


How Different Aspects of Motor Dysfunction Influence Day-to-Day Function in Huntington's Disease

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ABSTRACT

Purpose: This study examined the relationships between different aspects of motor dysfunction (chorea, dystonia, rigidity, incoordination, oculomotor dysfunction, dysarthria, and gait difficulties) and functional status in persons with Huntington's disease.

Methods: A total of 527 persons with Huntington's disease completed the Unified Huntington's Disease Rating Scale motor, total functional capacity, and functional assessments.

Results: Confirmatory factor analysis indicated that a 4-factor model provided a better model fit than the

existing 5-factor model. Exploratory factor analysis identified the following 4 factors from the motor scale: dystonia, chorea, rigidity, and a general motor factor. Regression indicated that dystonia ($\beta = -0.47$ and -0.79) and rigidity ($\beta = -0.28$ and -0.59) had strong associations with function, whereas chorea had modest correlations ($\beta = -0.16$ and -0.15).

Conclusions: Dystonia and rigidity have stronger relationships with functional status than chorea in persons with Huntington's disease. The findings underscore the need for further research regarding the effects of dystonia and rigidity on functioning. © 2019 International Parkinson and Movement Disorder Society

Key Words: chorea; dystonia; HDQLIFE; Health-related quality of life; Huntington's disease; motor function

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease characterized by progressive motor, behavioral, and cognitive decline.¹ Motor dysfunction is multifaceted, involves all body regions, and profoundly affects day-to-day function. Most studies and interventions focus on chorea,^{2,3} which can appear as fidgety, jerky, or dance-like movements. Chorea and dystonia are the only motor symptoms known to respond to pharmacotherapy.^{4,5} By mid-stage to late-stage HD, motor problems steadily worsen^{1,6} even if chorea remains controlled.⁷ Motor dysfunction is a major driver of functional loss in HD.^{6,8,9}

The Unified Huntington's Disease Rating Scale (UHDRS) Motor Scale is one of the most commonly used assessments in HD. Although the motor scale includes clinician ratings of eye movements, chorea, dystonia, rigidity, speech, gait, postural stability, and bradykinesia, prior research suggests that the motor scale could be consolidated and further improved.^{10,11} The present study builds on this research by examining UHDRS motor and function ratings in a large sample of people with HD. The goal was twofold: (1) repeat a factor analysis on the UHDRS motor scale, comparing it with the 5 factors identified previously,¹⁰ and (2) determine which motor factors best relate to functional status in HD.

Methods

Participants

A total of 527 individuals with premanifest or manifest HD were included in this analysis. Participants were at least 18 years of age, able to read and comprehend English, and capable of providing informed

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consent. Participants were recruited from 8 HD treatment centers and through the Predict-HD study.¹² Electronic medical records,¹³ the National Research Roster for HD, and community outreach were used to bolster recruitment efforts.

Measures

The UHDRS motor scale is a 15-item clinician rating scale.¹⁴ Total scores range from 0 (no motor difficulties) to 124 (greater motor difficulties). Participants with a diagnostic confidence level on this scale of 4 (≥99% confidence of unequivocal motor signs) were classified as manifest HD.

The UHDRS Total Functional Capacity (TFC)¹⁵ is a 5-item clinician rating of day-to-day functional status. TFC scores were used to examine functional status and to classify manifest HD participants as either early stage (sum scores of 7–13) or later stage (sum scores of 0–6).

The UHDRS Functional Assessment (FA) includes 25 items for common tasks related to occupation, finances, average daily living, domestic chores, and care level. Clinician-rated scores range from 0 to 25 (higher scores indicate better function; note that FA scores were missing for the n = 170 Predict-HD participants that were enrolled in this study given established ceiling effects in premanifest HD).

The Stroop Color Word Interference Test¹⁶ provides measures of psychomotor speed and executive function; higher scores reflect better performance. We examined raw scores on the 2 processing speed components (color raw score plus word naming raw score).

Statistical Analyses

Confirmatory factor analysis (CFA) was used to determine whether we could replicate the published 5-factor structure.¹⁰ Good fit was defined as (1) comparative fit index >0.90, (2) root mean square error of approximation <0.1,¹⁷⁻²⁰ and (3) residual correlations <.15.²¹⁻²³ This was followed by an exploratory factor analysis (EFA) with a promax rotation. Eigenvalues >1 and the number of factors before the break in the scree plot helped identify discrete factors. Item loadings (criterion >0.4) established which items belonged to which factor. In cases with substantial cross-loadings, the item with the highest loading was retained. Given that the existing 5-factor model was based solely on a sample of manifest HD participants,¹⁰ CFA was conducted using only manifest HD participants in this sample; EFA was conducted using the combined sample. These analyses were conducted using MPLUS 6.11.²⁴

Linear regression (using SAS 9.4, SAS Institute Inc.100 SAS Campus DriveCary, NC 27513-2414, USA) was used to examine the relationship of the identified factors (through the procedure described previously) and functional outcomes (TFC and FA). A total of 8 sets of simple linear regression models were conducted; each of the 4 factors that were identified as part of the previous analysis

were regressed on both outcomes of interest (TFC and FA). Two separate multiple linear regression models were conducted that included multiple predictors (the discrete factors identified in the previous analysis) and the criterion measure (TFC or FA). All simple linear regression and multiple regression models were conducted twice: once without covariates and then again with Stroop added as a covariate.

Results

Table 1 provides descriptive data for the sample.

The initial CFA (in manifest HD participants) did not support the existing 5-factor model (comparative fit index = 0.93; tucker lewis index (TLI) = 0.93; root mean square error of approximation = 0.14). The follow-up EFA (using the full sample) supported a 4-factor model (Table 2). CFA (using the full sample) on this new 4-factor model indicated a small

TABLE 1. Demographic data for the HDQLIFE participants

Variable	Premanifest, n = 204	Early, n = 198	Late, n = 125	All, N = 527
Age, y; M (SD) ^a	42.7 (12.0)	51.4 (12.7)	54.7 (12.0)	48.8 (13.2)
Sex				
Female	65.4	53.5	57.6	59.0
Male	34.6	46.5	42.4	41.0
Ethnicity ^a				
Not Hispanic or Latino	92.7	92.9	96.8	93.7
Hispanic or Latino	1.5	4.6	0.8	2.5
Not provided	5.9	2.5	2.4	3.8
Race ^a				
White	97.5	96.5	92.8	96.0
African American	0.0	2.0	6.4	2.3
Other	2.0	1.5	0.0	1.5
Unknown	0.5	0.0	0.8	0.2
Education, y; M (SD) ^a	15.9 (2.9)	14.7 (2.8)	14.2 (2.6)	15.1 (2.9)
Marital status ^a				
Single, never married	15.8	15.2	11.8	14.6
Married	67.4	52.9	61.3	60.5
Separated/divorced	13.8	25.1	23.5	20.4
Widowed	0.0	2.6	3.4	1.8
Living with partner	3.0	4.2	0.0	2.7
Years since diagnosis		n = 154	n = 75	N = 230
M (SD)	–	3.14 (3.74)	5.99 (4.62)	4.05 (4.25)
CAG repeats ^a	n = 190	n = 145	n = 56	N = 391
M (SD)	42.2 (2.9)	43.1 (3.9)	44.4 (6.6)	42.9 (4.1)

Entries in the table represent percentage of participants unless otherwise specified. Premanifest participants (M = 42.7, SD = 12.0) were significantly younger than early stage (M = 51.4, SD = 12.7), who were significantly younger than late-stage participants (M = 54.7, SD = 12.0; $F_{2, 524} = 44.25, P < 0.0001$); early-stage (M = 14.7, SD = 2.8) and late-stage (M = 14.2, SD = 2.6) participants had 1 to 1.5 years less education relative to premanifest HD participants (M = 15.9 years, SD = 2.9; $F_{2, 502} = 15.78, P < 0.0001$). The late-stage group had more African Americans than the early-stage and premanifest groups (Fisher's exact $P = 0.0005$); the early-stage group had fewer married participants than the premanifest or late-stage groups, and the premanifest group had fewer widowed participants than the manifest groups, $\chi^2(8, N = 527) = 21.9, P = 0.0051$; there were marginal differences for gender, $\chi^2(2, N = 527) = 5.27 (P = 0.07)$, and ethnicity (Fisher's exact $P = 0.06$).

^aSignificant group differences for this variable. M, mean; SD, standard deviation.

TABLE 2. Factor loadings for the Total Motor Scale

Item	Factor 1, chorea	Factor 2, dystonia	Factor 3, rigidity	Factor 4, general factor	Siesling factor loading
Ocular pursuit–horizontal	0.049	–0.267	(0.439)	0.833	1
Ocular pursuit–vertical	–0.005	–0.198	(0.422)	0.859	1
Saccade initiation–horizontal	–0.039	–0.092	0.016	1.013	1
Saccade initiation–vertical	–0.021	–0.099	0.022	0.997	1
Saccade velocity–horizontal	–0.105	0.153	0.271	0.783	1
Saccade velocity–vertical	–0.106	0.140	0.281	0.770	1
Dysarthia	0.060	0.339	0.014	0.593	1 & 2
Tongue protrusion	0.099	0.143	–0.053	0.665	1
Finger taps–right	0.173	0.258	–0.161	0.690	1
Finger taps–left	0.176	0.258	–0.177	0.692	1
Pronate/supinate hands–right	0.066	0.285	–0.063	0.716	1 & 2
Pronate/supinate hands–left	0.099	0.298	–0.067	0.690	1
Luria (fist-hand palm test)	0.081	0.222	–0.068	0.622	1
Rigidity arms–right	0.022	0.249	0.820	0.050	1 & 5
Rigidity arms–left	0.040	0.228	0.805	0.102	1 & 5
Bradykinesia–body	–0.032	0.342	0.107	0.581	1 & 5
Maximal dystonia–trunk	0.086	0.493	0.194	0.234	4
Maximal dystonia–RUE	0.059	0.919	0.149	–0.087	4
Maximal dystonia–LUE	0.033	0.919	0.129	–0.053	None
Maximal dystonia–RLE	–0.065	0.906	0.001	0.115	4
Maximal dystonia–LLE	–0.021	0.880	0.040	0.092	None
Maximal chorea–face	0.649	–0.128	–0.013	(0.440)	2
Maximal chorea–BOL	0.645	–0.155	–0.010	(0.465)	2
Maximal chorea–trunk	0.738	–0.046	0.053	0.230	3
Maximal chorea–RUE	0.916	0.068	–0.156	0.095	3
Maximal chorea–LUE	0.949	0.050	–0.161	0.063	None
Maximal chorea–RLE	0.969	0.066	0.248	–0.186	3
Maximal chorea–LLE	0.991	0.051	0.251	–0.197	None
Gait	0.076	(0.431)	0.022	0.519	1
Tandem walking	0.074	0.377	0.001	0.541	1
Retropulsion Pull Test	0.017	0.336	0.051	0.501	2

Bold indicates primary factor loadings (values in parentheses indicate that the item loaded on to more than 1 factor). RUE, right upper extremity; LUE, left upper extremity; RLE, right lower extremity; LLE, left lower extremity; BOL, buccal-oral-linguistic.

improvement in model fit (comparative fit index = 0.94; TLI = 0.94; root mean square error of approximation = 0.13). The Akaike information criterion provided additional support for the 4-factor model over the 5-factor model (Akaike information criterion = 12,945.58 in the 5-factor model vs. Akaike information criterion = 12,769.22 in the 4-factor model) with regard to manifest participants. Factor 1 included the 7 chorea items (ie, chorea), factor 2 included the 5 dystonia items (ie, dystonia), factor 3 consisted of 2 rigidity items (ie, rigidity), and factor 4 consisted of the remaining 17 items representing general motor function (ie, general).

Findings from the simple linear regression models indicated that each of the 4 factors were significant predictors of the TFC and FA scales (Supplemental Table A). When cognition was considered in the models, the pattern of findings was the same except for chorea (which was no longer a significant predictor of the FA Scale; Supplemental Table B). We thus concluded that more dystonia, rigidity, and general motor manifestations are associated with worse function.

Next, all 4 factors plus cognition were entered into the same multiple linear regression model. The general factor was removed from the model because of its high collinearity. Therefore, the refined multiple linear regression model examined the impact that chorea, dystonia, and rigidity had on overall function (as evaluated by the TFC and FA) while controlling for cognition. For this combined model (controlling for cognition), dystonia and rigidity remained significant predictors of both the TFC and FA; dystonia was the stronger of the 2 predictors for both (Supplemental Table C).

Discussion

The purpose of this study was to examine the factor structure of the UHDRS Motor Scale and to determine which motor factors are most associated with functional status in people with HD. To this end, our analyses indicated that a 4-factor model provided a slightly superior fit to the previously published 5-factor structure.¹⁰ In

addition, the factor structure of the 4-factor model was more readily interpretable than the factor structure of the 5-factor model. Our model included all chorea items on a single factor, whereas the chorea factor from Siesling's model did not include the face or buccal-oral-lingual items (in the Siesling model these factors loaded with the dysarthria, pronate/supinate right hand, and retropulsion test items).¹⁰ Furthermore, although both models included a more general factor, the rigidity items cross-loaded on this factor for the Siesling model (these items clearly comprised a solitary factor in our findings), as did the dysarthria and pronate supinate right-hand items (which clearly loaded on our general factor).¹⁰ We suspect that the substantial discrepancy in sample size likely contributes to the different outcomes of the 2 studies (we included 527 premanifest and manifest participants, whereas the Siesling study only included 69 manifest participants), and we suspect that the Siesling analysis may have been underpowered (ie, given that the minimal sample size criteria for EFA is typically ~5 people per item analyzed²⁵⁻²⁷). Future studies are needed to evaluate the replicability of our results.

A strength of this study is the large cross-sectional sample across the full TFC spectrum, and not just earlier disease. The TFC score in particular inexorably declines as HD advances²⁸; in fact, it is used as a surrogate for disease severity and stage after motor diagnosis. The positive association of all identified individual motor factors with lower function is not surprising; HD is a progressive disease, and all individual motor features are expected to appear and then worsen to varying degrees with time. What is novel in our analysis is the relative associations of individual motor factors with functioning (and thereby disease stage). We found the most striking association between dystonia (accounting for 9% and 14% of the variance in TFC and FA, respectively, after controlling for cognition) and functioning. Rigidity (accounting for 1% of the variance for both TFC and FA after controlling for cognition) and chorea (accounting for 1% of the variance in TFC and FA) more weakly related to functioning and disappeared entirely when cognition was added to the model. This suggests that although chorea is the hallmark motor manifestation of HD, and one of the only motor manifestations with treatments approved by the Food and Drug Administration,^{4,5} it is not necessarily the most functionally debilitating motor abnormality. Thus, treatments that target dystonia and rigidity have potential to substantially improve function in these individuals.

We acknowledge several study limitations. Although this study employed multisite data collection, the participants reflected a convenience sample that may not be readily generalizable to the broader HD population. Furthermore, our results do not imply that dystonia and rigidity are necessarily major drivers of HD functioning. It may be that these are motor markers of later stage disease that themselves do not contribute much to loss of function. The

general factor encompasses a large and diverse set of motor elements, including eye movements, speech, motor sequencing, upper limb coordination, gait, and balance. Many of these are clearly critical to human function; their elimination in the combined regression model was the result of the strong correlation of this factor with the other 3 factors not because of their lack of importance.

Despite these limitations, the findings suggest that research examining motor function in HD should focus more broadly on the multifaceted nature of motor dysfunction including dystonia and rigidity. Although chorea can impair day-to-day function in these individuals, dystonia and rigidity may have a greater impact on function. As such, more extensive longitudinal analysis of motor progression, including disease-specific quality of life measures such as HDQLIFE Chorea^{29,30} and HDQLIFE Speech and Swallowing,^{29,31} would shed light on how specific motor factors contribute directly to various facets of function loss. Our study also underscores the need for further research regarding the effects of dystonia and rigidity on functioning in HD. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Prodromal Marker Progression in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Sample Size for Clinical Trials

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ABSTRACT

Objective: To estimate prodromal marker progression in idiopathic rapid eye movement sleep behavior disorder patients with prodromal Parkinson's disease (PD) to calculate sample size for neuroprotective trials.

Methods: Patients with polysomnogram-proven idiopathic rapid eye movement sleep behavior disorder

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