Cognition in Huntington's disease

The influence of motor behaviour and time

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Chapter 1

Introduction and aims

In 1872 the first official publication on Huntington's disease (HD) appeared in The Medical and Surgical Reporter[1]. In his essay 'On chorea', George Huntington described a hereditary form of chorea which he noted while at work as a general practitioner in Long Island, USA. This disease became known as Huntington's Chorea, and was renamed into Huntington's disease in the eighties of the last century.

Manifest versus premanifest

Huntington's disease is a progressive neurodegenerative disease with an autosomal dominant mode of inheritance. The pathology leads to a triad of progressive clinical symptoms: motor, cognitive and psychiatric. In 1983 the genetic defect was mapped to chromosome 4, and one decade later the Huntington's Disease Research Group succeeded in generating an exact location for the HD gene[2]. With the availability of genetic testing it became possible to identify gene carriers who are still without clinical symptoms and signs, but who will inevitably progress into manifest disease. These so-called premanifest gene carriers play an important role in the understanding of the earliest damage caused by HD. Studying and mapping these early changes has become an important goal in the search for a cure for the disease.
Knowledge of the earliest conversion from healthy to disease may help to identify the fields that degenerate first, even before the appearance of overt clinical symptoms. This knowledge about the earliest pathophysiological, metabolic or functional changes could lead to the development of pharmacological agents targeting these specific fields. Currently, pharmacological research is focused on discovering disease modifying and/or disease slowing compounds, to prolong and improve the

quality of life for patients suffering from HD[3]. Identifying markers for the transition from premanifest to manifest is important for the timing of the start of therapeutic agents in individual patients. In the view of drug side-effects and health care costs it is of importance to start drug treatment at the right moment.
A key challenge in HD research is its heterogenic presentation among patients. Even when belonging to the same family, no prediction can be made about an individuals initial symptoms, age at onset, clinical presentation or disease duration. To date, no single symptom or sign has been identified as generalised marker of definite onset of disease. Most likely early changes on pathophysiological measures of the brain in combination with changes on several clinical functional measures will help to more precisely pinpoint the onset in the individual person[3].

Clinical features

HD symptoms can be separated in three domains: motor, behavioural and cognitive. The most characteristic and debilitating motor symptoms are the choreatic, or dance-like, movements. Starting as subtle twitches in arms, legs, face or trunk, and often (consciously or unconsciously) masked by other normal movements, they progress in severity throughout the whole body over several years, severely debilitating patients in their daily activities[4,5]. Other motor impairments include, amongst others, bradykinesia and dystonia[5,6]. Although the clinical diagnosis is often based on the appearance of the first overt motor abnormalities (together with a positive family history and genetic test) subtle motor abnormalities have been detected in premanifest subjects also. Here, chorea, defective oculomotor functioning, bradykinesia and dystonia have been shown to differentiate premanifest gene carriers from healthy control subjects[7,8,9].
Behavioural changes are also well recognized in HD gene carriers, sometimes more so by partners and family members than by the patients themselves. Among the most common psychiatric symptoms associated with HD are depression, apathy and aggression or irritability, resulting in progressive personality changes[10,11]. Particularly, symptoms such as depression, anxiety and obsessive-compulsive behaviour can already be seen in premanifest subjects[12].
he third main area of decline in HD is cognition. HD patients become progressively more disabled on several areas of cognitive functioning, eventually leading up to full blown dementia. HD belongs to the group of subcortical dementias, and patients often exhibit a frontal syndrome and the associated disabilities reflect the neuropathological damage to fronto-subcortical connections[13]. Typically, executive dysfunctioning (i.e. difficulties with planned behaviour, attentional impairment and disinhibition) is one of the first cognitive symptoms to appear, together with marked reductions in psychomotor and mental processing speed[14,15,16]. This is opposed to the picture of cognitive decline that we see in dementias of the cortical type, such as Alzheimers disease (AD), where severe memory loss, aphasia and

agnosia are most pronounced early on in the disease process[13]. In HD, memory deficits are also common, but less prominent than in AD[15]. Language is relatively spared until the latest stages of the disease, but will eventually also deteriorate, alongside other cognitive functions. A robust finding, which has even been found in individuals in the premanifest phase, is defective recognition of negative emotions[17]. But subtle changes in psychomotor speed, executive functioning and memory have also been detected before clinical disease onset[18 19 20]. However, variability in observed premanifest cognitive changes is large and no agreement is reached yet from the studies performed.

Nowadays, consensus is starting to form among scientists and clinicians that changes in any of the three main HD domains can already be detected in the premanifest phase, before the motor symptoms are severe enough to warrant a clinical diagnosis. The area of cognition is one of the largest research fields in HD literature, evident by the large body of articles on cognition in both manifest and premanifest HD[21]. Next to psychiatric disturbances, cognition is also one of the symptoms most debilitating for patients in daily life, even more so than the unwanted movements[6 14].

Genetics

HD is caused by an expanded and unstable trinucleotide (CAG) repeat in the huntingtin gene, leading to an expanded polyglutamine stretch in the huntingtin protein[22]. CAG repeats from 36 repeats on are associated with HD, but only repeats from 39 on are considered fully penetrant, where individuals will develop symptoms and signs of the disease within their lifetime. Repeats from 36 to 39 are regarded as a grey area, where the disease may or may not manifest[23 24]. Abnormal CAG repeat lengths have been found to be inversely related to age at onset, and they can account for up to 70% of the variability in age at onset. The remaining variability is likely influenced by both other genetic influences and environmental factors[6].
In most cases, clinical manifestation of the disease occurs in mid-life (between 30 and 50 years of age) and inevitably leads to death in approximately 15 to 30 years. To date, no cure is available for HD, and patients receive symptomatic treatment only[3 25].

Neuropathology

ven though the exact neuropathology of HD is not yet completely known, the earliest and most pronounced neuropathology is found in the striatal parts of the basal ganglia (e.g. caudate nucleus and putamen) and progresses throughout the course

of the disease[23,26]. Subsequently, neuronal loss and atrophy spread throughout the cerebral cortex, affecting both grey and white matter[27,28]. In the later stages of the disease the entire brain is affected to a greater or lesser extent, resulting in up to 25% brain weight loss in the most advanced stages[23].
Magnetic Resonance Imaging (MRI) studies have indicated that brain abnormalities in HD develop long before overt clinical symptoms and signs appear. Both structural[29,30] and functional[31,32] brain changes have been found in premanifest gene carriers up to 20 years from their estimated disease onset[33].

Motoric influence on cognitive tests

That cognitive test performance is influenced by affective disorders, such as depression, is well recognized in the literature[34], for example in Parkinsons disease (PD)[35]. Therefore, depression score is often taken into account when differences in cognitive functioning between groups are studied. However, the influence of motor disturbances on cognition has not received much attention, even though it probably has a negative impact on cognitive outcome, because almost all cognitive test require some form of motoric response (e.g. speaking, drawing, writing).
With HD primarily being a movement disorder, and together with the subtle motor changes already recognized in premanifest HD gene carriers[7], the influence of motor impairments on cognitive functioning in HD must not be neglected when doing cognitive research. However, in very few studies on cognition in HD the influence of motor impairment is accounted for.

Aims of this thesis

The main aim of this thesis was to gain more insight into the course of cognitive functioning in HD, especially in the premanifest phase. Furthermore, we aimed to minimize the influence of HD specific motor disturbances on cognitive scores, by taking the motoric influence into account making use of several different approaches.

We studied the cognitive construct of attentional control in both premanifest and manifest HD gene carriers using the Sustained Attention to Response Task (SART), a cognitive test of attention and inhibition with minimal motor demands. Moreover, the P300, an event related potential independent from motor influence, was recorded simultaneously with the SART, to more accurately measure cognitive processes free from motor influences. We investigated possible differences in attentional control and P300 characteristics between premanifest, manifest and control subjects cross-sectionally (**chapter 2**). Furthermore, we studied potential change in attentional control and P300 in our groups over a three-year follow-up

period (**chapter 3**). In **chapter 4** we studied longitudinal change in premanifest gene carriers on several cognitive tests over a seven-year follow-up period. We further investigated the natural progression of cognition by studying both manifest and premanifest subjects over a ten-year period, and compared their longitudinal change on three cognitive and one motor domain to control subjects in **chapter 5**. In **chapter 6** we explored whether differences exist in the cognitive and global profiles of two different HD motor phenotypes; predominant hypokinetic-rigid HD and choreatic HD. In **chapter 7** we present the results of a longitudinal study where we investigated the possible negative influence of motor functioning on cognition by creating an extra 'high motor low cognition' conditions for existing tests of executive functioning. We subtracted these motor conditions from the original test scores to be able to isolate more 'pure' cognitive functioning. To conclude, a general discussion and future perspectives are presented in **chapter 8**.

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Chapter 2

Deficient Sustained Attention to Response Task and P300 characteristics in early Huntington's disease

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Abstract

Objective Evidence for the extent and nature of attentional impairment in premanifest and manifest Huntington's disease (HD) is inconsistent. Understanding such impairments may help to better understand early functional changes in HD and could have consequences concerning care for HD patients. We investigated attentional control in both early and premanifest HD.

Method We studied 17 early HD subjects (mean age: 51 yrs), 12 premanifest HD subjects (mean age: 43 yrs), and 15 healthy controls (mean age: 51 yrs), using the Sustained Attention to Response Task (SART), a simple Go/No-go test reflecting attentional and inhibitory processes through reaction time (RT) and error rates. Simultaneously recorded EEG yielded P300 amplitudes and latencies.

Results The early HD group made more Go errors ($p<0.001$) and reacted slower ($p<0.005$) than the other groups. The RT pattern during the SART was remarkably different for early HD subjects compared to the other two groups ($p<0.005$), apparent as significant post-error slowing. P300 data showed that for early HD the No-go amplitude was lower than for the other two groups ($p<0.05$).

Conclusions Subjects with early HD showed a reduced capacity to effectively control attention. They proved unable to resume the task directly after having made an error, and need more time to return to pre-error performance levels. No attentional control deficits were found for the premanifest HD group.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurological disorder characterized by progressive motor, cognitive and behavioural abnormalities. While the clinical diagnosis is based on the presence of motor signs, deficits in the other functional domains are widespread[1,2]. The discovery of the HD gene[3] allows gene-carriers to be identified in the premanifest phase of the disease, i.e., before symptoms and signs appear. Deficits in cognition such as psychomotor slowing, memory decline and executive dysfunctioning have been reported in both manifest and premanifest individuals[4], but inconsistently[5].

Attentional processing may well be abnormal in HD, but results are conflicting: some authors reported attentional and inhibitory deficits in both patients and premanifest gene carriers[6,7], while others did not[8]. The conflict may be due to the complex nature of the widely applied neuropsychological tests such as the symbol digit modalities test, the Stroop colour-word task and the trial making test. These assess attention and inhibition, they also tap into psychomotor speed, implicit learning, and visuomotor integration.

Studies of attentional processing showed deficits in focused attention[9,10], shifting attention[11,12], and inhibition, with sometimes reduced inhibition[12] and sometimes increased inhibitory control[13]. Due to such methodological differences it is difficult to come to a conclusion about overall attentional processing in HD. Moreover, attention and inhibition are functionally very closely related and rely heavily on each other, i.e. attention often is a prerequisite of correct inhibition. This interdependence lead us to investigate attention and inhibition together in the context of attentional control, a construct overarching the two terms[14,15].

The Sustained Attention to Response Test

The Sustained Attention to Response Test (SART) is a test of attention control assessing both attentional and inhibitory processes[16,17,18]. Participants are requested to press a button when a number (1-9) appears on a screen except when that number is a 3. The need to withhold responses only to rare stimuli means that the task relies heavily on attentional control. Pressing a button is simple in terms of motor control, important in HD, as motor disturbances can interfere with the determination of cognitive deficits. The SART demonstrated deficiencies in attention, in disorders such as traumatic brain injury[19], schizophrenia[20], attention deficit hyperactivity disorder[21] and narcolepsy[22].

The P300

There is a growing need in HD research for sensitive, objective and quantifiable assessments. Electroencephalography (EEG) has the advantages of low cost, non-invasiveness and high temporal resolution. Event-related potentials (ERP) are

EEG-based potentials reflecting the neurophysiologic substrate of mental processes such as stimulus identification, processing and response initiation[23]. We focused on the P300 peak, which is most commonly evoked by rare stimuli interspersed in a series of frequent ones. Although the exact neural origin is not entirely clear, the P300 is often linked with processes of attention[24 25 26]. Some authors have suggested P300 amplitude to reflect the amount of attentional resources allocated to the stimulus, while the latency is linked to the stimulus evaluation time, or more general, speed of cognitive processing of the stimulus[27]. In previous work P300 latency was increased and its amplitude decreased in manifest HD compared to healthy controls in a visual search task[28] and a visual Go/No-go task[29]. However, no P300 abnormalities were found in premanifest HD or those at risk in auditory odd-ball paradigms[30 31].
The P300 can be elicited by Go/No-go tasks such as the SART. Studies in healthy individuals found that simultaneous SART and EEG assessment resulted in good indexes for attentional and inhibitory processes[32]. Only one previous study has used the combination of SART and P300 in premanifest HD[33], but found no differences in P300 characteristics between the premanifest HD group and controls. They concluded that possibly their premanifest group was not yet close enough to disease onset and that with progressive basal ganglia degeneration closer to onset differences would have emerged. Indeed, magnetic resonance imaging measurements of grey and white matter structures showed changes before the appearance of overt clinical signs of HD[34 35].

We hypothesized that both premanifest and manifest (early) HD groups show impaired attentional control in comparison with control subjects as measured by a heightened error rate on the SART. Furthermore, we aim to further strengthen this hypothesis by showing altered P300 characteristics (i.e. lowered amplitude and increased latency) in both HD groups in accordance with deviant SART results. Due to the motor disturbances in HD we expected the SART reaction times for the early HD group to be longer.

METHODS

Subjects

Thirteen subjects with premanifest HD (PMHD), 18 with early manifest HD (MHD) and 17 age-matched healthy controls, relatives that were tested as gene-negative, were included, all above the age of 18 years. Participants were recruited from the outpatient neurologic clinic of the Leiden University Medical Centre and had been genetically tested for HD. Gene carriers were considered premanifest when they had 5 points or less on the total motor subscale of the Unified Huntingto‘s Disease Rating Scale (UHDRS)[36]. The manifest group consisted of early HD sub-

jects (Shoulson-Fahn stages 1 and 2)[37]. Disease burden was calculated using the formula 'age(CAG-35.5)'[38]. Exclusion criteria were major psychiatric disorders, neurological co-morbidity, a score of ≤ 25 on the Mini-Mental State Examination and medication with known effects on the EEG (e.g. neuroleptics). The study was approved by the local Medical Ethical committee and all participants gave written informed consent.
All participants underwent neurological, SART and EEG assessments. Depression was measured using the short version of the Problem Behaviour Assessment for HD[39]. The motor part of the UHDRS was administered by a clinician (SvdB) blinded for genetic status.
One PMHD, one MHD, and one control subject were excluded because of excessive muscle artefacts on the EEG. One additional control was excluded because of epileptiform abnormalities on the EEG. Data of 12 PMHD, 17 MHD and 15 controls were analyzed.

Sustained Attention to Response Task

For the SART, subjects were seated in a comfortable chair one meter from a computer screen, with a computer keyboard placed in easy access of the dominant hand. Numbers from 1 to 9 were shown 25 times on a computer screen. Subjects were asked to respond to the appearance of every number by pressing the spacebar ('Go' trials), except when the number 3 was shown ('No-go' trials). When the number 3 was displayed, participants were instructed to withhold their response. Reaction time (RT) was recorded whenever the spacebar was pressed. To ensure accurate measurement of RT a cathode ray screen was used together with a purpose built hardware device that allowed precise measurement of the build-up time of the screen information and hence of RT in relation to the visual stimulus. Subjects were instructed that accuracy and speed were equally important. Before the start of the test subjects performed a practice run consisting of 25 numbers from 1 to 9 in random order. Stimuli were shown for 250 milliseconds followed by a blank screen for 900 milliseconds (detailed description of the task see[16]). Outcome measures for the SART were RT and error rates. Overall RT refers to mean RT over all trials performed. The mean RT for correct Go trials and incorrect No-go trials were also computed. Error rate data consisted of overall error rate (the total number of errors as a percentage of the total number of trials performed), error rate Go (total of Go errors as percentage of total number of trials) and error rate No-go (total of No-go errors as a percentage of total number of trials).

ERP recording and analysis

All EEGs (Nihon Kohden 2110 EEG apparatus) were recorded between 12.00 and 14.30 hrs, except for one control subjects tested late in the morning. Twenty-one Ag/AgCl electrodes were placed according to the 10/20 convention. ECG,

respiration and horizontal eye movement leads were also recorded. The EEG was band-pass filtered from 0.16-70 Hz before display and analysis. Sample frequency was 200 Hz and A-D precision 12 bits. For the P300 analysis we used the midline sites Fz (frontal), Cz (central) and Pz (parietal) with linked mastoids as reference. The computer controlling the SART paradigm wrote synchronization signals to the EEG machine, allowing averaging to take place offline after controlling for signal quality. Data were averaged over epochs of 1200 ms, starting 200 ms before stimulus onset. Individual trials with eye blink artefacts or suspected muscle artefacts (peak amplitudes more than 75 μV) were excluded from P300 analysis. The P300 component was defined as the maximum positivity between 350 and 650 ms. This time-frame was based on visual inspection of the averaged ERPs. ERP analysis, including peak detection, was performed automatically using an in-house developed program written in MATLAB (The MathWorks, Natick, USA). Peak amplitudes were measured relative to a 200 ms baseline before stimulus onset. Outcome measures consisted of amplitude and latency data. The mean amplitudes and latencies for all trials, all Go trials and all No-go trials were calculated averaging the data from the midline electrodes.

Statistical analysis

SPSS for Windows version 17.0 was used for data analysis. Analyses of demographic variables were performed using parametric and non-parametric tests where appropriate. Group differences for mean SART RT and error rate and P300 amplitude and latency data were calculated using univariate analysis of covariance (ANCOVA) with age as a covariate. Upon visual inspection of the RT patterns for the four trials preceding and the four trials following a No-go trial different patterns were observed. To investigate possible group differences in these patterns a secondary analysis was performed. For this purpose the difference (delta) between the mean RT just before and just after both correct and incorrect No-go trials was calculated for each subject. The delta scores for the three groups were analyzed again using ANCOVA with age as covariate. The Bonferroni method was used to correct for multiple testing. The level of significance was set at $p \leq 0.05$. P-values $> 0.05 < 0.1$ were reported as trend significant.

RESULTS

Clinical characteristics

There were no differences between groups for sex, age, IQ and level of education (Table 1). Disease burden differed significantly between PMHD and MHD ($p<0.0001$). Two subjects (one premanifest, one early HD subject) were rated as mildly depressed; depression did however not differ between groups (data not

shown in table).

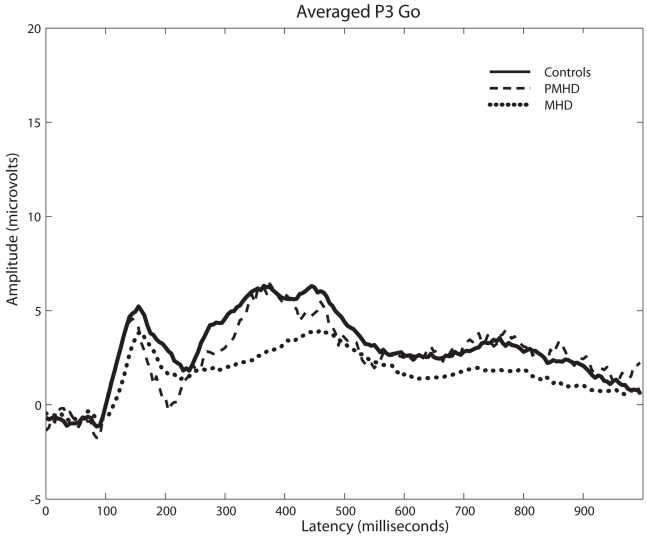
Table 1: Descriptive statistics of controls, premanifest and manifest participants

Characteristic	Controls N=15	PMHD N=12	MHD N=17
Age	51 (10)	43 (10)	50 (11)
CAG	20 (3)	42 (2)	44 (3)
Male/female[a,b]	7/8	6/6	8/9
Level of education[a,b] (lower/middle/higher)	1/9/5	0/9/3	2/11/12
Intelligence Quotient (IQ)	107 (8)	105 (8)	101 (12)
Disease burden		251 (75)	404 (81)

Note. Descriptive statistics are presented as mean (standard deviation), except for [a] which is total number. IQ was measured by the National Adult Reading Test (Dutch version). Disease burden is age(CAG-35.5). [b]Pearson Chi Square Test.

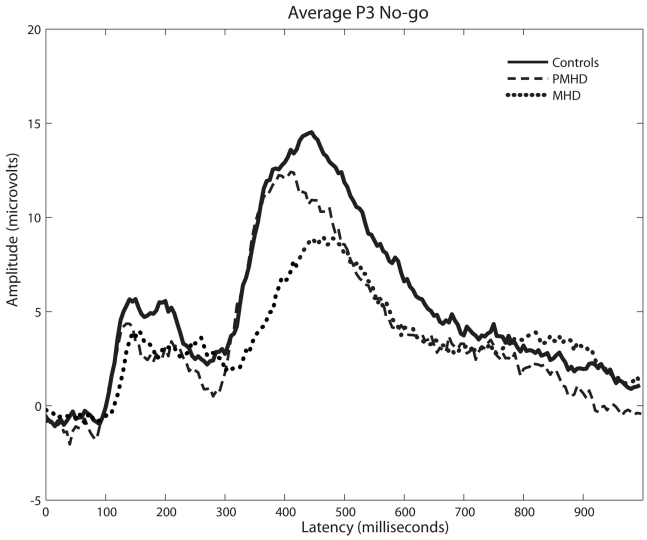
SART

Table 2 shows SART error rate and RT data. The overall error rate (i.e. all errors made, not differentiated for type) differed significantly between groups ($p<0.05$) (Table 2). The MHD group made significantly more errors of all types than both PMHD and controls ($p<0.05$). Further analysis revealed that only for Go-errors (i.e., subjects did not press the spacebar when they ought to) there was a group difference ($p<0.001$). Surprisingly, the number of No-go errors (pressing the spacebar when the number '3 appears') did not differ between groups. Concerning mean RT (i.e. mean RT for all pressed trials, not differentiated for correct or erroneous trials) there was a group difference ($p<0.005$), where the overall RT was significantly longer for MHD than for PMHD ($p<0.005$) and controls ($p<0.001$).



(a) Go

Note. P300 waves for the three groups during SART Go trials, averaged over the midline electrodes. Time point 0 denotes the point of stimulus presentation.



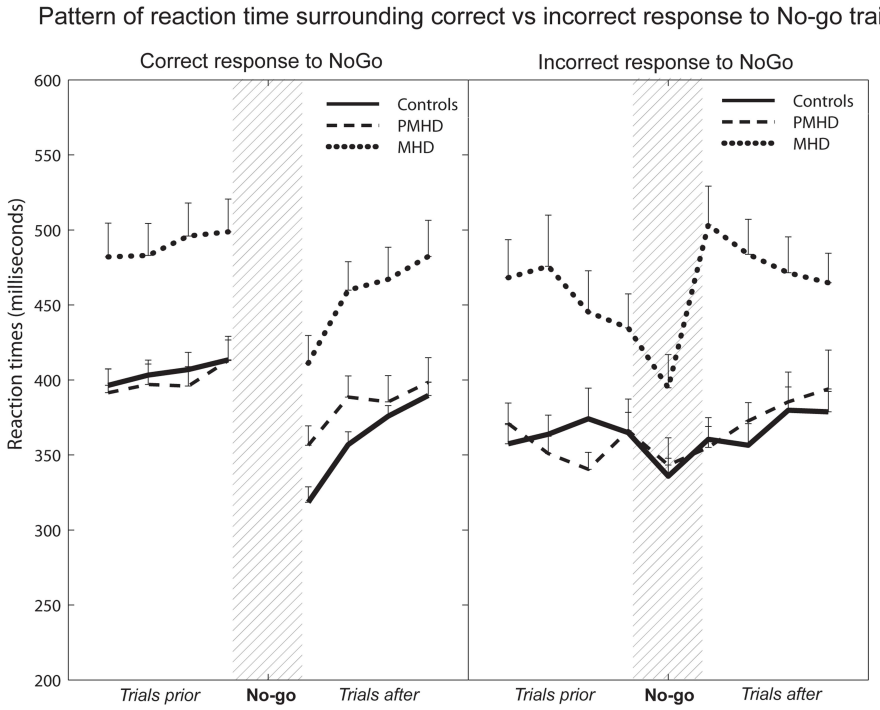
(b) No-go

Note. P300 waves for the three groups during SART No-go trials, averaged over the midline electrodes. Time point 0 denotes the point of stimulus presentation.

Figure 1: P300 waves per group (averaged)

P300

The number of epochs used for P300 analyses were not different between groups. P300 amplitudes were larger for No-go trials than Go trials (Table 2; Figures 1a/1b.). Overall P300 amplitude proved only trend significant between groups ($p<0.06$). Amplitude in No-go trials differed significantly between groups, with lower amplitude in MHD than in the other groups ($p<0.05$). For mean latency only a trend towards significant group differences for Go trials was observed ($p<0.06$).



Note. The reaction time for the four trials preceding and the four trials following No-go trails. Data are separated for RT patterns surrounding correct responses (i.e. not pressing at No-go stimulus) and incorrect responses (i.e. pressing at No-go stimulus), averaged per group.

Figure 2: RT patterns for trials before and after correct and incorrect No-go trial

Reaction time patterns before and after correct and incorrect No-go

Almost all Go errors (not pressing on 1-9) occurred directly following a No-go error (incorrectly pressing on 3), with MHD making significantly more of these errors than the PMHD group ($p<0.05$). The RT patterns for the four trials preceding and following both correct and incorrect No-go trials are shown in Figure 2. Analysis of covariance on the difference between the RT of the last trial before and the first trial after both correct and incorrect No-go responses revealed a significant result for incorrect No-go trials only ($p<0.01$). MHD had a significantly slower response to the first Go trial following an incorrect No-go trial compared to controls ($p<0.005$) and PMHD ($p<0.05$). P300 amplitude did not differ significantly for trials surrounding correct and incorrect No-go trials.

Table 2: Main and post-hoc effects for SART error rate and mean reaction time data and P3 mean amplitude and latency data

	Controls N=15	PMHD N=12	MHD N=17	p-value main effect	p-value MHD-controls	p-value PMHD-controls	p-value MHD-PMHD
SART							
Error rate	4.3 (1.8)	3.9 (2.5)	6.3 (2.8)	**0.021**	**0.027**	ns	**0.014**
Error rate No-go	27.7 (11.9)	25.8 (13.8)	32.9 (15.9)	ns	ns	ns	ns
Error rate Go	1.4 (0.98)	1.2 (1.3)	3.0 (1.4)	<**0.001**	**0.001**	ns	**0.001**
Mean RT	381 (34)	388 (48)	462 (77)	**0.001**	<**0.001**	ns	**0.004**
P300							
Amplitude	8.7 (2.8)	8.3 (4.4)	5.9 (3.2)	0.058	ns	ns	ns
Amplitude Go	7.9 (2.8)	7.8 (4.6)	5.4 (3.1)	ns	ns	ns	ns
Amplitude No-go	16.3 (4.9)	1.61 (4.5)	1.20 (5.6)	**0.046**	**0.023**	ns	0.064
Latency	414 (37)	401 (37)	439 (57)	ns	ns	ns	ns
Latency Go	408 (30)	405 (43)	445 (62)	0.059	ns	ns	ns
Latency No-go	430 (38)	424 (47)	447 (50)	ns	ns	ns	ns

Note. Data are mean (standard deviation). RT = Reaction time in milliseconds. Errors are percentage of errors out of total number of stimuli. Amplitude is μV. Latency is milliseconds. ns = not significant.

DISCUSSION

The main finding of this study was that attentional control is deficient in MHD, evident primarily through a heightened error rate on the SART. This behavioural deficit was corroborated by abnormalities of P300 characteristics.

SART error rate

As expected, MHD made more errors of any type than the other groups, indicative of defective attentional mechanisms. Unexpectedly, this was not caused by a high rate of No-go errors, but by significantly more Go errors. The only study using the SART in HD did not report about the type of errors made[33]. Even though they used different Go/No-go paradigms other studies also report on attentional deficits in manifest HD as measured by more Go errors for manifest HD compared to controls, but all have concomitantly also found more No-go errors, contrary to our findings[10,40]. Our findings are partly in line with studies using the SART in other brain disorders with known attentional deficits. Schizophrenic patients have also been found to largely make Go errors and not No-go errors[20]. However, patients with traumatic brain injury made significantly more errors of both types, with stronger evidence for No-go than Go errors[16,21]. So, our findings cannot be easily attributed to attentional deficits alone as earlier findings in other studies were not replicated. Therefore they were further investigated in reaction time pattern analyses.

Reaction time patterns surrounding No-go errors

As the SART is likely to provoke No-go errors, due to the repetitive nature of the task and the rarity of No-go stimuli, we further investigated the significant amount of Go errors made by the early HD group. Examination of these Go errors in MHD revealed that most were made directly following a No-go error. Analysis of the reaction time patterns for trials directly preceding and following a correct No-go trial (correctly withholding response to a three) revealed identical patterns for the three groups, although the MHD group reacted significantly slower than the PMHD or control groups. Prior to correct responses to a No-go trial RT was relatively stable for all three groups. Directly after such a correctly withheld response, RT was noticeably shorter. This speeding most likely represents action anticipation that is evoked by the repetitive nature of the SART. This primes the motor response; after having correctly withheld the response at the No-go trial, the response to the next Go trial is more quickly accessed, resulting in a quicker response[41]. Although the MHD group reacted slower, the general pattern was the same as for the other groups. This suggests that the cause of slowing is due to motor disturbances and not to different cognitive processing.
Interestingly, a different pattern emerged concerning incorrect No-go responses, i.e.

when participants incorrectly pressed the space bar in response to a three. For all three groups the trials directly preceding such a No-go error showed a shortened RT. We hypothesize that this pre-error speeding could mean that the task was performed fairly automatically, with less attentional control, eventually resulting in an error[16]. Remarkably, this pre-error speeding was more prominent in MHD than in the other two groups. This could indicate that subjects with MHD can sustain attention less well than the other groups. After such a No-go error RT returned to the pre-error level almost immediately for the PMHD and control groups, but not for the MHD group, showing a dramatic post-error slowing.

One proposition for this is that a No-go error induces MHD subjects to slow down in response time in the hope of making fewer errors. This is an unconscious cognitive strategy known as 'speed-accuracy trade-off' (SAT): low speed allows high accuracy[42]. That healthy controls performing the SART use this SAT strategy has also been put forward by Helton and colleagues[17]. At first glance one would then expect that subjects who choose 'accuracy over speed' would make fewer errors, but this was not the case. A more likely explanation is that there is an intrinsic deficit of attentional control in MHD. This is seen in the obvious drop in RT trials preceding an error. This could possibly reflect a drop in attentional control, in turn causing the No-go error. The post-error RT pattern shows that the PMHD and control groups are able to return to the task immediately and perform on pre-error level. The pattern of the MHD subjects however reflects a difficulty in recovery; it takes this group several trials to return to pre-error performance. This difficulty could be due to the realization of having made an error, i.e., the response evaluation, causes confusion; the subsequent quick return to a Go trial adds to this confusion, leading to a slower return to pre-error performance. Alternatively, this post-error slowing does not reflect cognitive confusion, but could be indicative of an inability to switch from a No-go to a Go response, and thus from inhibiting the response to activating it. Together with the fact that directly following a No-go error significantly more Go errors are made in the MHD group than in the other two groups we speculate that attentional and inhibitory deficits are the probable causes of inadequate attentional control in MHD. Adding to this theory of impaired attentional control we found, on further analysis, that in the trial directly following a No-go error trial, the early group made significantly more go-errors (8%) than both the premanifest (0.5%) and control groups (3%). Similar results in a task-switch and stop-signal task in MHD have been reported[12]. Post-error slowing was interpreted in that study as task-switch cost and a deficit in the 'inhibition of the just-performed response' respectively. The authors attributed these phenomena to deficient inhibition. These explanations are not mutually exclusive in that early HD subjects can use the speed-accuracy trade-off strategy to avoid making further errors, but that their cognitive abilities are deficient and they cannot use this strategy successfully.

Even though constructs such as attention and inhibition are not directly measurable and can only be derived from secondary measurements, we hypothesize that the

RT pattern around No-go errors in the MHD group seems to reflect a cognitive rather than a motor process as subjects with early HD are able to respond in the same manner as PMHD and controls in correctly withheld No-go trials, albeit slower. This similar pattern for all groups demonstrates that it is not a No-go trial per se that elicits a deviant reaction from early subjects. The problem seems to lie purely in the fact that an error was made.

P300 amplitude and latency

As stated before P300 amplitude is hypothesized to reflect the amount of attentional capacity that is being allocated to a stimulus[27]. If so, then P300 amplitude would be lower for incorrectly performed No-go trials. This was indeed the case for the MHD group, confirming a lowered attentional control during presentation of No-go stimuli. Our findings correspond well to those of Beste et al. and Jurgens et al.[29 33]. Münte et al.[28] also reported lowered P300 amplitude, however not in the context of a Go/No-go task.
P300 latency is thought to be linked to the speed of attentional processing[27]. In accordance with Münte et al.[28], P300 latency was significantly longer in MHD compared to the other groups for Go trials. This implies a low speed of attentional processing during Go trials is lessened for MHD. Together with a lowered attention during No-go trials this strengthens our hypothesis that the disturbed pattern observed surrounding No-go errors is of a cognitive rather than a motor nature.

Premanifest HD results

PMHD did not exhibit any attentional or inhibitory deficits. Explanations for this are that no attentional control deficits are yet present or that subtle changes in attentional control capacity are already present in PMHD, but that they are still too subtle to be measured with this method. Possibly these deficits gradually worsen and are better picked up in subjects closer to expected onset. This interpretation seems plausible as both SART and P300 data did show a nonsignificant trend towards worse performance in the premanifest group. The only reverse pattern concerned SART error rate, where PMHD subjects made fewer errors than controls. We hypothesize that this reflects a high motivation. Clinical experience suggests that PMHD subjects are highly motivated to perform to their best on the tests, as they may wish to prove that there they are still in the premanifest phase.

Practical implications and limitations

Patients with HD may experience more distress from the decline of their cognitive functions rather than the presence of motor disturbances. The results from this study indicate that patients with HD experience difficulties with recovering after an error and maintaining attentional control for a longer period, which adds to the

knowledge about cognition in HD and could have implication for daily care.
A limitation to the present study is the relative small number of subjects in the PMHD group and therefore having less statistical power. This could have obscured possible subtle differences from controls.
We conclude that there is an attentional control deficit in MHD. MHD subjects are cognitively not able to directly resume task requirements after having made an error and that they need more time to return to pre-error performance level. No attentional control deficits were found for the PMHD group.

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Competing Interests

The authors state that they have no conflict of interest.

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Chapter 3

Longitudinal pilot-study of Sustained Attention to Response Task and P300 in manifest and premanifest Huntington's disease

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Abstract

Background Earlier research has found cross-sectional attentional control deficits in manifest Huntington's disease (HD) using neuropsychological testing combined with simultaneous P300 registration. In the current pilot-study we investigate attentional control in premanifest and manifest HD over a three-year follow-up period.

Method Five manifest HD (MHD), 9 premanifest HD (PMHD) and 12 control subjects were included. Sustained Attention to Response Test (SART) and P300 registration resulted in number of errors, reaction time (RT), and P300 amplitude and latency. RT change patterns surrounding No-go trials were also investigated. Within-subject differences were tested using paired-samples t-tests and between-group results with ANCOVA on delta scores (follow-up - baseline scores).

Results MHD made more errors and were slower than controls and PMHD. Longitudinally, MHD showed an overall RT increase and a specific slowing on trials preceding a correct No-go trial. The latter was also seen in PMHD. P300 latency prolongation was found for controls on No-go and for MHD on Go trials. Directly preceding a correct No-go, MHD became significantly slower over time than controls and PMHD.

Conclusions Over three-years MHD subjects became slower on the SART and showed a prolongation of P300 latency on specific SART trials. Specific slowing of performance over time was also seen in PMHD, suggestive of compensatory mechanisms in this group.

INTRODUCTION

Huntington's disease (HD) is a neurodegenerative disease caused by a gene mutation located on chromosome 4[1]. Its clinical manifestation is heterogeneous, with symptoms and signs occurring in three domains: motor, psychiatry and cognition[2]. Attentional deficits in HD patients have been widely demonstrated[3 4 5]. In premanifest HD subjects, i.e. gene carriers without overt clinical symptoms, differences in attentional processing compared to controls have also been found[6], but with inconsistent results[7 8]. Reports on longitudinal change in attentional functioning in premanifest HD are few[9 10 11], and again contradictory results have been found[12 13].

A practical test to investigate attentional processing is the Sustained Attention to Response Task (SART)[14], a simple Go/No-go task with little motor involvement. The P300, an event-related potential (ERP) that can be deduced from the EEG, is proposed to be an electrophysiological substrate of attentional and inhibitory processes[15 16]. In combination, these two assessments have demonstrated ability to detect lapses in attention[17].
Hart and colleagues[18] combined the SART with a simultaneous P300 registration to investigate attentional functioning in both a manifest and a premanifest HD group cross-sectionally. They demonstrated that attentional control was deficient in manifest HD subjects, apparent in the inability to directly resume task requirements after having made an error. The manifest subjects showed higher error rates corroborated by abnormalities in the P300 signal. While the attentional control deficit in manifest HD was evident, the performance of the premanifest HD group did not differ from that of controls, and no P300 abnormalities were found.

Recent MRI studies reported early brain changes involving grey and white matter[19 20] in premanifest gene carriers even far from expected disease onset. This raises the possibility that these changes can also be measured with functional assessments, such as P300. Indeed, differences in ERPs between premanifest HD subjects and controls have been found[21]. A majority of these studies have found reduced neurophysiologic measures in the absence of abnormal clinical performance in the premanifest groups. This coincides with findings in MRI studies where pathological changes in premanifest HD gene carriers are seen before onset of clinical symptoms[20].
To date, one longitudinal study has been performed using electrophysiological assessment in HD. Here, somatosensory evoked potentials were studied in a group of manifest HD subjects. The amplitude of these potentials demonstrated progressive decline over the two year follow-up period[22]. To our knowledge, no longitudinal electrophysiological research has been performed in premanifest HD subjects yet.

The current pilot-study aimed to investigate attentional deficits in premanifest and manifest HD subjects longitudinally. Observed early brain changes in preman-

ifest HD literature lead us to expect possible longitudinal change for SART error scores and P300 characteristics over the three year interval in this group. For the manifest group we expected to find abnormalities similar to those found earlier by Hart and colleagues: longer reaction time, more errors, and a lower No-go P300 amplitude than controls and premanifest HD subjects. Furthermore, due to the progressive nature of HD we expect a longitudinal worsening of these outcome values.

METHODS

Participants

Five manifest (MHD), 10 premanifest (PMHD), and 13 control subjects participated in this pilot-study and were tested with a three-year interval using the same tests. All subjects completed the baseline and follow-up visit, with a mean follow-up time of 36.7 months. One PMHD and one control subject were excluded from longitudinal analyses due to excessive muscle artefacts visible during the ERP registration. Eventually, data of 5 MHD, 9 PMHD and 12 control subjects were analyzed. None of the PMHD subjects converted to manifest HD over the study period. All subjects were grouped at visit 1 and were subsequently analyzed in this group at follow-up.

All participants were recruited from our outpatient neurology clinic. The controls were gene-negative relatives. Genecarriers were considered premanifest if they had a CAG expansion of $>$39 and a total motor score (TMS) of 5 on the Unified Huntington's Disease Rating Scale (UHDRS)[23]. Disease burden was calculated using the formula 'age(CAG-35.5)'[24]. Exclusion criteria for all subjects were major psychiatric disorder, neurological co-morbidity, a score of $\leq$25 on the Mini Mental State Examination (MMSE)[25] and medication with known effects on the P300 (e.g. neuroleptics). The study was approved by the local medical ethical committee and all participants gave written informed consent (according to the declaration of Helsinki). Subjects underwent neurological examination including the complete UHDRS, P300 and SART assessment on both baseline (visit 1) and follow-up visit (visit 2). The MMSE was used to measure global cognitive functioning. Depression was measured with the depression part of the Problem Behaviours Assessment short version[26], where depressive feelings are scored by severity and frequency (score range 0-16). The neurological assessment was performed at both visits by clinicians specialized in HD, blinded for genetic status.

Sustained Attention to Response Test

The SART was administered during both visits under the same conditions. Subjects were seated in a comfortable chair one meter from a computer screen, with a

computer keyboard placed in easy access of the dominant hand. Numbers from 1 to 9 were each shown 25 times on a computer screen. Subjects were asked to respond to every number by pressing a spacebar ('Go' trials), except when the number 3 was shown ('No-go' trials). In the case of a No-go trial subjects were instructed to withhold their response. Accuracy and speed were instructed to be equally important. Before the test subjects were allowed to practice with 25 random trials. The numbers were shown for 250 milliseconds followed by a blank screen for 900 milliseconds[14]. Reaction time (RT) was recorded whenever the spacebar was pressed. To ensure accurate measurement of RT a cathode ray screen was used together with a purpose built hardware device that allowed precise measurement of the build-up time of the screen information and hence of RT in relation to the visual stimulus[18].
Outcome measures for the SART were reaction time (RT) and number of errors. 'Overall RT' refers to mean RT over all trials performed. Errors are divided into total number of errors, and errors on Go and No-go trials. For error processing analyses the mean RT of the trials directly preceding and directly following both correct and incorrect No-go trials were used ('3' is the No-go item in the SART). A delta score was also computed, which comprised the difference between the mean RT on the trials directly preceding and directly following both correct and incorrect (i.e. an incorrect response to a three) No-go trials.

ERP recording and analysis

Twenty-one Ag/AgCl electrodes were placed according to the 10/20 convention. ECG, respiration and horizontal eye movement leads were also recorded. The EEG was band-pass filtered from 0.16-70 Hz before display and analysis. Sample frequency was 200 Hz and A-D precision 12 bits. For the P300 analysis we used the midline sites Fz (frontal), Cz (central) and Pz (parietal) with linked mastoids as reference. The computer controlling the SART paradigm wrote synchronization signals to the EEG machine, allowing averaging to take place offline after controlling for signal quality. Data were averaged over epochs of 1200 ms, starting 200 ms before stimulus onset. Individual trials with eye blink artefacts or suspected muscle artefacts were excluded from P300 analysis. The P300 component was defined as the maximum positivity between 350 and 650 ms. ERP analysis, including peak detection, was performed automatically using an in-house developed program written in MATLAB (The MathWorks, Natick, USA). Peak amplitudes were measured relative to a 200 ms baseline before stimulus onset. P300 outcome measures consisted of amplitude and latency data. The mean amplitudes and latencies for all trials, all Go trials and all No-go trials were calculated[18].

Statistical analysis

Data analysis was done using IBM SPSS statistics for Windows, version 20.0. Demographic variables were compared between groups using ANOVA (continuous variables) and Pearson's χ^2 (categorical variables). Classification of the groups at baseline was used for all analyses. ANCOVA was done for cross-sectional SART and P300 analyses, where separate analyses were performed for baseline and follow-up visits. For SART error scores, the age and mean RT at time of visit were used as covariates. Age was chosen because of the known effect of aging on neuropsychological testing. With the inclusion of RT as covariate we assume to test more pure cognitive performance while controlling for possible differences in RT. For the RT, P300 and error processing analyses, age at time of visit was selected as covariate. Again, age has been proven to have an altering effect on both RT and P300 characteristics. For longitudinal analyses of between group effects, delta scores (follow-up visit score-baseline visit score) were calculated and analyses of covariance were performed on these scores. Age at baseline was used as covariate, except for the analyses of SART error scores where age and mean RT at baseline were selected. Significant main results were further investigated using Bonferroni post-hoc tests. Within subjects effects were investigated using paired samples t-tests. Effect sizes are reported as partial eta squared values. The level of statistical significance was set at $p \leq 0.05$. For both cross-sectional as longitudinal analyses Bonferroni correction was applied to correct for multiple testing.

RESULTS

Demographic data

Demographic and clinical data of baseline and follow-up visits are shown in Table 1. The groups were similar in terms of age, gender, education, and total functional, depression and MMSE scores on both visits. MHD subjects had a higher disease burden than PMHD subjects ($F(1, 12) = 12.41$, $p = 0.004$). The TMS of the MHD group was higher than the TMS of the PMHD ($F(2, 23) = 8.89$, $p = 0.002$) and control group (visit 1: $F(2, 23) = 8.89$, $p = 0.003$, and visit 2: $F(2, 23) = 8.89$, $p < 0.001$) on both visits.

Cross-sectional data

Cross-sectional data of the SART and P300 are shown in Table 2. MHD subjects made more total ($F(2, 21) = 4.07$, $p = 0.03$, $\eta_p^2 = 0.280$) and No-go errors ($F(2, 21) = 5.18$, $p = 0.02$, $\eta_p^2 = 0.330$) on both visit 1, and visit 2 ($F(2, 21) = 7.30$, $p = 0.004$, $\eta_p^2 = 0.410$, and $F(2, 21) = 8.80$, $p = 0.002$, $\eta_p^2 = 0.456$, respectively) compared to PMHD subjects and controls. Additionally, the MHD group reacted slower on visit 2 ($F(2, 22) = 9.51$, $p = 0.001$, $\eta_p^2 = 0.464$) compared to PMHD

subjects and controls.
Concerning the P300 characteristics MHD subjects showed a longer overall (visit 1 $F(2, 22) = 3.68$, $p = 0.04$, $\eta_p^2 = 0.250$), Go (visit 1 $F(2, 22) = 3.53$, $p = 0.047$, $\eta_p^2 = 0.243$ and visit 2 $F(2, 22) = 4.14$, p=0.03, $\eta_p^2 = 0.273$) and No-go (visit 1 $F(2, 22) = 4.64$, $p = 0.02$, $\eta_p^2 = 0.297$) latency than PMHD and control subjects. Also, the MHD group demonstrated a lower No-go amplitude than the control group on visit 1 ($F(2, 22) = 3.69$, $p = 0.04$, $\eta_p^2 = 0.251$).

Table 1: Descriptive statistics at baseline and follow-up visits

Characteristic		Premanifest HD N=9	Manifest HD N=5	Controls N=12
Age (years)	baseline	40.3 (10.0)	45.4 (10.7)	48.2 (9.7)
	follow-up	43.4 (9.7)	48.4 (10.7)	51.3 (9.7)
Gender, m/f[a]	baseline	3/6	2/3	5/7
Education (years)	baseline	12.3 (2.6)	14.4 (2.9)	11.9 (2.7)
CAG repeat length	baseline	41.3 (1.5)	44.4 (3.1)	20.0 (2.9)
Disease burden	baseline	232.2 (73.3)	382.5 (82.5)	
	follow-up	250.7 (75.8)	409.2 (90.7)	
Total motor score	baseline	1.6 (2.5)	6.4 (1.3)	2.0 (2.2)
(range 0-124)	follow-up	2.2 (1.5)	14.8 (7.7)	3.0 (3.4)
Total functional capacity	baseline	12.2 (1.1)	12.0 (1.4)	13.0 (0)
(range 0-13)	follow-up	11.8 (1.6)	12.0 (1.2)	12.8 (0.6)
PBA-s depression score	baseline	2.8 (2.9)	2.2 (3.3)	3.0 (3.5)
(range 0-16)	follow-up	1.0 (2.1)	2.0 (2.0)	1.1 (1.6)
Score MMSE	baseline	28.8 (0.8)	28.4 (0.9)	29.0 (1.0)
(range 0-30)	follow-up	28.8 (1.2)	28.6 (1.5)	29.4 (0.7)

Note. Data is presented as mean (SD), [a] is total number.

Longitudinal data

No between-group effects were found longitudinally for SART and P300 data. Concerning within-subjects differences, paired samples t-tests showed a significant mean RT increase over time on the SART for MHD participants ($t(4)$ = -9,56, p = 0.01, η_p^2 = 0.938).
A prolongation of the No-go P300 latency was found for controls ($t(11)$ = -3.56, p = 0.004, η_p^2 = 0.494) and of the Go latency for MHD ($t(4)$ = -2.82, p = 0.048, η_p^2 = 0.570). No significant changes were observed concerning P300 amplitude.

SART error processing analyses cross-sectional data

Data for the error processing analysis are shown in Table 3. Cross-sectionally, MHD subjects reacted slower on the trial directly following both correctly ($F(2, 22)$ = 3.75, p = 0.04, η_p^2 = 0.254) and incorrectly ($F(2, 21)$ = 5.49, p = 0.01, η_p^2 = 0.343) withheld responses to No-go trials (appearance of the number '3') compared to controls at visit 1. MHD subjects were also slower in reacting to the trial just preceding a correct No-go ($F(2, 22)$ = 6.03, p = 0.007, η_p^2 = 0.364) and following both correct ($F(2, 22)$, $p < 0.001$, η_p^2 = 0.544) and incorrect ($F(2, 22)$, $p < 0.001$, η_p^2 = 0.542) No-go trials, all compared to both controls and PMHD participants at visit 2.

SART error processing analyses longitudinal data

ANCOVA on delta scores revealed between group differences for trials preceding a correct No-go trial. RT in all groups became longer over time, but MHD subjects became significantly more so than the other groups ($F(2, 22)$ = 6.22, p = 0.007, η_p^2 = 0.361). Regarding within-subject effects paired samples t-tests showed that both MHD ($t(4)$ = -5.15, p = 0.007, η_p^2 = 0.815) and PMHD ($t(8)$ = -2.68, p = 0.03, η_p^2 = 0.418) participants became slower over time on trials directly preceding correct No-go trials.

Table 2: SART and P300 data: cross-sectional and longitudinal within-subjects and between-group analyses

SART	Group PMHD (N=9) MHD (N=5) Controls N=12	Baseline	Follow-up	Cross-sect baseline p-value	Cross-sect follow-up p-value	Longit[a] within-subjects p-value	Longit[b] between-group p-value
	PMHD	7.9 (4)	6.7 (3)			0.171	
Total error	MHD	12.0 (8)	12.4 (4)	<**0.05**	<**0.01**	0.889	0.267
	Controls	8.2 (5)	9.3 (3)			0.362	
	PMHD	6.9 (3)	6.4 (3)			0.559	
No-go error	MHD	10.8 (7)	8.8 (4)	<**0.05**	<**0.01**	0.417	0.140
	Controls	7.1 (4)	8.3 (3)			0.234	
	PMHD	1.0 (2)	0.2 (0)			0.211	
Go error	MHD	1.2 (2)	3.6 (4)	0.596	0.421	0.170	0.587
	Controls	1.1 (1)	0.9 (1)			0.732	
	PMHD	361.4 (32)	374.9 (33)			0.098	
Mean RT	MHD	422.9 (81)	481.9 (84)	0.055	<**0.01**	<**0.01**	0.174
	Controls	371.2 (29)	379.9 (39)			0.435	

Table continued on next page.

Table 2: **(Continued)** SART and P300 data: cross-sectional and longitudinal within-subjects and between-group analyses

P300	Group PMHD (N=9) MHD (N=5) Controls N=12	Baseline	Follow-up	Cross-sect baseline p-value	Cross-sect follow-up p-value	Longit[a] within-subjects p-value	Longit[b] between-group p-value
	PMHD	380 (18)	394 (36)			0.138	
Latency	MHD	435 (46)	451 (58)	**<0.05**	0.089	0.313	0.760
	Controls	406 (39)	413 (39)			0.407	
	PMHD	391 (34)	420 (47)			0.080	
Lat No-go	MHD	449 (62)	474 (45)	**<0.05**	0.081	0.453	0.850
	Controls	408 (22)	432 (33)			**<0.001**	
	PMHD	375 (21)	396 (36)			0.119	0.204
Latency Go	MHD	430 (45)	454 (53)	**<0.05**	**<0.05**	**<0.05**	
	Controls	409 (41)	406 (30)			0.646	
	PMHD	10.2 (5)	9.6 (4)			0.597	0.674
Amplitude	MHD	7.8 (3)	8.2 (2)	0.427	0.736	0.630	
	Controls	9.6 (3)	8.9 (3)			0.222	
	PMHD	17.3 (6)	16.5 (5)			0.534	
Amp No-go	MHD	10.9 (3)	14.1 (6)	**<0.05**	0.406	0.223	0.111
	Controls	17.8 (4)	17.6 (5)			0.742	
	PMHD	9.6 (5)	9.1 (5)			0.628	
Amplitude Go	MHD	7.6 (3)	7.8 (2)	0.449	0.698	0.769	0.767
	Controls	8.3 (3)	7.9 (3)			0.221	

Note. Data is presented as mean (SD). [a]paired samples t-tests; [b]ANCOVA on delta-scores. RT = reaction time in milliseconds. Amplitude is in microvolts (μV). Latency is in milliseconds, MHD=manifest HD, PMHD=premanifest HD.

Table 3: SART error analysis data: cross-sectional and longitudinal within-subjects and between-group analyses

	Group PMHD (N=9) MHD (N=5) Controls N=12	Baseline	Follow-up	Cross-sect baseline p-value	Cross-sect follow-up p-value	Longit[a] within-subjects p-value	Longit[b] between-group p-value
Correct 3							
RT	PMHD	336 (21)	392 (43)			<**0.05**	
before	MHD	426 (92)	535 (128)	0.070	<**0.01**	<**0.01**	<**0.01**
	Controls	409 (43)	416 (67)			0.760	
RT	PMHD	314 (57)	349 (37)			0.054	
after	MHD	381 (76)	421 (70)	<**0.05**	<**0.001**	0.223	0.099
	Controls	317 (18)	310 (23)			0.442	
Incorrect 3							
RT	PMHD	338 (45)	350 (48)			0.391	
before	MHD	350 (39)	444 (194)	0.777	0.185	0.278	0.115
	Controls	349 (35)	364 (53)			0.625	
RT	PMHD	414 (85)	360 (36)			0.092	
after	MHD	476 (104)	529 (108)	<**0.05**	<**0.001**	0.435	0.118
	Controls	338 (54)	363 (59)			0.414	

Note. Data are mean (SD). Reaction time are milliseconds. [a]paired samples t-tests; [b]ANCOVA on delta-scores, MHD=manifest HD, PMHD=premanifest HD, RT = Reaction Time.

DISCUSSION

In this pilot-study we present preliminary data on longitudinal SART and simultaneous P300 assessment in HD. To our knowledge we are the first to perform a longitudinal ERP study in premanifest HD. We found that over a course of three years MHD subjects showed an increase in RT on the SART, and exhibited a prolongation of the P300 latency on specific trials of the SART. PMHD subjects only showed specific increase in reaction time just before having prevented a possible error on the SART.

In the MHD group we replicated the findings of the cross-sectional study by Hart et al.[18] on the SART and P300 in HD where MHD subjects make more errors on the SART than both other groups, and took longer to react to the trials (follow-up visit). The increase in reaction time is not surprising, and is likely to reflect motor slowing. This conclusion is strengthened by only specific, and not overall, RT increase in the PMHD subjects. In the earlier study the authors hypothesized that the observed slowing could reflect a speed-accuracy trade-off, a (conscious or unconscious) strategy applied by MHD participants to maintain task requirements[27]. The increase in RT seen in the current MHD cohort does however not prevent these subjects from making more mistakes than the other two groups. So, there is no task-related benefit from the motor slowing. One explanation for this absence of benefit could be that the employment of the speed-accuracy trade-off has reached a maximum. If this level is reached the impairment can no longer be compensated and task-related benefit is absent.
The MHD group also showed the most pronounced RT increase over time, which was expected in view of the neurodegenerative nature of HD. Neurodegeneration is also reflected in the neurophysiologic data, as demonstrated by the cross-sectionally longer P300 latencies compared to the other groups, and the latency prolongation over time on Go trials. The P300 latency has been linked to stimulus evaluation time, or generalized, cognitive processing speed[28], so a lengthened latency in the MHD group could reflect reduced processing speed. Deficits in processing speed have also been demonstrated by other authors using other paradigms[29 30].

Cross-sectionally, premanifest subjects perform equally to control subjects, evident by the lack of cross-sectional results. Interestingly, in the PMHD group we did find specific slowing over time. During follow-up this group became slower in reacting to trials directly preceding correct No-go trials (i.e. correctly withholding the response to the appearance of a '3'). This slowing was also seen in the MHD group, but only MHD subjects produced more errors than controls. The exact significance of such specific deterioration is difficult to explain, but as the PMHD subjects make the same number of errors as controls and increase in RT where controls do not, this could mean that it takes more attentional demands for PMHD subjects to maintain task performance. As PMHD subjects can keep up with the

demands of the SART it could mean that the RT increase is the result of some kind of compensatory mechanism. That it reflects pure motor slowing is less likely as in this case we would have expected increased RT on more variables.
A candidate compensatory mechanism here could be speed-accuracy trade-off, a strategy that was used by MHD subjects in the cross-sectional study[18]. That growing attentional demands could translate into increased RT is well described in speed-accuracy trade-off literature[27]. Additionally, the controls did not slow over time on these specific trials, and produced a similar amount of errors as the PMHD subjects. This strengthens our hypothesis that some kind of compensation is utilized by the latter group. This proof of early compensation by means of speed-accuracy trade-off in PMHD complements our earlier hypothesis that in the current MHD cohort the maximum level of compensation (by means of speed-accuracy trade-off) is reached and no more task-related benefits are observed.
That compensatory mechanisms are at work in PMHD has been suggested before[31]. In another basal ganglia disorder, Parkinsons disease (PD), compensatory mechanisms responsible for delaying overt symptom onset have long been accepted[32]. Here, even several compensatory networks have been identified postponing the final appearance of parkinsonism[33]. Looking at our overall raw data we also see that for SART errors and mean RT scores the premanifest subjects perform better not only than the MHD, but also than the control subjects. This could reflect overall compensation to perform at pre-disease level.

The significant post-error slowing that was found in the previous cross-sectional study was not replicated in the present study. An explanation for this could be that the manifest group, consisting of five subjects, was too small to make this difference visible. Also, individual differences in such a small sample could have large effects. This is evident in the differences in RT patterns surrounding incorrect responses to a No-go trial, where at baseline some post-error slowing was visible (albeit not statistically significant) for MHD and PMHD, while it was absent at follow-up.

As our preliminary data derived from small pilot groups our conclusions should be considered with caution. Generalization of our results is limited as, due to the sample sizes, statistical power is low and the impact of individual fluctuations in scores more influential.
The combination of cognitive testing (SART) with simultaneous P300 registration is a strength of this study, in the way that the P300 is independent of motor slowing whereby conclusions about cognitive functioning can be made more easily. Following the specific result in the PMHD group we recommend replication of this pilot-study with larger numbers of participants in order to be better able to understand the transition from premanifest to manifest HD.

In conclusion, this pilot-study partly replicated the findings from the cross-sectional

study by Hart and colleagues[18] that MHD subjects perform worse than both PMHD and control subjects on tests of attentional control. MHD subjects are slower and make more mistakes on the SART, and show longer P300 latencies. Longitudinal change in attentional control was observed for specific trials in the PMHD subjects, which could be suggestive of compensatory mechanisms in this phase of HD.

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Chapter 4

Seven-year clinical follow-up study of premanifest carriers of Huntington's disease

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Abstract

Detecting subtle clinical abnormalities in the 'premanifest' phase of Huntington's disease (HD) is of importance in the development of instruments to monitor early therapeutic intervention trials. The current study examined changes in motor function, cognition and behaviour over a period of seven years in premanifest carriers of the HD gene mutation. Twenty-nine carriers without unequivocal motor signs of HD and 43 non-carrier controls were prospectively examined four times. The assessments consisted of the Unified Huntington's Disease Rating Scale (UHDRS) and an extensive neuropsychological test battery addressing global cognitive function, memory, language and executive function. Rate of Change (RoC) analysis was performed to measure longitudinal differences between carriers and non-carriers. Carriers performed consistently worse on executive function (Symbol Digit Modalities Test, Stroop, Trail Making Test and Wechsler Adult Intelligence Scale-Revised arithmetic). Over the years, carriers showed a decline in memory and concentration function (Wechsler Memory Scale) and in motor function (UHDRS motor scale). Changes over time could be particularly ascribed to carriers converting to manifest HD. These results demonstrate that standardized motor assessments and objective memory and concentration tasks are sensitive to change over a period of 7 years, specifically in carriers converting to manifest HD. Executive tasks also showed subtle cognitive abnormalities in premanifest HD, but a decline over time could not be demonstrated.

INTRODUCTION

Huntington's disease (HD) is a hereditary neurodegenerative disease that becomes manifest in midlife and is characterised by motor disturbances, cognitive decline and behavioural dysfunction. HD is caused by the abnormal expansion of a trinucleotide (CAG) repeat in the gene for the protein huntingtin[1]. The genetic defect leads to cerebral cell death, especially in the basal ganglia. Although the clinical diagnosis of HD is based on the first appearance of motor signs, a positive family history and confirmation by DNA-testing, subtle changes in motor function, cognition and behaviour are known to precede manifest disease. Detecting these very early changes is of importance in the development of instruments to monitor early therapeutic intervention trials and to obtain more insight into the phase of clinical disease onset.

Cross-sectional reports showed that carriers of the HD gene mutation without manifest motor signs (further labelled as carriers) perform significantly worse than non-carriers on certain motor scores, neuropsychological tests and behavioural assessments[2,3,4,5,6,7,8,9,10,11]. Furthermore, some studies showed relationships between fewer years to estimated onset of diagnosable clinical disease and worse motor and cognitive function[2,7,12,13,14].
Longitudinal follow-up is however necessary to really understand the pattern of evolving motor, cognitive and behavioural abnormalities in the phase of HD clinical onset. First of all, to find out if clinical markers that are sensitive in detecting premanifest abnormalities show a decline over time and might be suitable as outcome measures in future therapeutic trials. Secondly, to monitor whether carriers, converting to manifest HD, display specific clinical changes.

To date, several longitudinal studies have been undertaken. The duration of follow-up however has been brief in the vast majority of longitudinal studies and results show discrepancies. In accordance with other studies we failed to demonstrate clinical markers for premanifest HD in our previous 3-year follow-up study[15,16,17]. Others did detect a significant decline over time in motor function, executive function, attention and memory[18,19,20,21]. The longest follow-up study to date (10 years) demonstrated that the most rapid decline on motor and cognitive domains was found in individuals approaching clinical disease onset[13].

With the present observational study we aim to give more insight in the clinical onset phase of the disease as the number of reports on clinical decline in premanifest HD using long-term follow-up with a comprehensive assessment battery is limited. The objective was to follow a premanifest HD carrier group for 7 years in order to determine if our assessment battery detects subtle clinical changes preceding diagnosable clinical HD. Furthermore, we examined whether the rate of decline on motor, cognitive and behavioural measures could be related to estimated proximity

to diagnosable clinical disease.

METHODS

Participants

In the original study, 134 participants were included (46 premanifest carriers, 88 non-carriers). They were referred to the Leiden University Medical Centre (LUMC) Department of Clinical Genetics, for predictive testing, and consented to participate in a three-year clinical follow-up study[17]. Carriers were considered to be premanifest in the absence of unequivocal motor signs on the Unified Huntington's Disease Rating Scale (UHDRS)[22]. A neurologist who was blind to genetic status and trained in the administration of the UHDRS performed the motor examination and filled in a score ranging from 0-3 (0= normal, 1= minor soft signs, 2= probable HD, 3= unquestionable HD). Carriers with a rating of 3 at baseline were diagnosed with HD and excluded from the study. One hundred six participants (33 carriers, 73 non-carriers) attended all follow-ups in the three-year period. Seven years after the start of the original study these participants were invited to take part in an additional follow-up. Twenty-nine carriers and 44 non-carriers consented to continue follow-up. Four carriers and 29 non-carriers did not re-enter the study after the original three year follow-up (Figure 1). One non-carrier was excluded for analyses since he had a minor stroke. This seven year follow-up study, therefore, reports on 29 carriers who were premanifest at baseline, and 43 non-carriers who served as controls. Carriers who were rated as unquestionable HD on the UHDRS after seven years were considered converters to manifest HD. The study was approved by the local Medical Ethical Committee. Written informed consent was obtained from all participants.

Procedure

All participants were evaluated with the UHDRS, including motor and behavioural assessment, and an extensive set of neuropsychological tests covering global cognitive function, memory, language and executive function (Tables 2 and 3)[17,22]. The number of estimated years to clinical diagnosis (EYTD) was calculated using a CAG- and age-based predictive model designed by Langbehn et al.[23].

Motor assessment

The UHDRS motor rating was filled in by a neurologist (range 0-3). A Total Motor Score (TMS) was calculated by summing all motor items of the UHDRS[17]. Analysis of TMS subscales was restricted to eye movement, voluntary movement and chorea[22].

Neuropsychological assessment
Neuropsychological tests included Mini Mental State Examination (MMSE)[24]; Wechsler Adult Intelligence Scale-Revised (WAIS-R)[25] subtests Information, Digit span, Arithmetic, Picture arrangement, Block design; Wechsler Memory Scale (WMS)[26]; Verbal fluency (FAS)[27]; Boston naming test[28]; Symbol Digit Modalities Test (SDMT)[29]; Trail Making Test[30], consisting of a simple (TMT-A) and a more complex (TMT-B) version; Stroop colour-word test[31]. Reaction time measures were both derived from a simple reaction time paradigm and a complex 'choice' reaction time paradigm (go/no go paradigm)[32]. A psychologist administered the cognitive tests[17].

Behavioural assessment
Behavioural and mood complaints were limited to the total behavioural score (TBS) that was obtained by adding the products of the frequency and severity for each item from the behavioural assessment of the UHDRS, administered by a psychologist[11]. Analysis of individual items from the behavioural assessment were restricted to four frequently reported neuropsychiatric symptoms; sadness, anxiety, aggression and irritability[33].

Statistical analysis

SPSS for Windows (release 16.0) was used for data analysis. Cross-sectional group differences at baseline and after 7 years were analysed with parametric or non-parametric tests when appropriate. Clinical group comparisons were corrected for age at assessment using ANCOVA. For longitudinal analyses we used the method reported by Solomon et al. (2008) since it accounts for slight differences in follow-up period. For each clinical score the change over the 7-year period was calculated for each participant. This Rate of Change (further labelled as RoC) was computed as follows: RoC= ($score_2$-$score_1$)/ (age_2-age_1). Differences in RoC between carriers and non-carriers were analysed using ANCOVA with correction for age at baseline. To assess the relationship between EYTD and RoC, Pearson correlation coefficients were calculated. The level of statistical significance was set at $p \leq 0.01$. A more liberal level of significance of $0.01 < p \leq 0.05$ was also reported to be of marginal interest to maximize any opportunity of finding trends towards group differences. Effect sizes are displayed as partial eta squared values ($_p\eta^2$), eta squared values (η^2) and *r*-values.

RESULTS

Group characteristics at study entry

The mean time interval between baseline and seven-year follow-up was 7.3 years (range 6.3-8.5 years). The group characteristics are described in Table 1. Carriers were younger than non-carriers (p= .015, η^2= .082). No group differences emerged for gender and education.

Table 1: Characteristics of carriers and non-carriers at baseline

	Carriers N=29	Non-carriers N=43	P-value
Male/female[a]	11/18	18/25	ns
Age (years)	37.9 (9.1)	43.8 (10.4)	**0.015**
Education (years)	12.0 (2.9)	11.9 (2.8)	ns
CAG repeat length[b]	42.9 (39-49)	20.7 (16-30)	
Estimated years to clinical diagnosis[b]	15.6 (4.3-36.4)	-	

Note. Values in the table are means with SD or range[b] between parentheses. Independent t-tests were used except where Pearson χ^2-test was used [a].

Cross-sectional results

Carriers did not differ from non-carriers with respect to the UHDRS motor rating at baseline (p= .99, r= -0.002) or after seven years (p= .12, r= -0.192) (Table 2). Five carriers (17%) converted to unquestionable HD on the UHDRS during follow-up. Two converters were rated as normal at baseline. Three converters were rated as probable HD at baseline. One carrier who was rated as probable HD at baseline was rated as normal after 7 years. Three non-carriers were rated as probable HD at baseline and five after 7 years. None of the non-carriers was rated as unquestionable HD. From the three carriers where motor assessment was missing at baseline, two were rated as normal after 7 years and one carrier showed minor soft signs.

Mean clinical scores are displayed in Table 3. At baseline, carriers showed more complaints in aggression than non-carriers (p= .024, ${}_p\eta^2$= .073). They also performed worse on the WAIS-R arithmetic subsection (p= .031, ${}_p\eta^2$= .065), SDMT (p=.002, ${}_p\eta^2$= .128), TMT-A (p= .006, ${}_p\eta^2$= .104), TMT-B (p= .024, ${}_p\eta^2$= .072), Stroop word (p= .008, ${}_p\eta^2$= .097) and Stroop interference (p=.01, ${}_p\eta^2$= .089). After seven years carriers additionally showed more motor abnormalities

compared to non-carriers on the UHDRS TMS (p= .012, ${}_p\eta^2$= .096), and on the UHDRS eye movement (p= .026, ${}_p\eta^2$= .076), voluntary movement (p= .029, ${}_p\eta^2$= .073) and chorea subsection (p= .005, ${}_p\eta^2$= .118). Also, worse scores on the MMSE (p= .015, ${}_p\eta^2$= .083), WMS memory quotient (p= .001, η^2= .147), WMS concentration (p= .001, ${}_p\eta^2$= .161), WMS logical memory (p= .025, ${}_p\eta^2$= .07) WMS visual reproduction (p= .042, ${}_p\eta^2$= .059) and Stroop colour (p= .009, ${}_p\eta^2$= .097) emerged in carriers. Cross-sectional differences at baseline on aggression and Stroop word could not be demonstrated after seven years. Without the five carriers who converted to manifest HD, baseline differences remained, except for TMT-B (p= .144, ${}_p\eta^2$= .033). In the analyses after seven years, differences remained only on UHDRS TMS (p= .04, ${}_p\eta^2$= .071) WMS memory quotient (p=.007, η^2= .105), WMS concentration (p=.006, ${}_p\eta^2$= .114) and Stroop colour (p= .027, ${}_p\eta^2$= .075).

Table 2: Frequencies of UHDRS motor ratings in carriers and non-carriers at baseline and after 7 years

	Carriers N=29	Carriers N=29	Non-carriers N=43	Non-carriers N=43
UHDRS rating	Baseline	Seven years	Baseline	Seven years
Normal	19	15	29	24
Minor soft signs	3	5	9	8
Probable HD	4	4	3	5
Unquestionable HD	-	5	-	-

Note. Values are expressed as number. UHDRS= Unified Huntington's Disease Rating Scale. Out of 29 carriers 3 motor assessments were missing at baseline. Out of 43 non-carriers two motor assessments were missing at baseline and six at follow-up.

Table 3: Mean (SD) performances on motor, behavioural and cognitive assessment at baseline and seven-year follow up in carriers and non-carriers

	Baseline				**Seven years**			
	Carriers N=29	Non-carriers N=43	P-value	${}_p\eta^2$	Carriers N=29	Non-carriers N=43	P-value	${}_p\eta^2$
Motor[b]								
UHDRS TMS	6.9 (7.8)	6.3 (5.7)	.124	.037	8.0 (15.5)	2.8 (2.7)	**.012***	.096
Eye movement	2.2 (3.3)	1.9 (2.8)	.113	.039	1.8 (4.2)	0.9 (1.3)	**.026***	.076
Voluntary mov.	2.1 (2.1)	1.9 (2.0)	.135	.035	2.1 (3.9)	0.9 (1.3)	**.029***	.073
Chorea	1.2 (2.5)	0.9 (2.1)	.363	.013	2.6 (5.2)	0.5 (0.8)	**.005****	.118
Behaviour[b]								
UHDRS TBS	9.0 (13.4)	5.2 (7.2)	.484	.007	9.6 (13.1)	8.1 (12.6)	.786	.001
Sadness	1.9 (2.8)	1.3 (2.2)	.989	.00	2.0 (3.2)	2.0 (3.0)	.436	.009
Anxiety	1.3 (2.7)	1.0 (1.9)	.702	.002	1.8 (2.8)	1.3 (2.5)	.873	.00
Aggression	1.5 (3.0)	0.2 (0.8)	**.024***	.073	1.6 (3.0)	0.8 (2.3)	.558	.005
Irritability	1.4 (2.8)	1.0 (2.1)	.696	.002	1.6 (2.7)	1.7 (2.7)	.383	.011

Table continued on next page.

Table 3: **(Continued)** Mean (SD) performances on motor, behavioural and cognitive assessment at baseline and seven-year follow up in carriers and non-carriers (continued)

	Baseline				**Seven years**			
	Carriers N=29	Non-carriers N=43	P-value	${}_p\eta^2$	Carriers N=29	Non-carriers N=43	P-value	${}_p\eta^2$
Neuropsychology								
MMSE	28.2 (1.1)	28.6 (1.3)	.248	.019	28.3 (1.3)	29.0 (1.2)	**.015***	.083
W-R Information	10.4 (3.0)	10.8 (1.8)	.932	.00	10.6 (2.8)	10.9 (2.0)	.899	.00
W-R Digit span	8.1 (2.6)	8.9 (2.2)	.076	.045	8.4 (3.0)	9.3 (2.1)	.078	.044
W-R Arithmetic	10.6 (3.3)	12.3 (2.5)	**.031***	.065	10.6 (3.4)	12.4 (2.6)	**.023***	.073
W-R Picture arr.	8.8 (2.5)	9.2 (2.6)	.217	.022	9.3 (2.7)	9.2 (3.1)	.347	.013
W-R Block design	11.8 (3.0)	11.7 (2.9)	.591	.004	11.6 (3.3)	11.9 (2.9)	.118	.036
WMS MQ[a]	115.2 (15.6)	122.1 (14.7)	.062	.05	113.8 (19.0)	127.8 (15.3)	**.001****	.147
WMS Concent.	7.7 (1.8)	8.4 (1.2)	.107	.037	6.8 (2.1)	8.4 (1.2)	**.001****	.161
WMS Logic. mem.	9.4 (3.1)	10.1 (3.2)	.237	.02	8.2 (3.3)	10.0 (3.6)	**.025***	.07
WMS Visual rep.	11.1 (2.3)	11.2 (2.2)	.686	.002	10.2 (3.3)	11.2 (2.2)	**.042***	.059
WMS Ass. learning	18.0 (2.2)	18.0 (2.6)	.719	.002	17.2 (2.9)	17.5 (3.0)	.600	.004
WMS Verbal fluency	33.7 (9.4)	34.2 (11.5)	.869	.000	34.8 (14.0)	37.4 (12.0)	.387	.011
Boston naming	26.6 (2.6)	26.1 (4.6)	.712	.002	27.1 (2.5)	27.7 (2.0)	.308	.015
SDMT	48.2 (10.8)	53.2 (10.1)	**.002****	.128	53.3 (15.8)	58.7 (10.5)	**.006****	.103

Table continued on next page.

Table 3: **(Continued)** Mean (SD) performances on motor, behavioural and cognitive assessment at baseline and seven-year follow up in carriers and non-carriers (continued)

	Baseline				**Seven years**			
	Carriers N=29	Non-carriers N=43	P-value	$_p\eta^2$	Carriers N=29	Non-carriers N=43	P-value	$_p\eta^2$
Neuropsychology								
TMT-A (sec)[b]	38.3 (14.8)	31.2 (9.4)	**.006****	.104	33.0 (17.6)	28.4 (9.4)	**.035***	.063
TMT-B (sec)[b]	59.6 (22.9)	51.4 (17.4)	**.024***	.072	66.1 (47.1)	52.1 (23.2)	**.017***	.079
Stroop colour	74.0 (11.7)	77.4 (10.8)	.054	.053	71.5 (14.6)	77.6 (13.3)	**.009****	.097
Stroop word	95.5 (16.5)	103.4 (14.4)	**.008****	.097	96.1 (20.4)	101.2 (15.7)	.086	.043
Stroop interfer.	42.1 (10.4)	45.2 (8.5)	**.01****	.089	41.5 (9.8)	45.6 (8.8)	**.001****	.150
RT simple (milliseconds)	428.5 (70.5)	422.2 (63.7)	.298	.017	484.6 (113.5)	455.8 (80.2)	.135	.036
RT complex (milliseconds)	568.1 (84.8)	552.7 (85.0)	.146	.033	640.8 (127.6)	615.0 (106.2)	.112	.041

Note. Mean scores (SD). Raw scores are displayed except for WMS memory quotient, which is calculated with a correction for age. ANCOVA corrected for age except for [a]. *p$\leq$ .05, **p $\leq$.01. Effect sizes are displayed as partial eta squared ($_p\eta^2$) values. [b]Higher scores correspond with worse performance. MMSE=Mini Mental State Examination, MQ=Memory Quotient, RT=Reaction time; simple=reaction time single stimulus conditions; complex=reaction time complex conditions, SDMT=Symbol Digit Modalities Test (number correct), TBS=Total Behavioural Score, TMS=Total Motor Score, TMT=Trail Making Test, UHDRS=Unified Huntington's Disease Rating Scale. WMS=Wechsler Memory Scale, W-R=Wechsler Adult Intelligence Scale-Revised.

Longitudinal results

The Rates of Change (RoC) on the motor, behavioural and cognitive tests are displayed in Table 4. Carriers demonstrated a greater rate of decline compared to non-carriers on the UHDRS TMS (p= 0.024, ${}_p\eta^2$= .083) and chorea subsection (p= .008, ${}_p\eta^2$= .114), the WMS memory quotient (p= .015, ${}_p\eta^2$= .084), WMS concentration (p= .007, ${}_p\eta^2$= .101) and WMS visual reproduction (p= .045, ${}_p\eta^2$= .057). Without the carriers who converted to manifest HD, the only remaining significant decline in carriers compared to non-carriers was on WMS concentration (p= .041, ${}_p\eta^2$= .063).

Associations between estimated years to clinical diagnosis and Rates of Change

Table 5 shows that proximity to estimated clinical diagnosis (EYTD) in carriers was associated with a greater rate of decline on WAIS-R Information (p= .033, r= .397), WMS memory quotient (p= .024, r= .426) (Figure 2), WMS concentration (p= .034, r= .396), WMS logical memory (p= .016, r= .444), WMS visual reproduction (p= .012, r= .461) and Reaction time complex condition (p= .046, r= -.410). Excluding the carriers who converted to manifest HD, associations remained between EYTD and rate of decline on WMS memory quotient (p= .045, r= .421), WMS logical memory (p= .028, r= .448) and WMS visual reproduction (p= .005, r= .553).

Table 4: Mean (SD) Rate of Change (RoC) in carriers and non-carriers between baseline and 7-year follow-up

Motor[b]	Carriers N=29 RoC	Non-carriers N=43 RoC	P-value	$_p\eta^2$
UHDRS TMS	0.217 (1.440)	-0.475 (0.639)	**.024**[*]	.083
Eye movement	-0.037 (0.401)	-0.141 (0.294)	.431	.011
Voluntary movement	0.012 (0.375)	-0.149 (0.252)	.103	.045
Chorea	0.235 (0.523)	-0.052 (0.328)	**.008**[**]	.114
Behaviour[b]				
UHDRS TBS	0.164 (2.178)	0.380 (1.485)	.634	.003
Sadness	0.025 (0.581)	0.093 (0.313)	.634	.003
Anxiety	0.079 (0.556)	0.043 (0.326)	.554	.005
Aggression	0.019 (0.457)	0.084 (0.321)	.388	.011
Irritability	0.039 (0.493)	0.091 (0.375)	.401	.010
Neuropsychology				
MMSE	0.012 (0.213)	0.057 (0.200)	.319	.014
W-R Information	0.030 (0.236)	0.007 (0.129)	.706	.002
W-R Digit span	0.048 (0.260)	0.057 (0.225)	.994	.000
W-R Arithmetic	-0.006 (0.321)	0.016 (0.296)	.728	.002
W-R Picture arrangement	0.067 (0.255)	0.004 (0.314)	.745	.002
W-R Block design	-0.028 (0.314)	0.035 (0.228)	.156	.029
WMS MQ[a]	-0.265 (1.813)	0.760 (1.593)	**.015**[*]	.084
WMS Concentration	-0.134 (0.236)	0.004 (0.148)	**.007**[**]	.101
WMS Logical memory	-0.170 (0.369)	-0.015 (0.298)	.065	.049
WMS Visual reproduction	-0.129 (0.327)	0.008 (0.313)	**.045**[*]	.057
WMS Associative learning	-0.119 (0.330)	-0.046 (0.368)	.656	.003
WMS Verbal fluency (FAS)	0.187 (1.181)	0.428 (1.131)	.174	.027
Boston naming test	0.074 (0.193)	0.211 (0.622)	.351	.013
SDMT	0.709 (1.440)	0.723 (0.780)	.827	.001
TMT-A (seconds)[b]	-0.781 (2.073)	-0.375 (1.105)	.446	.008
TMT-B (seconds)[b]	0.860 (4.552)	0.088 (2.364)	.172	.027
Stroop colour	-0.325 (1.478)	0.027 (0.985)	.125	.034
Stroop word	0.112 (1.730)	-0.369 (1.409)	.300	.016
Stroop interference	-0.077 (1.201)	0.071 (0.775)	.470	.008
RT simple (milliseconds)	6.706 (11.411)	4.229 (7.995)	.627	.004
RT complex (milliseconds)	7.893 (8.229)	8.953 (12.164)	.796	.001

Note. Mean RoC (SD). ANCOVA corrected for age at baseline. [*]$p \leq .05$, [**]$p \leq .01$. Effect sizes are displayed as partial eta squared ($_p\eta^2$) values. Positive scores indicate an improvement over time and negative scores indicate deterioration over time, except for [b] where positive scores indicate deterioration and negative scores indicate an improvement. MMSE= Mini Mental State Examination, MQ= Memory Quotient, RoC= Rate of Change, RT= Reaction time; simple= reaction time single stimulus conditions; complex= reaction time complex conditions, SDMT= Symbol Digit Modalities Test (number correct), TBS= Total Behavioural Score, TMS= Total Motor Score, TMT= Trail Making Test, UHDRS= Unified Huntington's Disease Rating Scale. WMS= Wechsler Memory Scale, W-R= Wechsler Adult Intelligence Scale-Revised.

Table 5: Correlations between estimated years to clinical diagnosis (EYTD) and rate of Change (RoC) in carriers

	r-value	P-value
Motor[b]		
UHDRS TMS	-.266	.189
Eye movement	-.264	.193
Voluntary movement	-.218	.286
Chorea	-.222	.276
Behaviour[b]		
UHDRS TBS	-.043	.828
Sadness	-.137	.486
Anxiety	.104	.598
Aggression	-.241	.217
Irritability	.062	.753
Neuropsychology		
MMSE	.233	.224
W-R Information	.397	**.033***
W-R Digit span	.082	.672
W-R Arithmetic	.338	.073
W-R Picture arrangement	.124	.529
W-R Block design	.267	.170
WMS MQ[a]	.426	**.024***
WMS Concentration	.396	**.034***
WMS Logical memory	.444	**.016***
WMS Visual reproduction	.461	**.012***
WMS Associative learning	-.002	.990
WMS Verbal fluency (FAS)	.089	.645
Boston naming test	.130	.501
SDMT	.289	.129
TMT-A (seconds)[b]	-.171	.376
TMT-B (seconds)[b]	-.328	.082
Stroop colour	.166	.398
Stroop word	.345	.067
Stroop interference	-.022	.910
RT simple (milliseconds)	-.214	.315
RT complex (milliseconds)	-.410	**.046***

Note. Pearson correlation coefficients (r-value) with $^{*}p \leq .05$. Positive scores indicate an improvement over time and negative scores indicate deterioration over time, except for [b] where positive scores indicate deterioration and negative scores indicate an improvement. MMSE= Mini Mental State Examination, MQ= Memory Quotient, RT= Reaction time; simple= reaction time single stimulus conditions; complex= reaction time complex conditions, SDMT= Symbol Digit Modalities Test (number correct), TBS= Total Behavioural Score, TMS= Total Motor Score, TMT= Trail Making Test, UHDRS= Unified Huntington's Disease Rating Scale. WMS= Wechsler Memory Scale, W-R= Wechsler Adult Intelligence Scale-Revised.

DISCUSSION

This longitudinal study with a follow-up of seven years demonstrated a significant decline in motor functioning, memory, and concentration in premanifest carriers of the HD gene mutation. Cognitive changes over time could be primarily ascribed to carriers who converted to manifest HD.

Cross-sectional results at baseline were comparable to previous studies demonstrating abnormalities in carriers in executive function, specifically attention, cognitive flexibility, psychomotor speed, and inhibitory processes, as assessed with WAIS-R arithmetic, SDMT, TMT and Stroop[5,6,34]. Without the carriers who converted to manifest HD during the study, cognitive abnormalities at baseline could still be demonstrated. This indicates that subtle cognitive deviations, especially on executive functions, are present, even long before the onset of HD motor signs and may be related to early deficits in the basal-ganglia circuitry[15,35]. After seven years additional cross-sectional differences emerged, with carriers showing more motor abnormalities on the UHDRS motor section and worse performance on memory and concentration tasks from the WMS, compared to non-carriers[2,6,7,10,13].

Remarkably, we could not demonstrate a significant decline on the executive tasks that proved sensitive for the earliest cognitive manifestations of HD at baseline. Also, we did not find an association between estimated years to clinical diagnosis and rate of change on these tasks. Practice effects on these type of tasks and familiarity with the test procedures might compensate for subtle cognitive deficits[19]. This is important for the interpretation of longitudinal data. A follow-up study by Paulsen et al. (2001) showed an improvement on executive tasks in individuals at-risk for HD and a decline in converters[36]. This is in accordance with our finding that differences between groups at follow-up, could be ascribed in particular to carriers who converted to manifest HD during the study. Indeed, previous longitudinal studies that did demonstrate a decline on these tasks displayed a much higher rate of carriers converting to manifest HD[20,21,36,37]. Duff et al. (2007) suggest that the amount of individual practice effects in longitudinal studies might provide valuable information on cognitive status and predict long-term cognitive outcome[38].

The WMS memory quotient shows an absence of practice effects in carriers compared to non-carriers, suggesting cognitive dysfunction in carriers. Indeed, we did demonstrate a decline in memory function and concentration on the WMS compared to non-carriers. These changes over time could be attributed to the carriers who converted to manifest HD, except for the decline on the concentration subtest. Also, when estimations of age at clinical diagnosis were used, an association with rate of change on the WMS could be demonstrated. Memory decline in individuals approaching clinical disease onset is confirmed by other studies[7,12,13]. The fact that we could not detect cross-sectional differences between carriers and non-carriers at

baseline on memory tasks is in line with the observation by Snowden at al. (2002) that memory function shows a precipitous decline around the time of clinical onset[20]. Perhaps, concentration changes evolve more slowly and precede the effect on memory tasks. It can be argued, however, that the concentration subtest of the WMS does not reflect selective attention but rather general cognitive slowing, since it is a timed task.

Interestingly, many longitudinal studies reported mainly on motor and executive tasks, specifically psychomotor speed and cognitive flexibility[21 36 39]. This is also reflected in the broadly used UHDRS cognitive section that is highly influenced by motor speed. Our findings confirm the importance of these tasks in detecting premanifest abnormalities. However we advocate the addition of memory tasks for this purpose since memory decline may be a sign of conversion to manifest HD and these tasks have the advantage to lack the motor component.

Behavioural changes could not be demonstrated in the current study. Complaints about aggression on the UHDRS behavioural section at baseline disappeared in subsequent years and confirm the variability in occurrence of psychiatric symptoms[17]. Furthermore, as many objective, quantitative cognitive tasks are available, these are more prominently represented in the present study design. In current studies, more attention is paid to behavioural and mood changes using extensive batteries of neuropsychiatric questionnaires including the Problem Behaviours Assessment for Huntington Disease (PBA-HD)[8 40]. Also, in motor functioning more continuous measures of motor function should be included in clinical studies since reliability of the UHDRS motor assessment is somewhat limited, especially when motor signs are very subtle[41]. This is reflected in the large number of non-carriers in our study that are rated with minor soft signs or probable HD. Converters to manifest HD in the current study mainly developed signs of chorea. We suggest that the appearance of subtle choreatic movements is an important specific feature for the motor examiner when diagnosing unquestionable HD. In a recent study, quantitative voluntary neurophysiological motor tasks proved sensitive for subtle motor deficits in carriers more than a decade before estimated clinical onset and might be used more commonly in premanifest HD research[8].

In the evaluation of longitudinal results of the current and previous studies, many discrepancies appear. Heterogeneity in closeness to clinical disease onset within and between studies and differences in the studied measures are probably the most important factors. Follow-up studies should show international uniformity in inclusion criteria and assessment protocol. Furthermore, longitudinal studies combining clinical and biological measures will provide more insight into the processes underlying clinical changes and may lead to a combination of measures suitable for objectively tracking premanifest HD. Ongoing international, multicentre, multidisciplinary trials are an important example in improving research

on the subject and in realising fast recruitment of study samples with sufficient power. PREDICT-HD[6], TRACK-HD[8], COHORT (http://www.huntington-study-group.org/ClinicalReserach/ClinicalTrialsObservationalStudiesinProgress/COHORT/tabid/83/Default.aspx) and REGISTRY (http://www.euro-hd.net/html/registry) are longitudinal observational studies on clinical and biological markers in the evolution of HD. Longitudinal data on these impressive studies will contribute substantially to the knowledge on the phase of onset of HD.

Conclusion

Standardized motor assessments and objective memory and concentration tasks prove sensitive for change, specifically in the phenoconversion phase. Executive tasks were found to be sensitive for subtle cognitive abnormalities in premanifest HD, a decline over time could, however, not be demonstrated on these tasks. Strengths of the current study are the lengthy follow-up and the comprehensive assessment battery, enabling us to detect changes over time. For the purpose of therapeutic trials, however, suitable instruments are still needed to track changes over shorter intervals. Extended follow-up periods appear useful only for clinical purposes since information about clinical disease onset and progression is of crucial importance in improving the psychosocial support for patients and their families. Because of discrepancies between studies and the discontinuous evolvement of clinical changes, uniformity in international research through multi-site collaborative research models will improve premanifest HD research substantially and point to a selection of specific clinical measures sensitive to change in premanifest HD.

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Chapter 5

Cognition in Huntington's disease in manifest, premanifest and converting gene carriers over ten years

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Abstract

Background Cognitive decline in Huntington's disease (HD) remains an area of inconsistencies, especially far from disease onset.
Objective To clarify the course of cognition in premanifest HD.
Methods Twenty-six premanifest HD, 19 manifest HD, and 87 control subjects were followed for ten years, using an extensive cognitive battery. Differences in baseline levels and change over time, on four factors (motor speed, global cognition, executive functioning (EF), and memory) were examined, using multilevel regression analyses. Converters were additionally analysed as a separate group. Also, the influence of motor speed and predicted years to disease onset on the cognitive factors was studied.
Results Manifest HD subjects showed lower baseline scores compared to controls on the motor speed (p=0.002), memory (p<0.001) and EF (p<0.001). They additionally deteriorated over the ten-year follow-up on memory (p=0.01). Converters deteriorated on EF (p=0.04). Further analyses of premanifest subjects far from and close to predicted onset revealed lower baseline scores for the close group on EF, as compared to controls (p=0.001). They also deteriorated on memory (p=0.01). Motor speed substantially mediated the results of the three cognitive factors; when added as covariate to the model several baseline and slope differences for the cognitive factors ceased to be significant.
Conclusions Memory and EF are highly sensitive for ascertaining deterioration in premanifest HD gene carriers, especially in subjects close to onset. Lack of deterioration for the subjects further away from onset suggests that both domains are largely unaffected in those far from onset. Also, motor influence on cognition is substantial and should be taken into account in cognitive HD research.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease causing selective neuronal damage resulting in motor abnormalities, psychiatric disturbances and cognitive decline[1]. Due to its genetic basis subjects at risk for HD can be tested for presence of the HD gene[2]. Consequently, gene carriers without a clinical diagnosis of disease onset, so-called premanifest carriers, can be identified and studied. In recent years the transition from premanifest to manifest HD has become a main area of interest. As we move forward towards clinical trials with possible disease modifying effects it is important to better understand the course of HD symptoms, including that of cognition.

Since the localization of the HD gene[3] a large number of studies on cognition in premanifest HD have been published. Many cross-sectional studies have reported differences between premanifest and control subjects, with defective emotion recognition and reduced psychomotor speed being the most robust findings[4,5,6]. Concerning attention, memory and executive functioning inconclusive findings have been reported. For example, Verny et al.[7] found premanifest deficits on executive functioning and memory tasks compared to controls, whereas Witjes-An et al.[8] and Soliveri et al.[9] did not report such differences. In subjects close to their predicted age of disease onset, memory and executive deficits have been quite consistently found. In individuals further from predicted onset results are less robust, although psychomotor speed reduction and impaired emotion recognition have been observed[10,11].

Few studies have assessed cognitive functioning in HD during follow-up periods of more than five years[12,13,14,15], despite the potentially informative nature of longer longitudinal studies, given the slow progressive nature of HD. These studies showed large differences in the kind and extent of the included cognitive batteries, duration of follow-up and number of participants included. Moreover, results are heterogeneous. Snowden et al.[12] found that colour naming on the Stroop task declines, Jurgens et al.[15] reported diminished concentration on a subtest of the Wechsler Memory Scale, in contrast to Brandt et al.[13] who found no cognitive decline over time.

As the development and progression of cognitive impairment associated with premanifest HD remains an area of uncertainty, specifically in the period far from disease onset, longitudinal research with substantial follow-up periods and comprehensive test batteries is important to increase our understanding of cognitive functioning in this critical period in HD. We assessed cognitive functioning at five time points during ten years of follow-up, allowing us to model the course of cognitive functioning and to compare the decline of (pre)manifest HD subjects with that of healthy controls. During the follow-up period we expect the HD groups

to decline on tasks of memory and executive functioning compared to controls. For further analyses the premanifest group will be divided in those who converted to manifest disease over the study period, and those who remained premanifest. Furthermore, we will investigate the difference in cognitive change between premanifest HD subjects far from predicted disease onset and those close to onset as compared to controls, as we hypothesized that the predicted duration until disease onset at baseline is inversely associated with the rate of decline on certain cognitive scores. The effect of motor functioning on cognition will also be investigated.

METHODS

Subjects

At baseline 134 subjects participated (46 gene-carriers, 88 controls)[8] (Figure 1), 106 completed three-year follow-up[16] and 72 participants completed seven-year follow-up[15]. Ten-year follow-up was completed by 68 participants (26 gene carriers, 42 controls). In this study we investigated all subjects over ten-year follow-up. Gene carriers were grouped at baseline into either premanifest HD gene carriers or manifest HD patients using the total motor score (TMS) of the Unified Huntington's Disease Rating Scale (UHDRS)[17]: subjects with scores below 6 points were considered to be premanifest, scores of 6 and higher were considered manifest[18]. Control subjects were tested non gene-carrying relatives.

Drop-outs over the ten-year period are described in Figure 1. Of the 134 subjects one female gene-carrier was excluded from analyses as the TMS was not ascertained at baseline, precluding a correct assignment to one of the HD groups. One male control was excluded as he suffered from cardiovascular disease and consequent cognitive dysfunction. The remaining 132 subjects were included and grouped as follows: 19 manifest HD, 26 premanifest HD (of whom 5 converted to manifest HD over the study period), and 87 control subjects.

Predicted years to disease onset were estimated using the formula by Langbehn et al.[19]. The formula (age*(CAG repeat length-35.5)) was used to calculate disease burden for the HD groups. The sadness score of the UHDRS behavioural section was used as depression measure. The study was approved by the local ethics committee and all participants gave written informed consent according to the Declaration of Helsinki.

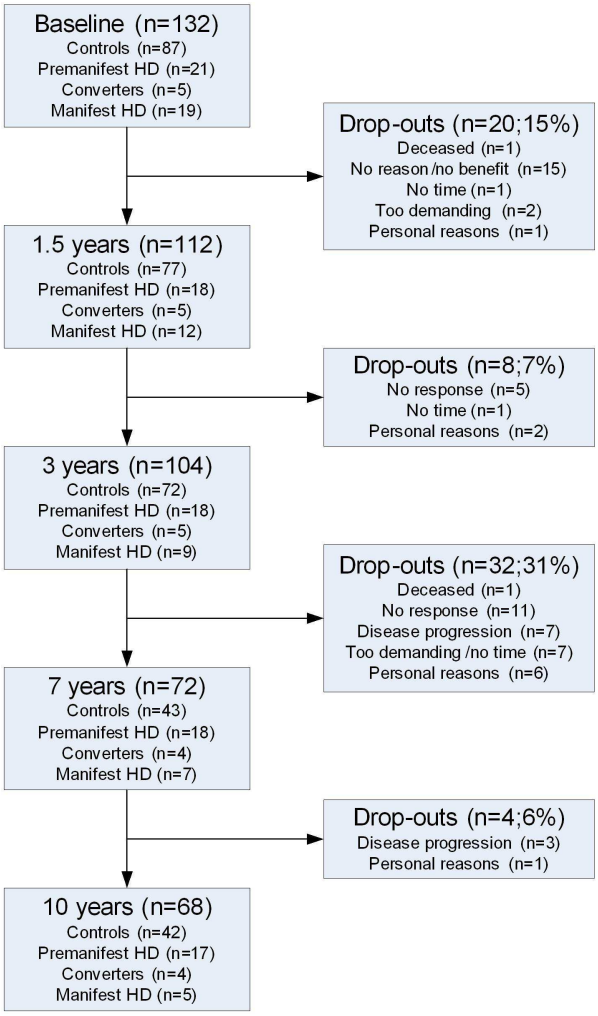

Figure 1: Flowchart of the participants and drop-outs over 10 years of follow-up

Procedure

Following the baseline visit subjects attended follow-up visits after 18 months, three, seven and ten-years. During baseline, three and ten-year follow-up visits an extended cognitive battery was administered. For 18 months and seven-year follow-up a shorter battery was applied.
All participants underwent UHDRS motor, behavioral and functional assessments

at all visits. The motor part was administered by a trained clinician. The cognitive battery included tests objectifying almost all cognitive domains. For global functioning the Mini Mental State Examination (MMSE) and the Wechsler Adult Intelligence Scale revised (WAIS-R) were used, the latter generating a total intelligence quotient (TIQ), performance (PIQ) and verbal (VIQ) intelligence quotients. Memory tests included the Wechsler Memory Scale (WMS) and the Dutch version of the California Verbal Learning test, namely the 'Verbale Leer- en Geheugen test (VLGT)'. From the WMS a memory quotient (MQ) can be derived. The VLGT consists of a main list to be learned (list A) and directly reproduced, and an interference condition (list B). Subjects are tested on direct recall, short term recall, long term recall and long term recognition. The Boston Naming (BNT) task was used for measuring picture naming abilities. For executive functioning the Stroop test (color, word and interference conditions), Symbol Digit Modalities test (SDMT), letter fluency ('f', 'a', 's'), and Trail Making test (TMT) (A and B) were used. A reaction time (RT) test, where participants were instructed to react as quickly as possible by releasing a 'rest' button and pressing a reaction button after hearing a tone (condition 1, 14 times) and seeing a light (condition 2, 14 times), was administered resulting in a RT score, from now on referred to as 'motor speed'. For detailed description of study procedures see Witjes-Ané et al.[8].

Statistical analyses

IBM SPSS for Windows 20.0 was used for data analysis. Group comparisons for demographic variables were done using ANOVA, χ^2 and Kruskal-Wallis tests for continuous, categorical and skewed data, respectively. Data pre-processing involved reverse coding for TMT A&B and RT and logarithm (loge) transformation of non-normally distributed scores (i.e. TMT A&B, MMSE, BNT, and the short- and long-term recall and recognition subtests of the VLGT). For longitudinal analyses all cognitive scores were standardized to z-scores. These z-scores were subsequently combined into factors by averaging the component test results.
To make the data on the extensive cognitive battery more comprehensible and to reduce Type I error caused by multiple testing (19 individual cognitive tests were administered) we decided to perform a factor analysis to combine inter-correlated cognitive tests into factors. Based on results from previous cognitive studies in HD, we were interested in the progression of performance on one motor construct and three cognitive constructs (global cognitive functioning, memory, executive functioning) in our cohort. The tests that are known, according to existing cognitive HD research, to capture these constructs were pre-selected to be entered in the factor analysis. The correlation coefficients of the variables had to be substantially large (correlation coefficient 0.30) to be assigned to a specific factor. Principal components analysis (using varimax orthogonal rotation) revealed four factors: (1) 'motor speed' (i.e., RT z-score) (2) 'global cognition' (composed of WAIS TIQ,

MMSE, verbal fluency), (3) 'memory' (composed of WMS MQ, VLGT list A, list B, short- and long-term recall and recognition) and (4) 'executive functioning' (composed of SDMT, Stroop interference, TMT B).
Because the time points were dependent for each participant, multilevel regression analyses (i.e. linear mixed models) were used to investigate differences in baseline levels and slopes between groups on the four factors. Firstly, a crude model was constructed (model 1). Secondly, a multivariate model was constructed adjusting for age, gender, and the three categories of education (model 2). Lastly, we repeated the multilevel regression analyses for the three cognitive factors, in which we additionally adjusted for motor speed, in order to study the pure effect independent from the decline in reaction time[20] (model 3). We calculated the strength of the mediating effects of motor speed by averaging the percentage change in beta-coefficients of the significant test results between models 2 and 3. In the multilevel analyses we used a compound symmetry covariance structure consisting of up to five time points (i.e. lower level) and the subjects (i.e. higher level). The four factors were used as continuous variables, and standardized mean differences versus controls (with standard error [SE]) are presented (Figure 2). Main analyses compared the whole premanifest HD group and the manifest HD group to controls for differences at baseline and rate of decline (i.e. slope; time*group interaction effects). Secondary analyses involved the premanifest HD group being divided into those who continued to be premanifest during the study, i.e. continual premanifest HD, and those who converted to manifest HD, i.e. converters, for comparison to controls. Additionally, the subjects whom were in the premanifest HD group at baseline were divided into 'close to onset' and 'far from onset' using a median-split of 'predicted years to onset' (median is 15.2 years), and compared to controls to test for possible influence of closeness to predicted disease onset on the cognitive factors. Post-hoc multilevel analysis on the separate cognitive tests were performed to investigate which cognitive tests are responsible for significant results in the factor analyses. Beta-coefficients in the tables can be interpreted as follows: baseline differences refer to how many standard deviations an HD group differs from the controls at baseline, and slope differences refer to how many standard deviations the change in the HD groups differed from the change in the control group over the ten-year period. All tests were two-tailed with $p<0.05$ denoting statistical significance.

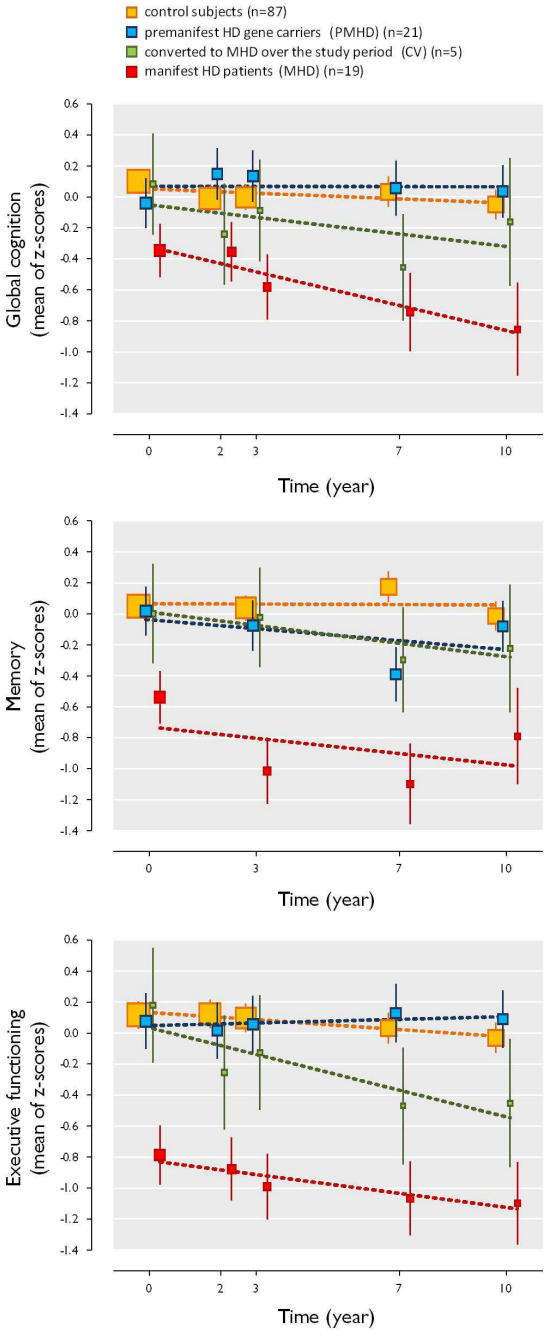

Figure 2: Scores for continual premanifest HD, converters, manifest HD and controls on the cognitive factors over 10-years of follow-up

RESULTS

Baseline demographics

The mean (± SD) age at baseline of the whole group of HD subjects combined was 39 (± 11) years and 64% were female (Table 1). At baseline the groups were comparable for gender, educational level, total functional capacity (TFC), and depression scores. premanifest HD subjects were younger than manifest HD (p=0.03) and control (p=0.04) subjects. The manifest HD group had a higher TMS than the controls (p<0.001). The burden of the manifest HD subjects was higher compared to the premanifest HD subjects (p=0.008). Raw cognitive scores are given in supplementary Table 1.
The subjects who completed the ten-year follow-up (n=68) were comparable to the drop-outs (n=64) on age at baseline (p=0.92), gender (p=0.48) and education (p=0.12). The drop-outs showed lower TFC (p=0.006) and higher TMS scores (p=0.02) (data not shown).

Table 1: Baseline demographics for the groups

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	p-value
Age, yrs	42 (11)	35 (7)	44 (14)	**0.02**
Gender, m/f	39 (45)/48 (55)	7 (27)/19 (73)	9 (47)/10 (53)	0.23
CAG repeat length	20 (4)	43 (3)	44 (3)	**<0.001**
Higher education	27 (31)	9 (35)	4 (21)	0.12
Depression score	0 (0; 1)	0 (0; 2)	0 (0;1)	0.06
TMS	6 (7)	3 (2)	18 (8)	**<0.001**
TFC	13 (13;13)	13 (13;13)	13 (13;13)	0.06
Disease burden[a]		259 (89)	332 (79)	**0.008**
Predicted onset[b], yrs		16 (8)		

Note. Data are mean (SD) for continuous variables, number (%) for gender and education and median (interquartile range) for TFC and depression score. ANOVA was used for comparisons of age, CAG and TMS variables χ^2-tests for gender and education variables and Kruskal-Wallis tests for depression score and total functional capacity variable. TFC = total functional capacity, TMS = total motor score. [a]Based on formula '(CAG-35.5)*age)' by Penney et al. (1997). [b]Based on survival analysis formula by Langbehn et al. (2004).

Baseline differences and change over time for premanifest HD and manifest HD on the four factors

The baseline differences and change over the ten-year follow-up period for the premanifest HD and manifest HD groups compared with the controls are presented

in Table 2. The analyses adjusted for age, gender and education showed lower baseline scores for the manifest HD group on the motor speed factor (Table 2B). The scores were on average 0.72 SD (SE=0.22; p=0.002) lower than the scores of the controls. For the executive functioning and memory factors the same pattern was found; for executive functioning factor the scores were 0.79 SD (SE=0.17; p<0.001) lower and for the memory factor 0.61 SD (SE=0.17; p<0.001) lower. Only for the latter factor both HD groups showed a difference in change over time compared to that of controls. The manifest HD group deteriorated with on average 0.61 SD (SE=0.24; p=0.01) over ten-year follow-up. The premanifest HD group deteriorated with 0.32 SD (SE=0.15; p=0.04). Post-hoc analysis to investigate which individual cognitive tests caused significant factor results revealed that for the memory factor both short and long term memory on the VLGT and the WMS MQ showed lower baseline scores for the manifest subjects compared to the controls (SD between 0.79 and 0.69, p-values between 0.001 and <0.001) (Supplementary Table 2A). Concerning change over time the premanifest subjects deteriorated on long term recognition of the VLGT (0.48 SD [SE=0.23, p=0.04]), and the manifest subjects deteriorated in the WMS MQ (0.70 SD [SE=0.23; p=0.003]). The significant baseline difference on the executive functioning factor was driven by worse baseline scores for the SDMT (0.85 SD [SE=0.20; p<0.001]) and TMT-B (0.77 SD [SE=0.20; p<0.001]).

To partition out the influence of motor functioning on cognition motor speed was added as an additional covariate to the multilevel regression analyses on the cognitive factors (Table 2C). Now, only the manifest HD group showed lower baseline scores compared to controls on the executive functioning (-0.73 SD (SE=0.17); p<0.001) and memory (-0.62 (SE=0.17); p<0.001) factors. The adjustment for motor speed resulted in a reduction in size of the statistically significant beta-coefficients by on average 20.2%. This indicates a substantial mediating effect of the reduction in motor speed over time on the cognitive factors. Supplementary Table 2B shows the data of the individual cognitive tests adjusted for age, gender, education and the motor factor. Here, post-hoc analyses revealed that the memory factor was driven by significant baseline differences for the manifest group compared to the controls on both the direct and the short and long term recall of the VLGT (SD between 0.76 and 1.08; p-values between 0.01 and <0.001) and the WMS MQ (0.75 SD [SE=0.21; p<0.001). The executive functioning factor was driven by worse baseline scores for the manifest group on both the SDMT (0.82 SD [SE=0.20; p<0.001]) and the TMT-B (0.74 SD [SE=0.21; p<0.001]).

Table 2: Changes over 10-year follow-up in cognitive and motor factors for premanifest and manifest HD compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	p-value
2a Crude				
Motor				
Baseline difference	Ref.	-0.16 (SE 0.20)	-0.80 (SE 0.24)**	**0.004**
Slope difference	Ref.	-0.13 (SE 0.18)	0.27 (SE 0.34)	0.51
Global Cognition				
Baseline difference	Ref.	0.00 (SE 0.15)	-0.39 (SE 0.17)	0.08
Slope difference	Ref.	-0.03 (SE 0.13)	-0.49 (SE 0.21)	0.07
Executive functioning				
Baseline difference	Ref.	-0.12 (SE 0.18)	-0.95 (SE 0.20)***	**<0.001**
Slope difference	Ref.	0.12 (SE 0.10)	-0.26 (SE 0.16)	0.08
Memory				
Baseline difference	Ref.	-0.03 (SE 0.15)	-0.68 (SE 0.18)***	**0.001**
Slope difference	Ref.	-0.34 (SE 0.15)*	-0.60 (SE 0.24)*	**0.01**
2b. Adjusted age, gender, education				
Motor				
Baseline difference	Ref.	-0.08 (SE 0.20)	-0.72 (SE 0.22)**	**0.007**
Slope difference	Ref.	-0.13 (SE 0.18)	0.25 (SE 0.34)	0.55
Global Cognition				
Baseline difference	Ref.	0.04 (SE 0.14)	-0.32 (SE 0.16)	0.12
Slope difference	Ref.	-0.03 (SE 0.13)	-0.51 (SE 0.21)	0.05
Executive functioning				
Baseline difference	Ref.	-0.27 (SE 0.16)	-0.79 (SE 0.17)***	**<0.001**
Slope difference	Ref.	0.11 (SE 0.10)	-0.28 (SE 0.16)	0.08
Memory				
Baseline difference	Ref.	-0.08 (SE 0.15)	-0.61 (SE 0.17)***	**0.002**
Slope difference	Ref.	-0.32 (SE 0.15)*	-0.61 (SE 0.24)*	**0.007**
2c. Adjusted age, gender, education, motor speed				
Global Cognition				
Baseline difference	Ref.	0.03 (SE 0.14)	-0.28 (SE 0.16)	0.21
Slope difference	Ref.	0.06 (SE 0.14)	-0.49 (SE 0.25)	0.11
Executive functioning				
Baseline difference	Ref.	-0.25 (SE 0.15)	-0.73 (SE 0.17)***	**<0.001**
Slope difference	Ref.	0.11 (SE 0.10)	-0.21 (SE 0.19)	0.24
Memory				
Baseline difference	Ref.	-0.12 (SE 0.15)	-0.62 (SE 0.17)***	**0.002**
Slope difference	Ref.	-0.17 (SE 0.15)	-0.44 (SE 0.28)	0.20

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. * $p<0.05$, ** <0.01, *** <0.001 indicate significant differences compared to the control group in post-hoc tests.

Table 3: Changes over 10-year follow-up in cognitive and motor factors for premanifest subgroups compared to controls

	Controls N=28	PMHD N=21	MHD N=40	P-value	Controls N=28	Close N=10	Far N=11	P-value
	3A. Continual premanifest subjects and converters compared to control subjects				**3B. Premanifest subjects close to and far from predicted disease onset compared to control subjects**			
Motor[a]								
Baseline diff.	Ref.	0.03 (SE 0.22)	-0.16 (SE 0.39)	0.90	Ref.	0.15 (SE 0.26)	-0.16 (SE 0.26)	0.63
Slope diff.	Ref.	-0.08 (SE 0.19)	-0.36 (SE 0.41)	0.64	Ref.	0.04 (SE 0.22)	-0.42 (SE 0.27)	0.25
Global Cognition[a]								
Baseline diff.	Ref.	0.08 (SE 0.16)	-0.04 (SE 0.28)	0.86	Ref.	0.11 (SE 0.19)	-0.01 (SE 0.19)	0.83
Slope diff.	Ref.	0.06 (SE 0.14)	-0.36 (SE 0.25)	0.30	Ref.	0.07 (SE 0.16)	-0.14 (SE 0.17)	0.60
Executive functioning[a]								
Baseline diff.	Ref.	-0.29 (SE 0.17)	-0.14 (SE 0.30)	0.22	Ref.	0.11 (SE 0.19)	-0.64 (SE 0.19)**	**0.003**
Slope diff.	Ref.	0.27 (SE 0.10)*	-0.59 (SE 0.19)**	**<0.001**	Ref.	0.04 (SE 0.12)	0.18 (SE 0.14)	0.40
Memory[a]								
Baseline diff.	Ref.	-0.15 (SE 0.16)	0.06 (SE 0.28)	0.62	Ref.	-0.13 (SE 0.19)	-0.08 (SE 0.19)	0.75
Slope diff.	Ref.	-0.21 (SE 0.16)	-0.83 (SE 0.30)	**0.02**	Ref.	-0.16 (SE 0.19)	-0.53 (SE 0.21)*	**0.04**

Table continues on next page.

Table 3: **(Continued)** Changes over 10-year follow-up in cognitive and motor factors for premanifest subgroups compared to controls

	Controls N=28	PMHD N=21	MHD N=40	P-value	Controls N=28	Close N=10	Far N=11	P-value
	3A. Continual premanifest subjects and converters compared to control subjects				**3B. Premanifest subjects close to and far from predicted disease onset compared to control subjects**			
Global Cognition[b]								
Baseline diff.	Ref.	0.06 (SE 0.16)	-0.07 (SE 0.28)	0.90	Ref.	0.08 (SE 0.19)	-0.03 (SE 0.19)	0.90
Slope diff.	Ref.	0.12 (SE 0.14)	-0.24 (SE 0.30)	0.47	Ref.	0.08 (SE 0.16)	0.03 (SE 0.20)	0.88
Executive functioning[b]								
Baseline diff.	Ref.	-0.27 (SE 0.17)	-0.16 (SE 0.29)	0.25	Ref.	0.08 (SE 0.19)	-0.60 (SE 0.19)**	**0.004**
Slope diff.	Ref.	0.21 (SE 0.11)	-0.46 (SE 0.22)*	**0.01**	Ref.	0.01 (SE 0.12)	0.25 (SE 0.15)	0.25
Memory[b]								
Baseline diff.	Ref.	-0.19 (SE 0.16)	-0.04 (SE 0.28)	0.51	Ref.	-0.14 (SE 0.19)	-0.17 (SE 0.19)	0.57
Slope diff.	Ref.	-0.15 (SE 0.16)	-0.31 (SE 0.33)	0.47	Ref.	-0.13 (SE 0.18)	-0.25 (SE 0.22)	0.45

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. * $p<0.05$, ** <0.01, *** <0.001 indicate significant differences compared to the control group in post-hoc tests. [a] is adjusted for age, gender, education; [b] is adjusted for age, gender, education, motor speed.

Baseline differences and change over time for continual premanifest HD and converters on the four factors

Next we analysed converters (n=5) separated from the continual subjects premanifest HD (n=21). The baseline and slope data for the analysis with the converters separated from the original premanifest HD group are shown in Table 3A. Figure 2 depicts data for all four groups. The analysis adjusted for age, gender and education showed a deterioration over time on the executive functioning factor for the converter group (-0.59 SD (SE=0.19); p=0.002) as compared to controls, while the continual premanifest HD group improved with on average 0.27 SD (SE=0.10; p=0.01) compared to controls. The converters group also deteriorated over time on the memory factor, with 0.83 SD (SE=0.30; p=0.006).
Post-hoc analysis on the individual cognitive tests adjusted for age, gender and education (Supplementary Table 3A) showed the significant slope difference for memory factor was caused by significant deterioration for the converter group compared to the controls on the WMS MQ of 0.88 SD (SE=0.27; p=0.001). The executive functioning factor was driven by the SDMT, where the converters deteriorated with on average 0.70 SD (SE=0.26, p=0.008).

With the introduction of motor speed as additional covariate the deterioration for the converter group, now 0.46 SD (SE=0.22, p=0.04), remained (Supplementary table 3B). The improvement of the continual premanifest HD group of now 0.21 SD (SE=0.11, p=0.052) was only borderline significant. Post-hoc analyses on component tests of the executive functioning factor revealed that the deterioration for the converter group was solely caused by lower scores for this group on the SDMT, of on average 0.64 SD (SE=0.30, p=0.04).

Baseline differences and change over time for subjects close to and far from predicted disease onset compared controls on the four factors

Table 3B presents the baseline and slope differences of the motor speed and cognitive factors for the premanifest HD group divided into close to and far from predicted disease onset. For the executive functioning factor, analysis adjusted for age, gender and education showed lower baseline scores for the close to onset group of 0.64 SD (SE=0.19; p=0.001) compared to controls. The 'close' group also showed a deterioration over the ten-year follow-up of 0.53 SD (SE=0.21; p=0.01) on the memory factor compared to controls. Investigation of the individual cognitive tests making up the factors revealed that the significant slope difference for the memory factor was based on the 'close' group deteriorating with on average 0.61 SD (SE=0.19); p=0.001) compared to controls over the ten-year follow-up (Supplementary Table 4A). Significant baseline differences on the executive functioning factor were the result of lower baseline scores of 0.77 SD

(SE=0.23; p=0.001) for the 'close' group compared to the control group on the SDMT.

When motor speed was added to the analyses on the cognitive factors results showed that lower baseline scores for the close to onset group on the executive functioning factor persisted. The scores were on average 0.60 SD (SE=0.19; p=0.002) lower as compared to control subjects. Again, this result was mainly based on the 'close' group scoring 0.73 SD (SE=0.22; p=0.001) lower on the SDMT compared to the controls (Supplementary Table 4B).

DISCUSSION

The present study reports on ten-year follow-up of cognitive functioning in premanifest and manifest HD. We found that manifest HD subjects scored significantly worse than controls on the factors of motor, executive functioning and memory. Over the ten-year follow-up they also showed deterioration on the memory factor, while change over time on the other factors was comparable to that of controls. Additionally, the premanifest subjects who converted to manifest disease were the only group to show significant deterioration over the ten-year follow-up period compared to the control subjects on the executive functioning factor and to lesser extent on the memory factor, whereas the premanifest participants who remained without clinical diagnosis showed no such change.

That the manifest HD group had lower mean baseline scores on the motor speed, executive and memory factors is not surprising as deficits in these areas of functioning are well established[21,22]. Longitudinally, this group showed deterioration on the memory factor, which is in line with other longitudinal studies on cognition in manifest HD[15,23]. When we controlled for motor functioning all factors ceased to show deterioration for this group. That in our fully adjusted model the deterioration on all cognitive factors did not differ from that of the control group seems counterintuitive, due to the neurodegenerative nature and the known cognitive deficits in manifest HD[24]. The most likely explanation is the selective attrition that takes place in longitudinal studies, where the subjects most vulnerable to cognitive decline have a larger chance of becoming lost to follow-up. Indeed, in our manifest HD group 14 out of the initial 19 were lost to follow-up, which likely resulted in a pronounced underestimation of the cognitive decline in this group.

The cognitive course over time for the subjects who were premanifest at baseline was most remarkable. Those who converted to manifest disease showed deterioration on both the memory and the executive functioning factors, as compared to controls. The decline on the executive factor was however most pronounced, a decline that was even greater than that of the manifest subjects. These results

are supported by the findings of Solomon et al.[14] who also performed a ten-year follow-up study. They used three cognitive tasks (i.e. subtests from the WAIS-R) and six motor and psychomotor tasks and found that their converter group showed greater rates of decline on the motor and psychomotor tasks compared with non-converters. Similarly, Rupp et al.[25] also reported faster deterioration for their converter group, especially in tests of psychomotor abilities.
In contrast, the subjects in our study who remained premanifest over the ten year follow-up showed no deterioration on any of the cognitive factors or the individual cognitive tests. They even showed a slight improvement over time on the executive functioning factor compared to controls, which was lessened to borderline significant when we introduced the motor speed factor to the analysis. This result could reflect a biphasic or non-linear pattern of progress of executive functioning, where premanifest subjects are able to maintain test requirements to the same, or even better, extent as controls, but where a rapid decline occurs close to or directly after disease onset. Non-linear progression of premanifest test performance has also been suggested by other authors. Snowden et al.[12] and Paulsen et al.[26] found that decline on certain cognitive measures (i.c. memory and executive functioning) seems to accelerate close clinical disease onset. Rupp and colleagues also observed an improvement for their premanifest group, which was far from predicted disease onset[25]. Rupp et al. attributed this to learning effects, however, this is a less likely explanation for our premanifest group as no significant improvement was found on the other factors. However, the influence of practice effects cannot be ruled out, especially since alternative versions were only available and used for certain, but not all, tests (i.c. SDMT and TMT). As Duff et al. have demonstrated[27], the influence of practice effects in repeated testing should be considered as a clarification for our results. Another explanation could again be the selective drop-out of subjects who are cognitively and functionally already impaired, even though only 4 of the original premanifest subjects were lost to follow-up. Overall, our results indicate that tests of memory, and to a somewhat larger extent, executive functioning are likely to be most sensitive to subtle deteriorations during the premanifest and transition phases of HD.

Splitting the original premanifest group (including those who converted to manifest HD over time) into 'far' (more than 15.2 years from predicted disease onset) and close (15.2 or less years to onset) strengthened our hypothesis of non-linear progression for the memory and executive functioning factors. We found worse performance for the close group compared to the control group. This finding implicates that cognitive decline, and more specifically executive dysfunctioning and memory decline, is present and can be detected even before overt (motor-symptomatic) disease onset, an assumption that is also shared by other authors[28]. Our findings strengthen the idea proposed by Papp et al.[11] amongst others, that premanifest subjects should not be regarded as one group, but that at least two different subgroups (i.e. close to and far from predicted disease onset) exist that in-

deed demonstrate different cognitive profiles. Further analyses revealed that poorer performance on the SDMT contributed most to executive dysfunction. This finding corroborates other findings where the SDMT proved most sensitive to the earliest cognitive change in premanifest HD[23 29 30]. Our results suggest that the SDMT is a sensitive instrument to track disease progression over time, especially around clinical onset.

Besides the progression of cognitive factors over a ten-year period we were also interested in the effect that motor functioning has on cognition, especially in the premanifest phase of HD. As for most cognitive tests some kind of motoric response (e.g. writing, drawing, speaking) is required, and as subtle motor disturbances have already been found in premanifest groups[20 31], this effect is worth investigating. We approached this by using the test that we hypothesized to be mainly motoric and relatively free of cognitive effort; the simple reaction time (RT) test (i.e. responding as quickly as possible to a tone or a light in two separate conditions by pushing a response button) as a covariate in our analyses. We found evidence for substantial mediating effects of motor speed on all three cognitive factors. When we adjusted for motor speed, results on particularly the global cognition and memory factors ceased to be significant. Also, *p*-values became less significant. That differences weaken and disappear with the introduction of a motor measure, underlines the importance of taking this motor influence into account while investigating cognition in HD. Studies that do not take into account the influence of motor function in the HD groups could potentially result in an overestimation of the 'pure' cognitive effect.
This is one of the few cognitive studies where the effect of motor functioning on cognitive test scores is quantitatively studied. However, we acknowledge that the choice for motor speed was an arbitrary choice and that we did not a-priori investigate whether this variable indeed (only) measures motor speed. There is a possibility that this variable also measures some kind of cognitive construct as our memory results were also affected by the introduction of the motor speed variable. Memory tasks are often less dependent on motor abilities than executive tasks, as they often only require a verbal response. On the other hand, from our supplementary data on the individual cognitive tests we can see that the WMS MQ is especially affected by the introduction of the motor speed variable. One of the sub-tests making up the WMS MQ is visual reproduction, where the patients is required to draw from memory, and this element could be especially sensitive to motor speed influence. The other memory tests, e.g. direct and long term recall from the VLGT, seem to be less affected by the introduction of the motor variable, strengthening our hypothesis that we are controlling for motor functioning. Nonetheless, future research is needed to more thoroughly investigate the potential influence of motor functioning on cognitive testing.

However, we feel that our attempt to quantify the influence of motor functioning on

cognitive scores has provided some interesting insights on differential influences on cognitive measures in HD, even though our results should be interpreted with caution. If our hypothesis that our motor factor measures pure motor speed is correct, our results indicate that commonly used tests for global functioning and memory used in HD are sensitive for the progressive motor disturbances characteristic for HD, which reduces their ability to pick up cognitive decline. It is unlikely that no decline on these measures occurs in the premanifest phase, as memory decline, and to a lesser extent also global functioning decline, have consistently been found in premanifest HD gene carriers[24 32 33]. Indeed, without the correction for motor speed, both converters and subjects close to predicted disease onset also showed deterioration compared to controls on the memory factor. Our findings suggest however, that these results could have been mediated by motor functioning and are likely to be smaller in extend. Nonetheless, tests of executive functioning, and the SDMT in particular, do show sensitivity for motor disturbances, but remain sensitive enough to pick up cognitive decline, which makes them best suited for use in longitudinal follow-up studies and clinical trials.

Our study adds to the existing literature as one of the longest follow-up studies on cognition in both manifest and premanifest HD. The diverse battery of cognitive tests is also a strong aspect of this study. Moreover, adjusting for the influence of motor speed has provided insights about the negative impact of motor functioning on cognition. However, some limitations have to be mentioned. During the study half of the initial participants were lost to follow-up, introducing a potential attrition bias. Therefore, results of both manifest subjects and converters should be interpreted with caution as the numbers in these groups were small and variability in test scores is substantial. Additionally, the influence of medication use (e.g. neuroleptics) was not investigated in this study, even though the effect can be both beneficial and disadvantageous. To avoid overestimation of results, future studies are advised to administer a motor task alongside cognitive tasks, to be able to disentangle the influence of motor disturbances on cognitive functioning in HD.

We conclude that both memory and executive functioning are sensitive in picking up premanifest decline in subjects close to their predicted disease onset. The latter cognitive domain is specifically sensitive, with the SDMT proven to be the most sensitive individual test. Our results imply that the course of executive functioning in the premanifest stage is not uniform and that in subjects furthest away from disease onset changes are difficult to detect. Additionally, we have found evidence for influence of motor speed on cognitive outcome measures.

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Conflict of interest

The authors have no conflict of interest to report.

Table 4: Supplementary table: Raw cognitive test scores at baseline and ten-year follow-up

	Baseline				**Ten-year follow-up**			
	Controls N=87	Continual Premanifest HD N=21	Converters N=5	Manifest HD N=19	Controls N=42	Continual Premanifest HD N=17	Converters N=4	Manifest HD N=5
MMSE	29 (28;29)	28 (28;29)	29 (28;29)	28 (27;29)	29 (28;30)	29 (28;30)	29 (28;30)	28 (27;28)
SDMT	52 (9)	50 (10)	51 (17)	42 (12)	52 (8)	52 (7)	48 (10)	38 (16)
Verbal fluency	32 (11)	34 (10)	33 (14)	32 (9)	36 (12)	41 (14)	35 (7)	26 (12)
Stroop colour	76 (12)	75 (9)	76 (15)	67 (15)	79 (12)	79 (11)	64 (25)	66 (18)
Stroop word	100 (16)	99 (14)	93 (9)	94 (22)	103 (15)	102 (11)	76 (22)	86 (23)
Stroop interf.	44 (8)	43 (9)	46 (10)	39 (13)	46 (10)	47 (9)	41 (10)	38 (14)
TMT A (sec.)	32 (10)	38 (13)	35 (21)	48 (21)	27 (8)	26 (8)	38 (23)	44 (18)
TMT B (sec.)	54 (19)	57 (21)	54 (25)	87 (42)	49 (18)	51 (27)	69 (48)	84 (43)
VLGT list A	58 (9)	59 (9)	54 (7)	48 (11)	56 (13)	57 (12)	48 (18)	50 (12)
VLGT list B	7 (2)	7 (2)	9 (2)	7 (2)	6 (2)	7 (2)	6 (2)	5 (3)
VLGT ST recall	13 (12;15)	13 (11;15)	13 (9;14)	13 (11;13)	13 (10;15)	13 (10;14)	7 (5;7)	10 (9;10)
VLGT LT recall	13 (11;15)	14 (11;15)	12 (11;15)	10 (8;14)	14 (12;15)	14 (12;15)	8 (4;8)	11 (10;11)
VLGT LT recog.	15 (15;16)	16 (15;16)	15 (15;16)	15 (14;16)	16 (15;16)	16 (15;16)	15 (11;15)	13 (12;13)
Boston naming	27 (25;28)	27 (26;28)	29 (25;29)	26 (24;27)	27 (25;28)	26 (26;28)	29 (27;29)	28 (26;29)
WMS MQ	120 (13)	114 (17)	118 (13)	109 (18)	131 (12)	122 (18)	114 (23)	107 (12)
WAIS TIQ	104 (11)	101 (14)	104 (14)	95 (12)	114 (13)	110 (15)	109 (19)	101 (5)
WAIS PIQ	105 (11)	104 (13)	101 (12)	94 (14)	117 (14)	117 (12)	108 (18)	101 (13)
WAIS VIQ	103 (10)	99 (14)	106 (15)	96 (11)	110 (10)	104 (14)	109 (17)	98 (11)
Reaction time	418 (65)	432 (84)	435 (91)	473 (108)	450 (104)	488 (106)	457 (46)	432 (52)

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. * $p<0.05$, ** <0.01, *** <0.001 indicate significant differences compared to the control group in post-hoc tests. LT=long term, MMSE=mini mental state examination, PIQ=performal intelligence quotient, SDMT=symbol digit modalities test, ST=short term, TIQ=total intelligence quotient, TMT=trail making test, VIQ=verbal intelligence quotient, VLGT=verbale leer- en geheugen test, WAIS=Wechsler adult intelligence scale, WMS MQ=Wechsler memory scale memory quotient.

Table 5: Supplementary table: Changes over ten-year follow-up on cognitive tests for premanifest HD and manifest HD subjects compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	P-value	Premanifest HD N=26	Manifest HD N=19	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
MMSE							
Baseline diff.	Ref.	-0.18 (SE 0.16)	-0.31 (SE 0.19)	0.19	-0.16 (SE 0.17)	-0.25 (SE 0.19)	0.32
Slope diff.	Ref.	0.02 (SE 0.23)	-0.53 (SE 0.36)	0.33	0.09 (SE 0.24)	-0.43 (SE 0.44)	0.54
SDMT							
Baseline diff.	Ref.	-0.29 (SE 0.19)	-0.85 (SE 0.20)***	**<0.001**	-0.28 (SE 0.18)	-0.82 (SE 0.20)***	**<0.001**
Slope diff.	Ref.	0.08 (SE 0.14)	-0.23 (SE 0.22)	0.43	0.08 (SE 0.14)	-0.13 (SE 0.27)	0.72
Verbal fluency							
Baseline diff.	Ref.	0.27 (SE 0.22)	0.03 (SE 0.24)	0.47	0.22 (SE 0.21)	0.05 (SE 0.24)	0.58
Slope diff.	Ref.	0.02 (SE 0.15)	-0.54 (SE 0.24)	0.08	0.08 (SE 0.16)	-0.48 (SE 0.30)	0.19
Stroop colour							
Baseline diff.	Ref.	-0.15 (SE 0.20)	-0.68 (SE 0.22)**	**0.01**	-0.12 (SE 0.20)	-0.60 (SE 0.22)**	**0.02**
Slope diff.	Ref.	-0.08 (SE 0.14)	-0.18 (SE 0.24)	0.69	-0.02 (SE 0.15)	-0.12 (SE 0.28)	0.91
Stroop word							
Baseline diff.	Ref.	-0.31 (SE 0.23)	-0.41 (SE 0.29)	0.20	-0.29 (SE 0.22)	-0.35 (SE 0.28)	0.26
Slope diff.	Ref.	0.19 (SE 0.14)	-0.15 (SE 0.24)	0.28	0.25 (SE 0.15)	-0.09 (SE 0.29)	0.22
Stroop interference							
Baseline diff.	Ref.	-0.26 (SE 0.21)	-0.51 (SE 0.26)	0.1	-0.22 (SE 0.20)	-0.38 (SE 0.26)	0.24
Slope diff.	Ref.	-0.03 (SE 0.01)	0.16 (SE 0.16)	0.16	0.20 (SE 0.17)	-0.44 (SE 0.32)	0.14
TMT A							
Baseline diff.	Ref.	-0.25 (SE 0.13)	-0.36 (SE 0.15)*	**0.03**	-0.25 (SE 0.13)	-0.35 (SE 0.15)*	**0.02**
Slope diff.	Ref.	0.10 (SE 0.15)	-0.47 (SE 0.24)	0.09	0.22 (SE 0.16)	-0.15 (SE 0.30)	0.30

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Table 5: **(Continued)** Supplementary table: Changes over ten-year follow-up on cognitive tests for premanifest HD and manifest HD subjects compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	P-value	Premanifest HD N=26	Manifest HD N=19	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
TMT B							
Baseline diff.	Ref.	-0.27 (SE 0.19)	-0.77 (SE 0.20)***	**0.001**	-0.26 (SE 0.18)	-0.74 (SE 0.21)***	**0.002**
Slope diff.	Ref.	0.02 (SE 0.16)	-0.33 (SE 0.27)	0.44	0.02 (SE 0.17)	-0.13 (SE 0.32)	0.91
VLGT list A							
Baseline diff.	Ref.	-0.17 (SE 0.19)	-0.79 (SE 0.22)**	**0.001**	-0.19 (SE 0.20)	-0.76 (SE 0.23)**	**0.004**
Slope diff.	Ref.	0.07 (SE 0.22)	0.12 (SE 0.43)	0.92	0.19 (SE 0.23)	0.08 (SE 0.45)	0.70
VLGT list B							
Baseline diff.	Ref.	-0.17 (SE 0.23)	0.00 (SE 0.41)	0.77	-0.16 (SE 0.23)	-0.01 (SE 0.44)	0.78
Slope diff.	Ref.	0.08 (SE 0.26)	-0.98 (SE 0.57)	0.19	0.19 (SE 0.27)	-0.96 (SE 0.58)	0.16
VLGT short term recall							
Baseline diff.	Ref.	-0.37 (SE 0.23)	-0.68 (SE 0.40)	0.10	-0.42 (SE 0.22)	-1.08 (SE 0.41)**	**0.01**
Slope diff.	Ref.	-0.09 (SE 0.20)	0.26 (SE 0.43)	0.73	-0.03 (SE 0.20)	0.54 (SE 0.43)	0.44
VLGT long term recall							
Baseline diff.	Ref.	-0.13 (SE 0.18)	-0.69 (SE 0.20)**	**0.004**	-0.15 (SE 0.19)	-0.76 (SE 0.21)***	**0.002**
Slope diff.	Ref.	-0.07 (SE 0.19)	-0.26 (SE 0.39)	0.78	0.03 (SE 0.20)	-0.22 (SE 0.39)	0.83
VLGT long term recognition							
Baseline diff.	Ref.	0.03 (SE 0.17)	-0.38 (SE 0.19)	0.11	0.02 (SE 0.17)	-0.37 (SE 0.20)	0.15
Slope diff.	Ref.	-0.48 (SE 0.23)*	-0.75 (SE 0.44)	**0.043**	-0.40 (SE 0.24)	-0.82 (SE 0.45)	0.07
BNT							
Baseline diff.	Ref.	0.12 (SE 0.18)	-0.43 (SE 0.21)	0.07	0.11 (SE 0.19)	-0.40 (SE 0.21)	0.11
Slope diff.	Ref.	0.05 (SE 0.18)	0.10 (SE 0.32)	0.92	0.03 (SE 0.18)	-0.24 (SE 0.34)	0.75

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Table 5: **(Continued)** Supplementary table: Changes over ten-year follow-up on cognitive tests for premanifest HD and manifest HD subjects compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	P-value	Premanifest HD N=26	Manifest HD N=19	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
WMS MQ							
Baseline diff.	Ref.	-0.26 (SE 0.18)	-0.70 (SE 0.21)**	**0.003**	-0.34 (SE 0.18)	-0.75 (SE 0.21)***	**0.001**
Slope diff.	Ref.	-0.27 (SE 0.14)	-0.70 (SE 0.23)**	**0.004**	-0.13 (SE 0.15)	-0.50 (SE 0.28)	0.17
WAIS TIQ							
Baseline diff.	Ref.	0.02 (SE 0.18)	-0.78 (SE 0.20)***	**0.001**	-0.03 (SE 0.19)	-0.76 (SE 0.20)***	**0.001**
Slope diff.	Ref.	-0.09 (SE 0.13)	-0.42 (SE 0.24)	0.18	0.06 (SE 0.13)	-0.53 (SE 0.26)	0.09
WAIS PIQ							
Baseline diff.	Ref.	-0.08 (SE 0.20)	-0.84 (SE 0.22)***	**0.001**	-0.13 (SE 0.20)	-0.85 (SE 0.22)***	**0.001**
Slope diff.	Ref.	0.03 (SE 0.16)	-0.74 (SE 0.29)*	**0.043**	0.12 (SE 0.17)	-0.65 (SE 0.33)	0.09
WAIS VIQ							
Baseline diff.	Ref.	0.07 (SE 0.18)	-0.62 (SE 0.19)**	**0.004**	0.04 (SE 0.18)	-0.61 (SE 0.20)**	**0.007**
Slope diff.	Ref.	-0.09 (SE 0.12)	-0.57 (SE 0.22)*	**0.039**	0.03 (SE 0.13)	-0.76 (SE 0.25)**	**0.007**

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. BNT = Boston naming task, MMSE = mini mental state examination, PIQ = performal intelligence quotient, Ref. = Reference group, RT = reaction time. SDMT = symbol digit modalities test, TIQ = total intelligence quotient, TMT = trail making test, VIQ = verbal intelligence quotient, VLGT = verbale leer- en geheugen test, WAIS = Wechsler adult intelligence scale, WMS MQ = Wechsler memory scale memory quotient. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ indicate significant differences compared to controls in post-hoc tests.

Table 6: Supplementary table: Changes over ten-year follow-up on cognitive tests for continual premanifest HD and converter subjects compared to controls

	Controls N=87	Continual Premanifest HD N=21	Converters N=5	P-value	Continual Premanifest HD N=21	Converters N=5	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
MMSE							
Baseline diff.	Ref.	-0.19 (SE 0.18)	-0.22 (SE 0.32)	0.48	-0.19 (SE 0.18)	-0.17 (SE 0.32)	0.53
Slope diff.	Ref.	0.06 (SE 0.24)	-0.15 (SE 0.45)	0.90	0.14 (SE 0.25)	-0.26 (SE 0.32)	0.73
SDMT							
Baseline diff.	Ref.	-0.30 (SE 0.20)	-0.20 (SE 0.36)	0.30	-0.29 (SE 0.20)	-0.23 (SE 0.35)	0.31
Slope diff.	Ref.	0.27 (SE 0.14)	-0.70 (SE 0.26)**	**0.002**	0.20 (SE 0.15)	-0.64 (SE 0.30)*	**0.03**
Verbal fluency							
Baseline diff.	Ref.	0.38 (SE 0.24)	0.12 (SE 0.42)	0.28	0.33 (SE 0.23)	0.06 (SE 0.41)	0.36
Slope diff.	Ref.	0.14 (SE 0.16)	-0.47 (SE 0.30)	0.15	0.18 (SE 0.17)	-0.45 (SE 0.35)	0.19
Stroop colour							
Baseline diff.	Ref.	-0.17 (SE 0.22)	-0.15 (SE 0.38)	0.71	-0.13 (SE 0.21)	-0.22 (SE 0.38)	0.75
Slope diff.	Ref.	0.11 (SE 0.15)	-0.88 (SE 0.28)**	**0.003**	0.03 (SE 0.15)	-0.33 (SE 0.32)	0.54
Stroop word							
Baseline diff.	Ref.	-0.20 (SE 0.25)	-0.51 (SE 0.42)	0.39	-0.18 (SE 0.24)	-0.55 (SE 0.41)	0.36
Slope diff.	Ref.	0.37 (SE 0.15)*	-0.63 (SE 0.28)*	**0.002**	0.32 (SE 0.16)	-0.24 (SE 0.33)	0.08
Stroop interference							
Baseline diff.	Ref.	-0.26 (SE 0.23)	-0.17 (SE 0.39)	0.51	-0.22 (SE 0.23)	-0.17 (SE 0.39)	0.60
Slope diff.	Ref.	0.30 (SE 0.17)	-0.47 (SE 0.32)	**0.047**	0.27 (SE 0.18)	-0.23 (SE 0.37)	0.23
TMT A							
Baseline diff.	Ref.	-0.29 (SE 0.15)	-0.07 (SE 0.26)	0.15	-0.28 (SE 0.14)	-0.09 (SE 0.25)	0.15
Slope diff.	Ref.	0.27 (SE 0.16)	-0.62 (SE 0.30)*	**0.02**	0.33 (SE 0.17)	-0.39 (SE 0.36)	**0.07**

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Table 6: **(Continued)** Supplementary table: Changes over ten-year follow-up on cognitive tests for continual pre-manifest HD and converter subjects compared to controls

	Controls N=87	Continual Premanifest HD N=21	Converters N=5	P-value	Continual Premanifest HD N=21	Converters N=5	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
TMT B							
Baseline diff.	Ref.	-0.28 (SE 0.20)	-0.09 (SE 0.36)	0.38	-0.27 (SE 0.20)	-0.11 (SE 0.36)	0.43
Slope diff.	Ref.	0.17 (SE 0.18)	-0.61 (SE 0.33)	0.09	0.10 (SE 0.18)	-0.47 (SE 0.38)	0.36
VLGT list A							
Baseline diff.	Ref.	-0.22 (SE 0.21)	-0.12 (SE 0.38)	0.56	-0.25 (SE 0.21)	-0.21 (SE 0.38)	0.46
Slope diff.	Ref.	0.11 (SE 0.23)	-0.12 (SE 0.47)	0.89	0.14 (SE 0.24)	0.63 (SE 0.56)	0.48
VLGT list B							
Baseline diff.	Ref.	-0.35 (SE 0.25)	0.57 (SE 0.42)	0.10	-0.36 (SE 0.25)	0.51 (SE 0.41)	0.11
Slope diff.	Ref.	0.28 (SE 0.27)	-0.88 (SE 0.55)	0.13	0.29 (SE 0.28)	-0.18 (SE 0.64)	0.54
VLGT short term recall							
Baseline diff.	Ref.	-0.43 (SE 0.25)	-0.38 (SE 0.41)	0.19	-0.44 (SE 0.25)	-0.45 (SE 0.41)	0.15
Slope diff.	Ref.	-0.01 (SE 0.21)	-0.53 (SE 0.42)	0.46	-0.01 (SE 0.21)	-0.11 (SE 0.49)	0.98
VLGT long term recall							
Baseline diff.	Ref.	-0.21 (SE 0.20)	-0.01 (SE 0.36)	0.57	-0.23 (SE 0.20)	-0.13 (SE 0.36)	0.53
Slope diff.	Ref.	0.05 (SE 0.20)	-0.70 (SE 0.41)	0.22	0.04 (SE 0.20)	-0.05 (SE 0.47)	0.98
VLGT long term recognition							
Baseline diff.	Ref.	0.02 (SE 0.17)	-0.04 (SE 0.31)	0.99	0.00 (SE 0.17)	-0.13 (SE 0.31)	0.92
Slope diff.	Ref.	-0.44 (SE 0.23)	-0.70 (SE 0.47)	0.07	-0.45 (SE 0.23)	-0.07 (SE 0.54)	0.16
BNT							
Baseline diff.	Ref.	0.09 (SE 0.20)	0.07 (SE 0.19)	0.63	0.11 (SE 0.20)	0.26 (SE 0.36)	0.70
Slope diff.	Ref.	0.07 (SE 0.19)	-0.00 (SE 0.35)	0.93	-0.00 (SE 0.19)	0.24 (SE 0.41)	0.84

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Table 6: **(Continued)** Supplementary table: Changes over ten-year follow-up on cognitive tests for continual premanifest HD and converter subjects compared to controls

	Controls N=87	Continual Premanifest HD N=21	Converters N=5	P-value	Continual Premanifest HD N=21	Converters N=5	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
WMS MQ							
Baseline diff.	Ref.	-0.33 (SE 0.19)	-0.08 (SE 0.35)	0.23	-0.41 (SE 0.19)	-0.17 (SE 0.35)	0.10
Slope diff.	Ref.	-0.13 (SE 0.15)	-0.88 (SE 0.27)**	**0.006**	-0.06 (SE 0.15)	-0.49 (SE 0.32)	0.30
WAIS TIQ							
Baseline diff.	Ref.	0.02 (SE 0.20)	0.10 (SE 0.35)	0.96	-0.02 (SE 0.20)	-0.00 (SE 0.35)	0.99
Slope diff.	Ref.	-0.01 (SE 0.14)	-0.41 (SE 0.24)	0.24	0.02 (SE 0.14)	0.30 (SE 0.32)	0.65
WAIS PIQ							
Baseline diff.	Ref.	0.05 (SE 0.21)	-0.26 (SE 0.37)	0.74	-0.00 (SE 0.21)	-0.36 (SE 0.37)	0.62
Slope diff.	Ref.	0.09 (SE 0.17)	-0.50 (SE 0.31)	0.20	0.12 (SE 0.18)	0.08 (SE 0.40)	0.79
WAIS VIQ							
Baseline diff.	Ref.	-0.05 (SE 0.19)	0.42 (SE 0.35)	0.45	-0.08 (SE 0.20)	0.36 (SE 0.35)	0.52
Slope diff.	Ref.	0.01 (SE 0.13)	-0.51 (SE 0.23)	0.08	0.05 (SE 0.13)	-0.11 (SE 0.30)	0.86

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. BNT = Boston naming task, MMSE = mini mental state examination, PIQ = performal intelligence quotient, Ref. = Reference group, RT = reaction time. SDMT = symbol digit modalities test, TIQ = total intelligence quotient, TMT = trail making test, VIQ = verbal intelligence quotient, VLGT = verbale leer- en geheugen test, WAIS = Wechsler adult intelligence scale, WMS MQ = Wechsler memory scale memory quotient. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ indicate significant differences compared to controls in post-hoc tests.

Table 7: Supplementary table: Changes over ten-year follow-up on cognitive tests for premanifest HD subjects far from and close to predicted onset compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	P-value	Premanifest HD N=26	Manifest HD N=19	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
MMSE							
Baseline diff.	Ref.	-0.14 (SE 0.21)	-0.25 (SE 0.21)	0.45	-0.15 (SE 0.22)[a]	-0.24 (SE 0.22)[a]	0.50
Slope diff.	Ref.	0.10 (SE 0.28)	-0.09 (SE 0.31)	0.87	0.10 (SE 0.32)[a]	0.03 (SE 0.37)[a]	0.95
SDMT							
Baseline diff.	Ref.	0.19 (SE 0.23)	-0.77 (SE 0.23)**	**0.001**	0.16 (SE 0.22)	-0.73 (SE 0.22)**	**0.003**
Slope diff.	Ref.	0.12 (SE 0.17)	0.02 (SE 0.18)	0.78	0.13 (SE 0.17)	-0.04 (SE 0.20)	0.69
Verbal fluency							
Baseline diff.	Ref.	0.41 (SE 0.28)	0.23 (SE 0.28)	0.31	0.33 (SE 0.28)	0.20 (SE 0.28)	0.45
Slope diff.	Ref.	-0.03 (SE 0.19)	0.09 (SE 0.20)	0.88	-0.03 (SE 0.19)	0.28 (SE 0.23)	0.45
Stroop colour							
Baseline diff.	Ref.	0.13 (SE 0.26)	-0.47 (SE 0.25)	0.13	0.13 (SE 0.25)	-0.44 (SE 0.25)	0.15
Slope diff.	Ref.	-0.16 (SE 0.18)	0.02 (SE 0.20)	0.63	-0.17 (SE 0.17)	0.22 (SE 0.21)	0.28
Stroop word							
Baseline diff.	Ref.	-0.11 (SE 0.29)	-0.46 (SE 0.30)	0.31	-0.10 (SE 0.29)	-0.46 (SE 0.29)	0.30
Slope diff.	Ref.	0.22 (SE 0.18)	0.14 (SE 0.20)	0.42	0.18 (SE 0.19)	0.34 (SE 0.22)	0.24
Stroop interference							
Baseline diff.	Ref.	0.02 (SE 0.27)	-0.54 (SE 0.27)	0.14	0.02 (SE 0.27)	-0.51 (SE 0.27)	0.16
Slope diff.	Ref.	-0.03 (SE 0.01)	-0.08 (SE 0.20)	0.09	-0.09 (SE 0.20)	0.66 (SE 0.24)**	**0.02**
TMT A							
Baseline diff.	Ref.	-0.07 (SE 0.17)	-0.42 (SE 0.17)	0.06	-0.09 (SE 0.17)	-0.42 (SE 0.17)	0.05
Slope diff.	Ref.	0.14 (SE 0.19)	0.03 (SE 0.21)	0.76	0.15 (SE 0.19)	0.30 (SE 0.23)	0.38

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Table 7: **(Continued)** Supplementary table: Changes over ten-year follow-up on cognitive tests for premanifest HD subjects far from and close to predicted onset compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	P-value	Premanifest HD N=26	Manifest HD N=19	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
TMT B							
Baseline diff.	Ref.	0.06 (SE 0.24)	-0.55 (SE 0.24)	0.06	0.04 (SE 0.24)	-0.53 (SE 0.24)	0.08
Slope diff.	Ref.	-0.00 (SE 0.21)	0.04 (SE 0.23)	0.99	-0.07 (SE 0.21)	0.13 (SE 0.25)	0.80
VLGT list A							
Baseline diff.	Ref.	-0.19 (SE 0.25)	-0.22 (SE 0.25)	0.58	-0.20 (SE 0.25)	-0.27 (SE 0.26)	0.48
Slope diff.	Ref.	0.17 (SE 0.27)	-0.08 (SE 0.31)	0.75	0.18 (SE 0.27)	0.21 (SE 0.33)	0.71
VLGT list B							
Baseline diff.	Ref.	-0.33 (SE 0.28)	0.03 (SE 0.30)	0.47	-0.31 (SE 0.27)	0.02 (SE 0.30)	0.50
Slope diff.	Ref.	0.27 (SE 0.31)	-0.18 (SE 0.37)	0.55	0.27 (SE 0.31)	0.09 (SE 0.39)	0.70
VLGT short term recall							
Baseline diff.	Ref.	-0.39 (SE 0.27)	-0.46 (SE 0.29)	0.18	-0.38 (SE 0.27)	-0.51 (SE 0.29)	0.15
Slope diff.	Ref.	0.03 (SE 0.24)	-0.27 (SE 0.28)	0.58	0.03 (SE 0.24)	-0.12 (SE 0.30)	0.91
VLGT long term recall							
Baseline diff.	Ref.	-0.24 (SE 0.24)	-0.11 (SE 0.24)	0.57	-0.25 (SE 0.24)	-0.17 (SE 0.24)	0.53
Slope diff.	Ref.	0.06 (SE 0.23)	-0.25 (SE 0.27)	0.59	0.06 (SE 0.23)	-0.04 (SE 0.28)	0.95
VLGT long term recognition							
Baseline diff.	Ref.	0.06 (SE 0.21)	-0.06 (SE 0.21)	0.91	0.08 (SE 0.21)	-0.13 (SE 0.21)	0.72
Slope diff.	Ref.	-0.60 (SE 0.27)	-0.36 (SE 0.30)	0.07	-0.60 (SE 27)	-0.08 (SE 0.32)	0.08
BNT							
Baseline diff.	Ref.	0.30 (SE 0.24)	-0.02 (SE 0.24)	0.43	0.29 (SE 0.24)	0.00 (SE 0.24)	0.48
Slope diff.	Ref.	0.00 (SE 0.22)	0.21 (SE 0.24)	0.88	0.02 (SE 0.22)	0.03 (SE 0.27)	0.99

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Table 7: **(Continued)** Supplementary table: Changes over ten-year follow-up on cognitive tests for premanifest HD subjects far from and close to predicted onset compared to controls

	Controls N=87	Premanifest HD N=26	Manifest HD N=19	P-value	Premanifest HD N=26	Manifest HD N=19	P-value
		A. Adjusted - Age, gender, education			**B. Adjusted - Age, gender, education, motor speed**		
WMS MQ							
Baseline diff.	Ref.	-0.29 (SE 0.24)	-0.28 (SE 0.23)	0.28	-0.31 (SE 0.23)	-0.41 (SE 0.23)	0.12
Slope diff.	Ref.	.00 (SE 0.18)	-0.61 (SE 0.19)**	**0.005**	0.03 (SE 0.17)	-0.40 (SE 0.21)	0.15
WAIS TIQ							
Baseline diff.	Ref.	0.03 (SE 0.24)	0.05 (SE 0.24)	0.98	-0.00 (SE 0.24)	-0.01 (SE 0.24)	0.99
Slope diff.	Ref.	0.17 (SE 0.16)	-0.40 (SE 0.17)*	**0.02**	0.19 (SE 0.16)	-0.16 (SE 0.19)	0.28
WAIS PIQ							
•Baseline diff.	Ref.	0.18 (SE 0.25)	-0.21 (SE 0.25)	0.48	0.14 (SE 0.25)	-0.28 (SE 0.25)	0.40
•Slope diff.	Ref.	0.14 (SE 0.20)	-0.24 (SE 0.22)	0.34	0.15 (SE 0.20)	0.04 (SE 0.24)	0.74
WAIS VIQ							
•Baseline diff.	Ref.	-0.07 (SE 0.24)	0.16 (SE 0.23)	0.72	-0.08 (SE 0.24)	0.12 (SE 0.24)	0.81
•Slope diff.	Ref.	0.18 (SE 0.15)	-0.42 (SE 0.16)**	**0.007**	0.20 (SE 0.15)	-0.26 (SE 0.18)	0.10

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. BNT = Boston naming task, MMSE = mini mental state examination, PIQ = performal intelligence quotient, Ref. = Reference group, RT = reaction time. SDMT = symbol digit modalities test, TIQ = total intelligence quotient, TMT = trail making test, VIQ = verbal intelligence quotient, VLGT = verbale leer- en geheugen test, WAIS = Wechsler adult intelligence scale, WMS MQ = Wechsler memory scale memory quotient. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ indicate significant differences compared to controls in post-hoc tests.

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Chapter 6

Better global and cognitive functioning in choreatic versus hypokinetic-rigid Huntington's disease

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Abstract

Understanding the relation between predominantly choreatic and hypokinetic-rigid motor subtypes and cognitive and general functioning may contribute to knowledge about different motor-phenotypes in Huntington's disease. In the European Huntington's Disease Network Registry study, 1882 subjects were classified as being predominantly choreatic (N=528) or hypokinetic-rigid (N=432), according to their score on items of the total motor score a priori labelled as choreatic or hypokinetic-rigid; the other 922 patients were of a mixed type. The relationship between motor type and cognitive (verbal fluency, symbol digit modalities, Stroop colour, word and interference tests) and functional (total functional capacity) capacity was investigated using multiple linear regression. Motor subtype contributed significantly to the total functional capacity score (partial r^2: 7.8%; $p<0.001$) and to the five cognitive scores (partial r^2 values ranging from 2.0-8.4%; all p-values <0.001), patients with a predominantly choreatic motor phenotype performing better in all areas than patients with a hypokinetic-rigid motor phenotype.

INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative disorder, caused by an unstable expansion of a CAG trinucleotide repeat on chromosome 4[1]. Although motor disturbances often stand out, the clinical presentation is also determined by behavioural problems and dementia[2].
HD is generally categorized as a hyperkinetic disorder[3]. Hypokinesia, however, also plays an important role in the motor presentation[4 5]. Clinically, three motor subtypes can be distinguished: choreatic, hypokinetic-rigid and mixed-motor type. It has been reported that the predominantly rigid type, typically seen in juvenile HD[6], is less common in adult-onset HD than chorea-predominant HD[7]. Nevertheless, some authors have stated that it is not chorea but hypokinesia-rigidity that is the core movement disorder in HD[8 9 10]. Most probably hyperkinesia and hypokinesia co-exist in HD, one of the two being predominant[10 11].

Because of the progressive nature of HD, motor symptoms worsen. Clinical observation suggests that this process is not uniform and that patients who present with predominantly choreatic or hypokinetic-rigid motor symptoms show different cognitive and functional profiles, a notion already stated by Brandt[12].
Several studies have investigated HD motor subtypes, but as the classification methods are heterogeneous, no uniform conclusions about the relation between motor type and clinical functioning can be drawn. Hyperkinesia in HD was found to be both related[13] and unrelated[9] to cognitive functioning, whereas hypokinesia was associated with cognitive[9 14] and functional impairment[4 5 8 15].

Investigating the cognitive and functional profiles of both motor types may add to the existing knowledge about motor functioning in HD patients, and may have implications for patient management.
We investigate the relationship between the predominant motor type and cognitive and general functioning and hypothesize that patients with predominantly choreatic motor characteristics function better than hypokinetic-rigid patients on both cognitive and general levels. We also examine the use of neuroleptics in both groups[16 17], and assess whether the motor phenotype is associated with disease duration.

METHODS

We used on-site, monitored data from the first visit of subjects with a CAG of $\geq$36 and a Unified Huntington's Disease Rating Scale (UHDRS)[18] total motor score (TMS) of $>$5, as recorded in the European Huntington's Disease Network Registry study. The number of subjects fulfilling these criteria was 1882. Variables consisted of the motor, function and cognitive parts of the UHDRS, CAG repeat

length, date-of-birth, gender, medication and educational level.
To enable classification into predominantly choreatic or hypokinetic-rigid motor phenotypes, certain TMS items were selected: for the choreatic subtype the items of the chorea scale, adding up to 28. For hypokinetic-rigidity finger taps, pronate-supinate hands, bradykinesia, rigidity, items measuring speed of movement and rigidity, again with a maximum of 28.
For subjects to be subdivided into predominantly choreatic or hypokinetic-rigid types, the total scores for the two subtypes had to differ by at least one standard deviation (i.e. 4 points). If the difference was smaller, it was considered to be a mixed motor type. This resulted in 528 choreatic, 432 hypokinetic-rigid and 922 mixed subjects. As we were interested in differences between predominantly choreatic and hypokinetic-rigid motor types, the mixed group was not included in analyses. The use of neuroleptic medication was scored as '1 = present' or '0 = absent'.

SPSS 17.0 was used for data analysis, and independent sample t-tests for group differences on demographic variables were performed, except for gender and neuroleptics (χ^2-test) and total functional capacity (Mann-Whitney U-test). Multiple linear regression models were constructed to evaluate the contribution of motor type to either cognition (verbal fluency, symbol digit modalities (SDMT) and Stroop colour, word and interference tests) or global functioning (total functional capacity; TFC). Age, gender, CAG repeat length, disease duration, TMS, and education were used as covariates and entered in one block. Motor type was entered as a binary variable. Partial correlation coefficients were calculated to examine the contribution of the separate covariates. To investigate whether the distribution of motor types was constant overt the disease course, disease duration was divided into quartiles and the distribution was examined with a χ^2-test. Statistical significance was set at $p<0.05$. For regression analysis the p-value was divided by six to correct for multiple testing, resulting in $p<0.008$.

RESULTS

Demographic analysis showed that the choreatic group was older, more often male, had been educated for longer ($p<0.005$), had a higher age at disease onset, shorter disease duration and lower CAG repeat (all p-values <0.001) compared to the hypokinetic-rigid group (Table 1). The choreatic group had a higher TFC and lower TMS ($p<0.001$). In all cognitive tests, hypokinetic-rigid subjects had lower scores than choreatic subjects ($p<0.001$). There was no difference between groups with regard to the number of participants using neuroleptic drugs.

Table 1: Demographics of whole group and of separate motor groups

	Whole group	Choreatic	Hypokinetic-rigid	P choreatic vs hypokinetic-rigid
N	1882	528	432	
Age (yrs)	50.6 (11.6)	52.2 (11.0)	49.8 (12.5)	<**0.005**
Gender f/m (%m)[a]	929/953 (51)	224/304 (58)	225/207 (48)	<**0.005**
Neuroleptics yes/no (%yes)[a]	1237/645 (66)	344/184 (65)	302/130 (70)	0.067
Years of education	11.2 (3.6)	11.4 (3.8)	10.8 (3.3)	<**0.005**
Age at disease onset (yrs)	43.6 (11.0)	45.2 (10.6)	41.7 (11.3)	<**0.001**
Disease duration (yrs)	7.0 (5.0)	6.9 (4.7)	8.1 (5.7)	<**0.001**
CAG large	44.1 (3.3)	43.7 (3.0)	45.0 (3.5)	<**0.001**
Total Functional Capacity[b]	9.0 (5)	10.0 (5)	6.0 (7)	<**0.001**
Total Motor Score	34.5 (18.4)	34.0 (16.4)	41.7 (19.8)	<**0.001**
Verbal fluency total score	17.7 (11.5)	19.4 (11.5)	13.7 (11.1)	<**0.001**
SDMT total score	20.6 (12)	22.8 (11.2)	15.4 (11.7)	<**0.001**
Stroop color total score	40.8 (17.5)	44.4 (17.2)	33.0 (17.0)	<**0.001**
Stroop word total score	55.2 (22.7)	60.5 (22.2)	44.3 (21.9)	<**0.001**
Stroop interference total score	22.2 (12)	24.7 (12.0)	17.4 (11.5)	<**0.001**

Note. Data are mean (standard deviation), expect for [a] (total number) and for [b] (median and interquartile range). Analyses are independent samples t-test, except for a (χ^2 test) and b (Mann-Whitney U-test). SDMT = Symbol Digit Modalities Test.

Linear regression analyses on cognitive functioning, taking differences in age, sex, education, disease duration, CAG and TMS into account (Table 2b-e), revealed that motor subtype was a predictor of all cognitive tests (all $p<0.001$). Patients in the hypokinetic-rigid group had significantly worse scores on all tests than those in the choreatic group. As revealed by the squared partial correlation coefficients, motor subtype was the second most contributing variable after TMS in all models ($p<0.001$) except verbal fluency, where it was the third most contributing factor ($p<0.001$).

Table 2: a-d. Linear regression analyses on total functional and cognitive scores

	B	SE B	Partial r^2	P-value
2a. Total Functional Capacity Score				
Constant	19.00	2.23		<**0.001**
Age (yrs)	-0.03	0.01	.000	<**0.005**
Gender	0.29	0.16	.003	0.075
Education (yrs)	0.10	0.02	.018	<**0.001**
Disease duration (yrs)	-0.14	0.02	.062	<**0.001**
CAG	-0.09	0.04	.005	0.029
Total Motor Score	-0.10	0.01	.297	<**0.001**
Motor subtype	-1.50	0.17	.078	<**0.001**
2b. Total Verbal Fluency Score				
Constant	48.08	8.71		<**0.001**
Age (yrs)	-0.08	0.05	0.003	0.070
Gender	-1.05	0.63	0.003	0.094
Education (yrs)	0.65	0.09	0.055	<**0.001**
Disease duration (yrs)	-0.11	0.07	0.003	0.116
CAG	-0.40	0.16	0.007	0.010
Total Motor Score	-0.27	0.02	0.157	<**0.001**
Motor subtype	-2.87	0.65	0.020	<**0.001**
2c. Symbol Digit Modalities Score				
Constant	70.49	7.60		<**0.001**
Age (yrs)	-0.26	0.04	0.045	<**0.001**
Gender	-0.56	0.55	0.001	0.303
Education (yrs)	0.56	0.08	0.053	<**0.001**
Disease duration (yrs)	-0.13	0.06	0.005	0.032
CAG	-0.52	0.14	0.015	<**0.001**
Total Motor Score	-0.33	0.02	0.278	<**0.001**
Motor subtype	-4.67	0.57	0.059	<**0.001**
2d. Stroop Colour Test Score				
Constant	84.96	12.07		<**0.001**
Age (yrs)	-0.24	0.06	0.014	<**0.001**
Gender	-0.93	0.87	0.000	0.286
Education (yrs)	0.53	0.12	0.020	<**0.001**
Disease duration (yrs)	-0.12	0.10	0.002	0.196
CAG	-0.16	0.22	0.001	0.454
Total Motor Score	-0.52	0.03	0.267	<**0.001**
Motor subtype	-7.39	0.90	0.066	<**0.001**

Table continues on next page.

Table 2: **(Continued)** e-f. Linear regression analyses on total functional and cognitive scores

	B	SE B	Partial r^2	P-value
2e. Stroop Word Test Score				
Constant	119.48	15.30		<**0.001**
Age (yrs)	-0.30	0.08	0.014	<**0.001**
Gender	-1.56	1.10	0.021	0.159
Education (yrs)	0.80	0.15	0.028	<**0.001**
Disease duration (yrs)	-0.37	0.12	0.096	<**0.005**
CAG	-0.35	0.27	0.002	0.206
Total Motor Score	-0.65	0.04	0.264	<**0.001**
Motor subtype	-10.62	1.14	0.084	<**0.001**
2f. Stroop Interference Test Score				
Constant	63.98	8.20		<**0.001**
Age (yrs)	-0.28	0.04	0.042	<**0.001**
Gender	-0.21	0.59	0.001	0.718
Education (yrs)	0.45	0.08	0.031	<**0.001**
Disease duration (yrs)	-0.13	0.07	0.004	0.043
CAG	-0.30	0.15	0.000	0.038
Total Motor Score	-0.32	0.02	0.229	<**0.001**
Motor subtype	-4.73	0.61	0.059	<**0.001**

Note. B=regression coefficient, SE B=standard error of B, r^2=squared partial correlation coefficients.

Motor subtype also contributed significantly to general functioning (TFC) ($p<0.001$) when the covariates were taken into account (Table 2a), and was the second most contributing variable after the TMS (partial $r^2=.078$, $p<0.001$). Together, independent variables explained 56% of the variance in TFC ($p<0.001$). Hypokinetic-rigid subjects performed significantly worse on TFC than choreatic subjects.

A χ^2-test revealed significant differences in the distribution of choreatic and hypokinetic-rigid subjects across disease duration quartile groups ($p= 0.008$), and shifted from slightly more choreatic than hypokinetic-rigid in the first three quartiles (I and II: 59% versus 41%, III: 56% versus 44%) to slightly more hypokinetic-rigid than choreatic in the last quartile (45% versus 55%).

DISCUSSION

We investigated the differences in clinical and cognitive performance between predominantly choreatic and hypokinetic-rigid HD patients. We found motor subtype defined by either predominantly chorea or hypokinesia-rigidity characteristics to be an independent predictor of both cognitive and general functioning, with choreatic patients functioning significantly better.

Investigating function and cognition in relation to predominantly choreatic or hypokinetic-rigid HD has not previously been carried out in this way. Earlier studies did, however, find that higher hypokinesia-rigidity scores were related to poorer cognitive and general functioning[4,5,14]. The lack of relation between choreatic movements and cognitive and functional impairment found in previous studies[9,13,15] seems to be in line with our finding that chorea in HD is characterized by better performance in both areas.
Clinically different motor subtypes have also been identified in Parkinsons disease (PD): tremor-dominant subtype (characterized by mild disease progression), akinetic-rigid subtype (where cognitive impairment is more severe), and postural instability and gait difficulty subtype (associated with cognitive impairment and severe disease progression)[19,20]. Comparable to our results, the hypokinetic PD subtypes are associated with poorer functioning than the subtype related to more hyperkinetic features.

The distribution of motor types across disease duration quartiles revealed a shift from slightly more choreatic than hypokinetic-rigid subjects in the first three quartiles to slightly more hypokinetic-rigid than choreatic subjects in the last quartile. Although these findings are based on group comparisons and do not necessarily reflect the probability that an individual patient follows the same course (i.e. the distribution across motor types of patients in the highest quartile of disease duration may already have been present in these same patients earlier in the disease), the alternative explanation that it does reflect the increasing probability that a patient converts from a more choreatic to a more hypokinetic-rigid motor type as disease duration lengthens is very well possible. This would support earlier findings on motor phenotype progression[7,21]. However, even if patients have an increased probability to convert to a more hypokinetic-rigid motor type with advancing disease, it does not account for our findings that the choreatic motor type is associated with better global and cognitive functioning because differences in disease duration were taken into account in the regression analyses. Furthermore, the differences in profiles can also not be explained by the influence of neuroleptic medication, as its use was comparable between groups.

Conclusions about our findings should be drawn with caution. The Registry database, due to its international nature, does not provide sufficient nor uniform

information about the dosages or indications for use of neuroleptics. Although neuroleptic use did not differ between groups, we cannot exclude the possibility that choreatic subjects are falsely assigned to the hypokinetic-rigid group due to medication-induced hypokinesia. Also, longitudinal analyses are essential to investigate the progression of choreatic and hypokinetic-rigid motor symptoms during the course of the disease. Replication of our results and further in-depth study of medication usage and degree of motor impairment is needed to ensure that the functional differences found can reliably be ascribed to different motor profiles.

To summarise, in a large cohort of patients with Huntington's disease, we found that predominantly choreatic HD is characterized by better global and cognitive functioning than hypokinetic-rigid HD, differences that could not be explained by differences in age or disease duration. Further research is, however, necessary.

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Competing interest

None.

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Chapter 7

The influence of motor dysfunction on executive functioning in manifest and premanifest Huntington's disease

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Abstract

Objective Motor disturbances can be present in both manifest and premanifest Huntington's disease (HD). We aimed to investigate the role of motor functioning on executive functioning in order to understand the progression of actual cognitive dysfunction in HD.

Methods Forty manifest HD (MHD), 21 premanifest HD (PMHD) and 28 control subjects were tested twice, with a one-year interval. For the Symbol Digit Modalities test (SDMT) and Figure Fluency test (FFT) extra conditions were designed to measure motor involvement. Subtraction of this motor score from the original test score resulted in isolation of the cognitive component. Groups were compared on motor, cognitive and original test scores. Additionally, PMHD far from ('far') and close to ('close') expected disease onset were investigated.

Results MHD showed lower baseline scores on the SDMT original (p=0.03) and motor isolation (p=0.006) parts, and deterioration over one-year follow-up on the original SDMT (p=0.001) compared to controls. PMHD showed lower baseline scores on the SDMT motor part (p=0.008) and deterioration on the SDMT original (p=0.001) and cognitive isolation (p=0.02) parts. Secondary analyses revealed that the premanifest findings were the result of worse scores by the close to predicted onset group only.

Conclusions We found evidence for the presence of motor disturbances which influence executive functioning in HD. Isolation of the cognitive component still revealed cognitive deterioration in the premanifest group, caused by decline of scores of premanifest subjects that are close to their predicted clinical disease onset. The SDMT proved most sensitive to premanifest decline, even over one-year follow-up.

INTRODUCTION

Huntington's disease (HD) is generally described as a hyperkinetic movement disorder, where unwanted movements are often the most characteristic signs of the clinical profile[1]. Next to these motor abnormalities cognitive decline and psychiatric disturbances are also part of the triad of symptoms belonging to HD[2]. Due to its autosomal dominant genetic nature, children with an HD parent are at 50% risk of inheriting the gene. Since 1993 it is possible to be tested for the presence of the HD gene, and individuals carrying the gene, but not yet displaying clinical symptoms of the disease (so-called premanifest gene-carriers), can be identified[3]. Much cognitive research has focused on executive dysfunctioning as it is one of the main areas of dysfunctioning in manifest HD[4,5]. Impairments of planning, organisation and problem solving (key executive functions) have been found in HD patients, increasing with disease progression[6,7,8]. In premanifest HD subjects, executive problems have also been identified[9,10]. As almost all commonly used tests of executive functioning require a motor response, often by means of verbal or written answers, it is important to investigate its possible confounding effect on cognitive scores. Especially since subtle motor changes have been found in premanifest HD gene-carriers years before overt clinical disease onset[11,12].
We aim to measure actual cognition that is relatively free from motor disturbances in premanifest and manifest HD. By estimating the motor component of two executive functioning tasks and subsequently subtracting this motor part from the actual test score we strive to measure more pure cognitive scores. We hypothesize to find worse scores on the original conditions of the executive tests used, for the HD groups compared to controls. When the motor component is isolated from the cognitive component we expect that both groups will show differences compared to controls on the motor conditions, and that cognitive results remain, albeit less strong. If premanifest results emerge we expect that the differences will be the result of worse performance in the subjects close to predicted disease onset.

METHODS

Participants

Gene-positive subjects who visited the outpatient neurology department at the Leiden University Medical Centre for their annual clinical evaluation were asked to participate in this study. Gene-negative spouses and siblings were recruited to participate as controls. Eighty-nine subjects agreed to participate, of which 61 were gene-positive and 28 controls.
Gene-positive subjects were grouped into either premanifest or manifest HD groups at baseline, according to their total motor score (TMS) on the Unified Huntington's Disease Rating Scale (UHDRS)[13]. Scores of 5 or less are premanifest scores,

6 or higher are manifest scores. This resulted in 40 manifest HD (MHD), and 21 premanifest HD (PMHD) participants. The premanifest group was further subdivided into those far from ('far', n=11) and close to ('close', n=10) predicted disease onset by means of a median-split of the variable 'predicted years to onset' (median=10.2 years). Predicted years to disease onset were estimated using the data provided by Langbehn et al[14].
Of the initial 89 participants, 67 returned for follow-up assessment. Three PMHD subjects converted to manifest HD after one year, based on their TMS. Fifteen MHD subjects were not able to complete the study due to disease progression. Consequently, 5 controls, which were partners of these MHD drop-outs, were not willing to participate alone. One premanifest subject was not able to complete follow-up because of personal reasons. As a result one extra control subject (partner of PMHD drop-out) was also lost to follow-up.

Procedure

Participants were tested twice, with a one year interval. At both visits all participants were assessed using the UHDRS for neurological functioning, the Mini Mental State Examination (MMSE)[15] as an indicator of global cognitive functioning and the Becks Depression Inventory - BDI-II[16] to detect the presence of a depression. The following cognitive tests were performed: the Symbol Digit Modalities test (SDMT)[17] and the Figure Fluency test (FFT)[18]. To isolate the cognitive component of these executive tasks we designed extra 'high motor and low cognition load' conditions for the SDMT and FFT (for complete description see 'isolation cognitive components' below). The study was approved by the local ethics committee and all participants gave written informed consent.

Isolation cognitive components

For the traditional SDMT, participants have to match numbers to symbols, according to a given key. They are instructed to match as many numbers to symbols in subsequent order in 90 seconds. To isolate the cognitive part of the SDMT we substituted the symbols with the numbers they represent in the original test, and asked participants to copy the numbers below, in subsequent order, again for 90 seconds (removing the cognitive task of matching a symbol to a number). We calculated time per stimulus on the SDMT by dividing the total time by the total amount of correctly matched symbols (90/total correct SDMT). Next, we calculated motor time per stimulus by dividing the total time by the total amount of numbers copied on the extra condition (90/total correct extra condition). The cognitive time per stimulus was calculated by subtracting the motor time per stimulus from the time per stimulus on the SDMT.
For the Figure Fluency test, subjects are instructed to generate as many unique designs as possible by connecting two or more dots displayed in a fixed pattern,

on a form with 35 of these dot patterns. Subjects have to generate as many different designs in one minute and avoid duplicating earlier ones. There are five conditions (each with a one minute time-limit), where the dot patterns are different from the one before and additional distracting stimuli are added, such as already drawn lines. Subjects are instructed to ignore these distracters. To isolate the cognitive component (i.e. non-verbal fluency), we created an extra condition where pre-drawn designs of different numbers of connected dots are presented and subjects are asked to accurately trace as many designs as possible in one minute. Designs range from two connected dots to complex designs of multiple connected dots. We calculated time per stimulus on the FFT by dividing the total time of the five conditions (300 seconds) by the total amount of correctly and uniquely generated designs on all five conditions (300/total amount correct FFT). We also calculated the motor time per stimulus by dividing the 60 seconds time-limit of the extra condition by the total amount of correctly traced designs (60/total amount correct extra condition). Cognitive time per stimulus was calculated by subtracting the motor time per stimulus from the time per stimulus on the FFT.

Statistical analysis

Analyses were performed using IBM SPSS version 20. Continuous demographic variables were analysed using ANOVA. Chi-square tests were used for gender and education variables. The skewed score of the total functional capacity (TFC) variable was analysed with the Kruskal-Wallis test. Multilevel regression analysis (i.e. linear mixed models) with a compound symmetry covariance matrix was performed to study group differences on SDMT and FFT scores. Both crude and corrected models were constructed. Covariates comprised age, gender, education, BDI-II score and TFC. The two-level structure consisted of the two time points (i.e. lower level) and the subjects (i.e. higher level). The PMHD and MHD groups were compared to controls for differences at baseline and differences in the rate of decline (time*group interaction effects). To facilitate interpretation of the differences, the raw test scores were converted into z-scores. Therefore, beta-coefficients in tables can be interpreted as follows: for baseline differences it refers to how many standard deviations an HD group differs from the controls at baseline, and for the rate of decline it refers to how many standard deviations that an HD group changes during the follow-up period as compared to the controls. Positive values denote deterioration (i.e. during follow-up the reaction times on the tests increased, so subjects became slower). Secondary analyses comprised the premanifest group divided into 'close' and 'far' to predicted disease onset compared to controls to investigate the influence of closeness to motor-manifest disease onset. All tests were two-tailed with $p<0.05$ denoting statistical significance.

RESULTS

Baseline demographics

Baseline demographics are presented in Table 1. The MHD group had lower TFC compared to controls and PMHD subjects ($p<0.001$). They also showed higher TMS scores compared to both PMHD and control subjects ($p<0.001$), and higher depression scores compared to controls ($p=0.02$). Scores on the MMSE showed that all groups were non-demented (i.e. MMSE<25 is indicative of cognitive impairment).

SDMT baseline differences and rate of decline for the HD groups compared to controls

In the analyses corrected for age, gender, education, depression and TFC scores (Table 2A) the MHD group showed lower baseline scores of on average 0.53 *SD* (*SE* 0.24, $p=0.03$). Lower baseline scores for the MHD compared to the control group were also found for SDMT motor isolation score (0.71 *SD* (*SE* 0.25), $p=0.006$). Longitudinally, this group showed a deterioration over the one-year follow-up of 0.47 *SD* (*SE* 0.13, $p=0.001$) compared to controls on the original SDMT.

Table 1: Demographics whole group

	Controls N=28	PMHD N=21	MHD N=40	P-value
Age (yrs)	50 (8)	45 (9)	49 (10)	0.150
Gender (m/f)	13/15	8/13	13/27	0.508
Education (% high)	14	29	25	0.204
CAG		42 (2)	43 (3)	
Total motor score	2 (2)	3 (1)	26 (16)	**<0.001**
Total functional capacity score	13 (0)	13 (0)	11 (6)	**<0.001**
BDI-II score	4 (5)	5 (5)	8 (7)	**<0.02**
MMSE score	30 (2)	29 (1)	29 (3)	
Disease burden[a]		282 (57)	366 (68)	
Expected yrs to disease onset[b]		10 (6)		

Note. Data are Mean (SD), except for gender (number), education (percentage) and total functional capacity, MMSE and expected years to disease onset (median and interquartile range). ANOVA was used for age and TMS variables. χ^2-test was used for gender and education variables. Kruskal-Wallis test was used for total functional capacity score. PMHD = premanifest HD, MHD = manifest HD, BDI-II = Becks Depression Inventory II, MMSE = Mini Mental State Examination. [a]Based on formula '(CAG-35.5)*age)' by Penney et al. (1997). [b]Based on survival analysis formula by Langbehn et al. (2004).

The PMHD group showed lower baseline scores of 0.67 *SD* (*SE* 0.25, p=0.008) on the SDMT motor isolation score, as compared to controls. Longitudinally, this group also showed a deterioration of 0.48 *SD* (*SE* 0.14, p=0.001) on the original SDMT, again compared to controls. The same pattern was seen for the SDMT cognition isolation score, where the PMHD group deteriorated with on average 0.52 *SD* (*SE* 0.21, p=0.02) compared to controls.

FFT baseline differences and rate of decline for the HD groups compared to controls

For the FFT, group differences were only found for the motor isolation score (Table 2A). Here, both the MHD and the PMHD group showed lower baseline scores as compared to controls. The MHD group had lower scores of on average 0.58 *SD* (*SE* 0.24; p=0.02). The PMHD group scores were 0.63 *SD* (*SE* 0.24; p=0.01) lower.

Comparison of premanifest subjects close to and far from their predicted age at disease onset

Table 2B presents baseline differences and rate of decline on the SDMT and FFT for the close and far groups compared to controls. The corrected analyses showed significant deterioration over time for the close group on the original SDMT score compared with controls. Over the one-year follow-up they deteriorated with on average 0.65 *SD* (*SE* 0.18, p=0.001). The SDMT cognitive isolation analysis showed that the close group deteriorated with 0.59 *SD* (*SE* 0.27, p=0.03) compared to controls. Considering the FFT, the close group showed lower baseline scores compared to controls on the motor isolation condition only (*SD* 0.66 (*SE* 0.29) p=0.03).

Table 2: Differences at baseline and change over time for PMHD and MHD and for PMHD close and far compared to controls

	Controls N=28	PMHD N=21	MHD N=40	P-value	Controls N=28	Close N=10	Far N=11	P-value
Crude Model	**2A. Premanifest and manifest HD subjects compared to controls**				**2B. Premanifest HD subjects close to and far from predicted disease onset compared to controls**			
SDMT original								
Baseline diff.	Ref.	-0.22 (SE 0.26)	0.85 (SE 0.22)***	<0.001	Ref.	0.04 (SE 0.29)	-0.52 (SE 0.30)	0.19
Rate of decline	Ref.	0.49 (SE 0.14)**	0.41 (SE 0.14)**	0.001	Ref.	0.66 (SE 0.18)**	0.35 (SE 0.18)	0.003
SDMT motor isolation								
Baseline diff.	Ref.	0.58 (SE 0.26)*	1.12 (SE 0.23)***	<0.001	Ref.	0.65 (SE 0.30)	0.50 (SE 0.31)	0.06
Rate of decline	Ref.	0.01 (SE 0.18)	-0.12 (SE 0.17)	0.71	Ref.	0.12 (SE 0.18)	-0.14 (SE 0.18)	0.46
SDMT cognition isolation								
Baseline diff.	Ref.	-0.54 (SE 0.27)*	0.51 (SE 0.23)*	<0.001	Ref.	-0.30 (SE 0.29)	-0.81 (SE 0.30)**	0.03
Rate of decline	Ref.	0.55 (SE 0.21)*	0.31 (SE 0.20)	0.04	Ref.	0.59 (SE 0.26)*	0.53 (SE 0.26)*	0.04
FFT original								
Baseline diff.	Ref.	0.05 (SE 0.27)	0.86 (SE 0.24)***	<0.001	Ref.	0.09 (SE 0.30)	-0.01 (SE 0.31)	0.95
Rate of decline	Ref.	0.09 (SE 0.15)	0.17 (SE 0.21)	0.71	Ref.	0.25 (SE 0.28)	-0.02 (SE 0.28)	0.63
FFT motor isolation								
Baseline diff.	Ref.	0.48 (SE 0.27)	0.94 (SE 0.24)***	0.001	Ref.	0.58 (SE 0.28)	0.36 (SE 0.29)	0.10
Rate of decline	Ref.	-0.05 (SE 0.16)	0.00 (SE 0.15)	0.94	Ref.	-0.06 (SE 0.21)	0.01 (SE 0.21)	0.95
FFT cognition isolation								
Baseline diff.	Ref.	-0.18 (SE 0.27)	0.63 (SE 0.24)**	0.003	Ref.	-0.15 (SE 0.30)	-0.22 (SE 0.31)	0.74
Rate of decline	Ref.	0.04 (SE 0.27)	0.22 (SE 0.25)	0.65	Ref.	0.34 (SE 0.34)	-0.21 (SE 0.34)	0.40

Table continues on next page.

Table 2: **(Continued)** Differences at baseline and change over time for PMHD and MHD and for PMHD close and far compared to controls

	Controls N=28	PMHD N=21	MHD N=40	P-value	Controls N=28	Close N=10	Far N=11	P-value
Corrected model	**2A. Premanifest and manifest HD subjects compared to controls**				**2B. Premanifest HD subjects close to and far from predicted disease onset compared to controls**			
SDMT original								
Baseline diff.	Ref.	-0.04 (SE 0.24)	0.53 (SE 0.24)*	0.04	Ref.	-0.02 (SE 0.32)	-0.19 (SE 0.36)	0.87
Rate of decline	Ref.	0.48 (SE 0.14)**	0.47 (SE 0.13)**	0.001	Ref.	0.65 (SE 0.18)**	0.33 (SE 0.18)	0.003
SDMT motor isolation								
Baseline diff.	Ref.	0.67 (SE 0.25)**	0.71 (SE 0.25)**	0.008	Ref.	0.60 (SE 0.32)	0.72 (SE 0.36)	0.06
Rate of decline	Ref.	0.00 (SE 0.19)	-0.04 (SE 0.18)	0.97	Ref.	0.12 (SE 0.19)	-0.15 (SE 0.19)	0.47
SDMT cognition isolation								
Baseline diff.	Ref.	-0.42 (SE 0.26)	0.24 (SE 0.26)	0.045	Ref.	-0.25 (SE 0.31)	-0.51 (SE 0.35)	0.32
Rate of decline	Ref.	0.52 (SE 0.21)*	0.38 (SE 0.20)	0.038	Ref.	0.59 (SE 0.27)*	0.54 (SE 0.27)	0.04
FFT original								
Baseline diff.	Ref.	0.20 (SE 0.25)	0.52 (SE 0.25)	0.12	Ref.	0.10 (SE 0.31)	0.34 (SE 0.35)	0.62
Rate of decline	Ref.	0.08 (SE 0.22)	0.26 (SE 0.20)	0.43	Ref.	0.25 (SE 0.29)	-0.01 (SE 0.29)	0.65
FFT motor isolation								
Baseline diff.	Ref.	0.63 (SE 0.24)**	0.58 (SE 0.24)*	0.018	Ref.	0.66 (SE 0.29)*	0.66 (SE 0.32)	0.03
Rate of decline	Ref.	-0.06 (SE 0.16)	0.06 (SE 0.15)	0.77	Ref.	-0.07 (SE 0.20)	0.03 (SE 0.21)	0.92
FFT cognition isolation								
Baseline diff.	Ref.	-0.07 (SE 0.26)	0.30 (SE 0.27)	0.35	Ref.	-0.19 (SE 0.31)	0.12 (SE 0.34)	0.72
Rate of decline	Ref.	0.01 (SE 0.27)	0.32 (SE 0.25)	0.35	Ref.	0.34 (SE 0.35)	-0.20 (SE 0.35)	0.43

Note. Data are standardized mean differences versus controls (standard errors). In all multilevel regression analyses a compound symmetry covariance matrix (CS) was used. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ indicate significant differences compared to the control group in post-hoc tests. SDMT = Symbol Digit Modalities test, FFT = Figure Fluency test, BDI-II = Becks Depression Inventory, Ref. = Reference group, TFC = Total Functional Capacity.

DISCUSSION

In this study we showed that there is a significant influence of motor disturbances on the SDMT for both manifest and premanifest subjects. Additionally, isolation of the cognitive component of this test showed a deterioration of executive functioning over the one-year follow-up for the premanifest group only. Secondary analyses revealed that the subjects closest to predicted clinical disease onset showed rapid decline while those further away from diagnosis performed similar to healthy controls.

To our knowledge, O'Rourke et al. have been the first in HD literature to investigate the cognitive domain of executive functioning, while minimizing the influence of non-cognitive factors of the test[19]. They used the Trail Making Test (TMT), which consists of two parts. Part A is hypothesized to rely on visuoperceptual abilities and visual search, and part B additionally relies on executive functioning abilities[20]. Amongst other derived scores, they subtracted the score on part A from that of part B to isolate the executive functioning components of the test. Contrary to our results, they concluded that the TMT primarily measures cognition in premanifest HD, and is not significantly affected by motor or psychiatric disturbances. One explanation that they offered is that motor deficits in the premanifest phase are too subtle to influence cognitive test outcome.
However, our study showed that isolation of the motor component of both the SDMT and the FFT resulted in motor scores that were significantly slower compared to controls for both manifest and premanifest participants. Even premanifest subjects proved to be more than 0.5 *SD* slower than controls, indicative of the presence of motor abnormalities in our premanifest group. No differences were found for the rate of decline of the motor components of both the SDMT and the FFT, which implies that motor dysfunctioning is stable over a one-year period. Moreover, we found that these motor abnormalities have an influential effect on the overall test score: when the motor component was subtracted from the original SDMT score to isolate the actual cognitive component of the test, no significant results remained for our manifest subjects. However, the premanifest group did show a decline of the cognitive component score over the one-year follow-up. Thus, even when the motor influence was taken into account, premanifest subjects deteriorated on their performance of the SDMT over one year.
No cognitive differences or deterioration in the manifest group was observed. This could mean that most rapid decline has already taken place preceding disease onset, and that deterioration of executive functioning stabilizes to a rate similar to that of controls in the manifest phase of the disease. Another explanation could be that the motor disturbances associated with manifest HD have become thus pronounced that they prevent from any cognitive effect to be measured. Indeed, we did find lower baseline scores for the manifest group on both the original SDMT score and on the motor isolation part. And, when the cognitive part was isolated by

subtracting the motor part from the original SDMT score, no significant differences remained. Therefore, it seems that motor functioning is the main contributor to the overall score on the SDMT in manifest HD.
So, on the one hand, we have found that motor disturbances are already present in the premanifest phase of the disease, revealed by slower motor component scores for the premanifest group compared to the control group. That subtle motor abnormalities are present in premanifest subjects was also observed by Biglan et al[21], in their study on data from the PREDICT-HD study. On the other hand, executive functioning deterioration also already occurs in this phase of HD, even when the influence of motor functioning is minimized. To date, cognitive HD literature has not yet reached consensus about the nature and extent of premanifest cognitive changes. Our study adds to the discussion with proof that executive functioning is one of the cognitive domains most sensitive to premanifest changes.

Secondary analyses revealed that the premanifest differences were the result of worse performance of the premanifest subjects that were predicted to be close to disease onset. This group showed a deterioration on the original condition of the SDMT, but also on the cognitive part of this test. Subjects further away from predicted onset performed at the same level as controls on all components of the executive functioning tests. Here, either no change takes place, or changes in executive functioning are too subtle to pick up with the tests used in this study. Altogether, our results point in the direction of a biphasic deterioration of executive functioning, with performance that is comparable to healthy controls in premanifest subjects more than 10 years from predicted disease onset, and a rapid deterioration close to clinical (motor-manifest) disease onset. Furthermore, decline is rapid as it is measurable over a one-year interval.
This is an assumption that is shared by other authors that have investigated cognition in the premanifest phase. They found that deterioration of several cognitive domains (e.g. executive functioning, memory) is most pronounced and rapid just before clinical disease onset, and is often the result of the performance decline of premanifest subjects who are about to convert to manifest HD[22 23].

Another important finding is that, using the SDMT, we were able to detect premanifest change on its original and isolated cognitive parts over a follow-up period of only one year. The SDMT is a test of executive functioning that has consistently been found to be impaired in both manifest and premanifest HD[24 25]. Cross-sectional as well as longitudinal[24 26 27] studies have reported poorer scores on the SDMT for premanifest gene-carriers. Outcome measures that are sensitive to change over short periods of time are of vital importance in the design and implementation of future clinical trials. Ideally, the effect of disease modifying or even slowing agents are to be measured over time periods as short as possible considering study costs and patient well-being. Our study indicates that the SDMT is a candidate cognitive outcome measure sensitive to premanifest change

in executive functioning.

Apart from differences on the motor part of this test, the FFT did not reveal any results for the HD groups on both the original and the cognitive conditions. One possible explanation could be that the FFT measures an executive construct different from that of the SDMT, and results are therefore not comparable. Indeed, a fundamental difference between the two tests is that the SDMT has a key with the correct answers that is provided alongside the test and which participants can refer to while completing the task. For the FFT, on the other hand, self-directed planning and organisation is needed to generate as many unique figures as possible. Additionally, due to its self-directed instead of key-directed component, the FFT seems to rely on more complex executive functioning abilities that even healthy controls find difficult to complete. As a result, the FFT seems not well suited to differentiate between healthy subjects and HD gene carriers.

With this study we have provided evidence that motor functioning contributes to performance on the SDMT. Consequently, cognitive findings in HD could be overestimated when this negative influence is not taken into account. Our findings implicate that the results of previous studies that have used the SDMT and have not controlled for the influence of motor functioning should be interpreted with caution. Also, in the design of future studies incorporating executive tasks with a high motor load, ways of minimizing motor influence should be considered to be better able to unravel actual cognitive performance. The extra motor conditions are of an experimental design. To isolate the motor component of the executive tasks used in this study we designed an extra 'low cognition - high motor' load conditions that mimic the motor requirements of the original task. However, no validation of these extra conditions were performed. Considering our findings, investigation of possible other ways of minimizing or controlling for motor contribution on cognitive tests deserves recommendation.

Concluding, we have found evidence for the presence of motor disturbances which are of influence on the score of the SDMT. These motor disturbances are stable over a one-year period. With isolation of the cognitive component of the SDMT we revealed cognitive deterioration in the premanifest group only, caused by deteriorating scores of premanifest subjects that are close to their predicted clinical disease onset. Lack of deterioration in subjects more than 10 years from onset suggests a biphasic course of progression for executive dysfunctioning. The FFT was not found to be able to pick up premanifest cognitive change.

Competing interests

None.

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Chapter 8

General discussion and future perspectives

Understanding the course of cognitive decline is of great importance in the study of HD, to gain knowledge to improve specialized care for HD patients and to aid the design of future clinical trials. Research in the premanifest phase of the disease is of particular importance as many pathophysiological mechanisms remain unclear. Furthermore, investigation of the influence that HD motor disturbances have on cognitive test results will help to entangle the actual cognitive effect from other influential factors.

Course of cognitive functioning

Impaired cognitive abilities such as mnestic deficits and executive dysfunctioning have consistently been found in manifest HD[1]. However, the results in the premanifest phase are not that clear-cut. Several longitudinal studies on cognition show cognitive deficits in premanifest gene carriers even decades before estimated age at disease onset[2], while others do not detect differences between their premanifest and control groups[3 4]. With the ever growing understanding of HD genetics we move closer to clinical intervention studies to investigate agents with possible disease modifying or disease slowing effects. Increasing the knowledge about phenotypical progression of symptoms remains however important as there is not yet a uniform agreement, especially in the areas of cognition and psychiatry.

Executive functioning most sensitive to premanifest change
In our cognitive studies we have found strong evidence that the cognitive domain of executive functioning is most sensitive to premanifest cognitive deterioration.

Ten-year follow-up of cognition (**chapter 5**) showed that the executive functioning factor was the only factor to show results in the premanifest group. Interestingly, when studying the premanifest group as a whole, results were not different from that of controls. Only when the subjects who converted to manifest disease over the ten-year follow-up were analysed separately from the subjects who remained premanifest during the study, informative differences emerged. The converters showed a significant deterioration over time compared with the control subjects, while the scores of the continual premanifest subjects were comparable to control scores. Likewise, when we divided the premanifest group into those subjects who at baseline were far from expected disease onset and those who were close to onset, only the subjects close to expected onset showed lower baseline scores compared to controls, on the executive functioning factor only.
Further analyses revealed that the above findings were the result of poorer performance of the converter and close to onset groups on the Symbol Digit Modalities test (SDMT). Large premanifest effects on the SDMT were also found in our one-year follow-up study where we tested possible decline on both the SDMT and the Figure Fluency test (**chapter 7**). Even when we controlled for the influence of motor functioning, only the SDMT proved sensitive to premanifest change in the close to predicted onset group. The SDMT is a widely used test of executive functioning, and has often been found to be sensitive to change in the premanifest phase of HD. Our results support other findings that the SDMT is a well suited cognitive instrument to catch early cognitive decline in HD.

The above results lead us to hypothesize that progression of executive functioning in the premanifest phase evolves in a non-linear manner. Subjects that are further away from disease onset are able to maintain test requirements to the level of controls, while subjects close to disease onset show a rapid decline in performance. Additionally, the lack of deterioration over time for the manifest group suggests that most rapid deterioration of executive functioning abilities occurs around disease onset. Furthermore, in our study on cognition over a seven-year follow-up period (**chapter 4**) we found additional evidence for non-linear decline of memory functioning. Here, the observed memory decline over time in the premanifest group could be fully attributed to the gene carriers who converted to manifest disease over the follow-up time. Premanifest subjects who remained without clinical motor symptoms did not show memory deficits compared to controls, they only showed lower scores on a sub-test supposed to measure concentration abilities. That progression of cognitive symptoms does not evolve in a linear manner has also been reported by other authors. Snowden et al.[5] and Paulsen et al.[2] have both observed a more rapid decline of memory and executive functioning, respectively, in subjects approaching motor symptomatic disease onset, as compared to gene carriers further away from disease onset. Furthermore, Rupp et al. have reported on a longitudinal study where those closest to onset showed the largest rates of decline on cognitive measures[6].

Evidence for compensatory mechanisms

In this thesis we provide evidence for possible cognitive compensatory mechanisms in HD. In the cross-sectional study on the SART and simultaneous P300 registration (**chapter 2**) we observed a pronounced post-error slowing of reaction time for the manifest HD group, which could be indicative of a compensatory strategy to prevent the occurrence of errors. This so-called 'speed accuracy trade-off', where a slowing in reaction time raises the amount of correct responses, could be an explanation for our findings. The slowing indeed seems to prevent the manifest HD group from making more No-go errors compared to both premanifest gene carriers and controls. The post-error slowing that we observed could not be ascribed to mere motor slowing. Indeed, the manifest group was slower to react to the appearance of stimuli overall. For the reaction time pattern of trials surrounding correctly responded No-go trials a significantly slower but similar pattern of reaction was observed for the manifest group compared to the premanifest gene carriers and the controls. However, when studying the pattern around incorrectly responded No-go trials, the responses were not only slower, but a different pattern also emerged. The difference in reaction time patterns surrounding correct No-go trials and No-go trials where an error has been made, leads us to hypothesize that the observed post-error slowing can indeed be caused by a compensatory mechanism such as speed accuracy trade-off.

In the longitudinal study on the SART and P300 (**chapter 3**) we no longer found evidence for compensation in the manifest group. Manifest subjects showed slower responses compared to premanifest gene carriers and controls, and also slowed more over time compared to both other groups. As there was no observed benefit from the slowing (i.e. less errors), we assumed that in this group of patients the neurodegenerative damage has become too large to effectively apply compensatory strategies. In contrast, we did find evidence for compensation taking place in our premanifest group. Only on specific trials we found a slowing over time in this group, and as there was no increase in errors over time, we hypothesized that this could reflect the implementation of the compensatory speed accuracy trade-off strategy.

That compensatory mechanism are at work in HD, and especially in the premanifest phase of the disease, is an idea that is receiving growing evidence. Using functional MRI, both cognitive[7] and motoric[8] compensation has been reported, as well as cognitive compensation using event related potentials[9]. In other neurodegenerative diseases such as Parkinson's and Alzheimer's disease compensatory mechanisms have also been found, sometimes referred to as the "cognitive reserve hypothesis". Furthermore, the unexpected lack of functional changes in premanifest gene carriers in the TRACK-HD study has resulted in the TRACK-ON HD study, especially designed to investigate possible compensatory mechanisms in the premanifest phase of HD.

Influence of motor functioning on cognition

HD is primarily known as a movement disorder, and clinical disease onset is in most cases based on the appearance of motor symptoms characteristic for the disorder. However, subtle disturbances in motor functioning have also already been found in premanifest subjects[10]. And as almost all cognitive tests require some kind of motoric response, often by means of verbal or written answers, investigating the influence of motor changes on cognitive functioning could provide important information on cognitive functioning.

Evidence for negative effect of motor on cognition
In our ten year longitudinal study on the course of cognition in HD (**chapter 5**) we investigated the influence of motor speed on cognition by adding this variable as a covariate in the cognitive statistical model. We found that the significant cognitive results diminished by 20% when motor speed was taken into account, opposed to the model without this motor measure. Here, several results that ceased to be significant, while those who remained significant lessened in strength. We concluded that motor speed has a substantial influence on cognitive test results, accounting for up to 20% of the significance of cognitive results when not statistically accounted for.
In another study we created additional conditions for existing cognitive tests of executive functioning, the SDMT and the Figure Fluency test (FFT) (**chapter 7**). These extra conditions were designed in such a way that the cognitive load was minimal while the motor demands were relatively similar to the original test. By subtracting this motor condition from the original test score we expected to measure a more 'pure' cognitive score. Our results showed there was a substantial (negative) influence of motor functioning on cognition, especially in the manifest HD group. When the actual cognitive component was isolated by subtraction of the motor component, no cognitive results remained for this group. For the premanifest group the influence of motor disturbances could also be detected, however, cognitive differences could still be measured. From these two studies we can conclude that the influence of motor functioning in HD has a negative effect on cognitive outcomes. Even in premanifest subjects, where motor disturbances are very subtle, cognitive outcomes are impacted by these abnormalities. Even though the motoric effect is substantial, we have also always measured a cognitive effect in premanifest subjects in both studies.

Two motor phenotypes with different clinical profiles
There is not only an influence of motor functioning on cognition, we have also found evidence for the existence of different motor subtypes of HD, with different cognitive profiles (**chapter 6**). When we divided a large group of manifest HD subjects into either choreatic or hypokinetic-rigid HD according to the motor signs that were predominant in these subjects, we found that the hypokinetic-rigid group

performed significantly worse on tests of global and cognitive functioning, compared with the choreatic group. Furthermore, we established that these differences were not caused by differences in age, disease duration and use of neuroleptic drugs, which strengthened our hypothesis that fundamental different clinical profiles exist between predominant choreatic and predominant hypokinetic-rigid HD.

Future perspectives

To date, many clinical trials investigating the efficacy of agents designed to enhance functioning in HD subjects are implemented in different stages of manifest disease. If we however want to move forward to disease modification or even prevention, inclusion of subjects in the premanifest phase is vital. Already a small number of clinical trials is aimed at preventative therapies in the premanifest phase (e.g. Pre-QUEST and PREQUEL [http://clinicaltrials.gov/ct2/home]), and the expectation is that this number will rise in the coming years. From our studies we can conclude that early changes in executive functioning are already visible in subjects nearing clinical onset, and that decline is rapid. Clinical trials investigating agents designed to improve cognitive functioning in HD should therefore make use of tests of executive functioning, preferably including the SDMT, to be best able to capture drug induced change.
Furthermore, our results prove that subjects close to their predicted disease onset are most suitable as key research group in future clinical trials. Firstly, as they show the most rapid decline in executive functioning opposed to premanifest subjects further from onset and subjects further into the manifest phase of HD, drug-induced disease modifying effects may potentially be measured over relatively short periods of follow-up time. Secondly, as they are the group to deteriorate most rapidly they are also the group that would probably show maximum benefit from drug intervention, especially when disease slowing agents will become available. Parallel to drug development projects, observational studies such as Track(-On) HD and Predict-HD are searching for the optimum time point in the course of HD to first introduce drug treatment. Our results on the course of cognition add to the knowledge from these multicentre studies.

To avoid overestimation of cognitive results we advocate that to control for a quantitative measure of motor functioning, such as reaction time, in cognitive studies, to be able to entangle the influence of motor influence on cognition in HD. Our findings also implicate that the results of previous cognitive studies which have not included some measure of motor functioning have to be interpreted with some caution. As a substantial part of the cognitive effect in these studies is possibly the result of (subtle) motor disturbances, the findings should not be regarded as 'pure' cognitive effects.

The existence of two different motor subtypes with different clinical profiles has implications for both care and scientific research. Concerning clinical care for HD patients, hypokinetic-rigid patients need more specialized care as they have been proven to be both generally and cognitively worse. Because a patient with predominant hypokinetic-rigid motor symptoms is more likely to have cognitive deficits, this patient is also more likely to benefit from repeated instructions, or cognitive training, to maintain a relatively good quality of life for a longer period of time. Instead, patients with predominant choreatic symptoms may need less cognitive care, even though they are often times motorically very affected.
The knowledge about different clinical profiles for patients with different predominant motor symptoms is also of importance for the design of future clinical trials. Studies using cognitive or global functional (e.g. total functional capacity scale) outcome measures which have mostly included patients with predominant choreatic HD motor symptoms will show different results from when mostly predominant hypokinetic-rigid HD patients or even a mix of the two groups are included.

Limitations
One general point of caution has to be noted. In all of the studies included in this thesis we have made the division of premanifest or manifest according to a cut-off point of the score on the total motor score (TMS), the subscale of the Unified Huntington's Disease Rating Scale measuring motor functioning. It may well have been that certain subjects already experienced a non-motor clinical onset, such as severe cognitive impairment or behavioral disturbances. Indeed, Orth et al.[11] investigated age at onset in the REGISTRY study and found that out of the 423 subjects studied 28% (120) had a non-motor onset of disease. The motor-based division that we have used could have introduced a selection bias, where subjects who may have been manifest based on cognitive or psychiatric criteria, but were nonetheless included in the (motor)premanifest group, possibly confounding study results. We question if the TMS should continue to be used as golden standard for group division in HD. Studies using broader criteria to make a distinction between manifest and premanifest may maximize both study and treatment outcomes.
Furthermore, it should be mentioned that the studies reported in this manuscript show some overlap in participants. A group of subjects (n=26) who participated in the longitudinal study on P300 and SART performance also participated in the seven and ten year cognitive follow-up study. Also, for the one-year follow-up study on executive functioning in both premanifest and manifest HD 15 subjects already also already participated in the seven and ten year follow-up study. This raises the question of practice effects, a well-known challenge in HD research. Due to the relative rarity of the disease HD subjects are often recruited for multiple studies using identical tests. This also makes that the results from the mentioned studies are not fully independent, which potentially limits generalizability.

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Summary

Huntingtons disease (HD) is an autosomal neurodegenerative disorder caused by the expansion of the huntingtin gene located on chromosome 4. The clinical picture is characterized by a triad of symptoms: motor disturbances, behavioural changes and cognitive decline. Disease manifestation occurs in mid-life, having a devastating effect on an individuals work, family and personal life. To date, no means of curing or even slowing the disease are available and inheriting the gene inevitable leads to disease and a premature death. With the chromosomal mapping of the disease in 1983 and the discovery of the huntingtin gene in 1993, it became possible to be tested for the presence of the gene. When tested positive, and without overt signs and symptoms of the disease, an individual is called a premanifest gene carrier. In these premanifest gene carriers subtle changes in motor, behavioural and cognitive functioning have been found, along with early changes in structure and function of the brain.

Even though almost all cognitive tests require some form of motor response, often by means of written or verbal answers, there is little attention for the influence of motor functioning on cognitive test outcome in HD. Furthermore, because it is known that subtle motor deficits can occur in the premanifest phase of HD, understanding the possible negative effect of motor on cognitive functioning is necessary when trying to understand the progression of cognitive decline in all stages of HD.

In this thesis we have studied cognitive functioning in both patients and premanifest gene carriers, making use of several different techniques. Furthermore, we have investigated the influence of the known (subtle) motor deficits on cognitive scores by controlling for several measures of motor functioning.

The event related potential (ERP) P300, a positive peak visible on the EEG approximately 300 milliseconds following the presentation of a stimulus, is thought to be a neurophysiologic measure of attentional processing. The peak latency is hypothesized to be linked to speed of stimulus evaluation, or more generally, to speed of attentional processing, and its amplitude to the amount of attention allocated to the stimulus. A key feature of the P300 is that it is a measure of

attentional processing that is independent of motor influences. We have registered the P300 simultaneous to a test of attention, the Sustained Attention to Response task (SART) (**chapter 2**). Seventeen patients, 12 premanifest gene carriers and 15 controls were assessed. We found attentional control to be deficient in patients, as demonstrated by more errors being made by this group. Further investigation revealed post-error slowing in case of a certain type of error, which could be induced by a cognitive compensatory strategy called speed-accuracy trade-off. Furthermore, the observed attentional control deficits during the SART were corroborated by a reduced P300 amplitude and prolonged P300 latency, indicative of lowered attentional capacities.

The findings on the SART with simultaneous P300 registration were further studied in a longitudinal pilot-study (**chapter 3**). A subset of participants (five patients, nine premanifest gene carriers and 12 controls) from the cross-sectional study was also tested over a three year interval to investigate the progression of attentional control in HD. Patients showed heightened error rates and prolonged reaction times compared to the other two groups. There was however, no evidence for compensation in the form of speed-accuracy trade-off, as proposed in our cross-sectional study, because the slowing in reaction time did not prevent the occurrence of errors. One explanation that we offered was that due to disease progression the employment of the compensation strategy has reached a maximum in the patient group and is no longer effective in reducing error rates. On the other hand we observed slowing of reaction time on the trials just before having prevented an error in the premanifest gene carriers. As no slowing was found on other trials, and the slowing was not accompanied by elevated error rates, we hypothesized that compensatory mechanisms may be at work here.

The progression of cognitive functioning in the premanifest phase of HD was studied in a longitudinal study (**chapter 4**). The 29 premanifest gene carriers and 43 control participants who completed the seven-year follow-up were analyzed in this study. They were tested four times, using an extensive battery of tests covering most areas of cognitive functioning such as memory and executive functioning. We found that the premanifest gene carriers deteriorated on the domains of memory and concentration. These changes could primarily be ascribed to the carriers who converted to manifest disease over the study period. When these subjects were excluded from the analyses only the concentration sub test of the Wechsler Memory Scale was found to deteriorate over time for the premanifest gene carriers. We concluded that most cognitive change probably takes place in the phase close to disease onset.

Further study of this cohort resulted in an additional ten-year follow-up of patients and premanifest gene carriers (**chapter 5**). The tests used in this study were combined into four factors by means of factor analyses: three cognitive (global cog-

nition, executive functioning and memory) and one motor factor (motor speed). The progression of premanifest gene carriers (n=26), patients (n=19) and control subjects (n=87) over ten-years on the four factors was studied using multilevel regression analyses. The patients showed lower baseline scores compared with controls on all cognitive factors. When the converters were analyzed separately from the participants who remained premanifest during the whole follow-up, we found that only the converters deteriorated over time as compared with controls on the executive functioning + memory factors. Furthermore, when the premanifest group was divided in those close to and those far from expected disease onset, we observed a deterioration on the executive functioning factor for the subjects close to disease onset. We concluded that the executive functioning factor is most sensitive to premanifest cognitive progression, especially around disease onset. Another important outcome of this study was that the influence of motor functioning on cognitive test scores is substantial and should be taken into account in cognitive research in HD.

We also investigated the different cognitive and functional profiles between two motor subtypes of HD: predominantly choreatic HD and predominantly hypokinetic-rigid HD (**chapter 6**). We divided the subjects from the REGISTRY study database into the two motor types, which resulted in 528 choreatic and 432 hypokinetic-rigid subjects. Using regression analyses we found that the hypokinetic-rigid group performed worse on a measure of global functioning, as well as on several measures of cognitive functioning. As the analyses were controlled for age and disease duration, and because both groups were comparable considering use of neuroleptics, we concluded that different profiles exist between the two motor types of HD. Here, predominantly choreatic HD subjects are functionally and cognitively better than predominantly hypokinetic-rigid HD subjects, which could have implications for both scientific research and clinical care.

To investigate the influence of motor functioning on cognitive functioning we designed an extra condition that measures motor functioning for two tests of executive functioning (the symbol digit modalities test [SDMT] and the figure fluency test [FFT]) (**chapter 7**). Subsequently we subtracted the motor condition from the original test score, which we hypothesized would result in a more pure cognitive score. Forty patients and 21 premanifest gene carriers were compared to 28 control subjects. We found a substantial negative influence of motor functioning on executive task performance, especially in patients. However, even in the premanifest group there motor disturbances were measurable. With the isolation of the actual cognitive component we found deterioration on the SDMT only, caused by deteriorating scores of subjects that were close to their predicted age at disease onset.

A general discussion and future perspectives are discussed (**chapter 8**). In sum-

mary, we advocate that the domain of executive functioning is best targeted in future clinical trials as this cognitive domain is most sensitive to premanifest change. The SDMT is recommended as a suitable executive test to serve as outcome measure. As most rapid deterioration of executive functioning is found in subjects approaching their clinical disease onset, this group is put forward as key research group in clinical trials. Following our findings of substantial negative effects of motor functioning on cognition, we advise future cognitive studies to always control for motor functioning in cognitive testing, to be able to entangle the influence of motor disturbances on cognition in HD. Lastly, the existence of two different HD motor phenotypes, namely predominant choreatic and predominant hypokinetic-rigid HD, with different clinical profiles brings about implications for both clinical care and scientific research.

Samenvatting

De ziekte van Huntington (ZvH) is een autosomale dominante neurodegeneratieve aandoening die wordt veroorzaakt door een abnormale expansie van het huntingtine gen, dat zich bevindt op chromosoom 4. Het klinisch beeld wordt getypeerd door een trias van symptomen: bewegingsstoornissen, gedragsveranderingen en cognitieve achteruitgang. De ziekte uit zich doorgaans ongeveer tussen de 30 en 50 jaar. In deze belangrijke periode van het leven heeft de ziekte dan ook een zeer ingrijpend effect op het werk, gezins- en persoonlijke leven van een persoon. Tot op heden is er geen genezing mogelijk en is er geen manier om de progressie van de ziekte te vertragen of veranderen. Het erven van het gen leidt dan ook onherroepelijk tot ziekte en een vroegtijdig overlijden. Met de chromosomale lokalisatie van de ziekte in 1983, en de ontdekking van het gen in 1993, is het mogelijk geworden om op de aanwezigheid van het gen te worden getest. Wanneer iemand het gen heeft, maar nog geen uiterlijke symptomen van de ziekte vertoont, noemen wij iemand een premanifeste gendrager. Eerder onderzoek heeft aangetoond dat bij deze premanifeste gendragers subtiele veranderingen op motorisch, gedrags- en cognitief gebied al aanwezig kunnen zijn, en dat deze samengaan met vroege veranderingen in zowel structuur en functie van het brein.

Hoewel bijna alle cognitieve testen enige vorm van motorische respons vergen, vaak door verbaal of schriftelijk antwoord te moeten geven, is er weinig aandacht voor de invloed van motoriek op cognitieve testscores bij de ZvH. Bovendien is het bekend dat subtiele motorische afwijkingen al in de premanifeste fase van de ziekte aanwezig kunnen zijn. Dit maakt dat het onderzoeken en daarmee begrijpen van de mogelijk negatieve invloed van motoriek op cognitief functioneren noodzakelijk is wanneer we de progressie van cognitieve achteruitgang in alle stadia van de ZvH in kaart willen brengen.

Dit proefschrift beschrijft het onderzoek dat wij hebben uitgevoerd naar cognitief functioneren in zowel de premanifeste als de manifeste fase van de ZvH, waarbij we gebruik hebben gemaakt van diverse meettechnieken. Bovendien hebben wij de invloed van de (subtiele) stoornissen in de motoriek op cognitieve scores onderzocht door verschillende maten van motoriek in ogenschouw te nemen in onze

analyses.

De P300 is een 'event related potential', dat wil zeggen een potentiaal dat is gerelateerd aan een gebeurtenis, en kan worden afgeleid uit het EEG. Het is een positieve piek die ongeveer 300 milliseconden na de presentatie van een stimulus kan worden gezien op het EEG. Er wordt verondersteld dat het een neurofysiologische maat is voor diverse aandachtsprocessen. De latentie waarmee de piek zijn hoogste punt bereikt wordt gekoppeld aan de snelheid waarmee een stimulus wordt gevalueerd, of anders gezegd, aan de snelheid van aandachtsverwerking. De P300 amplitude wordt daarentegen gekoppeld aan de hoeveelheid aandacht die aan een stimulus wordt besteed. Een belangrijke eigenschap van de P300 is dat het een maat voor aandachtsprocessen is die onafhankelijk is van de invloed van motoriek. Wij hebben de P300 geregistreerd tijdens een aandachtstest, de Sustained Attention to Response test (SART), waarbij zeventien patiënten, 12 premanifeste gendragers en 15 controle personen werden onderzocht (**hoofdstuk 2**). Wij vonden dat de aandachtscontrole was aangedaan bij de patiënten, hetgeen bleek uit het hoge aantal fouten dat deze groep maakte. Uit verder onderzoek bleek dat er sprake was van een vertraging in reactietijd direct na het maken van een specifiek type fout. Dit kan het gevolg zijn van een bepaalde cognitieve compensatiestrategie genaamd 'speed-accurracy trade-off'. Bovendien ging dit gebrek aan aandachtscontrole gepaard met een verlaagde P300 amplitude en een vertraagde latentie, wat verder bewijs is voor verlaagde aandachtscapaciteiten.

In een longitudinale pilot-studie hebben wij de cross-sectionele resultaten van de SART met gelijktijdige P300 registratie verder onderzocht (**hoofdstuk 3**). Een deel van de deelnemers aan de cross-sectionele studie (vijf patiënten, negen premanifeste gendragers en 12 controles) werden na drie jaar nogmaals getest om de progressie van aandachtscontrole bij ZvH te onderzoeken. Nu maakten de patiënten wederom meer fouten en waren zij langzamer vergeleken met de andere twee groepen. Aanwijzingen voor compensatie strategieën in de vorm van speed-accurracy trade-off, zoals verondersteld in onze eerdere studie, werden nu echter niet gevonden. De vertraagde snelheid waarmee de patiënten reageerden voorkwam niet dat er fouten werden gemaakt. Een verklaring hiervoor kan zijn dat het gebruik van de strategie maximaal profijt heeft bereikt en geen voordelen meer oplevert vanwege de progressie van de ziekte in de groep patiënten. Aan de andere kant vonden we bij de premanifeste gendragers ook vertraging, en wel specifiek vlak voordat het maken van een fout werd vermeden. Omdat er verder geen vertraging in reactietijd werd gevonden, en omdat de geobserveerde vertraging niet samenging met het maken van meer fouten, concludeerden wij dat hier wel sprake kan zijn van een compensatiemechanisme.

De progressie van cognitief functioneren in de premanifeste fase van de ZvH hebben we onderzocht in een longitudinale studie (**hoofdstuk 4**). De analyses betreffen de

29 premanifeste gendragers en 43 controle deelnemers die de zeven jaar follow-up afmaakten. Zij werden vier keer getest met een uitgebreide batterij van cognitieve testen die bijna alle gebieden van het cognitief functioneren, zoals bijvoorbeeld geheugen en executief functioneren, omvatten. Wij vonden dat de premanifeste gendragers op de domeinen van geheugen en concentratie verslechterden over tijd. Deze verslechtering werd echter vooral veroorzaakt door de deelnemers die gedurende de studie manifest werden. Wanneer de analyses werden herhaald zonder deze zogenaamde 'converters' bleek dat de premanifeste gendragers over tijd alleen verslechterden op de concentratie sub-test van de Wechsler Memory Scale. Hieruit concludeerden wij dat de meeste cognitieve verandering waarschijnlijk vlak voor het begin van de ziekte plaatsvindt.

Verdere studie van dit cohort resulteerde in een tienjarige follow-up van patiënten en premanifeste gendragers (**hoofdstuk 5**). De testen die werden gebruikt in deze studie werden door middel van factor analyse samengebracht in vier factoren: drie cognitieve (globale cognitie, executief functioneren en geheugen) en een motor factor (motor snelheid). De progressie van de premanifeste gendragers (n=26), patiënten (n=19) en controle personen (n=87) op deze vier factoren over tien jaar werd onderzocht met behulp van multilevel regressie analyse. De patiënten lieten lagere baseline scores zien op alle cognitieve factoren. Toen de converters apart werden geanalyseerd van de deelnemers die premanifest bleven gedurende de studieperiode, bleek dat alleen de converters verslechterden over tijd op de executief functioneren factor, vergeleken met controles. Bovendien, toen de premanifeste groep werd verdeeld in deelnemers dichtbij en veraf van hun verwachte leeftijd waarop de ziekte zal beginnen, bleek dat er alleen een verslechtering op het gebied van executief functioneren werd gevonden voor de deelnemers dicht bij verwacht ziektebegin. Wij concludeerden dat executief functioneren het cognitieve domein is dat het meest sensitief is voor cognitieve veranderingen in de premanifeste fase, vooral rondom het begin van de ziekte. Een andere belangrijke bevinding van deze studie was dat er een substantiële invloed van motoriek op cognitieve test scores is en dat er rekening gehouden dient te worden met deze negatieve invloed bij het doen van cognitief onderzoek bij de ZvH.

Ook onderzochten wij de verschillen in de profielen met betrekking tot globaal en cognitief functioneren tussen twee motorische subgroepen in de ZvH: predominant choreatisch en predominant hypokinetisch-rigide (**hoofdstuk 6**). Wij verdeelden de deelnemers van de Europese REGISTRY studie in deze twee typen: dit resulteerde in 528 choreatische en 432 hypokinetisch-rigide deelnemers. Met behulp van regressie analyse vonden wij dat de hypokinetisch-rigide groep slechtere scores had op de maten voor globaal functioneren en op alle testen voor het cognitief functioneren. In de analyses werd gecontroleerd voor onder andere leeftijd en ziekteduur, en omdat het gebruik van neuroleptica in beide groepen gelijk was, concludeerden wij dat de twee motorische subtypen verschillen laten zien in cogni-

tief en globaal functioneren. Predominant choreatische patiënten zijn functioneel en cognitief beter dan de patiënten met het predominante hypokinetisch-rigide type. Dit verschil in klinisch profiel kan gevolgen hebben voor zowel de zorg als het wetenschappelijk onderzoek bij de ZvH.

Om de invloed van motoriek op cognitief functioneren te onderzoeken hebben wij voor twee testen van het executief functioneren (Symbol Digit Modalities test [SDMT] en Figure Fluency test [FFT]) een extra conditie ontwikkeld die hoofdzakelijk motoriek meet (**hoofdstuk 7**). Vervolgens hebben wij deze motorische conditie afgetrokken van de test score van de originele test, om een meer pure cognitieve score te meten. De scores van veertig patiënten en 21 premanifeste gendragers werden vergeleken met de scores van 28 controle deelnemers. Wij vonden een flinke negatieve invloed van motoriek op cognitie, vooral bij de patiënten. Maar ook in de premanifeste groep waren motorische stoornissen meetbaar. Isolatie van de cognitieve score resulteerde in een verslechtering voor alleen de SDMT, welke werd veroorzaakt door slechtere scores van de personen die dicht bij de leeftijd waren waarop voorspeld was dat de ziekte klinisch zou beginnen.

Tot slot worden de algemene discussie en toekomstperspectieven besproken (**hoofdstuk 8**). Samengevat pleiten wij ervoor dat toekomstig medicijn onderzoek zich het beste kan richten op executief functioneren, omdat dit het meest gevoelige domein is voor premanifeste cognitieve veranderingen. De SDMT wordt aangeraden als meest geschikte uitkomstmaat voor executief functioneren. Omdat de meest snelle premanifeste achteruitgang wordt gemeten in personen die dicht bij klinisch begin van de ziekte zitten, lijkt deze groep het best geschikt als onderzoeksgroep in medicatie onderzoek. Naar aanleiding van onze bevindingen dat er een substantiële negatieve invloed van motoriek op cognitie is, adviseren wij om altijd te controleren voor motorisch functioneren bij cognitief onderzoek, om beter in staat te zijn om de 'echte' cognitieve effecten te scheiden van andere invloedrijke factoren. Tot slot brengt het bestaan van twee verschillende motor fenotypen, namelijk predominant choreatisch en predominant hypokinetisch-rigide HD, met verschillende klinische profielen consequenties voor zowel zorg als wetenschappelijk onderzoek met zich mee.

Dankwoord

Zonder deelname van gendragers, patiënten en controle deelnemers is een onderzoek als dit niet mogelijk, dus allereerst een hartelijk dank aan alle deelnemers die trouw en gemotiveerd bij hebben gedragen aan het onderzoek. Ook de samenwerking met het Europese Huntington netwerk (EHDN) is van grote waarde geweest voor mijn onderzoek. Daarnaast wil ik alle (ex-)collega's van de Neuropsychologie, Klinische Neurofysiologie en Neurologie bedanken voor hun steun en motiverende woorden tijdens de afgelopen jaren. Ook mag de steun en houvast die ik in de afgelopen periode heb mogen ontvangen van familie en vrienden natuurlijk niet onderschat worden, bedankt allemaal!

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E.P. Hart, E.M. Dumas, E.J. Giltay, H.A.M. Giltay, R.A.C. Roos. Cognition in Huntington's disease in manifest, premanifest and converting gene carriers over ten years (2013) Journal of Huntington's disease 2, 137-147

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Curriculum Vitae

Ellen 't Hart werd op 28 augustus 1983 geboren te Gouda. Na het behalen van haar VWO diploma aan het Coenecoop College te Waddinxveen (2001) koos zij voor de studie Italiaanse Taal- en Letterkunde aan de Universiteit Leiden. In 2003 verbreedde zij haar interesses van de Italiaanse taal naar de sociale wetenschappen en startte zij een tweede studie, Psychologie, tevens aan de Universiteit Leiden. Naast het studeren ging zij roeien bij Koninklijke Studenten Roeivereeniging 'Njord' en zat zij van 2005 tot 2006 als Ab-actis in het bestuur. In 2008 studeerde zij af als Italiaans taal- en letterkundige na een thesis te hebben geschreven over één van de toneelstukken van Nicollò Macchiavelli; 'La Clizia'. Ondertussen had zij ook gekozen voor een afstudeerrichting in de psychologie: neuropsychologie. Zij deed zowel haar wetenschappelijke als haar klinische stage in het Leids Universitair Medisch Centrum op de afdelingen Neurologie en Neuropsychologie. Gedurende haar wetenschappelijke stage deed zij onderzoek naar de ziekte van Huntington onder begeleiding van Dr. Caroline Jurgens. Zo kwam zij in aanraking met deze neurodegeneratieve ziekte en raakte zij tevens betrokken bij het internationale TRACK-HD onderzoek. Na haar afstuderen als neuropsycholoog (2009) ging zij als onderzoeker aan het werk bij de TRACK-HD studie en startte zij niet lang hierna haar promotietraject onder leiding van Prof. Dr. R.A.C. Roos. Haar focus lag vanzelfsprekend bij de ziekte van Huntington, en wel specifiek bij het cognitief functioneren van premanifeste gendragers en de invloed van motoriek hierop. Als lid van het Europese Huntington Netwerk (EHDN) werd zij actief lid van de Cognitive Phenotype Working Group en werd zij in 2012 uitgenodigd om op de EHDN plenary meeting te spreken over haar onderzoek. Meerdere Huntington projecten volgden, waaronder de tevens internationale projecten TRACK-ON HD en Paddington. Vanaf 1 januari 2014 zal zij als Clinical Scientist beginnen bij de afdeling CNS van het Centre for Human Drug Research te Leiden.