J Neurol (2017) 264:32–39
DOI 10.1007/s00415-016-8310-1

ORIGINAL COMMUNICATION

Exercise effects in Huntington disease

Sebastian Frese[1,2] · Jens A. Petersen[1] · Maria Ligon-Auer[1] · Sandro Manuel Mueller[1,2] · Violeta Mihaylova[1] · Saskia M. Gehrig[1,2] · Veronika Kana[3] · Elisabeth J. Rushing[3] · Evelyn Unterburger[1] · Georg Kägi[4] · Jean-Marc Burgunder[5] · Marco Toigo[2,6] · Hans H. Jung[1]

Received: 4 July 2016 / Revised: 7 October 2016 / Accepted: 8 October 2016 / Published online: 17 October 2016

Abstract Huntington disease (HD) is a relentlessly progressive neurodegenerative disorder with symptoms across a wide range of neurological domains, including cognitive and motor dysfunction. There is still no causative treatment for HD but environmental factors such as passive lifestyle may modulate disease onset and progression. In humans, multidisciplinary rehabilitation has a positive impact on cognitive functions. However, a specific role for exercise as a component of an environmental enrichment effect has been difficult to demonstrate. We aimed at investigating whether endurance training (ET) stabilizes the progression of motor and cognitive dysfunction and ameliorates cardiovascular function in HD patients. Twelve male HD patients (mean ± SD, 54.8 ± 7.1 years) and twelve male controls (49.1 ± 6.8 years) completed 26 weeks of endurance training. Before and after the training intervention, clinical assessments, exercise physiological tests, and a body composition measurement were conducted and a muscle biopsy was taken from M. vastus lateralis. To examine the natural course of the disease, HD patients were additionally assessed 6 months prior to ET. During the ET period, there was a motor deficit stabilization as indicated by the Unified Huntington's Disease Rating Scale motor section score in HD patients (baseline: 18.6 ± 9.2, pre-training: 26.0 ± 13.7, post-training: 26.8 ± 16.4). Peak oxygen uptake ($\dot{V}O_{2peak}$) significantly increased in HD patients ($\Delta\dot{V}O_{2peak} = +0.33 \pm 0.28$ l) and controls ($\Delta\dot{V}O_{2peak} = +0.29 \pm 0.41$ l). No adverse effects of the training intervention were reported. Our results confirm that HD patients are amenable to a specific exercise-induced therapeutic strategy indicated by an increased cardiovascular function and a stabilization of motor function.

Keywords Unified Huntington disease rating scale (UHDRS) · Endurance training · Motor function · Cardiovascular function · Peak oxygen uptake ($\dot{V}O_{2peak}$)

S. Frese, J. A. Petersen, M. Toigo and H. H. Jung contributed equally.

✉ Hans H. Jung
hans.jung@usz.ch

1 Department of Neurology, University Hospital and University of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland

2 Institute of Human Movement Sciences and Sport, ETH Zurich, Zurich, Switzerland

3 Institute of Neuropathology, University Hospital and University of Zurich, Zurich, Switzerland

4 Department of Neurology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

5 Department of Neurology and Swiss Huntington Disease Centre, University of Bern, Bern, Switzerland

6 Balgrist University Hospital, Department of Orthopedics, University of Zurich, Zurich, Switzerland

Introduction

Physical activity has the potential to ameliorate cardiovascular health and other aspects of physical health, encompassing postural control, gait and health-related quality of life in several neurodegenerative diseases [1, 11] including Huntington Disease (HD; [3, 5, 6]). In transgenic HD mice, enhanced physical exercise delays the onset of specific motor deficits [10], attenuates neuropathological changes, improves gait function and coordination [12], and certain cognitive deficits may be rescued by wheel running initiated during adulthood [21]. By contrast, one study demonstrated a negative effect of exercise on motor

performance [22]. In HD patients, multidisciplinary rehabilitation has been suggested to have a positive impact on cognitive functions relating to verbal learning and memory [9]. However, it remains unclear by which mechanisms exercise exerts its effects [5, 22]. Our aim was to investigate by a systematic, supervised approach the effect of endurance training (ET) on motor and cognitive impairment as well as on cardiovascular function in HD patients.

Methods

Thirteen male HD patients and fifteen age-matched male controls were recruited. One HD patient and three controls prematurely finished the study due to loss of motivation. Twelve patients with a genetically verified diagnosis of HD (mean ± SD, age: 54.8 ± 7.1 years; height: 1.74 ± 0.05 m; CAG repeat number: 39–45) and twelve controls (age: 49.1 ± 6.8 years; height: 1.79 ± 0.05 m) completed the study. Inclusion criteria were male gender, serum levels of phosphocreatine kinase (CK) below 300 U/l and motor and cognitive skills that allowed to give written informed consent and to perform ET. Exclusion criteria included contraindications of an ET such as cardiovascular, metabolic or orthopedic disorders. Demographic data (date of birth, gender, etc.), medical history, co-morbid conditions, current medication, and HD-mutation (CAG repeat analysis, size of the alleles, laboratory performing the analysis, date of the analysis) were assessed during the screening phase. All patients and controls gave their written informed consent. The protocol was approved by the local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects (ClinicalTrials.gov NCT01879267). A pre-trial power analysis revealed that 12 patients and 12 controls were necessary to achieve a statistical power of 80 % at a significance level of 5 %. The power analysis was based on an expected average increase in peak oxygen uptake ($\dot{V}O_{2peak}$) of 8–10 % after 6–8 weeks of endurance training and a coefficient of variation for repeated measurements of $\dot{V}O_{2peak}$, determined in our laboratory, of 5.7 %.

HD patients performed ET following an observation period of 6 months while controls performed only the identical ET. The 6 months of ET were divided into three training periods that were interspersed with one regeneration week. During the first 10 weeks, participants conducted 30 min of constant intensity cycling at a cycling power corresponding to 65 % $\dot{V}O_{2peak}$ three times per week. After the first regeneration week, participants completed high-intensity interval trainings (i.e. 4 × 4 min cycling at a power eliciting 90–95 % of peak heart rate) according to Helgerud et al. [13], three times a week for a total of 8 weeks. The last 6 weeks of endurance training consisted of two interval sessions and one constant-load training per week, adapted from Russell et al. [24]. During the regeneration weeks, the participants conducted two constant-load trainings at 50 % $\dot{V}O_{2peak}$ for 30 min. To maintain sufficient training stimulation, power was increased based on the individual level of the participants as monitored by the perceived exertion using a CR10 scale [4].

Assessments

HD patients and controls were assessed before and after the ET period. To examine the natural course of the disease, HD patients were additionally assessed 6 months prior to the ET. The severity of motor signs in HD patients was quantified using the Unified Huntington's Disease Rating Scale (UHDRS) motor section [15]. Neuropsychological tests were carried out in a fixed sequence and included the verbal-fluency test [8], the Hopkins Verbal Learning Test-Revised (HVLT-R; [2]), the dementia rating scale 2 (DRS-2), formerly the Mattis dementia rating scale [20, 19], the Symbol-Digit Modalities Test [26], the Stroop color naming, word reading and interference tests [27], the trail making test part A and B [23], and the category-fluency task [7].

Fasting venous blood samples were taken at the beginning of the natural course observation period as well as before and after ET. Several metabolic parameters were measured including lactate, glucose, HbA1c, thyroid stimulating hormone (TSH) and creatine kinase (CK). To recognize possible accelerated muscle turnover during the training period, CK levels were measured weekly [17]. HD patients with CK levels >300 U/l were excluded from the study. Before and after the training period, we determined segmental body composition using dual-energy X-ray absorptiometry (DXA; Lunar iDXA™, GE Healthcare, Madison, WI, USA) according to the manufacturers specifications.

To determine $\dot{V}O_{2peak}$ and peak cycling power, a maximal graded cycling test was conducted on an electromagnetically braked ergometer (Ergoselect 200K, Ergoline, Bitz, Germany). Prior to the test, participants were resting on the bicycle ergometer for 3 min equipped with a facemask, which covered their mouth and nose (Hans Rudolph, Shawnee, KS, USA). The facemask was connected with an anti-bacterial filter (PALL PRO1087, Pall, East Hills, NY, USA) to an Innocor™ device (Innocor™, Innovision, Odense, Denmark). During the ergometer trials, pulmonary gas exchange and ventilation were measured breath by breath. The graded cycling test started at 25 W and involved power increases of 25 W every 2 min. The participants were advised to maintain a

constant cadence (70–80 revolutions per min; rpm) throughout all cycling tests. Volitional exhaustion was reached when the participants voluntarily stopped pedaling or when the pedaling frequency could no longer be sustained within ±5 rpm. Endurance capacity was assessed by a constant-load test. After 3 min of rest (measurement of ventilation, gas exchange, and heart rate at rest), participants started pedaling with their individually preferred cadence, which was recorded during the graded cycling exercise test. The power of the initial 5 min "warm-up" stage was 40 % peak power of the graded cycling exercise test. Subsequently, the power was increased to 85 % peak power for the constant-load test. The participants pedaled until volitional exhaustion, which was defined as the point in time at which the participants stopped pedaling or at which they were no longer able to maintain their cadence (±5 rpm). Time-to-exhaustion was recorded.

Minimally invasive percutaneous muscle needle biopsies were taken before and after the training period in HD patients and controls. In consenting HD patients, an additional muscle biopsy was taken before the natural course observation period. The non-dominant vastus lateralis muscle was biopsied as described previously [16] using a 6-mm Bergstrom muscle biopsy needle (Dixons Surgical Instruments, Essex, UK) modified to include suction. Participants were placed in supine position. After local anesthesia with 8–10 cc of 1 % lidocaine, a small incision was made into the lateral mid-thigh ~15 cm from the lateral superior border of the patella. Two muscle samples were taken from the same insertion site of the biopsy needle by rotating the needle. One muscle sample was mounted in embedding medium and frozen in pre-cooled isopentane for histochemical examinations. The second muscle sample was fixed in glutaraldehyde and embedded in Epon for semithin sections. Seven micrometer cryostat sections of muscle biopsies were stained with hematoxylin and eosin, with modified Gömöri trichrome and with enzyme histochemical methods for succinic dehydrogenase and combined cytochrome oxidase/succinic dehydrogenase according to standard methods. For eventual ultrastructural analysis, a small piece of skeletal muscle tissue (<1 mm^3) was fixed in 2.5 % glutaraldehyde in phosphate buffered saline (PBS) for 1 h. Specimens were then postfixed in 2 % osmium tetroxide for 40 min. After dehydration in increasing concentrations of ethanol (50–100 %), they were embedded in Epon and polymerized at 60 °C for at least 24 h. Toluidine blue semithin sections (70 nm) from two randomly chosen blocks were cut from each biopsy.

Statistics

Data were checked for normality with a Q–Q-plot. All data were summarized using descriptive statistics as mean values ± standard deviation or minimum and maximum values for continuous variables. To detect differences between baseline and pre-training within the HD group, paired sample *t* tests were conducted. An analysis of variance with repeated measures was performed to determine changes between groups over time during the training intervention. SPSS 21.0 statistical software (SPSS, Chicago, IL, USA) was used for all statistical calculations. A value of $P < 0.05$ was set as statistical significance.

Results

All participants tolerated the ET well, and CK levels remained below 300 U/l during the course of the study. Further laboratory analyses as depicted above revealed no abnormalities at baseline as well as before and after ET (data not shown). During the natural course observation period, the UHDRS motor score increased markedly in HD patients (Fig. 1). The UHDRS motor score did not further increase during the ET period in the entire patient group ($P = 0.770$), indicating a motor deficit stabilization (baseline: 18.6 ± 9.2, pre-training: 26.0 ± 13.7, post-training: 26.8 ± 16.4; Fig. 1). We reanalyzed the data excluding the two patients with 39 CAG repeats and the statistical results were not altered.

During the observation period, absolute and relative $\dot{V}O_{2peak}$ decreased significantly in HD patients, whereas peak cycling power output was not altered (Table 1). In both HD patients and controls, absolute and relative $\dot{V}O_{2peak}$ as well as absolute and relative peak power output

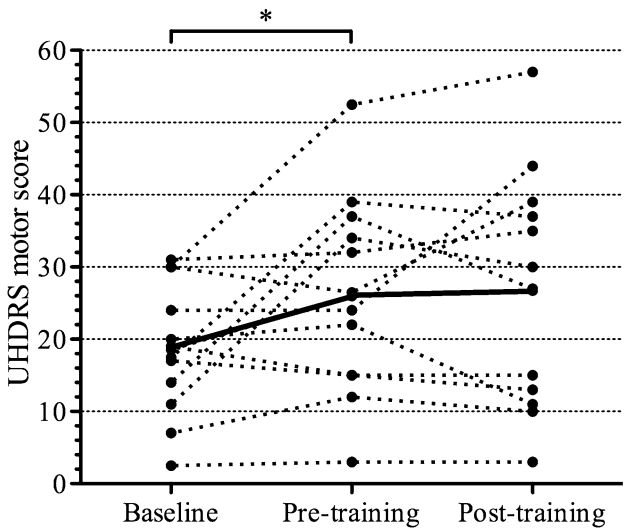

Fig. 1 Individual scores (*full dots* and *dotted lines*) of the Unified Huntington's Disease Rating Scale (UHDRS) motor section for twelve HD patients at baseline, pre- and post-training. *Solid line* represents mean value for all HD patients. *$P < 0.05$, significantly different between baseline and pre-training

Table 1 Results of the cycling exercise tests for Huntington's disease (HD) patients and healthy controls

	HD ($n = 12$)			Controls ($n = 12$)		ANOVA for training intervention		
	Baseline	Pre-training	Post-training	Pre-training	Post-training	Time effect	Group effect	Time × group
GXT								
VO_{2peak} (l min^{-1})	2.71 ± 0.49	2.54 ± 0.38*	2.87 ± 0.42	3.03 ± 0.59	3.32 ± 0.44	$P < 0.001$	$P = 0.013$	$P = 0.823$
$VO_{2peak,\ rel}$ (ml kg^{-1} min^{-1})	35.0 ± 8.0	32.9 ± 7.2*	37.6 ± 7.8	36.5 ± 5.7	40.1 ± 3.6	$P < 0.001$	$P = 0.215$	$P = 0.557$
P_{Peak} (W)	168 ± 40	165 ± 37	197 ± 31	218 ± 50	256 ± 37	$P < 0.001$	$P = 0.002$	$P = 0.496$
$P_{peak,rel}$ (W kg^{-1})	2.17 ± 0.59	2.13 ± 0.59	2.57 ± 0.51	2.62 ± 0.47	3.10 ± 0.40	$P < 0.001$	$P = 0.018$	$P = 0.713$
CLT								
Time to exhaustion (s)	754 ± 274	640 ± 170	1335 ± 525	915 ± 271	1951 ± 721	$P < 0.001$	$P = 0.018$	$P = 0.713$

Data are presented as mean ± SD. Absolute and relative peak oxygen uptake ($\dot{V}O_{2peak}$) as well as absolute and relative peak cycling power output (P_{peak}) were obtained during a graded cycling exercise test (GXT). Time to exhaustion (s) was determined during a constant-load cycling exercise test (CLT)

* $P < 0.05$, significantly different between baseline and pre-training

Table 2 Body composition results for Huntington's disease (HD) patients and healthy controls

	HD ($n = 12$)			Controls ($n = 12$)		ANOVA for training intervention		
	Baseline	Pre-training	Post-training	Pre-training	Post-training	Time effect	Group effect	Time × group
BMI (kg m^{-2})	26.1 ± 4.3	26.1 ± 4.6	25.7 ± 4.4	26.2 ± 4.1	26.0 ± 3.7	$P = 0.098$	$P = 0.906$	$P = 0.467$
Total body mass (kg)	79.1 ± 13.3	79.2 ± 14.1	78.0 ± 13.5	83.7 ± 13.3	83.2 ± 12.1	$P = 0.088$	$P = 0.373$	$P = 0.482$
Total lean mass (kg)	56.9 ± 6.9	56.7 ± 7.5	56.3 ± 7.0	59.0 ± 6.6	59.6 ± 6.1	$P = 0.480$	$P = 0.332$	$P = 0.042$
Body fat (%)	24.0 ± 7.4	24.0 ± 7.0	23.3 ± 6.8	25.2 ± 4.9	24.1 ± 4.4	$P = 0.012$	$P = 0.670$	$P = 0.529$
Total fat mass (kg)	19.3 ± 8.7	19.5 ± 8.8	18.7 ± 8.5	21.6 ± 7.2	20.4 ± 6.3	$P = 0.012$	$P = 0.556$	$P = 0.681$
Arms lean mass (kg)	7.5 ± 1.1	7.5 ± 1.3	7.4 ± 1.3	7.8 ± 1.1	7.7 ± 1.0	$P = 0.029$	$P = 0.580$	$P = 0.742$
Arm fat (%)	22.0 ± 6.8	21.9 ± 6.7	22.0 ± 6.3	22.7 ± 4.2	22.8 ± 3.8	$P = 0.642$	$P = 0.724$	$P = 0.990$
Legs lean mass (kg)	19.5 ± 2.7	19.4 ± 2.9	19.3 ± 2.7	20.6 ± 2.6	21.0 ± 2.8	$P = 0.044$	$P = 0.214$	$P = 0.006$
Leg fat (%)	20.4 ± 6.6	20.4 ± 6.6	20.4 ± 6.0	23.0 ± 4.4	21.8 ± 3.9	$P = 0.102$	$P = 0.357$	$P = 0.070$
Trunk lean mass (kg)	26.3 ± 3.0	26.2 ± 3.1	26.2 ± 3.0	27.0 ± 2.9	27.3 ± 2.4	$P = 0.356$	$P = 0.411$	$P = 0.264$
Trunk fat (%)	28.2 ± 9.7	28.7 ± 9.2	27.2 ± 9.4	29.6 ± 7.4	28.1 ± 7.0	$P = 0.011$	$P = 0.782$	$P = 0.927$
Android lean mass (kg)	3.8 ± 0.6	3.9 ± 0.6	4.0 ± 0.6	3.8 ± 0.5	4.0 ± 0.4	$P = 0.031$	$P = 0.984$	$P = 0.237$
Android fat (%)	31.8 ± 10.9	31.7 ± 10.2	29.0 ± 10.9	35.2 ± 9.3	30.9 ± 9.4	$P < 0.001$	$P = 0.507$	$P = 0.247$
Gynoid lean mass (kg)	8.5 ± 1.2	8.6 ± 1.2	8.7 ± 1.1	8.4 ± 0.9	9.0 ± 0.8	$P < 0.001$	$P = 0.825$	$P = 0.007$
Gynoid fat (%)	25.3 ± 8.2	25.0 ± 7.9	23.0 ± 6.6	30.2 ± 5.5	25.3 ± 4.9	$P < 0.001$	$P = 0.151$	$P = 0.021$

Data are presented as mean ± SD

BMI body mass index

increased during the training period (Table 1). There were significant group differences for absolute $\dot{V}O_{2peak}$, absolute and relative peak cycling power output as well as time-to-exhaustion at 85 % peak cycling power but no significant time × group interactions (Table 1). Furthermore, there was a time ($P = 0.013$) and a group effect ($P = 0.003$) for oxygen cost of exercise (HD patients: 15.9 and 14.7 ml O_2 W^{-1} and controls: 14.0 and 13.0 ml O_2 W^{-1} for pre- and post-training, respectively), but no time × group interaction ($P = 0.794$).

Segmental body composition determined by dual-energy X-ray absorptiometry remained constant during the observation period in HD patients (Table 2) and there were no group differences between HD patients and controls. During the training period, there were time effects for total body fat, total fat mass, trunk fat, android fat and gynoid fat, showing a decrease in fat content in both training groups. A significant time × group interaction was only present for gynoid fat indicating a higher decrease in the healthy controls. Significant time effects were present for

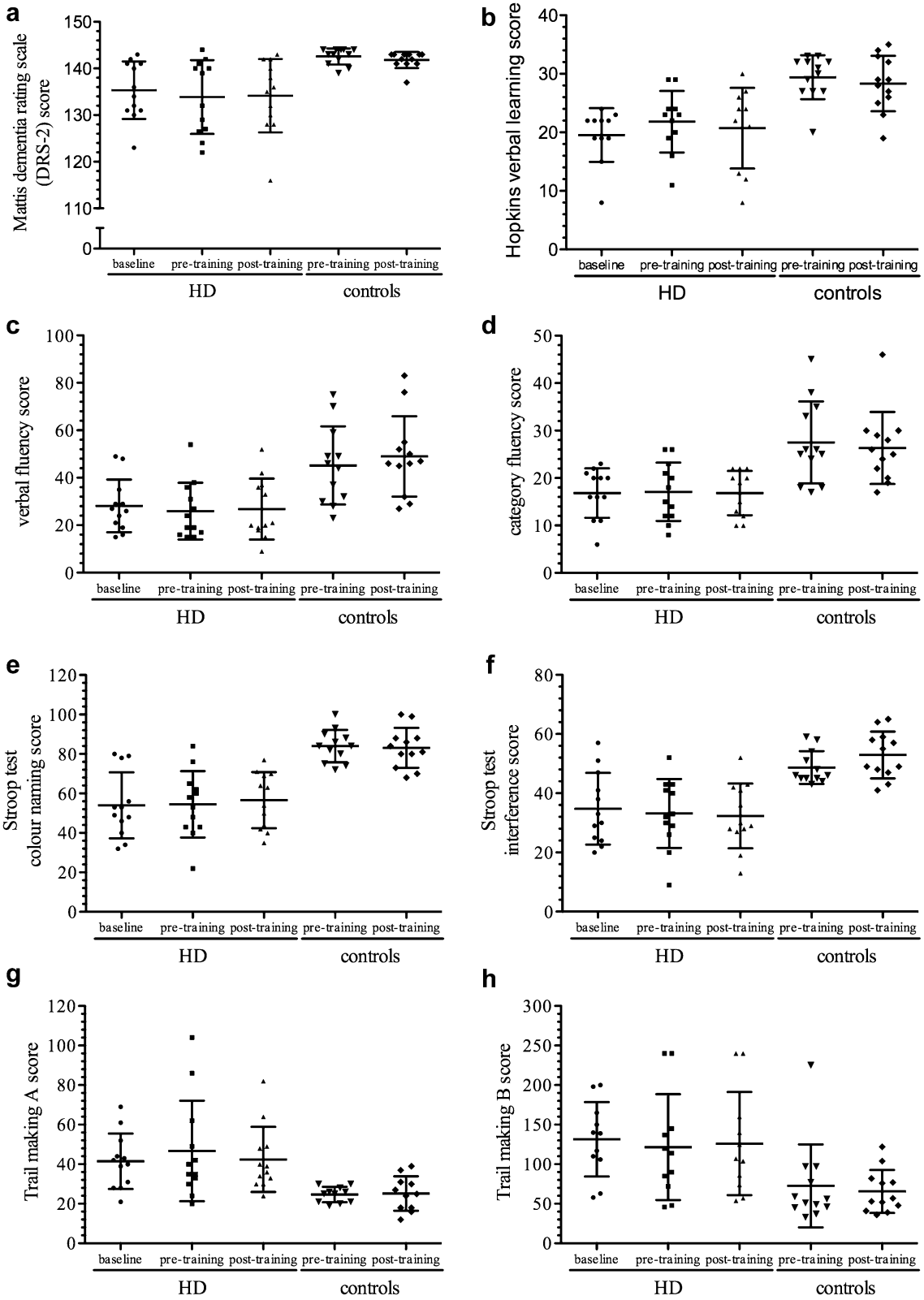

Fig. 2 Scatter *dot plots* of the scores for the **a** Mattis dementia rating scale ($n = 12$), **b** Hopkins verbal learning ($n = 11$), **c** verbal fluency ($n = 12$), **d** categorical fluency ($n = 12$), **e** Stroop test color naming ($n = 12$), **f** Stroop test interference ($n = 12$), **g** Trail making A ($n = 12$), and **h** Trail making B ($n = 11$) tests for HD patients at baseline, pre- and post-training as well as for healthy controls ($n = 12$) pre- and post-training

Table 3 Results of the neuropsychological tests for Huntington's disease (HD) patients and healthy controls

	HD ($n = 12$)			Controls ($n = 12$)		ANOVA for training intervention		
	Baseline	Pre-training	Post-training	Pre-training	Post-training	Time effect	Group effect	Time × group
Verbal fluency	28.2 ± 11.1	25.9 ± 12.0	26.8 ± 12.8	45.2 ± 16.5	49.0 ± 16.9	$P = 0.077$	$P = 0.002$	$P = 0.267$
Category fluency	16.8 ± 5.2	17.1 ± 6.2	16.8 ± 4.7	27.5 ± 8.6	26.3 ± 7.6	$P = 0.433$	$P = 0.001$	$P = 0.611$
Stroop test color naming	54.0 ± 16.8	54.5 ± 16.8	56.6 ± 14.2	84.0 ± 8.2	83.1 ± 10.1	$P = 0.598$	$P < 0.001$	$P = 0.183$
Stroop test word reading	77.4 ± 19.0	77.3 ± 19.8	76.0 ± 20.4	99.8 ± 0.6	99.3 ± 2.0	$P = 0.385$	$P = 0.001$	$P = 0.691$
Stroop test interference	34.8 ± 12.1	33.2 ± 11.7	32.3 ± 10.9	48.7 ± 5.5	52.9 ± 7.9	$P = 0.182$	$P < 0.001$	$P = 0.053$
Trail making A	41.5 ± 14.0	46.7 ± 25.4	42.4 ± 16.4	24.6 ± 3.9	25.2 ± 8.7	$P = 0.383$	$P = 0.006$	$P = 0.262$
Trail making B (HD: $n = 11$)	131.5 ± 47.0	121.5 ± 66.9	126.1 ± 65.1	72.7 ± 52.4	65.6 ± 27.1	$P = 0.902$	$P = 0.014$	$P = 0.572$
Hopkins verbal learning (HD: $n = 11$)	19.5 ± 4.6	21.8 ± 5.3	20.7 ± 6.9	29.4 ± 3.8	28.3 ± 4.7	$P = 0.281$	$P = 0.001$	$P = 0.997$
Cumulative word learning (HD: $n = 10$)	70.1 ± 24.1	110.5 ± 61.7	99.9 ± 67.1	222.8 ± 71.5	196.0 ± 109.1	$P = 0.327$	$P = 0.002$	$P = 0.667$
Symbol digit modalities	38.2 ± 11.0	39.6 ± 13.7	37.4 ± 13.7	50.3 ± 5.3	51.0 ± 9.2	$P = 0.540$	$P = 0.011$	$P = 0.213$
DRS-2 total score	135.3 ± 6.2	133.9 ± 7.9	134.2 ± 7.9	142.6 ± 1.7	141.8 ± 1.8	$P = 0.808$	$P = 0.001$	$P = 0.581$
DRS-2 subscore attention	36.3 ± 1.0	35.9 ± 1.1	34.6 ± 3.0	36.8 ± 0.4	36.7 ± 0.5	$P = 0.080$	$P = 0.009$	$P = 0.168$
DRS-2 subscore initiation/ perseveration	33.1 ± 4.3	32.0 ± 5.0	32.3 ± 4.3	36.8 ± 0.6	36.4 ± 1.7	$P = 0.971$	$P = 0.002$	$P = 0.499$
DRS-2 subscore memory	22.9 ± 1.7	22.8 ± 2.1	23.5 ± 1.5	24.4 ± 0.9	24.1 ± 0.9	$P = 0.564$	$P = 0.025$	$P = 0.142$
DRS-2 subscore conceptualization	37.3 ± 1.9	37.3 ± 1.3	37.8 ± 1.5	38.7 ± 0.9	38.7 ± 0.8	$P = 0.379$	$P = 0.010$	$P = 0.379$
DRS-2 subscore construction	5.7 ± 0.5	5.9 ± 0.3	5.9 ± 0.3	5.83 ± 0.4	6.0 ± 0.0	$P = 0.328$	$P = 1.000$	$P = 0.328$

Data are mean ± SD

arms, legs, android, and gynoid lean mass, indicating increases in lean mass in the whole cohort, with exception of arms lean mass, which showed a slight decline. Significant time × group interactions for legs and gynoid lean mass were based on increases within the healthy controls, while the values remained constant in the HD group.

HD patients performed worse than controls for all assessed neuropsychological tests, namely Mattis dementia rating scale (DRS-2), the DRS-2 initiation/perseveration subscale score [25], the verbal and category fluency test [14], the Hopkins verbal learning test [18], the Stroop tests [18], the trail making test part A and B, and the symbol digit modalities test (Fig. 2; Table 3). Solely for the DRS-2 subscore construction HD patients attained similar values as compared to healthy controls. There were neither time effects nor time × group interactions for all assessed neuropsychological variables.

Histological analysis of cross-sections of vastus lateralis muscle fibers showed no clear pathological changes. There were scattered ragged red fibers in one patient post-training. Rare cytochrome oxidase (COX)-negative fibers were detected in HD patients and controls at baseline as well as in pre- and post-training biopsies. Increased subsarcolemmal staining on Gömöri trichrome-stained sections, suggestive of mitochondrial proliferation was observed post-training in HD patients and controls. Semithin sections from a few HD patients and controls showed increased intracellular lipid.

Discussion

Our exercise physiological data indicate that HD patients had a similar trainability for the assessed cycling variables as compared to healthy controls. ET was well tolerated by

HD patients and no adverse events were reported. In particular, no clinically relevant weight loss or elevated CK levels were observed during ET. This is of importance since ET appeared to accelerate disease onset in a transgenic mouse model [22], and a case report suggested a detrimental training effect in a semi-professional marathon runner with premanifest HD who developed rhabdomyolysis earlier than the predicted disease onset [17]. In this cohort, ET improved cardiovascular function and endurance capacity in both HD patients and controls. HD patients reached post-training values for $\dot{V}O_{2peak}$ and peak cycling power approaching pre-training values of controls. Our results indicate that HD patients are capable of increasing their cardiovascular fitness to the level of age-matched controls, and may also profit from a concomitantly improved quality of life. During ET, segmental body composition in HD subjects was only slightly altered. Notably, total lean mass and leg lean mass was not reduced during the ET intervention, indicating that neither weight loss nor skeletal muscle wasting was induced by ET in the HD patients.

The UHDRS motor score stabilized during the ET period, indicating the possibility of a beneficial effect of ET on motor function in at least a subgroup of patients. This result is supported by previous studies that reported positive effects of exercise on motor readouts in the R6/1 mouse model [10, 21]. By contrast, we could not observe an effect of ET on any of the investigated neuropsychological variables. However, the high variability within both groups and the relatively small number of participants might be a responsible factor for our outcome. In line with these results, there were no significant alterations in the UHDRS behavior and functional abilities components during the entire study period in HD patients (data not shown). Overall, the effects of ET on all assessed cognitive variables were rather small. Therefore, to detect significant differences for these variables a larger cohort and/or a longer training period might be necessary.

The histopathological analyses revealed no significant morphological differences between HD patients and controls. The only possible ET-related change was the presence of subsarcolemmal caps observed in trichrome-combined COX/SDH and SDH-stained sections, suggestive of mitochondrial proliferation, which can also be observed in healthy controls after ET. Although not conclusive, these findings may represent a morphologic correlate of ET-related improved mitochondrial metabolism in HD patients, which in turn may promote cardiorespiratory and muscular function. However, a further analysis of the effects of ET on the mitochondrial function in HD is warranted.

To date, neither the quantity nor the quality of physical interventions that are beneficial for HD patients can be conclusively defined. Namely, it is not known if aerobic, anaerobic or combined ET should be applied. Nevertheless, our results demonstrate that physical training in HD patients is safe and that HD patients are amenable to exercise-induced therapeutic effects. Our study is limited by the small number of participants; however, the results of our study justify further investigation of exercise effects in HD patients. Larger multicenter trials might help identifying patients which will benefit from ET.

Acknowledgments We thank Dr. Niels Hagenbuch and Prof. Burkhardt Seifert of the Epidemiology, Biostatistics and Prevention Institute (University of Zurich) for their support and assistance during the statistical analyses. The study was supported by the Swiss National Science Foundation (320030_135539) and the Jacques and Gloria Gossweiler Foundation.

Compliance with ethical standards

Conflicts of interest None. The results of this study do not constitute endorsement by ACSM. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Ethical standards All patients and controls gave their written informed consent. The protocol was approved by the ethics committee of the Canton of Zurich (KEK-ZH-Nr. 2009-0119) and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects (ClinicalTrials.gov NCT01879267)

Funding The study was supported by the Swiss National Science Foundation (320030_135539) and the Jacques and Gloria Gossweiler Foundation. The funding sources had no role in writing of the manuscript or in the decision to submit it for publication.

References

1. Baker LD, Frank LL, Foster-Schubert K et al (2010) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 67:71–79
2. Benedict RHB, Schretlen D, Groninger L, Brandt J (1998) Hopkins verbal learning test revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 12:43–55
3. Bohlen S, Ekwall C, Hellstrom K et al (2013) Physical therapy in Huntington's disease—toward objective assessments? Eur J Neurol 20:389–393
4. Borg E, Kaijser L (2006) A comparison between three rating scales for perceived exertion and two different work tests. Scand J Med Sci Sports 16:57–69
5. Busse M, Khalil H, Brooks S, Quinn L, Rosser A (2012) Practice, progress and future directions for physical therapies in huntingtons disease. J Huntingt Dis 1:175–185
6. Busse M, Quinn L, Debono K et al (2013) A randomized feasibility study of a 12-week community-based exercise program for people with Huntington's disease. J Neurol Phys Ther 37:149–158
7. Butters N, Granholm E, Salmon DP, Grant I, Wolfe J (1987) Episodic and semantic memory: a comparison of amnesic and demented patients. J Clin Exp Neuropsychol 9:479–497

8. Butters N, Wolfe J, Granholm E, Martone M (1986) An assessment of verbal recall, recognition and fluency abilities in patients with Huntington's disease. Cortex 22:11–32
9. Cruickshank TM, Thompson JA, Dominguez DJ et al (2015) The effect of multidisciplinary rehabilitation on brain structure and cognition in Huntington's disease: an exploratory study. Brain Behav 5:e00312
10. van Dellen A, Cordery PM, Spires TL, Blakemore C, Hannan AJ (2008) Wheel running from a juvenile age delays onset of specific motor deficits but does not alter protein aggregate density in a mouse model of Huntington's disease. BMC Neurosci 9:34
11. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL (2008) The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Mov Disord 23:631–640
12. Harrison DJ, Busse M, Openshaw R, Rosser AE, Dunnett SB, Brooks SP (2013) Exercise attenuates neuropathology and has greater benefit on cognitive than motor deficits in the R6/1 Huntington's disease mouse model. Exp Neurol 248:457–469
13. Helgerud J, Hoydal K, Wang E et al (2007) Aerobic high-intensity intervals improve VO_{2max} more than moderate training. Med Sci Sports Exerc 39:665–671
14. Hodges JR, Salmon DP, Butters N (1990) Differential impairment of semantic and episodic memory in Alzheimer's and Huntington's diseases: a controlled prospective study. J Neurol Neurosurg Psychiatry 53:1089–1095
15. Huntington Study Group (1996) Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 11:136–142
16. Item F, Nocito A, Thony S et al (2013) Combined whole-body vibration, resistance exercise, and sustained vascular occlusion increases PGC-1alpha and VEGF mRNA abundances. Eur J Appl Physiol 113:1081–1090
17. Kosinski CM, Schlangen C, Gellerich FN et al (2007) Myopathy as a first symptom of Huntington's disease in a Marathon runner. Mov Disord 22(11):1637–1640. doi:10.1002/mds.21550
18. Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbusche E, Dom R (2004) Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation–a longitudinal follow-up study. J Neurol 251:935–942
19. Mattis S (1988) Dementia Rating Scale: professional manual. Psychological Assessment Resources Inc, Odessa
20. Mattis S (1976) Mental status examination for organic mental syndrome in the elderly patient. In: Bellack L, Karasu T (ed) Geriatrics psychiatry: a handbook for psychiatrists and primary care physicians. New York, pp 77–121
21. Pang TY, Stam NC, Nithianantharajah J, Howard ML, Hannan AJ (2006) Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. Neurosci 141:569–584
22. Potter MC, Yuan C, Ottenritter C, Mughal M, van Praag H (2010) Exercise is not beneficial and may accelerate symptom onset in a mouse model of Huntington's disease. PLoS Curr 2:RRN1201
23. Reitan R (1958) Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 8:271–276
24. Russell AP, Feilchenfeldt J, Schreiber S et al (2003) Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle. Diabetes 52:2481–2874
25. Salmon DP, Kwo-on-Yuen PF, Heindel WC, Butters N, Thal LJ (1989) Differentiation of Alzheimer's disease and Huntington's disease with the Dementia Rating Scale. Arch Neurol 46:1204–1208
26. Smith A (1973) Symbol digit modalities test manual. Western Psychological Services, Los Angeles
27. Stroop J (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18:643–662