University and Rehabilitation Clinics Ulm

Neurology

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Implementation and Evaluation of Two Distinct Electronic Motion Detection Devices for the Assessment of Abnormal Movements in Huntington's Disease

Dissertation

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submitted by

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Dedicated to my family

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List of Abbreviations

ANOVA	Analysis of Variance
BDNF	brain-derived neutrophic factor
CAG	Cytosin, Adenosin, Guanin
CAPIT	Core Assessment Protocol for Intracerebral Transplantation
CM-Pf	centromedian parafascicular thalamic complex
CNS	Central Nervous System
GPe	Globus Pallidus externus
GPi	Globus Pallidus internus
HD	Huntington's Disease
mHTT	mutant Huntingtin
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
UHDRS	Unified Huntington's Disease Rating Scale
PPN	pedunculopontine nucleus
RKU	Rehabilitations- und Universitätsklinikum Ulm
STN	subthalamic nucleus
TFC	Total Functional Capacity

1. Introduction

Huntington's Disease (HD) is a progressive hereditary autosomal-dominant neurodegenerative disorder of the central nervous system. It is caused by an expanded trinucleotide repeat in the HD gene located on chromosome 4 [47]. Three main symptom groups are commonly recognized:
1. movement disorders (hypo- ;-hyperkinesia), 2. organic psychiatric symptoms, and 3. cognitive decline (dementia) [11]. In addition, weight loss is also a common and clinically significant feature [81].

The HD gene mutation results in a in a long polyglutamine tract in the N-terminus of the encoded protein Huntingtin (htt) [47]. The disease is fully penetrant for a repeat length > 39, the age of motor symptom onset typically lies between 35 and 45 years of age, but is difficult to predict exactly. Interestingly, age of symptom onset correlates inversely with the length of the triplet repeat tract [19] [45], while repeat length does not correlate with the rate of the disease progression itself [66].

Motor symptoms are usually the first signs that can be clearly attributed to HD, but observational studies show that the disease almost always starts with subtle cognitive and behavioral dysfunctions which can precede a formal clinical diagnosis by up to 15 years [46]. Once clinically manifest, HD relentlessly progresses, albeit in unpredictable form, until patients die after approximately 15-20 years later typically from complications like aspiration, pneumonia and cardiovascular disease [82].

Because of the large variation in the clinical phenotype, it is challenging to assess stage and disease progress objectively. The established clinical tools are validated rating scales, most importantly the Unified Huntington's Disease Rating Scale (UHDRS) [37]. The scale consists of a combination of motor, behavioral, cognitive and functional assessments. These clinical rating tools are inherently observer dependent and thus susceptible to subjective errors. Whilst the benefit lies in breadth and ability to capture a wide variety of deficits, the categorical design of a rating scale also often prevents detection of subtle changes in patient performance [32].

To generate an UHDRS score correctly, considerable time is required from patients, physicians and caregivers (10-20 minutes) [37, 39]. It is also limited by poor sensivity to change over time and nonlinearity of subscores [39].

The research community has made efforts to deconstruct the UHDRS into simpler subscales, or to determine study outcomes from subitems in the hope that these would increase e.g. sensivity towards change over time and reduce in inter-individual variability [49]. The need for a time efficient, simple, inexpensive and easy-to-use objective measurement of clinical phenotype to supplement standard clinical assessment remains unmet and has increased with the advent of potentially disease modifying therapeutic approaches.

The movement disorder in HD is complex and evolves over disease progression. Although (worsening) chorea remains the most striking motor feature, patients also suffer from general paucity of movement including a delay in movement onset (akinesia), slowing of movement (bradykinesia), generally reduced movement (hypokinesia) and imprecision in the force and trajectory of movements once executed [60]. Chorea in HD starts as involuntary movements in the distal extremities, spreading to proximal muscle groups over time, ultimately culminating in frank dystonia.

Dysfunction and subsequent atrophy in specific parts of the basal ganglia circuits, mainly the Globus pallidus externus (GPe) and the subthalamic nucleus (STN), underlies these motor impairments [16, 17, 25].

Initiation and execution of voluntary targeted movements are impaired in all clinically manifest stages of HD and even in presymptomatic mutation-carrier subjects [70]. Full-body chorea also influences targeted movements [21]. Consequently, HD patients are performing poorly in device-assisted motor tests which measure targeted movements e.g. fingertapping or coordination movements like reposition-of-pins tests [69].

The results of such objective motor measurements are not HD specific but can function as markers of clinical manifestations of neurodegeneration and can help evaluate motor functions objectively [69]. Since patients experience impairment of

targeted movement as impairment of function it can serve as a proxy of functional status.

1.1.1 History

The first doctors to describe clinical symptoms of Huntington's Disease were Dr. Oscar Waters 1842 in New York, and the Norwegian physician Dr. Lund in 1860 [48]. The Disease is named after the physician George Huntington from New York. In a time even before Mendel's discoveries of the laws of inheritance, he described Huntington's disease in 1872 as hereditary, and as distinction from the chorea minor [36]. His essay was also praised as an excellent clinical description for its time [59].

Over a hundred years later, Gusella et al. used a polymorphic DNA marker and a very large pedigree from Venezuela to localize the genetic defect of HD on the short arm of chromosome 4 in 1983 [29]. A further ten years later, the Huntingtin gene was identified, cloned, and characterized in an epochal study by the Huntington's Disease Study Group [47]. The last 30 years have been dedicated to identifying the activities and the toxicity of the mutant protein Huntingtin in the human cell and its interaction with neurons, and why corticostriatal neurons are the most vulnerable to it.

Today, great progress has been made in understanding the biological processes and symptoms of Huntington's Disease, and for the first time, specific drugs for silencing the HD mutation are in the clinical testing phase (NCT03342053; NCT03225833).

1.1.2 Epidemiology

HD is among the most common monogenetic adult onset diseases. In Europe, the prevalence of clinically manifest gene carriers is approximately 10 per 100,000 [87]. In Japanese (≈0,4 per 100,000), Finnish (≈2 per 100,000) [75] and African (6:10 million) populations HD is far less frequent [31]. In Germany, the prevalence is about 10,000 with an incidence of 6-12 per 100,000 [33].

Age of symptom onset is typically between 35 and 45 years of age, though it may occasionally start at younger than 10 or over 60 years [31]. Men and women are affected equally.

1.1.3 Genetics

HD is a paradigmatic autosomal-dominant hereditary disease. The trinucleotide repeat causing it is located in the HTT-gene on chromosome 4 which codes for the likely pathogenetic agent – a mutant form of the protein huntingtin [47]. The CAG-repeats result in the huntingtin harboring an excessively long polyglutamine stretch near the N-terminus [47].

For > 39 repeats the disease will develop with nearly 100% certainty, i.e. complete penetrance. In the general population, the CAG-repeat length lies between 17-20 repeats in the HTT gene [40]. With 20-26 repeats, a person will not develop any symptoms and counts as normal. 27 to 35 repeats, termed intermediate range, still do not cause HD, even though a few cases have been described [30].

Alleles of 27 repeats or higher are meotically unstable and can expand to pathogenic length in the subsequent generation.
The phenomenon of younger manifestation age and possibly also more severe symptoms in the following generations is called anticipation and is much more frequent in paternal transmission.

1.1.4 Pathophysiology at the whole-brain and striatal level

HD is characterized by striatal degeneration and specific neuronal loss in layers V and VI of the cerebral cortex, which disrupt network activity in several cortico-basal ganglia circuits [84]. Bilateral, symmetrical atrophy of the striatum is observed in 95% of HD brains, with the tail of the caudate being more affected than the head [10]. This, in turn, is associated with neuron loss in associated regions.

Widespread brain degeneration is apparent in end-stage autopsies. Neuronal atrophies in many regions, including hippocampus, neocortex, cerebellum, substantia nigra and brainstem nuclei is a well described feature [83, 85].

There is also diffuse loss of white matter in cerebral areas. Accordingly, patients suffer from dyskinetic movements, behavioral disorders, and cognitive defects. Volumetric MRI analyses, performed in on-going prospective studies of gene carriers or persons-at-risk reveal that the earliest atrophies still take place in the striatum and the cerebral white matter [7, 78].

Striatal atrophy is the basis for staging the severity of disease according to the Vonsattel system [85]. Striatal neurons seem more susceptible to the disease than interneurons. The medium spiny neurons, which make up 95% of the neuron population of the striatum, and their GABAergic striatal efferents are most severely affected. Other major neuronal populations, like the aspiny cholinergic neurons, are relatively preserved [22]. Defects in energy metabolism, sensitivity to oxidative stress and the cytotoxic effects of glutamate also seem to affect neuronal death in HD [41].

Subpopulations of medium spiny projection neurons are characterized by their neurotransmitter receptors, primary projection targets and coexpressed neuropeptides.

Postmortem HD brain material analysis suggests that the decline of these neuron subpopulations follows a sequential pattern. In early stages, the striato-globus pallidus externus (GPe) and striato-substantia nigra projecting neurons seem to be hit [7, 38, 85], and striato-globus pallidus internus (GPi) projecting neurons are spared until late. This temporal order of neuronal loss results in the different phases of motor function symptoms of clinical HD (please refer chapter 1.2.1: Motor Symptoms and Basal Ganglia Circuits).

The cause of neuronal cell death in Huntington’s Disease, regardless of regional patterns, is the expanded HTT gene and its product or products.

1.1.5 Physiology and Pathophysiology at the molecular level

Findings suggest that Huntington's Disease derives from either a toxic gain of function and/or a toxic loss of function of the Huntingtin protein. Huntingtin is expressed in all mammalian cells and is found widespread throughout the CNS, but also appears commonly in liver, pancreas, lungs, muscle and testes [12]. It plays an important role in neuronal differentiation during embryogenesis [90], but its adult function is not fully understood.

Wild-type Huntingtin seems to regulate the function of the cortico-striatal connection through transcription and promotion of axonal transport and vesicle delivery of BDNF (brain-derived neurotrophic factor) [72]. It scaffolds Dynein/ Dynactin to regulate transport of cell organelles in axons and dendrites within neurons. Huntingtin also seems to protect cells from autophagocytosis and apoptosis [72].

Due to the expanded polyglutamine chain in mutated Huntingtin (mHTT), the folding and spatial conformation of the protein changes. mHTT is at higher risk of proteolysis than the wildtype - in vitro experiments have shown polyglutamines are prone to aggregation, a process which proceeds faster with a higher number of polyglutamin repeats [74].

The pathophysiology which leads to selective neuronal dysfunction in HD and eventually neurodegeneration has not yet been elucidated, but several mechanisms might play key roles. Aggregates of truncated huntingtin seem to be toxic to the cell. Prolonged huntingtin aggregation leads to an unmanageable amount to degradate via proteolysis or autophagic vacuolization [61].

Mutated huntingtin can enter the nucleus [18] and perturb gene transcription [77]. In the cytoplasm, mHTT interacts with cytoskeletal elements and transport proteins, possibly causing vesicular transport trafficking to fail [13]. mHTT also interacts with proteins that regulate apoptosis, mitochondrial function, tumor suppression, and axonal transport [26, 62, 79]. Excitotoxicity through NMDA-Receptor stimulation by mHTT and following unbalanced calcium influx also seems to push cells towards death [91]. All these mechanisms might affect neuronal death in HD, and different

neuronal populations might be vulnerable to different aspects. These pathological pathways are found in similar variants in other neurodegenerative diseases, e.g. Alzheimer's' Disease and Parkinson's syndrome.

1.2 Clinical Picture and Natural History

The classic clinical triad in HD consists of 1) progressive motor disorder 2) progressive cognitive decline (dementia) 3) psychiatric symptoms (depression, anxiety, suicidal tendencies, and/or occasionally psychosis). Weight loss is a common feature and can serve as an indicator for progression as well [81].
The course of HD can be divided into premanifest and manifest phases [67]. 15-20 years before symptom onset HD patients are clinically indistinguishable from controls and may then enter a 'prodromal' period (Fig. 1).

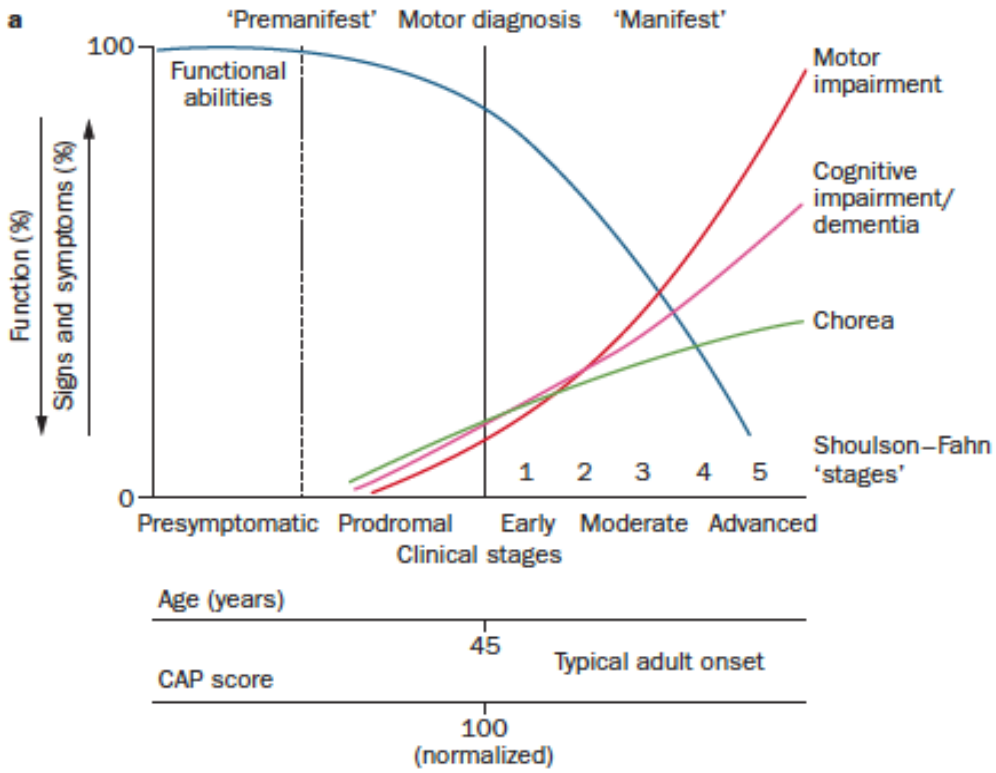

Figure 1: Periods of Huntington's Disease. (from Ross, Aylward et al. "Huntington Disease: Natural History, Biomarkers and Prospects for Therapeutics." [In eng]. Nat Rev Neurol 10, no. 4 (Apr 2014): 204-16, used with permission)

There, the relatives and partners of HD patients tend to notice subtle changes, reporting restlessness or fidgeting and that they become more irritable, while patients themselves feel they take longer to accomplish usual tasks at work [23]. Almost

always, patients are not diagnosed before visible motor symptoms become apparent [63].

1.2.1 Motor symptoms and Basal Ganglia Circuits

Generally, the motor disorder in HD can be divided into two broad areas.
The first component consists of involuntary movements, especially chorea. It is most prominent in adult or late-onset HD and gives the disease its most characteristic clinical appearance. Chorea often begins as fleeting, suppressible, random fidgety movements, most recognizable in the distal extremities [10].

With time, chorea involves larger and more proximal muscles. Particularly violent chorea can present as ballism and may result in falls and exhaustion. In the end stages, chorea tends to slow and may be replaced by severe dystonia. Patients can develop fixed, dystonic contraction of limb and axial muscles leading to immobility and contractures. Often HD patients are not aware of their involuntary movements, some deny them altogether [34, 76].

The second component involves voluntary movements, including incoordination, rigidity and bradykinesia [10]. This component is more noticeable in early-onset or rare juvenile HD as well as in the late stages of the more common adult-onset HD, progresses more steadily than chorea and also correlates better with functional ability [65, 66].

Bradykinesia means general slowness and reduced scaling of movement, mimical apraxia, less spontaneous gesturing, reduced arm swing; and small steps [24].
Fine motor skills show abnormalities early after the beginning of the clinical stages and decrease with disease progression.
Patients experience delay of movement onset, slowing of movement and imprecision in force and trajectory of movement when executed [60]. Learning of complicated motor skills is critically impaired. Loss of voluntary motor control progresses until complete inability to perform any purposeful motor act.
Saccadic eye movement occurs early and persists throughout the disease. Saccades are slow to initiate, often requiring a blink or head movement to break fixation [44].

Motor symptoms in HD patients differ greatly. Juvenile patients may lack chorea altogether. Chorea early in the adult-onset disease may change to superimposed dystonia, bradykinesia and poor postural reflexes when the disease progresses.

The basal ganglia circuit impairment in HD gives the disease its characteristic motor symptoms, and neurodegeneration in these areas can also be helpful in understanding the progression of the described symptoms.

The term basal ganglia in the strictest sense refers to nuclei set deep in the brain hemispheres (the striatum or caudate-putamen and globus pallidus), whereas related nuclei are found in the diencephalon (subthalamic nucleus), mesencephalon (substantia nigra), and pons (pedunculopontine nucleus).

The basal ganglia network can be described as multiple parallel loops and re-entering circuits whereby motor, associative, and limbic territories control movement, behavior, and emotions (Fig. 2, p. 10) [42, 55].

This architectural (structural) and functional organization is differently applied to certain systems: Firstly, the ‘goaldirected’ system, the selection of pre-frontostriatopallidal activity during performance and acquisition of new activities and tasks. Then, there is the habit system, where reinforcement learning creates habitual responses automatically performed by the motor circuit. The third is for stopping a current activity and switching to a new one if needed, which is primarily regulated by the inferior frontal cortex/substantia nigra-cortical loop.

Abnormalities and dysfunctions in these domains lead to the characteristic motor symptoms, and the motor function impairment we see in HD [6]. They can also be the cause of the obsessive-compulsive disorders and alterations of mood [80]. Reduced activity in the subthalamic nucleus-GPi projection, or focal lesions of the subthalamic nucleus can cause choreatic or ballistic movements [17].
The previously described early loss of striato-GPe projecting neurons leads to reduced activity of the subthalamic nucleus, which in turn can also be associated with involuntary movements.

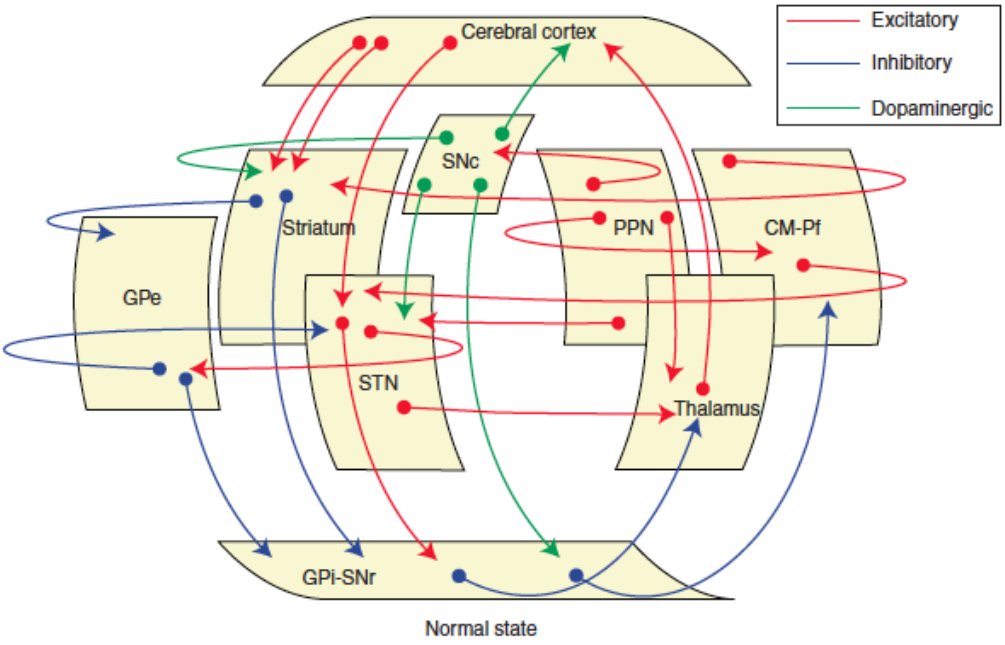

Figure 2: Schematic representation of the basal ganglia circuits; (CM-Pf = centromedian-parafascicular thalamic complex; GPe = Globus pallidus externus; GPi = Globus pallidus internus; PPN = pedunculopontine nucleus; SNc = Substantia nigra, pars compacta; SNr = Substantia nigra, pars reticulata; STN = subthalamic nucleus; from Lanciego et al., "Functional Neuroanatomy of the Basal Ganglia", Cold Spring Harb Perspect Med 2012, used with permission) [42]

The indirect pathway seems to play the major role for the induction of dyskinesia in HD.

Chorea in HD worsens over time, it peaks and declines, only to be accompanied by dystonia and bradykinesia.
These later symptoms might derive from generalized loss of striatal neurons and white matter, and neurons/nuclei from other related parts of the basal-ganglia [28].

1.2.2 Cognitive symptoms

Cognitive symptoms in HD often spare long-time memory, but impair critically needed functions like organizing, planning, ability to multi-task, focusing, and learning new skills [56]. All these dysfunctions can disrupt working ability and social life well before motor onset and gradually worsen over time.

Patients will eventually develop frank dementia. Dementia in HD presents as executive dysfunction, with initiation and perseveration of thoughts as well as

constructional praxis being impaired [58]. In contrast to Alzheimer's Disease, HD patients have better episodic memory and language function [58].

Huntington patients often times show a surprising lack of insights into their own cognitive (as well as motor) disabilities [34], which might partly be due to dysfunction of striatal neurons despite potent frontal-lobe input.

1.2.3 Psychiatric symptoms

Psychiatric symptoms vary greatly, and do not correlate with chorea or cognitive decline, nor do they show a steady progression. Patients suffer from affective illness, anxiety disorders, delusional behavior and occasionally even hallucinations [57]. Manic symptoms can develop. In retrospect, relatives of HD patients often recognize personality changes years before diagnosis, describing irritability, outbursts and obsessive-compulsive behavior [23].
Depression in HD is typical and suicide risk is estimated to be about 5-10 times that of the general population [2].

1.2.4 The Westphal variant

The Westphal variant of Huntington's disease (HD) is a distinct clinical entity of HD characterized by a rigid-hypokinetic syndrome and is associated with a juvenile onset of disease (< 20 years) (please refer chapter 1.1.3, p. 4). It shows a more progressive course of disease and may present seizure disorders and myoclonus. As described, it is characterized by longer triplet repeat length, often through paternal transmission.

1.3 Treatment of HD

1.3.1 Symptomatic Treatment

There is currently no cure for HD. Despite research advances in the understanding of the molecular process, there is currently no drug to halt or even slow clinical progress.

Some symptoms can be treated pharmacologically, whereas others can be adressed through non-pharmacologic measures.

Most approachable with drug treatment are psychiatric symptoms and prominent chorea. Dopamine receptor blockers have been prescribed the most, e.g. risperidone or olanzapine, intended to treat outbursts, irritability and psychosis.
Antichoreic drugs such as tetrabenezine offer patients with severe chorea some respite from their constant involuntary movements [73].

Of essential matter is counselling of patients, partners, relatives and caregivers. Frank discussions are needed to help cope with the complex issues of family, career and financial planning.

1.3.2 Disease-Modifying Drugs

As of yet, there are no disease modifying drugs for HD.
But for the first time, HD affected patients and families can lay hope on new drugs altering the mHTT producing mechanism, aspiring to stop the process which causes the disease.

Studies are underway testing huntingtin lowering drugs, the prime example being ‘HTTRx’, which is an antisense oligonucleotide that sticks to the mutated Huntingtin gene mRNA, rendering it unable to be read [64]. HTTRx is applied per intrathecal injection at 4 week intervals for a 13 week treatment period. This phase II study was completed in October 2017 [National Clinical Trial (NCT) 02519036].

1.4 The UHDRS

The Unified Huntington’s Disease Rating Scale, or UHDRS is a multidimensional Rating System to quantify the severity of Huntington’s Disease symptoms [37]. It was developed to allow a standardized and comparable assessment of HD symptoms and progression. The autonomy, overall capability and the psychological findings as

well as the cognitive abilities and the motor status of the Huntington patients are assessed. It is divided into six subsections:

Motor Assessment
Cognitive Assessment
Behavioral Assessment
Independence Scale
Functional Assessment
Total Functional Capacity

For each section, a score is generated. An examined health worker interviews, observes and tests the patient and summarizes each item score for the different subsections. An example of the motor questionnaire of the UHDRS can be found in the appendix.

For the purpose of this thesis I will focus on the Motor assessment and the TFC.

1.4.1 Motor Assessment

The motor part of the UHDRS consists of 15 subitems, each of which is rated on a 0-4 scale by best estimation of the assessing physician. 0 means normal movement, 4 is severely pathological [71]. The full UHDRS Motor Assessment Scale as used in our study can be found in the Appendix. Fingertapping and Pro/Supination of hands is listed in the UHDRS as follows:

FINGER TAPS (right and left):

0 = normal (≥15/5 sec.)
1= mild slowing and or reduction in amplitude (11-14/5 sec.)
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5 sec.)
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements (3-6/5 sec.)
4 = Can barely perform the task (0-2/5 sec.)

PRONATE/SUPINATE-HANDS (right and left):

0 = normal
1 = mild slowing and/or irregular
2 = moderate slowing and irregular
3 = severe slowing and irregular
4 = cannot perform

These were the two items we approached with our electronic motion capture program.

1.4.2 Total Functional Capacity Scale and 'Shoulson and Fahn' – Scale

The progression of the disease is documented and assessed with the total functional capacity scale (as shown below). This scale is included in the UHDRS [37] and reflects functional status and the degree of independence of a person in 5 areas: Work, Handling Finances, Housekeeping, Activities of daily Life, and the Need for Care. The TFC is assessed in a personal conversation, supplemented by details of relatives and caregivers if necessary and possible.

Each area is rated 0 – 2, or 0 – 3. The scale ranges from 0 - 13, with higher values representing better functionality. In prodromal HD however, the TFC has been shown to not be sensitive enough to early changes [9].

FUNCTIONAL CAPACITY :

- OCCUPATION
  0 = unable 1 = marginal work only 2 = reduced capacity for usual job 3 = normal

- FINANCES
  0 = unable 1 = major assistance 2 = slight assistance 3 = normal

- DOMESTIC CHORES
  0 = unable 1 = impaired 2 = normal

- ADL
  0 = total care 1 = gross tasks only 2 = minimal impairment 3 = normal

- CARE LEVEL
  0 = full time skilled nursing 1 = home or chronic care 2 = home

The Shoulson and Fahn-Scale divides the TFC score into 5 stages of the disease, in which lower values represent better functionality (Table 1, Fig. 1, p. 7). Importantly, these stages are purely descriptive characterizations based on continuously changing functional capacity rather than on biology.
This staging does not relate to biological events with specific implications for prognosis and treatment.

Table 1: Shoulson and Fahn – Scale (TFC= total functional capacity)

TFC Score	Stage
11-13	I
7-10	II
3-6	III
1-2	IV
0	V

1.4.3 Differences between disease markers

There are different types of disease markers to describe. What is a biomarker?
In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”[1]

When used as outcomes in clinical trials, biomarkers are considered to be surrogate endpoints; that is, they act as surrogates or substitutes for clinically meaningful endpoints. But, not all biomarkers are surrogate endpoints, nor are they all intended to be. Biomarkers as surrogate endpoints need constant re-evaluation since we as of yet do not fully understand the biological molecular processes behind them.

A trait marker represents the properties of the behavioral and biological processes that play an antecedent, possibly causal, role in the pathophysiology of a neurological or psychiatric disorder, whereas a state marker reflects the status of clinical manifestations in patients.

1.5 Challenges for trial design

The availability of a pipeline of promising drug candidates brings new urgency to the problem of quantifying motor symptoms in HD. Our goal was to address the following thematic: How can disease severity and progression in HD – focusing on the motor symptoms - be objectively measured?
The study aimed to compare measuring methods – electronically and manually by a physician - of simple, single motor tasks (single UHDRS items) and compare them to the total functional capacity. Can they serve as an objective state or trait biomarker in HD?

We took advantage of the fact that almost all HD patients at the Ulm Outpatient Clinic are participating in the ENROLL-Study, and its predecessor, the REGISTRY-Study. The ENROLL-HD (NCT01574053; REGISTRY in europe) study is a worldwide prospective observational study of HD patients and families. These studies give powerful tools to observe clinical progress and investigate the effects of certain drugs, infections or other factors. Participants are assessed regularly with the UHDRS.

1.6 Hypothesis

Given that finger taps [3, 50, 68] and (dys-) diadochokinesis [52] are two relatively strong simple markers for motor impairment and movement changes in HD, I hypothesized that measurement of these two objectively on an electronic motion detection device could be just as valuable and reliable as the UHDRS in assessing clinical presentation and progress of motor symptoms.

It could be, further validated, a useful tool for self-evaluation for HD patients.

I wanted to examine if our objective tests on a handheld electronic device (i.e. a relatively new-generation smartphone) could
i) generally show differences between patients and controls
ii) show correlation with HD patients total functionality scale and thereby functional stage
iii) be an adequate objective tool of measurement of two specific UHDRS motor scale items (1.fingertapping – 2. pro/supination cycles).

Furthermore, the impact of age and sex was analyzed.

2. Methods

2.1 Study Design

The HD cohort consisted of 39, [23 male and 16 female] patients which were recruited from the Outpatient clinic at the RKU Neurology Department. The age ranged from 22 to 80 years old with an average of 53.25 (SD 12.28). The control group consisted of 25, [9 male and 16 female] persons with an age average of 42.66 (range 27 – 74, SD 12.27).

Controls with no known neurological diseases were recruited from friends or family accompanying patients to the clinic and clinic staff. We captured two movement patterns from our test subjects in three steps with a handheld electronic motion capturing device (further described in the next chapter) by a standardized protocol starting with the first patients during their control visits in March 2014 until April 2017. The investigations were carried out with approval of the Ulm Ethics Committee of 28 June 2017 (Application 87/2014).

Everyone from the HD cohort was either a manifest HD Patient who was seen on a regular basis in Ulm or a premanifest diagnosed carrier of CAG Repeats >36 and who had at least one study visit. Missing data of any sort was not replaced.

	HD	Control
n (m/f)	39(23/16)	25 (9/16)
age (+/-SD)	53.25 (14,39)	42,66 (12,27)
TFC (+/-SD)	9.5 (3,52)	-

Medical treatment of the patient study group was not recorded at any time.

2.2 Fingertapping and Pro-/Supination Cycles: The gMed App

We used a custom-made electronic motion capture smartphone app to assess participants:

It was programmed especially for this project for devices with in-built motion detection sensors. It uses the android system and can function on any android smartphone.

Our App was modeled after selected items from the UHDRS motor test. The UHDRS motor score test items includes finger tapping and pronation/supination (left and right), gait, tongue protrusion and tandem walking [37]. The App was designed to imitate two motor test items: the finger tapping and pronation/supination cycles (UHDRS Appendix 2, Finger taps 1-4; Pro/Supinate Hands 0-4).

Both are performed in a set time frame (5 seconds; 10 seconds; 30 seconds). It was developed as a simple touchscreen recognition and gravity detection software and uses the in-built gravity sensor (Tri-Axis Digital Accelerometer [15]) of current smartphones.
It recognizes rapid tapping on the screen and counts each individual tap. It uses the built-in gravity sensor to sense rotation cycles while the test person performs pronation and supination alternately if the device is held in hand.

Participants were instructed to tap as fast as they could with their index finger on any part of the touchscreen for 30 seconds, first with the right and then the left hand, with the phone lying on an open table in front of them (Fig. 4A-B, p. 20).
After, they were instructed to perform 30 seconds of alternating pro- and supination cycles as fast as possible while holding the phone in the testing hand (Fig. 5A-B, p. 21). The results were sent real-time from the smartphone to our self-developed software program and database on a laptop nearby.

The total number of taps and the total number of cycles counted, as well as the time in between was recorded and shown as graphs. The gMed Software depicted the data as shown on the next page (Fig 3A-C, p. 20).

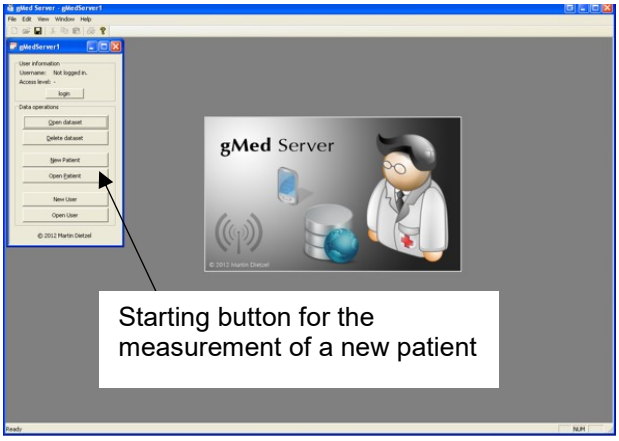

Figure 3A: gMed Opening Screen (RKU Ulm, 2014)

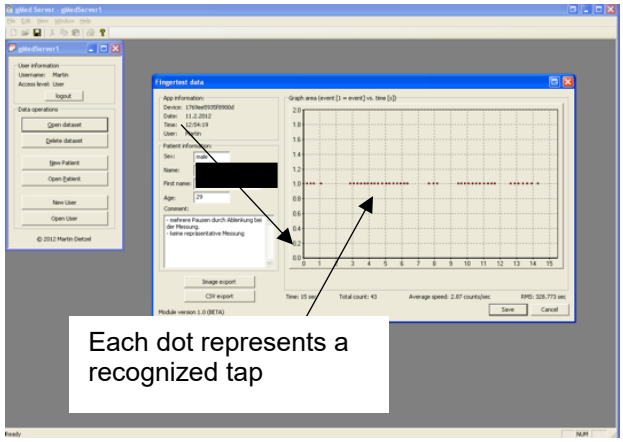

Figure 3B: Example of a Fingertap Test (RKU Ulm, 2014)

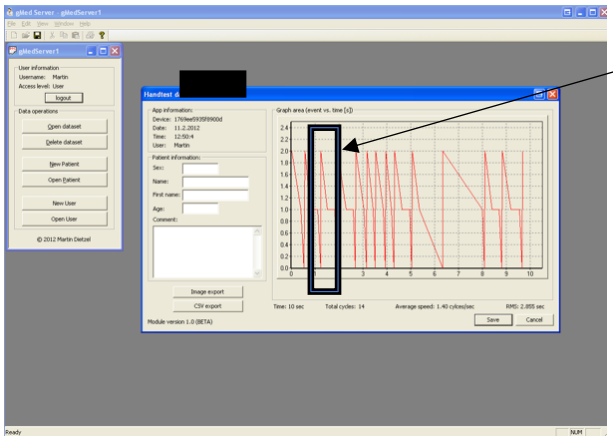

Figure 3C: Example of a Handrotation Test (RKU Ulm, 2014)

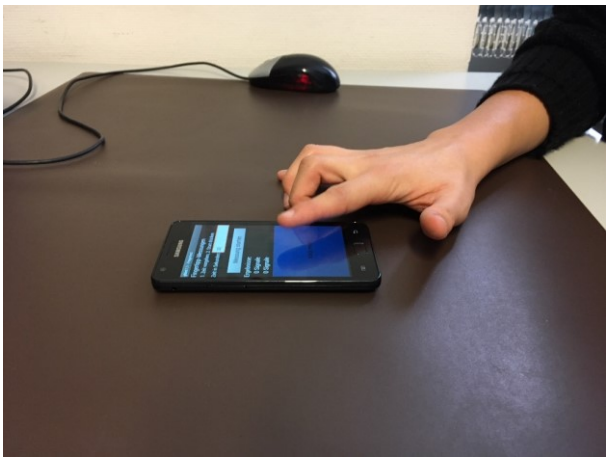

Figure 4A (and 4B): Example Setup of a Fingertap Test (RKU Ulm, 2017)

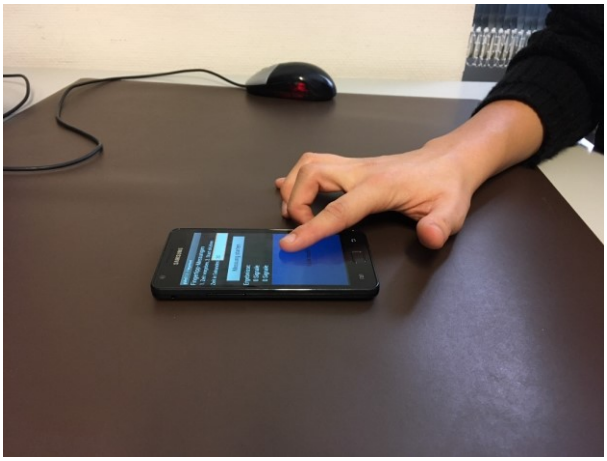

Figure 4B

Figure 5A (and 5B): Example of a Handrotation Test (RKU Ulm, 2017)

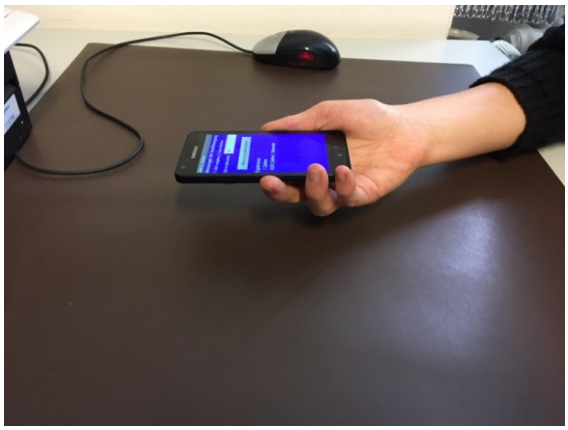

Figure 5B

The data set for each patient included:

1. Age
2. Sex
3. Tapping: Total Count per 30s
4. Tapping: Average (counts/sec)
5. Pro/Supinate Cycles: Total Count per 30s
6. Pro/Supinate Cycles: Average (cycles/sec)
7. UHDRS motor item score: Tapping 0-4
8. UHDRS motor item score: Pro/Supinate Hands 0-4
9. TFC Stage 1-5 (from UHDRS)

Each data set was saved in excel tables. We tested the subject's right hand first, the left hand after. An example data set of one HD patient is shown on the next page (Table 2).

Table 2: example data set of a male patient (RKU Ulm, Huntington Outpatient Clinic, 09/2015) (fingtapr = UHDRS motor item ‘tapping’ score right hand; fingtapl = UHDRS motor item ‘ tapping’ score left hand; prosupr = UHDRS motor item ‘pro/supination’ score right hand; prosupl = UHDRS motor item ‘pro/supination’ score left hand)

Name	----------
Dataset Nr.	169
ENROLL NR	xxx-xxx-xxx
Age	54
Sex	m
Date	29.09.2015
Hand tested	Right hand
Time Fingertest	30s
Total Tap Count	114
Average Speed (counts/sec)	3.80
Time Handtest	30s
Total Cycle Count	46
Average Speed (cycles/sec)	1.53
visit date UHDRS	29/09/15
TFC score	9
fingtapr	2
fingtapl	2
prosupr	2
prosupl	2
HD Stage	stage II

2.3 Statistical Analysis

All statistical analysis was done using standard spreadsheet and statistics software (Microsoft Excel, Graph Pad Prism [27]). The tests were performed as indicated. Due to non-Gaussian distribution, the correlation coefficient according to Spearman (r) is used for the correlation analysis in the X and Y tables. For ANOVA analysis, values were transformed logarithmically (Y=log(Y)).
Results were considered statistically significant if $p < 0.05$.

3. Results

3.1. The Study Group

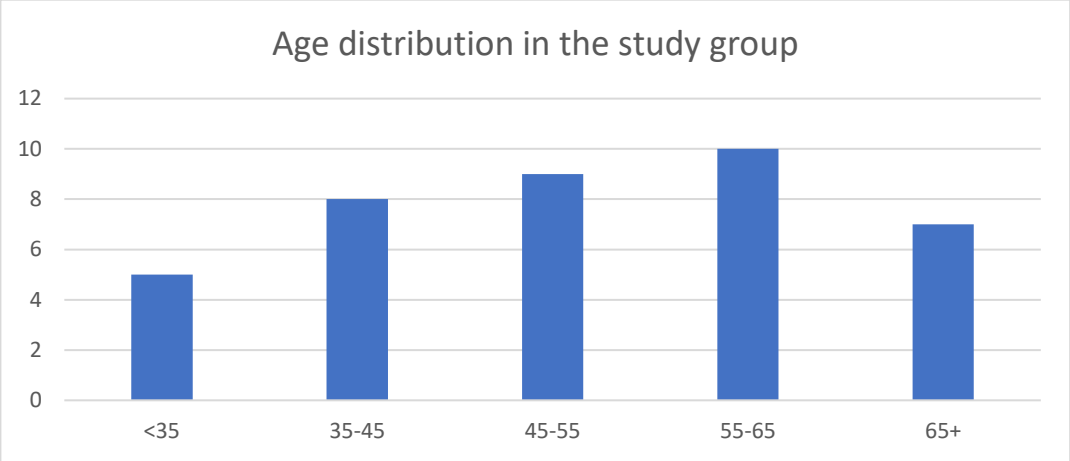

Figure 6: Age (x-axis) distribution in the study group by 10-year differences between 35 and 65, y-axis = number of patients
(RKU Ulm, Huntington Outpatient Clinic, March 2014 – April 2017)

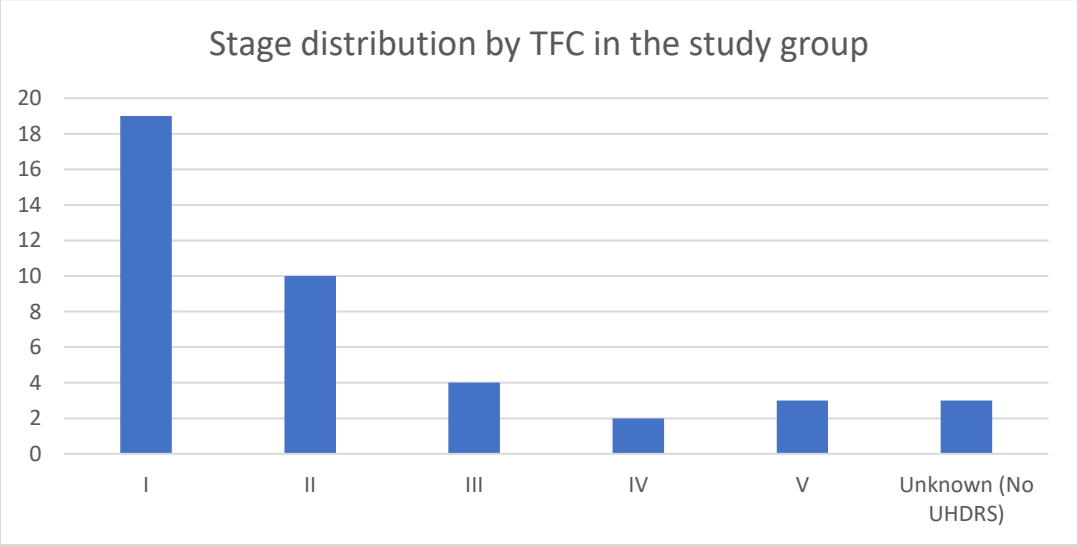

Figure 7: HD (Huntington's Disease) stage (x-axis; calculated by total functional capacity) distribution in the study group 1-5; (Stage I (n=19), stage II (n=10), stage III (n=4), stage IV (n=2), stage V (n=2), and unknown stage (n=3); (y-axis = number of patients) (RKU Ulm, Huntington Outpatient Clinic, March 2014 – April 2017)

From the HD patients, the UHDRS score assessed closest to the electronic motion capture measurement date was collected. Most scores (>80%) were assessed in a 3 months span near the finger/handtest performance, and more than half were assessed with the UHDRS on the same day. The Shoulson and Fahn-Scale stage

was calculated according to the UHDRS. Most patients fell into categories of mid-to-earlier stages (Fig. 7, p. 24).

3.2. Fingertapping Results

We divided the fingertap data sets into different groups. This table (Table 3) shows the basic data for right hand taps in 30 seconds.

Table 3: Right hand index finger taps in 30 seconds, HD patients vs. control (HD=Huntington's Disease) (RKU Ulm, 2014-2017)

	HD (all stages)	control	Mann-Whitney U	p-value
Number of values	39	25	133.5	<0,0001
Mean	119,7	172,8		
Std. Deviation	47,27	27,63		
Std. Error of Mean	7,771	5,525		

Firstly, when looking at total tap counts per 30 seconds, there is significant difference between HD patients and controls (refer Tbl. 3 and Fig. 8). HD patients could perform significantly less taps on the touchscreen in 30 seconds with either hand. Figures 8 and 9 show the boxplots of total tap count per 30 seconds from either hand of HD patients compared to controls.

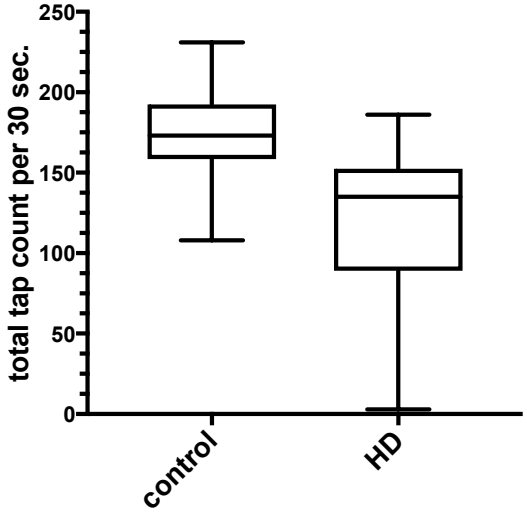

Figure 9: Boxplots of total number of taps in 30 seconds, HD(Huntington's Disease) patients (n=39) vs control (n=25) (RKU Ulm, 2014-2017)

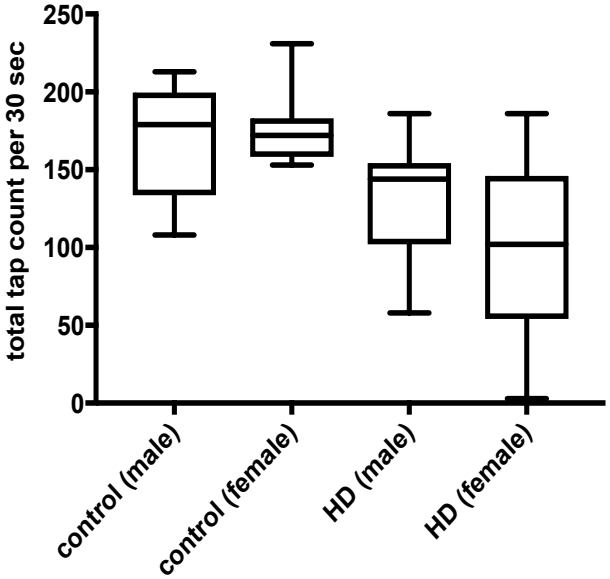

Figure 8: Boxplots of total number of taps in 30 seconds by sexes, HD(Huntington's Disease) patients (n=39) vs. control (n=25) (RKU Ulm, 2014-2017)

Control persons had a measurably higher number of total taps in our test, regardless of gender as well (Fig. 9, p. 25). In all box & whiskers graphs shown, the box always extends from the 25th to 75th percentiles. The whiskers in our graphs are set from the minimum to maximum tap number from each group. The line in the middle of the box is plotted at the median.

Looking at the comparison for each single hand, the correlation of the right hand UHDRS item score and the objectively measured right hand tap count by our device produced a spearman r value of r = -0,5442, the left hand correlation between these two showed r = -0,8027 (Fig. 10, 11).

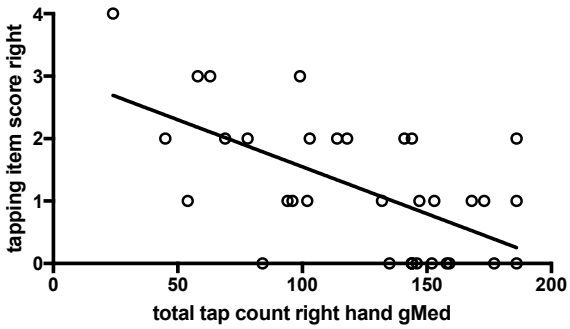

Figure 10: total tap count right hand correlates with UHDRS (Unified Huntington's Disease Rating Scale) right hand tapping item score in HD (Huntington's Disease) patients (r = -0,5442; p = 0,0009, n=39) (RKU Ulm, 2014-2017)

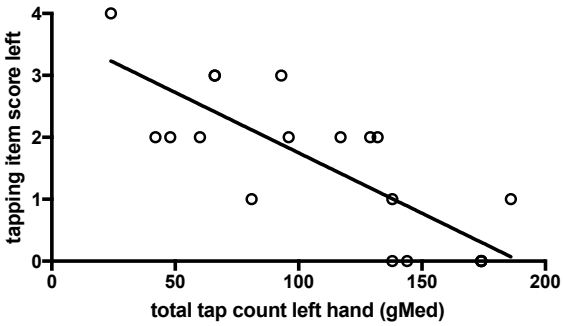

Figure 11: total tap count left hand correlates with UHDRS (Unified Huntington's Disease Rating Scale) left hand tapping item score in HD (Huntington's Disease) patients (r = -0,8027, p < 0,000, n=22) (RKU Ulm, 2014-2017)

When comparing fingertaps from both hands of patients to their 'tapping' item score together, Fingertapping scores measured with the electronic device correlate strongly (p < 0,0001) with the respective UHDRS item "tapping" score (Scale 1-4) (Fig. 12).

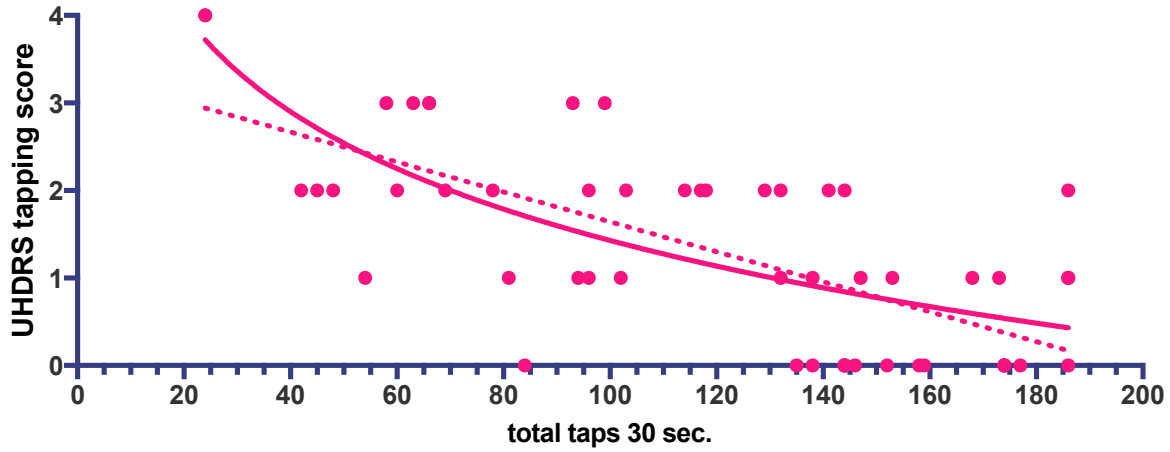

Figure 12: fingertapping scores from both hands correlate with their UHDRS (Unified Huntington's Disease Rating Scale) item score (r = -0,6737, p < 0,0001) (RKU Ulm, 2014-2017)

3.2.1 Fingertapping and Total Functional Capacity (=Stage)

Looking at the tap count by stage, mean tap count decreases from stage I to III (Table 4).
Notably, the tap count is still relatively stable from stage 1-4 and then shows a sudden decline as the participants are no longer able to easily perform the test and/or generate an exceptionally low tap count (Fig. 13).

Table 4: Mean tap counts by HD (Huntington's Disease) stage (RKU Ulm, 2014-2017)

	stage I	stage II	stage III	stage IV	stage V	unknown
Number of values	19	10	4	2	2	2
Minimum	54	45	48	103	3	126
25% Percentile	102	64	60	103	3	126
Median	144	106,5	107	123,5	13,5	135,5
75% Percentile	159	142,3	144,3	144	24	145
Maximum	186	186	153	144	24	145
Mean	136,3	105,9	103,8	123,5	13,5	135,5
Std. Deviation	38,2	48,07	43,96	28,99	14,85	13,44
Std. Error of Mean	8,764	15,2	21,98	20,5	10,5	9,5
Sum	2590	1059	415	247	27	271

n = 4 patients classified as the late stages IV-V. Our Stage IV-classified patients performed relatively well.

In Tukey's test of comparison for differences among means all stages were significantly different compared to stage V. Comparing the other stages (1-4) showed no statistical significance (Table 5).

Table 5: Tukey's test of comparison, tap columns by stage (RKU Ulm, 2014-2017)

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Adjusted P Value
stage I vs. stage II	0,1314	-0,1061 to 0,369	No	0,5585
stage I vs. stage III	0,1338	-0,2007 to 0,4684	No	0,8292
stage I vs. stage IV	0,02823	-0,4239 to 0,4803	No	>0,9999
stage I vs. stage V	1,185	0,7331 to 1,637	Yes	<0,0001
stage II vs. stage III	0,002368	-0,3574 to 0,3621	No	>0,9999
stage II vs. stage IV	-0,1032	-0,5743 to 0,3679	No	0,9848
stage II vs. stage V	1,054	0,5827 to 1,525	Yes	<0,0001
stage III vs. stage IV	-0,1056	-0,6322 to 0,4211	No	0,9898
stage III vs. stage V	1,051	0,5247 to 1,578	Yes	<0,0001

stage IV vs. stage V	1,157	0,5488 to 1,765	Yes	<0,0001

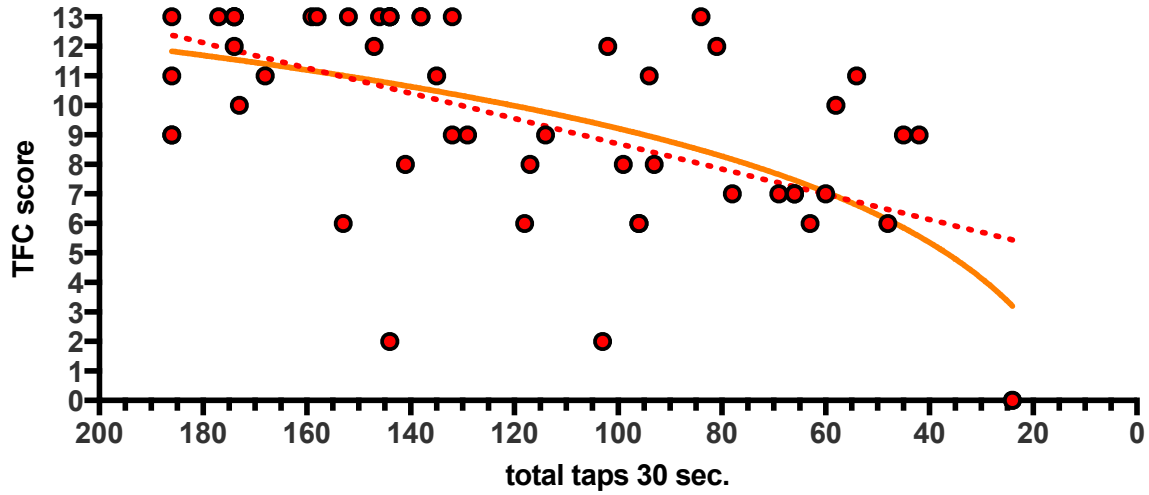

Figure 13 : fingertapping scores from both hands correlate with total functional capacity (r = 0,5604, p < 0,0001) in HD (Huntington's Disease) patients (n=39) (RKU Ulm, 2014-2017)

Importantly, from any stage, the total number of taps in 30 seconds correlated with the independence score, the total functional capacity of the patient; r = 0,5604, p < 0,0001 (Fig. 14).

Figure 14 also shows the slight decline of tap count with decreasing total functional capacity (and thereby higher stage of disease).

3.3 Pro-/Supination Rotation Results

We divided the pro/supination data sets into different groups: HD patients (n=36, 3 sets incomplete) and controls (n=25). From each group, basic statistic values were determined. This table (Table 6) shows the basic data for right hand cycles (alternating pro/supination as fast as possible) in 30 seconds.

Table 6: Hand rotation (pro/supination) count in 30 seconds; HD (Huntington's Disease) patients vs. control (RKU Ulm, 2014-2017)

	HD	control	Mann Whitney U	p-value
Number of values	36	25	170	<0.0001
Mean	40,33	75,92		
Std. Deviation	27,95	30,55		
Std. Error of Mean	4,659	6,11		

Lower 95% CI of mean	30,88	63,31
Upper 95% CI of mean	49,79	88,53

The mean count of patients is significantly lower than controls (refer Table 6). Figures 15 and 16 depict the boxplots of mean cycle count between groups and by sex.

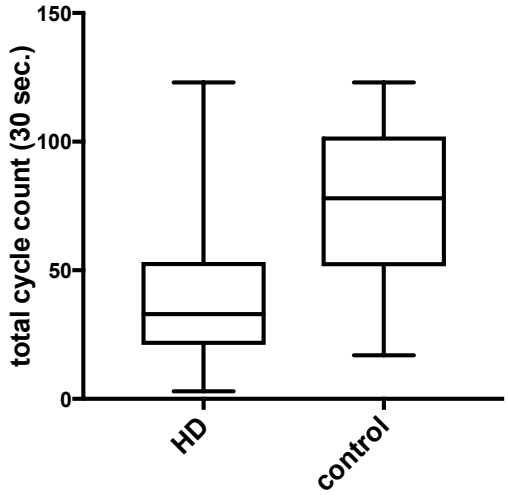

Figure 14: Boxplots of total cycle count (pro/supination) in 30 sec., HD (Huntington's Disease) patients vs control (RKU Ulm, 2014-2017)

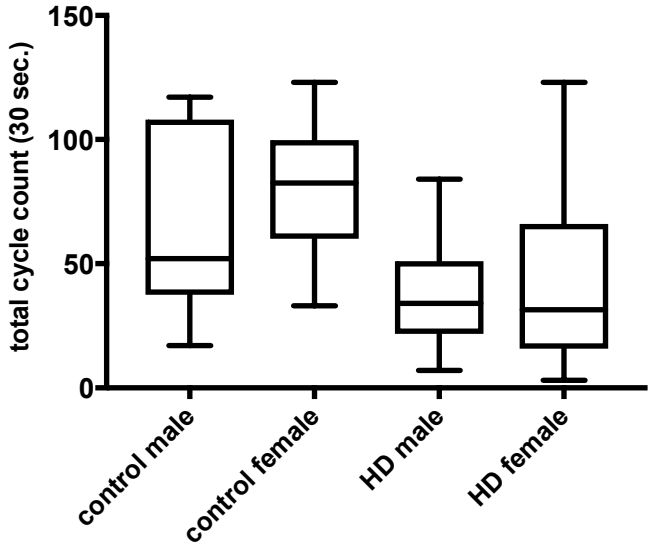

Figure 15: Boxplots of total cycle count (pro/supination) in 30 sec. by sexes, HD (Huntington's Disease) patients vs control (RKU Ulm, 2014-2017)

The assessed UHDRS item score of pro/supinate hands of the HD patients (ranging from 1-4) correlated strongly with the respective cycle count of the electronic motion capture device (Fig. 17 and 18). The left-hand correlation (cycle count gMed left hand - UHDRS item left hand) showed a spearman r value of r = -0,92, the right hand (cycle count gMed right hand – UHDRS item right hand) comparison produced r = -0,5414 (Fig. 17 and 18).

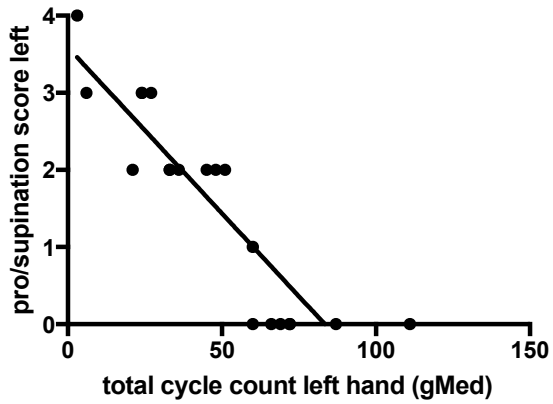

Figure 16: Left hand cycle count correlates with respective UHDRS (Unified Huntington's Disease Rating Scale) item score (r = - 0,9252, p < 0,0001) (RKU Ulm, 2014-2017)

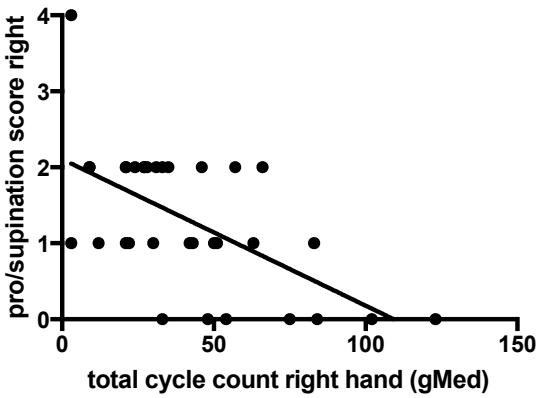

Figure 17: Right hand cycle count correlates with respective UHDRS (Unified Huntingon's Disease Rating Scale) item score (r = -0,5414, p < 0,0011)(RKU Ulm, 2014-2017)

When not focusing on a specific side, item score and electronically assessed cycle count presents the following Figure (Fig. 19); the parameters correlate inversely with the r-value of -0,687:

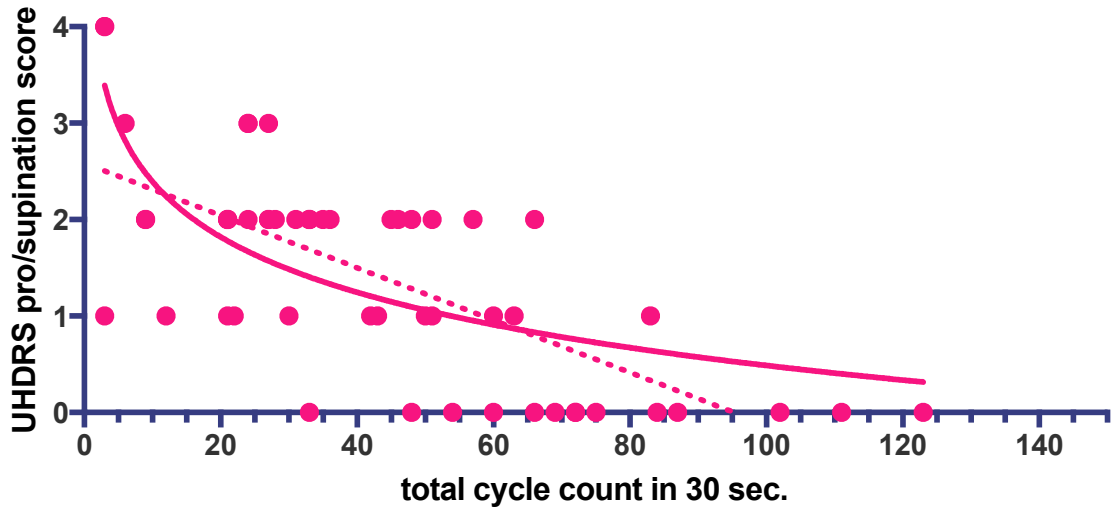

Figure 18: Total cycle count measured with an handheld electronic motion device correlates with respective UHDRS (Unified Huntington's Disease Rating Scale) item scores (r = -0,687, p<0,0001) (RKU Ulm, 2014-2017)

3.3.1 Pro/Supination Rotation Count and Total Functional Capacity (=Stage)

When looking at the hand rotation count means measured in the different stages, there is an apparent decline as well (Fig. 20). Subjects classified as later stages of HD with the UHDRS performed less rotation cycles. The decline from stage 1-3 in

absolute medians is constant compared to the tapping test (Fig. 20, refer Fig. 13, p. 27). Like tapping, a sudden drop occurs in stage V patient scores (Fig. 20)

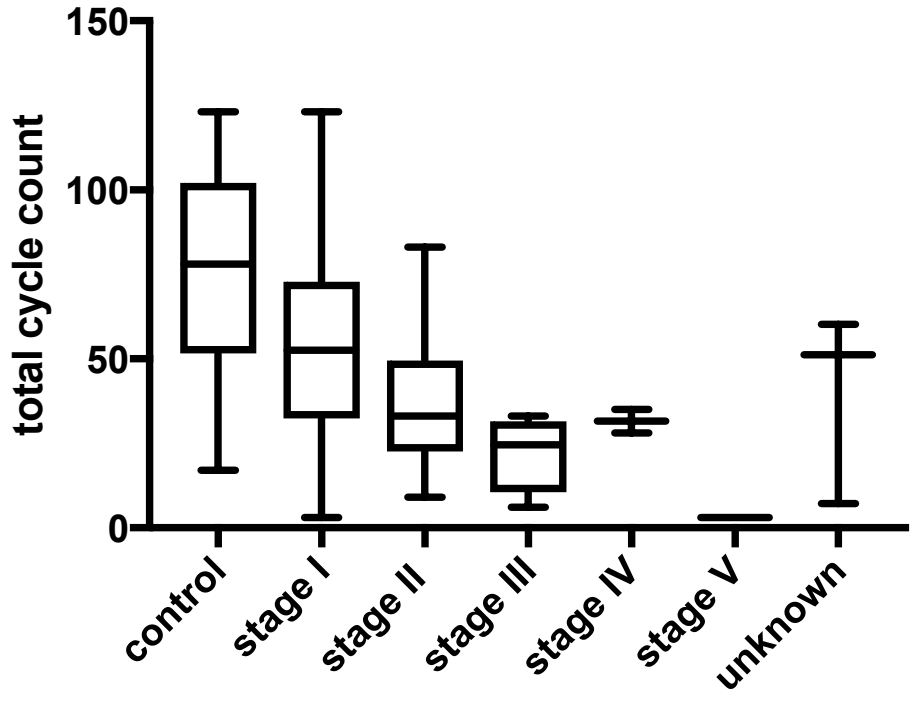

Figure 19: boxplots of cycle count by stage (RKU Ulm, 2014-2017)

Values were transformed (Y=log(Y)) for analysis with ANOVA. In Tukey's test of comparison, the means of all
stages were significantly different to the last stage (V), while there was no significant difference between the others (Table 7).

Table 7: Table 7: Tukey's Test of Comparison, Cycle count by stage (RKU Ulm, 2014-2017):

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Adjusted P Value
stage I vs. stage II	0,1559	-0,1354 to 0,4472	No	0,6113
stage I vs. stage III	0,3795	-0,04345 to 0,8024	No	0,1022
stage I vs. stage IV	0,1574	-0,5279 to 0,8426	No	0,9833
stage I vs. stage V	1,176	0,4906 to 1,861	Yes	<0,0001
stage II vs. stage III	0,2236	-0,2198 to 0,667	No	0,6696
stage II vs. stage IV	0,001456	-0,6966 to 0,6995	No	>0,9999
stage II vs. stage V	1,02	0,3219 to 1,718	Yes	0,0010
stage III vs. stage IV	-0,2221	-0,9846 to 0,5403	No	0,9534
stage III vs. stage V	0,7964	0,03394 to 1,559	Yes	0,0359
stage IV vs. stage V	1,018	0,0847 to 1,952	Yes	0,0251

The total rotation count measured in 30 seconds per App correlated strongly with the total functional capacity of the assessed UHRDS of the HD patients (r = 0,6182, p > 0,0001) (Fig. 21).

Figure 21 includes a fitted nonlinear semilog curve, depicting the decreasing hand rotation count with declining total functional capacity.

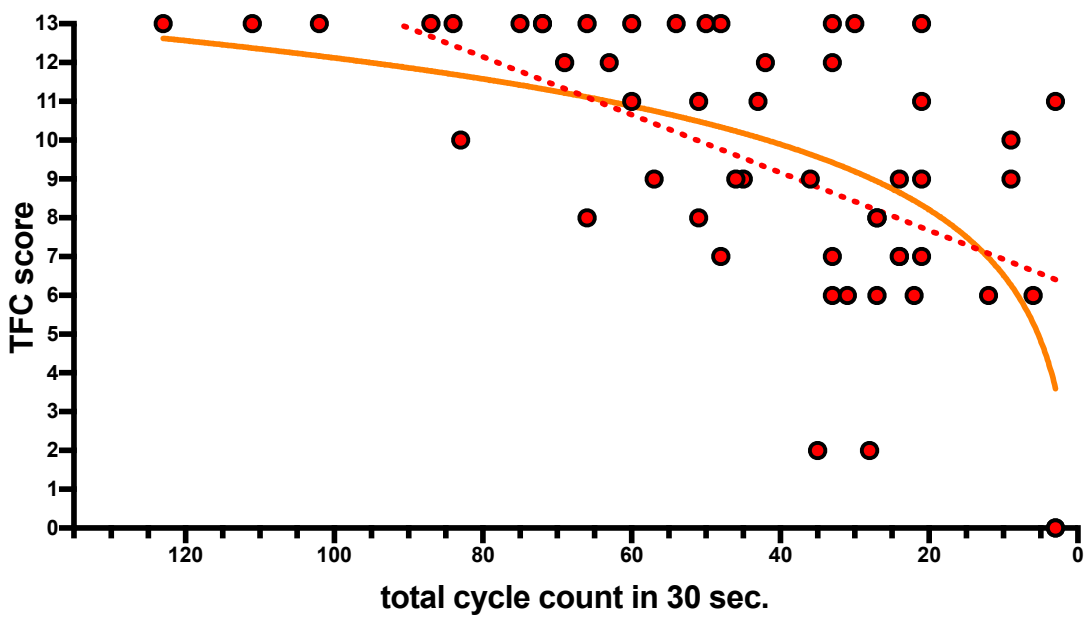

Figure 20: Hand cycle counts measured with gMed App correlates with total functional capacity (r = 0,6182, p < 0,0001).

3.5. Fingertapping and Age

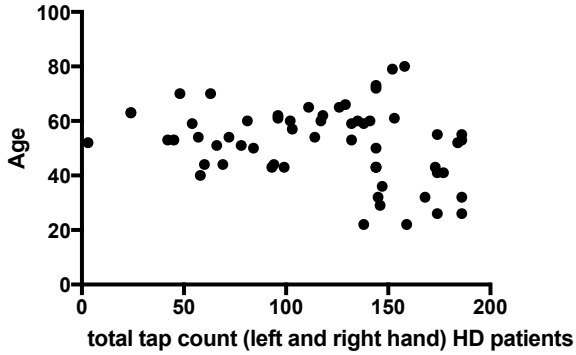

Figure 21: In the HD (Huntington's Disease) group, age correlates slightly with tap count in 30 seconds (n=39) (RKU Ulm, 2017)

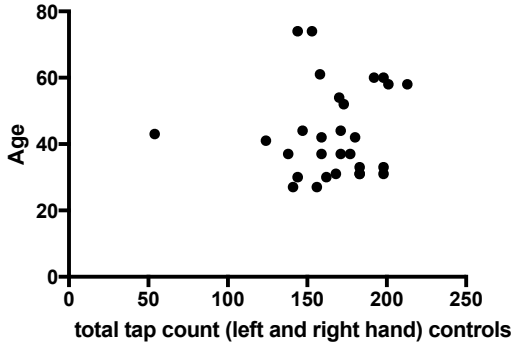

Figure 22: Age does not correlate with tap count in the control group (n=25) (RKU Ulm, 2017)

In HD patients, age correlates in an inverse manner with the index finger tap count measured by the gMed App in 30 seconds (Fig. 22; r = -0,291, p = 0,0254) while this is not true for the control group (Fig. 23; r = 0,0938, p = 0,628; Fig. 24). All Figures (Fig. 22-24) show on the y-axis age in years and on the x-axis their tap count from each hand in 30 seconds.

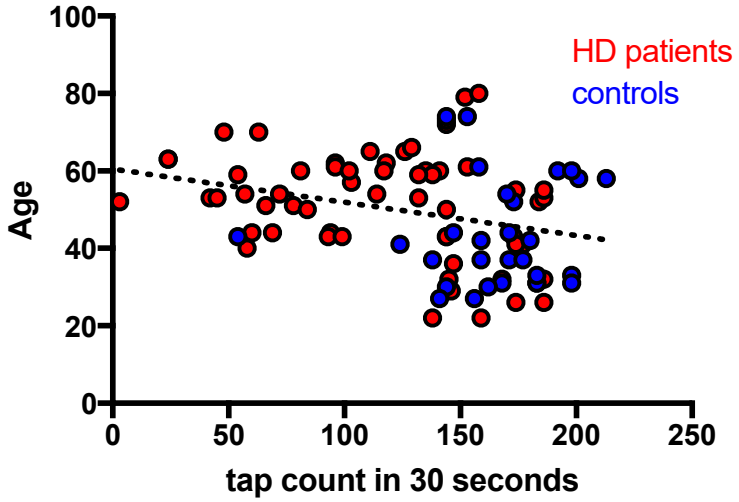

Figure 23: The tap count from HD (Huntington's Disease) patients correlates with age, but not controls (RKU Ulm, 2014-2017)

3.6 Pro/Supination Rotation Count and Age

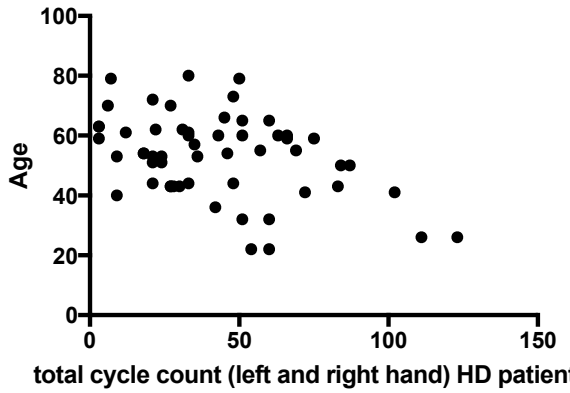

Figure 24: In the HD (Huntington's Disease) group, age correlates slightly with hand rotation count (n = 39) (RKU Ulm, 2017)

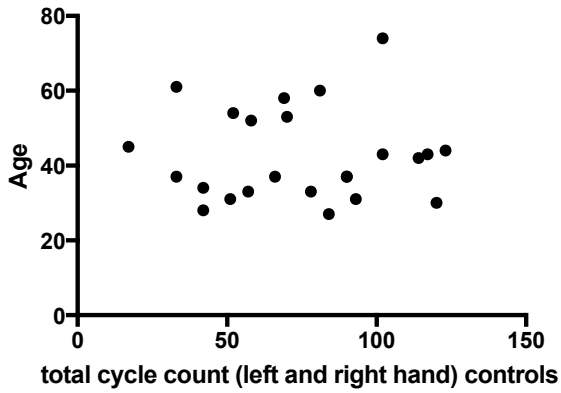

Figure 25: Age does not correlate with total cycle count in 30 sec. in the control group (n = 25) (RKU Ulm, 2017)

Hand rotation performance (=cycle count) also correlates inversely with age in the HD group (Fig. 25: r = -0,3192; p = 0,0165). This is not the case for the controls (Fig. 26: r = -0,0248, p = 0,9802). On all Figures (25-27) the y-axis shows age in years.

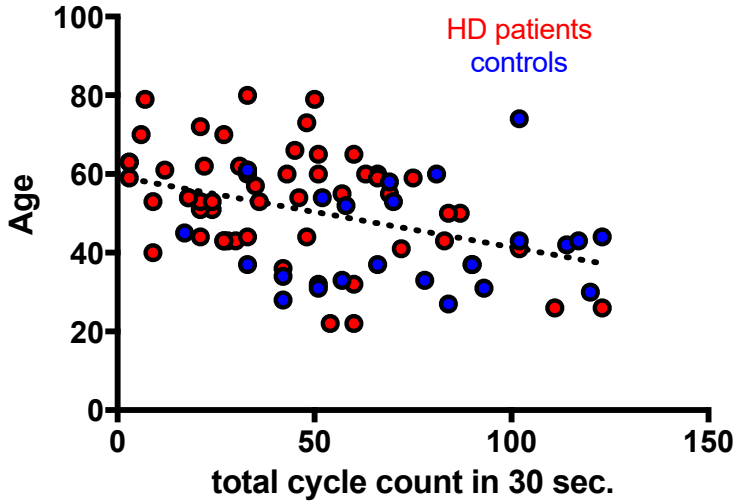

Figure 26: rotation cycle count and age, HD (Huntington's Disease) patients vs. control (RKU Ulm, 2014-2017)

4. Discussion

In the present thesis I tested the hypothesis that the movement disorder of HD can be captured and quantified with a simple handheld motion detection device. I found that the objective measurement of two distinct movement patterns, fingertapping and pro/supination, can distinguish robustly between symptomatic and non-symptomatic individuals and correlates with the total functional capacity measured by the UHDRS.

This finding has important practical implications. The quantitative assessment of motor phenotype in HD is the prerequisite for any therapeutic or symptomatic intervention trials. The available methods and tools are very limited in their sensitivity and specificity. Thus the development of useful tools is an urgent research priority in the field. This challenge has been approached in a number of ways:
Several studies indicate simple motor tasks as a useful marker for progression of HD over time [3, 14, 52, 69]. Some versions of these tests are computer-based, but the methodologies vary widely.

Garcia Ruiz and colleagues tested HD patients and controls during the CAPIT (Core Assessment Protocol for Intracerebral Transplantation) protocol [43], including finger dexterity, pro/supination, movement between two points “MTP” (=tapping), and gait tests and found them significantly different – also the results, similar to our results, showed correlation to the total functional capacity of patients [24].

Michell, Goodman and colleagues researched the relation between whole-hand tapping of two 30cm apart buttons in 30 seconds of HD patients in Cambridge with their motor UHDRS score and independence score in 2007 [50]. Not only did they find it well correlated with the UHDRS motor items and functionality scale – it also showed high reproducibility [50]. Collins and colleagues also proved tapping to be a reproducible parameter in their following longitudinal study in 2014 [14].

Diadochokinetic movements also differ significantly between HD patients and controls [52]. All these tests take the reductionist approach of measurement of a

simple movement that is specifically impaired in HD and use this as an index of motor status.

For my study I selected fingertapping and pronation/supination for two reasons: a) these two had emerged as the most sensitive items in the (motor assessment of the) UHDRS and were put forward as candidates for a simplified test battery [49] and b) conveniently they are two items that can by far be most readily emulated on a cell phone.

4.1 Tapping

Fingertapping is an elementary, uncomplicated movement. PET-Scans measuring regional cerebral blood flows have localized the functional anatomic structures of tapping as the gyri pre- and postcentralis, motor-associated regions and the cerebellum [88] [8].
As pointed out in the introduction, basal ganglia dysfunction, projecting to these areas, could be one of the causes of decreasing tapping rates in neurodegenerative diseases like HD [3, 16].

Using methods such as fMRI and DW-MRI studies have shown that the functional and also inhibitory connectivity between the left putamen and the left and right primary sensorimotor areas is reduced in HD patients while performing right hand fingertapping [25].
Saft et al. showed a correlation between a person's ability to tap a single target in a set time frame and caudate atrophy, as well as their CAG repeat length in 2006 [69].

We know that in early stages, the striato-GPe projecting neurons are one of the first populations to diminish, resulting in loss of inhibition of the subthalamic nucleus [85]. This is one of the causes of involuntary movements – but might also interfere in the coordination of quick fingertapping.

The total tap counts per 30 seconds we assessed electronically, regardless which hand was used, was significantly lower in the HD group compared to the control group. Furthermore, we found it also correlating strongly with the UHDRS item score

assessed by trained investigators (pl. refer Fig. 12, p. 26). While this may be no surprising finding (and is compatible with our knowledge of clinical HD), the power of correlation exceeded my expectations. Accordingly, this test is an objective measure of this item.

Until now, this item scale consists of only a 5 point range – making it susceptible for subjective errors and rendering it inadequate for small changes.

Most importantly, the digitally captured tap count also correlated highly positively with total functional capacity from the UHDRS (pl. refer Fig. 14, p. 28). This reinforces the point that these markers can reveal functional status of HD patients and demonstrates the validity of this item as our read-out. Our tapping test can serve as a supportive state biomarker of functional status in HD.

I envision that this quick test can be of use diagnostically and as a quantitative marker of disease progression.
A good case can be made for measuring the subjects dominant hand since their tap scores should be slightly better [35].

4.2 Pro/Supination

The hand rotation (pro/supination) task was clearly more demanding for our test subjects compared to tapping. While pro/supination is a straightforward movement pattern as well it is much more difficult to capture with our methodology, mainly because the device (the cell phone) itself is moved, whereas for tapping it is at rest: Subjects had to focus on holding the phone firmly, and at an optimal right angle.

This was more challenging, especially for older or more affected patients. It also obviously involves the coordination of more muscle groups than simple tapping (and so does not present anomalies in the same way).

Patients and controls also showed significant differences in their hand rotation count. The mean count of patients proved significantly lower compared to the control group. Similar to tapping, it also correlated strongly with the respective UHDRS item

‘pro/supination’ (pl. refer Fig. 19, p. 30). Again, it can serve as an objective measurement of said item.

The rotation count correlated strongly with the TFC and thereby stage of disease, this with an even higher r-value than fingertapping (pl. refer Fig. 21, p. 32). This might reflect higher complexity of the pronation/supination movement compared to tapping, which might be more vulnerable to the underlying disease progress.

Previous studies have shown that more complex movements, for example ‘reposition of pins’, are more affected by cognitive impairment than simple tasks, such as tapping in HD [3, 4, 69]. This is not surprising, since planning and executing these movements requires certain cognitive performance to align visual and spatial information and generate an internal movement pattern [20]. These cognitive processes are mediated by striatal dopamine release [53].

Dopamine serves also as a regulator of various aspects of the cognitive brain functions in the prefrontal cortex within the striatofrontal interconnections. It plays a key role not only in movement behavior but also affects cognitive functions and controls attention through the frontal lobe and the basal ganglia [54].
Selective lesions in these areas could cause deficits in executing more complex movements which require more planning and different muscle groups [54].

4.3 Comparison

Both electronic motion capture measurement methods can be used to assess highly informative UHDRS items. They provide a more objective, detailed information of these motor abilities.

Both approaches did reveal statistically significant quantitative difference between the four Shoulson and Fahn-Stages.
In our study fingertap counts and handrotation counts from patients from all symptomatic stages were significantly lower than controls. Thus, in early stages, measuring these parameters could help to objectively define motor symptom onset.

Consider, though, that HD patients showed smaller overall motor UHDRS scores at an earlier time point than abnormities in only their tapping scores in a study by Andrich et al. [3]. This could mean that measurement of tapping only is not sufficient enough to capture motor symptom onset alone. Possibly, pro/supination performance could be more sensitive than fingertapping in this instance.

In addition to the motor deficits, the UHDRS also records other manifestations of HD, the cognitive and psychiatric deficits, and the ability of self-reliance. Therefore it still covers a wider range of HD symptoms than just motor assessment, which is not to be neglected to be measured in the future. This is especially the case because specific drugs for HD are available for the first time, which might also completely change the clinical picture of the disease. It would be a cruel outcome, indeed, if CNS-targeted therapies are efficacious in reducing classic signs of HD, only to have mutation carriers die of other consequences in peripheral organ systems.
Still, as of yet, early phases of HD do not affect the cognitive scores of the UHDRS significantly [4].

The Cognitive Score within the UHDRS consists of five subtests which are assessed as individual items, rendering certain items more important than others. I did not assess whether cognitive ability affects tapping scores or hand rotation scores, but this relationship might be of interest.

Assessing of HD patients with quick motor tests also holds advantages over ‘wet’ biomarkers as they are not dependent on sample quality, or sample handling and processing.
Another attractive application is the potential for easy and rapid self-evaluation by HD patients themselves – on personal smartphones for example. It requires no special training, is easy to understand and implement, inexpensive and much less time-consuming than e.g. the (motor part of the) UHDRS. With instructions for relatives and caregivers at home, patients could do this test by themselves without the need of medical staff.

In today's digital world, nearly every individual is already equipped with the measuring device – the smartphone. Especially smartphone applications, 'apps', are very easy and inexpensive to acquire, distribute and use.

Inevitably, our study had limitations. It is always possible to increase the sample size. Yet, despite the comparatively small cohort size our sample contained subjects from all stages, thus representing the full spectrum of the disease. Importantly, the power of the study was sufficient to detect differences between groups. In this regard the small sample size highlights the power of the methodology.

Secondly, our method of measurement reflects the state-of-the-art in 2012, and has naturally not kept up with the staggering speed of technological progress. The touchscreen and (basic) g-sensor of a simple smartphone is improvised from today's (2018) standpoint and lacks precision in exact cycle or tap count. Patients tended to have difficulties in particular with performing the rotation task, e.g. losing grip on the phone or holding it at the wrong angle. This might have distorted results and could be remedied with simple improvements like a glove.

Furthermore, longitudinal studies with progress documentation and regular tests are needed to fully validate these methods of measurement.
Also, the time frame of 30 seconds could be changed to find the optimal time for quick assessment without fatigue and with enough power.

Finally, consider that these tasks can be affected by mood and compliance, subject to a practice effect, and can be impaired in patients with coexisting conditions like rheumatological or orthopaedic problems [86]. Over long time scales, these factors would likely play a minor role but have to be considered. Especially for the hand rotation, joint problems could have an effect since it involves more and bigger joints whereas for simple tapping this is less likely. It is also acknowledged, too, that measuring of tapping and hand rotation is focusing on the upper limbs in a disease which can affect the limbs differently [21].

Note also that both parameters declined more prominently with age in patients than control subjects (p. 36, 37).

Kinetic studies from large healthy populations have shown that tapping rates decrease with age physiologically after ca. 35 years of age [35], but, not unexpectedly, HD accelerates this process significantly (Fig. 24, p. 33).

4.4 Outlook

Further research is necessary to investigate i) the power of method of simple motor tests in neurodegenerative diseases ii) the reliability of an objective version of measuring these, using motion detection devices. Here, a joint approach with bioengineering and information technology as well as medical knowledge is needed.

It must be shown if instrumental tests like ours can be used in evaluation of medical treatment or serve as respectable read-outs in similar diseases and variants.

Assessing of simple motor tasks like tapping or whole-hand rotation with objective standardized devices will be integrated in the normal regular assessment of HD patients and at-risk-individuals.

Also, the global whole-body impression (balance and gait) of HD patients and other neurological diseases with any movement impairment as of yet is difficult to objectively measure. But most recently, this topic is receiving increasing attention. Andrzejewski and colleagues are one of the first to try measuring whole-body movement in HD, equipping patients with 5 accelerometer-based body sensors with results showing clear differences between controls and patients [5]. Mirek et al. also performed a gait and trunk analysis of HD patients using passive markers attached to specific anthropometric points directly on the skin based on the newest biomechanical models [51]. Our team from the Huntington Outpatient Clinic at the RKU Ulm also are performing gait and balance analysis using the Kinect System [89] (pl. refer p. 53).

5. Summary

An electronic motion recognition software on a handheld device is an objective and useful tool in assessing motor impairment in Huntington's Disease.
Our data provide evidence that the measurement of these distinct two parameters (tap count or pro/supination cycle count) distinguishes clearly between controls and HD.
In addition, the read-outs correlate significantly not only with the respective Unified Huntington's Disease Rating Scale motor item score but also with the total functional capacity. The use of a standard new-generation smartphone offers a simple and rapid evaluation of motor status.

Assessment of pro/supination and tapping is easy at practically all but the last stages of the disease since the instruction and implementation is intuitive.

Importantly, both of our two tests capture only on the motor symptoms of HD. In contrast, the UHDRS also tests cognitive and psychiatric symptoms as well as a global clinical performance. Electronic motion capture can, however, serve as full, even improved, surrogates for main parts of the motor assessment (of the UHDRS).

Longitudinal studies starting in the presymptomatic phase are needed to determine if our methodology can be used to objectively and directly measure motor onset, still one of the most important clinical milestones in HD.

It has been pointed out before that these single UHDRS items (tapping and pro/supination) are affected by inter-rater variability. This provides further motivation to explore the methods of electronic motion capture assessment.

In our study the effect of medication was not taken into account, because it was not relevant for testing the underlying hypothesis. However, testing the effect of available antichoreatics on motor function could be the most immediate application of our approach. With improving electronic motion caption devices, whole-body or single

limb movement analysis for clinical assessment in different movement disorders might come into use in a standardized way in clinic not too far in the future.

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Appendix

1. Full Motor Assessment Score and Independence Scale from the 1999 Modified Unified Huntington's Disease Rating Scale (as used in the PREDICT-HD Study)

PREDICT-HD
MODIFIED UNIFIED HUNTINGTON'S DISEASE
RATING SCALE '99 (UHDRS)

08

All items must be completed.

PARTICIPANT NO. ☐☐☐☐ SITE NO. ☐☐☐ VISIT NO. ☐☐

TIME (24 hour clock) ☐☐ : ☐☐ EVAL. DATE ☐☐ MM ☐☐ DD ☐☐☐☐ YEAR

I. MOTOR ASSESSMENT

1. OCULAR PURSUIT — Horizontal 1a. ☐ Vertical 1b. ☐
   0 = complete (normal)
   1 = jerky movement
   2 = interrupted pursuits/full range
   3 = incomplete range
   4 = cannot pursue

2. SACCADE INITIATION — Horizontal 2a. ☐ Vertical 2b. ☐
   0 = normal
   1 = increased latency only
   2 = suppressible blinks or head movements to initiate
   3 = unsuppressible head movements
   4 = cannot initiate saccades

3. SACCADE VELOCITY — Horizontal 3a. ☐ Vertical 3b. ☐
   0 = normal
   1 = mild slowing
   2 = moderate slowing
   3 = severely slow, full range
   4 = incomplete range

4. DYSARTHRIA 4. ☐
   0 = normal
   1 = unclear, no need to repeat
   2 = must repeat to be understood
   3 = mostly incomprehensible
   4 = anarthria

5. TONGUE PROTRUSION 5. ☐
   0 = can hold tongue fully protruded for 10 seconds
   1 = cannot keep fully protruded for 10 seconds
   2 = cannot keep fully protruded for 5 seconds
   3 = cannot fully protrude tongue
   4 = cannot protrude tongue beyond lips

6. FINGER TAPS — Right 6a. ☐ Left 6b. ☐
   0 = normal (≥ 15/5 sec.)
   1 = mild slowing and or reduction in amplitude (11-14/5 sec.)
   2 = moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5 sec.)
   3 = severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements (3-6/5 sec.)
   4 = can barely perform the task (0-2/5 sec.)

7. PRONATE/SUPINATE HANDS — Right 7a. ☐ Left 7b. ☐
   0 = normal
   1 = mild slowing and/or irregular
   2 = moderate slowing and irregular
   3 = severe slowing and irregular
   4 = cannot perform

8. LURIA (fist-hand-palm test) 8. ☐
   0 = ≥ 4 in 10 seconds, no cue
   1 = < 4 in 10 seconds, no cue
   2 = ≥ 4 in 10 seconds with cues
   3 = < 4 in 10 seconds with cues
   4 = cannot perform

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9. RIGIDITY-ARMS — 9a. Right ☐ 9b. Left ☐
0 = absent
1 = slight or present only with activation
2 = mild to moderate
3 = severe, full range of motion
4 = severe with limited range

10. BRADYKINESIA-BODY — 10. ☐
0 = normal
1 = minimally slow (? normal)
2 = mildly but clearly slow
3 = moderately slow, some hesitation
4 = markedly slow, long delays in initiation

11. MAXIMAL DYSTONIA
0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged
11a. TRUNK ☐
11b. RUE ☐
11c. LUE ☐
11d. RLE ☐
11e. LLE ☐

12. MAXIMAL CHOREA
0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged
12a. FACE ☐
12b. BOL ☐
12c. TRUNK ☐
12d. RUE ☐
12e. LUE ☐
12f. RLE ☐
12g. LLE ☐

13. GAIT — 13. ☐
0 = normal gait, narrow base
1 = wide base and/or slow
2 = wide base and walks with difficulty
3 = walks only with assistance
4 = cannot attempt

14. TANDEM WALKING — 14. ☐
0 = normal for 10 steps
1 = 1 to 3 deviations from straight line
2 = > 3 deviations
3 = cannot complete
4 = cannot attempt

15. RETROPULSION PULL TEST — 15. ☐
0 = normal
1 = recovers spontaneously
2 = would fall if not caught
3 = tends to fall spontaneously
4 = cannot stand

16. WEIGHT (kg) — 16. ☐☐☐.☐

17. DIAGNOSIS CONFIDENCE LEVEL — 17. ☐
To what degree are you confident that this participant meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a participant at risk for HD?
0 = normal (no abnormalities)
1 = non-specific motor abnormalities (less than 50% confidence)
2 = motor abnormalities that may be signs of HD (50 - 89% confidence)
3 = motor abnormalities that are likely signs of HD (90 - 98% confidence)
4 = motor abnormalities that are unequivocal signs of HD (≥99% confidence)

18. **Motor Examiner** — 18. ☐☐☐☐
STAFF CODE

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V. INDEPENDENCE SCALE

Please indicate the most accurate current level of participant's independence 69. ____

(only increments of 5 are acceptable)

100: No special care needed
090: No physical care needed if difficult tasks are avoided
080: Pre-disease level of employment changes or ends; cannot perform household chores to pre-disease level; may need help with finances
070: Self-care maintained for bathing; limited household duties (cooking and use of knives); driving terminates; unable to manage finances
060: Needs minor assistance in dressing, toileting, bathing; food must be cut for participant
050: 24-hour supervision appropriate; assistance required for bathing, eating, toileting
040: Chronic care facility needed; limited self-feeding, liquified diet
030: Participant provides minimal assistance in own feeding, bathing, toileting
020: No speech; must be fed
010: Tube fed; total bed care

VI. FUNCTIONAL CAPACITY

70. OCCUPATION 70. ____
0 = unable
1 = marginal work only
2 = reduced capacity for usual job
3 = normal

71. FINANCES 71. ____
0 = unable
1 = major assistance
2 = slight assistance
3 = normal

72. DOMESTIC CHORES 72. ____
0 = unable
1 = impaired
2 = normal

73. ADL 73. ____
0 = total care
1 = gross tasks only
2 = minimal impairment
3 = normal

74. CARE LEVEL 74. ____
0 = full time skilled nursing
1 = home or chronic care
2 = home

INFORMATION SOURCES

75. Was the Functional Capacity information obtained from: 75. ____
1 = participant only
2 = participant and family/companion

76. **Functional Examiner** 76. ____
STAFF CODE

7/18/02

Table of Figures

Abstract

Binder
Julius M.

Implementation and Evaluation of Two Distinct Electronic Motion Detection Devices for the Assessment of Abnormal Movements in Huntington's Disease

Problem

Huntington's Disease (HD) is a severe neurodegenerative disorder in which the impairment of voluntary movement causes significant functional disability. Clinical assessment of motor dysfunction currently relies on semiquantitative rating scales, which are time consuming and susceptible to subjective errors.
This thesis presents a study to determine if capturing two simple movements (fingertapping and pro/supination) with electronic motion detection software on a handheld device is useful in assessing abnormal movements in HD and possibly other neurodegenerative diseases.

Methods

We emulated two items from the Unified Huntington's Disease Rating Scale (UHDRS) Motor Assessment score, the finger tapping test and pro/supination cycle test by recreating them on a custom-made smartphone app and comparing them to UHDRS scores and total functional capacity assessed by EHDN-trained investigators.
The app measured a) the total number of taps on the smartphone touchscreen in a given time frame (30 sec.) b) the total number of rotation cycles when the phone was in hand during pro/supination movement (30 sec.)
From March 2014 to April 2017 n=39 HD patients from all functional stages (calculated by UHDRS) from the RKU Ulm Neurology Outpatient Clinic and n=25 controls were tested.

Results

Symptomatic HD patients had a significantly reduced number of taps compared to controls. Tap count decreased with advanced stages of the disease. The count correlated strongly with the UHDRS "tapping" item score and also, with total functional capacity. The rotation cycle count of whole-hand pro/supination rotation count also proved significantly different in HD symptomatic patients vs control. It correlated strongly with the respective UHDRS "pro/supination" score and with the total functional capacity as well. Both test scores declined with age more rapidly in HD patients compared to controls.

Conclusion

Measurement of hand rotation count and fingertaps on electronic motion detection devices allows for the objective assessment of clinical motor symptoms in HD. Both measurements (taps and cycles) can serve as proxies of motor function or impairment over disease progression. With simple tests on electronic motion capturing devices physicians and researchers are handed a useful tool to assess (motor functions of HD) patients quickly and objectively.

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