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Abstract

Background: Understanding the contribution of anticipatory postural adjustments (APA) on walking ability in individuals with Huntington's disease (HD) may provide insight into motor planning and the functional consequences of HD-specific cortical-basal ganglia pathway dysfunctions. **Research Question.** How do inertial measurement unit (IMU)-derived APAs and first step parameters differ between individuals with HD and controls under no load and cognitive load conditions, and what is their relationship to gait speed and clinical measures?

Methods: 33 individuals with manifest HD and 15 age-matched healthy controls wore three Opal APDM IMUs during a 14-meter walk during a no load and cognitive load condition. APA acceleration amplitudes, APA durations, first step range of motion (ROM), and first step duration were compared, along with their relationship to gait speed. **Results:** Individuals with HD had greater APA acceleration amplitudes, smaller first step ROM and longer first step durations compared to healthy controls. No differences in APA durations were present between groups in both conditions; cognitive loading did not affect the APA parameters. Mediolateral APA acceleration amplitudes were a significant predictor of gait speed and were related to disease-specific measures. **Significance:** Larger acceleration amplitudes and smaller first step ROMs of greater duration, accompanied by the preservation of APA durations, reveal a discrepancy in movement scaling in HD. Additionally, the mediolateral component of the APA is likely a rate-limiting factor that drives a compensatory response in gait initiation. Further research is needed to explore the neural correlates of HD-related movement scaling.

Keywords. Huntington's disease, gait initiation, motor, inertial sensors, cognitive load, accelerometers

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Availability of data and material: Upon request from the authors

Introduction

Huntington's disease (HD) is an inherited neurodegenerative disease that leads to basal ganglia pathway dysfunction of striatal origin, resulting in progressive motor and cognitive disturbances [1]. Gait-related impairments begin in the early stages and worsen through disease progression [2]. Gait initiation, i.e., the preparation and execution of the first step of a gait sequence, reflects the complex integration of movement planning and execution. Anticipatory postural adjustments (APAs) are the first component of gait initiation and are used to stabilize posture in preparation and allowance for lifting the initial stepping leg. APAs are marked by the period of time when the center of mass accelerates laterally and forward, by shifting the center of pressure backward and towards the stance leg just prior to toe-off. Validated accelerometry measures indicate that adequate amplitudes and durations of APAs facilitate first step execution by minimizing balance disturbances [3,4]. Appropriately timed and scaled gait initiation is necessary to maintain stability as an individual transitions from a static posture to dynamic locomotion [5,6].

Individuals with early and mid-stage HD have inadequately scaled APAs and first steps in a gait sequence [6]. Specifically, Delval et al (2007) report decreased accelerations of the center of mass and decreased velocity of the center of mass at heel contact (first step) in individuals with manifest-HD compared to controls during cued and self-triggered gait initiation. However, the duration of APAs was only different during self-triggered conditions [6]. APA acceleration amplitudes and smoothness could provide insight into functional consequences of disease-specific basal ganglia pathway dysfunction, however these have not yet been explored in HD.

Cognitive interference is the relative degradation in motor performance caused by the addition of a cognitive load during a motor task [7,8]. Evaluation of cognitive interference can provide key insights into how attentional and neural resources are distributed. Previous studies have shown that deficits in gait initiation are exacerbated with the addition of an executive functioning task in individuals with PD [9,10]. Similar and yet distinct cortical striatal changes are present in HD, however, the cognitive-motor consequences of these changes have yet to be explored within the context of gait initiation in HD [11].

APAs play an integral role in overall gait quality, specifically in gait speed and in the maintenance of dynamic stability during step execution. Mediolateral APAs play a crucial role in controlling mediolateral stability during gait initiation in healthy controls [12], but this relationship has not been explored in HD. Sufficient motor planning is necessary for the adequate integration of temporal and force parameters of both the anticipatory and voluntary movement, and a mismatch of these parameters may be a reflection of a motor planning deficit.

In this study, we aimed to: 1) determine inertial measurement unit (IMU)-derived measures of APA acceleration amplitudes and durations, and first step range of motion (ROM) and durations as previously identified via force plate measures, in individuals with manifest HD and healthy controls; 2) evaluate gait initiation parameters under an additional cognitive load in individuals with manifest HD compared to healthy controls; and 3) explore the relationship between APA acceleration amplitudes and smoothness, and the contribution of APA amplitudes to gait speed. We hypothesized that IMU-derived measures of APA acceleration amplitudes, but not durations, would be greater, and initial step length would be smaller with shorter durations in individuals with manifest-HD when compared to healthy controls. We further hypothesized

there would be a larger magnitude of motor deficits of gait initiation parameters when under a cognitive load (e.g., dual task), as evidenced by increased APA amplitudes and durations, and decreased first step lengths compared to walking under no cognitive load (e.g., single task).

Methods

Subjects

Individuals with HD were recruited from the New York State Psychiatric Institute in New York, NY, Wayne State University in Detroit, MI, and the George Huntington Institute in Munster, Germany. Inclusion criteria were: 1) age 18 years or older, 2) diagnosis of HD as confirmed by the individual's neurologist, 3) capacity to consent, 4) Total Functional Capacity (TFC) [13] score of 7 or greater, 5) ability to walk 10 meters independently without any assistive device. Exclusion criteria: 1) diagnosis of juvenile-onset HD, 2) history of co-morbid neurological conditions, 3) acute orthopedic conditions or injuries, 4) inability or unwillingness to give written informed consent. The protocol for this study was approved by the respective institutions. All participants signed written informed consent.

Demographic and clinical measures

Demographic data and Unified Huntington Disease Rating Scale (UHDRS) TFC and Total Motor Score (TMS) [13] were obtained within three months of testing (Table 1). Participants completed two cognitive assessments: Symbol Digit Modality Test (SDMT) [14] and Delis-Kaplan Executive Function System (D-KEFS) [15].

Experimental Setup and Protocol

Opal inertial measurement unit (IMU) sensors (APDM, Inc., Portland, OR) were secured to the dorsum of the feet bilaterally at the level of the metatarsals, and the lumbar region of each participant via velcro straps. Participants started walking at the sound of a tone, walked to a 7-meter mark, turned and walked back to the start, completing 14 meters. The walking condition consisted solely of the 14-meter walk (no-load). For the walking condition with an added cognitive load, participants were instructed to begin walking while performing the D-KEFS verbal fluency task with category switching. Participants were asked to alternatively name items of fruit and furniture while walking the same 14-meter distance. Responses were recorded and scored for correct numbers of switches in the walking period as compared to the performance of the D-KEFS category switching test in sitting. Each condition consisted of a single trial with the simple walking task always preceding the more complex walking with the D-KEFS.

Extraction of IMU-based measures

Raw signals from the accelerometers were set to horizontal and vertical coordinates by the sensors' pre-existing algorithms, which utilize the magnetometers and gyroscopes to identify x, y, and z reference positions. The lumbar and ankle accelerometry streams were extracted and processed in Matlab (Mathworks R2018A). Accelerometry streams, sampled at 128Hz, were filtered through a 3.5Hz cut-off, zero-phase, low-pass Butterworth filter. This filtering profile is consistent with previous uses of APDM IMU sensors in identifying APAs [16].

APDM Mobility Lab software was unable to apply the standard algorithm for APA processing in most HD participants, secondary to the excessive movements during static stance prior to gait initiation. We, therefore, extracted APAs in a custom Matlab program by constructing a time window 1000ms prior to the time of toe-off of the first stepping leg, as

defined as the first peak acceleration in the anterior direction of the ankle sensor. Within this time frame, the maximum value in the mediolateral lumbar accelerometry stream indicated the amplitude of the medial-lateral (ML) APA. Our process of extraction of APAs from raw accelerometry streams was modeled after the work of Mancini et al.[17]. The onset of the APA was defined as the time point at which the ML accelerometry stream reaches 20% of the identified maximum value within the predetermined time window (Fig. 1). Therefore, the duration of the APA was defined as the length of time between the time of onset to the time of toe-off of the first stepping leg. The anterior-posterior (AP) component of the APA occurs after the first peak of the ML component; amplitudes of the AP component were thus determined by finding the maximum AP value of the lumbar stream within the time window after the maximum ML peak value and toe-off of the first stepping leg. All accelerometry streams were visually inspected as a second measure to ensure that peak values were determined within appropriate time windows. Duration windows below 10ms and above 7500ms, along with amplitudes below .01(G-units) and above .9(G-units), were not considered as potential APAs [16].

INSERT FIGURE 1 HERE

Spatiotemporal parameters of the first step were derived using angular velocities extracted from the ankle gyroscope of the first stepping leg [16]. First step duration was defined as the length of time from APA end, as defined as toe-off, to heel strike of the first stepping leg [16]. Specifically, first step duration was defined as the time-to-peak angular velocity from APA end to heel strike. The spatial feature of the first step was assessed using the first step range of motion (ROM), by integrating the angular velocity of the ankle sensor from APA offset to heel-strike within the gyroscope stream. Smoothness of the APA in the ML direction was defined as

average jerk (m/s^3) within the APA period. Specifically, peak acceleration in the ML direction was divided by the duration of the APA.

Statistical Analysis

Statistical analyses were performed in SPSS (SPSS Inc. Released 2018. SPSS for Mac, Version 25.0. Chicago, SPSS Inc). Levene's test was utilized to assess the homogeneity of variance for amplitudes and durations ($p > .05$). Gait initiation parameters for the no-load and cognitive-load conditions were analyzed for HD and control groups using a two-way repeated measures ANOVA, with a post-hoc Tukey HSD. Pairwise comparisons of means were used to assess amplitudes and duration across conditions within and between participant groups. A regression analysis was used to determine the degree to which APA parameters could predict gait speed during the 14-meter walk in HD participants. Pearson correlations were utilized to assess correlations between all APA variables and clinical measures. Differences in age and cognitive measures between groups were compared using independent t-tests. Kernel density estimations were calculated and visually depicted as violin plots using the online platform, Plot-ly. The violin plots represent the distribution of the data and associated variability within each group across conditions. Dashed lines within each plot represent the median, while any black dots represent data outliers. The significance value was set at $p < 0.05$ for all analyses.

Results

Forty-eight participants were recruited for this study as part of the iWEAR-HD project, including 33 individuals with manifest HD (20 males, mean age 54.67 ± 12.57), and 15 healthy controls (8 males, mean age 53.2 ± 13.18). The aforementioned sample size is large enough to indicate gait-

related differences in HD and other rare diseases, as demonstrated by previous gait studies [2,6]. Table 1 provides demographic and disease-specific measures. There was no difference in age between the HD and control groups ($p < 0.05$). There was a significant difference in both measures of cognitive function (DKEFS and SDMT) ($p < 0.01$). We recorded medications for all participants, and provide the number of individuals on medications to specifically address the movement disorder (e.g. chorea).

INSERT TABLE 1 HERE

Mean values and standard deviations of all outcome measures of groups across task conditions are listed in Table 2. In line with previous research, there was a significant difference in gait speed between HD and controls ($F(1,43)=6.76, p=0.013$), and a significant main effect for task condition ($F(1, 43)=90.27, p < 0.001$), where gait speed decreased under the cognitive load condition for both groups. There was no significant interaction ($p=0.39$). There was a significant main effect for APA acceleration amplitudes between groups, with HD having greater ML ($F(1, 46) = 38.49, p < .001$) and AP ($F(1, 46) = 78.51, p < .001$) amplitudes (Fig. 2). There were no main effects for task condition and no interaction effects for APA acceleration amplitudes ($p > .05$). For APA durations, there was no main effect for group or task conditions ($p > .05$) (Fig. 3).

INSERT TABLE 2, FIGURE 2 and FIGURE 3 HERE

The HD group had significantly larger first step duration values ($F(1,46)= 26.20, p < .001$) and smaller first step ROM values ($F(1,46)=12.67, p = .001$) compared to healthy controls (Fig.

4). There was no main effect of task conditions and no interaction effects for first step parameters ($p > .05$).

INSERT FIGURE 4 HERE

The HD group had a greater AP average jerk ($F(1,46)=26.68$, $p < .001$) compared to the control group, however there was no significant difference in the ML direction ($F(1,46)=2.21$, $p=.144$). There was no main effect of task conditions and no interaction effects for either AP or ML average jerk ($p > .05$).

Results of the linear model assessing the role of APA and first step parameters in HD did not indicate a significant model ($R^2=.1019$, $F(4, 26)=1.851$, $p=.15$). However, ML eAPA acceleration amplitudes ($\beta = -2.150$, $p=.04$) were a significant predictor of gait speed. Results of a similar analysis among controls found that no APA and first step parameter were significant predictors of gait speed ($p=.29$). Results of the repeated measures ANOVA on gait speed during the 7-meter walk indicated a significant main effect for both groups ($F(1,46)=7.551$, $p=.01$) and condition ($F(1,46)= 60.54$, $p=.00$).

Lastly, we examined the relationships between APA amplitudes and durations, and their relationship with disease-specific measures of cognition and function. APA ML amplitude and duration under the no-load condition were significantly correlated ($p=.348$, $p=0.47$), but not under cognitive load conditions ($r=.089$, $p=.624$). APA AP amplitudes were not correlated with duration under no load and cognitive load conditions ($p > 0.05$). APA ML amplitudes under the cognitive load condition were significantly correlated with TFC ($r=-.442$, $p=0.01$) and TMS ($r=0.452$, $p=0.009$). APA ML amplitudes under the no load condition were significantly

correlated with TMS ($r=.350$, $p=0.049$) and SDMT ($r=0.390$, $p=0.025$). APA durations and APA AP amplitudes were not correlated with any of the disease-specific measures ($p>0.05$).

Discussion

Our results confirm previous findings [6] that individuals with HD exhibit greater APA acceleration amplitudes, but not durations, in both the ML and AP directions when compared with healthy controls. Individuals with HD displayed smaller ROM values and larger first step durations that remained unaffected by cognitive loading. The preservation of APA duration between groups may come as a result of inadequate force modulation in the ML direction causing the prioritization of first step completion in the HD group. The large correlations between ML APA and APA duration may indicate a dominant rate-limiting factor within gait initiation. The larger accelerations values in HD, with the absence of time scale adjustments, reflects a disintegration between the APA and the associated voluntary movement initiation.

Maintenance of APA duration between groups and conditions with a cognitive load further indicates a mismatch in APA and step initiation. This mis-scaling between duration and acceleration amplitudes remained unaltered as a result of cognitive load, indicating consistent spatiotemporal mis-scaling despite cognitive interference. This is in contrast to individuals with PD, where first step durations but not APAs are vulnerable to a cognitive load [9]. We speculate that the cognitive task did not interfere with the gait initiation due to motor prioritization and perhaps due to a lack of overlap in the resources required to initiate gait and facilitate working memory in preparation for the recitation of the cognitive task. Motor deficits appear to be unaffected by a cognitive load during gait initiation, however, numerous studies have reported effects during continuous walking [18–20]. Gait initiation requires a subset of neural pathways

and resources distinct from that of continuous gait in HD [21]; this may explain why it responded to cognitive loading in a way that was different from the way that gait speed responded. The cognitive loading led to a significant decrease in gait speed in both groups.

The ML APA maintains equilibrium as weight is shifted onto the stance leg and is followed by an AP APA, which maintains equilibrium during the first step. As weight is shifted onto the stance leg, deceleration of the body is needed to prevent continuous acceleration, which would cause destabilizing displacement of the body in the direction of the stance leg. Continuous acceleration towards the stance leg without the appropriate deceleration or a compensatory response could ultimately lead to a lateral fall [12]. In healthy populations, adequate force modulation decelerates the body as weight is shifted onto the stance leg, followed by an acceleration back towards the midline, allowing for smooth backward and forwards AP APA accelerations through the completion of the first step [12]. However, large and highly variable AP accelerations among the HD group may reflect a compensatory strategy in response to the initial and exceeding ML APA accelerations. A large AP APA acceleration is an effective compensatory strategy to overcome a lack of ML deceleration and continuous displacement. By accelerating quickly in the AP direction, first step completion is expedited, ultimately preventing dynamic instability and reducing the time spent solely on the stance leg [12]. Furthermore, high correlations between ML APA accelerations and APA durations indicate that the ML APAs dominate the majority of the APA time window and may be a rate-limiting factor for gait initiation. ML APA as a significant predictor of gait speed may also imply that ML shifting is rate-limiting through the entirety of the gait cycle, although we interpret these results of the linear model with caution.

Our results are in line with the underlying pathophysiology of HD. Individuals with HD exhibit hyper-thalamocortical drive within the basal ganglia – supplementary motor area (SMA) circuit [22–24], resulting in excessive excitatory input into the SMA, putatively causing impairments of force modulation and excessive amplitudes of voluntary movements [23]. Hyper-excitation of the SMA may also contribute to excessive changes in accelerations, which is representative of jerk. Specifically, we quantified this as the mean jerk in the ML and AP directions as changes in acceleration over time. Individuals with HD exhibited larger jerk values particularly in the AP direction when compared to healthy controls. Our results show that individuals with HD exhibit overall increases in acceleration during the preparatory phase of movement initiation, indicating an impairment of dynamic balance. These large peak accelerations might be explained by the emergence of chorea within a voluntary movement or a standalone deficit in motor planning.

We observed exceedingly large and variable AP APAs and a strong relationship between ML APAs and APA durations, suggesting a compensatory phenomenon in response to heightened dynamic instability. However, the generalized disintegration of APA and first step accelerations and durations may also come as a result of an HD-specific impairment of force modulation. The strong correlations between ML APAs and APA durations argue against embedded chorea since we would not expect to see involuntary movements appropriately scaled and correlated with a time scale of volitional movement. Therefore, it is likely that the predictability of ML APA amplitude on gait speed in individuals with HD reflects a disease-specific motor planning deficit. This argument is further strengthened by the breakdown in scaling with the addition of a cognitive load.

Limitations

This study has several limitations. First, we used only one gait initiation cycle rather than an average of multiple trials, which may limit the reproducibility of the results. Next, several disease-specific factors could influence the results. Persons with HD may take medications that influence movement or dampen the severity of chorea. Representative medications are listed in Table 1 although we did not specifically control for these medications. In HD, medication prescription is typically symptomatic and there is little knowledge of the effect of commonly prescribed medications on posture and gait. We indicated those individuals who were on medication to treat the movement disorder in HD, however the relatively small number of participants limits further analysis.

Our sample includes a wide range of UHDRS-TMS scores and chorea subscores, which is representative of the HD population. Future research may help to better understand the contextual role of chorea during movements and whether they are enveloped within a voluntary movement. Additionally, future work could examine motor phenotypes (i.e., choreatic vs rigidity) to determine if there are differential responses in APAs with gait initiation. In addition, while we did not measure global cognitive function, we used the DKEFS and SDMT. The SDMT is well-established as a measure of cognitive dysfunction in HD. Finally, we note that the cognitive load used here may have been insufficiently demanding. Another possible explanation could be that participants may not have started the cognitive task until they had taken several steps; this may explain why we observed no effect of cognitive interference on gait initiation. If the participant was not engaged in the cognitive task until after the first step, there would be minimal or no interference during APA. Future work should examine either the use of

a motor dual-task or a cognitive dual-task that demands engagement prior to the initiation of gait to ensure interference at step initiation for all participants. Examination of the neural correlates associated with time-scale discrepancies in APAs during gait initiation in individuals with HD is also of interest; some cognitive tasks could force reliance on resources and circuitry shared with the SMA, thereby dampening any prefrontal compensatory mechanisms that would normally attenuate hyper-excitation of the premotor areas.

Summary

This study aimed to investigate APAs during gait initiation during no-load and cognitive-load conditions in individuals with HD and healthy controls. Results indicated disintegration of acceleration amplitudes and durations of APAs among the HD group as compared to healthy controls, which remained preserved across conditions. Findings indicate force modulation impairments specific to HD pathology.

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Table 1. Participant demographics and disease-specific measures

	Huntington's Disease (n=33)	Controls (n=15)
Male: Female	20:13	8:7
Age (yrs) (mean± SD) range	54.7 ± 12.6 (30-79)	53.2 ± 13.2 (33-74)
UHDRS Total motor score (TMS)	39 (15)	--
UHDRS Total functional capacity (TFC)	11 (2)	--
DKEFS Score (Total Correct)	10(3)*	16(3)
Symbol Digit Modality (SDMT)	28(12)*	56(16)
Medications to treat movement disorder		
Tiaprid/Tiapridex	n=1	--
Austedo/duetetrabenazine	n=2	--

*Significant difference between groups ($p < 0.01$)

All values represent mean (SD). Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) ranges in scores from 0 to 120, with lower scores reflecting less motor impairment. Unified Huntington's Disease Rating Scale-Total Functional Capacity (UHDRS-TFC) ranges in scores from 0 to 13, with higher scores indicating greater functioning. Delis-Kaplan Executive Function System (DKEFS) scores list the amount of total correct answers, that were recited after gait initiation during the walking task.

Table 2: Mean (SD) Anticipatory Postural Adjustment (APA) and first step values across groups and conditions (2x2 repeated measures ANOVA)

	HD (n=33)	Control (n=15)	Main effect for group (HD vs Control)	Main effect for task condition (no-load vs cognitive-load)	Group x Task interaction
Gait Speed					
No-load	1.10(0.20)	1.32(0.26)			
Cognitive-load	0.86(0.22)	1.03(0.37)	p=0.013	p<0.001	p=0.39
APA ML amplitudes (g)					
No-load	0.12(0.05)	0.06(0.02)			
Cognitive-load	0.13(0.05)	0.06(0.03)	p<.001	p=.73	p=.42
APA AP amplitudes (g)					
No-load	0.51(0.22)	0.05(0.01)			
Cognitive-load	0.55(0.22)	0.05(0.01)	p<.001	p=.53	p=.54
APA duration (s)					
No-load	0.43(0.21)	0.35(0.16)			
Cognitive-load	0.48(0.22)	0.37(0.19)	p=.07	p=.39	p=.66
First Step ROM (radians)					
No-load	24.16(2.11)	26.52(2.53)			
Cognitive-load	23.64(2.21)	26.10(2.60)	p=.001	p=.05	p=.84
First Step Duration (sec)					
No-load	0.53(0.05)	0.47(0.04)			
Cognitive-load	0.54(0.04)	0.47(0.04)	p<.001	p=.31	p=.63
APA Jerk ML					
No-load	3.03(1.37)	2.02(1.05)			
Cognitive-load	3.37(2.09)	2.78(4.46)	p<.001	p=.26	p=.66
APA Jerk AP					
No-load	15.33(12.76)	1.71(0.79)			
Cognitive-load	14.64(10.25)	1.97(1.44)	p<.001	p=.89	p=.77

ML=mediolateral; AP=antero-posterior; ROM=range of motion

Figure Legends

Fig.1 Example acceleration stream from the lumbar sensor of a single control participant (A) and HD (B) participant. The duration of the APA is marked by the grey vertical lines within each accelerometry stream. APA start times were derived from the lumbar stream within a duration window 1000ms prior to the time of toe-off of the first stepping leg, as defined as the first peak acceleration in the anterior direction of the ankle sensor. Within this time frame, the maximum value in the mediolateral lumbar accelerometry stream indicated the amplitude of the medial-lateral (ML) APA. APA end is the end time indicated by toe-off.

Fig. 2 Violin plots of kernel density estimations of APA acceleration amplitudes in the mediolateral (A) and anteroposterior (B) directions. The dotted line represents the median, with the tips representing lower and upper adjacent values. Larger accelerations in HD versus control participants are noted in both directions, with particularly larger amplitudes and variance among anteroposterior APAs. ** $p < 0.001$.

Fig. 3 Violin plots of kernel density estimations of APA durations, which are preserved across conditions and groups ($p = .66$). In contrast to APA amplitude values, the variability of the duration within each group appears to be consistent. The dotted line represents the median, with tips representing lower and upper adjacent values. Data outliers are represented with black dots within each plot.

Fig. 4 Violin plots of kernel density estimations of first step range of motion (A) and first step duration (B). First step durations were larger in the HD group as compared to controls, in

contrast to APA durations ($p < 0.001$). The HD group exhibited significantly smaller first step ROM (B) in comparison to healthy controls, however, the first step range of motion is preserved across conditions. * $p < 0.01$; ** $p < 0.001$