

## Research Report

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# Cognitive Performance After a One-Year Multidisciplinary Intensive Rehabilitation Program for Huntington's Disease: An Observational Study

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### Abstract.

**Background:** Studies of physical therapy and multidisciplinary rehabilitation programs for Huntington's disease (HD) have shown improvements in gait function, balance, and physical quality of life. There is a gap in the literature on effects of cognitive interventions and the potential to improve cognitive performance.

**Objective:** To assess changes in cognitive performance among patients with early to middle stage HD as secondary analyses from a one-year multidisciplinary rehabilitation program. The program included cognitive stimulation as a non-specific cognitive intervention in addition to physical interventions.

**Methods:** A one-year rehabilitation program that included comprehensive neuropsychological assessments was completed by 31 out of 37 participants with early to middle stages of HD. Socio-demographic and clinical information was recorded. A battery of neuropsychological tests was used to measure cognitive functions before and after the intervention. Descriptive statistics was used for sample characteristics. Paired sample *t*-tests and nonparametric Wilcoxon Signed ranked tests were used to compare cognitive measures at both time points.

**Results:** Scores on the Symbol Digit Modalities Test (SDMT) were significantly lower post intervention. There were no significant differences in all other measures. Scores on the Stroop color naming and California Verbal Learning Test-II (CVLT-II) long-term delayed recall tasks showed tendencies towards lower scores post intervention.

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**Conclusions:** An intensive multidisciplinary rehabilitation program for patients with HD was generally well tolerated and feasible, with no indication of negative effects on cognition. Neuropsychological measures overall remained stable following an intensive multidisciplinary rehabilitation program, however continued progression of cognitive impairment was evident on the SDMT, suggesting that disease progression is not halted. Randomized controlled trials are needed to verify these findings.

Keywords: Huntington's disease, rehabilitation, cognition, multidisciplinary

## INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by progressive development of movement disorder, psychiatric disturbances and cognitive impairment (dementia). Disease presentation varies greatly with variation in age at onset, rate of progression and severity of symptoms [1–3]. There is currently no disease modifying treatment and patients are dependent on comprehensive coordinated long-term care including non-pharmacological and pharmacological symptomatic interventions [4, 5]. During the last decade, there has been increasing interest in physical therapy and multidisciplinary rehabilitation programs in patients with HD [6–11]. Rehabilitation programs are associated with positive effects on gait, balance, depression, quality of life and cognitive impairment in other progressive neurodegenerative diseases such as Parkinson's disease [12–14]. Additionally, such interventions have been proposed to potentially reduce or stabilize disease progression in persons with neurodegenerative diseases [10]. The rationale for conducting studies of physical therapy and rehabilitation, including cognitive training, in neurodegenerative diseases is based on the principle of neuroplasticity [15, 16].

To date, the primary focus of studies on multidisciplinary rehabilitation interventions in patients with HD in early to middle phase has been on physical outcome measures such as gait and balance [6–9, 11]. Research indicates that such interventions result in maintained or improved motor performance including gait function, balance and functional performance. Additionally, positive outcomes regarding symptoms of anxiety and depression, health related quality of life (HRQOL), and maintained function in Activities of Daily Living (ADL) have been reported [6–9]. Programs, both among early and middle stage HD, have generally been feasible and tolerable [17]. Cognitive impairment is a hallmark of HD, and patients develop progressive cognitive decline starting with subtle specific signs and evolving to

more severe specific cognitive impairments eventually resulting in global cognitive impairment and dementia. Cognitive impairments are generally most prominent in domains of psychomotor speed, executive functions and memory [18–20]. Subtle cognitive decline, observed 10–15 years earlier, may precede the onset of motor symptoms, which today still are the basis for a clinical diagnosis of HD [21, 22]. Cognitive impairment has been described as the most debilitating symptom of HD, affecting functional ability already early in the disease [23]. Recently, Andrews et al. 2015 drew attention specifically to cognitive interventions as a method to increase neural compensation and thereby positively affect cognitive performance in HD. Three primary forms of cognitive interventions were described including cognitive training, cognitive stimulation and cognitive rehabilitation [15].

Despite the debilitating effects of cognitive impairment in HD, studies using comprehensive batteries of cognitive measures and investigating cognitive interventions are still sparse. Studies that have been published have briefly reported on screening tools for cognitive function, including the Mini-Mental State Examination (MMSE), or a limited number of specific cognitive measures indicating maintained or improved cognition after intervention in HD patients [6–9, 24]. To date, only one study has been published where the aim was to evaluate whether multidisciplinary rehabilitation can specifically reduce further decline of cognitive deficits and brain changes in patients with manifest HD. Their findings support a positive impact on cognitive functions of verbal learning and memory in patients with manifest HD [25].

Addressing a gap in the literature, the aim of this study was to conduct secondary analyses among patients with early to middle stage HD who had participated in a multidisciplinary rehabilitation program that included cognitive stimulation as a non-specific cognitive intervention. Specifically we aimed to assess change in participants' cognitive performance as part of secondary analyses following

completion of a one-year multidisciplinary rehabilitation program.

## METHODS

The present report is based on a previous study [7]. For more a more detailed description of the elements of the overall the rehabilitation program we refer to the previously published study [7].

### *Participants and recruitment procedures*

A total of 37 patients, aged 18 years and older were enrolled in a one-year program followed by a five-day evaluation stay approximately one year later. Patients were recruited by disseminating information about the project on the web-sites of two rehabilitation centers (Vikersund Kurbad and Rehabiliteringssenteret Nord-Norges Kurbad), the website of the Centre for Rare Disorders, the National Advisory Service for HD, and by announcements through the Norwegian patient association for HD (Landsforeningen for Huntington sykdom). Participants were recruited nationwide through specialized health care (i.e. through neurologists and psychiatrists from regional hospitals) and primary health care (i.e. the patients' General Practitioner (GP)). The inclusion criteria for enrollment in the rehabilitation program entailed the following: a) being 18 years old or older, b) genetically confirmed clinical diagnosis of HD, c) Early to middle-stage of HD corresponding to stages I – III on the Shoulson and Fahn Total Functional Capacity Scale (TFC) [26], d) no diagnosis of severe psychiatric illness and e) no general cognitive impairment (dementia) at the time of admission and f) mostly full independence in ADL (a score of 1–3 on the ADL function; 0) completely independent of care, 1) able to complete gross ADL-tasks independently, 2) minimally reduced function for ADL-function or 3) normal function). Physicians referring patients to the program were asked to perform a pre-admission clinical evaluation of the patients, primarily to determine the level of ADL functioning. This was done in accordance with a form specifically composed for referral to the rehabilitation program, which included guidelines for completion of the form and clearly specified the inclusion criteria. No evaluation of cognitive function by means of clinical instruments as part of the referral process pre-admission was required. Participants were enrolled in the rehabilitation program at one of the two sites based on where the referral came from and the patients'

preference. Written and oral information about the program was provided to both the participants and their family members and all participants provided written informed consent to take part in the study.

Approval for the project was obtained from the NSD Data Protection Official for Research (reference number 26587), after the ethics committee considered that a formal approval from the committee was not necessary (reference 2010/2629-7).

### *Procedures for data collection*

The study was conducted during the years 2010–2012. Participants were included in groups of four to six patients. During the first stay, socio-demographic information was recorded, including age, gender, years of education, marital status, number of children, smoking, and whether they had an *Individual Plan* (individual plan for coordinating long-term healthcare). Furthermore, baseline disease characteristics were collected for estimated disease duration (based on date of received clinical diagnosis as extracted from the patients' medical record), and for the functional capacity, the level of motor impairment, and behavioral symptoms, using the standardized assessments of the Unified Huntington's Disease rating scale (UHDRS) [27]. The TFC of the UHDRS was employed to determine disease stage using the following consensus: TFC of 11–13: stage I, TFC of 7–10: stage II and TFC of 3–6 of stage III [26, 28].

### *The rehabilitation program*

The rehabilitation program was an intensive multidisciplinary program consisting of three inpatient stays of three weeks each during one year. Throughout each stay, the participants had a daily program of up to eight hours including lunch and breaks. The multidisciplinary teams consisted of physio-, occupational- and speech therapists, a dietician, a social worker and a neuropsychologist, nurses and a neurologist. In collaboration with the patient, the team set short- and long-term rehabilitation goals. Family members were invited to participate during the first few days of the initial admission as well as the evaluation stay. All participants received a schedule with the intervention activities planned for the three-week stays at the beginning of each admission. The program consisted of group activities (46 %) and individual training activities (29 %), as well as scheduled time for daily independent training as prescribed

by one of the therapists (25%). The scheduled program of intervention activities and approximate time use (excluding the above mentioned scheduled 25% of independent training) comprised of: a) 45 physiotherapy sessions of 30 minutes (38%), each divided equally (19% each) between aerobic exercise (i.e. activities in a swimming pool, cycling, walking) and exercises to improve balance and coordination, b) 10 Occupational therapy group sessions (45 minutes each) and two hours of individual training (13%), c) 7 hours of individual speech therapy follow-up and 1 hour as a group session, including orofacial stimulation, oral motor training, voice training and guidance and evaluation regarding eating and drinking, spelling words forwards and backwards etc. (13%), d) 1 hour of individual and 1 hour group activities and follow up with the (neuro)psychologist (3%), and e) on average 5 hours educational group sessions related to aspects of HD by different relevant professionals (8%). The majority of the cognitive stimulation activities were implemented in consultations and collaboration between the occupational therapist and the (neuro)psychologist (details described below). Assessments by the multidisciplinary team and individual follow-up by different professionals according to patients' individual needs (i.e. dietician, neurologist, social worker) were conducted during the in-patients stays, but are not included in the estimated time dedicated to the different intervention elements described above. All participants were assigned a contact person (a nurse or physiotherapist) who monitored attendance and was able to answer questions. Except in special circumstances, all participants attended all activities. Dieticians made dietary adjustments if patients had a Body Mass Index (BMI) <21 or had dysphagia/difficulties with chewing. Medication adjustments were made, and additional individual follow up for patients and family members was provided if needed during the course of the program.

#### *Cognitive stimulation*

Although the main focus when designing and conducting this intensive multidisciplinary rehabilitation program was the physical training, the program purposefully included cognitive interventions to specifically maintain or strengthen cognitive functions. One can distinguish three types of cognitive interventions: cognitive training, cognitive rehabilitation and cognitive stimulation [15]. The present study included cognitive stimulation. The program

was designed to include non-specific approaches in order to increase cognitive and social functioning. The cognitive stimulation in the program included a variety of activities, both individually and in groups, with the aim of stimulating cognitive function. Memory games, word games, number games, and activities requiring collaboration between the participants to solve a problem were utilized [15]. Table 1. shows a more detailed description of the activities of cognitive stimulation including the time dedicated to the activities and by which professionals they were conducted. In total, participants received 12.5 hours of cognitive stimulation, which represents one-fifth of the total time dedicated to intervention activities. Participants planned what food was to be made and how to prepare it (i.e. which ingredients were needed etc.) thus determining and executing the action chain for making food. Participants who wanted to, received training in the use of a diary to write down memories, appointment etc. The participants received a plan for homework between the three-week stays that was developed in collaboration between the participant and psychologist and/or occupational therapist. These included taking up a leisure time activity (usually a hobby the patient would re-kindle or learn/start doing). Patient discussion groups covering topics such as symptoms and changes in cognitive function, psychological and psychiatric difficulties, their experiences of such difficulties, and how to manage these, compensatory strategies, the meaning / implications of changes in life as well as ADL and social function were conducted.

#### *Cognitive outcome measures*

During the first stay and at the evaluation stay approximately one year later, a neuropsychological assessment was conducted to assess cognitive function at baseline and this was repeated after completion of the one-year program. The same investigator (MRvW) conducted all assessments. The cognitive test battery included neuropsychological tests measuring a broad range of cognitive domains, and feasible in terms of time (max two hours) and effort. This comprehensive testing allowed us to identify specific impairments in cognitive abilities and thus allow for individual tailoring of the general rehabilitation program (i.e. does a patient need extra reminders for attending the scheduled activities). The neuropsychological report describing the patients' cognitive function (strengths and weaknesses) provided information and guidance to other professional

Table 1  
Description of the cognitive stimulation activities per three-week rehabilitation stay

Cognitive stimulation activities	Individual (hours / three-weeks stay)	Group (hours per three-week stay)	Professional
Determining and preparing homework exercise, writing a diary, taking up a hobby / leisure activity, cross-word puzzles	1		Neuropsychologist
Kitchen training: making food. Planning and completion of chain to make recipes as teams; composing grocery list, buying groceries/ingredients, making the food	2	6 × 0,75	Occupational therapist
Memory games Cross-word puzzles Playing games, number games, word games, board games, alias game, four on a row Using supporting aids for cognition i.e. using a diary Following up on homework activities			
Spell words backwards, count backwards, figure copying, repetition of long words, cross-word puzzles	1		Speech therapist
Discussion groups (sharing experiences on the program, exchange experience with other participants, social games, discussions at the end of the stay, take home experiences etc.)		4 × 0,75	Occupational therapist
Discussion group (sharing experiences on management of symptoms including use of aids (electronic and / or on paper)		1	Neuropsychologist
Total hours per stay	4	8,5	

team members working with the patients. In addition, this report provided advice on care and support needs in the local community (i.e. advice on need for assistive technology for cognition), and presented results from a broader range of cognitive measures in order to examine the potential changes on cognitive abilities after completion of the rehabilitation program. By incorporating the neuropsychological reports (from the first stay and evaluation stay) into the extensive medical report the referring clinician and/or GP could use these for further follow up of the patients locally [7].

We employed the following neuropsychological measures covering the domains of psychomotor speed, attention, executive function (divided attention, inhibition, cognitive regulation and initiation, and cognitive flexibility), working memory, verbal learning, short-term and long-term memory and recognition, and general verbal function, as part of the cognitive battery in the present study:

a) *Trail Making Test part A and part B (TMT A & TMT B)*, a paper and pencil task requiring the participant to correctly connect numbers 1 to 25 in ascending order as fast as possible (part A) and to

correctly connect letters and numbers in alternating and ascending order as fast as possible (part B) [29]. The total score for each part is the total time to complete the task. They were employed as tasks measuring psychomotor speed, visual scanning, divided attention, and cognitive flexibility [30].

b) *Stroop, color-naming, word-reading and interference* parts, requiring the participant to correctly name as many colored boxes (red, green, blue), read as many color-words written in black ink (red, green, blue), and name as many correct colors of the ink of incompatible color-words as possible within 45 seconds. The number of correctly named colors and read color-words within this time represent the total scores. These tests tap into domains of psychomotor speed, effectiveness of focused attention, and inhibition [27].

c) *Symbol Digit Modality Test (SDMT)*, also a paper and pencil task requires the participant to correctly match symbols with numbers as fast as possible using a reference key. The number of correctly matched symbols within 90 seconds generated the total score on the task. This

measures psychomotor speed, working memory, and visual tracking/attention [27].

- d) *Phonemic fluency (FAS)*, where the participant is asked to generate as many words as possible within 1 minute starting with letters, F, A and S respectively. The total number of correct words on the three letters indicates the total score on the test. It measures verbal fluency, self-regulation, organization and flexibility [27].
- e) *Semantic word fluency (animals)*, which requires the participant to generate as many different animals as possible within 1 minute and is scored as the total number of correct animals was also employed as a measure of self-regulation and flexibility [29].
- f) *Digit Span Forwards and Digit Span backwards* of the Wechsler Intelligence Assessment Scale-3rd edition (WAIS-III), where one is asked to correctly repeat strings of numbers of increasing length in the same and in backwards order, were used as measures of attention and working memory. The total scores reflect the longest span of correctly repeated strings forwards and backwards, respectively [31].
- g) *California Verbal Fluency Test- Second edition (CVLT-II)*, which was employed as a measure of verbal learning and memory (CVLT-II). The test generates scores for i) total learning (the number of words from four categories recalled over five consecutive trials), ii) total short-term recall (number of words recalled after a short distraction), iii) long-term recall (number of words recalled after an interval of 20 minutes), and iv) recognition score, (number of words from the memorized list recognized among words which are related to or unrelated to the four word categories). We used parallel forms for the baseline and evaluation assessment.
- h) *Vocabulary* (WAIS-III) requiring participants to explain the meaning of different words to assess general semantic knowledge and verbal comprehension [31].

Longer time needed to complete timed tasks (TMT A and B) indicates worse functioning, while for the remaining cognitive tasks, higher scores correspond to better performance. The Stroop tests, SDMT and FAS are part of the UHDRS cognitive assessment [27]. These measures have also been described in our previous publications, but are included in the present report as well for a more comprehensive picture and

in depth interpretation of the changes in cognitive measures following this program [7, 8].

### *Statistical analysis*

Descriptive statistics of mean values and standard deviations (SD) and frequencies and proportions were calculated for the socio-demographic and disease characteristics. In order to compare change between baseline and follow-up visit for the cognitive measures, we employed paired samples *t*-tests for dependent samples for normally distributed variables and non-parametric Wilcoxon Signed rank test for non-normally distributed variables. Results of the analyses are reported as means and SD, mean difference between assessments, including 95% confidence intervals (CI's), standardized *t* value (*t* (Z)) and *p*-value. We validated our main results by performing analyses on two sub-groups: a) the entire sample excluding two patients with other neurological conditions that may have influenced cognitive performance and b) sub-analyses based on the MMSE score at the time of admission. We excluded four patients with global cognitive impairment (MMSE < 20) based on Norwegian guidelines for MMSE criteria for general cognitive impairment, as global cognitive impairment originally was described as an exclusion criterion [32].

The significance level was set at 0.05. All analyses were performed using the 22.0 version of IBM SPSS for Windows (IBM SPSS, Armonk, New York).

## **RESULTS**

### *Sample characteristics*

A total of 31 patients (84%) completed the one-year rehabilitation program and were available for neuropsychological testing one year later (evaluation stay). Fourteen patients were men (45.2%) and 17 were female (54.8%) with a mean age of 52.2 years and on average 11 years of education. Average time since symptom start was seven years and at enrollment nine (29%) were in disease stage I, 17 (54.8%) in stage II, and five (16.2%) patients were in stage III with a TFC of 6. Average TFC score was 9.2. Mean UHDRS motor score was 35.6 (range: 7–75) and mean UHDRS behavioral assessment score was 9.5 (range: 0–34). Mean MMSE score was 25.4 (range: 17–29). The average duration between the first cognitive assessment at the beginning of the first 3-week

stay of the program and the second assessment during the evaluation stay was 370 days.

### *Changes in cognitive measures*

Table 2 shows the results for the mean change between the raw scores at baseline and evaluation stay of the cognitive measures for the entire sample of 31 patients. For each test, the number of patients included in the calculations represents the number of patients who completed the tests at both time points.

The majority of the subjects completed tests both at the first admission and at the 1-year follow up and all subjects completed Vocabulary of the WAIS-III. However, for three tests, the Trail making test part B, Digit span backwards and the Digit span forwards, only 17, 17 and 18 patients, respectively, completed the tests.

Slight changes in raw test scores were found between the baseline and the one-year evaluation stay. The majority of the changes show overall slight declines in scores, except for the phonemic fluency test (FAS) (cognitive regulation and flexibility) and the TMT B test (divided attention and psychomotor speed), revealing slight improvement of 1.68 (almost 2 words) and of 1.11 (over 1 second) respectively. Results for Vocabulary, CVLT-II recognition and Digit Span backwards remained unchanged between test-points. Of those cognitive tasks indicating a decline, only the SDMT reached statistical significance (mean difference (SD) = 2.27 (0.83),  $p$ -value: 0.02). Stroop color naming task (psychomotor speed and automatization) and the long-term delayed free recall (long-term verbal memory) tasks showed a tendency towards significant decline in raw score with  $p$ -values of 0.08 and 0.07 respectively. Results remained unchanged when conducting sub-analyses of the study sample excluding two patients with additional neurological conditions and the four participants with and MMSE score of <20.

## **DISCUSSION**

Overall, the present investigation shows that patients in early to middle stages of HD maintained a similar level of cognitive functioning before and after completing a multi-disciplinary rehabilitation program that included cognitive stimulation. Two tests showed tendencies towards decline, the Stroop color naming task and the long-term delayed recall as measured by the CVLT-II, with slightly lower scores at the second time point, and one statistically significant

decline for the SDMT. The overall maintenance of cognitive function is similar to the findings of previous studies [9, 25]. Additionally, previous studies also revealed changes for the Stroop color naming task and for long-term delayed recall, measured using the Hopkins Verbal Learning Test (HVLT) [9, 25]. However, contrary to the findings in our study, the authors of these two studies reported better scores for these two measures [9, 25]. Thompson et al. 2013 showed better raw scores for Stroop color naming while raw scores on the HVLT had declined [9]. Cruickshank et al. 2015 found improvement on HVLT long-term delayed recall that reached significance [25]. The significant difference in scores (Total correct) found for the SDMT in our study, as reported in our previous report [7], has not been found by Thompson et al. and Cruickshank et al. [9, 25]. Yet, inspecting the raw scores of the participants in the intervention group and in the control group in the study of Thompson et al., a slight decline is also observed in their SDMT score [9].

Differences in study results can possibly be explained by different sample sizes and varying composition of the study populations with respect to disease duration and stage. Moreover, the use of different outcome measurements may contribute to different results. The CVLT-II was used in the present study and the inclusion of a word list of 16 words is more demanding compared to the HVLT, comprising a list of only 12 words [9, 25]. The results from previous studies as well as this study propose that Stroop color tasks and a measures for long-term delayed recall are sensitive measures for change in these cognitive functions. The results regarding the SDMT could be considered comparable as tendencies in the studies are in the same direction as the results of the present study, but reaching significance in our larger study sample. The SDMT is a sensitive test measure for cognitive decline in pre-manifest and manifest patients with HD [33, 34]. Our result for the SDMT may indicate that multidisciplinary rehabilitation interventions may not halt the progression of cognitive decline related to psychomotor speed and working memory, and thus supports the sensitivity of the test to measure change over time.

We found that nearly half of the study subjects did not complete three of the tests (TMT B, Digit span forwards and backwards). This was because they were unable to carry out the complete test battery resulting in the assessor terminating or shortening the assessment. The battery was conducted in the same consecutive order by the same assessor, who

Table 2  
Mean change score in cognitive functions

Variable $n_{\text{tot}} = 31$	No of cases	Evaluation(I) (range, SD)	Baseline(J) (range, SD)	Mean diff (I-J) (SE)	t (Z)	P	95 % CI for the difference	
							Low	Upper
FAS <sup>a</sup>	29 of 31	21.44 (5–51, 12.13)	19.75 (4–49, 10.83)	1.69 (1.33)	–1.25	0.21	–4.37	0.93
SDMT <sup>a</sup>	30 of 31	21.73 (6–47, 9.35)	24.00 (11–49, 8.73)	<b>– 2.27 (0.83)</b>	2.69	<b>0.02*</b>	0.7	3.96
Stroop color naming <sup>a</sup>	29 of 31	43.72 (18–70, 13.32)	46.21 (18–76, 14.23)	–2.48 (1.33)	–1.87	0.08**	–0.07	5.03
Stroop word reading test <sup>a</sup>	29 of 31	63.44 (21–100, 21.51)	64.34 (37–102, 18.8)	–0.90 (1.48)	–0.60	0.56	–2.10	3.72
Stroop interference <sup>a</sup>	26 of 31	26.15 (11–42, 8.28)	25.96 (13–50, 8.52)	0.19 (0.86)	0.18	0.87	–2.38	1.84
Vocabulary Wais III <sup>b</sup>	31 of 31	31.16 (12–47, 9.82)	31.00 (12–48, 10.01)	0.16 (0.66)	–0.24	0.67	–	–
Trail Making Test A (time) <sup>b</sup>	29 of 31	63.17 (24–177, 36.39)	59.48 (29–136, 27.83)	3.68	–0.4	0.7	–	–
Trail Making Test B (time) <sup>b</sup>	17 of 31	149.18 (51–286, 67.6)	150.30 (62–324, 69.4)	–1.11	–0.35	0.74	–	–
Word fluency Animals <sup>b</sup>	27 of 31	11.63 (3–21, 4.89)	12.63 (4–30, 4.74)	–1.00	–1.04	0.31	–	–
CVLT-II total learning <sup>a</sup>	29 of 31	30.28 (14–52, 9.59)	32.34 (13–50, 9.18)	–2.07 (1.54)	1.33	0.2	–0.86	5.17
CVLT-II short delay free recall <sup>a</sup>	28 of 31	6.17 (2–13, 2.81)	6.67 (1–13, 3.04)	–0.50 (0.46)	1.01	0.28	–0.43	1.39
CVLT-II long delay free recall <sup>a</sup>	28 of 31	6.25 (2–14, 3.01)	7.18 (0–14, 2.99)	0.93 (0.48)	1.90	0.07**	–0.07	1.86
CVLT-II recognition <sup>a</sup>	28 of 31	13.54 (7–16, 1.89)	13.54 (10–16, 1.79)	0.00 (0.38)	0.00	1.0	–0.71	0.75
CVLT-II false positives <sup>a</sup>	28 of 31	7.71 (0–20, 5.76)	7.25 (0–20, 5.85)	0.46 (0.90)	–0.52	0.64	–2.21	1.29
Digit span forwards <sup>a</sup>	18 of 31	5.28 (3– 8, 1.27)	5.44 (3– 8, 1.58)	–0.17 (0.32)	0.48	0.65	–0.50	0.83
Digit Span backwards <sup>a</sup>	17 of 31	3.41 (2–5, 0.72)	3.41 (2–4, 0.51)	0.00 (0.17)	0.00	1.00	–0.35	0.35

<sup>a</sup>Paired *T* test. 95 % confidence intervals (CI) and *P* values calculated by percentile bootstrapping method. <sup>b</sup>Wilcoxon signed – rank test (Non parametric). Listed *p* values are from *t* tests and Wilcoxon signed- rank test (\**p* < 0.05, \*\**P* < 0.1). Abbreviations: FAS (Fatigue Assessment Scale), SDMT (Symbol Digits Modalities Test), WAIS (Wechsler Adult Intelligence Scale- vocabulary), CVLT-II (The California Verbal Learning Test).

made decisions regarding discontinuation or reducing the assessment battery based on the specific condition of the patient with respect to variations in mental capacity, fatigue and endurance, which were observed and taken into account when conducting the assessment. Shorter tests or tests earlier in the order of the assessment battery were more likely to be completed than those at the end. Although we have previously shown that this intensive multidisciplinary rehabilitation program was well tolerated and feasible, the reduced number of patients completing the full neuropsychological assessment suggests that the use of an extensive test battery was less tolerated. In future research, it may be necessary to compromise on the extensiveness of neuropsychological test included both in the clinical and research context [7, 8]. A qualitative study of participants' experiences with a multidisciplinary rehabilitation program found that some patients with HD experienced the cognitive test battery as demanding and exhausting [17]. This is not unexpected given the nature of the disease, which also affects the patients' ability to maintain focus over a longer period of time. Research in the area of cognition and cognitive assessment in patients with HD has generated valuable information regarding qualities of neuropsychological tests in terms of sensitivity for identifying impairment in cognitive function and tracking this over time. Based on this research, proposals for cognitive assessment strategies have been presented [34–38]. This is of great value when designing and planning studies including cognitive outcomes. Unfortunately, much of this knowledge was not yet available at the time of the planning of this project.

#### *Limitations and strengths*

The present study has several limitations. The study is not a registered randomized clinical trial, but a clinical observational study across two institutions without a control group. Therefore, there are restrictions regarding the specific details of the intervention, i.e. the time adhered to each intervention activity of cognitive stimulation by the individual patients. On the other hand, the design allowed flexibility, regarding performing slight adjustments to interventions based on the clinical status of the participant. There is only one pilot study by Thompson et al. that included a control group [9], but the study was very small with only 9 patients and 11 controls. To our knowledge, the present study is the largest study reporting on a broad range of cognitive measures after a

multidisciplinary rehabilitation program. However, the sample was still small and the study suffers from lack of power. There was large heterogeneity with respect to functional capacity with disease stages ranging from I to III. Consequently, within the sample, there was likely a significant variation in the ability to benefit from the (cognitive) interventions of the program. The capacity to profit from neural compensation and brain plasticity in more advanced stages is less compared to early or pre-manifest patients. Thus, based on the present study, we cannot tease apart potential positive changes for different disease stages of HD patients or other factors (i.e. motor score). Additionally, the study does not allow teasing apart potential changes in cognition as a result of physiotherapy exercises, in particular aerobic exercise, which has been reported to be beneficial for cognition in studies in PD, and effects as a result of cognitive stimulation [39]. Further, it is worth noting that at the time of the planning of this project, information regarding neuropsychological tests most suitable as endpoints was not available. Thus if the study had been started today, the test battery would probably have consisted of more sensitive tests. Finally, the selection of cognitive measures did not necessarily correlate well with the specific activities that were targeted in the cognitive stimulation. As described by Andrews et al. 2015, cognitive stimulation is a non-specific cognitive intervention, contrary to cognitive training and cognitive rehabilitation which are aimed at improving specific cognitive functions or deficits, which allow the selection of specific cognitive measures where changes are expected to be found [15].

#### *Recommendations for future research*

There is a need for studies conducted on larger study samples, ideally including imaging techniques in line with the study of Cruickshank [25]. Further, in order to tease apart potential effects of the elements of multidisciplinary rehabilitation interventions, more detailed descriptions of the interventions in more homogeneous populations of patients with HD should be included with longer study periods and with a healthy control group. Additionally, the batteries of cognitive outcome measures should be selected carefully capturing cognitive domains that correspond to the cognitive interventions. The outcome measures should also be sufficiently sensitive to assess changes in cognitive function over time. Finally, potential beneficial effects on social life and functioning

resulting from multidisciplinary rehabilitation intervention programs and in particular cognitive interventions deserve more attention. Despite some general indications that the multidisciplinary program contributed to this in a positive way as reported in the qualitative study, this deserves more structured and quantitative evaluation [17].

### Conclusion

There was a significant decline over the one-year period in the SDMT, a measure known to be sensitive for change in cognitive function in pre-manifest and manifest patients with HD, however there was no indication that the rehabilitation program worsened or had negative effects on other measures of cognition in patients with early to middle stage HD. As half of the patients were not able to complete all the scheduled tests, we recommend a shorter battery, at least for research purposes. In addition, studies with larger and more homogeneous samples, and with appropriate control groups, are needed to further tease apart who will benefit the most from an intensive rehabilitation program. Studies should also evaluate to what extent a multidisciplinary and cognitive rehabilitation program for HD patients will result in positive changes such as improvement or maintenance in cognitive function over time.

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### CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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