Machine learning aided classification of tremor in multiple sclerosis

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Summary

Background Tremors are frequent and disabling in people with multiple sclerosis (MS). Characteristic tremor frequencies in MS have a broad distribution range (1–10 Hz), which confounds the diagnostic from other forms of tremors. In this study, we propose a classification method for distinguishing MS tremors from other forms of cerebellar tremors.

Methods Electromyogram (EMG), accelerometer and clinical data were obtained from a total of 120 [40 MS, 41 essential tremor (ET) and 39 Parkinson's disease (PD)] subjects. The proposed method - Soft Decision Wavelet Decomposition (SDWD) - was used to compute power spectral densities and receiver operating characteristic (ROC) analysis was performed for the automatic classification of the tremors. Association between the spectral features and clinical features (FTM - Fahn-Tolosa-Marin scale, UPDRS - Unified Parkinson's Disease Rating Scale), was assessed using a support vector regression (SVR) model.

Findings Our developed analytical framework achieved an accuracy of up to 91.67% using accelerometer data and up to 91.60% using EMG signals for the differentiation of MS tremors and the tremors from ET and PD. In addition, SVR further revealed strong significant correlations between the selected discriminators and the clinical scores.

Interpretation The proposed method, with high classification accuracy and strong correlations of these features to clinical outcomes, has clearly demonstrated the potential to complement the existing tremor-diagnostic approach in MS patients.

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Keywords: Multiple sclerosis tremor; Essential tremor; Parkinson's disease tremor; Electromyogram; Accelerometer

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Introduction

Multiple sclerosis (MS) is a debilitating neuro-inflammatory and degenerative disease of the central nervous system with focal lesions to grey and white matter and evolving cerebral networks dysfunction.[1] Tremor, characterized by the uncontrolled rhythmic movement of a body part with varying frequency and amplitude, is a common symptom affecting around half (47.5%) of the MS patients.[2,3] The most frequently observed tremor

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Research in context

Evidence before this study

Tremor is a common symptom affecting around half of the Multiple Sclerosis (MS) patients. The most frequently observed tremor types in MS are cerebellar tremors which overlaps with other tremor types like Essential tremor (ET) and Parkinsonian tremor (PT). Discrimination between these tremor types which all have the basis in dysfunction of the cerebellar system is a challenge not only for diagnostic purpose but also for having insight into the mechanisms of disability and neurobiological underpinnings. Previously, varying symptoms including measure of acquired ataxia, the degree of disability etc. caused by the disease have been investigated to estimate the scale of ailment. Several clinical and neurophysiological methods have been employed in the assessment of MS tremor, eg. finger-to-nose task, spiral drawing, handwriting and visual tracking or more complex accelerometric and EMG techniques. However, none of these measures of ataxia or the clinical assessments have provided consensus in the clinical routine or have enabled us in detangling different tremorgenesis or its underlying neural mechanism.

Added value of this study

The clinical neurophysiology of tremor can be assessed by obtaining various properties of the signals recorded using accelerometric (ACC) and electromyographic (EMG) techniques. Even though previous studies have computed several different properties using various algorithms - e.g. time-domain, frequency-domain, time-frequency and nonlinear analysis, the challenges remain for each of these methods. Here we utilize a technique - Soft Decision Wavelet Decomposition (SDWD) which we previously shown to effectively discriminate ET and PT, for the classification of MS tremor using both ACC and EMG signal. This proposed technique not only facilitates a method for clinical diagnostic crucial for the timely clinical intervention to slow the disease progression but also provides an insight in the neurobiology of the MS tremor and it's distinction from PD and ET.

Implications of all the available evidence

This study further solidifies the evidence that the fundamental tremor frequency and their harmonics are distinct oscillatory activity rather than pure harmonic frequencies due to waveform-characteristics. Moreover, the method able to discriminate tremor only using peripheral signals could further complement other diagnostic criteria for characterizing tremor in MS patients presently used in the clinical routine.

types in MS are intention (cerebellar) and postural tremors, with most of the patients experiencing them to different extent within five years of diagnosis.[4,5] The common body parts affected are the upper and lower extremities, head, trunk and vocal cords.[6,7] MS tremor is classically attributed to abundance of mostly brain stem, cerebellum or cerebellar peduncles lesions, with intensity of the tremor shown to be correlated with the number of lesions or its functional connections.[8–10] However, recent work further evidenced the inflammatory damage to the cerebello-thalamic and cortico-thalamic pathways, that might play an important role for tremor generation.[10,11] Specific frequency patterns have been postulated for tremor symptoms, while its often diverse and broadly ranges from 2.5 to 7.0 Hz predominantly for postural or intention tremor or even higher.[12,13]

The other common type of tremor which has cerebellar origins is essential tremor (ET).[14] The action evoked involuntary movement,[15] being the distinguishing feature of this type of tremor, is exhibited during voluntary movement of the muscle and the frequency ranges from 4 to 8 Hz.[16] ET is a pathological tremor and its cause is reported to be degeneration of cerebellum.[17] Similarly, parkinsonian tremor (PT), a characteristic of rest tremor in Parkinson's disease (PD), is another highly prevalent tremor whose frequency ranges between 4 and 6 Hz.[18] The movement of index finger and thumb together mimicking so-called pill-rolling motion is a distinct characteristic of this tremor[16] which ensues when muscles are at rest and supported against gravity.[19] Moreover, previous studies have indicated the cerebellar involvement in the tremorogenesis of PT as well.[20–22]

The description of these tremor types itself noticeably depicts the difficulty a clinician is confronted with in assessing MS tremor due to the variability and overlap with other tremor types. The measure of acquired ataxia, the degree of disability, in particular the lack of coordination in speech, walk, and balance caused by the disease can be used to estimate the scale of ailment.[23] However, these measures of ataxia are not enough for identification of the tremor type as the overlapping frequency range, etiology and the involved body parts make it an difficult enervating clinical assessment to undertake. Several clinical and neurophysiological methods have been employed in the assessment of MS tremor, simple neurological tasks like finger-to-nose task, spiral drawing, handwriting and visual tracking or more complex accelerometric and EMG techniques, Stewart - Holmes maneuver and digitized spirals.[24–27] Additionally, several tremor-rating scores are in use, like Bain Score for Tremor Severity (BSTS), Tremor and Coordination Scale (TACS), Fahn Tremor Rating Scale (FTRS) and Multidimensional Assessment of Tremor (MAT).[24,28–30] However, despite all these methods and tools, there is no unified rating score or consensus in the clinical routine for quantifying the MS tremor.

The clinical neurophysiology of tremor can be assessed by analyzing the signals recorded using Accelerometric (ACC) and Electromyographic (EMG)

	Patients	MS	PD	ET
Trial Data	Number	20	19	21
	Age: mean (range)	52.5 (35−84) yrs.	64.5 (40−90) yrs.	63.2 (27−94) yrs.
	Sex	10 M, 10 F	11 M, 8 F	12 M, 9 F
Test Data	Number	20	20	20
	Age: mean (range)	55.7 (43−79) yrs.	68.2 (52−85) yrs.	64.5 (32−86) yrs.
	Sex	7 M, 13 F	12 M, 8 F	11 M, 9 F
Clinical Scores (Mean ± SD)		3.54 ± 1.62 (FTM)	5.86 ± 2.76 (UPDRS- III)	9.42 ± 3.56 (FTM)

***Table 1*: Demographic details and summary of clinical parameters of all patients used in the study. Here, M - Male, F - Female, yrs. - years, MS - Multiple Sclerosis, PD - Parkinson's' disease and ET - Essential tremor, FTM - Fahn-Tolosa-Marin, UPDRS-III - Unified Parkinson's Disease Rating Scale, motor examination sub-score.**

techniques.[31] This analysis can be executed using different algorithms - namely time-domain,[32] frequency-domain,[33] time-frequency[34] and nonlinear analysis.[35] The time-domain methods for identification of tremor frequencies are particularly challenging in the case of EMG signal, which is comprised of numerous frequencies.[36] A better approach is to transform the signal into frequency domain by using the Fast Fourier Transform (FFT) technique.[37] However, a shortcoming of FFT-based methods is the assumption that the signal is stationary, which normally is not the case for physiological signals. In addition, they have limited time-frequency resolution and cannot distinguish between involuntary tremor and voluntary movements if their spectra overlap.[38] The Soft Decision Wavelet Decomposition (SDWD) method is an effective technique of wavelet transformation to overcome these limitations in analysing nonstationary signals obtained from neurological tremors.[39] This technique describes the signal as a combination of different functions of transient elements.[40] In our previous studies, we demonstrated that this method is able to discriminate between PT and ET with high classification accuracy of over 85% using both ACC and EMG signals.[41,42] Here, we propose this technique for the classification of MS tremor to Essential or Parkinsonian tremor which would facilitate an earlier diagnosis of MS, which is crucial for the timely clinical intervention to slow the disease progression.[43]

Methods

Data acquisition

Electromyogram (EMG), accelerometer (ACC) and clinical data were obtained from a total of 120 subjects encompassing 40 relapsing-remitting MS patients [mean (range) age: 52.5 (35−84) years], 41 ET patients [mean (range) age: 63.2 (27−94) years] and 39 PD patients [mean (range) age: 64.5 (40−90) years]. The diagnoses were confirmed by an experienced neurologist on established clinical standards.[44] The data were recorded for the diagnostic purpose at the Department of Neurology at University of Kiel, Germany. Further demographic details along with their clinical scores are shown in Table 1.

The data recording conditions were set to be uniform for all three groups. During the acquisition, the patients were asked to sit in an armchair with comfortable posture. The postural tremor was recorded from the more affected side, while subjects extended their hands and fingers in parallel with the resting forearm. The other types of tremors also found in MS patients (intention and rest tremor) were not evaluated in this study due to their limited added diagnostic value. Tremor was recorded for a period of 30 s in this posture where the hand was held against gravity. An accelerometer weighing 2 g was attached to the dorsum of the affected hand in the middle of the third metacarpal bone during the recording. For EMG, two electrodes were used, placed at flexor (EMG1) and extensor (EMG2) muscles, respectively. It was ensured that the EMG electrodes were placed closer to motor points of the ulnar part of the hand. All data were recorded at a sampling rate of 800 Hz and all EMG data were band-pass filtered between 50 and 350 Hz and full-wave rectified.[41]

Ethics

All patients gave written informed consent to be part of this research and the study protocols were approved by the local ethics committee of the University Hospital Schleswig Holstein, Kiel, Germany (reference number: A 143/13).

Data analysis

Data analysis was performed within the framework of the Soft Decision Wavelet Decomposition (SDWD) technique to estimate the power spectral density (PSD) as detailed in the previous studies.[45,46] Briefly, at the first step the signal is decomposed using a selected wavelet filter into two (low- and high-pass) sub-bands. All possible branches of this decomposition (further 2^m sub-bands) were obtained by choosing a parameter 'm' (in

this case 8) as per frequency resolution. A probability measure was assigned to each branch in the first decomposition (frequency sub-band) estimating how much information (power) is contained in each sub-band in relation to the total information (power). For each subsequent stage of decomposition, the probability measure of the resulting sub-bands was made equal to the product of the previous branch probabilities and the conditional probability. These probabilities derived from the estimator are interpreted as an approximate measure of PSD of the signal. Different measures of obtained PSD are used for the quantification between different tremors as mentioned in previous studies.[41,47]

For the classification, the recorded data were divided into training and testing sets with each subject randomly assigned to a set. The principle being: obtaining the desired features from the training set and checking the performance in the testing set. The training set consists of data from 20 MS, 21 ET and 19 PD patients, while the testing set consists of the data from the remaining 20 MS, 20 ET and 20 PD patients.

The SDWD algorithm was first applied to the ACC data of all subjects in the training set using 8-band decomposition to obtain 256 bands each covering 1.56 Hz (400/256). Among all the obtained bands, the first 6 bands B1 (0–1.56 Hz) to B6 (7.81–9.37 Hz) were of interest as the frequency ranges of all three tremor types fall within these bands. The spectral features that efficiently distinguish (discrimination factor) the MS tremor from ET and PT were estimated for all subjects. For this study, we included spectral measures of the obtained PSD as the discrimination factor. To set the best threshold on the discrimination factor under investigation, the threshold value was estimated analytically by evaluating the Receiver Operating Characteristics (ROC), selecting the optimal compromise between specificity and sensitivity. The obtained optimal threshold was then used to discriminate the tremors among two groups in the test data. The same procedure was repeated for the data obtained from EMG1 and EMG2. Finally, voting between the discrimination results of accelerometer, EMG1 and EMG2 was applied. The voting method is based on the binary classification of subjects to increase evaluation efficiency. For a particular datapoint to be assigned to a group, it needs to be classified in that category two times or more. The voting criterion employing different characteristics for sensitivity and specificity of tremor was reported previously.[48]

Statistics

To validate the significance of these discriminators, we further applied a support vector machine analysis to predict the clinical scores used in the diagnostic criteria for migraineurs. The Support Vector Regression (SVR)[49] was applied representing a machine–learning–based multiple regression method that could associate the observed and trained values and present the regression coefficient for the accuracy of the prediction. We used clinical features, Fahn-Tolosa-Marin (FTM) scale[50] in the case of ET and MS, and Unified Parkinson's Disease Rating Scale - Motor Examination sub-score (UPDRS-III)[51] for PD patients, as a dependent variable and SDWD-based discriminators as independent variables. The regression coefficient of 0.5 is considered a borderline significant result.

Statistical notes. Sample size of the study was determined by the availability of the data after quality control that were recorded for the diagnostic purpose at the Department of Neurology at University of Kiel, Germany. The group determination and inclusion and exclusion criteria was based on the clinical diagnosis from neurologists (co-authors: GD, SG).

Role of funders

The funders had no role or influence in study design, data collection, analyses, interpretation, or writing of the manuscript. The corresponding author (M. Muthuraman) had full access to all the data and the final responsibility for the decision to submit for publication.

Results

Discrimination between MS and (ET or PD) using accelerometer signal

Four different discriminators were determined for quantifying the differences between MS tremor to ET or PT using signals which were recorded using ACC. Out of these four discriminators, the latter two are effectively derived from the first two. The first two discriminators were chosen based on the uninformed search criterion, where all the possible combinations of adjacent bands were tested for the classification of the training data and the two best performing discriminators from this blind search were selected for subsequent analysis.

1. Discriminator 1 (DF1) comprised of the summation of the power in sub-bands B4, B5 and B6, while it encompassed the frequency range of 4.68–9.37 Hz.
2. Discriminator 2 (DF2) comprised of the summation of the power in sub-bands B1 and B2, while it covered the frequencies from 0 Hz to 3.12 Hz.
3. Discriminator 3 (DF3) is the difference of DF1 and DF2.
4. Discriminator 4 (DF4) is the difference of (B4+B6) and B2.

All discriminators were able to classify MS tremor with an accuracy of more than 85%, with DF4 yielding the best accuracy at 92%, followed by DF3 with 89%.

Discriminators		Successful classification				Total	Efficiency
		Trial data		Test data			
		MS	ET & PD	MS	ET & PD		
ACC	DF1	16/20	37/40	14/20	38/40	105/120	87.5%
	DF2	16/20	37/40	16/20	36/40	105/120	87.5%
	DF3	14/20	39/40	16/20	38/40	107/120	89.16%
	DF4	19/20	38/40	16/20	37/40	110/120	91.67%
EMG1	DF3	17/20	34/40	13/20	38/40	102/120	85%
	DF4	16/20	30/40	12/20	33/40	91/120	75.83%
EMG2	DF3	19/20	38/40	14/20	39/40	110/120	91.6%
	DF4	16/20	36/40	13/20	36/40	101/120	84.16%

***Table 2*: Classification results using all discriminators with both accelerometer (ACC) and electromyograph (EMG) data. Here, MS - Multiple Sclerosis, PD - Parkinson's' disease and ET - Essential tremor, DF - Discriminating factors. Please refer to supplementary Table 3 for positive and negative predictive value (PPV and NPV) for these classifications.**

Results of all four discriminators are detailed in Table 2 and the distributions of all these discriminators for both, the trial and test sets are shown in Figure 1. Furthermore, to statistically validate the performance of our discriminators, we employed the ROC analysis and results of this statistical analysis are highlighted in Figure 2. All four discriminators achieved an area under the curve (AUC) of more than 0.5 (mean: 0.877 ± 0.018) with a significance of $p < 0.05$. Here, the DF4 achieved the highest AUC with 0.89 followed by DF3 with AUC of 0.875.

Discrimination between MS and (ET or PD) using EMG signal

The two best discriminators from the accelerometer analysis DF3 and DF4 (see Table 2) were further used for the classification of tremors using two EMG signals. For EMG2 (extensor), the accuracy was higher than 84% for both discriminators, with DF4 yielding up to 92% accuracy. The EMG1 (flexor) signal did not perform well with discriminator DF3 (75% accuracy) in comparison to DF4 with accuracy of 85%. The distributions of the discriminator for both, trial and test data, are shown in Figure 1 and results are illustrated in Table 2. The ROC analysis employed on the discriminator to statistically validate the performance revealed significant ($p < 0.05$) results for both EMG signals and discriminators with AUC more than 0.5 (mean: 0.8337). Among the two discriminators, the DF3 performed the best with AUC of 0.8512 in comparison to DF4 with AUC of 0.8162 (Figure 2). The results of the voting between DF3 and DF4 for both accelerometer and electromyography signals are given in Table 3. We also did the voting between the DF3 and DF4 whose results are also included in Table 3.

Support Vector Regression (SVR) analysis

For the SVR analysis, both training and test data were used.[52] We took discriminators DF3 and DF4 for both the ACC data and the EMG data as the independent variable, owing to their performance, while clinicals scores were taken as the dependent variable. We observed a significant correlation ($r > 0.5$) between the discriminators, when combinations of all discriminators were taken as independent variables, and clinical scores for all tremor types [PD: UPDRS - $DF3_{acc}$: 0.72, UPDRS - $DF4_{acc}$: 0.73, UPDRS - $DF3_{EMG}$: 0.71 UPDRS - $DF4_{EMG}$: 0.74; ET: FTM - $DF3_{acc}$: 0.72, FTM - $DF4_{acc}$: 0.71, FTM - $DF3_{EMG}$: 0.73, FTM - $DF4_{EMG}$: 0.73; MS: FTM - $DF3_{acc}$: 0.75, FTM - $DF4_{acc}$: 0.76, FTM - $DF3_{EMG}$: 0.77, FTM - $DF4_{EMG}$: 0.75]. Furthermore, we also observed significant positive correlation when individual discriminators were taken as independent variable [PD: UPDRS - $DF3_{EMG}$: 0.55, ET: FTM - $DF3_{acc}$: 0.56, MS: FTM - $DF3_{acc}$: 0.54]. The high values of correlation show the strong positive relation of discriminators with clinical features of the MS, ET and PD further corroborating the effectiveness of our proposed method.

Discrimination between MS and ET (additional analysis)

As the MS tremor is most easily confused clinically with ET rather than with PT, we made an additional analysis to observe if the classification still holds when compared to only ET group without considering PT. We found the same results as above with the two best discriminators being DF3 and DF4 from the accelerometer analysis. The classification accuracy for these discriminators, even though were slightly reduced, were still above 80% for accelerometers and above 77% for EMG. All the results from the analysis are presented as Supplementary table 1 and 2.

Discussion

In the presented study, we propose and implement a highly efficient method to distinguish MS tremors from

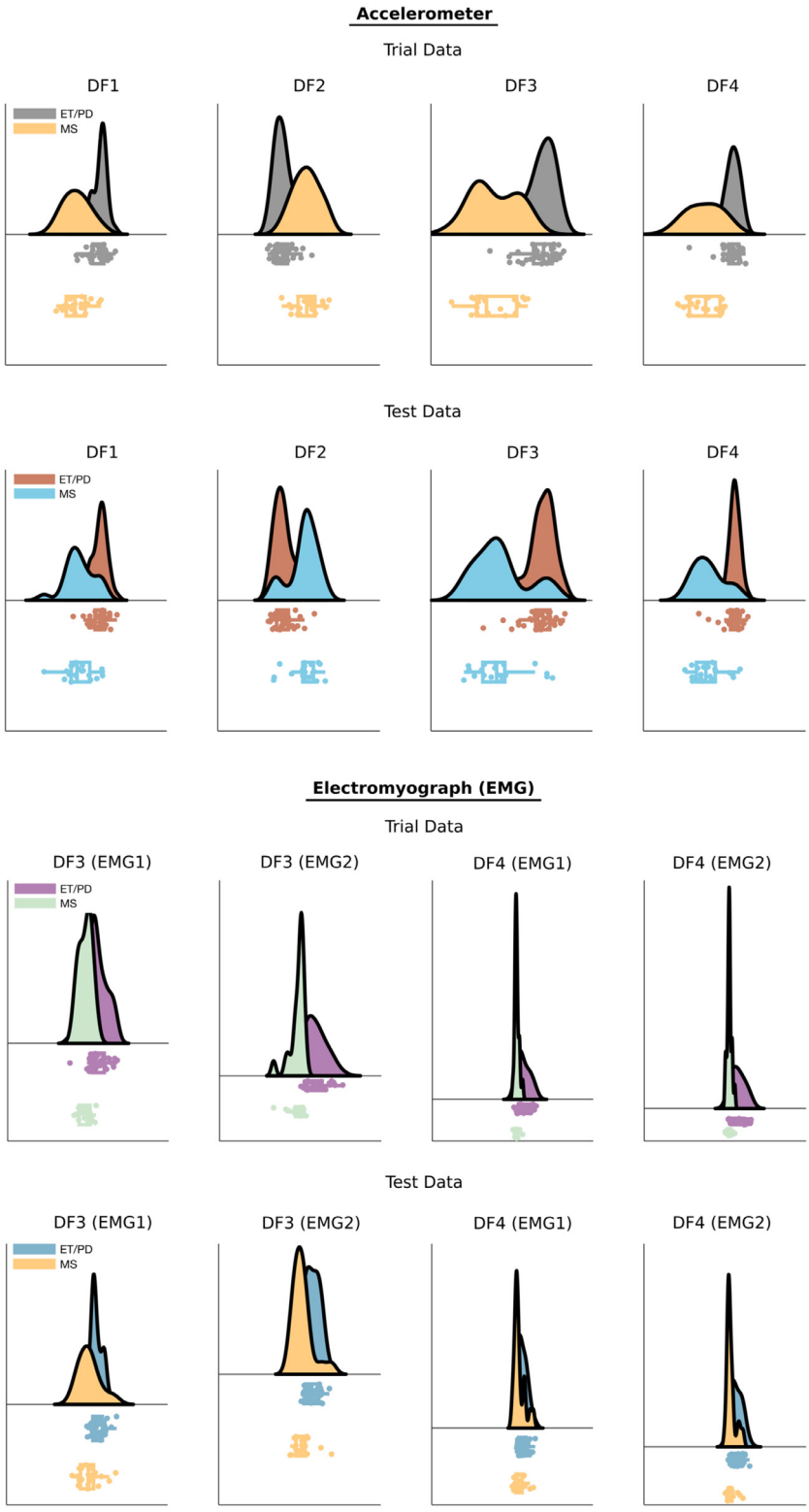

Figure 1. Discriminator distribution of trial and test data for all four discriminating factors (DF) using accelerometer data and two best DFs from accelerometer (DF3 and DF4) using EMG data.

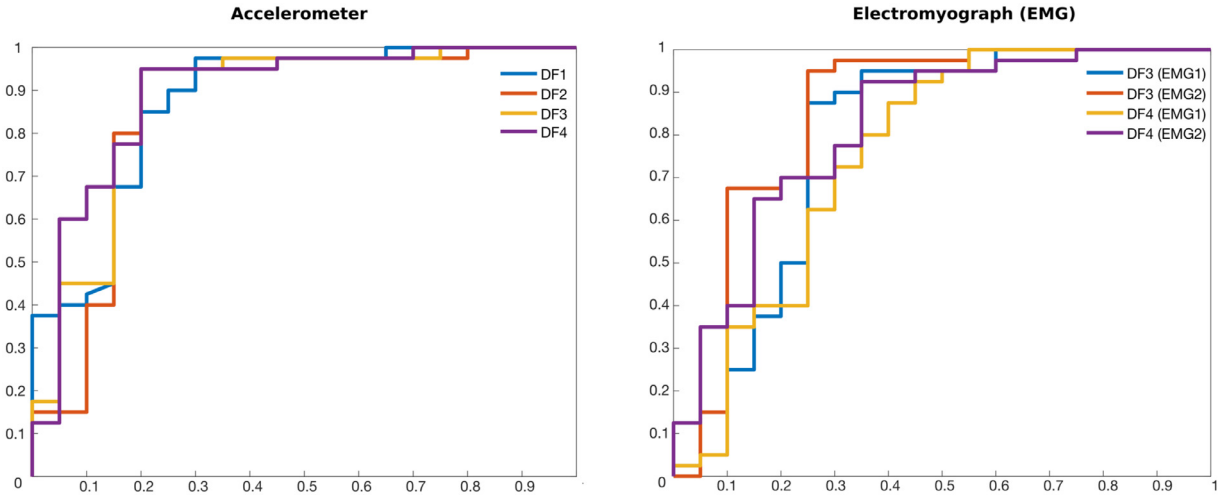

Figure 2. ROC analysis of all four discriminating factors using Accelerometer and two best DFs from accelerometer (DF3 and DF4) using EMG data.

other cerebellar tremors (e.g., ET) based on decomposing associated frequency spectra into sub-bands. We further showed that the proposed analytical framework performs similarly robustly for the discrimination with the rest tremor in PD. The performance of discriminators (DF_3 and DF_4) using both EMG and accelerometer data was found to be the best, yielding classification accuracy of more than 90%. Moreover, we show that these discriminators are strongly related to the clinical measures of MS, ET and PD, highlighting the diagnostic importance of the findings.

Tremor is a poorly understood movement disorder[53] with a lack of specific and robust biomarkers for diagnosis which makes the subsequent care and cure very challenging.[54,55] Even though several recent studies have indicated that the physiological sources of these tremors are different,[56–58] the overlapping frequencies and symptoms are some of the challenges for proper diagnosis. Presently, magnetic resonance imaging (MRI) based tools such as McDonald diagnostic are available, exploiting the association between the clinical symptoms, chemical composition of cerebrospinal fluid (CSF), and visual stimulation to the brain for the diagnostic of multiple sclerosis.[59] In addition, the multifocal neuroanatomical changes and the varied symptoms exhibited by this tremor, make a proper diagnosis even more challenging.[57] Our rationale for conducting this research was to exploit the non-invasive and relatively simple electrophysiological data obtained during clinical routine to effectively characterize MS tremor.

Previously, it was shown that electrophysiological methods like soft-decision wavelet-decomposition (SDWD) can be helpful in quantifying different types of tremors with overlapping frequency ranges.[36] The advantage of SDWD over conventional FFT-based techniques is better discrimination efficiency, particularly for the tremors where frequencies overlap.[60] The discrimination between the tremors in the case of PD and ET might not be extremely challenging, as PD is characterized by the rest tremor, while ET is more associated with manifestation in the form of action tremor. Moreover, previously it was shown that classification sensitivities as high as 90% could be reached for ET and PD tremor distinction.[61] However, quantification between ET/PT and MS tremor adds an additional layer of complexity with the overlapping frequency band and symptoms.

The method of Soft Decision Wavelet Decomposition is examined in the case of three types of tremors, namely MS, ET and PT. Among four discriminators applied, the highest classification accuracy was obtained from discriminators D_3 and D_4. Owing to their mathematical expression, discriminators D_3 and D_4 involve

Discriminators		Successful classification		
		MS	ET & PD	Total
ACC	DF3	29/40	77/80	106/120
	DF4	35/40	74/80	109/120
EMG1	DF3	30/40	72/80	102/120
	DF4	28/40	63/80	91/120
EMG2	DF3	33/40	77/80	110/120
	DF4	29/40	72/80	101/120
Voting	DF3	34/40	79/80	113/120
	DF4	31/40	77/80	108/120

***Table 3*: Classification results of DF3 and DF4, for both, trial and test, data using accelerometer (ACC) and electromyograph (EMG) signals and voting between them. MS - Multiple Sclerosis, PD - Parkinson's' disease and ET - Essential tremor, DF - Discriminating factors.**

the difference of sub-bands, hence effectively resulting in the discriminator encompassing a narrow frequency band. We believe that it is due to the specific and restricted frequency contents that discriminators DF3 and DF4 performed better than the other two discriminators. Furthermore, the ensemble discriminators comprised first-harmonic frequencies of the fundamental tremor frequency, which could have improved the efficiency of these discriminators. In the case of MS and ET, the harmonics of the tremor frequency were observed to be regular and at the multiples of the fundamental tremor frequency. Furthermore, in previous studies.[62,63] the harmonics of fundamental tremor frequency were observed to be irregular in the case of PT. This could be due to the fact that harmonic ratio in the case of PT is low.[64] The harmonics of the tremor frequency have also been reported to have a potential as a discriminator among different types of tremors.[62] Considering the difference in the harmonics, the accelerometer signal was very good in predicting the ET and MS tremors, whereas the EMG signal performed better for the prediction of PD tremor. This difference of performance could be due to the fact that both techniques, namely ACC and EMG measure, are different and perhaps complementary for the movement characteristics.[65] Owing to recent technological advancements, accelerometers have been found to be useful for numerous applications in biomedical research. However, they are not efficient in differentiating postures and are prone to gravitational artifact.[66] The use of the modulus accelerometer signal as in our study is advocated to overcome this limitation.[67] The electromyography signal was recorded using surface electrodes. The signal-to-noise (SNR) ratio of the EMG signal can be improved by employing intramuscular electrodes, however it has proven to be clinically impractical and challenging so far.[68]

SVR analysis between clinical features and discriminators revealed a strong and significant positive correlation, indicating reliable association with clinical diagnostic scores. The highest correlation was observed for the clinical scores of MS patients. The significant association of these discriminators thus clearly demonstrates the paramount importance of using these alongside the clinical measures for effective diagnosis of MS tremor. However, one should use caution in interpreting these associations as the clinical scores (UPDRS and FTM scores) used here for the correlations are focused on the severity of the diseases rather than differential diagnosis. The correlations observed for both ET and PT further highlight the importance of the previous findings[45,46] and reveal their clinical significance.

Limitations

Some potential limitations are: i) our method is unable to interactively learn and improve; ii) it can only be used offline (not possible yet to process the data in real time); iii) the result might be influenced by the selection of training data as it should be ensured that dataset representing 'true' picture must be used as training to get best accuracy; iv) necessity of more studies using the SDWD method for the discrimination of tremor in different diseases and with larger sample size to comprehensively validate the efficacy of our technique; v) the approach used in the study with the reduced dimension of the parameters (only to four classifiers), might have impact on the reduced accuracy. We utilized such approach with its advantage of being able to provide potential information in the underlying mechanism. However, in future, we encourage that other machine learning approaches without dimension reduction (e.g., whole frequency spectrum analysis using figure-based machine learning by convolution neural network) should be tested for improving the accuracy.

Conclusion

Only using the peripheral signals obtained from electromyography and accelerometers, we were able to differentiate MS tremor with an accuracy of more than 90% from other tremors like essential and Parkinsonian tremor. The frequency discriminators were excellent predictors of the clinical scores justifying the relevance of the parameters. We further gathered evidence that the fundamental tremor frequency and their harmonics are distinct oscillatory activity rather than pure harmonic frequencies due to waveform-characteristics. These discriminators could complement the other diagnostic criteria presently used in the clinics.

Contributors

The contribution of each author is depicted below using the CRediT taxonomy (http://credit.niso.org/).

AH: Formal analysis, Data curation, Software, Methodology.

ARA: Formal analysis, Data curation, Software, Methodology, Writing-original draft.

NK: Writing - Original draft, Writing- review and editing, Visualization, Methodology.

HD: Formal analysis, Software.

DB: Writing- review and editing, Resources.

AW: Writing- review and editing, Resources.

UH: Writing- review and editing, Supervision, Data curation.

GD: Writing- review and editing, Supervision, Data curation.

SG: Project administration, Funding acquisition, Supervision, Writing- review and editing.

MM: Project administration, Funding acquisition, Supervision, Writing- review and editing.

All authors read and approved the final version of the manuscript.

Data sharing statement

Patients' data used for the study could not be shared because of the agreement signed with the participants. However, partially analysed, deidentified electrophysiological data could be shared with appropriate request to corresponding author.

Declaration of interests

GD received royalties from Thieme publishers and consulting fees from Cavion, Insightec Inc. All authors report no competing interests. International Committee of Medical Journal Editors (ICMJE) developed electronic uniform disclosure form was filled by each author separately and submitted to the journal declaring no competing interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104152.

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