect on seizure frequency and intensity after initiating adjunctive brivaracetam treatment in several patients with drug resistant epilepsy. The significance was based on the ability to accurately detect seizure numbers and types in individual patients with difficult-to-observe predominantly nocturnal seizures. Results between seizure diaries and Nelli® hybrid system recordings varied in our patient population. Seizure diaries often underestimated seizure numbers compared to video recordings. Therefore, the ability of seizure diary usage to detect change in numbers of specific seizure types after therapy modification was inferior to video monitoring tool. The change in nighttime motor seizure count based on diary entries could be larger or smaller than the actual change (as suggested by the video monitoring). Finally, assessment of BRV treatment efficacy was improved by using the video/audio recording system. Further research with larger patient groups is still needed to improve the reliability of feature analysis.

Conflicts of interest

AK, and MZ are employees of Neuro Event Labs, the company that provided the equipment and technology used in the study. PO has

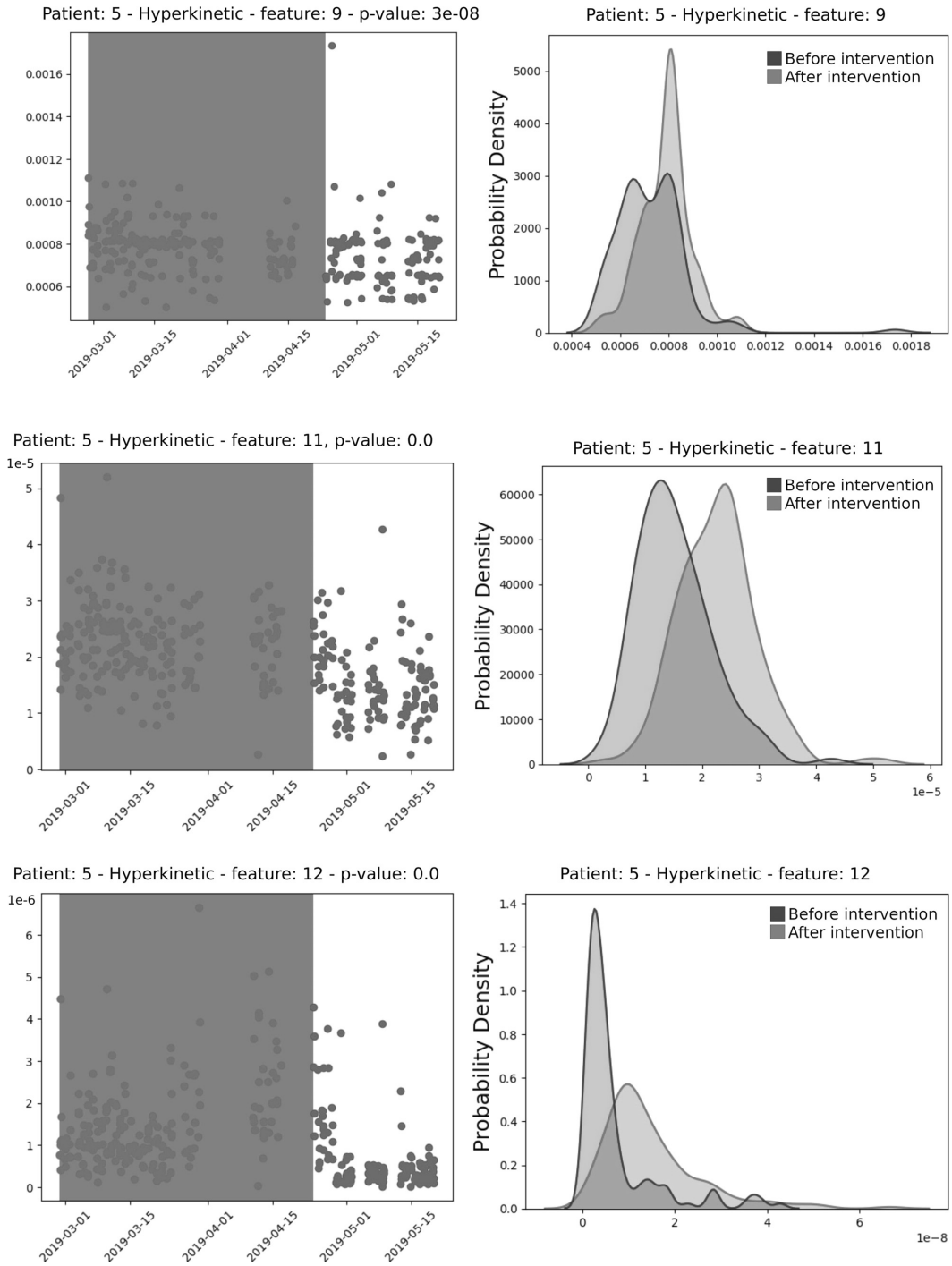

Fig. 3. part 1. Feature values (left) and Kernel density estimation (right) from intensity analysis for patient 5. Features 9, 11 and 12 are visual features calculated by using background subtraction method.part 2. Feature values (left) and Kernel density estimation (right) from intensity analysis for patients 7 and 9. Feature 1 is a visual feature calculated by using optical flow.

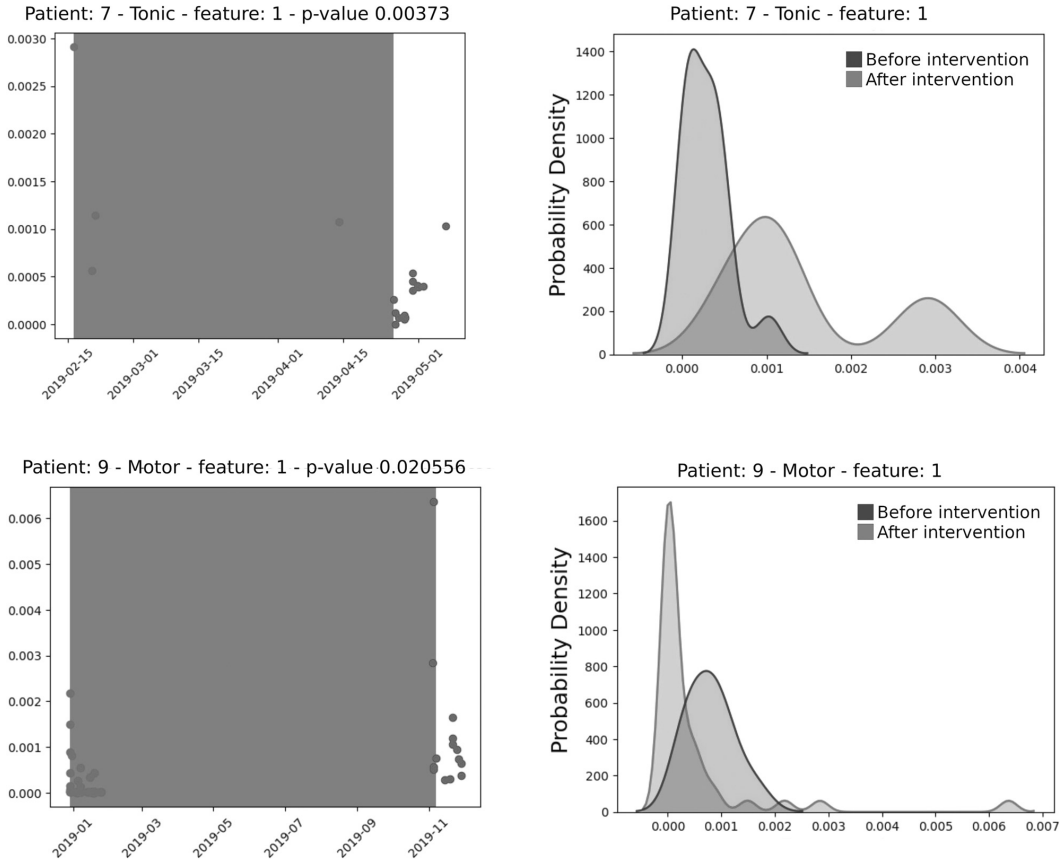

Fig. 3. (*continued*).

provided medical consultation for Neuro Event Labs. JP is a shareholder of Neuro Event Labs and has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for Arvelle, Novartis, LivaNova, Eisai, Medtronic, UCB, and Pfizer. Other authors claim no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eplepsyres.2022.106949.

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PUBLICATION IV

Characteristics of motion signal profiles of tonic-clonic, tonic, hyperkinetic and motor seizures

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Submitted.