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Head tremor in cervical dystonia: Quantifying severity with computer vision

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ABSTRACT

Background: Head tremor (HT) is a common feature of cervical dystonia (CD), usually quantified by subjective observation. Technological developments offer alternatives for measuring HT severity that are objective and amenable to automation.
Objectives: Our objectives were to develop CMOR (Computational Motor Objective Rater; a computer vision-based software system) to quantify oscillatory and directional aspects of HT from video recordings during a clinical examination and to test its convergent validity with clinical rating scales.
Methods: For 93 participants with isolated CD and HT enrolled by the Dystonia Coalition, we analyzed video recordings from an examination segment in which participants were instructed to let their head drift to its most comfortable dystonic position. We evaluated peak power, frequency, and directional dominance, and used Spearman's correlation to measure the agreement between CMOR and clinical ratings.
Results: Power averaged 0.90 (SD 1.80) deg^2/Hz, and peak frequency 1.95 (SD 0.94) Hz. The dominant HT axis was pitch (antero/retrocollis) for 50%, roll (laterocollis) for 6%, and yaw (torticollis) for 44% of participants. One-sided *t*-tests showed substantial contributions from the secondary ($t = 18.17$, $p < 0.0001$) and tertiary ($t = 12.89$, $p < 0.0001$) HT axes. CMOR's HT severity measure positively correlated with the HT item on the Toronto Western Spasmodic Torticollis Rating Scale-2 (Spearman's rho = 0.54, $p < 0.001$).
Conclusions: We demonstrate a new objective method to measure HT severity that requires only conventional video recordings, quantifies the complexities of HT in CD, and exhibits convergent validity with clinical severity ratings.

1. Introduction

Head tremor (HT) affects a large proportion of cervical dystonia (CD) patients. Estimates of the proportion vary over the range of 18–68% but are likely approximately 2/3 [1–7]. HT is more frequently associated with pain [1,2] and can have a substantial impact on disability [8] and

overall quality of life [3,9–11].

Clinical trials of new treatments targeting HT require quantified outcome measures. Current clinical methods for quantifying HT include the Tsui scale [12] and the revised version of the widely used Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), the TWSTRS-2. The Tsui scale includes one item for HT, but it has not undergone successful clinimetric testing [13]. The TWSTRS-2 is a modification of the standard TWSTRS [14] that is considered the standard measure of CD severity [15]. Although the TWSTRS-2 added an HT item to the TWSTRS, the item exhibited poor item-to-total properties [16]. When used by movement disorders specialists provided with specific training on the TWSTRS-2, the HT item demonstrates high inter-rater agreement [17]. Nevertheless, as with other rating scales, the TWSTRS-2 is susceptible to inter-rater variability because it is subjective. Objective methods to measure HT severity would circumvent this limitation and could provide insight into complex characteristics of an individual's HT.

Historically, objective methods to assess tremor include electromyography (EMG) [18], electromagnetic motion capture systems [19,20], and inertial measurement units (IMUs) including accelerometers and gyroscopic transducers [21–24]. These methods all require equipment, expertise, and suitable placement of the device on the participant. If we could instead quantify HT from video recordings, it would provide a digital method that requires only a conventional video camera. Once the technology is automated, no additional expertise would be necessary. Importantly, for forms of dystonia like CD, video-based approaches would also avoid sensory contact with the face or head that can modulate the very phenomenon we wish to capture. Collectively these features of a video-based approach would support large-scale, multi-site clinical trials, and allow remote assessments for telemedicine, making longitudinal follow-up less cumbersome.

The computer vision and machine learning fields have been developing methods for estimating the 3D orientation of the head ("head pose estimation") from digital images. We are leveraging those advances in head pose estimation technology to develop a video-based system to capture motor symptoms of dystonia (the Computational Motor Objective Rater; CMOR). In this study, we extend CMOR to estimate intrinsic HT severity from participant videos recorded in the clinic. The objectives of our study were twofold: first, to quantify spectral oscillatory power, peak frequency, and directionality of HT; second, to develop a model of overall HT severity with CMOR and evaluate its convergent validity with clinical assessments.

2. Methods

We analyzed clinical data and video recordings from 206 participants enrolled across 10 tertiary research centers that participated in a previous rating scale validation study (https://clinicaltrials.gov/ct2/show/NCT01373424) [16] conducted by the Dystonia Coalition between March 2011 and January 2013 [25]. All participants were assessed three or more months after their last BoNT injections, by which time much of the effect would normally have worn off. Videos of CD participants were recorded at 30 frames per second with image resolutions ranging from 512×288 to 1440×1080. Participants were examined and video recorded with a protocol that was standardized across all participants [26]. Participants were seated in a chair without head support with their feet resting on the floor, and hands resting in their laps. The camera was zoomed in enough to capture the upper body, including the head and both upper limbs. For the portion of the protocol evaluated in this study, the video was recorded at one angle from the front. All participants provided informed consent prior to participation in the original study in accordance with the Declaration of Helsinki. The protocols for this study were approved by the Human Research Protection Offices at the Washington University School of Medicine (WUSM), Rush University Medical Center (RUMC), and the University of California, San Diego (UCSD; protocol 111,255×).

One movement disorders neurologist at each of the 10 sites evaluated

HT in each of their participants using the TWSTRS-2. In the TWSTRS-2, HT was scored as absent (0), slight (1; amplitude less than 2 cm and present less than 50% of the exam), mild (2; amplitude less than 2 cm and present more than 50% of the time, or amplitude 2–4 cm but present less than 50% of the exam), moderate (3; amplitude 2–4 cm and present more than 50% of the time, or amplitude more than 4 cm and present less than 50% of the exam), or severe (4; amplitude more than 4 cm and present more than 50% of the exam) [14]. Independently, a movement disorders neurologist (CLC) assessed all video recordings for HT severity using ordinal scores ranging from absent = 0 to most severe = 10 (head tremor score; HTS). HTS does not have specific anchors like the TWSTRS-2 HT item but rather is a gestalt impression of HT severity. Although HTS is not validated, we used it in this study for two reasons: 1) there is one rater for all participants to circumvent inter-rater variability in our site raters' TWSTRS ratings, 2) the 0–10 scale is more fine-grained. Participants were retained for analyses only if there was concordance between CLC and the site raters about the presence of HT as evidenced by a HT score > 0.

Our video analyses were based on a 10 s segment of the video exam protocol in which participants were instructed to close their eyes and let their head drift to its most comfortable dystonic position. This was done to ensure that participants are not receiving visual feedback about their head movements and not trying to do anything that would modify their head movements, such as fighting against the tonic postural aspects of their CD [20,27]. Other parts of the exam may mask their HT because they involve instructions for the participant to perform other tasks that either implicitly or explicitly require volitional control of their head. Two independent video annotators, blind to the clinical ratings, marked these segments using the annotation software ELAN 4.9.4 [28,29]. For all subsequent analyses, we used the overlap between these two annotations and retained only participants with at least a 5 s segment.

All videos underwent a quality control review by three independent reviewers who were blind to the clinical ratings. We excluded participant videos if the video was deemed "unstable" i.e., excessive and/or irregular movement – in the form of either zooming, panning, and/or rotation – of the video camera. This primarily occurred in cases where the camera was hand-held rather than mounted on a tripod. Identification of this issue by at least two out of the three video quality control reviewers was used to exclude that participant from further analyses.

CMOR's current computer vision engine (CVE; OpenFace 2.0 [30]) estimated head pose from each video frame (Fig. 1A). OpenFace is an open-source computer vision tool dedicated to detecting facial landmarks and estimating head pose and eye-gaze for each frame of videos. It uses a deep neural network [31] to estimate the 3D projection of facial landmarks. The landmarks are then used with a generalized direct least-square method to infer the 3 angles of rotation that specify head pose. OpenFace has been validated for head pose estimation against a publicly available dataset (ICT-3DHP), which in turn provides ground truth from a combination of Polhemus Fastrak and Microsoft Kinect sensors [32]. Head pose is given as angle of rotation from frontal in each of three conventional axes: pitch, roll, and yaw. These are mapped to TWSTRS-2 items as illustrated in Fig. 1B: pitch (a "yes-yes" tremor, in the direction of rotation or antero/retrocollis), roll (a "side-to-side" tremor, in the direction of tilt or laterocollis), and yaw (a "no-no" tremor, in the direction of horizontal rotation or torticollis). We filtered video frames for CVE confidence in head pose estimation and biomechanical feasibility (Fig. S1). Frames with confidence levels above 0.7 out of 1.0 were considered for further processing. Because the CVE sometimes exhibits false positives (i.e., high confidence but clearly implausible head pose estimates), we constructed a biomechanically feasible filter incorporating both static thresholds and dynamic thresholds to identify periods in which head pose estimates from the CVE were biomechanically plausible. Static thresholds were used to identify plausible per-frame head pose estimates, using as feasible maxima (all in absolute value): pitch = 80°, roll = 70°, yaw = 90°, (yaw + roll) = 120°. Dynamic thresholds were used to identify plausible across-frame dynamics in the
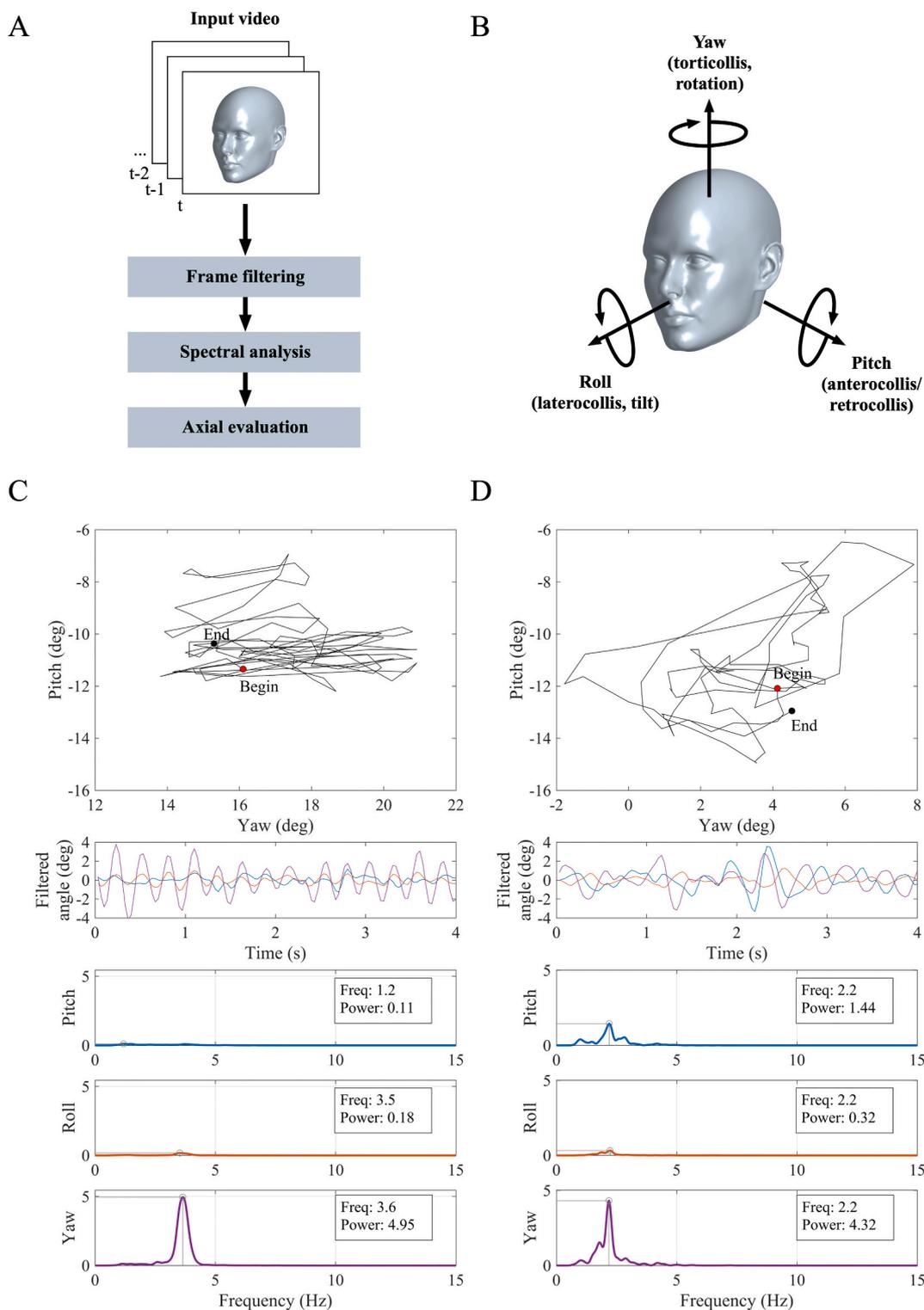
Fig. 1. A) Video processing pipeline. B) Three angles of head rotation corresponding to terminology from the TWSTRS: pitch (antero/retrocollis), roll (laterocollis, or "tilt"), and yaw (torticollis; 3D head model). C and D) Cyclograms, filtered time series, and power spectra for pitch, roll, and yaw in two CD participants with severe HT (TWSTRS-2 HT rating = 3, HTS = 7). Cyclograms and filtered time series are four representative seconds within the middle of the video segment. Spectral powers were generated from the entire duration of the segment. C) Uni-axial HT participant with peak power (deg^2/Hz) = 4.95, $\log_{10}$ peak power (deg^2/Hz) = 0.70, and $APR_{2,1}$ = 0.04. D) Multi-axial HT participant with peak power (deg^2/Hz) = 4.32, $\log_{10}$ peak power (deg^2/Hz) = 0.64, and $APR_{2,1}$ = 0.33.

form of excessive rotational velocity that would otherwise artifactually influence power spectral estimates. As a proxy for rotational velocity, a sliding window of 5 frames was applied across the entire time window to compute local standard deviations for all three axes. Frames with local standard deviations below 7 were considered plausible. Frames that pass

through *both* the CVE confidence and biomechanically feasible filter were used for all subsequent analyses. To mitigate any boundary artifacts, we removed ten frames from both ends of the longest contiguous duration of confident and biomechanically feasible frames. Based on the result of this frame filtering process, we excluded participants whose

longest contiguous period of good data was less than 2 s. The remaining frames from the frame filtering process (Fig. S1E) were used to formulate CMOR's HT metric.

The time series and spectral analyses are depicted in Fig. 1. Per Nyquist's theorem, the 30 FPS video frame rate should be able to veridically represent frequencies up to 15 Hz. Because most HT is considered to be above 1 Hz [33] and one report found a range of HT frequency from 2.3 to 6.4 Hz [21], we applied a 1–8 Hz third-order Butterworth bandpass filter to the entire duration of the longest contiguous period of good data. The corresponding power spectra, in units deg^2/Hz, were computed using Matlab's *pwelch* function with the following parameters: fast Fourier transform (FFT) overlap factor = 0.75, segment duration = 5, number of discrete Fourier transform points = 2^{12}, window = Bartlett, number of samples of overlap from segment to segment = (number of frames) × (FFT overlap factor). "Log peak power" was computed as log_{10} of the maximum power over the spectrum and "peak frequency" was the frequency at which that occurred. The log peak power and peak frequency were computed for each axis (pitch, roll, yaw). The axis with the highest peak power was designated the dominant axis (sometimes referred to as "primary" axis) [34].

To characterize the directionality of HT, we identified the dominant axis of rotation and the relative contribution from secondary and tertiary axes. We evaluated the proportion of participants with HT dominance in either pitch, roll, or yaw, with a Chi-square test. For each participant, we calculated an axis power ratio ($APR_{x,1} = \frac{maximum\ power_x}{maximum\ power_1}$), i. e., the relative power between the secondary (x = 2) or tertiary (x = 3) axes and the primary tremor axis. We evaluated the relative proportion of HT power among the primary, secondary, and tertiary axis by comparing $APR_{2,1}$ and $APR_{3,1}$ to a mean of 0 with one-sided *t*-tests.

We built the CMOR model of overall HT severity with the following variables: log peak power and frequency of the dominant axis, $APR_{2,1}$, and $APR_{3,1}$. We hypothesized that higher values of these variables would individually appear more severe to the clinician because a) the TWSTRS-2 HT item anchors refer to tremor amplitude, which would have a direct and positive correspondence to power, b) a faster HT (in terms of frequency) would, everything else being equal, be perceived as more debilitating for the participant, and c) more "mixed" HT, with higher values of APR, would involve a more complex pattern of optimal BoNT injections. We used the HTS and stepwise multiple regression with minimum Bayesian Information Criterion to determine which variables to retain. We tested how well the CMOR model developed with the HTS generalized to the TWSTRS-2 HT item because the TWSTRS-2 HT item demonstrated high inter-rater agreement [17]. Because the HTS range is 0–10 and the TWSTRS-2 ratings range is 0–4, we rescaled CMOR's HTS-based model by a factor of 0.4 so that it would be on the same scale as the TWSTRS-2 ratings. We evaluated the correlation between CMOR and both the HTS and TWSTRS-2 HT severity ratings using Spearman's rho. Post hoc, we identified cases where CMOR and the clinician assessments of HT severity were discordant as those participants whose CMOR estimate residuals of HT severity were more than twice the standard deviation. For these cases, we re-reviewed their clinical ratings and videos to identify reasons for the discrepancy. In all statistical tests, we used an alpha level of 0.05 to determine significance.

3. Results

3.1. Participant cohort

HTS ratings were missing for 3 participants, 0 for 101 participants and > 0 for 102 participants. TWSTRS-2 HT ratings were missing for 3 participants, 0 for 71 participants, and > 0 for 132 participants. There were 9 participants for whom HTS was greater than 0 but TWSTRS-2 HT was not, and 39 participants for whom TWSTRS-2 HT was greater than 0 but HTS was not. These findings illustrate differences that may occur with subjective scoring methods. Because of these discrepant

judgements about the presence of HT, we analyzed only participants who had HT ratings greater than zero from both neurologists ($N = 93$).

Two participants were excluded because video recording standards were not met, 10 because their video was deemed "unstable," and one because their segment duration was less than 5 s. All subsequent CMOR analysis therefore involved 80 participants. Demographics and overall motor severity for this cohort are provided in Table 1. Participants' clinical HT severity ratings averaged 4.8 (SD = 1.8, range 2–9) for HTS, and averaged 2.3 (SD = 0.8, range 1–4) for TWSTRS-2 HT.

3.2. HT characteristics

The distributions of log peak power and frequency are provided in Fig. 2A and B. Peak power was, 0.90 (SD 1.80) deg^2/Hz, and on a log_{10} scale, −0.69 (SD 0.76) deg^2/Hz, and peak frequency 1.95 (SD 0.94) Hz. The dominant HT axis was not uniformly distributed ($\chi^2 = 26.88$, $p < 0.0001$; Fig. 3A, D): it was pitch for 40 participants (50.00%), roll for 5 (6.25%), and yaw for 35 (43.75%; Fig. 3A). One-sided *t*-tests showed that both the secondary axis of rotation ($t = 18.17$, $p < 0.0001$; Fig. 3B) and the tertiary axis of rotation ($t = 12.89$, $p < 0.0001$; Fig. 3C) substantially contributed to HT. Examples of participants with unidirectional or multidirectional HT are shown in Fig. 1.

3.3. HT severity model

The multiple linear regression model for HTS revealed log peak power ($F = 82.03$, $p < 0.001$) and peak frequency ($F = 4.58$, $p = 0.035$) of the dominant axis to be significant factors whereas $APR_{2,1}$ ($F = 0.02$, $p = 0.903$), and $APR_{3,1}$ ($F = 0.17$, $p = 0.678$) were not significant factors for predicting HT severity. The CMOR overall HT severity metric was determined to be 5.29 + (1.64 ×log peak power) + (0.31 ×peak frequency). The CMOR metric was positively correlated with the HTS ($R^2_{adj} = 0.55$; Spearman's rho = 0.77, RMSE = 0.89, $p < 0.001$; Fig. 4A). The CMOR metric based on HTS, linearly rescaled for the TWSTRS-2 range, was also positively correlated with the TWSTRS-2 HT ($R^2_{adj} = 0.26$; Spearman's rho = 0.54, RMSE = 0.46, $p < 0.001$; Fig. 4B). The number of participants for whom CMOR and the clinician ratings were discordant was 5 for the HTS model, and 5 for the TWSTRS-2 model. However, these two groups of 5 participants were mutually exclusive. The correlation between TWSTRS-2 HT and HTS is shown in Fig. S2.

Given the high proportion of patients with APRs >0, in post hoc analysis we sought to determine whether a power metric that includes all three axes might better reflect clinician assessments than a power metric that uses only the dominant axis. Therefore, we calculated the log_{10} of the Euclidean sum of peak power across the three axes (hereafter referred to as the "Euclidean sum power") and compared this metric to the log peak power from the dominant axis. The multiple linear regression model for HTS revealed the Euclidean sum power metric ($F = 81.00$, $p < 0.001$), peak frequency ($F = 7.81$, $p < 0.05$) to be significant factors whereas $APR_{2,1}$ ($F = 0.15$, $p = 0.703$), and $APR_{3,1}$ ($F = 0.002$, $p = 0.967$) were not significant factors for predicting HT severity. The CMOR overall HT severity metric was determined to be 5.14 + (1.67 ×Euclidean sum power) + (0.33 ×peak frequency). The CMOR metric was positively correlated with the HTS ($R^2_{adj} = 0.55$; Spearman's rho = 0.77, RMSE = 0.89, $p < 0.001$). The CMOR metric based on HTS, linearly rescaled for the TWSTRS-2 range, was also positively correlated

Table 1
Participant characteristics.

| Demographics ($N = 80$)	Range	Mean (SD)
Age at Onset (yrs)	15–67	42.4 (13.4)
Age at Exam (yrs)	34–80	61.5 (10.4)
Disease Duration (yrs)	1–60	19.1 (12.3)
Sex (F/M)	64/16	
TWSTRS-2 total motor severity (possible 0–48)	4–29	17.5 (5.2)
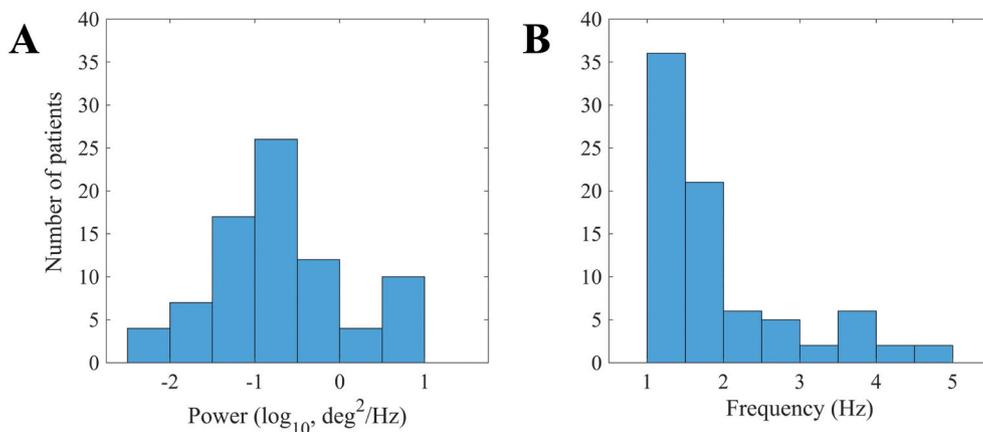
Fig. 2. Distributions of $\log_{10}$ peak power and peak frequency from the dominant axis.
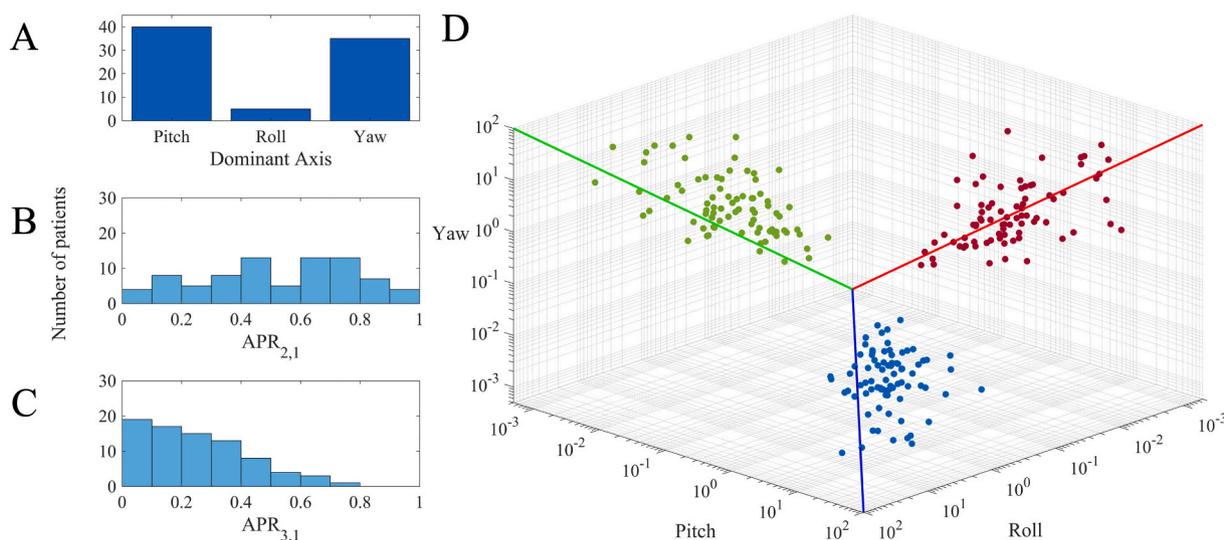

Fig. 3. Axis dominance based on peak spectral power. A) Distribution of dominant axis. B) and C) Distribution of relative power axis power ratio for the secondary ($APR_{2,1}$) and tertiary ($APR_{3,1}$) axes. D) 3D representation of Pitch and Yaw dominance over Roll, projected onto each of the three planes defined by pairwise axis combinations (magnitude in each axis is peak power (deg^2/Hz) plotted on a $\log_{10}$ scale).
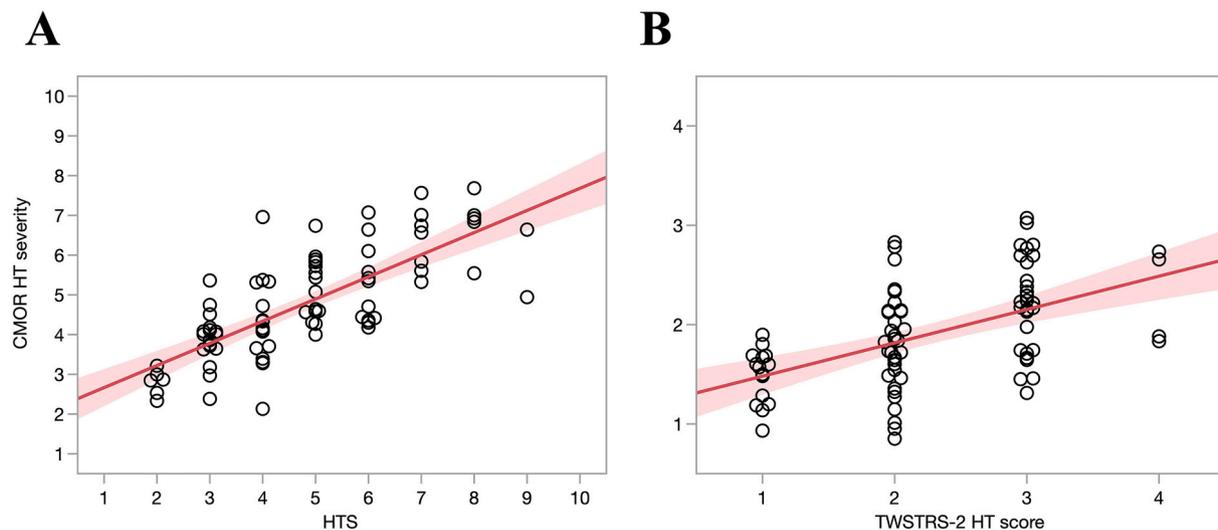
Fig. 4. Correlation between CMOR HT severity and clinical scores from A) HTS (Spearman's rho = 0.77, p < 0.001, $N = 80$), and B) TWSTRS-2 HT item (Spearman's rho = 0.54, p < 0.001, N = 80). The CMOR HT severity metric is scaled separately for each clinical rating scale (see Methods). Shaded regions are 95% confidence intervals for the linear regression.

with the TWSTRS-2 HT (R^2_{adj} = 0.27; Spearman's rho = 0.55, RMSE = 0.45, p < 0.001). In summary, the model using the dominant axis and the model using the Euclidean sum were almost identical.

4. Discussion

We used computer vision applied to conventional clinical video recordings to quantify HT severity in CD in the form of its power, frequency, and directional components. We also demonstrate that these measures from a brief examination period of approximately 10 s of observation can be combined in an overall HT severity score that exhibits convergent validity with clinical ratings of HT severity.

The first objective of this study was to quantify and characterize HT; we determined the log peak power of HT and its corresponding frequency and identified the relative contribution to severity from each of the 3 axes. With the TWSTRS-2, clinicians quantify HT by taking into account a combination of HT amplitude and percentage of time HT is observed [14]. To reflect what clinicians measure in the clinical setting, we incorporated conventional spectral power of tremor amplitude (deg^2/Hz) in our CMOR HT model. As the CMOR HT peak power feature is based on a log scale, our results are consistent with the previously demonstrated logarithmic relationship between HT amplitudes measured with inertial measurement units and ordinal 0–4 clinical tremor ratings [21].

In addition to amplitude, we characterized the frequency of the peak power. Previous studies of CD participants with HT found mixed results for peak frequency. In two separate studies, participants had peaks averaging 4.4 (SD 0.8) Hz [20] and 4.5 (SD 1.0) Hz [35]. In contrast to these previous studies, the average peak frequency for our cohort was much lower at 1.95 (SD 0.94) Hz. The discrepancy between our results and previous results may be explained by differences in HT subtypes. In the study by Shaikh et al., the cohort consisted of 5 participants with jerky head oscillations and 9 participants with a combination of jerky and sinusoidal head oscillations. Analysis of sinusoidal head oscillations resulted in peaks averaging 4.4 (SD 0.8) Hz [20]. From the same cohort, analysis of non-sinusoidal head oscillations resulted in 11 out of 14 participants with peaks between 1 and 2 Hz [33]. This is consistent with our results, in which over 70% of participants had peak frequencies below 2 Hz. Because dystonic HT has been defined as an irregular, jerky movement [33,36], it may be that the high concentration of participants with peak frequencies between 1 and 2 Hz in our cohort represents a predominance of "jerky" HT in CD [33,37]. In future work, these complex, irregular characteristics of HT in CD should be quantified.

Historically, HT in CD has been characterized as "no-no"(yaw), "yes-yes" (pitch), or mixed axis head oscillations [13,36]. It is difficult for clinicians to quantify mixed axis HT, but knowledge of how multiple axes contribute to HT may help determine optimal botulinum toxin injection sites for reducing HT. Although previous studies [38,39] have mainly provided descriptive results of HT directionality, our results elaborate HT directionality in an objective, quantitative way. We found that the predominant axis is mainly in either pitch or yaw, with relatively few participants exhibiting HT that is dominant in roll. Additionally, most of our cohort had "mixed" HT. Most participants' HT contained substantial relative power in not only their primary but also their secondary axis of rotation, and some participants even exhibited substantial power in their tertiary axis of rotation. Our results are qualitatively similar to those previously found in HT in the context of essential tremor (ET). In ET, mixed directionality HT was more common (54.9%) than either purely pitch (17.6%) or yaw (27.5%) [38]. Of the 28 participants in that study with mixed tremor, 6 had predominantly yaw tremor, 3 had predominantly pitch, and 19 had a roughly balanced mix of yaw and pitch. Thus, CMOR may be useful for assessing the directionality of HT for not only CD but also ET.

The second objective of this study was to develop a model of overall HT severity with CMOR and evaluate its convergent validity with clinical assessments. In our multiple linear regression model, only log peak power and peak frequency of the dominant axis were significant factors for predicting HTS scores. The log peak power had much higher influence than peak frequency. When assessing HT, clinicians generally emphasize HT amplitude, consistent with the higher influence from power. Although frequency is not included in the wording for the TWSTRS-2 anchors, our results suggest that clinicians may also be influenced by HT frequency when assessing HT severity. In terms of the axial distribution of HT, post hoc analysis revealed that the CMOR model using the dominant axis and the CMOR model using the Euclidean sum were almost identical. This suggests that clinicians may more heavily weight a single dominant axis among antero/retrocollis, laterocollis, and torticollis, despite the majority of patients exhibiting power in multiple axes of rotation. In conjunction with the fact that the APRs were not included in the models, our results suggest that directional contributions to HT are not taken into account in clinician assessments of severity. Although frequency and directional contributions to HT are not easily quantified through simple observation, they are captured with CMOR. Relatedly, subjective observations of overall HT severity are susceptible to inter-rater variability. HTS and TWSTRS-2 HT ratings were discordant with CMOR (i.e., outliers defined as residuals in the CMOR estimate of HT severity that were more than twice the standard deviation) in 5 of 80 participants, and the 5 participants were different for the two ratings. We did not see artifactual CMOR results in any of these 10 participants. Collectively, this suggests that the discordance between CMOR and the clinical rating was because of divergent ratings between the clinicians rather than discordance between the rating and CMOR.

This study has a few limitations. First, because we sought to examine HT, the observation periods used for the CMOR HT ratings represent only a subset of that used for the clinical ratings. For the clinical ratings, HT is observed throughout the entire exam rather than a specific segment of the assessment. For CMOR we used only a single 10 s segment in which participants were instructed to close their eyes and let their head drift to its most comfortable dystonic position. This approximates the null point where dystonic activity is typically minimized. For participants whose HT is not static, the segment we used may not be representative of all other parts of the exam. Relatedly, conventional spectral power measures reflect spectral power cumulatively aggregated over the full time window. As such, they do not distinguish between brief, transient, high amplitude oscillations and chronic low amplitude oscillations. Examining these features would be interesting for future studies and could be more reliably examined with much longer observation periods. With longer time periods, it would be practical to determine whether the contribution of the various axes is static or dynamic. Nevertheless, CMOR HT severity measures generated from these short segments had sufficient distribution to demonstrate convergent validity with clinical scores. Using other segments such as turning the head in a direction that maximizes tremor [27] may yield different tremor characteristics. Future studies using CMOR could easily evaluate multiple segments separately, a task for clinicians that is susceptible to bias and that becomes increasingly tedious as the number of time segments is increased. Second, CMOR is based on camera coordinates, not body coordinates. If the participant's trunk is not square to the camera, CMOR will over- or underestimate directional contributions in HT. This issue could be addressed by ensuring that the participant's trunk is squared to the camera or by integrating other computer vision technology that also infers the orientation of the trunk. Additionally, future endeavors include expanding upon computer vision tools to estimate trunk posture to determine HT relative to the trunk. Third, the present study requires substantial quality review and time-step annotations before the video is analyzed. In future studies, this could be circumvented by either a closed-loop, interactive examination protocol that is more tightly integrated with video recording starts and stops and/or technology that automatically annotates video segments based on the audio channel. Fourth, the videographer's adherence to the protocol influences CMOR's ability to quantify HT. When the camera is not

stabilized, the present formulation of CMOR may be unable to accurately estimate head pose dynamics and infer the participant's true HT severity. However, a clinician may be able to infer the participant's true HT severity despite the unstable camera. Improvements to future studies could include improved protocol and recording adherence on the part of the examiners and/or additional computer vision and AI technology incorporated into CMOR that disambiguates subject and camera motion. Fifth, our study may have under-sampled participants with mild HT because we included only participants on which the raters agreed about the presence of HT. Nevertheless, the majority of participants retained in our analyses were still mild and thus represented a substantial contribution to the model.

In future studies, we plan to extend CMOR beyond quantifying overall HT severity to detecting HT, capturing the mix of jerky and sinusoidal subtypes of HT, and evaluating HT stability and task dependency. There is poor recognition of CD symptoms even among expert neurologists [40], including the presence of HT as evident from the large discrepancy between expert raters in our study. Objective measurements obtained with computer vision methods have been shown to detect and differentiate tremor [41]. Objective detection of HT can reduce the time from onset of symptoms to diagnosis and treatment. Additionally, objectively characterizing HT subtypes may be important for understanding the relationship between HT and pain in CD, because HT severity and pain severity were correlated in CD participants with sinusoidal tremors but not for those with jerky tremors [42]. The subtype of HT – whether it appears jerky or sinusoidal or both – may also help inform diagnosis. Previous studies have attempted to characterize and differentiate dystonic tremor from ET, yet classification remains elusive [43–45]. In cases where HT is the only visible sign, these two tremulous movement disorders are sometimes mistaken for each other, and this can lead to suboptimal treatment. Objective differentiation of HT subtypes and the distinction from ET may reduce incidence of misdiagnoses and accelerate optimally targeted treatment. Although previous studies using objective measures distinguish between jerky and sinusoidal HT, they used complex instrumentation and cohorts of up to only 14 participants [20,33,46]. If CMOR can be expanded to distinguish between jerky and sinusoidal HT in CD, it would require only conventional video recordings, enable the distinction to be used across multiple centers, and scale up to cohort sizes in the hundreds or thousands. In addition to detecting and subtyping HT, it would be interesting to determine whether HT is stable for a given task and/or depends on the task. For example, we could assess any changes in HT for a given task that is repeated two or more times separated by time and/or other tasks. Likewise, we could assess any changes in HT between two different tasks. Both of these would facilitate development of a minimal clinically important change (MCIC) that is based on CMOR, analogous to an MCIC previously formulated for the TWSTRS motor overall score [47], and inform precisely how examination protocols are designed to enable sensitive and reliable outcome measures in clinical trials.

Objective methods for quantifying HT can provide a reliable outcome measure for clinical trials. As a complement to subjective rating scales, objective measures like CMOR do not suffer from the variability intrinsic to subjective measures, allow for more sensitive outcome measures, and can improve the efficiency of clinical trials. Because CMOR only needs conventional video recording, it can facilitate multi-center clinical trials and ultimately be extended to telemedicine.

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