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Research paper

Electrophysiological testing aids the diagnosis of tremor and myoclonus in clinically challenging patients

Cheryl S.J. Everlo [a,b,*], Jan Willem J. Elting [a,b], Marina A.J. Tijssen [a,b], A.M. Madelein van der Stouwe [a,b]

[a] Department of Neurology, University Medical Center Groningen, Groningen, the Netherlands
[b] Expertise Center Movement Disorders Groningen, University Medical Center Groningen (UMCG), Groningen, the Netherlands

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ABSTRACT

Objective: We investigated how clinical neurophysiological testing can help distinguish tremor and myoclonus and their subtypes.

Methods: We retrospectively analysed clinical and neurophysiological data from patients who had undergone polymyography (EMG + accelerometry) to diagnose suspected tremor or myoclonus. We show a systematic approach, which includes contraction pattern, rhythm regularity, burst duration and evidence of cortical drive.

Results: We detected 773 patients in our database, of which 556 patients were ultimately diagnosed with tremor (enhanced physiological tremor n = 169, functional tremor n = 140, essential tremor n = 90, parkinsonism associated tremor n = 64, cerebellar tremor n = 19, Holmes tremor n = 12, dystonic tremor n = 8, tremor not further specified n = 9), 140 with myoclonus and 23 with a combination of tremor and myoclonus. Polymyography confirmed the presumptive diagnosis in the majority of the patients and led to a change of diagnosis in 287 patients (37%). Conversions between diagnoses of tremor and myoclonus occurred most frequently between enhanced physiological tremor, essential tremor, functional tremor and cortical myoclonus.

Conclusions: Neurophysiology is a valuable additional tool in clinical practice to differentiate between tremor and myoclonus, and can guide towards a specific subtype.

Significance: We show how the stepwise neurophysiological approach used at our medical center aids the diagnosis of tremor versus myoclonus.

1. Introduction

Patients presenting with tremor are frequently seen by neurologists, as tremor is the most common movement disorder in adults (Louis and Ferreira, 2010). Tremor is defined as a rhythmic, involuntary, oscillatory movement of a body part over a joint (Bhatia et al., 2018). Despite this clear description, classification of the different types of tremor (e.g. enhanced physiologic tremor (EPT), essential tremor (ET), parkinsonism associated tremor (PT), dystonic tremor (DT), functional tremor (FT), etc) can be challenging. Furthermore, one of the most important differential diagnostic considerations in tremor is myoclonus. Myoclonus is defined by sudden, brief, shock-like, involuntary movement caused by muscular contraction (positive myoclonus) or inhibition (negative myoclonus) (Apartis, 2013). Although neurological examination can

provide information regarding frequency, regularity, amplitude and activating conditions of these involuntary movements, clinical distinction between subtypes of tremor and myoclonus can still be challenging in some cases. For example the clinical diagnostic accuracy for essential tremor is 63% at best (Jain et al., 2006). Besides that, patients presenting with an irregular or jerky tremor can be difficult to diagnose, as are patients with a proximal tremor, polyminimyoclonus or asterixis (Deuschl et al., 1998; Zutt et al., 2015). Differentiating between tremor and myoclonus is important as it guides further clinical decision making and treatment (Wardt et al., 2020; Zutt et al., 2015).

Electrophysiological investigations can be employed to support, clarify or distinguish clinical suspicion of various movement disorders. Polymyography, by which we mean a combination of electromyography and accelerometry, is frequently used to establish tremor. It can also be used to further define subtypes (van der Stouwe et al., 2016). Moreover, electrophysiological testing can help to determine myoclonus and subsequently subclassify myo-

* Corresponding author at: Department of Neurology, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.
  E-mail address: c.s.j.everlo@umcg.nl (C.S.J. Everlo).

clonus to its anatomical substrate (cortical, subcortical, spinal or peripheral) by combining poly-EMG and EEG (Zutt et al., 2018).

However, although polymyography is recommended when clinical distinction between tremor and myoclonus is difficult, the literature indicating *how* polymyography can distinguish these two movement disorders is limited. In this study, we report retrospectively on a large population of patients evaluated with polymyography for suspected tremor or myoclonus using a stepwise clinical neurophysiological approach, which we will illustrate with an illuminative case.

2. Material & methods

2.1. Patients

In this retrospective study, we examined the clinical neurophysiology database of the University Medical Center Groningen, a tertiary referral center, for patients who were evaluated using polymyography to diagnose suspected tremor or myoclonus. Data was collected between January 1st, 2008 and December 31, 2019. Patients were included when tremor and/or myoclonus were mentioned by the attending neurologist in the presumptive diagnosis. It is important to notice that these are all syndromic diagnoses, conform axis 1, rather than etiological diagnoses (Bhatia et al., 2018). Patients were excluded when their syndromic diagnosis, presumptive or final, was not specified, unclear or missing due to a lack of correspondence. Age at recording, sex, presumptive diagnosis, polymyography result and final diagnosis, after possible additional diagnostic tests, were extracted from the clinical records. The study was registered at the UMCG Research Register under study number 201900338. Whether patients objected to scientific use of their clinical data was checked by an official privacy officer at our institution and patients were excluded if so. Informed consent was obtained from the patients whose cases are used for illustration.

2.2. Polymyography

All recordings were performed following standardized polymyographic evaluation focused on tremor-like movement disorders. The movement disorder was evaluated at rest, during different postural positions, and while performing specific tasks (e.g. weight loading, pointing tasks, entrainment by tapping motions or distraction by performing a mental task (serial sevens)). Data were recorded using Brain RT software (OSG BVBA, Rumst, Belgium). Accelerometers were placed on either the index fingers or the dorsal side of both hands. Accelerometry was used to ana-

lyse frequency, using fast Fourier transformation. Surface EMG was recorded with Ag/AgCl surface electrodes placed over four muscle groups of the affected limb. Needle EMG does not typically play a role in our investigations of movement disorders patents. In some patients an electro-encephalogram (EEG) was immediately performed simultaneously, because myoclonus was suspected, in other cases it was performed additionally during a second visit. Videos were taken using an E-series Sony camera (SNC-EP580 1080p/30 FPS PTZ). The recordings were assessed and reported by one of two experienced clinical neurophysiologists based on continuous recordings of accelerometry, surface EMG, video and, if available, EEG.

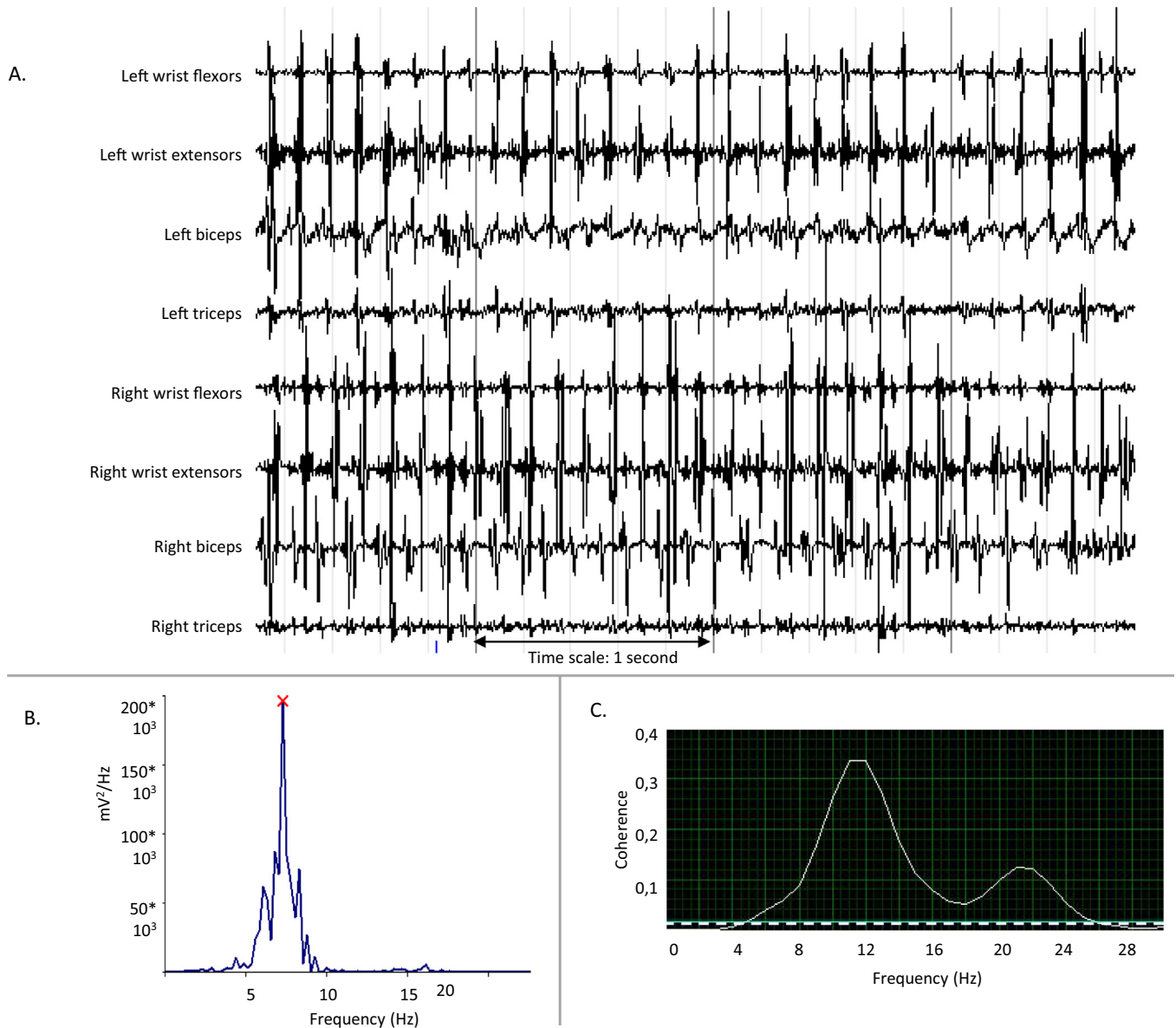### 2.3. Steps to distinguish myoclonus from tremor using polymyography

To indicate how clinical neurophysiologists at our centre arrive at a conclusion when differentiating tremor versus myoclonus using polymyography, we provide an overview of the diagnostic steps taken in Table 1. First of all, the agonist–antagonist contraction pattern is determined. Consistently synchronous discharges in agonists and antagonists indicate myoclonus, whereas tremor is presumed when alternating bursts are present (Fig. 1A). Note that the contraction pattern of a rest tremor in essential tremor is reported to be synchronous and that this characteristic is used in some clinics to differentiate it from a rest tremor in Parkinson disease (Nisticò et al., 2011). However, in our experience there will always be a moment of alternating contractions in tremor at some point during the registration. It should also be pointed out that co-contraction can be a feature of dystonia, in which case it consists of phasic, synchronous bursts of activity of variable duration (>250 ms) instead of the short bursts as seen in myoclonus (van der Veen et al., 2021). Secondly, regularity with which the movements are repeated is considered: an irregular pattern without a clear peak in the frequency spectrum and with high frequency variability fits with myoclonus; while a regular rhythm, a clear peak in the frequency spectrum and relatively low frequency variability are characteristics of tremor. (As a caveat, frequency variability > 1.75 Hz is possible and even has diagnostic value for EPT and FT versus other tremor syndromes (Schwingenschuh et al., 2016; van der Stouwe et al., 2016)). If at this point the movement disorder under investigation is definitely tremor, activating conditions and specific signs such as frequency change on loading of the affected limb or entrainment are investigated. Please see Table 1 of our previous publication for the core and supportive criteria used to differentiate between tremor subtypes at our center (van der Stouwe et al., 2016). If the possibility of a myoclonus remains, burst duration is determined, as this is used to localise the anatom-

Table 1

Stepwise approach to electrophysiological testing to differentiate myoclonus from tremor as used at the University Medical Center Groningen.

	Myoclonus	Tremor
1. Contraction pattern Determine the agonist–antagonist contraction pattern	Predominantly synchronous Never alternating	Predominantly alternating Sometimes synchronous
2. Rhythm Determine the regularity of the rhythm	Irregular No narrow peak in frequency spectrum High frequency variability	Regular Narrow peak in frequency spectrum Low frequency variability*
3. Bursts Determine the burst duration	<100 ms → cortical myoclonus, peripheral myoclonus>100 ms → subcortical myoclonus, spinal myoclonus	Tremor bursts will be dependent on tremor frequency: 1000/tremorfrequency = usually > 100 ms.
4. Cortical drive Determine if there is evidence for cortical myoclonus by EEG-EMG co-registration	Confirmative of cortical origin: • Jerk-locked back averaging • EEG-EMG coherenceSupportive of cortical origin: • Giant somatosensory evoked potentials • Enhanced long-latency reflexes (C-reflex)**	Not applicable.

*Note that tremor frequency variability > 1 Hz is possible in tremor, particularly in enhanced physiological tremor and functional tremor.
**Very rarely, a subcortico-cortical myoclonus can have enhanced latencies as well (i.e. Creutzfeldt-Jacob disease, limbic encephalitis).

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Fig. 1. Example of a patient with myoclonus (see clinical description in Box 1) A. Synchronous agonist–antagonist contraction pattern in both forearms, where two burst durations are distinguished (30–60 ms and 80–150 ms). B. Broad peak in the frequency spectrum between 5 and 10 Hz indicating an irregular rhythm. C. Significant EMG-EEG coherence. Dotted line indicates significant coherence at the given frequency.

ical substrate of myoclonus. Currently, there is consensus that cortical myoclonus bursts are shortest (<100 ms (Zutt et al., 2018) or even < 50 ms (Latorre et al., 2018; Shibasaki et al., 1978)), although evidence is lacking to support the exact cut-off point (van der Veen et al., 2021). Finally, in some cases, evidence of a cortically driven myoclonus is investigated by means of EEG-EMG co-registration (Fig. 1C). Jerk-locked back averaging, EMG-EEG coherence, giant somatosensory evoked potentials and enhanced long-latency reflexes (C-reflex) can all confirm a cortical origin of myoclonus (Grosse et al., 2003; Latorre et al., 2018; Shibasaki, 2012; Shibasaki and Hallett, 2005; van Rootselaar et al., 2005; Wilkins et al., 1985; Zutt et al., 2017).

2.4. Statistical analysis

Patient characteristics are described using means, standard deviations and percentages. To determine the influence of polymyography on diagnosis, we focused on the change of diagnosis in the diagnostic process by comparing the presumptive

diagnosis, the polymyography result and the final diagnosis, and report percentages of confirmation or change of diagnosis.

3. Results

3.1. Patient characteristics

In this study, 773 patients with suspected tremor or myoclonus were included, with a mean age of 49 years (range: 0–91 years, SD: 23). Of all patients, 52% were male and 48% female (Table 2). Below, we will discuss our results per diagnostic phase first, and then we will discuss the changes in diagnoses that occurred due to polymyography.

3.2. Presumptive diagnosis

The presumptive diagnosis (that is, the clinical diagnosis before polymyography) was tremor in 557 patients, divided into the following subtypes: EPT (n = 138), ET (n = 164), PT (n = 81), cerebellar

Table 2
Patient characteristics.

Characteristic	N (%)	
Total number of patients	773	
Males	400 (52%)	
Females	373 (48%)	
Age (in years)		
Mean/SD/Range	49/23/0-91	
Diagnosis	Presumptive diagnosis N (%)	Final diagnosis N (%)
Tremor	557 (72%)	556 (72%)
EPT	*138*	*169*
FT	*95*	*141*
ET	*164*	*90*
PT	*81*	*64*
CT	*15*	*19*
HT	*9*	*12*
DT	*21*	*8*
Multiple tremors	*15*	*44*
Tremor not further specified	*19*	*9*
Myoclonus	167 (22%)	140 (18%)
*Myoclonus**	*138*	*-*
Cortical myoclonus	*-*	*76*
Subcortical myoclonus	*-*	*9*
Peripheral myoclonus	*-*	*2*
Cortical and subcortical myoclonus	*-*	*2*
Functional myoclonus	*29*	*40*
Not specified	*-*	*11*
Other	49 (6%)	77 (10%)
Tremor + myoclonus	*16*	*23*
Functional movement disorder	*13*	*15*
Chorea	*-*	*12*
Remaining	*20*	*27*

SD: standard deviation. EPT: enhanced physiological tremor, FT: functional tremor, ET: essential tremor, PT: parkinsonism associated tremor, CT: cerebellar outflow tremor, HT: Holmes tremor, DT: dystonic tremor. * total of the following myoclonus subtypes: cortical, subcortical, peripheral, not specified.

outflow tremor (CT, n = 15), Holmes tremor (HT, n = 9), DT (n = 21), multiple tremors (n = 15), FT (n = 95) and tremor not further specified (n = 19). Myoclonus was the presumptive diagnosis in 167 patients, of which 29 were suspected to have a functional myoclonus. Thirteen patients were thought to suffer from a tremulous/jerky functional movement disorder. In sixteen patients, determining the clinical diagnosis was challenging and both tremor and myoclonus were mentioned as presumptive diagnosis. The presumptive diagnosis of the remaining 20 patients varied from structural lesion to dystonia and tics (Table 2).

3.3. Final diagnosis

Tremor was the final diagnosis in 556 patients, divided into the following subtypes: EPT (n = 169), FT (n = 141), ET (n = 90), PT (n = 64), CT (n = 19), HT (n = 12), DT (n = 8), multiple tremors (n = 44) and tremor not further specified (n = 9). The final diagnosis was myoclonus in 140 patients, subclassified in to cortical myoclonus (n = 76), subcortical myoclonus (n = 9), peripheral myoclonus (n = 2), cortical and subcortical myoclonus (n = 2), functional myoclonus (n = 40) and not specified (n = 11). The final diagnoses of the remaining 77 patients were tremor plus myoclonus (n = 23), functional movement disorder (n = 15), chorea (n = 12), and a remaining group of 27 patients (Table 2).

3.4. Changes in diagnosis

While polymyography confirmed the presumptive diagnosis in 54% (n = 420) patients (presumptive diagnosis = polymyography result = final diagnosis), it led to a change in diagnosis in 37%

(n = 286) patients (presumptive diagnosis ≠ polymyography result = final diagnosis). In 30 patients (4%) there was a change in diagnosis during the process, but polymyography had not influenced this change. In 37 patients (5%) there was no change in diagnosis despite the polymyography result, mostly due to additional laboratory or imaging results, or due to the clinical view of the consulting neurologist. We have depicted all changes in diagnosis (n = 316) in Fig. 2. A few observations stand out. In absolute numbers, when the presumptive diagnosis changed, the conversions from essential tremor to enhanced physiological tremor are most numerous (41 out of 89 presumptive ET diagnoses changed to the final diagnosis of EPT (47%)). Moreover, frequent changes between functional movement disorders to enhanced physiological tremor occurred (7 out of 16 presumptive FMD diagnoses changed to EPT (44%), and 13 out of 44 vice versa (30%)). Similarly, presumptive diagnoses of myoclonus were reconsidered as functional movement disorders quite frequently (in 14 out of 56 presumptive myoclonus diagnoses (24%)). Presumptive diagnoses of myoclonus changed into final diagnoses of enhanced physiological tremor relatively frequently (7 out of 56 presumptive myoclonus diagnoses changed to EPT (12%)).

3.4.1. Unexpected changes

Most of the changes were in line with the clinician's expectations as reflected by their initial differential diagnosis, but there were also some unexpected changes. On the one hand, in 17 of the 158 patients for whom only myoclonus was listed as presumptive diagnosis, it was entirely unexpected that tremor was the final diagnosis. The majority of these tremor diagnoses were EPT (35%) or FT (18%). HT, DT, PT and ET were smaller groups (all 6%) (Fig. 3A). In all cases polymyography contributed to this change of diagnosis. On the other hand, in 13 of the 526 patients with tremor as presumptive diagnosis, the final diagnosis unexpectedly included myoclonus. Initially, most of these patients were thought to suffer from ET (n = 5) or EPT (n = 4). In the majority of these cases of unexpected myoclonus, the anatomical subtype was cortical myoclonus (Fig. 3B). In all these cases the polymyography result led to the change of diagnosis.

3.4.2. Polymyography results in clinically difficult cases

As a subanalysis, we focus on the group of clinically difficult cases, that is, the 57 patients in whom the neurologist hesitated between tremor and myoclonus based on their clinical consultation, as was reflected by the inclusion of both in their differential diagnosis. In such cases, polymyography was requested with the question "tremor or myoclonus?". Polymyographic evaluation indicated tremor in 31 patients (56%), myoclonus in 12 cases (22%), tremor and myoclonus in 8 patients (15%), mixed functional movement disorder in 2 patients (4%), and a different or no movement disorder in 4 patients (7%) (Fig. 4A). To be more specific, the most common tremor diagnosis was EPT (45%) (Fig. 4B). The most likely anatomical substrate of myoclonus was cortical in half of the cases (Fig. 4C). The group "combined tremor and myoclonus" mostly consists of mixed functional movement disorders or a combination of an enhanced physiological tremor with myoclonus.

4. Discussion

In this study, we retrospectively investigated how clinical electrophysiological testing can help in distinguishing between tremor and myoclonus, which we illustrated with two illustrative cases (Box 1 and 2, Figs. 1 and 5). We evaluated the diagnostic process in a large population of 773 patients with suspected tremor or myoclonus to pinpoint where the clinical challenges are, or in other words: in which cases misdiagnosis happens most easily.
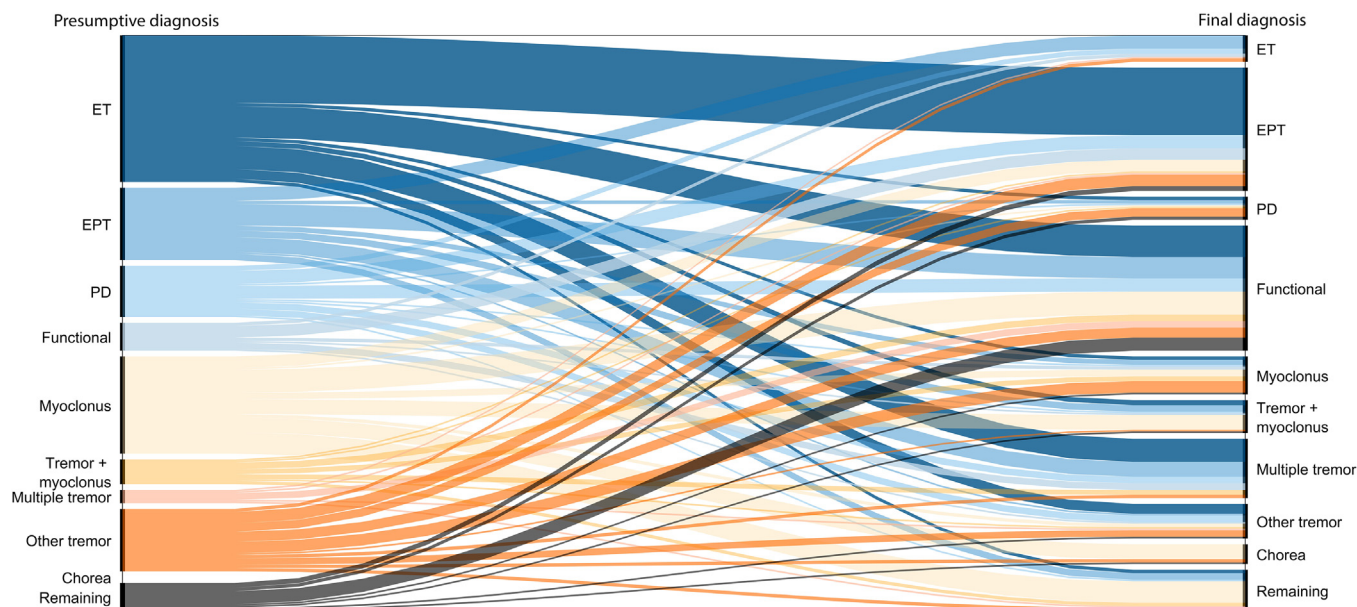
Fig. 2. Changes between presumptive (left) and final (right) diagnosis (N = 316). Essential tremor (ET), enhanced physiological tremor (EPT) and parkinsonism associated tremor (PT).
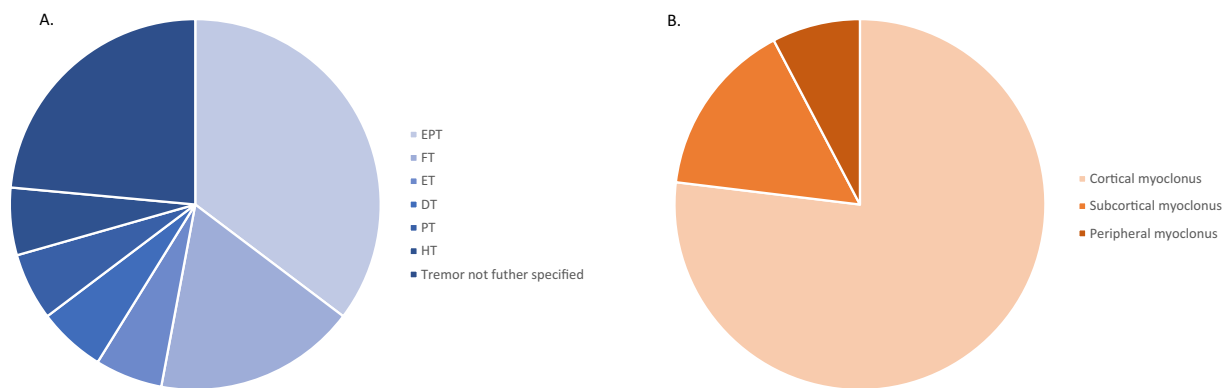

Fig. 3. A. Tremor subtypes as unexpected final diagnosis when myoclonus was the presumptive diagnosis (n = 17). The presumptive myoclonus diagnosis was not specified into a likely anatomical substrate in most cases and is therefore not reported. B. Myoclonus subtypes as unexpected final diagnosis when tremor was the presumptive diagnosis tremor (n = 13). Presumptive tremor diagnoses were ET (n = 5), EPT (n = 4), PT (n = 2) and tremor not further specified (n = 2).

First, we found that in the majority of all cases the presumptive diagnosis was confirmed by polymyography, whereas in 37% of all cases polymyography changed the diagnosis during the diagnostic pathway. While, it is important to realize that other diagnostic tests can also influence the final diagnosis, an important lesson that is illustrated by the case we describe is that clinical electrophysiological characterization of a clinically challenging movement disorder can guide further clinical decision making (Wardt et al., 2020): in this case, F-DOPA-PET would not have been necessary if the movement disorder had been established as polyminimyoclonus rather than tremor. All in all, our findings underline there is a definite place for clinical neurophysiologic assessment in the diagnostic workup of movement disorder patients.

Secondly, we saw some interesting patterns emerge regarding the confusion or misdiagnosis of tremor versus myoclonus. When tremor is the final diagnosis while myoclonus was clinically suspected, EPT and FT are the most common subtypes. Similarly, when myoclonus is the unexpected final diagnosis since tremor was clin-

ically suspected, ET and EPT are the most common presumptive diagnostic considerations. In these patients, the anatomical substrate of the final diagnosis which was seen most frequently is cortical myoclonus. If the final diagnosis showed a combined tremor and myoclonus, this mostly consisted of functional movement disorders or a combination of EPT and myoclonus (not further defined into its anatomical substrate). Reasons we suspect EPT, ET and FT are the tremor syndromes most easily mistaken for (cortical) myoclonus (and vice versa) are the high variability of their tremor frequencies and the overall variability in clinical appearance of FT (van der Stouwe et al., 2016), as well as the distal aspect of EPT that may clinically be mistaken for cortical myoclonus (Raethjen et al., 2000; Zutt et al., 2015). Our findings underline that EPT, ET, (cortical) myoclonus and a functional movement disorder belong in the same differential diagnosis.

We have shown how polymyography is used for the distinction of tremor versus myoclonus in our medical center, in Table 1. We realise that not all of the steps we describe can be substantiated
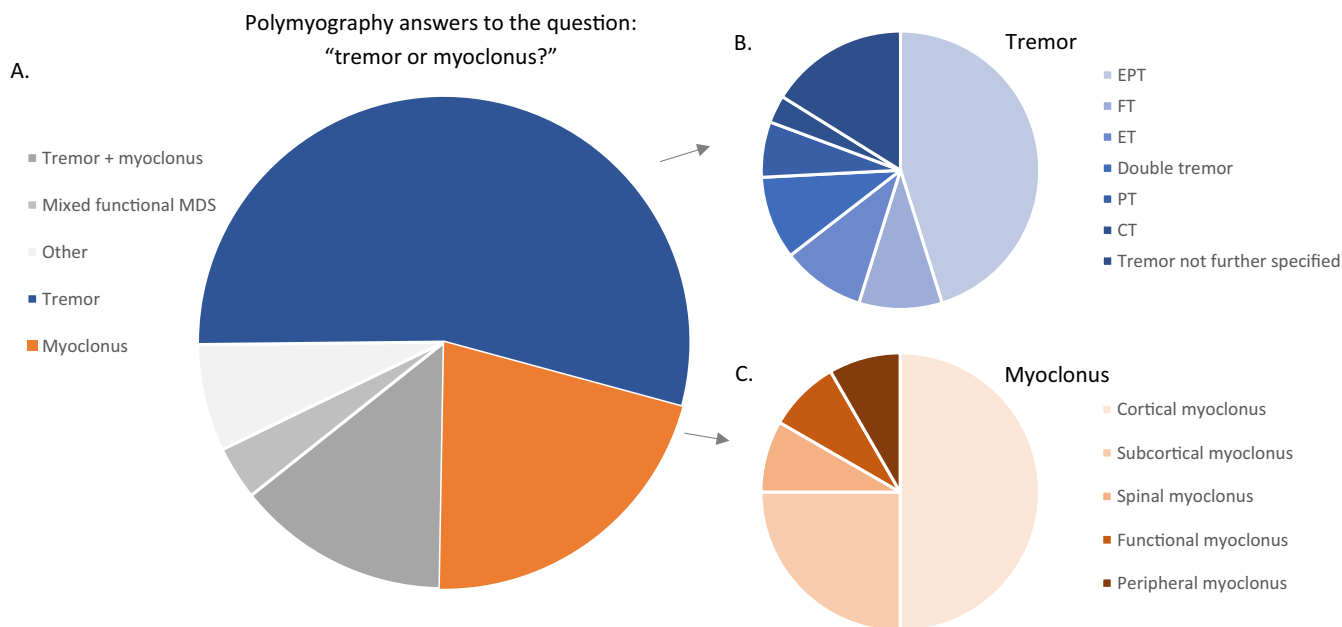
Fig. 4. A. Polymyography results when the clinician requested polymyography with the question "tremor or myoclonus?" (n = 57). B. Tremor subtypes (EPT n = 14, FT n = 3, ET n = 3, Double tremor n = 3, PT n = 2, CT n = 1, tremor not further specified n = 5). N = 36 because in three patients polymyography revealed two different tremors. C. Myoclonus split into its most likely anatomical substrates (cortical myoclonus n = 6, subcortical myoclonus n = 3, spinal myoclonus n = 1, functional myoclonus n = 1, peripheral myoclonus n = 1).

by high level evidence, nevertheless, based on the available evidence and expert opinion of our clinical neurophysiologists we find this to be a workable approach. To our knowledge, no other electrophysiological criteria for distinction have been published. This stepwise approach can be compared to or incorporated at other medical centers.

4.1. Limitations

As with the majority of studies, the design of this study is subject to limitations. Here, limitations relate to our diagnostic "gold standard", which is the final diagnosis. Naturally, patients can be misdiagnosed. However, as this is a tertiary referral center for movement disorders and patients are thus seen by experienced neurologists and clinical neurophysiologists, we are confident that misdiagnoses were at a minimum. Moreover, there is a risk of circularity when retrospectively investigating the parameters on which diagnoses are made, as these parameters themselves helped to establish the diagnosis. This risk is unavoidable in retrospective studies such as this, and therefore a prospective, if possible, even blinded, study would be of additional value. Nevertheless, we believe our study is a useful contribution to the literature as it reports on a large, general population of patients suspected to have tremor or myoclonus, that has not been restricted to age or subtype. Results can therefore be related to the actual clinical setting of a patient presenting with a 'hard-to-diagnose' movement disorder, either tremor or myoclonus.

4.2. Conclusions

In this article we show how polymyography can be used to differentiate between tremor and myoclonus. It is particularly helpful where clinical examination alone has its pitfalls: in the distinction between enhanced physiological tremor, essential tremor, func-

tional tremor and (cortical) myoclonus. In a stepwise approach to electrophysiological testing, look for myoclonus characteristics such as a synchronous contraction pattern and an irregular rhythm, and use EMG burst durations and signs of cortical drive when combined with EEG. With these steps, neurologists and clinical neurophysiologists are provided with a valuable tool to differentiate between tremor and myoclonus.

Box 1. Illustrative case 1.

A 72-year-old woman was referred to our medical center with symptoms suspicious for Parkinson's disease. She had an extensive medical history and took 18 drugs (including amiodarone, oxycodone and clomipramine). For six months, she had suffered from a largely symmetrical, progressive tremor of her arms and legs. She had noticed some cognitive slowing and had mild memory complaints. Neurological examination revealed a postural, delicate, high frequency, distal tremor of both hands, legs and around her mouth. Grade 1 rigidity and possible subtle bradykinesia was found, while her gait was normal. Because Parkinson's disease was suspected, an F-DOPA-PET-scan was done but did not reveal the expected presynaptic dopaminergic defect: therefore, a polymyography was performed (Fig. 1). During the polymyography, a predominantly synchronous contraction pattern of agonists and antagonists was seen, indicating myoclonus rather than tremor. This was supported by the irregular rhythm and variable frequency (6.1–8.3 Hz). Burst duration was never longer than 100 ms, implicating a cortical origin of the myoclonus. This cortical substrate was confirmed by the existence of EEG-EMG coherence. A cortical polyminimyoclonus was the final diagnosis, illustrating how electrophysiological testing led to this patient's diagnosis of myoclonus rather than the originally suspected parkinsonism associated tremor.
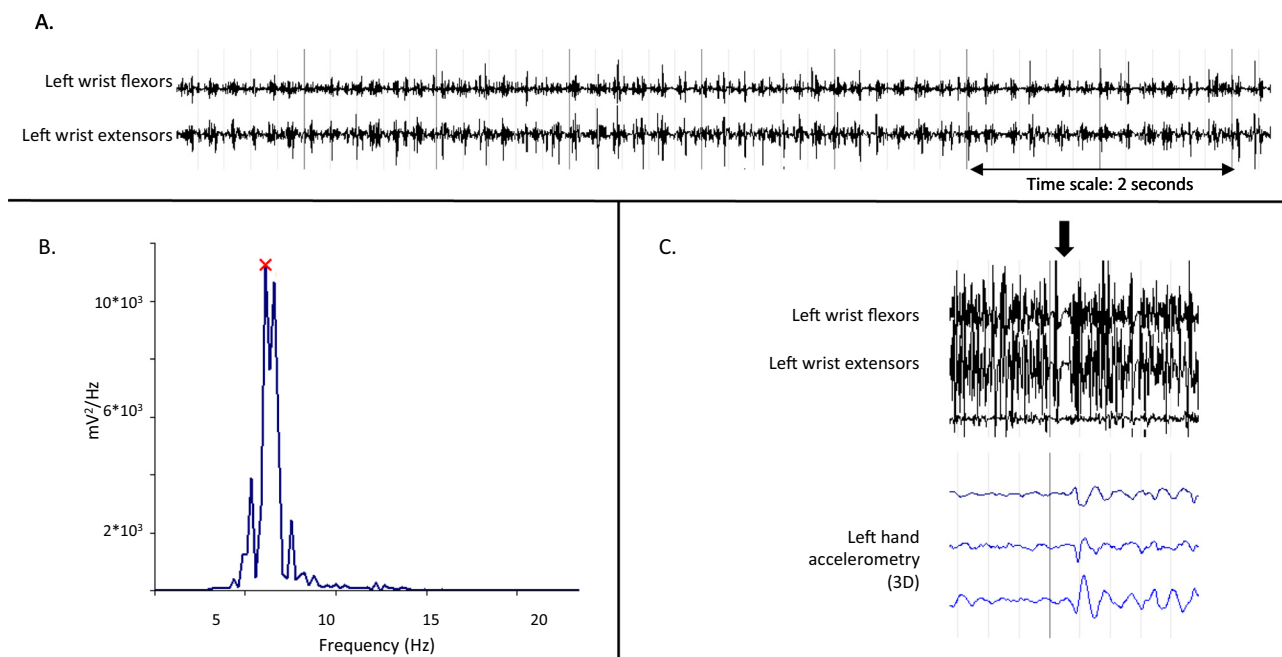
Fig. 5. Example of a patient with myoclonus: illustrative case 2. A) Synchronous agonist–antagonist contraction pattern in the left forearm (burst duration was highly variable between 40 and 100 ms). B) Broad peak in the accelerometry frequency spectrum between 4 and 8 Hz indicating an irregular rhythm. C) Negative myoclonus, as indicated by the arrow: a brief loss of muscle tone, followed by a brisk movement as can be seen in the accelerometry trace. This negative myoclonus could be verified in the simultaneously recorded video (not shown).

Box 2. Illustrative case 2.

A 19-year-old man presented with tremor and muscle cramps, present since a couple of years, that affected his hands, arms and legs. His symptoms worsened at the end of the day and after exercise, and were alleviated by alcohol consumption and sporadic use of propranolol. On neurological examination, a postural tremor was found, which increased after sustained pinching and had a subtle irregular or even jerky quality. Clinically, the differential diagnosis included enhanced physiological or essential tremor and myoclonus or myoclonus dystonia. Polymyography was performed to help make the distinction (Fig. 5). The contraction pattern was synchronous throughout the registration, in line with a diagnosis of myoclonus rather than tremor. With regard to burst duration, both subcortical (low frequency, broad EMG bursts (80–150 ms)) and cortical (high frequency, narrow EMG bursts (30–60 ms)) were present. Cortical drive was confirmed by means of back-averaging and EMG-EEG coherence analysis. This case illustrates how polymyography can enable the diagnosis of myoclonus, in a patient whose movement disorder is clinically indistinguishable from tremor. As there was a family history of similar symptoms, genetic testing was performed and revealed a SGCE mutation, fitting with a diagnosis of myoclonus dystonia.

5. Authors' roles

Research and project conception (C.S.J.E., A.M.M.S., J.W.E., M.A.J.T.), organization (C.S.J.E., A.M.M.S.), execution (C.S.J.E.), manuscript preparation (C.S.J.E., A.M.M.S.), review and critique (J.W.E., M.A.J.T.).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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