Title

Handwriting Movement Abnormalities in PreManifest Huntington's Disease

Authors

Haque, Ameera
Corey-Bloom, Jody
Park, Sungmee
et al.

Publication Date

2017

Peer reviewed

Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Handwriting Movement Abnormalities in Symptomatic and Premanifest Huntington's Disease

Michael Caligiuri, PhD,[1,] Chase Snell, BS,[2] Sungmee Park, BS,[2] and Jody Corey-Bloom, MD, PhD[2]*

ABSTRACT: Background: Kinematic measures of handwriting movements are sensitive to mild subclinical motor abnormalities stemming from a wide range of disorders involving the basal ganglia including Huntington's disease (HD). Prior research has not investigated handwriting movements in at-risk individuals in the premanifest stage of HD.

Objectives: The purpose of this study was to examine whether handwriting movement abnormalities are present prior to clinically manifest chorea in HD.

Methods: A total of 38 symptomatic HD, 30 gene-positive premanifest, and 25 healthy control participants completed handwriting tasks consisting of circles, loops, sentences, and spirals with a noninking pen on a digitizing tablet. Multiple measures of pen stroke kinematics and pressure were measured along with the cognitive and motor status of each participant. Burden of pathology and CAG × age product scores were obtained from each participant with HD.

Results: Participants with HD exhibited significantly longer and more variable stroke durations, decreased handwriting smoothness, and increased and more variable pen pressures when compared with the healthy controls. We found significant positive associations between stroke duration and both burden of pathology and CAG × age product. Results from a discriminant function analysis revealed a 7-factor model that distinguished premanifest from healthy controls with 85% accuracy. Factors in the model included greater variability in stroke amplitude, velocity and pen pressure, higher levels of pen pressure, longer stroke durations, and lower velocities for combinations of handwritten circles, sentences, and spirals.

Conclusions: These findings support the clinical utility of dynamic measures of handwriting kinematics as a potential early behavioral biomarker in HD.

Huntington's disease (HD) is an inherited progressively disabling disorder that leads to disturbances with behavioral control, cognition, and motor function. Although not the first to describe the disease, George Huntington published the most thorough description of the condition in 1872. The movement disorder in HD is a hyperkinetic disorder characterized by dyskinesia, the random involuntary movements of the limbs and trunk. Early motor signs appear as restlessness, twitching, and a desire to move about. Fine motor control, including handwriting, becomes less controlled with declining coordination. Later in the course of the illness, motor signs devolve into dystonia, chorea, slowness of voluntary movements, inability to regulate the speed or force of movements, inability to initiate movement, slowed reactions, difficulty speaking and swallowing, impaired balance ability, and eventually muscle rigidity.

It has been nearly 20 years since the last publication on handwriting abnormalities in HD appeared in the literature. Work by Phillips and colleagues[1–3] constitute the bulk of this literature. Phillips and colleagues[1] employed kinematic analyses to characterize handwriting movements in 12 patients with HD. Participants

[1]*Department of Psychiatry, University of California San Diego, La Jolla, California, USA;* [2]*Department of Neurosciences, University of California San Diego, La Jolla, California, USA*

***Correspondence to:** Dr. Michael P. Caligiuri, Department of Psychiatry (0603), University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093; E-mail: mcaligiuri@ucsd.edu

Keywords: Huntington's disease, handwriting, kinematics.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 27 February 2019; revised 1 July 2019; accepted 8 July 2019.
Published online 16 August 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12824

were instructed to write the letter "l" at a specified size using linked cursive script. Samples were digitized, and nearly a dozen kinematic parameters were automatically extracted from the digitized samples. The investigators reported that handwriting movements in HD were characterized by longer stroke durations, greater variability in stroke amplitude, duration, and velocity, and an increase in the number of submovements (an index of handwriting smoothness and efficiency) when compared with age-comparable healthy individuals. The investigators did not find any associations between the handwriting kinematic abnormalities and clinical status or medication, suggesting a weak predictive value of handwriting kinematics as markers of disease progress in HD. In a subsequent study, Phillips and colleagues[2] examined whether these impairments worsened during continuous sequential handwriting as is observed in the micrographia of Parkinson's disease (PD). Given that the basal ganglia pathophysiology in HD overlaps with PD at least in advanced cases, the investigators hypothesized that handwriting in HD should contain micrographic features. Although the investigators observed that stroke duration increased progressively with continuous writing, there was no consistent finding of progressive decrease in stroke size as there is in PD micrographia. Nonetheless, at least 1 of their HD patients exhibited clear micrographia. A few years later, Iwasaki and colleagues[4] reported micrographia in a 72-year-old HD patient, lending support to the possibility that HD and PD share a common basal ganglia pathology that presents with handwriting abnormalities. In light of the sparse research on handwriting movements in HD, questions remain as to whether the assessment of handwriting movements can be used to detect abnormalities in the premanifest (PM) stage of the disease and serve as a harbinger of disease progress.

The present study had the following 3 aims: (1) confirm prior research on handwriting movement abnormalities in HD, (2) examine the relationships between handwriting movement abnormalities and clinical features in symptomatic HD patients, and (3) test whether features and their variability extracted from analyses of pen-stroke movement and pressure can distinguish PM individuals at risk for developing symptomatic HD from healthy individuals. Based on prior research, we hypothesized that symptomatic HD participants will deviate significantly from normal healthy subjects on multiple parameters of handwriting movement. In addition, we hypothesized gene-positive individuals in the PM stage of the disease can be distinguished with a high degree of accuracy from healthy individuals with no family history of HD based on measures of handwriting movements.

Methods

Participants

The study enrolled 38 symptomatic HD participants and 30 gene-positive, asymptomatic individuals currently in the PM stage of the illness. A total of 25 healthy individuals with no family history of HD served as normal control (NC) participants. The HD and PM participants were recruited through an ongoing HD clinic at the University of California San Diego. Healthy participants were recruited from staff and caregivers. Prior to participation, all participants signed informed consent approved by the University of California, San Diego institutional review board. Table 1 shows the demographic and clinical characteristics of the study participants.

Clinical Assessments

All participants underwent clinical assessments of cognitive, motor, and behavioral signs and symptoms using the Unified Huntington's Disease Rating Scale (UHDRS)[5] and Mini-Mental State Exam.[6] Confirmatory genetic findings including CAG repeats to assess disease penetrance for HD and PM participants were available for the study. Two additional measures derived from the CAG score and considered to be valid indices of disease progression were calculated for each HD and PM participant. These included the Penney Burden of Pathology (BOP)[7] calculated from the product of age × [CAG − 35.5] and the CAG × age product.

Handwriting Assessments

Following the clinical assessments, participants completed the procedure for quantifying handwriting movements. The procedure has been found to be particularly sensitive to extrapyramidal signs associated with antipsychotics in psychiatric patients.[8–10] The handwriting assessment involves minimal decision-making on the part of the examiner, and stimulus delivery and task sequence are automatically delivered. The procedure extracts multiple spatial, temporal, and pressure variables from each stroke of pen movement during natural handwriting and drawing. Pen movements were recorded using a noninking pen and Wacom digitizing tablet (https://www.wacom.com/en-us) connected to a notebook computer. The tablet had a writing surface area of 30 cm × 22.5 cm, a sampling rate of 120 Hz, and root mean square accuracy of 0.01 cm. The test battery used in the present study consisted of the following 5 different writing patterns: simple loops written from left to right ("llllllll"), complex loops ("lleellee"), rapid

TABLE 1 *Clinical and demographic characteristics for 25 normal control (NC), 30 premanifest (PM) gene-positive, and 38 symptomatic Huntington's disease (HD) participants*

Group	Age, y	Gender, F:M	UHDRS	MMSE	CAG	BOP	CAP
NC	44.72 (20.82)	18:7	0.88 (1.64)	28.95 (1.20)			
PM	45.17 (13.14)	18:12	3.73 (3.57)	28.23 (1.63)	41.67 (3.11)	259.15 (92.99)	342.26 (100.33)
HD	55.74 (13.26)	25:13	28.79 (15.22)	26.18 (3.34)	43.00 (3.05)	386.47 (100.65)	489.03 (97.93)

Shown are means (with standard deviations) or individual counts.
UHDRS, Unified Huntington's Disease Rating Scale; MMSE, Mini-Mental State Exam; CAG, gene base repeats; BOP, Penney Burden of Pathology; CAP, CAG × age product.

overlay circles, Archimedes' spiral, and the sentence "Today is a nice day." All tasks were completed with the participant's self-reported dominant hand. The tasks were administered in random order with a fixed block of 5 trials for each. Handwriting traces were recorded and processed using MovAlyzeR software (Neuroscript LLC, Tempe, AZ; http://www.neuroscript.net/).

The participants were seated comfortably at a table with the digitizing tablet positioned to allow natural writing for a given participant. Participants were free to position the tablet to improve comfort and create a normal writing environment. Prior to the start of data collection, each participant was shown a visual copy of the task, given instructions, and provided with a practice period to ensure familiarity with writing on the tablet using an inkless stylus. Delays in initiating the trial or trials where the participant stopped before the trial ended were readministered. The recording window for each trial was 10 seconds with a 2-second intertrial interval. With 5 tasks each with 5 trials, the full handwriting assessment lasted approximately 10 minutes. Handwriting assessments were considered sufficient if a participant completed at least 3 trials with 5 or more pen strokes per trial. Under these criteria, the number of participants with HD excluded from analysis varied with the task and ranged from 1 for simple loops and spirals to 5 for sentences. The number of PM participants excluded from analysis ranged from 1 for simple loops and spirals to 3 for sentences. Only 1 NC participant met the exclusion criteria and only for maximum speed circles and sentences.

Single-trial samples of the 5 handwriting tasks from 1 NC participant and 1 participant with HD are shown in Figure 1. The participant with HD selected for this exemplar was 35 years old with a CAG repeat of 49, a BOP of 472.5, UHDRS total score of 40 (9 on the chorea items), and an Mini-Mental State Exam score of 21. These exemplars contrast the dysfluent pen movements in the HD participant when compared with the NC participant across the 5 tasks.

Handwriting samples were subjected to automatic processing and analysis using Movalyzer software. Handwriting patterns were low-pass filtered at 12 Hz, and time derivatives were estimated. Reduction and analysis of the handwriting kinematics involved the extraction of multiple variables from each vertical pen stroke from each trial of each handwriting task. Variables included the mean and variability (standard deviation across strokes and trials) for movement duration (in seconds), peak vertical velocity and average velocity (in cm/s), vertical amplitude (in centimeters), average normalized jerk (smoothness), and pen pressure (in tablet units). Normalized jerk is unitless as it is normalized for stroke duration and length. Average normalized jerk was calculated using the following formula[11]:

$$\sqrt{\left(0.5\times\sum\left(\text{jerk}(t)^2\right)\times\text{duration}^5/\text{length}^2\right)}.$$

These features were computed for both upstrokes and downstrokes and then averaged across all vertical strokes of the trial

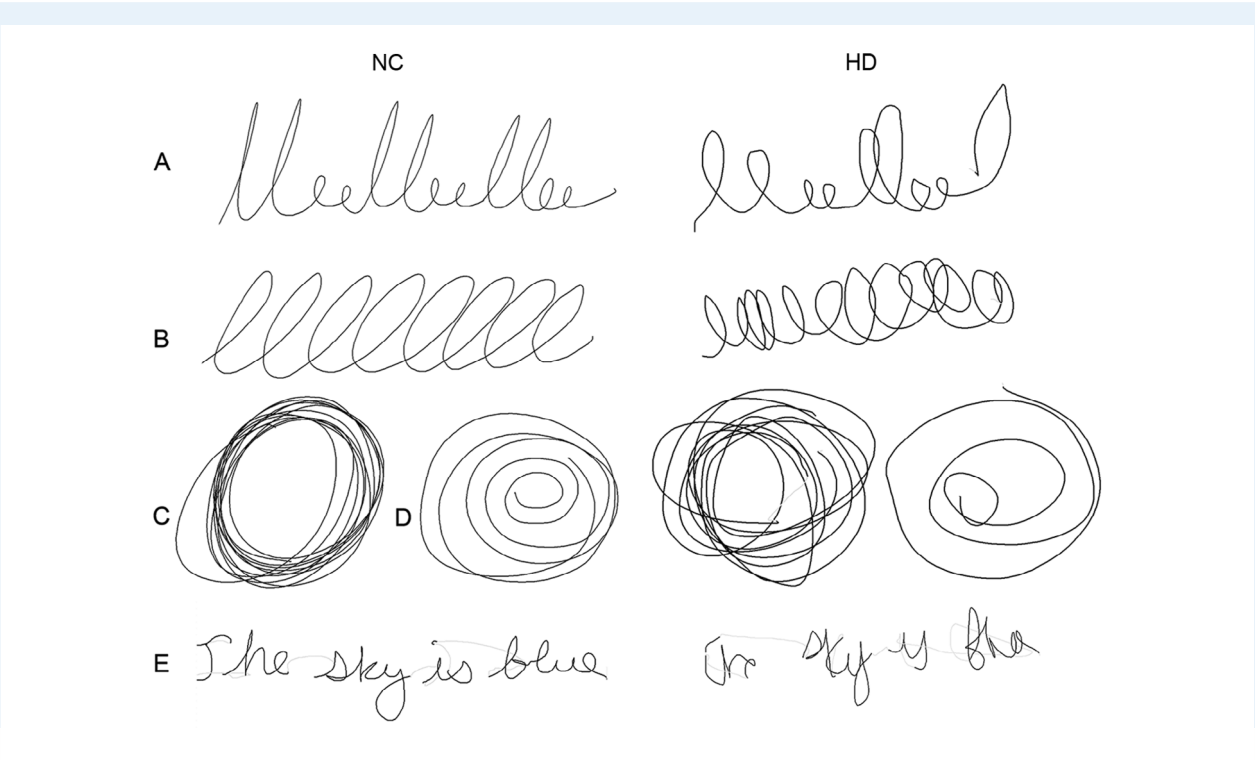

FIG. 1. Examples of the 5 handwriting tasks written by a healthy control participant (NC, left) and participant with Huntington's disease with moderate chorea (HD, right). The figure shows performance on the complex loops (A) simple left to right loops (B), overlay circles drawn at maximum speed (C), spirals (D), and the sentence (D) tasks.

and across trials. Completed trials contained at least 14 up and down pen strokes.

Results

The results are summarized in 3 parts. The first part reports findings from a statistical comparison of handwriting movement variables between HD and NC participants. Statistical relationships between clinical characteristics and abnormal handwriting movements for the participants with HD are reported in the second part. The third part contains the results of discriminant function analyses examining the sensitivity and specificity of the handwriting movement variables in PM participants.

Handwriting Abnormalities in HD

For comparisons of HD with NC participants, we restricted the NC participants' age to greater than 29 years to ensure comparable mean ages for the 2 groups, as prior studies have shown that age can influence many handwriting movement variables.[12] This resulted in retaining 15 of the 25 healthy participants having a mean age (standard deviation) of 60.00 (10.56) years, which was statistically comparable to the mean age of the participants with HD ($t = 1.11$; $P > 0.10$) reported in Table 1.

Tests of differences in the variances between the HD and NC participants for paired comparisons were found to be statistically significant for most variables, requiring us to reject the assumption of homogeneity of variance. Therefore, nonparametric tests (Mann-Whitney tests) were used to examine group differences on handwriting movement variables across the 5 conditions with $\alpha < 0.05$ for rejecting the null hypotheses. Table 2 shows the group means and standard deviations for the NC and HD participants.

Stroke Duration

The participants with HD exhibited significantly longer stroke durations when compared with the age-comparable healthy participants for the complex loops ($z = 3.52$; $P < 0.001$), overlay circles written at maximum speed ($z = 3.11$; $P < 0.01$), simple left-to-right continuous loops ($z = 3.13$; $P < 0.01$), sentence writing ($z = 3.82$; $P < 0.001$), and spirals ($z = 3.09$; $P < 0.01$). The participants with HD exhibited significantly larger mean variability in stroke duration on each of the 5 handwriting tasks when compared with the healthy participants.

Stroke Amplitude

None of the group differences in stroke amplitude were found to be statistically significant. With regard to the within-subject stroke–stroke variability in stroke amplitude, the participants with HD exhibited significantly larger mean variability scores in stroke amplitude for overlay circles, left-to-right loops, and sentences when compared with the healthy participants.

Peak Vertical Velocity

A significant group difference was observed in peak stroke velocity for the production of handwritten spirals only ($z = 2.26$; $P < 0.02$) with the participants with HD producing spirals with lower stroke velocities when compared with the healthy participants. The HD participants exhibited significantly larger mean variability in pen movement velocity for only spirals when compared with the healthy participants.

Average Normalized Jerk

The participants with HD exhibited significantly larger scores on the handwriting dysfluency measure when compared with the

TABLE 2 *Mean (with standard deviations) pen movement and pressure scores for 15 normal control (NC) and 38 age-comparable Huntington's disease (HD) patients for 5 handwriting tasks*

	Handwriting Condition				
Handwriting Task	Complex	Max Speed	Left–Right Loops	Sentence	Spirals
Duration					
NC	0.31 (0.06)	0.29 (0.09)	0.33 (0.07)	0.20 (0.04)	0.44 (0.11)
HD	0.44*** (0.14)	0.41*** (0.14)	0.46*** (0.15)	0.26*** (0.08)	0.58 (0.18)
Vertical size					
NC	2.16 (0.83)	5.66 (2.17)	3.27 (0.98)	1.00 (0.24)	5.06 (1.30)
HD	2.46 (1.28)	6.27 (1.98)	3.85 (1.72)	1.21 (0.46)	4.64 (1.19)
Peak velocity					
NC	12.13 (3.45)	32.72 (12.49)	17.57 (4.78)	9.19 (2.14)	18.38 (6.16)
HD	11.52 (5.14)	27.88* (12.15)	16.26 (5.86)	9.27 (3.02)	13.94* (5.46)
Average normalized jerk					
NC	23.70 (12.15)	13.09 (4.02)	18.86 (9.15)	24.71 (12.91)	26.00 (20.74)
HD	93.37** (125.62)	27.98** (24.73)	60.79*** (60.50)	53.79** (47.21)	62.99* (51.40)
Pen pressure					
NC	697.28 (164.01)	763.68 (157.67)	718.59 (130.07)	577.41 (142.23)	774.31 (142.33)
HD	828.56*** (147.31)	852.53** (151.27)	851.99*** (140.49)	676.13*** (138.94)	858.20** (146.77)

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$, significantly different from NC participants based on Mann-Whitney statistic.

age-comparable healthy participants for the complex loops ($z = 3.52$; $P < 0.001$), overlay circles written at maximum speed ($z = 2.83$; $P < 0.01$), simple left-to-right continuous loops ($z = 3.60$; $P < 0.001$), sentence writing ($z = 3.01$; $P < 0.01$), and spirals ($z = 3.64$; $P < 0.001$). The HD participants exhibited significantly larger mean variability scores on the handwriting fluency measure for each of the 5 handwriting tasks when compared with the healthy participants.

Pen Pressure

The participants with HD exhibited significantly larger mean pen pressures when compared with the age-comparable healthy participants for the complex loops ($z = 2.53$; $P < 0.01$), simple left-to-right continuous loops ($z = 3.09$; $P < 0.01$), sentence writing ($z = 2.16$; $P < 0.05$), and spirals ($z = 2.12$; $P < 0.05$). The HD participants exhibited significantly larger mean variability in pen pressure for complex loops, simple left-to-right loops, and sentences when compared with the healthy participants.

Clinical Relationships

We examined the relationships between clinical disease state variables and handwriting movement variables in the 38 symptomatic HD participants. Based on univariate Pearson product moment coefficients, scores on several of the handwriting movement variables were significantly correlated with and accounted for greater than 25% of the variability in clinical severity, including the UHDRS, BOP, and CAG × age product. Specifically, a greater UHDRS total score was associated with reduced stroke amplitude for rapid circles ($r = -0.56$; $P < 0.001$) and increased pen pressure variability for left–right loops ($r = 0.52$; $P < 0.001$). Greater BOP scores were associated with increased stroke duration for both complex loops ($r = 0.52$; $P < 0.001$) and left–right loops ($r = 0.51$; $P < 0.001$). Greater CAG × age product scores were associated with increased stroke duration for both complex loops ($r = 0.59$; $P < 0.001$) and sentences ($r = 0.51$; $P = 0.001$), increased variability in stroke duration for left–right loops ($r = 0.55$; $P < 0.001$), and increased handwriting dysfluency ($r = 0.51$; $P = 0.001$). None of the scores on handwriting movement variables were directly associated with the CAG repeat number.

Discriminating Gene-Positive PM from Gene-Negative Healthy Participants

Scores on the handwriting movement variables from 30 gene-positive PM individuals at risk for developing symptomatic disease and 25 healthy participants were entered into a stepwise discriminant function analysis to identify the most accurate multivariate model for distinguishing PM from NC participants. We restricted the variables entered into the analysis to those found to be abnormal in symptomatic HD participants as reported previously.

A backward stepwise analysis led to a 7-factor model having 90% sensitivity in classifying PM participants and 80% specificity in classifying NC participants, with an overall accuracy of 85.4% ($F_{7,47} = 6.70$; $P < 0.0001$). Table 3 shows the statistical results for the variables in the model.

Table 3 includes R^2 as a measure of the strength of the contribution by a given handwriting variable in discriminating PM from age-comparable and gender-comparable NC participants. Based on this measure, stroke duration, amplitude, and velocity for spirals were the 3 strongest predictors of HD risk status, accounting for between 75% and 87% of the variability in diagnosis. With regard to the specific variables found to discriminate PM from NC participants, correctly classified PM participants exhibited increased variability in stroke amplitude and reduced variability peak velocity for rapid circles, both increased variability and mean pen pressure for sentence writing, and increased stroke duration, decreased stroke amplitude, and decreased average velocity for spirals when compared with the NC participants.

Discussion

The present study tested the following 2 hypotheses: (1) that symptomatic HD participants will deviate significantly from normal healthy participants on multiple parameters of handwriting movement and (2) that gene-positive individuals in the PM stage of the disease can be distinguished with a high degree of accuracy from healthy individuals with no family history of HD on measures of handwriting movements. With regard to the first hypothesis, we found handwriting movements in HD patients were characterized by abnormalities across several kinematic features, including prolonged pen stroke duration, dysfluency, and greater variability in amplitude,

TABLE 3 *Results from a discriminant function analysis showing the 7 handwriting movement and pressure variables in the final model used to distinguish premanifest from normal comparison participants*

Handwriting Movement Variable	Task*	Wilks' Lambda	*F*	*P* Value	R^2
Variability in stroke amplitude	C	0.55	5.13	0.03	0.37
Variability in peak velocity	C	0.60	9.53	0.003	0.42
Mean pen pressure	S	0.56	5.37	0.03	0.16
Variability in pen pressure	S	0.54	3.72	0.06	0.15
Mean stroke duration	Sp	0.59	8.03	0.007	0.75
Mean stroke amplitude	Sp	0.57	6.86	0.01	0.75
Mean average velocity	Sp	0.55	5.16	0.03	0.87

*C, maximum speed overlay circle; S, sentence; Sp, spiral.

duration, velocity, and pen pressure relative to healthy participants. Although prior studies suggest that handwriting in HD may present with micrographia,[2,4] the HD participants in the present study did not demonstrate micrographia as a group. Our findings that the participants with HD produced handwriting movements with prolonged stroke durations, reduced velocity, and increased kinematic variability in the absence of micrographia were consistent with prior studies in HD.[1,2] Higher pen pressures and greater pen pressure variability during handwriting in HD have not been previously reported and constitute 2 features having the greatest departure from healthy handwriting motor behavior.

Our results supported the hypothesis that individuals in the PM stage of the disease with no clinically overt cognitive or motor signs can be distinguished with a high degree of accuracy from healthy individuals who are not carriers of the genetic mutation responsible for HD. Discriminant function analyses revealed a 7-factor model having 90% sensitivity in classifying PM participants and 80% specificity in classifying healthy participants, with an overall accuracy of 85.4%. The model was based on kinematic and pen pressure scores from the following 3 handwriting tasks: rapidly produced circles, sentences, and spirals. Pen stroke duration, amplitude, and velocity for handwritten spirals were the 3 strongest variables discriminating PM from NC participants, accounting for between 75% and 87% of the variability in diagnosis. This finding suggests that sensitive dynamic measures of handwriting can detect movement abnormalities in individuals prior to the clinical presentation of even mild motor dysfunction.

Prior research failed to uncover statistically significant associations between the handwriting kinematic abnormalities and clinical status or medication, leading investigators to conclude that measures of handwriting kinematics might not be useful as markers of disease progress in HD.[1,2] A lack of statistical significance from these studies was likely the result of small sample sizes. Even with substantially increased sample sizes, the present study detected only modest associations between disease severity (based on UHDRS total score) and several handwriting variables, including an inverse relationship with pen stroke amplitude and a positive relationship with pen pressure variability. Similarly, with regard to disease penetration, HD participants with higher BOP scores exhibited longer stroke durations. Increased stroke duration during handwriting could be the result of motor slowness or bradykinesia and/or the introduction of multiple inversions in velocity or acceleration during the production of a single pen stroke. The latter possibility has been observed in the handwriting of patients with tardive dyskinesia,[10] a hyperkinetic movement disorder having abnormal movement patterns that often resemble HD. In the present study, the number of acceleration inversions was obtained; however, because of its linear relationship with stroke duration in individuals with hyperkinesia, it was excluded from the analysis. Instead, we chose stroke duration, which may encompass the number acceleration inversions but is computationally easier to obtain in future replication studies.

The finding that handwriting abnormalities can be detected in PM participants has far-reaching clinical implications. Effective pharmacotherapy in any neuropsychiatric movement disorder depends on the early detection of pathology to offer the greatest chance of delaying the onset of debilitating signs and symptoms. The general focus of this effort has traditionally focused on biomarkers found using genetic, imaging, or laboratory assays. The present study suggests that the early detection of motor abnormalities in PM HD can be achieved using a behavioral biomarker. In addition, assessing the outcomes of novel pharmacotherapies in HD needs to include reliable quantitative procedures for assessing change in motor function. Indeed, research by Reilmann and colleagues[13,14] have demonstrated the benefits of quantitative motor assessments of disease progression in HD. These investigators developed a "choreomotography" task to quantify the extent to which choreatic movements interfered with a grip force task. As in the present study, scores on the choreomotography task were both abnormal in PM HD relative to healthy controls and were associated with disease burden scores.

Results from the present study require confirmation, particularly for the PM participants. Larger normative sample sizes in future studies are needed to help refine predictive models based on handwriting movements and applied pen pressure of the transition to symptomatic HD. Moreover, longitudinal studies are needed to enhance precision for the delay between the PM stage and the first clinically detectable chorea in HD gene carriers.

In conclusion, the findings of the present study support the clinical utility of dynamic measures of handwriting kinematics and pen pressures as potential early behavioral biomarkers of disease transition in HD. The tablet-based handwriting procedure deployed in this study is low cost and capable of providing fully automatic data collection, analysis, and reporting in the clinical environment.

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution 2. Statistical analysis: A. Design, B. Execution, C. Review and Critique 3. Manuscript preparation: A. Writing of the first draft, B. Review and Critique

M.C.: 1A 1B 1C 2A 2B 2C 3A 3B
J.C.-B.: 1A 1B 3A 3B.
S.P.: 1C
C.S.: 1C

Acknowledgments

We thank the patients, families, and volunteers from the University of California San Diego Huntington's Disease Society of America Center of Excellence and the University of California San Diego Shiley-Marcos Alzheimer's Disease Research Center (ADRC) for their participation in this research.

Disclosures

Ethical Compliance Statement: All authors have read and complied the Journal's Ethical Publication Guidelines. We

confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This research was reviewed and approved by the University of California San Diego institutional review board (Reference 170038). All participants signed informed consent prior to participating in this research.

Funding Sources and Conflicts of Interest: This research was supported by the University of California San Diego Huntington's Disease Society of America Center of Excellence and the University of California San Diego Shiley-Marcos ADRC National Institutes of Health P50 AG 0055131. None of the authors received direct financial support from these funding sources for their roles related to the research covered in this article.

Financial Disclosures of All Authors (for the Preceding 12 Months): Michael P. Caligiuri received grant funding from National Institute of Justice and a contract with a pharmaceutical company. Jody Corey Bloom received grant funding from National Institutes of Health P50 AG 0055131 and from contracts with pharmaceutical companies. Sungmee Park and Chase Snell have no financial disclosers to report for the preceding 12 months.

References

1. Phillips JG, Bradshaw JL, Chiu E, Bradshaw JA. Characteristics of handwriting of patients with Huntington's disease. *Mov Disord* 1994;9:521–530.
2. Phillips JG, Chiu E, Bradshaw JL, Iansek R. Impaired movement sequencing in patients with Huntington's disease: a kinematic analysis. *Neuropsychologia* 1995;33:365–369.
3. Slavin MJ, Phillips JG, Bradshaw JL, Hall KA, Presnell I. Consistency of handwriting movements in dementia of Alzheimer's type: a comparison with Huntington's and Parkinson's diseases. *J Int Neuropsychol Soc* 1999;5:20–25.
4. Iwasaki Y, Ikeda K, Shindo T, et al. Micrographia in Huntington's disease. *J Neurol Sci* 1999;162:106–107.
5. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996;11:136–142.
6. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Research* 1975;12:189–198.
7. Penney JB Jr, Vonsattel JP, Macdonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann Neurol* 1997;41:689–692.
8. Caligiuri MP, Teulings HL, Dean CE, Niculescu AB, Lohr JB. Handwriting movement analyses for monitoring drug-induced motor side effects in schizophrenia patients treated with risperidone. *Hum Mov Sci* 2009;28:633–642.
9. Caligiuri MP, Teulings HL, Dean CE, Niculescu AB, Lohr JB. Handwriting movement kinematics for quantifying EPS in patients treated with atypical antipsychotics. *Psych Res* 2010;77:77–83.
10. Caligiuri MP, Teulings HL, Dean CE, Lohr JB. A quantitative measure of handwriting dysfluency for assessing tardive dyskinesia *J Clin Psychopharmacol* 2015;35:168–174.
11. Teulings HL, Contreras-Vidal JL, Stelmach GE, Adler CH. Coordination of fingers, wrist, and arm in Parkinsonian handwriting. *Exp Neurol* 1997;146:159–170.
12. Caligiuri MP, Kim, C, Landy KM. Kinematics of signature writing in healthy aging. *J Forensic Sci* 2104;59:1020–1024.
13. Reilmann R, Kirsten F, Quinn L, et al. Quantitative assessment of progression in Huntington's disease: a 3-year follow-up study. *Neurology* 2001;57:920–924.
14. Reilmann R, Bohlen S, Kirsten F, et al. Assessment of involuntary choreatic movements in Huntington's disease—toward objective and quantitative measures. *Mov Disord* 2011;26:2267–2273.