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Review article

The diagnostic value of clinical neurophysiology in hyperkinetic movement disorders: A systematic review

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ABSTRACT

Introduction: To guide the neurologist and neurophysiologist with interpretation and implementation of clinical neurophysiological examinations, we aim to provide a systematic review on evidence of electrophysiological features used to differentiate between hyperkinetic movement disorders.
Methods: A PRISMA systematic search and QUADAS quality evaluation has been performed in PubMed to identify diagnostic test accuracy studies comparing electromyography and accelerometer features. We included papers focusing on tremor, dystonia, myoclonus, chorea, tics and ataxia and their functional variant. The features were grouped as 1) basic features (e.g., amplitude, frequency), 2) the influence of tasks on basic features (e.g., entrainment, distraction), 3) advanced analyses of multiple signals, 4) and diagnostic tools combining features.
Results: Thirty-eight cross-sectional articles were included discussing tremor ($n = 28$), myoclonus ($n = 5$), dystonia ($n = 5$) and tics ($n = 1$). Fifteen were rated as 'high quality'. In tremor, the basic and task-related features showed great overlap between clinical tremor syndromes, apart from rubral and enhanced physiological tremor. Advanced signal analyses were best suited for essential, parkinsonian and functional tremor, and cortical, non-cortical and functional jerks. Combinations of electrodiagnostic features could identify essential, enhanced physiological and functional tremor.
Conclusion: Studies into the diagnostic accuracy of electrophysiological examinations to differentiate between hyperkinetic movement disorders have predominantly been focused on clinical tremor syndromes. No single feature can differentiate between them all; however, a combination of analyses might improve diagnostic accuracy.

1. Introduction

Hyperkinetic movement disorders such as myoclonus, tremor, dystonia, chorea and tics are characterized by excessive and involuntary movements, each with their own clinical presentation. Identifying the movement disorder phenotype is important for identification of the etiology and for proper treatment strategies. To aid the diagnostic process, clinical neurophysiological tests such as electromyography and accelerometry may be performed. Numerous neurophysiological features have been proposed to be useful in the differential diagnoses, of which some found a place amidst the diagnostic criteria. While multiple cohort descriptions and reviews exist about the use of clinical neurophysiology in movement disorders, they mostly consist of expert opinion or explain how to perform tests, without systematic scientific substantiation [1] [–] [3]. To aid neurophysiologists with the interpretation and implementation of electrophysiological tests and to identify knowledge gaps, we aim to provide a critically appraised systematic review on the evidence of polymyography, accelerometry, and electroencephalography used in clinical practice to differentiate between movement disorders.

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2. Methods

2.1. Search strategy and quality assessment

A PRISMA systematic review was performed of all studies on accelerometry (ACC) or electromyography (EMG) features to discriminate between different hyperkinetic movement disorders. We focused on myoclonus, dystonia, chorea, tics and tremor, but also included ataxia. Furthermore, each of these movement disorders has a functional variant, such as functional tremor or functional myoclonus, which can be challenging to diagnose in some patients presenting with abnormal movements. For that reason, we discuss functional variants alongside each particular movement disorder, rather than "functional movement disorders" as a separate entity.

The search terms described in **A.1** were used in PubMed up until January 2021. We only selected diagnostic test accuracy studies as described by the Cochrane Collaboration [4]. These papers report the diagnostic accuracy of features that have been compared between two or more groups in a cross-sectional study or meta-analysis. We did not set a minimum for the numbers of patients investigated. Only articles published in English were included. A flow diagram of our inclusion process can be found in Figure A.5.

The quality of the papers was assessed with the QUADAS checklist as advised by the Cochrane Collaboration (Table A.2) [5]. This checklist leads to a classification of a study as either "high quality", "low quality", or "unknown". For specification see supplementary Table A.6.

2.2. Well-known phenomena with limited evidence

As consequence to our in- and exclusion criteria, no papers were included on a few well-known neurophysiological phenomena. However, to give a complete overview we will discuss these relevant papers as well. These consisted of the most recent research studying burst duration and synchronicity in myoclonus syndromes and co-contraction in dystonia, in a relative large patient cohort.

2.3. Grouping of results

We will discuss the evidence per movement disorder, presenting the electrophysiological features in four categories: 1) basic features, which can be easily determined using ACC and/or EMG in rest or during posture, 2) task-related features, the influence from the performance of internally and externally administered tasks on basic features, 3) advanced analyses, which can be calculated from multiple sensor signals derived from ACC and EMG, and 4) diagnostic tools, which consists of multiple criteria and a cut-off score to establish a final diagnosis. Table 1 describes the definition of the electrophysiological features discussed in this systematic review.

2.4. Statistical analysis

We adopted the group specific values and statistics stated in the included papers. Only the frequency and frequency variability were recalculated based on the original values stated in the included papers (see **Eq. A.3** and **Eq. A.4**) [6].

3. Results

3.1. Search results

Thirty-eight cross-sectional articles proved fit for inclusion. No meta-analyses were found. Fifteen papers were qualified as 'high quality' studies using the QUADAS guidelines, the remaining papers as 'unknown' (Table A.6).

One paper discussed the difference between two movement disorders, myoclonus and tics; the others compared clinical syndromes [7].

Table 1
Definitions of electrophysiological features.

Feature	Definition	Equipment
Basic features		
Presence of tremor activity	Visual inspection of the signal to determine the presence of tremulous burst activity	EMG
Frequency	The mean frequency as the frequency of the dominant peak in the power spectrum or subjective inspection throughout the registration measurement, in Hz	ACC or EMG
Frequency variability	Several measurements that give the variability of the frequency throughout the registration or specifically after changes in posture or externally administered tasks (i.e. loading), in Hz	ACC or EMG
Amplitude	The extent of the muscle activity or movement measured in voltage or power in gravity	ACC or EMG
Burst duration	The average duration of EMG bursts, in milliseconds	EMG
Synchronicity of bursts	The relative synchronicity of EMG burst within a muscle pair	EMG
Task-related features		
Intention component	A goal directed task in which a patient is asked to move their hand towards a prespecified goal. E.g., the finger-to-nose test, a movement of the index finger from a stretched-out hand towards their nose. The intention component is present if an amplitude increase is observed when the finger is approaching the goal.	ACC or EMG
Distractibility	The patient is distracted by a mental task, for example by serially subtracting seven from a hundred or by having a conversation, or a contralateral ballistic movement. Simultaneously, the patient holds the hands in a posture in which the movement disorder is evoked. Distractibility is established when a frequency shift or temporal disappearance of the tremor is present	ACC or EMG
Entrainment	The patient performs a tapping task at multiple frequencies with the least-affected hand while the most-affected hand is put in a position that evokes the tremor. A positive entrainment test is established when a notable frequency shift is recorded in the most-affected (non-tapping) hand or becoming the same frequency of the task.	ACC or EMG
Loading/weighting	A 500 g or 1000 g of weight is added to the wrist. The tremor frequency and amplitude is compared between a postural task in both a loaded and an unloaded condition to establish whether loading results in frequency or amplitude variability, in Hz or power.	ACC or EMG
Advanced analyses		
Autospectrum	A Fourier transformation of electromyography data	EMG
Standard coherence analysis	A normalized measure within the frequency domain expressing the dependence of two signals, between 0 and 1, where 0 represents complete independence and 1 represents complete dependence	EMG & EMG or EMG & EEG
Wavelet coherence analysis	The percentage of time in which significant coherence exists between EMG channels (PTSC) and the number of uninterrupted periods with coherence below the significance level (NOV)	EMG & EMG
Cumulant density	Time domain measure derived from the frequency domain by application of the inverse Fourier transform, informative of the timing relations between two signals	EMG & EMG

(*continued on next page*)

Table 1 (*continued*)

Feature	Definition	Equipment
Jerk-locked back-averaging	The presence of an averaged 'time-locked' biphasic potential on the contralateral motor cortex preceding the jerks on the EMG within the timeframe corresponding to the conduction period of the corticospinal tract (arms 15–25 milliseconds/legs ±40 ms)	EMG & EEG
Bereitschaftspotential	A slowly rising, negative cortical deflection started at least 1000 (early BP) or between 1000 and 500 ms (late BP) before the movement onset in the EMG	EMG & EEG
Event-related desynchronization	A reduction of beta and low gamma oscillations occurring prior to cued and self-paced movement	EMG & EEG

The papers included tremor ($n = 27$), myoclonus ($n = 5$), dystonia ($n = 5$), and tics ($n = 1$). Four papers only used descriptive statistics and were not taken into account for further review [8] [–] [11]. Table 2 summarizes the number of identified articles per movement disorder and highlights the diagnostic value of electrophysiological features that were substantiated by the articles with highest level of evidence and highest number of patients.

3.2. Tremor

Commonly encountered tremor syndromes included essential tremor ($n = 22$), parkinsonian tremor ($n = 19$), functional tremor ($n = 10$), enhanced physiological tremor ($n = 6$), and dystonic tremor syndromes ($n = 6$) [12]. The vast majority of authors compared parkinsonian to essential tremor. No diagnostic test accuracy study was found for orthostatic tremor for which a 15 Hz orthostatic-induced leg tremor is considered pathognomonic [13]. Table 3 describes the features with significant and clinical relevance, adopted from referred papers that can be used to differentiate clinical tremor syndromes.

3.2.1. Basic features

The **presence** of tremulous activity during rest, posture or movement is an important clinical characteristic. Confirmed with electrophysiology, parkinsonian tremor is significantly more often present at rest compared to essential tremor (71 % versus 0 % of patients) and significantly less at posture or action (8 % versus 79 % of patients) [14]. The phenomenon of a "re-emergent tremor" i.e., tremor temporarily diminishes while assuming a posture, has only been reported in parkinsonian tremor [15,16].

The tremor **frequency** is the most commonly investigated feature measured with ACC or EMG during rest, posture, action or the most provoking position. Only the high frequency (>9 Hz) of enhanced physiological tremor and low frequency (<4 Hz) of rubral tremor was significant and clinically useful to be discriminated from essential, parkinsonian and functional tremor [10,14] [–] [28]. Comparing the frequency during rest, posture or action did not seem to be of additional value [14,15,26,29]. Only in writing, frequency was higher in essential tremor compared to tremor associated with dystonia (i.e., tremor in non-dystonic limb), but not dystonic tremor (i.e., tremor in dystonic limb) [29]. The presence of harmonic frequencies was able to differentiate between parkinsonian and essential tremor with high diagnostic accuracy (91.7–94 %): the sum of all harmonic peaks in the power spectrum being higher in parkinsonian tremor [22].

The extent of frequency variability can be quantified with various methods ranging from easy to complex: frequency spread, as the absolute range of frequency [18]; tremor consistency, as the proportion of the time spend at the modal frequency [30]; tremor stability, as the area under the curve between two vertical lines at half peak power (full width at half maximum, FWHM) of the frequency spectrum [26,29]; power spectrum variability, as the power mean-deviation of the frequency spectrum [31]; and the Tremor Stability Index (TSI), as the absolute interquartile range of the cycle-by-cycle variation in tremor frequency of the ACC axis with the largest contribution to tremor variation (see

Table 2
Overview of the number of identified articles and features with most evidence and their diagnostic value.

Movement Disorder	Articles of good quality (N)	Articles of unknown quality (N)	Distinguish subtype with confidence compared to:	Features with most evidence	Diagnostic test accuracy		
					Sensitivity	Specificity	AUC-ROC
Tremor	10	18					
Essential tremor (ET)	9	13	Cohort of clinical postural tremor syndromes	Diagnostic tool [36]see Table 4	97.7 %	82.3 %	
Parkinsonian tremor (PT)	6	13	Essential tremor	Tremor Stability Index [25]	88–90 %	69–95 %	
Functional tremor (FT)	4	6	Organic tremor (ET, PT, EPT, DT)	Diagnostic tool A [20,37]see Table 4	89.5 %	95.9 %	
			Organic tremor (ET, PT, EPT)	Diagnostic tool B [23]see Table 4	100 %	93 %	
			Organic tremor (ET, PT, DT)	Diagnostic tool C [26]see Table 4			Good (0.809)
Enhanced physiological tremor (EPT)	2	4	ET, PT, FT	Diagnostic tool [23]see Table 4	84 %	94 %	
Dystonic tremor (DT)	4	2	–	–			
Orthostatic tremor	0	0	–	–			
Myoclonus	3	2					
Cortical myoclonus	2	2	Non-cortical myoclonus and healthy controls	Jerk-locked back-averaging [47–49]	44–75 %	100 %	
			Healthy controls	Corticomuscular coherence [47]	83.3 %	90 %	
Functional jerks	1	2	Cortical myoclonus	Bereitschaftspotential & Event Related Desynchronization [49,50]	80 %	100 %	Excellent (0.9–1.0)
Subcortical myoclonus	1	0	–	–			
Dystonia	3	2	Healthy muscles	Autospectrum [59]	88 %	100 %	
Tics	0	1	–	–			
Ataxia	0	0	–	–			
Chorea	0	0	–	–			

Table 3
Differentiating neurophysiological features of five clinical tremor syndromes.

Features	EPT	ET	PT	DT	FT	References
Basic features						
Presence of tremor activity, *in % of patients*						
In rest	–	0 %	71 %	–	–	
In posture/action						[14]
	–	79 %	8 %	–	–	
Mean frequency, Hz	7.72 ± 1.35	5.84 ± 1.05	5.07 ± 0.92	7.62 ± 1.41	7.62 ± 1.41	[10,14,17–26]
Phase of agonist-antagonist wrist muscle pair	–	synchronous	alternating	–	–	[14,19]
Frequency variability features						
Frequency spread, range in absolute frequency, Hz	2.44 ± 1.74	1.00 ± 0.45	0.87 ± 0.57	1.59 ± 0.82	2.24 ± 1.60	[23,24,32]
Tremor consistency, Proportion of time spend in modal frequency	–	↑	↑	–	↓	[30]
Tremor stability, the full width half maximum (FWHM)	–	↑	↑	↑↑	↓	[20,29,37]
Tremor Stability Index (TSI)	–	↑	↓	↑↑	–	[25,29]
Power spectrum variability	–	↑	↓	–	–	[31]
Task-related features						
Alteration in frequency						
Distractible, *in % of patients*	Organic tremor syndromes: 8 %				94 %	[23]
Entrainment, *in % of patients*	Organic tremor syndromes: 9–12 %				77–91 %	[20,23]
Decrease due to arm loading, *in % of patients*	42 %	Other tremor syndromes: 5 %				[15,18,23]
Alteration in amplitude						
Distractible, mental task	No alteration		↑	–	–	[15]
Distractible, contralateral ballistic movement	Organic tremor syndromes: less alteration				↓	[16,23]
Arm loading	Organic tremor syndromes: less alteration				↑	[20]
Intention component, *in % of patients*	~	42 %	Other tremor syndromes: 15 %			[23]
Advanced analyses						
Intermuscular coherence	↓	↑	↑	–	↑	[24]
Wavelet coherence analysis						
NOV (fragmentation)	↓	↓	↓	–	↑	
PTSC (stability)						[26]
	↑	↑	↑	–	↓	
Cumulant density of wrist and elbow extensors	synchronous	alternating	synchronous	–	synchronous	[24]

↑ higher; ↓ lower, compared to the other subtypes.
FT, functional tremor; EPT, enhanced physiological tremor; ET, essential tremor; PT, parkinsonian tremor; DT, dystonic tremor; NOV, number of valleys: the number of uninterrupted periods with coherence below the significance level was determined as the total number of upward crossings through the line of significant coherence; PTSC, the percentage of time that significant coherence existed between both EMG channels: this parameter was calculated as the number of time points with significant coherence divided by the total number of time points.

Fig. 1) [19,29]. Frequency spread was significantly higher in enhanced physiological and functional tremor compared to essential and parkinsonian tremor [17,18,32,33]. In other studies, tremor stability did not differ between functional and organic tremor as a group, but was significantly lower in functional compared to essential and parkinsonian tremor [26,30]. The power spectrum variability and the TSI showed both high accuracy to differentiate the more stable parkinsonian from the more variable essential tremor. The spectrum variability was found to have a 90 % sensitivity, 87 % specificity and AOC-ROC of 89 %; the TSI a 88 % sensitivity, 95 % specificity and a AUC-ROC of 90 % in the test and 69 % in validation cohort [19,31]. Finally, three variability features including frequency spread, FWHM and TSI are higher in dystonic than essential tremor and tremor associated with dystonia [17,29,32].

The **burst duration** of a muscle contraction is moderately correlated ($r = -0.5$) with tremor frequency [21]. This feature has been reported in five clinical tremor syndromes. The duration of a tremor burst (±80–110 m s) visible on the EMG does not show any significant or clinically relevant difference between essential, parkinsonian and functional tremor [25,26]. It can be useful for differentiation of longer bursts (>150 m s) in rubral tremor and of shorter bursts (<50 m s) in enhanced physiological tremor; however, only after determining the pattern of the appearance of these bursts as synchronous or alternating first [21].

Some authors hypothesize that tremor syndromes may be subdivided into two groups, **synchronous** or **alternating** tremor. Without clear specification of diagnostic accuracy, Milanov and colleagues stated that the synchronous group consists of essential, cerebellar and enhanced physiological tremor; the alternating group of parkinsonian, essential (type B with alternating activity), rubral and functional tremor [21]. This division has not been confirmed in other studies. On visual inspection of EMG, essential tremor seems to show a synchronous wrist antagonists pattern more often than parkinsonian tremor [14,15,25]. No consistent pattern was found in dystonic versus essential tremor [29].

The **amplitude** of the oscillatory movement has been measured in voltage or power. Overall the amplitude shows great variation and is dependent on EMG properties, as such no significant or clinical relevant difference was found between essential, parkinsonian, enhanced physiological, functional tremor, rubral, cerebellar and dystonic tremor syndromes [16,18,21,22,25,26,29,32,34].

3.2.2. *Task-related features*

The **tremor frequency** can be susceptible to change under a number of tasks. Changes in frequency can point either towards an unstable central tremor generator such as in functional tremor or a peripheral (reflex) component such as in enhanced physiological tremor. A notable frequency shift of >1 Hz or suppression during a mental or physical task (e.g. **distraction**) or a contralateral tapping task (e.g. **entrainment**) occurred in the majority (94 % and 77–91 %) of functional tremor patients, while it is rare in organic tremor patients (8 % and 9–12 %) [17,26]. **Loading** of the arm with a weight (500–1000 g) results in a decrease of >1 Hz in 42 % of enhanced physiological tremor patients opposed to 5 % of patients with parkinsonian, essential, dystonic, functional, Holmes or cerebellar tremor [15,17,24].

An **alteration in amplitude** can also be noticed by the neurophysiologist as consequence of several tasks. During a mental task, an amplitude increase was seen in parkinsonian but not essential or enhanced physiological tremor patients [15]. Furthermore, the amplitude and features representing tremor regularity decrease in parkinsonian tremor during arm loading and merge with values of healthy controls, making differentiation more difficult [34,35]. An amplitude decrement during a contralateral ballistic movement and amplitude

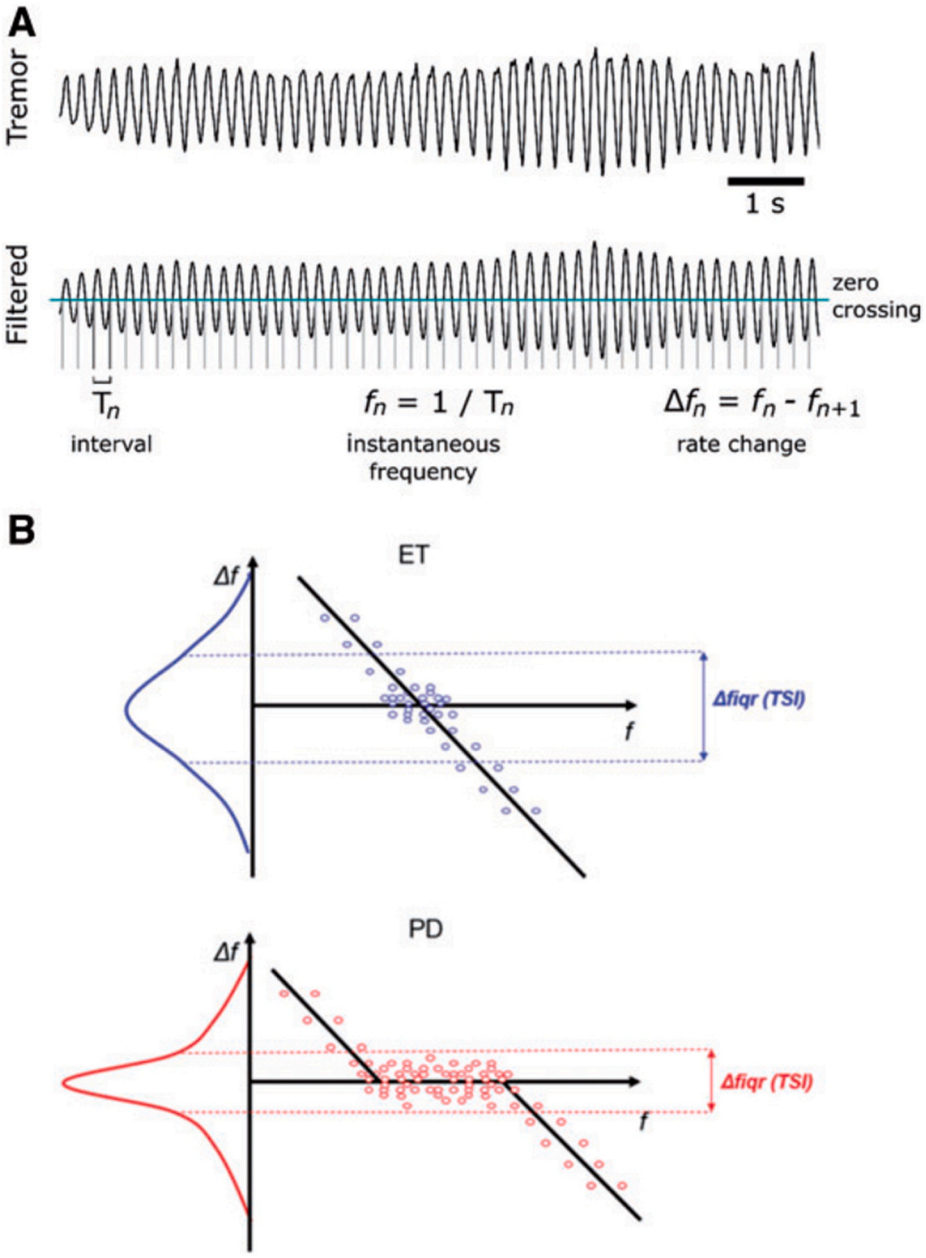

Fig. 1. Tremor stability index (TSI). This schematic illustration shows the (A) instantaneous frequency and variation in frequency and (B) the TSI, which is the absolute interquartile range of the cycle-by-cycle variation in tremor frequency of the ACC axis. Figure is copied from Ref. [19].

increase after loading is significantly more often present in patients with functional compared to organic tremor [16,17,26]. During the finger-to-nose maneuver, a tremor amplitude increase indicating intention tremor occurred more frequently in of essential tremor patients (42 % of 50 patients) compared to a combined group of six tremor subtypes (15 % of 160 patients) including eight cerebellar and four Holmes tremor. By omitting the cerebellar and Holmes tremor patients, the specificity of the intention component for essential tremor increased from 85 % to 92 % [17].

3.2.3. *Advanced analyses*

Coherence analysis has been investigated in several tremor subtypes. Significant **intermuscular coherence** between a unilateral muscle pair was more often present in parkinsonian (100 %), functional (94 %), and essential tremor (70 %) compared to enhanced physiological tremor (50 %) [18]. Coherence in bilateral muscle pairs occurred more frequently in functional (56 %) compared to organic tremors (4 %) [26]. The degree of coherence was significantly lower in dystonic tremor compared to essential tremor and tremor associated with dystonia [29]. **Wavelet coherence analysis** takes the variation in coherence over time into account (see Fig. 2) and is able to differentiate parkinsonian (*AUC* 0.874–0.998) and enhanced physiological tremor (*AUC* 0.883–0.998) from essential and functional tremor. Furthermore, it was more accurate in discriminating functional from organic tremor (*AUC-ROC* 0.809) than to standard intermuscular coherence (*AUC-ROC* 0.552) [20]. Focusing on the coherence phase to quantify the temporal delay of the **effect of voluntary movements** on tremor frequency, the tremor frequency was close to synchronized with that of the voluntary movement in tremor associated with dystonia, whereas it was close to alternating (e.g. out of phase) in essential tremor [29]. **Cumulant density** in Fig. 3, the direct counterpart of coherence, showed an alternating pattern of wrist and elbow extensors in essential tremor compared a synchronous pattern regarding this muscle pair in parkinsonian, enhanced physiological and functional tremor (91 % sensitivity, 64 % specificity) [18].

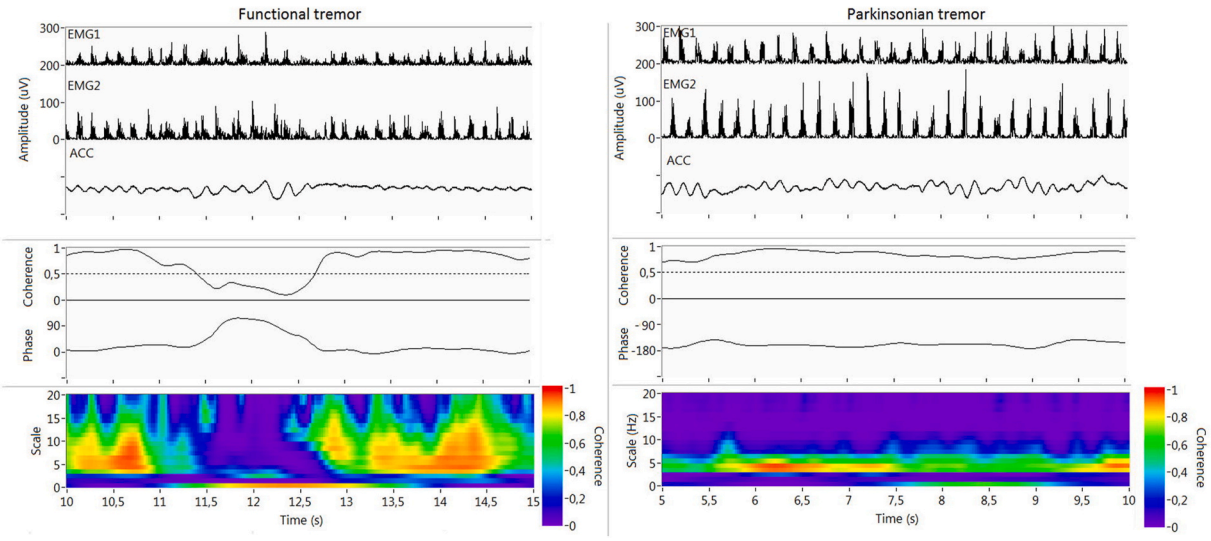

Fig. 2. Wavelet coherence analysis (WCA). WCA enables to detect variation in coherence and phase difference between two signals over time. For two patients, the scalogram displays wavelet coherence over time for frequencies from 0 to 20 Hz. Figure is copied from Ref. [20].

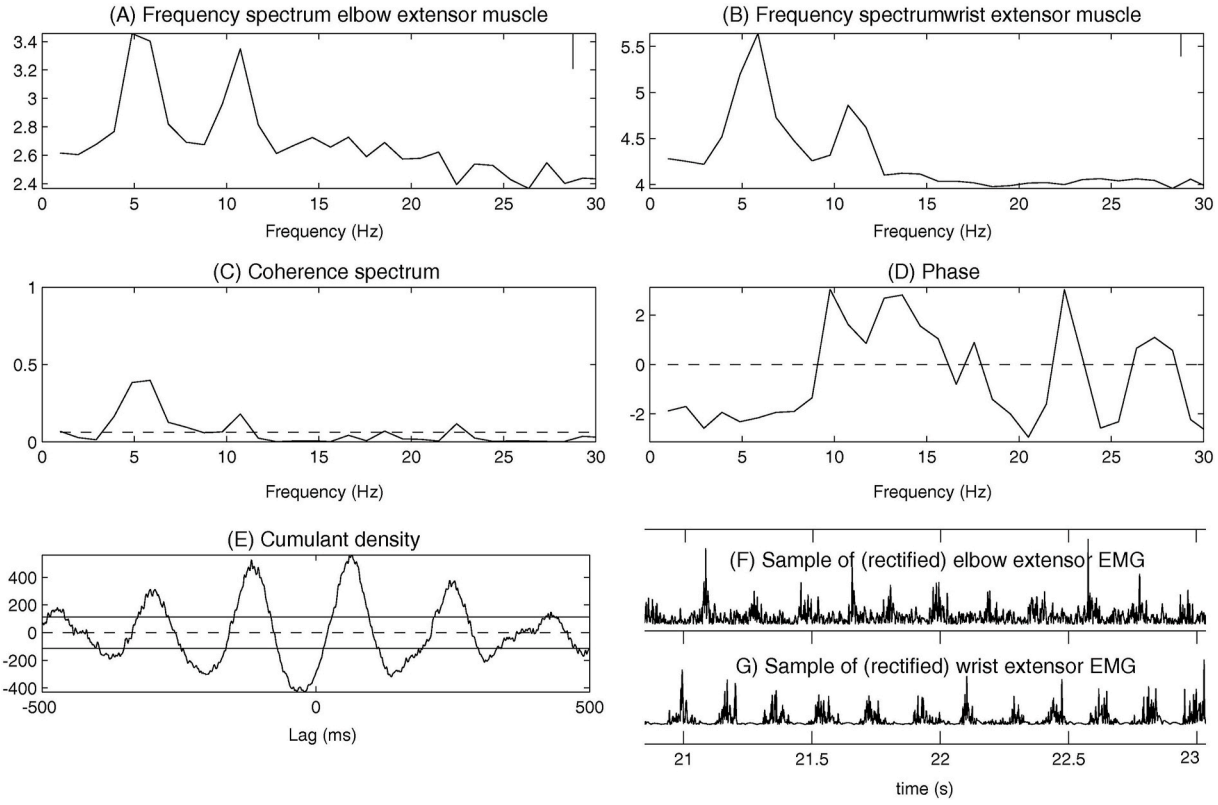

Fig. 3. Example of output of the coherence and cumulant analysis for an ET patient. Note the appearance of two peaks in the coherence spectrum (C), at the dominant tremor frequency and its first harmonic. The cumulant (E) shows a broad negative peak around zero for muscle pair including the wrist and elbow extensors and indicates an alternating pattern of muscle activity, as can be verified in the EMG (F and G). Figure is copied from Ref. [18].

3.2.4. *Diagnostic tools*

In recent years, tremor recognition by means of a **diagnostic tool** has been introduced in the field of tremor and it has been proposed by four papers of high quality for essential ($n = 1$), enhanced physiological ($n = 1$) and functional tremor ($n = 3$) (see Table 4). The diagnostic tool for essential tremor is based on the presence of six criteria and validated within a study population of 300 consecutively collected patients with postural tremor (97.7 % sensitivity, 82.3 % specificity) [36]. The scoring tool for enhanced physiological tremor consists of three criteria: the presence of at least two items indicated a diagnosis of EPT in a group of 210 patients with upper limb tremor (sensitivity 84 %, specificity 94 %) [17]. The three diagnostic tools proposed for discriminating functional from organic tremor vary. *Diagnostic tool A* contains six criteria based on basic and task-related features resulting in 10 points of which at least three points must be present for the diagnosis of functional tremor [26]. First based on 13 functional patients and 25 patients with an organic

Table 4
Diagnostic tools for essential tremor (ET), enhanced physiological tremor (EPT) and functional tremor (FT). The criteria and diagnostic values (sensitivity and specificity) are stated for each diagnostic tool.

Diagnostic tool for ET, (Gironell, 2004) [36]	
- Rhythmic bursts of postural tremor on EMG	AND
- Tremor frequency greater than or equal to 4 Hz	AND
- Rest tremor absent or, if present, frequency 1.5 Hz lower with respect to the postural tremor	AND
- Absence of latency from rest to postural position	AND
- Changes of the dominant frequency peak less or equal to 1 Hz after the weight load test	AND
- No changes in tremor amplitude after mental concentration	
All six criteria must be present for the neurophysiological diagnosis of ET. Sensitivity of 97.7 % and specificity 82.3 %	
Diagnostic tool for EPT (Van der Stouwe, 2016) [23]	
- Frequency decrease upon loading	
- Frequency >6 Hz	
- Frequency variability >1.75 Hz	
A score of ≥ 2 out of 3 positive tests suggests EPT Sensitivity of 84 % and specificity 94 %	
Diagnostic tool A for FT (Schwingenschuh, 2011 & 2016) [20,37]	
- Incorrect tapping performance at 1, 3, and 5 Hz	(max. 3 points)
- Entrainment, suppression, or pathological frequency shift at 1, 3, and 5 Hz	(max. 3 points)
- Pause or 50% reduction in amplitude or tremor with ballistic movements	(1 point)
- Tonic co-activation before tremor onset	(1 point)
- Coherence of bilateral tremors	(1 point)
- Increase of peak tremor frequency with loading	(1 point)
Cut-off score for a diagnosis of laboratory supported FT with 3 of 10 points. Sensitivity of 89.5 % and specificity of 95.9 %	
Diagnostic tool B for FT (Van der Stouwe, 2016) [23]	
- Frequency change during entrainment	
- Frequency change during distractibility	
- Frequency variability > 1.75 Hz	
A score of ≥ 2 out of 3 positive tests suggests FT Sensitivity of 100 % and specificity of 93 %	
Diagnostic tool C for FT (Kramer, 2018) [26] **– Wavelet coherence analysis**	
- Mean numbers of valleys >3.3; defined as the total number of upward crossing through the line of significant coherence	AND
- The percentage of time that significant coherence existed < 97 %	
Both calculated for the time that tremor activity was present in both EMG signals of the muscle pair Correctly classifies 83.7 % of all cases of organic and functional tremor	

tremor in 2011, the tool has been validated in 38 functional and 73 organic prospectively collected tremor patients in 2016 (sensitivity 89.5 %, specificity 95.9 %) [37]. *Diagnostic tool B* is based on 210 patients with upper limb tremor, and could diagnose functional tremor based on basic and task-related features in case two of three criteria were present (sensitivity 100 %, specificity 93 %) [17]. *Diagnostic tool C* is based on two features of wavelet coherence analysis and showed diagnostic accuracy of 83.7 % of all 98 cases of which 26 were diagnosed with functional tremor [20].

3.3. Myoclonus

The five papers that were included discuss cortical myoclonus, subcortical myoclonus and functional jerks.

3.3.1. Basic features

No basic features were compared in diagnostic test accuracy studies. The high diagnostic value of an **alternating** burst pattern in tremor versus a **synchronous burst pattern** in myoclonus has been described in expert opinion reviews [1]. In order to differentiate between clinical myoclonus syndromes, the threshold of 50 or 100 m s **burst duration** for *brief* cortical compared to *less brief* non-cortical myoclonic jerks has been implemented in the diagnostic neurophysiological criteria based on several case series [38–45]. However, the duration of orthostatic and peripheral myoclonic bursts also can be less than 100 m s [38,46].

3.3.2. Advanced analyses

In order to distinguish myoclonus subtypes, a simultaneous measurement of electroencephalography and electromyography is useful. **Jerk-locked back-averaging** has been studied to demonstrate a cortical correlate of myoclonic jerks and prove their cortical origin. A cortical correlate was found in 44–75 % of patients with cortical and none with subcortical or functional jerks [47] [–] [49]. A more advanced method to assess the cortical origin is **corticomuscular coherence** analysis, which was used in high-frequency myoclonus. A significant coherence between EEG and EMG of the intrinsic hand muscles was present in most patients with jerks due to a variety of non-progressive syndromes associated with cortical myoclonus, at a frequency of 14.4 Hz ± 2.6. Cortico-muscular coherence discriminated cortical myoclonus from healthy controls with a sensitivity of 83.3 % and specificity of 90 % [47]. Furthermore, the authors studied **intermuscular coherence** as a more simplistic measurement less influenced by signal artefacts than EEG-EMG, with even higher sensitivity (100 %) and specificity (95 %), to differentiate cortical myoclonus from healthy subjects [47]. We did not identify any papers comparing the results of inter- or cortico-muscular coherence analysis between cortical and sub-cortical myoclonus patients.

The **Bereitschaftspotential** is a slow rising potential seen in the EEG prior to a self-paced movement. A classical Bereitschaftspotential, identified by visual inspection, was identified in 47–86 % of patients with functional jerks and none with cortical or subcortical jerks [7,49,50]. The use of objective Bereitschaftspotential analysis, by means of automatic identification of the EEG deflection, showed similar sensitivity and specificity (51 % and 100 %) compared to the classical visual method (49 % and 100 %) [49]. Reduction of beta-low gamma oscillations prior to a self-paced movement is called **event related desynchronization**. Significant event related desynchronization was present in 62–65 % of patients with functional jerks and was not found in patients with organic myoclonic jerks [48] [–] [50]. Both objective Bereitschaftspotential and event related desynchronization showed 'good' *AUC-ROC* (i.e., *AUC* between 0.8 and 0.9) in discriminating functional from cortical myoclonus: combining both approaches resulted in an 'excellent' *AUC-ROC* [49].

3.4. Dystonia

We have included five papers focusing on differentiating muscles activity involved in clinical defined dystonic movements, such as cervical dystonia or myoclonus-dystonia, from muscle activity in healthy movements (i.e., dystonic versus non-dystonic muscles). The included papers did not study muscle activity pattern.

3.4.1. Basic features

Three patterns of muscle activity are used as diagnostic criteria for dystonic muscles: (1) tonic, an interference pattern with slight variation in amplitude and density, (2) phasic, synchronous bursts of activity of variable duration (>250 m s), (3) tremulous, rhythmic bursts with durations between 50 and 300 m s [51,52]. Furthermore, involuntary activation of contiguous muscles (i.e., **overflow**) and simultaneous contraction of agonist and antagonist muscles (i.e., **co-contraction**) are stated to be useful [51,53–56]. Overflow and co-contraction have been studied in ten patients with torsion dystonia, including focal, hemi, segmental, generalized distribution, compared with nine healthy controls [57]. During rapid elbow movements, co-contraction of the agonist (biceps) and antagonist (triceps) muscles and abnormal activation of the pectoralis major muscle were measured in an undefined proportion of the patients with help of EMG. This was not seen in healthy controls.

3.4.2. Advanced analyses

An **autospectrum** of needle EMG was studied in cervical dystonia patients compared to healthy controls. A significant peak at >10 Hz during sustained contraction of the m. Splenius capitis was not present in any of eight torticollis patients, while seven of eight healthy controls showed this phenomenon [58]. Even within-patient measurements show the presence of a peak in the 8–14 Hz frequency band during voluntary movement in 7 of 10 non-dystonic muscles compared to 2 of 9 dystonic muscles [59]. The use of autospectra for discriminating dystonic from non-dystonic muscles obtained a sensitivity of 88 % and specificity of 100 % in cervical dystonia patients [58].

Standard **intermuscular coherence** analysis has been used to differentiate dystonic from non-dystonic muscles. The diagnostic value of this analysis was found to be variable. A significant coherence peak within the 4–7 Hz band was seen between ipsilateral splenius capitis and contralateral sternocleidomastoid in 7 of 8 cervical dystonia patients opposed to 1 of 8 healthy controls [58]. This was confirmed in 7 of 8 other cervical dystonia patients and also present in the lower part of the leg of all ten patients diagnosed with DYT-*TOR1A* generalized mobile dystonia, but not in 11 patients with fixed dystonia, six with dystonia due to focal cerebral lesions and 15 healthy participants [58,60]. Contradictory, Tijssen et al. showed a significant peak in 8 of 10 healthy participants. The impact of an observed methodological difference, no transformation of raw EMG to TTL pulses before Fourier transformation, is unknown [58,59]. No peak was found in patients diagnosed with MYC/DYT-*SGCE* [61]. Although Tijssen et al. found no correlation between visible tremor in dystonia patients and the low frequency theta intermuscular coherence peak, two other studies found the significant peak to be present often in mobile dystonia [58] [–] [60].

3.5. Tics

One study compared the presence of Bereitschaftspotential in multiple jerky movement disorders: functional jerks, organic myoclonus and tics as part of Tourette syndrome. The classic Bereitschaftspotential, as described in section 3.3.0, was identified in a significantly larger proportion of functional jerks, 86 %, compared to 43 % of Tourette patients and none of patients with organic myoclonus. The proportion of Gilles de la Tourette patients in which a Bereitschaftspotential was found did not significantly differ from that of organic myoclonus. The onset of the Bereitschaftspotential was significantly earlier for functional myoclonus, starting on average 1.2 s prior to the EMG burst, compared to an onset of 0.9 s in tics [7].

4. Discussion

Here we present a systematic review on the diagnostic value of accelerometry and electromyography features in clinical practice for differentiating movement disorders and their clinical syndromes. A total of 38 papers were identified in which subtypes of tremor ($n = 27$), myoclonus ($n = 5$), and dystonia ($n = 5$) and tics ($n = 1$). None discussed ataxia or chorea.

Only one study directly compared movement disorders, comparing the Bereitschaftspotential in myoclonus and tics [7]. It could very well be that it is less difficult to distinguish between movement disorder phenotypes (e.g., tremor and myoclonus) than between clinical syndromes (e.g., essential tremor versus parkinsonian tremor) based on neurological examination alone, reducing the need for electrophysiological markers - however, in general movement disorder phenotype recognition has a poor interrater agreement [62,63]. The low number of included studies is due to the inclusion only of diagnostic test accuracy studies in which a comparison in neurophysiological features between groups has been made. Although numerous descriptive physiological and pathophysiological fundamental studies can support expert opinions ruling current practice, diagnostic test accuracy is preferred to substantiate diagnostic value.

Tremor is the movement disorder in which the application of neurophysiological features has been studied most. Researchers have foremost been interested in differentiating essential tremor from other clinical syndromes, mainly parkinsonian and dystonic tremor, and in differentiating functional from organic tremor. This interest could be explained by the relatively high incidence but broad clinical spectrum of both essential and functional tremor, which makes the clinical diagnosis difficult for physicians, necessitating additional diagnostic tools.

No single electrophysiological feature can be used to distinguish between all tremor subtypes. Fortunately, several diagnostic tools combining features have been created for the sole purpose to single out a specific tremor subtype, including functional, enhanced physiological and essential tremor. Independently, the basic and task-related features show great overlap between most clinical syndromes apart from the outliers enhanced physiological and rubral tremors. For the remaining tremor syndromes, including essential, parkinsonian, functional tremor and dystonic tremor syndromes, methods to detect frequency variability and advanced analyses have tried to resolve this issue. These analyses are often successful and accurate showing great promise for clinical utility, although the majority of studies have included and compared only two of these clinical tremor syndromes. This makes the overall diagnostic value of these advanced analyses difficult to interpret.

In **myoclonus** syndromes, advanced analyses are available to identify a cortical component preceding the jerk. Jerk-locked back-averaging can be used to confirm the cortical origin of jerks when visual inspection does not suffice. Its more advanced counterpart corticomuscular coherence can be used if the myoclonic jerks are high-frequent and rhythmic. If a functional myoclonic movement disorder is suspected, a Bereitschaftspotential is of good diagnostic value; especially with the addition of event related desynchronization. For both Bereitschaftspotential and event related desynchronization to be effective, a clear starting point for the burst or involuntary movement has to be present, making it less suitable for a high frequency functional movement disorder.

Dystonia has been studied in a limited amount of diagnostic test accuracy studies. Using an autospectrum with needle EMG, dystonic muscles can be identified with high sensitivity and specificity but this has only been studied in a low number of patients. Intermuscular coherence showed an inconsistent diagnostic value between multiple studies. Conclusively, these tests show promise for distinguishing dystonia from movements in healthy controls but should be validated in larger cohort studies.

No diagnostic test accuracy studies of high quality were found that discussed certain prominent neurophysiological phenomena such as synchronicity of bursts in myoclonus or tremor, the duration of burst in cortical myoclonus compared subcortical myoclonus, and the discriminative presence of co-contraction in dystonia. Although these phenomena are potentially and presumably characteristic for their movement disorder indicated by the high number of patients described in multiple case series, their diagnostic accuracy is currently unknown due to a lack of case-control studies. This example shows the need for diagnostic test accuracy studies to substantiate these phenomena's diagnostic values. In the meantime, interpretation of these phenomena should not be too stringent.

In conclusion, the accuracy of diagnostic neurophysiological tests in the field of hyperkinetic movement disorders using accelerometry and electromyography has most extensively been studied for differentiating between clinical tremor syndromes. With respect to myoclonus and dystonia syndromes, literature was rather limited. Overall, there is need to investigate the diagnostic accuracy of electrophysiology for hyperkinetic movement disorders.

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CRediT authorship contribution statement

S. van der Veen: Research project, Review, Critique, Writing – original draft. **M.R. Klamer:** Organization, Execution, Formal analysis, Review, Critique. **J.W.J. Elting:** Review, Critique. **J.H.T.M. Koelman:** Review, Critique. **A.M.M. van der Stouwe:** Conceptualization, Organization, Review, Critique. **M.A.J. Tijssen:** Conceptualization, Organization, Review, Critique.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.07.033.

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