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Tremor analysis with wearable sensors correlates with outcome after thalamic deep brain stimulation

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ABSTRACT

Introduction: Thalamic deep brain stimulation (DBS) provides excellent tremor control in most patients with essential tremor (ET). However, not all tremor patients show clinically significant improvement after DBS surgery. Currently, there is no reliable clinical or instrument-based measure to predict how patients respond to DBS. Therefore, we set out to provide a method for tremor outcome prediction prior to surgery.
Methods: We retrospectively analysed quantitative tremor data collected with inertial measurement units (IMU) in 13 patients who underwent DBS surgery in the ventral intermediate nucleus of the thalamus (VIM). All patients were diagnosed with either ET or ET-plus according to current diagnostic criteria of the movement disorder society. We used linear and logistic regression models to evaluate the influence of different tremor characteristics on tremor outcome.
Results: We found that the ratio between the amplitude of the first overtone and the amplitude of the fundamental frequency, denoted as the Harmonic Index, has a significant influence on tremor reduction after DBS surgery. This measure shows a strong correlation with the post-operative improvement of tremor outcome based on the Whiget Tremor Rating Scale.
Conclusion: Based on these findings, we propose a novel approach to predict tremor outcome after DBS surgery. Quantitative tremor assessment adds to the preoperative prediction of DBS response and might therefore have a relevant clinical impact in the management of patients suffering from pharmacoresistant tremor.

Introduction

Essential tremor (ET) is one of the most common movement disorders [1]. Besides pharmacological treatment [2–7], thalamic deep brain stimulation (DBS) in the ventral intermediate nucleus (VIM) is a well-established approach [8], providing excellent tremor control in most cases [2,4,6,9–12]. The success in post-operative tremor reduction depends on an accurate implantation of the DBS electrodes, careful patient selection and the correct diagnosis [13–15]. Nevertheless, the clinical outcome of DBS surgery varies considerably between patients and is usually not well predictable [8,10]. As a possible reason for this observation, patients with the clinical diagnosis of essential tremor have a broad variability in clinical phenotype [30]. Currently, there is no established clinical or instrument-based measure to predict how patients respond to DBS surgery.

Quantitative tremor analysis has been tested by several groups as an addition to clinical assessment of tremor disorders to provide objective and sensitive biomarkers for diagnosis and treatment response [16–18]. Using inertial measurement units (IMU), the long term fluctuation of tremor was analysed [19,20], showing for example, a decrease in tremor frequency over time for ET patients [21]. Other groups used IMUs to improve electrode placement during DBS surgery [22–24]. Furthermore, frequency content was measured with IMUs to classify patients with different tremor etiologies such as ET and Parkinson's disease (PD) [25,26]. In particular, analysing frequency peaks at integer multiples of the basic tremor frequency, i.e., the higher harmonic frequencies, which arise due to rhythmic processes containing nonlinear or asymmetric wave forms [27,28] has been proven useful in the diagnostic process and in the prediction of therapy response to dopaminergic medication [26]: in a previous study, we found a significant correlation between L-Dopa response and the Harmonic Index of tremor (Pearson $r = 0.64, p < .005$), proposing a non-invasive approach to predict L-Dopa response in PD tremor patients [28]. Importantly, we found that these harmonic oscillations could not only be found in PD but can also be present in ET [29].

In this study, we propose a new approach to assess tremor outcome after thalamic DBS surgery based on quantitative tremor analysis in patients diagnosed with either ET or ET-plus. Based on the assumption that sensitive technology-based assessments of tremor proves efficacious to reveal

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clinically relevant differences, we hypothesize that pre-operative tremor characteristics, measured with IMUs, will allow to predict tremor outcome after DBS surgery. To this end, we correlated DBS outcome with preoperative quantitative tremor analysis. To reduce variability due to different DBS targets (VIM and subthalamic nucleus) we exclusively investigated tremor control in DBS patients implanted in the VIM.

Method

Study cohort

We performed a retrospective analysis in 13 patients (7 female and 6 male, age: 57–81 years), who underwent DBS surgery in the VIM. 8 Patients were diagnosed with ET; 5 patients showing additional mild signs of parkinsonism (not fulfilling the diagnostic criteria for idiopathic PD) were classified as ET-plus according to the current tremor classification guidelines of the movement disorder society [30]. L-Dopa response to tremor was assessed in a standardised protocol, but none of the patients showed significant response in L-Dopa challenge tests (Table 1). The study was approved by the local ethics committee *(Kantonale Ethikommission*, KEK Number 2018–00618) and all patients gave written informed consent for study participation. Table 1 shows patients' demographic data and clinical characteristics.

Tremor assessment protocol

We recorded tremor data preoperatively using an IMU, a lightweight motion sensor, at a sampling frequency of 50 Hz. The IMU measures movements with a 3-axis accelerometer (ADXL345, Analog Devices, Norwood, MA, USA) and a 3-axis gyroscope (ITG-3200, InvenSense, San José, CA, USA) [31]. Two sensors were attached to the dorsal side of both hands using a Velcro® strap (Velcro, Manchester, NH, USA). We analysed resting, postural and intentional tremor by asking the patients to perform three standardised hand and arm movements: resting posture (both arms in an approximately 90-degree angle in the elbow with forearms fully supported by the table in front of the patient, hands rotated in a 90-degree angle with thumbs up), postural (elevated parallel arms and hands in horizontal posture with outstretched fingers pointing straight ahead) and intention (elevated arms in horizontal posture with outstretched fingers pointing towards each other, approaching the fingers as close as possible, without touching). Each posture was held for 60 s. Additionally, clinical assessment of tremor using the Whiget Tremor Rating Scale [32] was performed pre- and post-operatively. The pre-operative baseline (BL) quantitative (IMU) and clinical (Whiget Scale) assessment was performed on average 3.5 months ±1.8 prior to DBS surgery in medication OFF state. The post-operative (POST) clinical assessment was done 5 ± 1.9 months after DBS surgery (DBS ON, medication OFF state).

Table 1
Patients' demographic data and clinical details. DBS response shows if patients are significant responders (S, >50%) or moderate responders (M, 20–50%) to DBS. L-Dopa response [%] was calculated based on the tremor part of the MDS-UPDRS III: Movement Disorder Society – Unified Parkinson's Disease Rating Scale. Response was calculated based on the ON/OFF values of the preoperative L-Dopa challenge test [33].

ID	Age	Gender	Diagnosis	DBS response	Whiget ON/OFF	L-Dopa response [%]	Side Dominance
1	81	F	ET	M	27/43	NA	L
2	74	M	ET	S	7/31	NA	R
3	59	F	ET	M	18/36	NA	L
4	81	F	ET	S	28/40	NA	R
5	59	F	ET	S	12/41	NA	L
6	65	F	ET	M	27/28	NA	L/R
7	69	M	ET	M	23/30	NA	L
8	74	M	ET	M	23/37	NA	L
9	77	F	ET-plus	S	17/30	NA	L/R
10	57	M	ET-plus	S	9/16	11.1	R
11	75	M	ET-plus	S	4/19	NA	L
12	75	F	ET-plus	M	46/46	5.3	L/R
13	62	M	ET-plus	M	17/17	30	R

IMU-based tremor analysis

For the quantitative assessment of tremor, each posture was analysed separately. Therefore, we first identified the posture in the filtered accelerometer data (6th order lowpass Butterworth filter, cut-off frequency: 0.5 Hz) (Fig. 1A). For spectral analyses, a discrete Fast Fourier Transformation was applied to the accelerometer and gyroscope raw data (sampling rate 50 Hz, 5000 ms window length, periodogram analysis for the full time-epoch), as described previously [28]. We processed all variables in three spatial dimensions, for the left and right hand each, and used Matlab (MathWorks Inc., Natick, MA, USA) for these calculations.

We defined the following variables from our IMU data to analyse tremor for each hand posture as described above: we calculated the Width of the Maximum Amplitude from the accelerometer data and from the spectral analysis, the Coefficient of Variation of the magnitude in three frequency bands (1–4 Hz, 4–7 Hz and > 7 Hz, respectively), the Fundamental Frequency (basic tremor frequency), the Higher Harmonics (the frequencies at integer multiples of the basic tremor frequency), and the Harmonic Index (the amplitude of the first overtone divided by the amplitude of the fundamental frequency, Fig. 1C) [25,27].

Clinical outcome assessment

We defined two outcome variables based on the Whiget Tremor Rating Scale. As a scalable variable, we defined the relative improvement of tremor, based on the postoperative Whiget Tremor Rating Scale compared to the preoperative baseline condition (percentage of improvement). The binary variable DBS response was defined based on relative improvement of 50% or more in the post-DBS assessment. Thus, patients were classified in a dichotomous manner as *significant* responders to DBS (>50% improvement) and *moderate* responders (20–50% improvement), respectively. This cut-off was chosen to provide balanced groups with comparable size (6 significant and 7 moderate responders) for the further comparative analysis. None of the patients had post-operative signs of cerebellar syndrome (tremor, gait dysfunction or dysarthia).

Model-based analysis outcome prediction

For determining independent variables, the outcome groups (significant versus moderate responders) were compared using a Wilcoxon rank-sum test (Mann–Whitney *U* test). Independent variables showing no significant difference were removed from the data set to reduce the complexity of the model. The remaining 30 variables were then tested for inter-variable correlation. To reduce dimensionality in the regression model, highly correlated variables (bivariate correlation coefficient > 0.5) were reduced to one representative variable, the others were removed from the data set. For variables with high bivariate correlation (>0.5), we calculated the mean absolute correlation of each variable (with all other variables) and removed the variable with the largest mean absolute correlation to optimize the data set towards maximal independency. The bivarite correlation matrix of the remaining 30 variables resulted in 435 correlations (Supplementary Table S2). These steps were performed prior to correlation with clinical outcome parameters to prevent over-fitting of the retrospective model.

The remaining variables used for this study include the Harmonic Index (Wilcoxon rank-sum test: $p = .00019$), the fundamental frequency (Wilcoxon rank-sum: $p = .022$) and the width of the maximal spectral amplitude (Wilcoxon rank-sum: $p = .04$).

These remaining predictive variables, and the descriptive variables disease, age, gender and side of the tremor measurement (left/right) were used as co-variates in both a linear and a logistic regression model, to analyse the influence of each variable on the tremor outcome after DBS surgery (after testing for normality and homoscedasticity). We used the variable

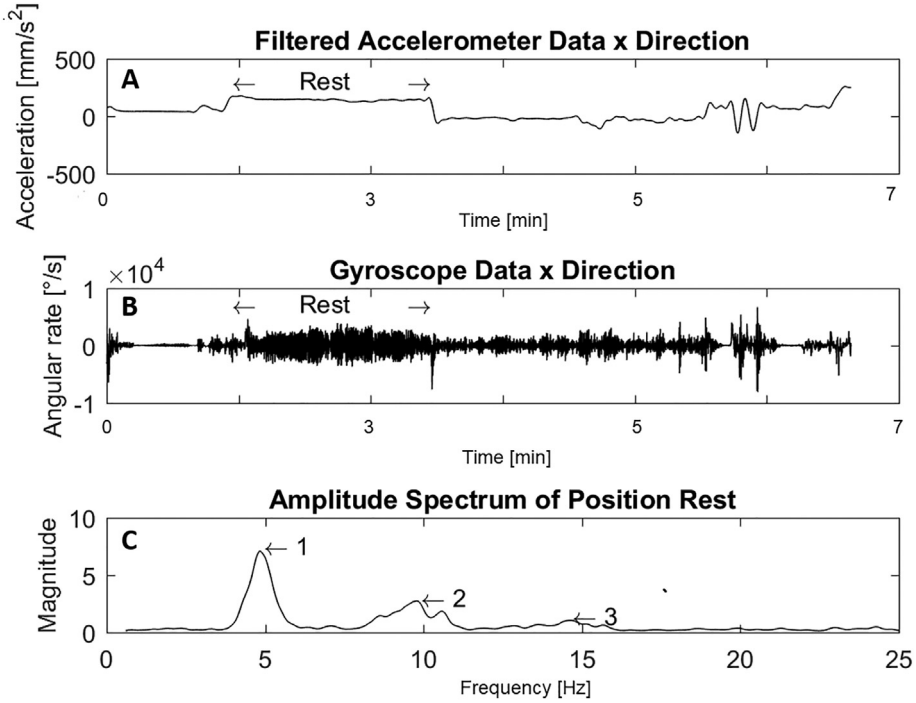

Fig. 1. Representative IMU data set from one patient. In A, the filtered (6th order lowpass Butterworth filter, cut-off frequency: 0.5 Hz) accelerometer data is shown for the spatial dimension x. In B the corresponding unfiltered gyroscope data is shown. C shows the amplitude spectrum of the posture Rest which was taken from the unfiltered accelerometer data as an illustrative example. A Hanning window was used for smoothing. The numbers 1, 2 and 3 denote the amplitude of the fundamental frequency and the amplitude of the first and second overtones respectively. The harmonic index was calculated by dividing the Magnitude of the first overtone (2) by the Magnitude of the fundamental frequency (1).

post-DBS improvement of tremor (%) as the dependent variable in the linear regression model and the binary outcome variable DBS response for the logistic regression model. For the bivariate post-hoc comparison of independent groups (ET versus ET-plus and significant versus moderate responders) we used Wilcoxon rank-sum statistics. Finally, we analysed the receiver operating characteristics (ROC) curve for the variables and calculated the Pearson's correlation between our variables and the post-DBS improvement of tremor (%).

Because tremor was clinically assessed and quantified on both extremities in 13 patients separately, we collected a data set with 26 observations. One data set was excluded from the data analysis, due to incorrect recording of the IMU during data acquisition (partial data loss). Furthermore, one IMU recording showed significant artifacts resulting in an outlier data point (> 4 standard deviations from median value) in the Harmonic Index variable and was excluded. Missing values were not replaced. Thus, all further analyses (multilinear model, bivariate comparison, ROC analysis) was based on 24 observations.

Results

In the linear regression model, we found that the Harmonic Index significantly contributes to the relative post-DBS improvement of tremor ($p = .0367$, Table 2) with a regression equation of $F(1,16) = 6.0477$, $R^2 = 0.35$. Patients' likelihood of showing a better improvement of tremor outcome after DBS surgery increased with a higher Harmonic Index. We found similar results in the logistic regression model, where the variable Harmonic Index showed a significant effect ($p = .0483$) (Table 2). In other words, an increase in the Harmonic Index corresponds to an increase in the likelihood of being a good responder to DBS.

Based on these findings, we performed a post-hoc comparative analysis of the Harmonic Index between both groups. Fig. 2A shows the Harmonic Index for significant versus moderate improvement after DBS surgery. A significantly higher Harmonic Index was found in the good responders' group as compared to the moderate responders ($p < .005$). The Harmonic Index for the two different patient groups ET and ET-plus is shown in Fig. 2B. In this direct comparison, no significant difference was observed ($p = .3472$). Bold values denote statistical significance at the $p < 0.05$ level.

We then calculated the bivariate correlation between the independent variables and the relative post-DBS improvement of tremor (%). This analysis revealed a significant correlation between the Harmonic Index and the post-DBS improvement of tremor (Pearson $r = 0.5$, $p = .013$) (Fig. 3A). For the other two variables, Fundamental Frequency (Pearson $r = -0.099$, $p = .64$) and Width of the Maximum Amplitude (Pearson $r = 0.044$, $p = .84$), we found no significant correlation with the response variable. Finally, we calculated the ROC curve and the corresponding area under the curve (AUC), to evaluate the specificity and sensitivity of our detection variable Harmonic Index to predict DBS outcome. The ROC curve shows an AUC of

Table 2
Output linear and logistic regression models.

Linear regression model				
Coefficients	Estimate/Betas	Std. Error	t value	Pr (>|t|)
Intercept	−8.30921	41.39874	−0.201	0.8435
Disease ET-plus	13.17162	9.68340	1.360	0.1926
Age	0.31225	0.50747	0.615	0.5470
Gender	−2.36342	9.39214	−0.252	0.8045
Fundamental Frequency	2.54839	3.21849	0.792	0.4401
Width Maximum Amplitude	0.01331	0.01348	0.987	0.3381
Harmonic Index	240.89217	105.66844	2.280	**0.0367**
Logistic regression model				
Coefficients	Estimate/Betas	Std. Error	Z value	Pr (> |z|)
Intercept	−5.093777	6.029128	−0.845	0.3982
Disease ET-plus	0.338960	1.270178	0.267	0.7896
Age	−0.004457	0.067568	−0.066	0.9474
Gender	0.594053	1.195296	0.497	0.6192
Fundamental Frequency	0.251974	0.451651	0.558	0.5769
Width Maximum Amplitude	0.001782	0.001890	0.943	0.3458
Harmonic Index	44.867327	22.717208	1.975	**0.0483**

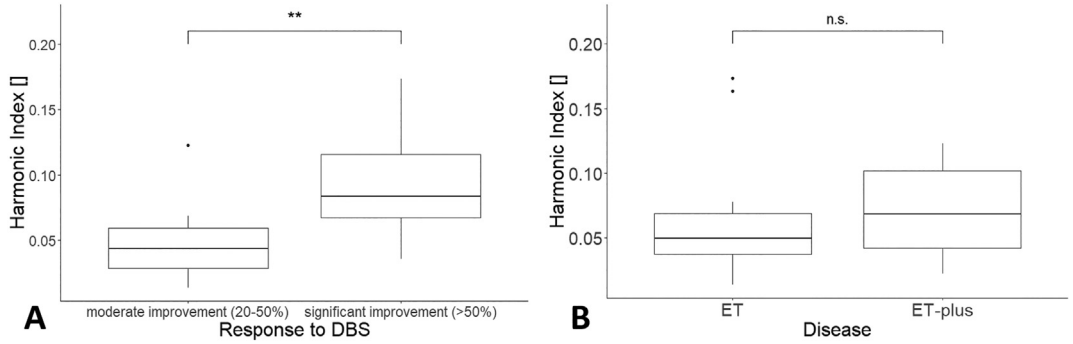

Fig. 2. A shows a boxplot comparing the variable Harmonic Index in the significant ($n = 10$) and moderate ($n = 14$) responder group with significant difference between the two groups ($p = .005908$, Wilcoxon rank-sum test). In B, Boxplot for comparing the variable Harmonic Index between the two diseases ET (n = 14) and ET-plus (n = 10). We found no significant difference between the two groups ($p = .3472$, Wilcoxon rank-sum test). In both panels, 24 observations in 13 patients (bilateral measurements, 2 removed traces) are displayed.

82.9%. For a threshold value of 0.036, the curve predicts significant improvement (>50%) with 100% sensitivity and 35.7% specificity. Tremor response was predicted with 80% sensitivity and 85.7% specificity at a threshold value of 0.063 (Fig. 3B).

Discussion

We investigated if tremor outcome after VIM-DBS can be predicted based on quantitative tremor assessment using predictive modelling of IMU data. We hypothesised that significant responders and moderate responders to DBS surgery show pre-operative differences in tremor characteristics, allowing for a prediction of tremor outcome after DBS surgery. The core finding of this study was that the Harmonic Index of the tremor frequency spectrum, as a readily available and single indicator, can be used to predict DBS response prior to DBS surgery. These findings were supported by linear and logistic regression models, both showing that significant responders to DBS surgery have a higher Harmonic Index than moderate responders. Overall, the Harmonic Index provides a significant prediction method for the tremor outcome after DBS surgery as seen in the ROC analysis (AUC = 82.9%) (Fig. 3B). Furthermore, we found this predictor to be independent from the underlying disease, as both ET and ET-plus patients show similar values for the Harmonic Index (Fig. 2B). These findings suggest, that the use of IMUs for quantitative tremor assessment and the subsequent frequency analysis of patients' tremor can not only be used to distinguish between different forms of tremor as suggested by previous studies [25,26], but also as an instrument-based measure to predict tremor outcome after DBS surgery. Comparing these findings with our previous study, proposing higher harmonic oscillations as an indicator for good response to L-Dopa in tremor patients [28], we suggest that higher harmonics in tremor may indicate responsiveness of tremor patients not only to pharmacological treatment, but also to surgical treatment. However, further research is needed, first to confirm these preliminary results in a larger sample, and then to investigate which mechanisms lead to the observed results.

There are several limitations of this study. The analytical models were calculated with a small data set ($n = 24$ observations) and an unbalanced patient distribution of ET and ET-plus patients. Furthermore, the statistical reduction of our variables should be carefully evaluated: the dimensionality reduction was inevitable to achieve numerically stable regression models, given the small number of independent observations. However, due to this reduction, numerous variables were excluded from the data set. In particular, the variability of IMU data in different postures (resting, postural and intention) was eliminated from the data set due to high inter-variable dependency. This approach might restrict the generalizability of our findings, since in other patient groups (e.g. PD or dystonia) tremor has generally a stronger postural dependence. Furthermore, for constructing the model we only selected variables that already showed a significant difference between the higher and the moderate responders to ensure the predictability of our models. For further investigations based on this study, tremor data of a larger patient group should be analysed to verify the outcome of our

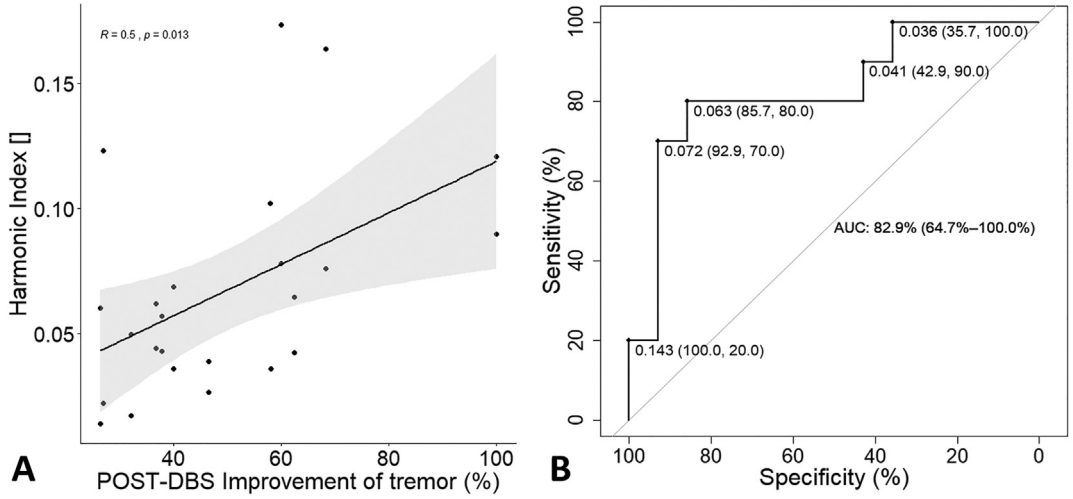

Fig. 3. A Pearson's Correlation between the variable Harmonic Index and the clinical outcome variable POST-DBS Improvement of tremor (%). A higher Harmonic Index correlates with the clinical tremor improvement after DBS surgery (Pearson $R = 0.5$, $p = .0013$, $n = 24$). B shows the ROC curve of the variable Harmonic Index with an AUC of 82.9%. Threshold values for 100% sensitivity and for 80% sensitivity are at 0.036 and 0.063 respectively.

models and potentially adapt them. Regarding the clinical implications of our findings, a further limitation is the absence of a systematic evolution of quality of life after DBS implantation. Thus, based on our data, we are not able to provide evidence that the (arbitrary) cut-off of 50% improvement in the tremor rating scale has a meaningful clinical correlate for all patients. Future studies might correlate the proposed tremor biomarker (Harmonic Index) with additional validated clinical outcome parameters including activities of daily living.

In summary, we propose a novel, non-invasive, instrument-based approach for pre-operative prediction of tremor response to VIM-DBS. Our findings encourage to further explore IMU data in a larger sample of patients to further explore quantitative tremor characteristics and their predictive value regarding tremor outcome after DBS surgery. To finally confirm our findings, future studies should assess the true predictive power of the Harmonic Index for treatment response to DBS surgery in a prospective controlled setting.

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Declaration of competing interest

None of the authors report competing interests related to this study.

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CRediT authorship contribution statement

Authors have made substantial contributions to the conception and design of the study (LLI), acquisition of data (LLI, DR, SM, LS, MO), analysis and interpretation of data (DR, LLI, RG, OL, CB, SM), drafting the article (DR, SM), revising it (all authors) and gave final approval of the submitted version (all authors).

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