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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