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Relationship between jerky and sinusoidal oscillations in cervical dystonia

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ABSTRACT

Introduction: Dystonia is often associated with repetitive jerky oscillations (i.e. dystonic tremor), while tremor is characterized by sinusoidal oscillations. We propose two competing predictions for dystonic tremor and sinusoidal tremor relationship. In any given patient, (1) the oscillation could be characterized as either sinusoidal or jerky based on the degree of distortion in the waveforms, (2) the oscillation consists of both sinusoidal and jerky waveforms mixed in a certain proportion that varies among individuals. We objectively test these predictions in patients with cervical dystonia.
Methods: We recorded head oscillations in 14 subjects with cervical dystonia using a high-resolution magnetic field search coil system. Distortion in the signal was used as a measure of jerkiness. A hierarchical clustering classified the oscillations based on distortion characteristics.
Results: Signal analysis in the frequency domain allowed identification of the components of the waveforms at frequencies other than the fundamental frequency. The distortion from the component at fundamental frequency was present in both low and high frequency range. Based on varying levels of distortions, i.e. jerkiness, the head oscillations were grouped into 4 clusters: one cluster with lowest distortion (sinusoidal waveforms), one cluster with highest distortion (jerky waveforms), and two intermediate clusters – one with distortion at low frequency and another with distortion at high frequency. The distribution of 4 clusters varied across subjects suggesting co-existence of sinusoidal and jerky waveforms.
Conclusion: These results support the prediction that jerky and sinusoidal waveforms concur in cervical dystonia. Amount of concurrence varies amongst patients.

1. Introduction

The dystonias are a group of disorders characterized by excessive muscle contractions leading to involuntary postures or oscillations that are jerky resembling the saw-tooth [1,2]. Tremors are defined by rhythmic oscillations of a body region, typically with a sinusoidal pattern [3,4]. Dystonia and tremor, although viewed as distinct disorders, share many relationships. One of the most controversial relationships between dystonia and tremor involves the concept of *dystonic tremor*. Dystonic movements sometimes have a tremor-like appearance because they can be intermittent, repetitive, and rapid. These tremor-like movements have been called *dystonic tremor*, a term with origins first summarized by Fahn in 1984 who emphasized on two features that distinguished dystonic tremors from other tremors [5]. First, the repetitive movements of dystonic tremors were viewed as being irregular in the domain of oscillatory train, in both oscillatory cycle frequency and amplitude fluctuate from time to time in a given patient. It was suggested that the irregularity in the oscillatory train differs from more common tremors, which are more regular. Second the *waveform shape* of the dystonic tremors was viewed as having a jerky quality (i.e. waveform shape domain), caused by a rapid movement in one direction followed by a slower movement in the opposite direction. This jerkiness contrasts with the waveform of other tremors, which are typically sinusoidal, due to a speed of movements in opposing

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directions being roughly similar. Because an irregular and jerky tremor could sometimes be the sole or dominant manifestation of dystonia, the co-existence of twisting movements or postures was not viewed as a core requirement for early definitions of dystonic tremor. This definition for dystonic tremor was changed drastically by a committee of the Movement Disorders Society in 1998 [6]. The committee considered the irregular oscillatory train and jerky waveform qualities used to define dystonic tremors to be too subjective for practical use. It was believed that grossly irregular and jerky movements were easy to identify as dystonic, but more subtle irregularity or jerkiness were more difficult to judge. The committee proposed an operational definition that could be more reliably applied in the clinic, so the irregular and jerky qualities were no longer viewed as core determinants of dystonic tremors. Instead, they emphasized that dystonic tremors should be accompanied by more obvious twisting movements or postures in the same body region.

The revised definition for "dystonic tremor" has not been universally adopted either. One reason is that the co-existence of twisting movements is very subjective. Some experts consider subtle tilting of the head or subtle hyperextension of the fingers to be evidence for dystonia, while others consider these features to be too subtle, and potential normal variations in motor behavior. For example, a recent commentary [7] claimed that 26% of the cases shown in a teaching video for essential tremor [8] also had subtle manifestations of dystonia. As a result of the disagreement in what constitutes dystonic tremor, some experts continue to use the original definition, emphasizing the irregular and jerky quality (i.e., Fahn's definition), regardless of any co-occurrence of dystonia [4,9,10]. Others use the newer definition, emphasizing any tremor that occurs in a dystonic body part, regardless of its irregular or jerky qualities [11,12]. Others use alternative terminology, such as tremor-dominant dystonia or tremulous dystonia [13].

The disagreements regarding such a fundamental diagnostic issue have led to enormous debate and a call for a more global re-evaluation of definitions for "dystonic tremor" [3,7,14,15].The irregularities in the oscillatory train, in form of cycle-by-cycle variability in frequency and amplitude is known and was compared between dystonia and other forms of tremor [16–19]. Here we propose a novel approach of distinguishing oscillations in dystonic patients based on the *quantitative analysis of waveform shape*. There are two mutually exclusive predictions. The first prediction is that in any given patient, the oscillation follows only one waveform pattern. Such waveform pattern may vary among patients forming a continuous spectrum ranging from pure sinusoidal shape in some patients to jerky (saw-tooth) shape in the others. The second prediction is the possibility that both sinusoidal and jerky waveform patterns coexist in the oscillation. In some patients, oscillations may have one waveform pattern more pronounced than the other, yet all individuals present a mixed oscillation profile consisting of waveforms of sinusoidal and jerky shape. Our experiment tested these predictions on objectively measured shapes of head oscillation waveforms in subjects with the most common form of focal dystonia, cervical dystonia (CD), which commonly presents with head oscillations. We quantitatively classified the waveforms in clusters according to the distortions in their shape (sinusoidal versus jerky or saw-tooth). According to the first prediction, in a given patient, there will be only one cluster of waveform shape; the quantitative characteristics of the waveform shape would vary among patients. According to the second prediction, in a given patient there will be more than one clusters, each of the clusters will be distinguished by differences in the waveform shape.

2. Materials and methods

2.1. Subjects

We recruited 14 patients (13 women and 1 man) with isolated CD. All were being treated with botulinum toxin. Measurements were performed 1 week prior to the next scheduled treatment. At the time of testing none were taking oral medications for tremor or dystonia. The study was approved by The Johns Hopkins University Institutional Review Board. All patients gave written informed consent. Clinical characteristics of the subjects are summarized in the Supplementary Table.

2.2. Head movement recordings

The head positions were recorded in a darkened room using the magnetic field search coil technique with a dual (three-dimensional) search coil (Skalar Medical) mounted on a bite bar as subjects sat within a stationary frame that held the external magnetic field coils [17,20]. Subjects were asked to look straight, then to the right and to the left in random order during recording. The angular position of the search coil with respect to the magnetic fields was digitized at 1000 Hz [21]. Head movements were recorded in the horizontal, vertical and torsional planes as the subjects viewed a front-projected LED target. Here, we focused on horizontal head movements (around an earth vertical axis passing through the center of the coil frame) because head movements of the subjects were predominantly horizontal. Recordings were preprocessed and analyzed using Matlab R2016b (MathWorks).

2.3. Signal processing

Preprocessing of head oscillation signals is summarized in Fig. 1A. Signals were smoothed with a moving average filter with a 100 ms long sliding window. This level of smoothing preserved the shape of the signals while removing minor artifacts related to signal acquisition (Step I in Fig. 1A). We then used a Butterworth bandpass filter with an order of 4 and cut-off frequencies 1 Hz and 100 Hz to remove extremely low and high-frequency signal noise. The signal of interest was oscillations that were superimposed on drifts in head positions. Therefore, smoothed and filtered signals were detrended in 10 s windows to remove large dystonic jerky head movements (Step II in Fig. 1A). Detrending realigned the signal along the abscissa with peaks of the oscillations taking positive and the troughs taking negative values.

Smoothed, filtered and detrended position signals were partitioned in shorter segments of 10 cycles, where a cycle was defined as the signal between 2 points on the time axis where data intersects the time axis and moves from a negative value to a positive value (Step III in Fig. 1A). Our aim was to segment the data into epochs with the shortest duration possible to have a high time-resolution in our analysis. However, with a segment of known fundamental frequency, we tested that 10 cycles were the necessary minimum signal length to perform a reliable frequency spectrum analysis.

2.4. Segment distortion analysis in frequency domain

Distortion alters the basic waveform of the signal, creating unequal amplification or attenuation of its amplitude at various other frequency components. Distortion analysis was performed to objectively assess the amount of jerkiness in the shape of head oscillations. Distortion calculation was based on 'harmonic distortion', an established concept in signal processing literature as a measure of deviation of a signal from a sine wave.

For each subject, distortion analysis of head oscillations started with a frequency spectrum analysis, which was applied to the whole signal (smoothed and detrended) and separately to each signal segment (Fig. 1B). For each segment, we obtained the component at the fundamental frequency (f_0, marked with blue in Fig. 1B), as well as the components at frequencies lower and higher than the fundamental frequency ($f < f_0$ and $f > f_0$, marked with red and green in Fig. 1B respectively). The latter two are the sources of the distortion in the signal. We calculated the low frequency distortion ($D_{f > f_0}$) and high frequency

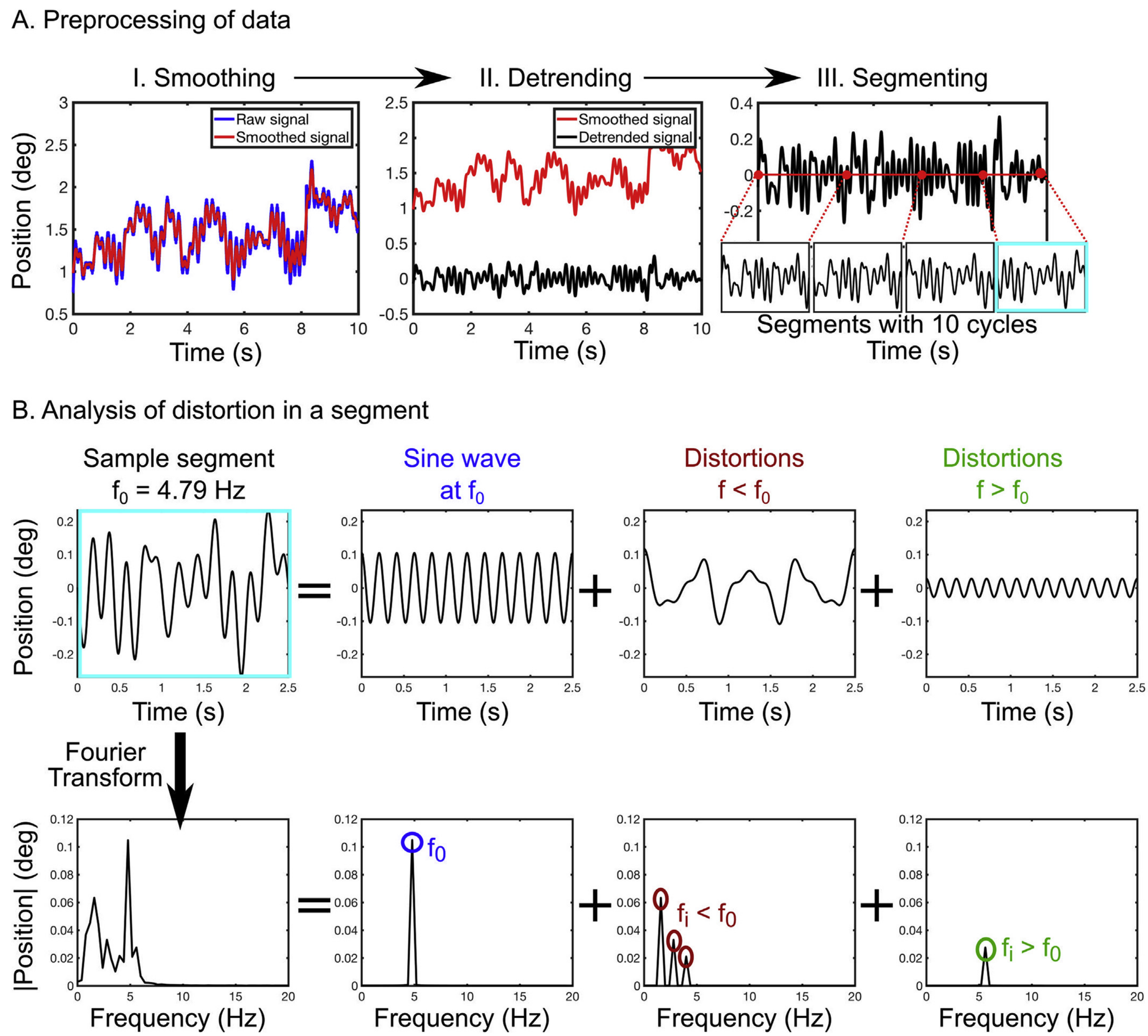

Fig. 1. A. Preprocessing of the data. Raw head oscillation recordings (shown in blue) were mildly smoothed using a moving average filter (Step I). Smoothed data (shown in red) were detrended to remove large drifts (Step II). Detrended data (shown in black) were then divided into segments of 10 cycles (20 zero-crossings) (Step III). **B**. Distortion analysis of the sample segment shown in the cyan box in A. The segment consists of a sinusoidal component at fundamental frequency (f_0), as well as low frequency distortions ($f < f_0$) and high frequency distortions ($f > f_0$). Fourier transform allowed us to obtain all these components. The fundamental component at f_0 is shown with a blue circle. The components at frequencies lower than the fundamental frequency ($f < f_0$) are shown with red circles. The component at a frequency higher than the fundamental frequency ($f > f_0$) are shown with a green circle. The components of the signal at $f < f_0$ and $f > f_0$ are compared to its fundamental component to quantify the amount of low and high frequency distortions in the signal, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

distortion ($D_{f>f_0}$) of the segment in terms of the strength of the distortion components relative to the strength of fundamental component (f_0) using the following equations:

$$D_{f<f_0}(\%) = 100*\frac{\sqrt{\sum_{f_i=f<f_0}\left(Amp_{f_i}^2\right)}}{Amp_{f_0}}$$

$$D_{f>f_0}(\%) = 100*\frac{\sqrt{\sum_{f_i=f>f_0}\left(Amp_{f_i}^2\right)}}{Amp_{f_0}}$$

$D_{f<f_0}$ and $D_{f>f_0}$ would take the value 0% for an undistorted sinusoidal head oscillation whereas a signal with large distortions at frequencies higher or lower than the fundamental frequency may take values greater than 100%.

Distortion was analyzed at segment-level to improve the resolution of the assessment since the characteristics of head oscillations within an individual may vary throughout the experiment. Segment-level analysis can therefore construct a more reliable profile of frequency components of the oscillations, improving the accuracy of distortion measurement. On the other hand, analyzing the whole signal at once might miss important information related to the shape characteristics of head oscillations.

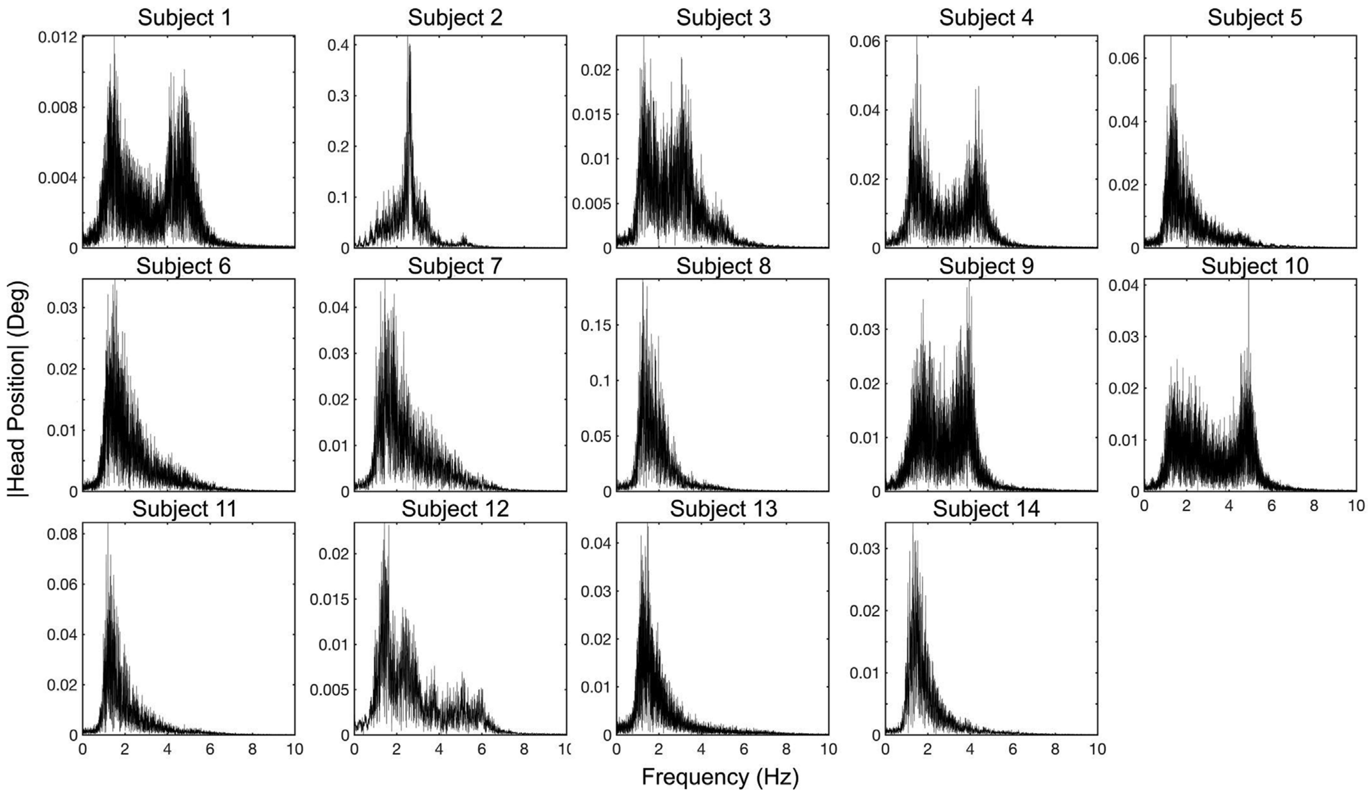

Fig. 2. Frequency spectra of subjects' head oscillations. Fast Fourier transformation was applied to the whole data (smoothed and detrended). Head oscillations occurred at frequencies between 1 Hz and 6 Hz.

Distortion was also evaluated separately for low and high frequency components to obtain additional information regarding the jerky characteristics of the head oscillations. In an individual with CD, these distortions may have different appearances. Jerky head oscillations mostly contain distortions at higher frequencies whereas sinusoids have distortions at lower frequencies. Separate analysis of low and high frequency distortions also prevents any bias that would be introduced by the location of the fundamental frequency of the head movement. For example, if the calculation were solely based on the components at higher frequencies, a subject with head oscillations at a high fundamental frequency (e.g. 5 Hz) would have a low percent distortion value because of the fundamental frequency's proximity to the upper end of the usual frequency range of head oscillations (1–6 Hz). Therefore, the head movement could be falsely interpreted as regular if the distortion at low frequencies were ignored. Hence, reporting distortion at low and high frequencies and considering them together to determine the extent of the jerkiness in an individual's oscillations avoid such bias.

2.5. Clustering of segments

Clustering was used to identify distinct levels of distortion in the whole population and objectively evaluate the amount of jerkiness of head oscillations of single subjects based on distortion levels. We used agglomerative hierarchical clustering algorithm (with Ward linkage method) to decompose the data into groups with similarities in features. Fundamental frequency (f_0), low frequency distortion ($D_{f<f_0}$) and high frequency distortion ($D_{f>f_0}$) obtained for all segments of each subject were used as the features in the clustering analysis. A dendrogram was used to determine the optimum number of clusters. Clustering algorithm assigned cluster labels to each segment indicating an inherent similarity in the distortion levels and fundamental frequencies. In the end of the clustering analysis, we were able to create an individualized profile quantifying jerkiness for each subject's head movement consisting of a unique distribution of oscillation segments with low and high levels of distortion.

3. Results

The goal of this study was to examine two conflicting but objectively testable predictions. One prediction is that in any given patient's head oscillation, one would expect only one waveform shape. The second prediction is that oscillation presents a mixture of distinct waveform shapes with a certain ratio; some patients may have more sinusoidal waveforms, others may have more jerky waveforms, and still others may have both.

Fig. 2 displays the frequency spectra resulting from fast Fourier transform (FFT) in 14 CD subjects. Based on the frequency distribution, which varied between 1 Hz and 6 Hz, each subject had one or more spectral peaks suggesting distorted shapes of head oscillations. To determine the amount and the dynamics of distortions in the shape of head movements throughout the experiment, we performed a segment-level distortion analysis, where FFT was applied to all 10-cycle-long oscillation segments separately to obtain their components at the fundamental frequency f_0 and at frequencies lower and higher than the fundamental frequency. Components of the signal at frequencies other than the fundamental frequency create the distortion in the signal. Hence their comparison to the fundamental component provided an objective measure of the amount of low and high frequency distortion in the signal. Sample segments from two exemplary subjects are shown in Fig. 3A and B, one subject having qualitative features of sinusoidal oscillations resembling the typical definitions of tremor (top plot in Fig. 3A), while the other having qualitative features of jerky oscillations appearing saw-tooth based on the early definitions of dystonic tremor (top plot in Fig. 3B). Scatter plots indicate the degree of distortion in the signal with two measures: distortion at high frequencies (left y-axis, shown in red) and distortion at low frequencies (right y-axis, shown in blue). Together with the histograms showing the distribution of the parameters on all three axes, this plot depicts a clear difference in

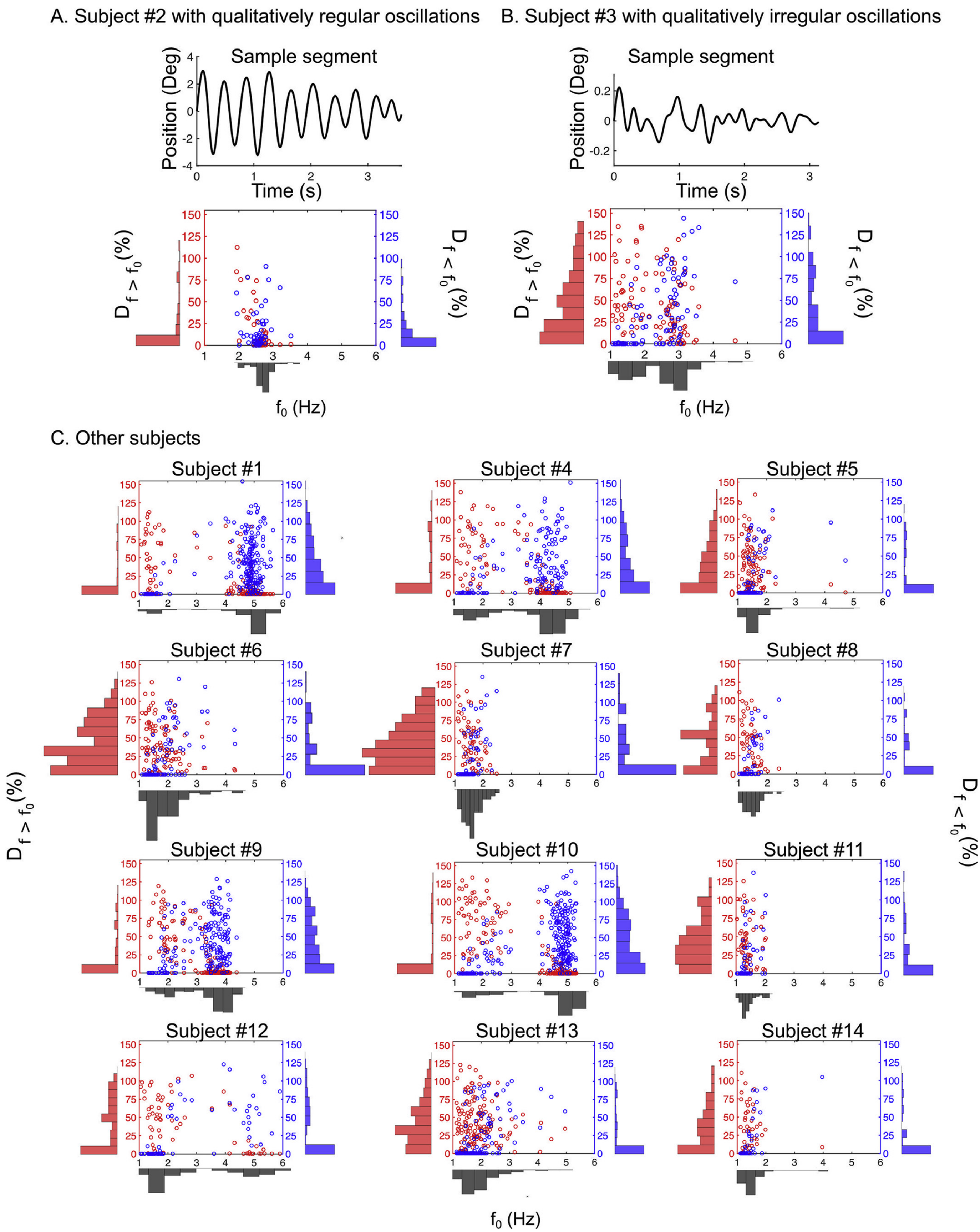

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Fig. 3. Distortion profiles of subjects' head oscillations. **A**. Smoothed and filtered sample segments of a subject with qualitatively sinusoidal head oscillations, and **B**. another subject with qualitatively jerky head oscillations (B) are shown as two exemplary subjects with different distortion profiles (top). Scatter plots (bottom) show fundamental frequencies of the corresponding subject's signal segments (f_0, x-axis) with distortion amount (in %) at frequencies higher than the fundamental frequency ($D_{f>f_0}$, left y-axis in red) and distortion amount at frequencies lower than the fundamental frequency ($D_{f<f_0}$, right y-axis in blue). Histograms next to the axes show the distribution of the data displayed on the corresponding axis. **C.** Distortion characteristics of all the other subjects are similarly represented in scatter histograms. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

distortion levels between the two subjects with qualitatively distinct head oscillations. Fig. 3C depicts the plots of all other subjects.

After obtaining the distortion characteristics of each subject's head oscillations, a clustering analysis was performed with the data that combined the signal segments of all subjects (N = 1593 segments). An agglomerative hierarchical clustering grouped the data into 4 clusters based on the similarity of segments in 3 characteristics (fundamental frequency of the segment, percent distortion at higher frequencies, percent distortion at lower frequencies) (see the Supplementary Figure for the dendrogram). The segments in the 4 clusters are demonstrated in Fig. 4A with a scatter plot of percent distortion at high vs. low frequencies. Cluster statistics (mean + standard deviation) of the 3 features are summarized in Fig. 4B. After considering the whole spectrum of oscillations, clustering algorithm was able to identify a cluster, Cluster 1, (N = 737, shown in black) with the lowest level of distortion (the most sinusoidal) and a cluster, Cluster 4, (N = 251, shown in orange) with the highest level of distortion (the most jerky or saw-tooth) when both higher and lower frequencies were considered. The algorithm discovered two additional clusters, Cluster 2 (N = 299, shown in maroon) and Cluster 3 (N = 306, shown in red). The former consisted of highly distorted segments at low frequencies with relatively lower levels of distortion at high frequencies (i.e., more sinusoidal and less jerky shape). The latter included the segments which are greatly distorted at high frequencies but comparatively undistorted at lower frequencies (i.e., less sinusoidal and more jerky shape). Clusters 2 and 3 verified the need to analyze the low and high frequency distortions separately as the level of distortion in some oscillation segments was different for low and high frequencies.

Fig. 4C demonstrates the whole signal (smoothed and detrended) plotted for each subject with segments color-coded by the colors assigned to the 4 clusters (the color gets lighter with increasing level of jerkiness). The percentage of segments belonging to each cluster with respect to subject's total number of segments was calculated and indicated in percentages in the figure (on the right side of each recording). Subjects were sorted by increasing jerkiness, i.e. decreasing percentage of segments assigned to Cluster 1, which includes the segments with low level of distortion. All subjects presented a mixed oscillation profile with the least distorted sinusoidal cluster (30–77%) and the 3 distorted clusters with a varying proportion (Cluster 2: 5–31%, Cluster 3: 7–37%, Cluster 4: 7–28%). It is important to note that qualitatively "sinusoidal" appearing head oscillations included segments with high level distortion, i.e. they had jerky characteristics (e.g., 8% of Subject #2's oscillations were assigned to the Cluster 4) and qualitatively jerky appearing head oscillations included segments with low level of distortion, i.e., they had sinusoidal characteristic (e.g. 30% of Subject #11's head movements were grouped into Cluster 1). Fig. 4C also provides information about the time dynamics of the distortion in the shapes of head oscillations. We observed no pattern in the timing of jerky oscillatory segments as they displayed a scatter distribution throughout the experiment. Finally, no linear relationship was found between the amplitude of the segment at its fundamental frequency and percentage distortion at higher and lower frequencies (Pearson's $r = -0.2195$ and -0.0945, $p > 0.05$). However, a one-way ANOVA comparing the mean amplitude (in dB) of the segments in different clusters revealed that the segments in the Cluster 1, i.e., sinusoidal oscillations, had significantly larger amplitudes ($F(3,1589) = 20.80$, $p < 0.001$) than the ones in the other 3 clusters (Cluster 1:-17.98 ± 9.48 dB vs. Cluster 2: -20.73 ± 7.57 dB, Cluster 3: -21.14 ± 9.77 dB, Cluster 4: -22.59 ± 9.00 dB) with no significant difference between the latter three clusters ($p > 0.05$).

4. Discussion

There are conflicting views on the relationship between the tremor and dystonia. The goal of our experiments was to delineate the relationships between the head oscillations in CD patients based on the-shape information, i.e., sinusoidal versus jerky. We examined two competing predictions: The first prediction was that in any given CD patient, there is only one type of oscillation shape, such oscillation shape varies among patients making a continuous spectrum ranging from pure sinusoidal shape in some patients to jerky (saw-tooth) shape in the others. Thus, any given patient will have only one quantitatively analyzed cluster of waveform shape. In contrast, the second prediction was that we would find a concurrence of distinct waveform shapes with a ratio varying among individuals; some patients may have one type more predominantly than the other, and still others may have both in similar proportion. Therefore, any given patient will have more than one clusterand each of the clusters will be distinguished by the degree of jerkiness in the waveform shape determined by a distortion analysis.

We objectively tested these predictions in quantitatively measured head oscillations from 14 CD subjects. The analysis involved a quantification of the waveform distortion (i.e. the quantification of the waveform shape amongst jerky versus sinusoidal) and further clustering the observations in various subgroups according to the level of jerky or sinusoidal features. Jerkiness of the head oscillations assessed with the quantity of distortion in the signal is a known feature of dystonic tremor; while minimal distortion is consistent with the sinusoidal shape. An objective and quantitative analysis of distortion in head oscillations depicted that CD patients have a co-existence of sinusoidal and jerky waveforms, the proportion of intensity of each subtype varied amongst patients. Segmentation of the head oscillation time series and the independent analysis of each segment allowed us to conclude that each time series (i.e. depicting individual patient) not only has mixture of variably shaped waveforms (i.e., sinusoidal versus jerky) but the amount of distortion in shapes unpredictably changes in the time series. The amount of distortions in shapes was objectively evaluated in each subject based on the levels determined by the clustering algorithm which identified 4 distinct levels of distortion after considering all segments in the data set. Each CD subject had a peculiar oscillation profile consisting of a unique distribution of segments with low and high levels of distortion (i.e., amount of jerkiness). These results provide a support for the second prediction that sinusoidal and jerky oscillations coexist in the same patient.

In conclusion, we suggest that a computational approach that uses waveform shape analysis and machine learning can quantitatively measure the amount of distortion in head oscillations and evaluate the differences in the shape of oscillations. Our findings implementing this approach provided an evidence for the prediction that sinusoidal and jerky oscillations may be two distinct but coexisting neurological phenomena in CD patients. The novel technique proposed in this study can be useful to identify the distinct waveform characteristics of other disorders, such as essential tremor, Parkinson's tremor, rubral tremor, and drug induced tremor.

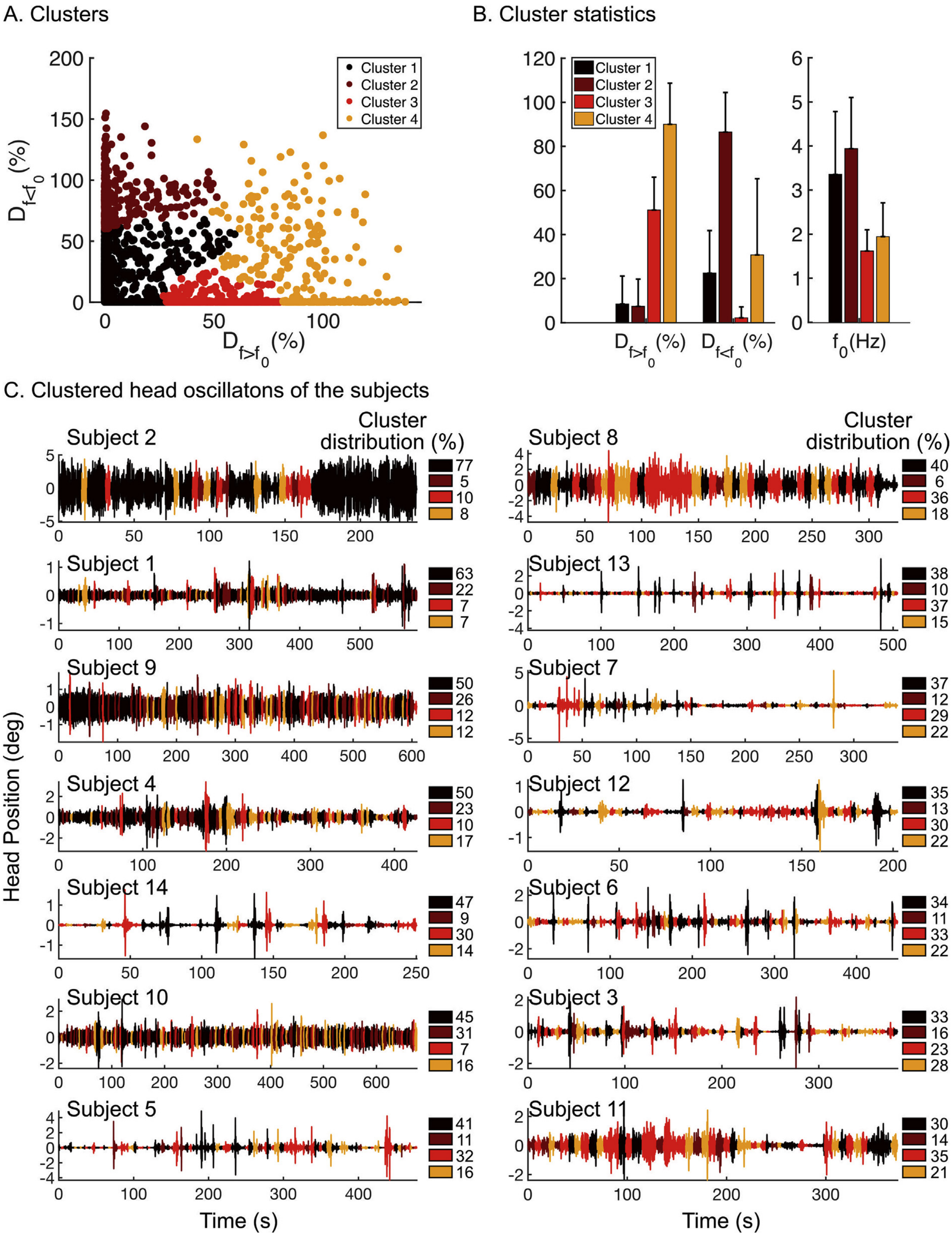

Fig. 4. Clustering Results. **A**. All segments were grouped into 4 clusters based on the similarity of segments in the fundamental frequency of the segment (f_0), its percent distortion at higher frequencies ($D_{f>f0}$, shown in x-axis), and its percent distortion at lower frequencies ($D_{f<f0}$, shown in y-axis). **B**. Grouped bar plot show the descriptive statistics (mean + standard deviation) of the 3 features used in the clustering analysis. Cluster 1 (shown in black) represents the least distorted segment group (most sinusoidal), while Cluster 4 (shown in orange) represents the most distorted segment group (most jerky) with large distortion values at both higher and lower frequencies. Segments in Cluster 2 (shown in maroon) are highly distorted at low frequencies but have relatively lower levels of distortion at high frequencies. Segments in Cluster 3 (shown in red) are greatly distorted at high frequencies but comparatively undistorted at lower frequencies. **C**. Recordings of the subjects with different levels of distortion. For each subject, segments were color coded by cluster assignment (the color gets lighter with increasing level of jerkiness). Cluster distribution in percentages is also depicted for each subject on the right side of the recording. Recordings are sorted by increasing jerkiness, i.e. decreasing percentage of segments belonging to Cluster 1 which includes segments with the lowest level of distortion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.024.

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