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Postural control and gait measures derived from wearable inertial measurement unit devices in Huntington's disease: recommendations for clinical outcomes

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Abstract

Background

Postural control impairments begin early in Huntington's disease yet measures most sensitive to progression have not been identified. The aims of this study were to: 1) evaluate postural control and gait in people with and without Huntington's disease using wearable sensors; and 2) identify measures related to diagnosis and clinical severity.

Methods

41 individuals with Huntington's disease and 14 age-matched peers performed standing with feet together and feet apart, sitting, and walking with wearable inertial sensors. One-way analysis of variance determined differences in measures of postural control and gait between early and mid-disease stage, and age-matched peers. A random forest analysis identified Features of Importance for Huntington's disease diagnosis. Stepwise and ordinal regressions were used to determine predictors of clinical chorea and tandem walking scores respectively.

Findings

There was a significant main effect for all postural control and gait measures comparing early stage, mid stage and age-matched peers, except for gait cycle duration and step duration. Total sway, root mean square and mean velocity during sitting, as well as gait speed had the greatest importance in classifying disease status. Stepwise regression showed that root mean square during standing with feet apart significantly predicted clinical measure of chorea, and ordinal regression model showed that root mean square and total sway standing feet together significantly predicted clinical measure of tandem walking.

Interpretations

Root mean square measures obtained in sitting and standing using wearable sensors have the greatest potential to serve as biomarkers of postural control impairments in Huntington's disease.

Highlights

- Sensor-derived postural control measures are discriminative in Huntington's disease
- Root mean square measures predict disease status and correlate to clinical measures
- Root mean square during sitting and standing are potential disease biomarkers

Introduction

Huntington's disease (HD) is a genetic neurodegenerative disorder marked by a triad of motor, behavioral and cognitive manifestations. (Bunner and Rebec, 2016; Tian et al., 2012) As a result of degeneration of the striatum, HD elicits hallmark motor deficits including impaired postural control from early in the disease process. Postural control deficits in HD are characterized by mis-scaling of accelerations and durations, and excessive excursions in both static and dynamic contexts, (Delval et al., 2011; Moisello et al., 2011; Salomonczyk et al., 2010) that interfere with stability. Although existing clinician-rated measures, such as items on the United Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), (Kieburtz, 1996) can provide insight into general balance performance (e.g. tandem walking and retropulsion pull tests), there remains a need for objective measures to accurately assess non-observable aspects of postural control. Objective markers of postural control provide insight into functional independence, and factor into important aspects of clinical decision making in HD, such as fall risk and the likelihood of nursing home admission.(Wheelock et al., 2003) Ultimately, precise and reliable measures can elucidate postural control impairments in HD and function as a marker for disease progression. (Salomonczyk et al., 2010).

Postural control encompasses the ability of an individual to maintain equilibrium during both static and dynamic tasks. (Dunsky et al., 2017; Lazarotto et al., 2020) During static tasks, which include sitting and standing, the motor system prioritizes maintaining the center of mass within the base of support to maintain stability. Dynamic tasks, such as walking and reaching, challenge the system to integrate the modulation of center of mass within the constraints of a volitional movement. Under both circumstances, the motor system aims to minimize the risk of

falls. In non-HD populations, properties of an individual's postural control, such as total sway and trunk velocity and acceleration, are tempered and scaled to the demands of a task. (Horak, 2006) Previous work in HD demonstrated an inability to appropriately scale postural control in the context of dynamic movements such as gait and reaching, (Delval et al., 2007; Mann et al., 2012) which can ultimately contribute to an increase in fall risk. (Grimbergen et al., 2008) Deficits in postural control are apparent early in HD and worsen with progressive striatal degeneration, which both directly and indirectly influence the output of the reticulospinal, vestibulospinal, and corticospinal tracts needed for voluntary postural control. (Jacobs and Horak, 2007) A deeper understanding of specific properties of postural control that are most impaired in persons with HD will lead to targeted rehabilitation programs for motor deficits that negatively affect function and contribute to fall risk (Grimbergen et al., 2008).

The presence of involuntary movements, such as chorea, creates a further challenge in measuring postural control in individuals with HD. Chorea consists of writhing involuntary movements of the face, neck, upper extremities, lower extremities, or trunk, and can cause a shift to the center of mass affecting postural control. (Berardelli et al., 1999) Chorea and postural control are typically assessed using subjective clinical ratings from the UHDRS-TMS. This test is inherently subjective, and ratings are typically non-linear, which limits the use of sensitive parametric statistical methods. Clinical rating scales also only provide a brief 'snapshot' into any disease, which remains problematic given the amount of heterogeneity of people with HD.

Quantitative analysis of movement has traditionally involved use of marker-based motion capture camera systems or use of force plates to measure spatiotemporal features of gait and postural control.(Miller et al., 2016) However, marker-based systems are costly, require an extensive setup time, and often require advanced programming skills for data processing. More

recently, wearable sensors have been shown to be capable of providing reliable and valid measurements of motor impairments, including postural control.(Kobsar et al., 2020; Simoes, 2011; Washabaugh et al., 2017) The benefits and utility of wearables has been demonstrated in people with neurodegenerative diseases such as Parkinson's disease (PD) to measure tremor, gait, and postural control. (Horak and Mancini, 2013; Washabaugh et al., 2017) Several recent studies have also demonstrated their clinical utility in individuals with HD. (Dalton et al., 2013; Porciuncula et al., 2020; Purcell et al., 2020; Tortelli et al., 2021; Trojaniello et al., 2015) IMUs can measure discrete biomechanical properties of postural control quality and impairments, such as jerk, total sway, and acceleration values, which may be more sensitive to motor impairments than current clinical measures. (Adams et al., 2017; Andrzejewski et al., 2016)

In order to address this need for quantitative measures of postural control, we analyzed postural control in sitting and standing conditions. The aims of this study were to 1) evaluate differences in postural control and gait between non-HD individuals and those with HD from wearable sensors; and 2) identify measures related to diagnosis and clinical measures of manifest HD. The aims addressed in this study will ultimately provide recommendations for candidate measures for use as clinical biomarkers.

Methods

Study Design

This cross-sectional study evaluated participants during one session at three sites (George Huntington Institute, Munster, Germany; Teachers College, Columbia University, New York, USA and Wayne State University, Detroit, Michigan, USA). The study was approved by the

Ethics or Institutional Review Boards at each site. Cardiff University was the study sponsor and the Wales Research Ethics Committee also approved the study protocol. The data presented here was part of a larger study integrating wearable technologies to quantify meaningful activity in Huntington's disease (iWEAR-HD).

Participants

Participants were included if they met the following inclusion criteria: 1) genetically confirmed diagnosis of HD; 2) Total Functional Capacity (TFC) score ≥7; 3) 18 years of age or older; and 4) able to walk 10 meters independently without assistance devices. Participants were excluded if they had: 1) A diagnosis of juvenile onset HD; 2) history of comorbid neurological conditions such as stroke or multiple sclerosis; 3) acute orthopedic conditions; and 4) the inability or unwillingness of participant or legal guardian to give written informed consent. Demographics of all participants are listed in Table 1.

TABLE 1 HERE

Procedures

UHDRS (TMS and TFC) (Kieburtz, 1996) were collected within three months of their study visit. If this was not available, the UHDRS was administered as a part of the study visit. The UHDRS TFC is a measure of functional ability, with scores ranging from 0 to 13, where higher scores indicate greater functioning. HD1 (early stage) manifest-HD was categorized as TFC scores of 11-13 while HD2 (mid stage) was TFC scores 7-10. These classifications were based on previous research that aimed to identify imaging measures as clinical outcome measures within HD. (Tabrizi et al., 2013) The UHDRS-TMS ranges in scores from 0 to 120,

with higher scores indicating a greater level of motor impairment. Each item is rated on a 0 – 4 scale with 0 = Absent, 1 = Slight/ Intermittent, 2 = Mild/Common or Moderate/Intermittent, 3 = Moderate/ Common, 4 = Marked/ Prolonged. The UHDRS chorea sub score was calculated from the UHDRS-TMS by summing trunk and extremities chorea scores (5 items). The UHDRS chorea sub score ranges from 0 – 20, with lower scores indicating little to no chorea and higher scores indicating greater chorea. Face and bucco-oral-lingual chorea scores were removed due to their lack of association with the postural measures of interest. Chorea sub scores were used to identify postural control measures that could best predict chorea. Clinical balance measures in this study were represented by UHDRS tandem walking scores. Tandem walking is rated on a 0-4 scale, where 0 indicates normal heel-to-toe walking for 10 steps and a score of 4 indicates an inability to attempt the motor task.

Participants were fitted with six Opal V2 IMUs (Ambulatory Parkinson's Disease Monitoring (APDM) opal sensors (ERT, Portland, OR, USA). Opal sensors have triaxial accelerometers that measure linear acceleration, a gyroscope to measure angular velocity, and a magnetometer for positional orientation.(Horak and Mancini, 2013). Data were processed using Mobility Lab 2.0© software (2015). Postural measures included total sway area, root mean square (RMS) of sway, mean velocity and jerk. Total sway area signifies the extent of movement around the center of gravity. RMS of sway is a time-domain measure, representing the average variance. Mean velocity is the average rate of change in position during a certain period of time. Jerk is a derivative of acceleration that reflects smoothness of movement. The wearable sensors captured movement as participants sat quietly for 30 seconds in an armless chair with their feet flat on the floor, hands resting in their lap, and their lower back away from the back of the seat. Participants also stood quietly for 45 seconds with their feet hip width apart

(standardized using the APDM foot plate) and 45 seconds with their feet together. During the gait task, participants walked 7 meters to a marking on the floor, turned around and returned to the initial position. Gait variables that were extracted from Mobility Lab included gait speed, percentage of time spent in stance and double support, and stride length.

Data Analysis

Statistical analyses were performed using R (Version 4.02; R Foundation for Statistical Computing, 498 Vienna, AT). Two methods were used to determine the most sensitive measures of dysfunction in postural control between individuals with HD and non-HD peers: Standardized Mean Difference (*SMD*) and Random Forest. The *SMD* is a measure of effect size determined by the following two equations:

$$SMD = \frac{\overline{X_1} - \overline{X_2}}{S}$$

$$S = \left(\frac{SD_1^2}{n_1} + \frac{SD_2^2}{n_2}\right) \times \left(\frac{n_1 \times n_2}{n_1 + n_2}\right)$$

where X_1 and X_2 are the means of the HD and non-HD groups, respectively. S is the pooled standard deviation of the groups, where SD_1, n_1, SD_2, and n_2 are the standard deviation and sample size of the HD group and the non-HD peer group, respectively. *SMD* values of >0.50 were retained as sensitive measures of UHDRS chorea sub score.

A Pearson correlation matrix was computed for participants with HD, which determined associations between all postural control and gait variables, in addition to TMS, TFC, UHDRS chorea subscore, and tandem walking score. A second Pearson correlation matrix was computed for non-HD peers, which included all postural control and gait variables. Furthermore, between-group differences in all postural control and gait variables were tested in the non-HD peer, HD1

(TFC<11), and HD2 (TFC 11-13) groups, using one-way analysis of variance (ANOVA). Post-hoc differences were assessed using Tukey's test.

The random forest model was conducted by using the 'randomForest' package on R. The random forest model is a machine learning approach that creates an ensemble of classification and regression trees using a training dataset. In this experiment, a classification tree was constructed using 80% of the total data. Once constructed, the remaining 20% of the data was used to test the error rate of the classification tree. The random forest yields a variable ranking metric termed 'mean decrease in Gini', which was used to represent features of importance of predictor variables and was compared to *SMD*s. Mean decrease in Gini was also used for feature selection to find a significant ordinal regression model to predict UHDRS tandem walking scores.

Finally, we wanted to determine which measures derived from IMUs were best able to predict clinical HD measures of chorea (UHDRS-TMS chorea subscore) and dynamic balance (UHDRS-TMS tandem walking). To determine wearable measures capable of predicting chorea, variables from the wearables (i.e., jerk, total sway area, RMS, mean velocity, gait speed, gait stride length) of all postural control and gait conditions were entered into a forward stepwise regression model, as chorea sub scores were treated as ratio data. Variables with multicollinearity (VIF $\geq$ 10) were removed from the stepwise regression. Lowest Akaike information criterion (AIC) was used for model comparison to determine the final regression model. To determine measures capable of predicting UHDRS tandem walking scores, the aforementioned variables of postural control and gait were entered into a random forest model. The parameters with the highest mean decrease index of Gini were entered into an ordinal regression model. Significance level was set at $P < 0.05$.

Results

There was a significant main effect for all postural control and gait measures comparing HD1 and HD2 and non-HD peers, except for gait cycle duration and step duration ($P > .05$) (Table 2). Post-hoc comparisons revealed a significant difference between the HD2 and non-HD peers for all measures, except jerk feet together ($P > .05$). Post-hoc comparisons between HD1 and non-HD peers revealed differences in RMS sitting ($P = .022$). Further, there were significant differences between HD1 and HD2 groups in RMS feet apart, RMS feet together, jerk feet apart, jerk sitting, and gait speed (Table 2).

INSERT TABLE 2 HERE

*SMD*s that compared differences between each HD group to non-HD peers are shown in Table 3. The highest *SMD*s found for both HD groups occurred in RMS feet apart (HD2: 19.94, HD1: 5.58), RMS feet together (HD2: 19.65, HD1: 6.36), and step duration (HD2: 6.44, HD1: 5.87).

INSERT TABLE 3 HERE

Pearson correlations were calculated for both HD and non-HD peers groups separately and are graphically represented in matrices found in Figure 1a and 1b.

INSERT FIGURE 1 HERE

Mean decrease in Gini derived from the random forest model showed that total sway sitting (3.57), RMS sitting (2.22), mean velocity sitting (2.09), and gait speed (1.32) had the greatest features of importance for accurate classification of individuals into either the HD or non-HD group.

Stepwise regression revealed a significant linear model, shown in Figure 2 in which RMS during standing feet apart ($\beta = 9.19$, $P < .001$) predicted chorea subscore (F (1, 38) = 11.74, $P <$ .0015, $R^2 = 0.216$). The random forest model revealed that RMS feet together (Odds Ratio: 6.74) and total sway feet together (Odds Ratio: -0.002) predicted UHDRS tandem walking scores ($\chi^2(2) = 13.38$, $P <.001$, Nagalkerke $R^2 = 0.30$).

INSERT FIGURE 2 HERE

Discussion

Consistent with previous findings, our results indicated significant differences between HD and non-HD peers across most variables of postural control that were measured within and across conditions. (Porciuncula et al., 2020; Salomonczyk et al., 2010; Tian et al., 1991) Individuals with HD performed significantly worse than non-HD peers on variables of postural control including greater sway area, greater acceleration values in static standing and sitting, and greater jerk values during quiet standing and sitting. These differences were more pronounced between non-HD peers and HD individuals with TFC scores below 11 (HD2). We found that RMS during standing feet apart best predicted UHDRS chorea subscore, and RMS and total sway during standing feet together best predicted UHDRS tandem walking scores. RMS, total sway, and mean velocity during sitting were postural measures most associated with an HD diagnosis. Given their ability to

predict preexisting clinical measures and HD diagnosis, we identified RMS measures in sitting and standing as candidate biomarkers of postural control. Among RMS measures, we determined that RMS during sitting is a suitable biomarker of postural control for its capacity to discriminate between high TFC groups and non-HD peers, and its feasibility for data collection within in an HD population.

RMS is the average composite value of acceleration of sway derived from the lumbar sensor. The *SMD* of RMS between non-HD and HD groups indicated a moderate effect size across all tasks (above .5) (Table 3). Interestingly, although RMS measures during standing successfully discriminated between HD1 and HD2, RMS during sitting remained the only variable with the discriminative capacity to discern between the HD (higher functioning) and non-HD peers. Although jerk values exhibited acceptable *SMD* values and differences between low and high TFC groups, within group variability was too large, as represented by large standard deviations, and therefore not included in the random forest tree model.

Often HD individuals with higher TFC scores do not exhibit motor symptoms that can be easily identified by clinicians. However, non-observable deficits in motor control are evident in pre-manifest and early-stage HD, (Delval et al., 2011; Salomonczyk et al., 2010) which are more easily captured by inertial sensors. (Andrzejewski et al., 2016; Fusca et al., 2018) Our findings on RMS values during sitting further confirm this and introduce the idea that static sitting may elicit more acceleration-based, measurable responses in force modulation impairments in HD. It is possible that in standing, the motor system prioritizes stability and fall prevention by introducing constraints to limit excessive sway. During sitting, the risk of fall is minimal relative to standing thereby decreasing the demand of constraints needed to prioritize stability. The overall result is that when seated, participants with HD could generate greater movement with less force

modulation without the risk of falling. Sitting minimizes the need for risk-related constraints, leaving greater room for non-consequential errors in sway, force modulation, and chorea.

The UHDRS chorea subscore used in this study was comprised of scores assessing the severity of chorea present in the trunk and extremities. Among the IMU-derived measures of postural control our findings indicated that RMS and mean velocity during sitting predicted chorea subscores. Aside from the association between lumbar total sway and visual trunk displacement, it is likely that pronounced chorea in extremities would be associated with greater displacement of the trunk due to postural disturbances and intersegmental dynamics. (Grimbergen et al., 2008; Kegelmeyer et al., 2017) Therefore, RMS and mean velocity during sitting may function as an indirect measure of chorea.

From our findings, we propose that RMS during sitting and standing derived from IMUs can serve as clinical outcome measures for postural control in individuals with HD. These measures are recommended due to their ability to predict both HD status and UHDRS tandem walking scores. These measures also had relatively low variability and larger discriminative validity, as determined by *SMD* values, relative to the remaining measures. Furthermore, the effect sizes of RMS values are consistent with previous findings indicating that larger accelerations and force productions within HD groups occur across motor tasks. (Moisello et al., 2011; Reilmann and Schubert, 2017) Our results show that IMU sensors can capture force modulation impairments, as represented by larger acceleration values, that are characteristic in HD. This further confirms the notion that IMU wearable devices can detect subtle differences in postural control that cannot be captured by clinical scales. The subjective nature of the UHDRS tandem walking score makes it unlikely that this clinical measure could detect more subtle changes in postural control in HD. Wearable-derived candidate measures of postural control were both associated with the

aforementioned clinical scales and captured non-observable and reliable measures of posture specific to HD as compared to non-HD peers, and characteristic of the disease. The wearable-derived outcome measures of postural control identified in this study can ultimately allow for the ability to discriminate between disease stages and potentially to evaluate intervention effectiveness as clinical endpoints.

Some limitations that can be addressed for future studies include the use of a single vs multiple trials. Results from our study are from a single trial of each task across participants. This may limit the generalizability as multiple trials can improve sensitivity of each measure. Future work should also address the reliability of these measures over the course of HD, including a pre-manifest HD group, where postural impairments are more subtle. Lastly, future work can determine whether these postural measures are sensitive to intervention. Identifying response to time with HD and intervention are integral next steps for evaluating the usability of these measures in clinical trials.

Conclusion

RMS measures derived from IMUs during sitting and standing were most related to HD status and severity and have the potential to serve as clinical outcome measures for postural control in HD. Measures of total sway area of FA and sitting are likely influenced by choreic movements, whereas RMS FT, jerk FA and RMS sitting are likely to best reflect postural control impairments. Differences in postural control variables were more pronounced between non-HD peers and HD individuals with TFC scores below 11. Future studies can determine sensitivity to time and intervention in these postural control measures.

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372 References
373
374 Adams, J.L., Dinesh, K., Xiong, M., Tarolli, C.G., Sharma, S., Sheth, N., Aranyosi, A.J., Zhu,
375 W., Goldenthal, S., Biglan, K.M., Dorsey, E.R., Sharma, G., 2017. Multiple Wearable
376 Sensors in Parkinson and Huntington Disease Individuals: A Pilot Study in Clinic and at
377 Home. Digit Biomark 1, 52–63. https://doi.org/10.1159/000479018
378 Andrzejewski, K.L., Dowling, A.V., Stamler, D., Felong, T.J., Harris, D.A., Wong, C., Cai, H.,
379 Reilmann, R., Little, M.A., Gwin, J.T., Biglan, K.M., Dorsey, E.R., 2016. Wearable
380 Sensors in Huntington Disease: A Pilot Study. JHD 5, 199–206.
381 https://doi.org/10.3233/JHD-160197
382 Berardelli, A., Noth, J., Thompson, P.D., Bollen, E.L.E.M., Currà, A., Deuschl, G., Van Dijk,
383 J.G., Töpper, R., Schwarz, M., Roos, R.A.C., 1999. Pathophysiology of chorea and
384 bradykinesia in Huntington's disease. Movement Disorders.
385 https://doi.org/10.1002/1531-8257(199905)14:3<398::AID-MDS1003>3.0.CO;2-F
386 Bunner, K.D., Rebec, G. V., 2016. Corticostriatal dysfunction in Huntington's disease: The
387 basics. Frontiers in Human Neuroscience. https://doi.org/10.3389/fnhum.2016.00317
388 Dalton, A., Khalil, H., Busse, M., Rosser, A., van Deursen, R., ÓLaighin, G., 2013. Analysis of
389 gait and balance through a single triaxial accelerometer in presymptomatic and
390 symptomatic Huntington's disease. Gait and Posture 37, 49–54.
391 Delval, A., Bleuse, S., Simonin, C., Delliaux, M., Rolland, B., Destee, A., Defebvre, L.,
392 Krystkowiak, P., Dujardin, K., 2011. Are gait initiation parameters early markers of
393 Huntington's disease in pre-manifest mutation carriers? Gait and Posture 34, 202–207.
394 https://doi.org/10.1016/j.gaitpost.2011.04.011
395 Delval, A., Krystkowiak, P., Blatt, J.L., Labyt, E., Bourriez, J.L., Dujardin, K., Destée, A.,
396 Derambure, P., Defebvre, L., 2007. A biomechanical study of gait initiation in
397 Huntington's disease. Gait and Posture 25, 279–288.
398 https://doi.org/10.1016/j.gaitpost.2006.04.001
399 Dunsky, A., Zeev, A., Netz, Y., 2017. Balance Performance Is Task Specific in Older Adults.
400 BioMed Research International 2017, 1–7. https://doi.org/10.1155/2017/6987017
401 Fusca, M., Negrini, F., Perego, P., Magoni, L., Molteni, F., Andreoni, G., 2018. Validation of a
402 Wearable IMU System for Gait Analysis: Protocol and Application to a New System.
403 Applied Sciences 8, 1167. https://doi.org/10.3390/app8071167
404 Grimbergen, Y.M.A., Knol, M.J., Bloem, B.R., Kremer, B.P.H., Roos, R.A.C., Munneke, M.,
405 2008. Falls and gait disturbances in Huntington's disease. Movement Disorders.
406 https://doi.org/10.1002/mds.22003
407 Horak, F.B., 2006. Postural orientation and equilibrium: what do we need to know about neural
408 control of balance to prevent falls? Age and Ageing 35, ii7–ii11.
409 https://doi.org/10.1093/ageing/afl077
410 Horak, F.B., Mancini, M., 2013. Objective biomarkers of balance and gait for Parkinson's
411 disease using body-worn sensors. Movement Disorders.
412 https://doi.org/10.1002/mds.25684
413 Jacobs, J. V., Horak, F.B., 2007. Cortical control of postural responses, in: Journal of Neural
414 Transmission. https://doi.org/10.1007/s00702-007-0657-0

415 Kegelmeyer, D.A., Kloos, A.D., Fritz, N.E., Chaudhari, A., Kostyk, S.K., 2017. Trunk Sway
416 Relates to Increased Fall Risk in Younger Individuals With Huntington Disease and to
417 Gait and Mobility Measures, in: NEUROTHERAPEUTICS.
418 Kieburtz, K., 1996. Unified Huntington's disease rating scale: Reliability and consistency.
419 Movement Disorders 11, 136–142. https://doi.org/10.1002/mds.870110204
420 Kobsar, D., Charlton, J.M., Tse, C.T.F., Esculier, J.-F., Graffos, A., Krowchuk, N.M., Thatcher,
421 D., Hunt, M.A., 2020. Validity and reliability of wearable inertial sensors in healthy adult
422 walking: a systematic review and meta-analysis. Journal of NeuroEngineering and
423 Rehabilitation 17, 62. https://doi.org/10.1186/s12984-020-00685-3
424 Lazarotto, L., Bobbo, G.Z.G., Siega, J., da Silva, A.Z., Iucksch, D.D., Israel, V.L., Bento, P.C.B.,
425 2020. Static and dynamic postural control: Comparison between community old adults
426 and people with Parkinson's disease. Physiother Res Int 25.
427 https://doi.org/10.1002/pri.1844
428 Mann, R.K., Edwards, R., Zhou, J., Fenney, A., Jog, M., Duval, C., 2012. Comparing movement
429 patterns associated with Huntington's chorea and Parkinson's dyskinesia. Experimental
430 Brain Research. https://doi.org/10.1007/s00221-012-3057-0
431 Miller, E., Kaufman, K., Kingsbury, T., Wolf, E., Wilken, J., Wyatt, M., 2016. Mechanical
432 testing for three-dimensional motion analysis reliability. Gait Posture 50, 116–119.
433 https://doi.org/10.1016/j.gaitpost.2016.08.017
434 Moisello, C., Perfetti, B., Marinelli, L., Sanguineti, V., Bove, M., Feigin, A., Di Rocco, A.,
435 Eidelberg, D., Ghilardi, M.F., 2011. Basal ganglia and kinematics modulation: Insights
436 from Parkinson's and Huntington's diseases. Parkinsonism and Related Disorders.
437 https://doi.org/10.1016/j.parkreldis.2011.06.021
438 Porciuncula, F., Wasserman, P., Marder, K.S., Rao, A.K., 2020. Quantifying Postural Control in
439 Premanifest and Manifest Huntington Disease Using Wearable Sensors. Neurorehabil
440 Neural Repair 34, 771–783. https://doi.org/10.1177/1545968320939560
441 Purcell, N.L., Goldman, J.G., Ouyang, B., Liu, Y., Bernard, B., O'Keefe, J.A., 2020. The effects
442 of dual-task cognitive interference on gait and turning in Huntington's disease. PLoS
443 ONE 15. https://doi.org/10.1371/journal.pone.0226827
444 Reilmann, R., Schubert, R., 2017. Motor outcome measures in Huntington disease clinical trials,
445 in: Handbook of Clinical Neurology. https://doi.org/10.1016/B978-0-12-801893-
446 4.00018-3
447 Salomonczyk, D., Panzera, R., Pirogovosky, E., Goldstein, J., Corey-Bloom, J., Simmons, R.,
448 Gilbert, P.E., 2010. Impaired postural stability as a marker of premanifest Huntington's
449 disease. Movement Disorders. https://doi.org/10.1002/mds.23309
450 Simoes, M.A., 2011. Feasibility of Wearable Sensors to Determine Gait Parameters. Department
451 of Mechanical Engineering Master of, 108. https://doi.org/10.1007/s13398-014-0173-7.2
452 Tabrizi, S.J., Scahill, R.I., Owen, G., Durr, A., Leavitt, B.R., Roos, R.A., Borowsky, B.,
453 Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J.C.,
454 Langbehn, D.R., 2013. Predictors of phenotypic progression and disease onset in
455 premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of
456 36-month observational data. The Lancet Neurology 12, 637–649.
457 https://doi.org/10.1016/S1474-4422(13)70088-7
458 Tian, J. -r., Herdman, S.J., Zee, D.S., Folstein, S.E., 2012. Postural stability in patients with
459 Huntington's disease. Neurology. https://doi.org/10.1212/wnl.42.6.1232

Tian, J.R., Herdman, S.J., Zee, D.S., Folstein, S.E., 1991. Postural control in huntington's disease (HD). Acta Oto-Laryngologica. https://doi.org/10.3109/00016489109131415

Tortelli, R., Rodrigues, F.B., Wild, E.J., 2021. The use of wearable/portable digital sensors in Huntington's disease: A systematic review. Parkinsonism Relat Disord 83, 93–104. https://doi.org/10.1016/j.parkreldis.2021.01.006

Trojaniello, D., Ravaschio, A., Hausdorff, J.M., Cereatti, A., 2015. Comparative assessment of different methods for the estimation of gait temporal parameters using a single inertial sensor: Application to elderly, post-stroke, Parkinson's disease and Huntington's disease subjects. Gait and Posture 42, 310–316. https://doi.org/10.1016/j.gaitpost.2015.06.008

Washabaugh, E.P., Kalyanaraman, T., Adamczyk, P.G., Claflin, E.S., Krishnan, C., 2017. Validity and repeatability of inertial measurement units for measuring gait parameters. Gait and Posture 55, 87–93. https://doi.org/10.1016/j.gaitpost.2017.04.013

Wheelock, V.L., Tempkin, T., Marder, K., Nance, M., Myers, R.H., Zhao, H., Kayson, E., Orme, C., Shoulson, I., 2003. Predictors of nursing home placement in Huntington disease. Neurology 60, 998–1001. https://doi.org/10.1212/01.WNL.0000052992.58107.67

Table 1. Participant Characteristics

	All Participants with HD (n=43)	TFC 7 -10 (n=28)	TFC 11-13 (n=15)	Non-HD peers (n=15)
Age(years)	56.9 (11.7)	55.9 (9.6)	50.9 (14.2)	53.1 (13.3)
Sex (M/F)	25/19	14/14	11/4	7/7
Height (cm)	173.6 (9.6)	172.3(9.4)	175.7 (9.5)	169.2 (10.8)
Weight(kg)	75.0 (14.8)	76.4(16.3)	73.2 (12.1)	79.6 (12.1)
UHDRS TMS	40.6 (16.2)	48 (12)	27 (14)	NA
UHDRS SDMT	27.5 (12)	22 (9)	37.5 (11)	NA
UHDRS Chorea Subscore	10 (5)	12 (5)	9 (5)	NA
UHDRS FA	22 (3)	20 (3)	24 (1)	NA
UHDRS Ind.	84 (9)	80 (10)	90 (6)	NA
# of Fallers	24	19	5	NA

Table 1: Demographics of all participants are represented as means(SD) except sex, which is reported number of participants. Unified Huntington's Disease Rating Scale (UHDRS) total motor score (TMS) is a sum of all sub scores rated on a 0-4 scale, where 0 represents an absence of impairment and 4 represents a pronounced impairment. UHDRS Symbol Digit Modalities Test (SDMT) measure executive functioning as represented by values correct from 0 to 110. UHDRS Chorea sub score is a sum of sub scores of 0-4, where 0 represents an absence of chorea and 4 represents pronounced presence, totaling in 28 points. UHDRS Functional Assessment (FA) scores are out of 25, where larger values represent higher functioning, and independence (Ind) scores, where higher scores represent greater independence, are rated 0-100.

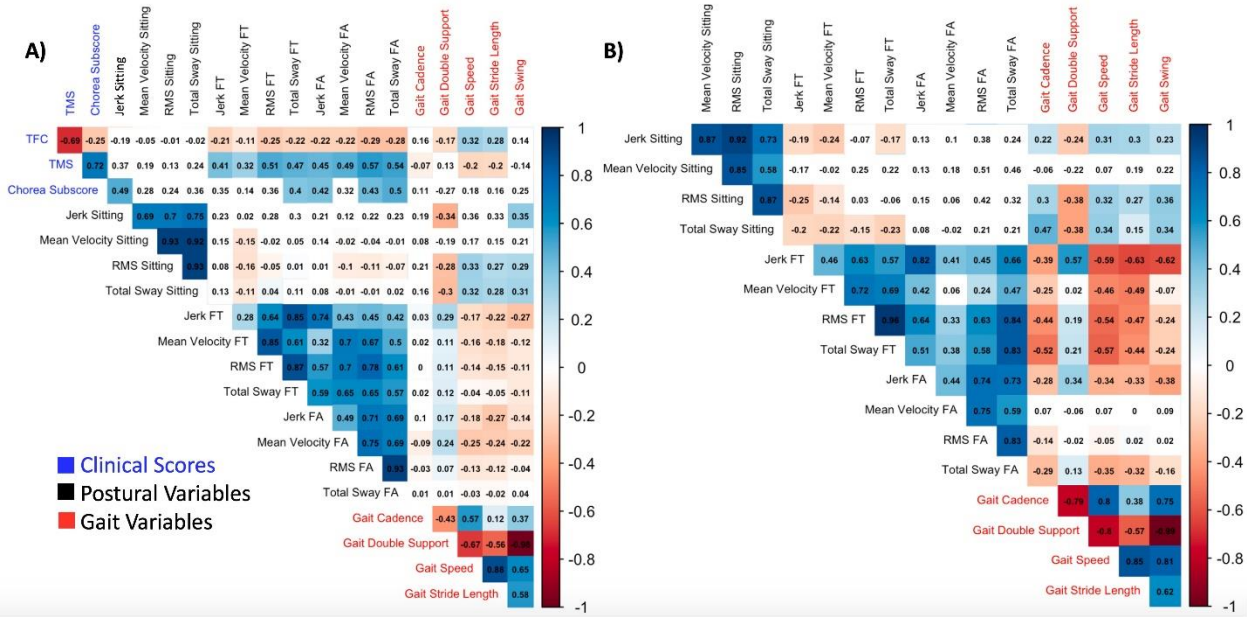
Table 2: Raw mean values, standard deviations, and coefficient of variation for all postural control and gait variables in persons with HD and non-HD peers. Standardized mean difference is a measure of effect size

		Non-HD Peers	**HD (TFC11-13)**	**HD (TFC<11)**	***SMD* (TFC11-13)**	***SMD* (TFC<11)**
RMS	Feet Apart	0.10(0.04)	0.21(0.19)	0.33(0.17)	5.58	19.94
	Feet Together	0.12(0.05)	0.25(0.19)	0.39(0.18)	6.36	19.65
	Sitting	0.06(0.05)	0.54(0.47)	0.63(0.60)	4.40	4.44
Jerk	Feet Apart	1.50(1.06)	22.0(37.6)	70.5(80.8)	0.029	0.030
	Feet Together	3.42(4.3)	19.6(25.4)	114.0(183)	0.049	0.0094
	Sitting	1.15(1.60)	36.7(31.8)	92.7(97.41)	0.070	0.028
Mean Vel.	Feet Apart	0.33(0.18)	0.45(0.41)	0.68 (0.49)	1.22	3.40
	Feet Together	0.32(0.15)	0.61(0.58)	0.80 (0.58)	1.59	3.63
	Sitting	0.11(0.11)	0.80 (0.71)	1.21 (1.24)	2.71	2.02
Total Sway	Feet Apart	1.80 (1.8)	14.8 (24.8)	36.6 (39.8)	0.042	0.062
	Feet Together	4.06(4.0)	20.4(27.0)	46.4 (51.7)	0.044	0.045
	Sitting	0.29 (0.37)	56.9 (66.8)	79.9(105)	0.025	0.021
Gait	Cycle Duration	1.06(0.12)	1.09(0.09)	1.10(0.13)	3.18	3.70
	Speed	1.32(0.26)	1.22(0.20)	1.04(0.21)	-1.84	-4.66
	Step Duration	0.53(0.06)	0.55(0.04)	0.56(0.07)	5.87	6.44
	Stride Length	1.37(0.19)	1.31(0.15)	1.14(0.19)	-1.76	-6.13

Table 3. Comparison of postural control and gait variables between Low TFC (LTFC; TFC <11), High TFC (HTFC; TFC≥11) and non-HD peer, using ANOVA and Tukey post-hoc pairwise comparison. * Denotes a main significant effect of group. Only significant pairwise post-hoc tests reported in table. D.F = Degrees of Freedom.

		D.F.	*F*-value	*p*-value	Tukey post-hoc
RMS	Feet Apart	(2,54)	11.13	<.001*	HD 2-HD 1: p = .04 HD 2-Non HD: p <.001
	Feet Together	(2,54)	13.24	<.001*	HD 2-HD 1: p = .027 HD 2-Non HD: p < .001
	Sitting	(2,55)	7.036	.0019*	HD 2-HD 1: p = .0016 HD 1-Non HD: p = .022
Jerk	Feet Apart	(2,54)	7.457	.0014*	HD 2-HD 1: p = .036 HD 2-Non HD: p =.0018
	Feet Together	(2,54)	4.593	.014*	HD 2-Non HD: p = .026
	Sitting	(2,55)	8.974	<.001*	HD 2-HD 1: p = .041 HD 2-Non HD: p < .001
Mean Vel.	Feet Apart	(2,54)	3.93	.026*	HD 2-Non HD: p = .027
	Feet Together	(2,54)	4.355	.0018*	HD 2-Non HD: p = .013
	Sitting	(2,55)	6.44	.0026*	HD 2-Non HD: p =.0017
Total Sway	Feet Apart	(2,54)	6.845	.0022*	HD 2-Non HD: p =.0022
	Feet Together	(2,54)	6.289	.0035*	HD 2-Non HD: p =.0034
	Sitting	(2,55)	4.742	.0126*	HD 2-Non HD: p =.0091
Gait	Cycle Duration	(2,54)	1.014	0.37	–
	Speed	(2,54)	8.271	<.001*	HD 2-HD 1: p = .04 HD 2-Non HD: p <.001
	Step Duration	(2,54)	0.862	.428	–
	Stride Length	(2,54)	8.881	<.001*	HD 2-Non HD: p <.001

Figure 1. a) Pearson correlation tables of all IMU derived postural control and gait, in addition to clinical measures, and UHDRS chorea subscores for patients with HD. b) Pearson correlation tables of all IMU derived postural control and gait for non-HD peers.



590 Figure 2: Linear regression plot indicating significant model, where UHDRS Chorea sub score is
591 predicted by Root Mean Square (RMS) Feet Apart.
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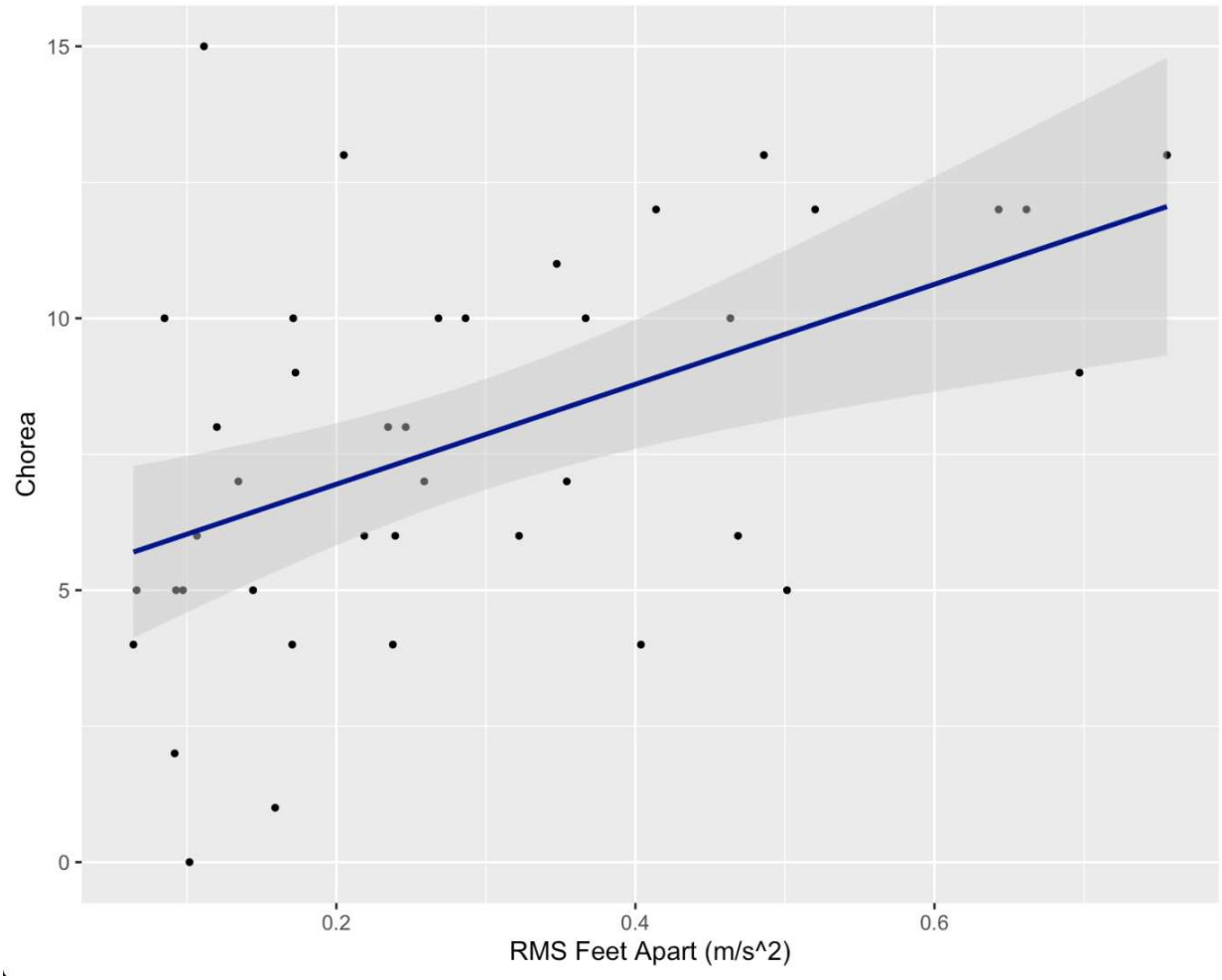

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