HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Parkinsonism Relat Disord. 2015 June ; 21(6): 561–566. doi:10.1016/j.parkreldis.2015.03.005.

Why are voluntary head movements in cervical dystonia slow?

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Abstract

Introduction—Rapid head movements associated with a change in fixation (head saccades) have been reported to be slow in cervical dystonia (CD). Such slowing is typically measured as an increase in time to complete a movement. The mechanisms responsible for this slowing are poorly understood.

Methods—We measured head saccades in 11 CD patients and 11 healthy subjects using a magnetic search coil technique.

Results—Head saccades in CD took longer to reach a desired target location. This longer duration was due to multiple pauses in the trajectory of the head movement. The head velocity of each segment of the (interrupted) head movement was appropriate for the desired total movement amplitude. The head velocity was, however, higher for the amplitude of the individual interrupted movements. These results suggest that brain programs the proper head movement amplitude, but the movement is interrupted by pathological pauses.

Conclusion—Voluntary head saccades have a longer duration in CD due to frequent pauses. The frequent pauses reflect pathological interruptions of normally programmed intended head movement.

Introduction

The dystonias are a group of disorders characterized by excessive muscle contractions leading to involuntary movements and abnormal postures [1]. Muscles of the neck are affected in cervical dystonia (CD) leading to abnormal twisting and turning of the head, often combined with jerky spasms or tremor-like movements [2]. In addition to these involuntary abnormal movements, several studies have shown that rapid voluntary

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Financial Disclosures

Authors have no other financial disclosures.

redirections of the head from one target to another (head saccades) take longer than normal in CD [3–5].

Although these studies have been interpreted to mean that head saccades in CD are slow, they did not take into account an important relationship between head saccade amplitude and velocity, known as the main sequence [6]. Specifically, the velocity of a head saccade depends on the intended amplitude of the movement. There are three different explanations for the increased time to complete head saccades in CD (Figure 1 and Table 1). The first involves abnormal central commands that encode head velocity. This hypothetical mechanism predicts that peak head velocity will be reduced for the desired amplitude of the head saccade in comparison to normal (red trace in Figure 1B,F). The second possible reason is a failure of the brain to program the head movement with an appropriate amplitude. Thus, instead of one adequately large movement the brain might program multiple small sequential movements (Figure 1C), resulting in frequent small pauses during the head saccade, increasing the time to reach the desired location. This mechanism predicts normal head velocities for the amplitudes of each segment of the movement (θn) (blue trace in Figure 1F), but peak velocity would be smaller compared to the larger desired movement ($\sum \theta n$, blue trace in Figure 1E). A third possible reason for slower head saccades is that a pathological process interrupts the normally programmed head movement, producing a series of concatenated movement bursts interspersed by brief pauses (Figure 1D). Upon resumption of the movement, the head continues to obey the kinematic parameters of the originally programmed head saccade. Because the main sequence rela+tionship predicts that larger amplitude movements have higher peak velocities than smaller ones, the third hypothesis predicts that the overall peak head velocity would be normally programmed for the desired total head movement; consequently, each smaller movement segment will appear unusually fast in relation to its amplitude (green traces in Figure 1 E,F).

To discriminate among these mechanisms, we performed a quantitative dissection of head saccades in 11 patients with CD and compared head velocities for different movement amplitudes. The results suggest that slowing of head saccades is caused by pathological interruptions of an otherwise normally planned movement. Thus the terms “slowing” or “bradykinesia” are not entirely appropriate.

Methods

We evaluated 11 healthy subjects and 11 with isolated focal CD (Table 2). Patients with secondary dystonia, segmental or generalized dystonia, or features suggestive of a neurodegenerative disorder were excluded. The Johns Hopkins University Institutional Review Board approved the study; all subjects gave written informed consent before participating.

Head movements were recorded using a three-axis search coil (Skalar, Delft, The Netherlands) mounted on a head-fixed bar. Subjects sat in the magnetic coil frame such that the mid-sagittal plane coincided with the center of the frame. The trunk was restrained with a cushioned chest bar, hence allowing the head to move on a stationary torso. Horizontal head movements were defined as those around an earth vertical axis passing through the

center of the coil frame (i.e., turning the chin to the right or left, or torticollis). Vertical head movements were those around an earth horizontal axis, passing through the center of the coil frame and parallel to the inter-aural line (i.e., flexion and extension of the head, or retrocollis-anterocollis). In this study we only quantified horizontal and vertical head movements. The angular position of the search coil with respect to the magnetic fields was digitized at 1000 Hz and the data were processed to compute the position of the head in three-dimensions [7].

Subjects wore a headband with an attached laser pointer. This setup used a head-fixed laser target to provide visual feedback about the spatial reference of the head position. Subjects were asked to aim their heads, using the head-fixed laser as a guide, at a light-emitting diode (LED) target located at 0°, and to turn the head as fast as possible (i.e., make a head saccade) toward LEDs located either to the right and left at 10°, 20°, and 30°, or up and down at 10° and 20°. Subjects made up to 2 head saccades to each eccentric target in either direction; hence up to 20 head saccades were recorded per subject. Three-dimensional head positions were further analyzed using Matlab® (The Mathworks™, Natick, MA). Mathematical derivations of angular head positions were used to compute head velocity and acceleration. Low-pass filtering and three-point averaging removed signal noise inherent to the mathematical derivations. Head saccades were interactively selected. Troughs in the velocity trace distinguished the breaks in the head saccades; those troughs reaching zero indicated a complete pause in the movement. A velocity criteria of 5°/s was used to determine the beginning of head saccade. Peak head velocity was defined as the maximum velocity achieved across the entire movement; when several local maxima were present in the velocity trace (i.e., when interruptions were present in the head saccade), this corresponded with the largest peak. We use a similar definition for peak acceleration. Statistical analysis was performed with the Matlab® statistics toolbox.

Results

Representative head movement traces

Figure 2A shows an example of a 30°-amplitude horizontal head saccade in a healthy control. There was one uninterrupted movement lasting approximately 250 ms, with a single velocity peak (Figure 2B) and a biphasic acceleration profile that had positive acceleration and negative deceleration peaks (Figure 2C).

Figure 2D depicts an example of a 30°-amplitude head saccade in a patient with CD, when moving in the same direction as their involuntary turning (pro-dystonic direction). The movement took 1088 ms; the longer duration was accompanied by frequent small pauses. The interruptions caused complete cessation of the movement as shown in the velocity trace where there are four peaks in horizontal head velocity and each peak is followed by a trough reaching zero (Figure 2E). These interruptions were also seen in the acceleration trace (Figure 2F).

Figure 2G shows a 30°-amplitude head saccade in a patient with CD moving in a direction opposite to their involuntary turning (anti-dystonic). This movement spanned over 1323 ms, it again was associated with pauses seen in the head position (Figure 2G), velocity (Figure

2H), and acceleration traces (Figure 2I). Results from this representative patient imply that the increased time required for head saccades in CD is due to frequent pauses or interruptions, but peak head velocity might not be reduced.

Summary of all patients and controls

Figure 3 summarizes the duration of head saccades compared with their amplitudes for all 11 CD and all 11 controls. The relationship between the logarithmic values of amplitudes and the actual values of the durations of such movements followed a linear trend. There was a significant difference between the populations of CD subjects and controls; the durations of identical sized head movements were larger in CD (ANCOVA, $p < 0.05$; Figure 3). These results confirm prior studies showing that head saccades in subjects with CD take longer than those of healthy subjects [3].

The main sequence relationship predicts that larger amplitude head movements have higher peak velocities [6]. Figure 4A shows considerable overlap between the main sequence of horizontal head saccades from 11 CD subjects and 11 healthy controls. The relationship between the logarithm of peak head velocities and the logarithm of the corresponding amplitudes followed a linear trend. There was no significant difference between the linear fits of the main sequence values for horizontal head saccades in the population of CD and healthy subjects (Figure 4A; ANCOVA $P > 0.05$). The main sequence of vertical head saccades from healthy subjects and CD also overlapped (Figure 4B); there were no significant differences (ANCOVA $P > 0.05$). These results imply that the peak velocity of the vertical and horizontal head saccades in subjects with CD is normal for the desired amplitude of the head movement.

We then assessed whether peak head acceleration is different for head saccades in CD compared to healthy controls (Figure 4C,D). We examined the relationship between peak head accelerations and the amplitudes of head movements. The logarithmic values of peak head acceleration and the actual values of the amplitude of desired movements formed a linear relationship. Such linear fits were compared between CD patients and healthy subjects for vertical and horizontal head saccades. There were no significant differences (Figure 4C,D; ANCOVA, $p > 0.05$).

The normal relationship of amplitude with peak acceleration and peak velocity of head saccades in subjects with CD argues against the first mechanism (Table 1 and Figure 1) and suggests that the increased duration of head saccades is not due to impaired central programming leading to low peak head velocity or peak acceleration for a given amplitude.

The example in Figure 2 showed interruptions in the head movement in both the pro-dystonic and anti-dystonic directions. The numbers of interruptions for all 11 CD subjects were similar in both directions (Figure 4E). The median number of interruptions was 2 for both pro-dystonic (95% confidence interval: 1.7 – 2.3) and anti-dystonic (95% confidence interval: 1.8 – 2.2) directions, and was not significantly different (ANOVA, $p > 0.05$). There were no interruptions in head movements of the healthy subjects (Figure 4E). Normal peak velocity and peak acceleration, but with increased numbers of breaks in ongoing head

saccades, suggests that increased duration to complete head saccades in CD results from the interruptions in the ongoing head movements.

We next asked whether CD patients program multiple small normal head saccades to achieve one desired head shift (mechanism 2) or a single "normal" head saccade that is interrupted and fragmented into multiple segments (mechanism 3). In order to discriminate between these two mechanisms, we compared the main-sequence relationship between the maximum velocities of the small segments of head movements with either the amplitudes of the corresponding segments of head movement or with the amplitude of the desired head movement. Mechanism 2 predicts that the main-sequence comparing the desired amplitude of head movement with maximum head velocity during each segment of the head movement will have a smaller slope, but the comparison of the maximum head velocities during the movement segments and the amplitudes of the corresponding segments will fall along the normal main sequence. In contrast, mechanism 3 predicts that the main sequence comparing the desired amplitude of head movement with maximum head velocity during the fastest segment will have a normal slope, but the main sequence comparing the amplitudes of movement segments with the corresponding head velocities will have a larger slope. The latter mechanism is plausible because the brain would have programmed head velocity based on the desired large amplitude of the head movement; following each interruption, the head attempts to resume the pre-programmed movement and continue to follow the intended velocity profile, causing each interrupted segment to exhibit a greater velocity than that typically associated with its amplitude.

The main sequence analysis of the maximum velocities of the small segments and the amplitude of desired head movement in CD was not significantly different from that of healthy subjects (ANCOVA, $p > 0.05$). In addition, the main sequence analysis of the maximum velocities of each small head-saccade segment with the amplitudes of those segments revealed an *increased* slope in CD as compared to matched amplitudes of the head saccades from the healthy subjects (healthy slope: 0.35; CD slope: 0.59; Figure 4F). The difference in the linear fit between slopes of the two populations was statistically significant (ANCOVA, $p < 0.05$). These results support mechanism 3, suggesting that central neural commands for head saccades in CD are appropriately programmed, but are pathologically interrupted.

Discussion

Many investigations reported slow voluntary movements in dystonia [3, 5, 8–13]. It was suggested that impaired central programming of motor commands leads to slow head movements in CD [3]. In focal limb dystonia, however, it was shown that slowing of limb movements is due to the co-activation of antagonistic muscles [8, 11–13]. Our results imply that the velocities of head saccades are normal in CD, but their longer durations result from frequent interruptions. The main sequence analysis comparing head velocity with amplitudes implied frequent interruptions of normally programmed ongoing head saccades, rather than abnormal programming as the explanation.

Our results conflict with a prior study that reported reduced velocity of head saccades in CD [3]. However, the range of head movement amplitudes was restricted in the patients evaluated in the previous study [3]. A well-known principle of cephalomotor and ocular motor control is that the velocity of a movement depends on its intended amplitude [6]. Thus, the apparently reduced velocities in the prior study could be due to the restricted range of amplitudes studied.

We observed that movement duration was dependent upon the amplitude of the head saccade. Hence, all patients had increased head saccade transit times relative to controls, and these times varied linearly with the amplitude of the head movement. Such dependence of the duration of the movement on head amplitude makes direct correlation of the transit time and disease duration unreliable. We did not find an influence of direction of head movement (pro- versus anti-dystonic) on duration, but only that head movement transit time increases with the amplitude of desired movements. Likewise, the number of breaks during the head saccade was also proportional to the movement duration and movement amplitude, but not to any other factor.

We can only speculate on the source of the interruptions of head saccades. One class of reticulospinal neurons (RSN) in the nucleus reticularis pontis caudalis and the dorsal nucleus reticularis gigantocellularis show a burst of discharge immediately prior to head movements [14–16]. These neurons receive monosynaptic excitatory projections from the superior colliculus [14] and project to the neck muscles. Their firing rate correlates with neck EMG activity [14]. Two subtypes of such neurons are identified; one subtype features a burst that correlates with the ipsilateral neck EMG activity, while the other subtype bursts with the contralateral EMG [14]. Cross-correlation analyses reveal strong positive and negative correlations of the burst with ipsilateral and contralateral EMG activity. The timing of the burst is related to the onset of agonist activity as well as the suppression of antagonist activity, suggesting reciprocal effects at a segmental level [14]. Activation of the excitatory burst neurons excites the agonist muscle, but the same signal also evokes discharge from the inhibitory neck burst neurons suppressing the activity of the contralateral antagonist muscle, hence facilitating a rapid head movement. One possibility is that premature activation of contralateral neck burst neurons excites the antagonistic muscle leading to interruption in an ongoing head saccade in CD. Indeed this hypothesis is consistent with the notion that breaks in the ongoing movement of a dystonic body region might be caused by intermittent co-activation of the antagonistic muscles [8, 10, 12, 13]. The RSN also receive inhibitory projections from the head movement related omnipause neurons [17]. In the ocular motor system the omnipause neurons remain active during sustained ocular gaze holding, but they are inhibited during eye saccades [18]. Electrical stimulation of primate omnipause during on going eye saccade activates an inhibitory latch circuit and interrupts ongoing eye saccade [19]. This phenomenon in the ocular motor system is similar to interruptions in head saccades as seen in CD, suggesting a second possible mechanism for interruption in an ongoing head saccade; pathologically premature activation of head movement-related omnipause neurons that project to head burst-related neurons.

Inhibitory reticulospinal bursts neurons receive projections from the deep cerebellar nuclei [20, 21]. The first possibility, i.e., the premature excitation of the antagonistic, inhibitory

burst neuron, might be attributed to an disturbed cerebellar signal [22]. Contemporary concepts of distorted cerebellar output in CD [23–25] to the inhibitory reticular spinal burst neurons favor the possibility of premature activation of the inhibitory burst neurons and interruption of ongoing head saccades.

In conclusion, we show that head saccades in CD have an increased duration, consistent with prior studies. However, a quantitative dissection of the temporal characteristics of these movements suggests that the brain programs a head saccade with normal velocity but it is frequently interrupted. The underlying mechanism that we hypothesize to explains the appearance of apparently “slow” head saccades in CD might also apply to the slowing of movements described in other forms of dystonia.

Acknowledgements

This research was supported by Dystonia Medical Research Foundation Clinical Fellowship Award (AS) and NIH U54 NS065710 (HJ).

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Highlights

- Voluntary head saccades have longer duration in cervical dystonia (CD).
- The longer duration is due to frequent pauses in head saccades.
- The frequent pauses reflect pathological interruptions of the intended movement.

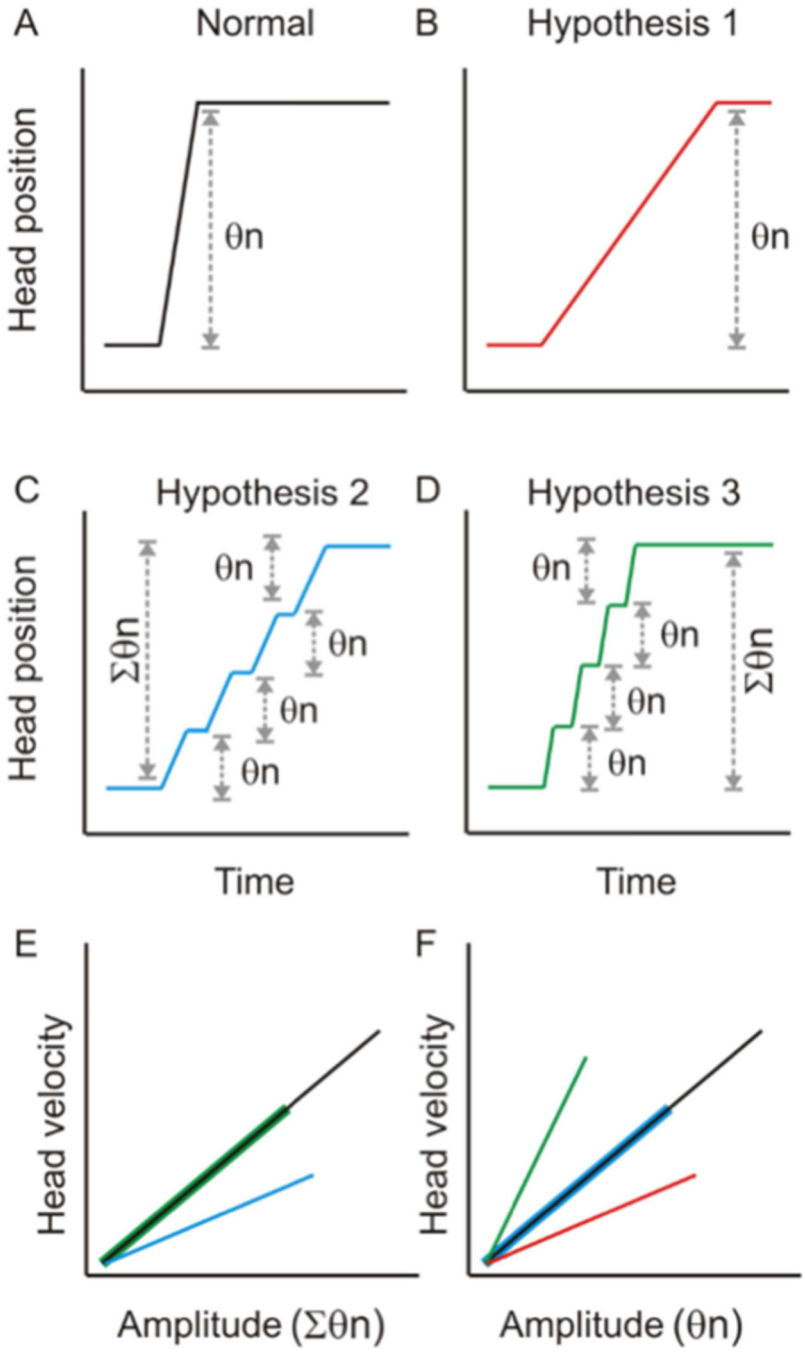

Figure 1.

Schematic illustration of three pontential mechanisms for slowing of head saccades in CD. In panels A-D head position is shown on the y-axis while corresponding time is on the x-axis. (A) Normal subject, head position is depicted as black line. The subject makes one head saccade with amplitude θn. (B) Mechanism 1, head saccades are slow in CD. The peak head velocity is reduced leading to increased movement time for the same movement shown in panel A. (C) Mechanism 2, the brain programs multiple head movements with small amplitude of head movement θ1 through θ4 to accomplish desired head movement with

amplitude θn (θn= θ1+ θ2+ θ3+ θ4). (D) Mechanism 3, the brain programs appropriate amplitude θn, but it is interrupted into smaller segments θ1 through θ4. Panels E and F depict schematic representations of each mechanism in terms of peak head velocity to amplitude (main-sequence) relationship. Amplitude in panel E corresponds to the desired head movement, while the amplitude in panel F corresponds to the amplitudes of each interrupted segment. In mechanism 2, the brain programs smaller head movements, their velocities are appropriate for the segments with smaller amplitude θ1 through θ4, but they are too slow for desired (large amplitude) head movement θn. The corresponding blue line in panel E depicts a smaller slope than the black line but the same slope as black line in panel F. In mechanism 3 (green line) the brain encodes head velocity that is appropriate for the desired head movement with the large amplitude but it is faster for the amplitude of small segments. Thus the corresponding line depicting the main sequence falls on the black line in panel E but it has a higher slope than black line in panel F.

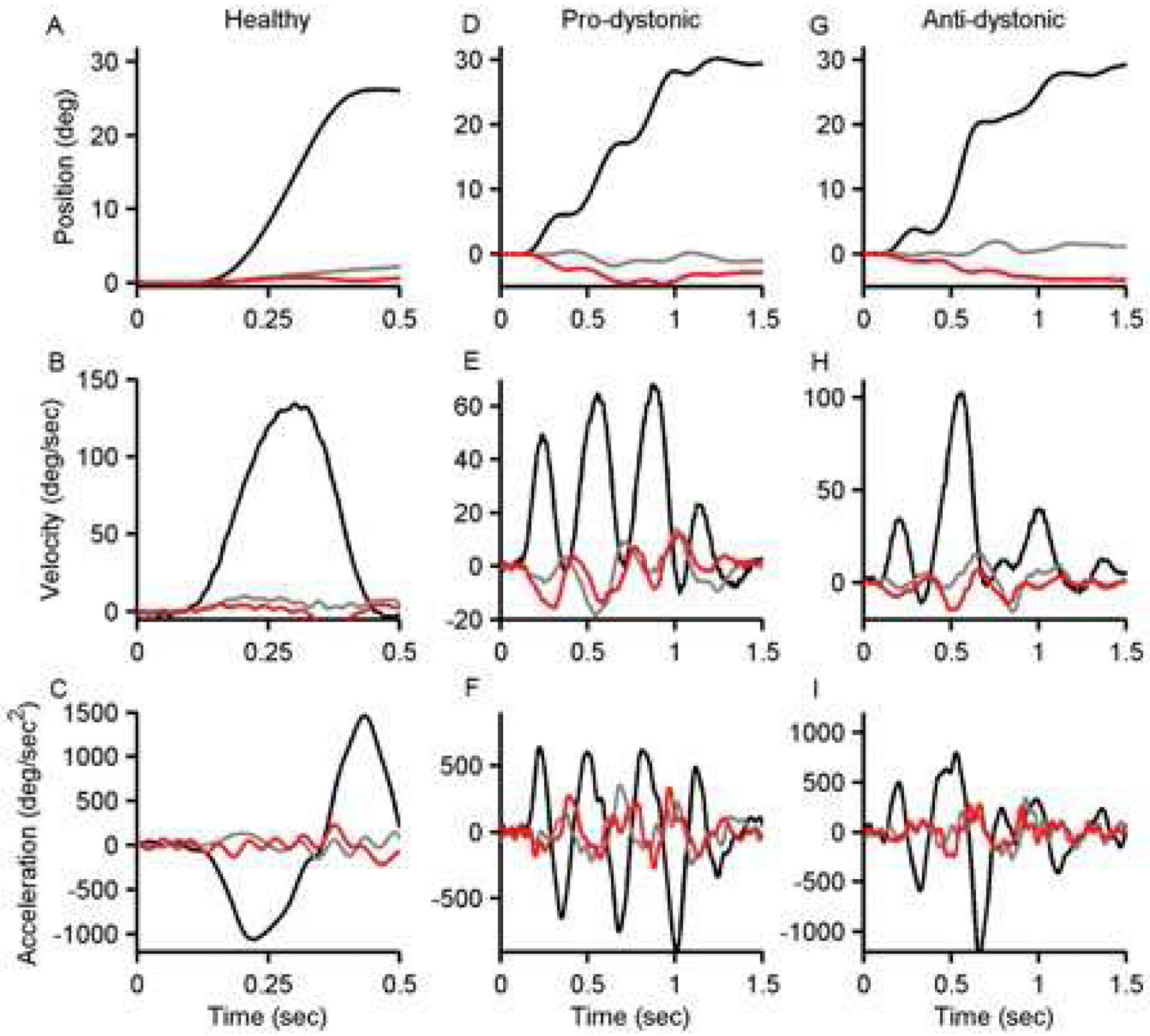

Figure 2.

Representative traces for rapid voluntary goal directed head movements (head saccades). Individual panels show a healthy subject (panels A, B, C) and in a CD patient in the pro-dystonic direction (panels D, E, F) and anti-dystonic direction (panels G, H, I). Included are head position (panels A, D, G); corresponding head velocities (panels B, E, H); and head accelerations (panels C, F, I). In each panel the black trace depicts horizontal movement, the red trace is vertical movement and the gray trace is torsional head movement.

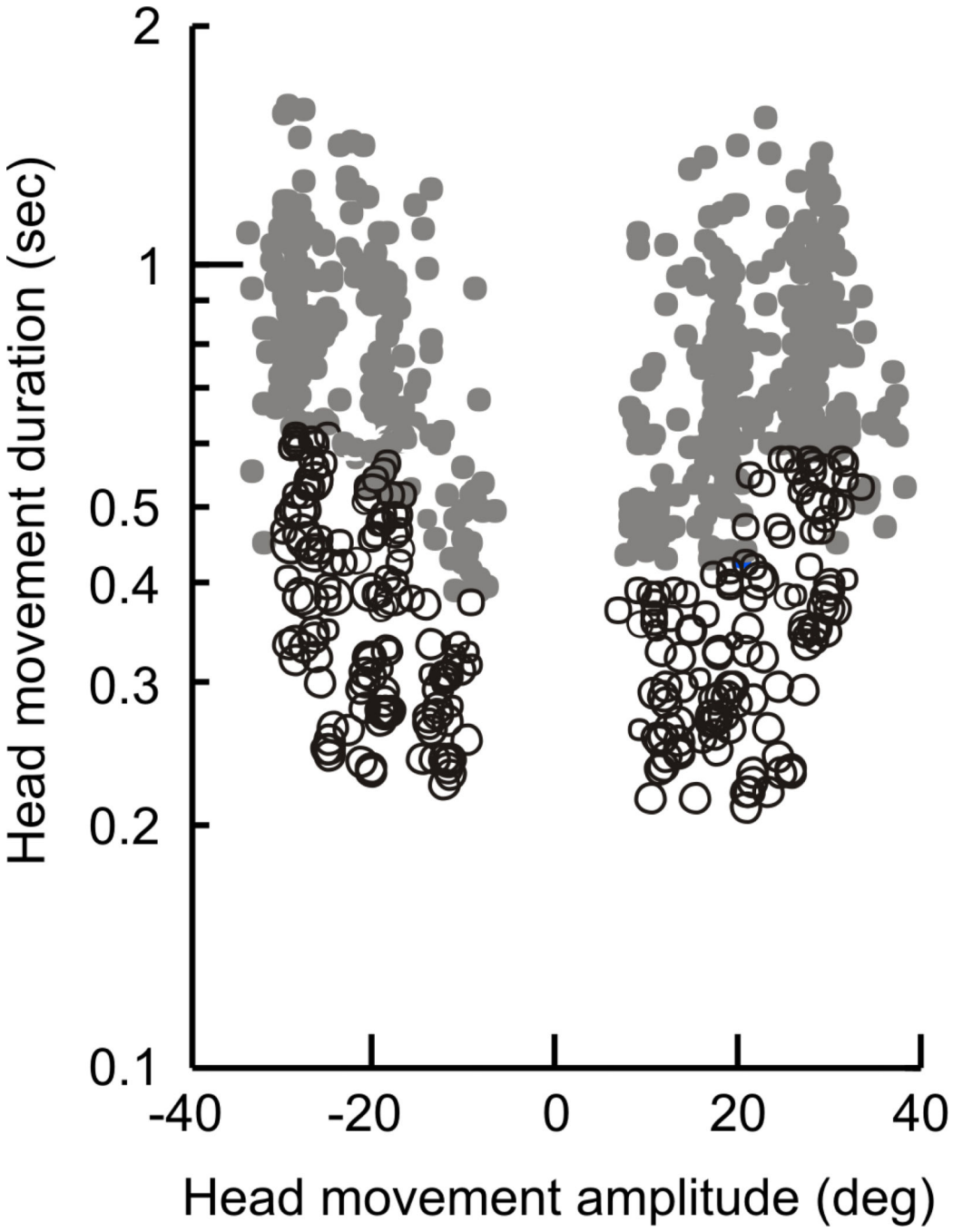

Figure 3.

Relationship of the duration of head movement with corresponding values of the head saccade amplitude. Gray symbols depict CD (n=11) while black open symbols are healthy subjects (n=11). Each data point depicts one head saccade.

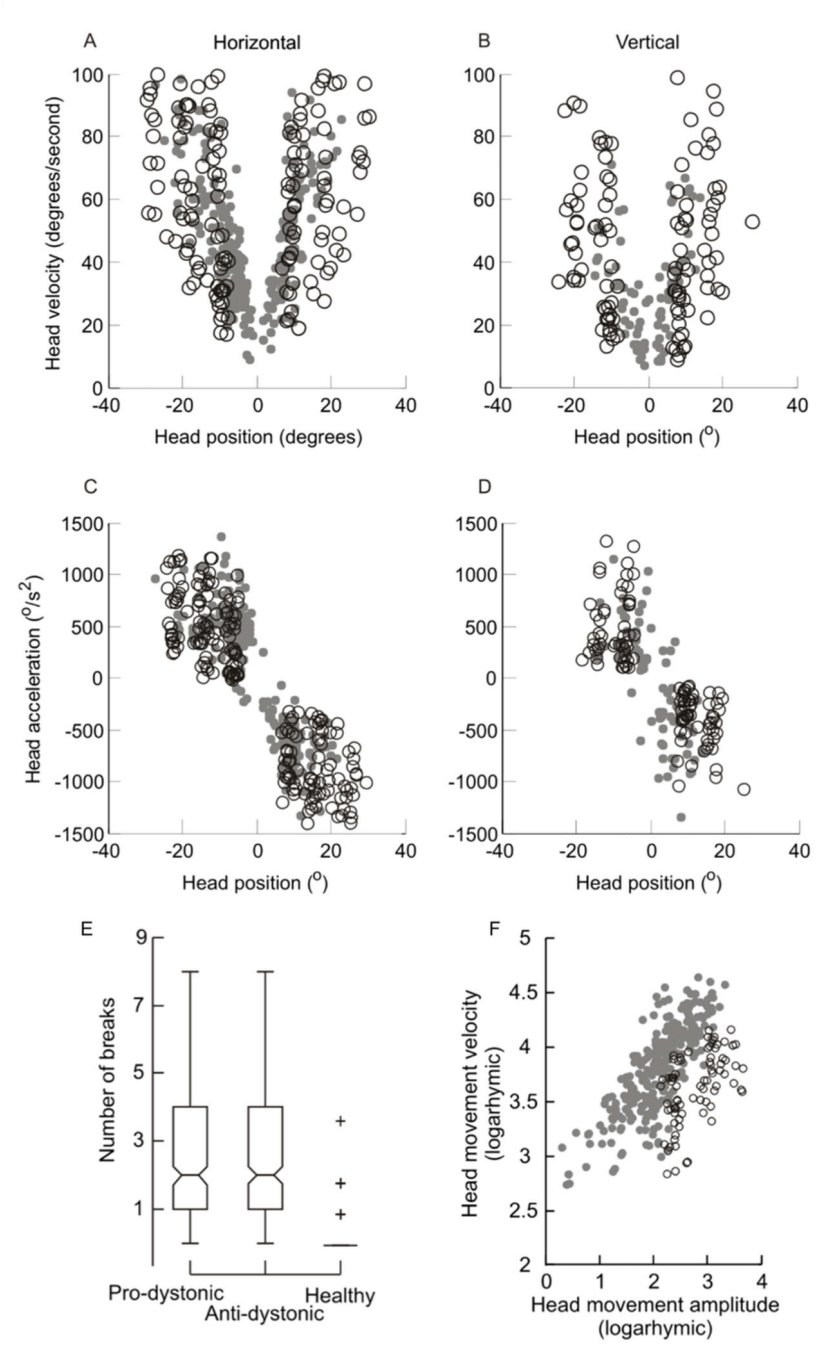

Figure 4.

Main-sequence relationships for head saccades in CD (n=11) and healthy controls (n=11). Gray symbols depict CD while black open symbols are healthy subjects. Each point shows one head saccade. Panel A shows horizontal head velocity with corresponding amplitude. Panel B shows vertical velocity with corresponding amplitude. Panel C shows the relationship of head acceleration with amplitude in the horizontal direction. Panel D shows the relationship of head acceleration with amplitude for vertical head saccades. Panel E compares the number of interruption in anti- and pro-dystonic directions in CD patients

(n=11) and healthy subjects (n=11) as separate box-whisker plots. The horizontal line in the center shows the median number of interruptions, and the notches depict 95% confidence intervals. The length of the boxes depicts interquartile length, while whiskers illustrate the entire data range. Plus symbols are outliers. Panel F compares logarithmic values of amplitude to logarithms of velocity of each segment of interrupted head sacccades in CD patients and healthy subjects. Gray symbols depict CD while black open symbols are healthy subjects. Each data point depicts one head saccade.

Table 1

Increased transit time during head movements

Possible reasons	**Slow head velocity command**	**Pauses during movement**	
Potential mechanisms	Brain programs slow head velocity	Brain programs small amplitude of head movements	Brain programs normal amplitude of head movements but there is an abnormal break in normally programmed head movement
Amplitude to velocity relationship (main-sequence relationship) as compared to normal	Decreased slope of main-sequence as compared to normal.	No change in slope of main-sequence as compared to normal.	Increased slope of main-sequence as compared to normal.

Table 2

Clinical presentation

Case	Age (years)	Sex	Duration of illness (years)	Direction of CD	Clinically apparent OHM?	Response to Botox	Duration since Botox (months)
1	48	F	12	TC Lt, RC	No	Moderate	3
2	87	F	25	LC Rt	Yes	Poor	3.5
3	58	F	2	TC Lt, AC	No	Good	3
4	74	F	12	LC Rt, TC Rt	Yes	Moderate	3
5	49	F	7	TC Lt, LC Lt	No	Good	3
6	57	F	12	TC Lt	Yes	Good	3
7	40	M	9	LC Rt, TC Lt, RC	No	Good	3
8	61	F	10	AC, LC Rt	No	Good	3
9	61	F	4	TC Rt	No	Moderate	3
10	59	F	19	TC Lt, LC Rt	Yes	Moderate	3
11	48	F	9	LC Rt, TC Lt	No	Good	3

Rt: Right; Lt: Left, TC: torticollis, AC: anterocollis, LC: laterocollis, RC: retrocollis