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Research report

Huntington's disease affects movement termination

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Abstract

Huntington's disease (HD) is a neurodegenerative disease affecting the striatum and associated with deficits in voluntary movement in early stages. The final portion of aiming movements is particularly affected in HD and one hypothesis is that this deficit is linked to attention or terminal control requirements. Sixteen patients with early HD and 16 age-matched controls were examined in aiming movements. Four conditions manipulated movement termination requirements (discrete movements with a complete stop vs. cyclical back-and-forth movements) and the presence of flankers around the target. Reducing movement termination requirements significantly attenuated deficits in the final movement phase in patients. The presence of flankers around the target affected the initial portion of movements but did not affect the two groups differentially. These results indicate that terminal control requirements affect voluntary movements in HD. This suggests that frontostriatal systems are involved in movement termination.

Keywords: Huntington's disease; Voluntary movement; Attention; Striatum; Frontostriatal systems; Cyclical movement; Discrete movement; Flankers

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease affecting the striatum at early stages. HD is associated with a number of problems in voluntary movements such as in aiming [38], grasping [4,34,36,37], and tracing [5,7,27]. HD patients also show problems in movement selection especially when movements require attention such as in sequential responses, novel contexts or when interference from competing responses is present [2,6,11,17,19,21,25,30,42,43].

Several studies have suggested that the final portion of aiming movements is significantly affected in patients with HD [18,33,38]. Patients with HD and even preclinical HD gene carriers show irregularity in the late portion of rapid aiming movements that is correlated with the initial aiming error, and this has been interpreted as a problem linked to on-line error correction based on feedback [38]. However, there are indications that error correction is not systematically affected in HD. For example, in tracing movements, which require continuous error correction, early HD patients show movement correction problems only when sensorimotor transformations are needed and not when movements are under direct visual control [27]. Similarly, patients with early HD show precision problems in early and late phases of aiming movements only when sensorimotor transformation is required [5]. In addition, data obtained on patients with Parkinson's disease suggest that the error correction deficit is mainly observed for larger consciously detected errors requiring attention [12]. These results suggest that HD does not affect error control per se, but movement control in situations requiring attention. The present study tested this hypothesis by examining the effects of target-related attention requirements on manual aiming movements in early HD.

Manual aiming recruits a series of complex processes. When the target varies from one trial to the other, target presentation first captures attention [1] and then the target is foveated, which improves its localization based on both retinal and extra-retinal information [31]. The foveation of the target refines attentional processing [23], movement programming and execution [22,29].

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Visual information and attention are particularly important in the final or corrective phase of the movement [8,46].

The final portion of aiming movement has been the subject of much research since the seminal work of Woodworth [46]. This phase involves predictive control using anticipated error information as well as feedback-based control [13]. It has been known for a long time that the final portion of a pointing movement requires more attention as well as ". . . a delicate current control" [46]. Considering that HD patients are known to exhibit problems in attention and in the executive control of action selection [26,41], one possibility is that these problems might contribute to the deficit observed in the final portion of aiming movements in HD.

Different movements produce different demands on the final portion of aiming movements. There is evidence that discrete movements (i.e. a single movement to the target) are controlled by different mechanisms than cyclical movements (back-and-forth movements between two targets) [35]. In healthy adults, cyclical movements are generally more precise and less irregular than discrete movements because of lower movement termination requirements [14,39,40]. Movement termination is an extra movement component which involves achieving simultaneous zero velocity and zero acceleration to stabilize the limb at the target. Cyclical movements produce significantly lower activation of frontostriatal systems than equivalent discrete movements suggesting that lower termination requirements allow cyclical movements to be performed more automatically (i.e. with less attention) than discrete movements [35]. If the voluntary movement deficit in HD is linked to the attentional demands of movement, performance should be more affected in discrete movements than in cyclical movements in patients with HD.

Aiming movements are also sensitive to the visual context. When aiming towards a target, irrelevant stimuli (flankers) in the vicinity of the target or the trajectory can increase reaction time and movement duration as well as steer movements away or towards them [44,45]. Pratt and Abrams [32] showed that the final portion was particularly affected by flankers. Tipper et al. [44] proposed that the perception of both target and flankers elicits parallel response preparation processes and thus the response to the flankers must be inhibited in order for the target response to be selected. It has been proposed that frontostriatal systems play a critical role in selection between response alternatives [26]. In HD, ocular saccades are sensitive to flankers surrounding the target [16]. Also, in aiming movements, reaction time is preferentially affected by distractors in patients with HD [3]. However, the previous studies on HD did not evaluate the effect of flankers on the final portion of aiming movements per se.

The present study will examine the hypothesis that the deficit observed in the final phase of aiming movements in HD is influenced by the attention requirements of the movement. Specifically, two factors which often affect voluntary aiming will be examined, including movement termination requirements and the presence of flankers surrounding the movement target.

Table 1
Clinical data for HD patients

Patient	Age (years)	Sex	UHDRS motor score (chorea index)	UHDRS cognitive score	Medication
1	49	F	20 (8)	166	Nil
2	58	M	44 (13)	124	Citalopram[a], Olanzapine[b] and Lorazepam[c]
3	48	F	–	127	Nil
4	39	M	46 (8)	103	Citalopram[a], Olanzapine[b] and Divalproex[d]
5	40	M	21 (2)	–	Nil
6	40	M	27 (4)	134	Bupropion[a], Citalopram[a], Olanzapine[b], Oxazepam[c] and Divalproex[d]
7	54	F	38 (17)	128	Nil
8	43	F	43 (8)	104	Topiramate[d]
9	53	M	21 (7)	212	Bupropion[a], Venlafaxine[a], Olanzapine[b] and Methylphenidate[e]
10	52	M	8 (0)	132	Escitalopram[a]
11	49	F	15 (1)	194	Venlafaxine[a]
12	48	F	32 (12)	167	Citalopram[a], Amitriptyline[a] and Irbesartan[f]
13	57	M	24 (12)	145	Nil
14	42	M	10 (5)	226	Mirtazapine[a] and Levetiracetam[d]
15	45	F	20 (9)	202	Venlafaxine[a]
16	41	M	16 (3)	148	Fluoxetine[a]

Note: UHDRS motor score range from 0 to 120 where 0 is normal. Maximal chorea score range from 0 to 28 where 0 is normal. In the cognitive score, higher values indicate better cognitive performance.

[a] Antidepressants.
[b] Antipsychotics.
[c] Benxodiazepines.
[d] Anticonvulsants.
[e] Stimulants.
[f] Antihypertensives.

2. Method

2.1. Participants

Sixteen genetically confirmed patients with early-stage HD ($M = 47.4$ years, S.D. = 6.0) were compared to 16 age-matched controls with no history of cerebral damage ($M = 45.9$ years, S.D. = 8.3). All participants had normal or corrected-to-normal vision and were right handed. Table 1 presents clinical data on the HD patients. For all participants, written informed consent to participate in the study was obtained according to the rules of the hospital.

2.2. Apparatus and procedure

Movements were performed with a pen on a digitizing tablet (Wacom, 30 cm × 30 cm) connected to a computer. The position of the pen was sampled at 94 Hz. The moving arm was hidden from view by an occluding screen and the displacement of the pen was monitored on a vertical computer screen in front of the participants (ratio 1:1). Participants sat upright in a chair and were directed to maintain a consistent initial position before each trial. In both the discrete and cyclical conditions, the starting base was first shown for 3.5 s. Participants were instructed to place the pen inside the starting base and wait for the target. The color of the starting base changed from gray to blue when it was reached. Participants were asked to make sure to touch the target on every trial and move at the fastest speed which would allow them to do so. This procedure was selected in order to avoid any possible confounding effect of a speed-accuracy tradeoff. A practice session was conducted before each condition (16 trials for the discrete condition, 8 trials for the cyclical condition) to make sure that these instructions were followed. The color of the target changed from white to gray when it was reached. An auditory signal (800 Hz, 20 ms) indicated the beginning of each movement. For cyclical movements, the end of the 10-s trial was also cued by the same auditory stimulus. The auditory cue did not affect the motor performance because the last few seconds of cyclical movements were not used in the analyses. In the discrete movement task (80 trials), participants performed simple aiming movements from the starting base to the target whereas the continuous movement task involved moving back and forth from the starting base to the target during 10 s (40 trials).

The target was a white circle with a black "X" inside its perimeter (diameter: 0.5 cm) at 45° in the upper right quadrant from the starting base. Flankers were present on half of the trials. Flankers were three empty white circles identical to the target (except for the X inside) located on the axis linking the starting base to the target (see Fig. 1). Participants were instructed to ignore the flankers when present. Targets and flankers were separated by a distance of 0.8 cm, and were presented at one of four possible locations (14, 14.8, 15.6, 16.4 cm from the starting base). The order of presentation of the targets/flankers was randomized within each block but was identical for the two conditions and for all participants. The order of presentation of the two conditions (discrete vs. cyclical) was also randomized across participants. Conditions were separated by a short pause.

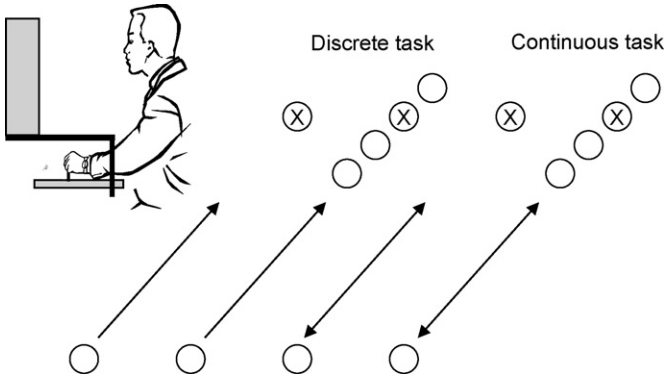

Fig. 1. Experimental setup.

2.3. Data reduction

The displacement data of the cursor over time were first smoothed using a Butterworth filter with a cutoff frequency of 7 Hz. The smoothed data were then numerically differentiated once to obtain the velocity profile of the aiming movement, a second time to obtain the acceleration profile and a third time to obtain the jerk profile.

In cyclical movements, the first upward movement was not used because the movement was not considered as being cyclical. Also, only the second and third upward movements of each 10-s trial were considered in the analysis to compare an equal number of segments in all participants and in both conditions (two upward movements/trial × 40 trials = 80 movements).

Each movement toward the target was then segmented in two sub-movements. The primary sub-movement is the trajectory between movement onset and the first negative-to-positive transition of the acceleration profile after peak velocity. The trajectory following that point was considered as the secondary sub-movement which reflects the final/corrective phase [15,28].

Temporal, kinematic and fluency measures were calculated in order to determine the influence of the movement condition and flankers on the execution of aiming movements in the two groups. The peak vertical velocity and movement time were calculated for each sub-movement as well as for the overall movement. The beginning of each movement was defined as the time at which relative velocity first reached 0.5% of peak velocity, whereas movement completion was defined as the time at which 0.1% of peak velocity was reached following peak deceleration. Measures of movement fluency included normalized jerk, absolute jerk and the number of acceleration–deceleration transitions. Optimal and smooth movement control is achieved by minimizing discontinuities in velocity and its higher-order derivatives such as acceleration and jerk [24]. Normalized jerk was calculated as follows

$$\sqrt{(1/2)\int \mathrm{dt}\ j2(t) \times \mathrm{duration}^5/\mathrm{length}^2}$$

Normalized jerk is unitless as it is normalized for stroke duration and size. This measure has been shown to be useful as an index of regularity in repetitive cyclical movements [42]. Normalization can only be performed for complete movements and is not meaningful for multiple sub-movements. To determine the irregularity in each sub-movement, absolute jerk and the number of acceleration–deceleration transitions were also calculated. Absolute jerk is the root mean square (RMS) value of absolute jerk across all samples of a movement or a sub-movement. Acceleration–deceleration transitions cause a segmentation of the movement, resulting in an intermittent, less efficient and less smooth movement. Acceleration–deceleration transitions and jerk measures were determined on the vertical axis [42].

3. Results

All measures were analyzed using a Group (HD vs. Controls) × Condition (Discrete vs. Cyclical) × Context (Flankers vs. No flankers) ANOVA with repeated measures on the last two factors. Only the significant effects are reported. All significant effects and interactions were further analyzed using the Scheffé procedure with a threshold of $p < 0.05$.

Patients with HD displayed longer movement duration than controls, $F(1, 30) = 9.55$, $p = .004$. Movements performed by patients with HD were also more irregular than controls as measured by normalized jerk, $F(1, 30) = 23.83$, $p = .00003$, and the number of acceleration transitions, $F(1, 30) = 6.43$, $p = .016$, and there was a trend for absolute jerk, $F(1, 30) = 3.70$, $p = .06$. Subsequent analyses showed movement time and fluency was more affected in discrete than in cyclical movements in patients but not in controls as shown by significant Group × Condition interactions on movement time, $F(1, 30) = 7.38$, $p = .01$, normalized jerk, $F(1, 30) = 11.5$, $p = .002$ and

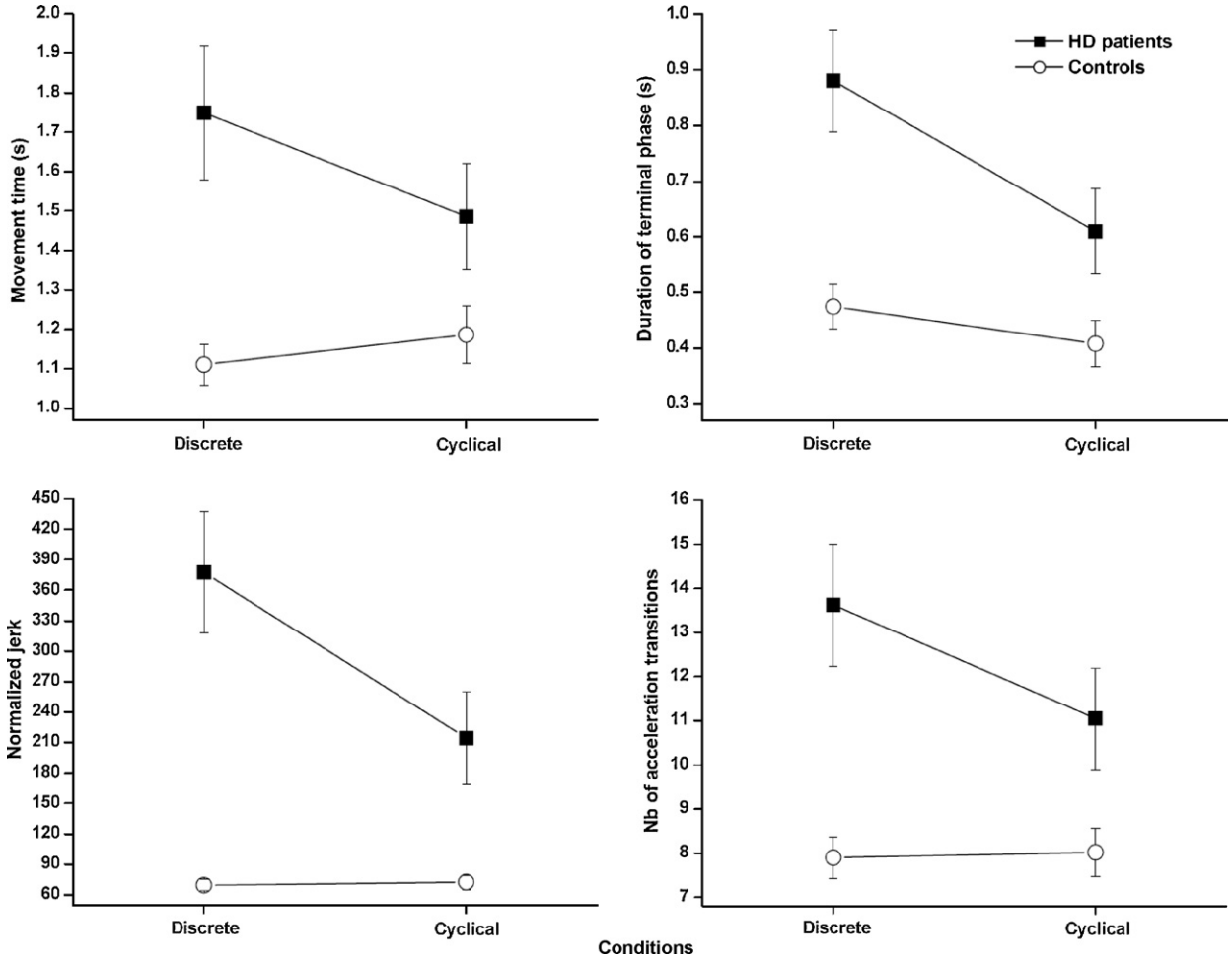

Fig. 2. Movement time, duration of the terminal phase, normalized jerk and number of acceleration transitions as a function of group and condition. Standard errors are represented by vertical bars.

the number of acceleration transitions, $F(1, 30) = 6.43$, $p = .016$ (see Fig. 2).

For the secondary sub-movement, Group × Condition interactions were also observed on the duration and the number of acceleration transitions (duration: $F(1, 30) = 16.03$, $p = .0004$; number of acceleration transitions: $F(1, 30) = 5.56$, $p = .02$). No significant interactions were observed for the duration, $F(1, 30) = 2.03$, $p = .16$, or the number of acceleration transitions: $F(1, 30) = 1.76$, $p = .19$) in the initial sub-movement. These results suggest that the effects observed on the overall parameters were mostly modulated by changes on the secondary sub-movement. To test whether medication could explain the effects observed, we compared the performance of five unmedicated patients to that of the rest of the patient group and all five patients showed scores that were equal or worse than the group average of patients for all measures.

When flankers were present, peak velocity was lower as compared to trials in which no flankers were presented, $F(1, 30) = 7.00$, $p = .013$. Additional analyses showed that the presence of flankers affected peak velocity during the initial sub-movement, $F(1, 30) = 6.80$, $p = .014$ but not the secondary sub-movement, $F(1, 30) = .005$, $p = .94$, suggesting that flankers mostly affected the initial portion of the movement. Movement was also smoother when flankers were present as measured by absolute jerk, $F(1, 30) = 4.28$, $p = .047$. Again, this effect was observed for the initial sub-movement, $F(1, 30) = 4.71$, $p = .038$ but not for the secondary sub-movement, $F(1, 30) = .04$, $p = .83$.

Correlations between scores of the UHDRS clinical evaluation (motor score, cognitive score) and the main movement measures were examined on 14 patients. A Bonferroni correction was used to correct for the number of correlations examined. No significant correlations were found between the cognitive score of the UHDRS and movement parameters, but this may be linked to insufficient statistical power. However, the UHDRS motor score showed significant positive correlations with normalized jerk, as well as with the duration and irregularity of the terminal phase in discrete movements (all rs > .66, all ps < .001). We further examined whether these correlations were linked to the presence of chorea, but found no significant correlation between the chorea index and movement parameters. Thus, the significant correlations observed appear to be more closely linked to general disease progression than to chorea.

In complementary analyses, we compared five patients with very little or no chorea to controls on the main movement parameters. We reproduced the key effects of an attenuated irregularity (NJ: $F(1, 20) = 22.19$, $p = .00012$; number of acceleration

transitions, $F(1, 20) = 8.37$, $p = .009$), and shorter secondary sub-movement duration, $F(1, 20) = 6.84$, $p = .02$, in cyclical movements as compared to discrete movements in patients.

4. Discussion

Patients showed increased movement time and irregularity as compared to controls in both discrete and cyclical movements. These results are mostly related to temporal and fluency anomalies during the secondary sub-movement, confirming that the final portion of aiming movements is clearly affected in patients with HD [18,33,38].

More importantly, our results also show that this aiming deficit in HD is significantly attenuated in cyclical movements, especially in the final portion of the movement. Discrete and cyclical movements involved reaching targets of identical size and location. The accuracy and speed requirements of the two movement types were also identical. The main difference between the two movements is that cyclical movements do not involve full termination of the movement. The present results indicate that patients with early HD can take advantage of reduced termination requirements of movements to significantly reduce deficits observed in aiming and thus that movement termination contributes to the voluntary movement deficit in HD.

The voluntary movement deficits in HD have been characterized in a number of ways. One suggestion has been that HD affects error feedback control [38]. Our results indicate that the aiming deficit in HD can be manipulated independently of error feedback control since precision requirements did not vary across the two types of movements examined here. This suggests that the deficit observed in the final part of aiming movements in HD is more generally linked to the control requirements of the movement than to error correction alone. There is evidence that discrete movements involve additional attentional or cognitive control processes linked to frontostriatal activity [35]. Frontostriatal brain systems, affected in HD, have critical roles in the attentional control of action [26]. Frontostriatal dysfunction in HD may affect attentional processes involved in the final phase of aiming movements leading to increased movement duration and irregularity. In line with other recent results, the present data suggest that HD affects the planning of sub-movements in demanding conditions [5,12,27].

In healthy adults, cyclical movements are often more precise and less irregular than discrete movements [14,39,40]. In the present study, no such advantage was observed in controls, possibly due to a floor effect linked to the parameters of the task, such as emphasizing precision over velocity and using medium target sizes.

The deficits observed in the present study cannot be attributed to medication or the presence of involuntary movements. None of our movement parameters correlated with the chorea index and HD patients with little or no chorea showed the same attenuation of the terminal phase deficit in cyclical movements as other patients. Also, involuntary movements in HD are often significantly inhibited during attentional engagement in a task [7,38]. The fact that the motor score of the clinical scale (UHDRS) significantly predicted patient performance supports the idea that the aiming deficit in HD is linked to disease severity and should be evaluated as a marker of progression in HD.

In the present study, patients were not preferentially affected by the presence of flankers. This may be because their movement deficits are mainly observed in the final part of the movement [27,38], whereas the flankers used in the present study mostly affected the initial portion of the movement. Flankers reduced peak velocity and absolute jerk in the first sub-movement but not in the second sub-movement. These results are contrary to the results obtained by Pratt and Abrams [32] showing that distractors affect the final portion of movements but are in line with results obtained by Glover and Dixon [20] showing that the contextual information surrounding the target mainly affects the initial part of the movement. It could be proposed that depending on the characteristics of the stimuli surrounding the target (location, salience, size, shape, . . .), their effect could be either beneficial or detrimental to the performance and affect different portions of the movement [9]. The flankers used in the present study may have helped guide and calibrate the movement rather than having a detrimental effect on performance. In that vein, some studies have shown that the visual context surrounding a target can help improve movement accuracy [10]. Therefore, slower movements may be linked to the need to process supplementary visual information rather than a detrimental consequence of movement control problems.

Early HD patients have more movement problems when indirect vision is used to guide movements (e.g. Lemay et al., 2006). One possible explanation is that indirect vision provides a level of cognitive demands in movement (e.g. mapping transformation, movement monitoring demands) which make their movement problem more detectable. However, whatever the reason for the presence of a movement problem in discrete movements in indirect vision, the present data indicate that cyclical movements reduce the movement deficit as does direct vision, suggesting that the aiming deficit in HD is linked to task demands.

Overall, the present results show that movement termination requirements contribute to the voluntary movement deficit in HD. This suggests that frontostriatal systems are involved in movement termination. This also suggests that deficit observed in the final portion of aiming movements in HD is more generally linked to attention requirements and not to error correction alone.

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