# The UHDRS and UHDRS-FAP assessments in Huntington's disease

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# CHAPTER 7

## Discussion and conclusions

## Focus of this thesis

In Huntington's disease (HD), detecting the course of motor, cognitive, and psychiatric symptoms is of great importance. If the presence, severity, and progression of symptoms and signs can be detected, the effect of therapeutic interventions can be monitored, which is useful in HD research and in clinical care. However, to measure change of symptoms and signs accurately, reliable and valid assessment scales are necessary. For the detection and monitoring of clinical features different rating scales are used, since the symptoms and signs of HD change as the disease progresses from premanifest stage to advanced stage. Therefore, the main aim of this thesis was to investigate the measurement properties of the Unified Huntington's Disease Rating Scale (UHDRS)[1] and of the Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP)[2] in various severity stages of HD and to give recommendations on which items or sections of the scales are, or are not, useful in which stage of the disease.

## Assessment of motor symptoms

The clinical assessment of motor symptoms in HD is usually performed with the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). The developers of the scale found a good interrater reliability, with an intraclass correlation coefficient (ICC) of 0.94.[1] Our study in a large cohort of raters, who participated in the annual online certification of the UHDRS-TMS, also showed a good, but lower, interrater reliability of the UHDRS-TMS (ICC = 0.847) (**chapter 2**). The lower interrater reliability in our study can more than likely be explained by the fact that the raters involved in our study had variable levels of experience, and were not all HD experts. Interestingly, we found a poor interrater reliability for all five dystonia items of the UHDRS-TMS (ICC < 0.400), suggesting that the rating of these items is difficult to interpret, probably as a consequence of the subjective nature of the response options (absent, slight, mild, moderate, or marked dystonia). Therefore, removing, changing, or combining some of the dystonia items, or providing clearer response options should be explored, as poor interrater reliability hampers the monitoring of progression of HD motor symptoms. A previous study on the internal consistency of the UHDRS-TMS showed that after elimination of all dystonia items the internal consistency hardly changed, thereby also questioning the importance of the dystonia items.[3] We believe that the dystonia items can be omitted in patients with mild to moderate HD, and should only be examined in patients with advanced HD, as dystonia often arises as the disease progresses. The annual online certification of the UHDRS-TMS also showed that the percentage of motor items scored correctly dropped significantly between baseline and follow-up (from 87.8% to 86.4%). However, a decrease of 1.4%

seems only marginally relevant. We recommend that raters should watch the teaching video of the UHDRS-TMS before each certification to be reminded of the established standards. The online video system allowed us to examine the interrater reliability of the UHDRS-TMS for a large number of raters. However, the use of video recordings was also a limitation of our study, since the raters did not perform an actual physical examination themselves and in real life the clinical presentation of a patient usually varies.

For the measurement of reliability, various parameters can be used, such as ICC, Cohen's kappa, and percentage agreement. We did not use percentage agreement, because this parameter does not take chance agreement into account. A weighted kappa can be used for categorical variables, such as the items of the UHDRS-TMS. The rationale for a weighted kappa is that misclassifications between adjacent categories are less serious than those between more distant categories. However, given that calculating a weighted kappa is cumbersome and complicated, especially if multiple raters are involved, we used the ICC, because the ICC is equivalent to a weighted kappa if a quadratic weighting scheme is used.[4,5]

Clinical diagnosis of HD is generally based on the appearance of motor symptoms. Therefore, the UHDRS-TMS is often used in HD gene carriers to distinguish between premanifest individuals and manifest patients for research purposes. However, oculomotor abnormalities have already been observed with eye-tracking equipment before disease onset.[6-9] Our study in premanifest HD gene carriers and healthy controls showed that horizontal ocular pursuit was the only affected item of the UHDRS oculomotor domain in premanifest individuals near to HD onset compared to controls (**chapter 3**). This finding suggests that horizontal ocular pursuit can be used to detect early clinical signs of HD in individuals who are at risk for developing HD in a much easier way than eye-tracking equipment. The fact that the other oculomotor items of the UHDRS-TMS did not show any differences between premanifest individuals and controls does not necessarily mean that they are not present, but more likely implies that these items are not sensitive enough to detect oculomotor abnormalities in premanifest HD gene carriers.

Apart from the UHDRS-TMS, other studies have focussed on more quantitative instruments to measure motor impairment, such as eye-tracking equipment, tongue force analysis, and quantitative-motor (Q-Motor) assessments.[6,10,11] Research has shown that Q-Motor measures were more sensitive than the UHDRS-TMS and exhibited no placebo effect.[12] While these objective instruments are useful for research purposes, in clinical practice the UHDRS-TMS seems a more feasible assessment.

## Assessment of patients with advanced HD

Severity of HD is usually classified into five stages using the Total Functional Capacity (TFC) subscale of the UHDRS: stage 1 (TFC 11-13), stage 2 (TFC 7-10), stage 3 (TFC 3-6), stage 4 (TFC 1-2), and stage 5 (TFC 0).[13] In patients with advanced HD (TFC stages 4 and 5), ceiling and floor effects of the UHDRS hamper the monitoring of changes over time.[14] Therefore, the UHDRS-FAP has been developed voor late stage HD.[2] Our cross-sectional study in advanced HD patients, residing in a nursing home or receiving day-care, showed that the motor scores of the UHDRS-FAP and UHDRS were the only subscales with a significantly worse score in TFC stage 5 compared to TFC stage 4 (**chapter 4**). The range of the UHDRS-FAP motor score was broader, the standard error of measurement (SEM) was lower, and the effect size r was higher than for the UHDRS motor score, suggesting that the UHDRS-FAP motor score differentiates better between patients in the highest TFC stages than the UHDRS motor score. Therefore, this subscale can possibly improve disease monitoring and, subsequently, care in patients with late stage HD in long-term care facilities. The cognitive and behavioral domains of both scales did not differ between TFC stages 4 and 5, and do not seem useful for differentiating between patients with advanced HD. We found a high internal consistency and high interrater reliability for the motor and cognitive scores of both scales, confirming previous findings.[1,2] The interrater reliability of the UHDRS-TMS in this study (ICC = 0.876) was similar to the one in our study on the UHDRS-TMS certification (ICC = 0.847). The behavioral scores of both scales showed low-to-moderate values for internal consistency and interrater reliability. This contradicts previous studies, which found high ICC values for an adjusted version of the UHDRS behavioral section.[15,16] However, they used a 'clinically relevant' interrater reliability, which means only differences larger than one point were included.

Our longitudinal study in late stage HD showed that the motor and cognitive scores of the UHDRS-FAP deteriorated during six months follow-up, while the motor and cognitive scores of the UHDRS did not show change (**chapter 5**). Previous research in late stage HD showed that both the UHDRS-FAP and UHDRS motor and cognitive scores deteriorated over time, but the slope was steeper with the UHDRS-FAP.[2] Both studies suggest that disease progression in advanced HD is better detected by the UHDRS-FAP than the UHDRS. Therefore, we recommend the use of the UHDRS-FAP motor and cognitive scores in nursing homes to optimize HD care by monitoring disease progression and by evaluating the effect of interventions in clinical care. The Functional Assessment Scale (FAS) and Independence Scale (IS) of the UHDRS, and the Care Dependency Scale (CDS)[17] also worsened over six months' time. Other studies in long-term care facilities also found a decline of the CDS in patients with dementia, and to a lesser extent in patients without dementia.[18,19] Interestingly, the behavioral scores of the UHDRS-FAP and UHDRS improved

in HD patients in TFC stages 4 and 5, suggesting that psychiatric symptoms fade away as the disease progresses. Previous studies also showed that depression and anxiety diminish in more advanced HD as emotions decrease and insight lessens.[20,21] Decline of psychiatric symptoms could also be caused partly by less communicative abilities of patients in late stage HD. Additionally, increased motor symptoms may lead to less strength and coordination to hit something, and therefore detection of irritability and agitation could be more complicated. For these reasons, the standard behavioral assessments do not seem suitable for advanced disease stages.

In the same cohort of late stage HD patients, we also examined the demographical and clinical differences between nursing home residents and day-care patients (**chapter 6**). None of the UHDRS-FAP or UHDRS subscales showed differences between the two groups, except for the FAS. This functional scale of the UHDRS demonstrated more dependency on care for common daily tasks for the institutionalized patients compared to the day-care participants. Interestingly, the most predictive factor for nursing home admission was not being married. This finding implies that a partner can assist with common daily tasks which a patient could not have done independently, resulting in being able to live at home longer. A systematic review on patients with dementia also showed that married patients had a lower risk of nursing home placement than patients without a partner.[22] Providing support to unmarried patients and their caregivers by home care services specialized in HD might increase the chance of the best possible care in the own environment before institutionalization and postpone nursing home admission. Furthermore, individual case management by social workers specialized in HD could also contribute to better care. Limitations of our studies in patients with advanced HD were the small sample size of 40 participants and the administration of the rating scales by two raters, which may have influenced the results due to interrater reliability.

## Future perspectives

The therapeutic interventions that are currently being developed and tested aim to slow down progression of HD. To measure change of clinical features accurately, reliable and valid assessment scales and measurement instruments are necessary. The UHDRS-TMS is widely used in therapeutic clinical trials and often serves as primary endpoint to assess efficacy of interventions. We showed that the UHDRS-TMS has a high interrater reliability, except for all dystonia items, which showed a poor interrater reliability. Future studies are required to explore how the dystonia items can be improved or to examine if objective motor assessments can measure dystonia more reliable than the UHDRS-TMS.

It is important to realize that sensitive assessment scales and measurement instruments differ from premanifest HD to early, moderate, and advanced HD. We demonstrated that for the identification of motor impairment in premanifest HD, horizontal ocular pursuit can be used, while the saccade initiation and saccade velocity items did not show deficits in premanifest HD. In late stage HD, however, we showed that the motor and cognitive sections of the UHDRS-FAP were more sensitive to detect changes than the motor and cognitive domains of the UHDRS. Although less interventional research is being performed in patients with advanced HD compared to patients in the early stages of the disease, the implementation of the UHDRS-FAP instead of the UHDRS in nursing homes to optimize clinical care is an important goal for the future. Additionally, the UHDRS-FAP should be investigated for a longer follow-up period.

Recently, proposals have been made for the use of measurement instruments that relate to health as the ability to adapt and to self-manage.[23] Therefore, we believe that the UHDRS-FAP should not only include sections on motor, cognitive, and behavioral symptoms, but should also assess functional status and include quality of life questionnaires. For the development of these sections, patients' and caregivers' input on what topics and questions should be included is important.

Identification of predictors for institutionalization may lead to interventions and treatment strategies that postpone the need for nursing home admission. We demonstrated that not having a partner was associated with nursing home placement in HD. However, we did not collect additional information about the partners or questioned the partners independently from the patients. Future research on the role of caregivers, cultural aspects, and financial costs may identify more predictors for institutionalization in HD. This information is of great importance since HD patients are usually younger than the average nursing home resident, and therefore the need for care and support is probably different.

## References


1. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

2. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

3. Siesling S, Zwinderman AH, van Vugt JPP, Kieburtz K, Roos RAC. A shortened version of the motor section of the Unified Huntington's Disease Rating Scale. Mov Disord 1997; 12: 229–234.

4. Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. Educ Psychol Meas 1973; 33: 613–619.

5. De Vet HCW, Terwee CB, Mokkink LB, Knol DL. Measurement in medicine. Cambridge: Univ Cambridge, 2011.

6. Blekher TM, Yee RD, Kirkwood SC, Hake AM, Stout JC, Weaver MR, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. Vision Res 2004; 44: 2729–2736.

7. Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, et al. Saccades in presymptomatic and early stages of Huntington disease. Neurology 2006; 67: 394–399.

8. Antoniades CA, Altham PME, Mason SL, Barker RA, Carpenter R. Saccadometry: a new tool for evaluating presymptomatic Huntington patients. Neuroreport 2007; 18: 1133–1136.

9. Hicks SL, Robert MPA, Golding CVP, Tabrizi SJ, Kennard C. Oculomotor deficits indicate the progression of Huntington's disease. Prog Brain Res 2008; 171: 555-558.

10. Reilmann R, Bohlen S, Klopstock T, Bender A, Weindl A, Saemann P, et al. Tongue force analysis assesses motor phenotype in premanifest and symptomatic Huntington's disease. Mov Disord 2010; 25: 2195–2202.

11. Reilmann R, Bohlen S, Kirsten F, Ringelstein EB, Lange HW. Assessment of involuntary choreatic movements in Huntington's disease – Toward objective and quantitative measures. Mov Disord 2011; 26: 2267–2273.

12. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. Handb Clin Neurol 2017; 144: 209–225.

13. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29: 1–3.

14. Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburtz K, et al. Rate of functional decline in Huntington's disease. Neurology 2000; 54: 452–458.

15. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 219–226.

16. Kingma EM, Van Duijn E, Timman R, Van der Mast RC, Roos RAC. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry 2008; 30: 155–161.

17. Dijkstra A, Buist G, Moorer P, Dassen T. Construct validity of the Nursing Care Dependency Scale. J Clin Nurs 1999; 8: 380–388.

18. Dijkstra A, Sipsma D, Dassen T. Predictors of care dependency in Alzheimer's disease after a two-year period. Int J Nurs Stud 1999; 36: 487–495.

19. Schüssler S, Lohrmann C. Change in care dependency and nursing care problems in nursing home residents with and without dementia: a 2-year panel study. PLoS One 2015; 10: 1–12.

20. Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, Snowden JS, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J Neuropsychiatry Clin Neurosci 2012; 24: 53–60.

21. Paulsen JS, Nehl C, Ferneyhough Hoth K, Kanz JE, Benjamin M, Conybeare R, et al. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci 2005; 17: 496–502.

22. Cepoiu-Martin M, Tam-Tham H, Patten S, Maxwell CJ, Hogan DB. Predictors of long-term care placement in persons with dementia: a systematic review and meta-analysis. Int J Geriatr Psychiatry 2016; 31: 1151–1171.

23. Huber M, Knottnerus JA, Green L, Van der Horst H, Jadad AR, Kromhout D, et al. How should we define health? BMJ 2011; 343: 1–3.