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Impact of Huntington's disease on working and driving

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Impact of Huntington's disease **on working and driving**

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Impact of Huntington's disease on working and driving

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CONTENTS

Chapter 1	General introduction and aims	9
Chapter 2	Reasons why Huntington's disease gene carriers decide to stop working or driving <i>submitted</i>	19
Chapter 3	Cognitive performance and apathy predict unemployment in Huntington's disease mutation carriers <i>The Journal of Neuropsychiatry and Clinical Neurosciences. 2018; 30(3):188-193</i>	33
Chapter 4	Driving with a neurodegenerative disorder: an overview of the current literature <i>Journal of Neurology. 2017; 264(8):1678-1696</i>	49
Chapter 5	Altered driving performance of symptomatic Huntington's disease gene carriers in simulated road conditions <i>Traffic Injury Prevention. 2018; 19(7):708-714</i>	87
Chapter 6	Predictors of simulated driving performance in Huntington's disease <i>Parkinsonism and Related Disorders. 2018 [e-pub ahead of print]</i>	109
Chapter 7	Comparable rates of simulator sickness in Huntington's disease and healthy individuals <i>Transportation Research Part F: Traffic Psychology and Behaviour. 2019; 60:499-504</i>	127
Chapter 8	General discussion	141
Summary		154
Nederlandse samenvatting		158
Dankwoord		164
List of publications		166
Curriculum Vitae		168

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General introduction and aims

Huntington's disease (HD) is a rare, autosomal-dominant inherited, neurodegenerative disorder caused by an extended cytosine-adenine-guanine (CAG) repeat length on chromosome four of the Huntingtin gene.¹ In the Caucasian population, the prevalence of HD is approximately 10 per 100,000 individuals.²⁻⁴ Currently there is only symptomatic treatment available for HD and no cure has yet been identified.⁵ Atrophy of the striatum (i.e., caudate nucleus, putamen, and nucleus accumbens) is most pronounced in HD and already occurs years before the predicted motor onset.⁶⁻⁸ In addition to striatal neuronal loss, MRI studies have revealed regional atrophy in cortical gray matter structures.^{8,9} Alterations in both striatal and cortical brain regions contribute to the clinical expression of HD.^{6,9-11}

Clinical features

HD is clinically characterized by a triad of symptoms including motor disturbances, cognitive decline and psychiatric symptoms. The disease generally manifests between the ages of 30 and 50 years, with a mean disease duration of 17 – 20 years,^{12,13} but there is also a juvenile and late-onset form of the disease.^{14,15} Longer CAG repeat lengths have been associated with earlier disease onset and more rapid progression.^{16,17}

The clinical hallmark of HD is the presence of chorea, which are unwanted, unpredictable jerky movements that can affect various parts of the body.¹⁸ In addition to chorea, hypokinesia, dystonia, bradykinesia and oculomotor signs can occur.¹² The presence and severity of these motor signs vary per individual.¹⁸ HD gene carriers can be divided into premanifest and manifest gene carriers based on the appearance of motor signs.¹⁰ By this definition, manifest gene carriers are those with a clinical motor diagnosis, whereas premanifest gene carriers are individuals with a positive gene mutation for HD, but without substantial motor signs.

Although HD is characteristically described as a motor disorder, cognitive and psychiatric symptoms can already be present years before the onset of motor signs.¹⁹⁻²¹ For patients and caregivers, changes in cognition and behavior are often more disturbing than motor impairments.^{22,23} In the past years, an increasing number of studies have focused on cognitive changes in HD.^{20,24} The first impairments in cognition are characterized by a deterioration in executive functioning, such as planning, flexibility, attention and concentration, and slower psychomotor speed.^{19,24,25} As the disease progresses, cognitive symptoms worsen, eventually resulting in dementia.

Depression, irritability, apathy and obsessive-compulsive disorder are the most common psychiatric and behavioral symptoms of HD.^{26,27} Up to 50% of the HD

patients report depressive symptoms at some point during the disease.²² Apathy is highly prevalent in HD and can already become apparent in the earliest phase.^{28,29} It usually increases with disease progression and has been associated with a decline in general functioning.^{22,28} Psychotic behavior has a relatively low prevalence in HD (3% - 11%) and is often reported in later disease stages.^{13,26}

Functional changes

Over time, HD causes severe impairments in daily functioning, such as an inability to work, manage finances, or drive a car. HD gene carriers without clinical manifestations of the disease frequently report limitations in work and managing finances, suggesting that these areas are the first to decline.³⁰ In general, functional decline is fastest in patients in the earliest symptomatic stages of HD.³¹ Lower cognitive functioning negatively affects the quality of life of both HD patients and caregivers, and is associated with a decrease in functional skills.^{32,33} Better cognitive performance is correlated with a less rapid decline in general functioning.³¹ Behavioral symptoms, particularly apathy, also interfere with daily life activities.²⁸ Although companions often observe functional changes, it is not always clear whether these changes are caused by HD. Premanifest gene carriers and their companions tend to attribute their decline in general functioning to factors other than HD, such as aging and lifestyle changes.³⁴ Decreased driving skills have been cited as one of the first functional changes by HD gene carriers.^{33,35} Since the disease onset typically occurs during midlife, activities such as working and driving can become affected at a relatively young age. Most studies that investigated quality of life or functional changes have focused on overall decline in general capacity rather than examining specific topics of daily activities. In addition, little is known about the personal motives of HD gene carriers for stopping working or driving.

Employment and Huntington's disease

Unemployment negatively affects psychological well-being and financial stability, and requires adaptation of daily routines.³⁶ More than 20% of the HD gene carriers expressed concerns about the impact of their gene status on employment.³⁷ Cognitive and motor functioning have both been associated with work disability in HD.³⁸ A previous study revealed that changes in speed of information processing, measured before and directly after work cessation, were most pronounced.³⁸ Further, higher depression scores, increased irritability, worse cognitive flexibility, and increased motor impairments were observed after stopping work. In this study, the average age at which the patient stopped working was 47 years, which is well before

the general retirement age of 65-67 years. However, the influence of HD symptoms on the ability to work still remains relatively unknown. Increasing the knowledge about work function in HD might assist gene carriers to accommodate to changes in work and delay unemployment.

Driving and Huntington's disease

Safe driving requires the interaction of cognitive, motor, behavioral and visual functions, which can be compromised in patients with HD and other progressive neurodegenerative disorders. The ability to drive a car reflects an individual's general functioning and is essential to maintain employment and social activities.^{39,40} Patients with a neurodegenerative disorder often adjust their driving habits to accommodate their disease.⁴¹ Some patients even decide to revoke their driver's license at an early stage. This has been associated with a loss of personal independence, lower self-esteem, and depressed mood.^{40,42}

Previous research showed that, compared to healthy individuals, patients with HD were less accurate, had slower reactions, and committed more errors in signaling, steering, braking, and speed adaptations when driving in a simulator and on the road.^{43,44} Cognitive dysfunction, in particular decreased psychomotor speed, less flexibility, and inattention, has been identified as a strong risk factor for impaired driving skills in HD patients.⁴⁵⁻⁴⁷ However, studies on driving competence in HD are still scarce and methods are heterogeneous. There is currently no consensus on which assessments should be used in the clinic as a screening tool to determine alterations in driving. Investigating the ability to drive is relevant given the progressive nature of HD, and because driving influences the quality of life and independence of patients. Although previous studies have hinted at diminished driving performance in premanifest gene carriers, this hypothesis has not been tested.

Aims and outlines of this thesis

The primary objective of this thesis was to study employment and driving ability in gene carriers with Huntington's disease (HD). We aimed to investigate predictors of work cessation and examine the influence of different symptoms and signs of HD on driving performance.

First, a status review was performed to explore reasons for work and driving cessation reported by HD gene carriers (**chapter 2**). The aim was to obtain more insight into personal motives of HD gene carriers for stopping working or driving and provide

guidance for clinicians when discussing potential work and driving cessation in the clinic. To further explore working status in HD gene carriers, we aimed to determine which symptoms of HD are predictors of work cessation (**chapter 3**).

Chapter 4, provides an overview of the available literature on previous studies investigating driving ability in neurodegenerative disorders, in particular Huntington's, Parkinson's and Alzheimer's disease. Here, the aim was to summarize the findings and identify the gap in the literature.

Based on the findings reported in chapter 2 and chapter 4, a cross-sectional study was conducted using a driving simulator to investigate differences in driving performance between premanifest HD gene carriers, manifest HD and controls. The aim of this study was to examine driving performance during simulated urban and motorway driving and to test various clinical predictors of driving ability. The results of this study are reported in **chapter 5** and **chapter 6**.

In **chapter 7**, the occurrence of simulator sickness is addressed. The aim was to investigate whether patients with HD are more susceptible to the occurrence of simulator sickness compared to controls.

The conclusions of this thesis are discussed in **chapter 8**. Here, recommendations for clinical implementation and future research are provided.

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Reasons why Huntington's disease gene carriers decide to stop working or driving

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Submitted

ABSTRACT

Background

In patients with Huntington's disease (HD), daily activities such as working and driving are affected at a relatively young age. Discussing the possibility of stopping work and driving is sensitive.

Objective

To explore why HD gene carriers decide to stop working or driving and to gain insight into their personal motives. Secondly, to investigate whether these motives differed between males and females.

Methods

Questionnaire responses of 191 HD gene carriers, who visited the outpatient clinic of the Leiden University Medical Center between 2016 and 2018, were used in this study. Self-reported reasons for work and driving cessation were explored and categorized according to gender.

Results

A total of 92 HD gene carriers (48% of the responders; 38 males and 54 females) had stopped working, due to reduced concentration (25%), problems with multi-tasking (22%), and slower reactions (21%). A total of 62 HD gene carriers (37%) had stopped driving a car (19 males and 43 females). They were significantly older ($p = 0.018$) and more often female ($p < 0.001$) compared to the active drivers. Males mainly reported difficulties with concentration (26.1%), whereas females stated anxiousness and insecurity as their primary reason for stopping driving (16.3%).

Conclusions

According to HD gene carriers, reduced concentration interferes with the decisions to stop working and stop driving. Gender differences and personal motives should be taken into consideration when discussing changes in daily life in the clinic.

INTRODUCTION

In patients with Huntington's disease (HD), activities of daily life, such as working and driving are affected at a relatively young age.^{1,2} Inability to work and decreased driving skills are among the first functional changes to be reported by HD gene carriers.^{3,4} Decreased occupational performance has been reported by more than two-thirds of the patients with HD and more than half of the HD patients are unable to work in their usual profession.³ In addition, HD gene carriers are concerned about the impact of their gene status on their employment.⁵ Not being able to work or a reduction in working time are associated with negative emotions, such as anger and a depressed mood. On the other hand, a reduction in the number of hours or the demands of work can also lower levels of stress.⁶ The clinical signs of HD, specifically apathy and executive dysfunction, have been shown to predict unemployment.⁷ Reasons why HD gene carriers decide to stop working have not been studied previously.

Patients with HD might be reluctant to stop driving, because this influences their independence and quality of life. Discussing in the clinic the possibility of stopping driving is, therefore, sensitive. In older adults, not being able to drive has been related to signs of depression.⁸ Furthermore, driving cessation does not only impact the independence of patients, but also has consequences for family members.⁹ Caregivers often have to compensate when the patient can no longer drive, influencing their lives and familial roles. In the Netherlands, patients with HD have the moral obligation to report a potential decline in driving performance to the national driver's licensing authority.¹⁰ By the means of a clinical and neurological examination, a neurologist or independent physician has to evaluate the patient's ability to drive. Based on this examination and the physicians' opinion, a formal driving test may become mandatory; patients have to undergo this at their own expense. If a patient passes the driving test, then the driver's license may be renewed for a maximum of five years. This process is comparable to that in other European countries.¹¹ Studies in older adults with dementia have shown that driving cessation is a gradual process with distinct stages, often starting with small alterations in driving behavior, such as avoiding certain situations (e.g., unknown roads, motorways).^{12,13} The number of driving restrictions usually increases, eventually resulting in complete cessation. Driving behavior is also influenced by self-monitoring and personal insight into driving capacity.¹⁴

Reasons for driving cessation have been classified into external and internal reasons. External reasons are those outside the individual, such as the influence of

family members, doctors, or lifestyle changes. Reasons within the individual, such as declining health or psychological factors (e.g., anxiety), are defined as internal reasons. In older adults, internal factors, especially a decline in health, seem to have the highest impact on changes in driving and the decision to stop.^{12,15} In general, women tend to stop driving at a younger age than men.^{15,16} Although previous studies have revealed driving impairments in HD, it remains, to our knowledge, unclear why HD gene carriers decide to stop driving.

The aim of this study is to explore why HD gene carriers stop working or driving, and to obtain a better understanding of their personal motives. Secondly, we aim to provide guidance for clinicians when discussing work and driving cessation with patients in the clinic and to increase awareness of these issues in the HD population.

MATERIALS AND METHODS

Between 2016 and 2018, HD gene carriers who visited the outpatient clinic of the Neurology Department at the Leiden University Medical Center in the Netherlands were asked to fill in a short survey containing items on symptoms and potential functional changes due to HD. The questionnaire was designed to provide the treating physician with insight into the patients' self-perception and general functioning.

The items on occupation (i.e., current working status, reason for work cessation, year of work cessation) and driving a car (i.e., type of driver's license, current driving status, reasons for driving cessation, year of driving cessation, and, for those still driving, preferred driving conditions (e.g., urban driving, not driving by themselves)) were used in the current study. Ethical approval for the use of the anonymous survey responses was obtained from the local medical ethics committee of the LUMC. Only those who worked in a paid job were selected for inclusion in the workers group. Gene carriers who stopped working due to HD-related symptoms were defined as not working. Gene carriers who stopped working because of other reasons (e.g., age) and those who had never obtained a driver's license were excluded from the analyses.

Reported reasons for work and driving cessation were described and percentages of these reasons were explored, separately for males and females. Age and gender differences between working and not working and drivers and not drivers were analyzed using separate logistic regression analysis with working or driving status as dependent variable. All analyses were performed using SPSS (version 23.0) for Windows.

RESULTS

Data of 191 HD gene carriers (77 males, 114 females) who filled in the questionnaire were used. The mean age was 50.2 years.

Work cessation

Of the 191 responses, 92 HD gene carriers (48%; 38 males, 54 females) retired from work due to signs of HD and 55 (25 males, 30 females) were still working in a paid job (Table 1). The median number of years of not working, defined as the difference between year of retirement and year the questionnaire was filled in, was 4.0 years. Women had been retired longer compared to men (5.5 years versus 3.0 years, respectively). HD gene carriers who stopped working were significantly older ($OR = 1.08$, $p < 0.001$) compared to gene carriers who were still working. There was no significant difference in gender ($OR = 0.84$, $p = 0.623$) between the working and not working group. Reduced concentration (25%), problems with multi-tasking (22%), and slower reactions (physical and mental; 21%) were the primary reasons noted for stopping working (Table 2). Here, no differences were observed between males and females; both mentioned reduced concentration most frequently.

TABLE 1 Demographics

	Working (N=55)	Not working (N=92)	Drivers (N=105)	Not driving (N=62)
Age (years)	44.4 ± 9.2	51.0 ± 9.3	48.5 ± 9.8	56.3 ± 10.2
Gender male/female	25/30	38/54	52/53	19/43
Years of not working (male/female)	NA	4.0 (3.0 / 5.5)	NA	NA
Years of not driving (male/female)	NA	NA	NA	3.5 (2.0 / 5.0)

Data are mean ± SD for age, number for gender, and median for number of years not driving and number of years not working for all participants and separately for males and females. NA: not applicable

TABLE 2 Self-reported reasons for stopping working by HD gene carriers

Reason for stopping working	Total number of times reported
Reduced concentration and attention/vigilance	N = 58 (25.4%)
Problems multi-tasking	N = 50 (21.9%)
Slower reactions (physical and mental)	N = 47 (20.6%)
Forgetfulness	N = 29 (12.7%)
Physical burden of the job became too heavy	N = 28 (12.3%)
Unspecified reason	N = 16 (7.0%)

Note: total number is not equal to the total number of gene carriers who stopped working N=92) because most gene carriers reported multiple reasons which were counted in all categories.

Driving cessation

Of the 191 HD gene carriers who filled in the questionnaire, 168 (97 females, 71 males) had obtained a driver's license. One hundred and five gene carriers were still driving, whereas 62 (37%) reported they had stopped of whom 43 (69.3%) were female and 19 (30.6%) were men (Table 1). One female temporarily stopped driving while waiting for a formal driving test. These data were not included in the analyses. HD gene carriers who stopped driving were significantly older (OR = 2.22, $p = 0.018$) and more often female (OR = 1.08, $p < 0.001$) compared to gene carriers who were still active drivers. The median period since driving cessation, defined as the difference between year of driving cessation and year the questionnaire was filled in, was 3.5 years for all HD gene carriers, 2.0 and 5.0 years for males and females, respectively.

Fourteen percent of the HD gene carriers reported multiple reasons for their decision to stop driving, and some (6.9%) reported a generic reason, such as "I prefer walking" or "I just stopped driving" (Table 3). Internal reasons for driving cessation were endorsed by 58.5% of the HD gene carriers (Figure 1A). For males, difficulties concentrating (26.1%) was the primary reason for stopping driving, whereas the most frequently answered reason for cessation reported by females was feeling of anxiety and insecurity (16.2%) (Figure 1B). Of the active drivers, 21.9% made minor alterations in their driving behavior; only driving in their own neighborhood and no motorway

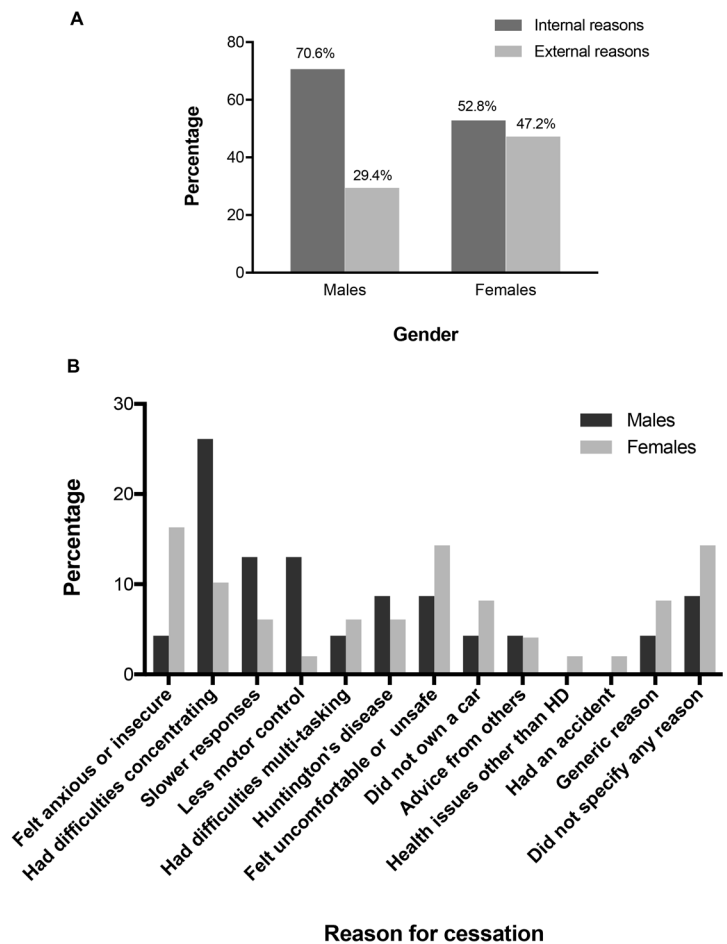
driving being most frequently noted (10.5%). Forty-six HD gene carriers (13 males, 33 females) stopped both working and driving. The mean age of this group was 53.9 years, with median period of unemployment of 7 years and median period of driving cessation of 3 years. In this group, the primary reported reason for stopping work was reduced concentration (26%), and the main reasons for stopping driving were reduced concentration (15%), anxiety (15%), and feeling uncomfortable/unsafe (15%).

TABLE 3 Reported reasons for driving cessation by HD gene carriers

Reason for stopping driving	Total (N=62)		Males (N=19)		Females (N=43)	
Had difficulties concentrating	11	15.3%	6	26.1%	5	10.2%
Felt anxious or insecure	9	12.5%	1	4.3%	8	16.3%
Felt uncomfortable or unsafe	9	12.5%	2	8.7%	7	14.3%
Slower responses	6	8.3%	3	13.0%	3	6.1%
Huntington's disease	5	6.9%	2	8.7%	3	6.1%
Did not own a car	5	6.9%	1	4.3%	4	8.2%
Less motor control	4	5.6%	3	13.0%	1	2.0%
Had difficulties multi-tasking	4	5.6%	1	4.3%	3	6.1%
Advice from others (e.g., family or physician)	3	4.2%	1	4.3%	2	4.1%
Health issues other than HD	1	1.4%	0	0%	1	2.0%
Had an accident	1	1.4%	0	0%	1	2.0%
Generic reason (e.g., 'prefer walking', 'just stopped driving')	5	6.9%	1	4.3%	4	8.2%
Did not specify any reason	9	12.5%	2	8.7%	7	14.3%

Note: Some HD gene carriers reported multiple reasons, therefore, the total number in the first column does not equal the number of gene carriers. The most frequently reported reasons per gender are presented in bold.

FIGURE 1 Reported reasons for driving cessation for males and females



Note: Figure 1A shows the percentage of internal and external reasons for driving cessation separately for males and females. Figure 1B shows percentages of all reported reasons for males and females separately.

DISCUSSION

Our study showed that reduced concentration, problems with multi-tasking, and slower reactions influenced the decision to stop working. No differences were observed between males and females. HD gene carriers who stopped driving were older and more often female compared to gene carriers who were still active drivers. Difficulty concentrating was the primary reason why males stopped driving, whereas females reported feelings of anxiety and insecurity as their main reason. Occupational changes have previously been reported as one of the earliest functional declines observed in HD, emphasizing the need for early discussion.³ Our results support the idea that cognitive functioning interferes more with activities of daily life than the characteristic motor symptoms of HD. Previous studies have also shown that cognitive decline, specifically in executive functions, is related to unemployment in HD.^{7,17} Most gene carriers reported a combination of multiple reasons for stopping working, implying that there is not a single factor that influences the decision to stop. In our study, women retired earlier than men, which is comparable to findings of studies in Parkinson's disease.¹⁸ It is important to educate patients, caregivers and employers to ensure that patients can maintain gainful employment for as long as possible. Making adjustments to the demands of work may offer a solution, but this might not be possible for all professions.

The fact that HD gene carriers worry about the effect of their gene status on their employment suggests that they might be reluctant to address work-related difficulties during a consultation with their physician.⁵ However, an early discussion about the future necessity to stop working and driving will allow the patient to anticipate functional changes due to HD, especially as the onset of clinical symptoms of HD occurs during mid-adulthood, a period of life when patients rely on the financial benefit of employment and the independence afforded by driving a car. The mean age of the HD gene carriers who stopped work in our study was 51 years, well below the general retirement age of 65-67 years. In addition, the mean age of the former drivers in our study was relatively young compared to other studies focusing on older adults and dementia.^{16,19}

Although males generally have the tendency to externalize their behavior, our study showed that males mostly reported internal reasons for driving cessation.²⁰ An explanation might be that males are more reluctant to stop driving because they rely more heavily on their car for work. In addition, males tend to be less risk averse compared to females.¹⁵ Decreased cognitive functioning has been related to driving impairments and might influence the decision to stop.^{21,22} This could also explain

the fact that, in our study, most males reported reduced concentration as their primary reason for driving cessation. Previous studies in older adults showed that their own opinion was the deciding factor to stop driving.^{19,23} Our findings suggest that gender influences this decision and that females might be more sensitive than males to external factors, such as the opinions of family or their physician. In addition, females also have the tendency to stop driving at a younger age and while in better health compared to males, which could explain our result that the duration of driving cessation was longer in females than in males.²⁴

We agree with previous studies stating that driving cessation is a gradual and dynamic process that not only involves patients and their relatives, but also the treating physician and the driver's licensing authority.^{12,23,25} In our cohort, gene carriers who still drove reported adaptations in their driving behavior, confirming this suggestion of gradual changes. The treating physician should include the topic of driving safety during routine visits and provide the patient with the right information to ease decision-making. Changes in the ability to drive safely should be discussed in an early phase of HD, without suggesting the patient simply stops driving following genetic confirmation. A study in patients with Alzheimer's disease (AD) showed that transportation and law-enforcement professionals were of the opinion that a diagnosis of AD, regardless of disease severity, was an indicator for driving cessation.²⁶ This suggests that driver's licensing authorities need to be well educated about the different stages of HD. We recommend an individual approach to discussing driving safety, acknowledging the differences between male and female perspectives observed in our study. The moral obligation to report changes in health has to be emphasized, because if the patient does not inform the national driver's licensing authority, this can affect their insurance if they are involved in a collision or traffic violation. Here, it is also important to consider the possible limited self-insight of patients with HD.^{27,28} Decreased awareness of impairments (i.e., anosognosia) could lead to an overestimation of the patient's own capacity or an under-reporting of functional impairments such as driving.²⁹ This could also have affected the results of the current study.

A limitation of our study is that the questionnaire was designed for use in the outpatient clinic as a screening questionnaire with different response options (multiple choice and open questions), and not specifically for research purposes. It contained global items on driving and not much information about driving restrictions by gene carriers who are still active drivers. Including more specific items or focus groups could be useful to further explore whether the decision to stop driving is indeed a process with distinct stages, as suggested in previous

studies.^{23,25,26} In addition, it would be interesting to compare our results with those of other European countries in view of the differences in regulations. Using a validated questionnaire is recommended. A more detailed approach, taking different types of professions into consideration and dividing patients into more working categories than the dichotomous employed versus unemployed categories, could provide more in-depth knowledge regarding the influence of HD on the ability to work. Due to the study design, we were unable to distinguish between different HD disease stages and no information was available regarding symptom severity. Nevertheless, our study provides greater insight into the daily life issues that patients with HD are confronted with and has implications for clinical care.

In conclusion, according to HD gene carriers, reduced concentration interferes with both the ability to work and drive. We identified that both internal and external reasons influence the decision to stop driving and that these reasons differ between males and females. Gender differences and personal situations should be taken into account in the clinic when discussing changes in daily life due to HD.

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Cognitive performance and apathy predict unemployment in Huntington's disease mutation carriers

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ABSTRACT

Background

Unemployment is common in those with Huntington's disease (HD), a genetic neurodegenerative disorder, and affects the patients' quality of life. HD is characterized by motor disturbances, cognitive dysfunction, and psychiatric symptoms.

Objective

The purpose of this article was to determine which clinical signs of HD are predictive of unemployment.

Methods

Data for employed ($N = 114$) and unemployed ($N = 106$) HD mutation carriers were used to investigate group differences. Univariate logistic regression analyses, adjusted for age and gender, were performed to determine individual predictors of unemployment. Subsequently, multivariate logistic regression analysis was performed entering all significant results from the univariate analyses into one fully adjusted model to determine the strongest predictors.

Results

HD mutation carriers with lower cognitive performances and higher apathy scores were more likely to be unemployed than were HD mutation carriers with higher cognitive scores and no signs of apathy. Motor functioning was an independent predictor of unemployment, but was not associated with unemployment in the fully adjusted model.

Conclusions

Cognitive impairments, especially in the executive domain, and apathy are independent determinants of unemployment in HD mutation carriers. Motor disturbances, the clinical hallmark of HD, did not appear to be the most important predictor for work cessation. This should be taken into consideration in clinical practice when evaluating HD patients' ability to work.

INTRODUCTION

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by a progressive decline in motor, cognitive, and psychiatric functioning. The mean age at onset is between 30 and 50 years, with a mean disease duration of 17-20 years.¹ The motor signs of HD are characterized by choreatic movements, dystonia, bradykinesia and hypokinesia, but the presence and severity can vary individually.² The clinical diagnosis of HD is currently based on the presence of unequivocal motor signs. Cognitive decline primarily involves deficits in the executive domain, eventually resulting in dementia.^{3,4} Executive functions include planning, organization, cognitive flexibility, and regulating behavior. Depression, irritability, apathy, and obsessive-compulsive disorders are the most common psychiatric and behavioral symptoms of HD.^{5,6} The cognitive and behavioral deficits can already be present years before the onset of motor signs.^{7,8}

At a relatively young age, individuals with HD become unable to work in their accustomed profession and this affects their quality of life.⁹ Around 65% of the patients with HD report some degree of decline in occupational performance.¹⁰ Gene mutation carriers without a clinical diagnosis also report changes in their work function, but they often attribute these changes to their working environment and personality traits, and not to signs of HD.¹¹ These results are not limited to the impact of total working cessation, but a reduction in work hours and increased sick leave were also reported as negative changes.¹² Cognitive and behavioral deficits, such as mental slowing, inattention, cognitive inflexibility, and apathy have been associated with a decline in everyday functioning in patients with HD.^{10,13-17} Only one study reported that cognitive and motor impairments are correlated with unemployment, but these results should be interpreted with caution due to the small sample size.¹⁸ The impact of HD symptoms on the ability to work is still unknown. Therefore, the aim of our study was to determine which HD related signs are specifically associated with unemployment in a large cohort of Dutch HD mutation carriers.

METHODS

Participants

Baseline data of 220 HD mutation carriers (Cytosine-Adenine-Guanine [CAG] repeat length ≥ 36) who participated in the Enroll-HD study at the Leiden University Medical Center (LUMC) were included. The Enroll-HD study is an on-going international,

longitudinal, observational study to improve the understanding of HD, identify markers of disease progression, assist in recruitment of clinical trials, and improve the health of HD patients.¹⁹ Data are collected on demographics, motor, cognitive, and neuropsychiatric symptoms. Participants are asked to attend annual visits. Additional details about the Enroll-HD study design are described elsewhere.^{19,20}

In this study, only participants with complete data on all assessments were included. Both participants with and without a clinical motor diagnosis (i.e., premanifest gene carriers and manifest HD) were included. The Medical Ethical Committee of the LUMC approved this study and written informed consent was obtained from all participants.

Current working status was determined on the basis of clinical information provided by the participants. Participants who worked either fulltime (i.e., 36–40 hours per week) or part-time (fewer than 36 hours per week) in a paid job were categorized as employed ($N = 114$). Participants who reportedly retired due to their ill health, caused by signs of HD, were categorized as unemployed ($N = 106$). The previous occupations of the unemployed participants were divided into physically demanding and nonphysically demanding jobs on the basis of the authors' judgement. Construction workers, nurses, and farmers are examples of physically demanding jobs. Examples of nonphysically demanding jobs are receptionists, administrative workers, and computer programmers. An overview of all job classifications is provided in Table S1 in the data supplement that accompanies the online version of this article.

Assessments

The total motor score of the Unified Huntington's Disease Rating Scale (UHDRS-TMS) was used to assess the degree of motor disturbances.²¹ Here, higher scores indicated more motor impairments (range=0–124). The UHDRS Total Functional Capacity (UHDRS-TFC) was used as a measure of general functioning.²¹ Lower scores indicated more functional disability. The cognitive scores included the total number of correct responses on the written Symbol Digit Modalities Test (SDMT),²² which was used to measure psychomotor speed and visual attention; the correct responses on the Stroop test (color, word, and interference),²³ measuring speed of processing and executive functions; and the completion time in seconds of the Trail Making Test Part B (TMT-B),²⁴ which was used to assess cognitive flexibility and executive functions. Lower total scores on the SDMT and Stroop test indicated worse performances. Lower completion times on the TMT-B indicated better performances. Behavioral and psychiatric problems were evaluated using the short version of the Problems

Behaviors Assessment (PBA-s).^{25,26} The PBA-s is a semi-structured interview to assess the following 11 symptoms: depression, suicidal ideation, anxiety, irritability, aggressive behavior, apathy, perseverative thinking, obsessive behavior, paranoid thinking, hallucinations, and disorientation. Severity and frequency scores are rated for each item on a 5-point scale (range = 0–4), with a score of zero meaning that the symptom is absent and a score of four indicates that the symptom is causing severe problems in daily life. Scores per item are derived by multiplying the severity and frequency of each item. In this study, the following previously defined constructs were used: depression, irritability, apathy, psychotic behavior, and executive dysfunction.¹⁹ Higher scores reflected more psychiatric and behavioral problems.

Statistical analyses

Differences between unemployed and employed HD mutation carriers were analyzed with independent sample t-tests, chi-square test, and Mann-Whitney U test, when applicable. Univariate logistic regression analyses were performed for each predictor variable, with working status (employed versus unemployed) as the dependent variable. Scores on the predictor variables were dichotomized at the median in high and low scores. For the UHDRS-TMS, higher scores than the median indicated more motor impairments. For the SDMT and Stroop test, lower scores indicated worse performances; for the TMT-B, higher scores indicated worse performances. For all neuropsychiatric domains, higher scores indicated more symptoms.

All univariate logistic analyses were adjusted for age and gender. Subsequently, the significant predictors resulting from the univariate logistic regression analyses were included in a multivariate logistic regression analysis, resulting in a fully adjusted model. The multivariate logistic regression analysis included age, gender, years of education, and HD group (premanifest or manifest) as covariates. All predictors were entered in one block (method=enter). This means that each predictor is entered in the model after correction for all other predictors that were included in the model. Significant results are, therefore, corrected for all predictors included. The significance threshold was set at $p < .05$ for all analyses. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS version 23.0 for Windows).

RESULTS

Demographic and clinical characteristics of all HD mutation carriers, employed, and unemployed participants are reported separately in Table 1. Sixty-seven participants (60 employed and 7 unemployed) were in the premanifest stage, and 153 participants (54 employed and 99 unemployed) were in the manifest stage of the disease, on the basis of their UHDRS-TMS (≤ 5 is premanifest). Of the 153 manifest HD participants, 59 (38.6%) were categorized in disease stage 1, 64 (41.8%) in disease stage 2, 23 (15.0%) in disease stage 3, and seven (4.6%) in disease stage 4, on the basis of the UHDRS-TFC.²⁷ None of the participants were classified in the latest stage, disease stage 5. Of the unemployed, 52 (49.1%) used to work in a physically demanding job, whereas 54 (50.9%) worked in less physically demanding environments (Table 1). The mean duration of unemployment was 6.9 years. The employed HD mutation carriers were significantly younger (mean=42.5 years) compared to the unemployed HD mutation carriers (mean=51.1 years). There were no significant differences between the two groups in gender and CAG repeat length. The unemployed HD mutation carriers showed significantly worse performances on the SDMT, Stroop test, and TMT-B. They also had significantly higher scores on the UHDRS-TMS and on the irritability, apathy and executive functioning scores of the PBA-s (Table 1).

TABLE 1 Demographic, Clinical, and Neuropsychiatric characteristics of the Huntington's disease participants^a

Characteristic	Whole group (N=220)	Employed (N=114)	Unemployed (N=106)	p-value
Demographic				
Gender (male/female) (%male)	96/124 (43.6%)	54/60 (47.4%)	42/64 (39.6%)	0.247
Age (years)	46.6 ± 11.1 (19–75)	42.5 ± 10.5 (19–66)	51.1 ± 10.0 (27–75)	<0.001
Years of education	14.8 ± 3.4 (8–25)	15.5 ± 3.4 (8–25)	14.1 ± 3.3 (8–23)	0.002
Duration of unemployment ^b	NA	NA	6.9 ± 6.6 (5; 0–29)	NA
Years to retirement after clinical diagnosis	NA	NA	-1.5 ± 6.1 (0; -24–11)	NA
Job demands: physical/non-physical (% physical)	NA	NA	52/54 (49.1%)	NA
Clinical				
CAG repeat length	43.1 ± 2.9 (36–60)	42.8 ± 3.1 (36–60)	43.5 ± 2.7 (36–55)	0.107
UHDRS-TMS	21.1 ± 21.2 (0–104)	9.54 ± 11.3 (0–57)	33.6 ± 22.4 (0–104)	<0.001
UHDRS-TFC	11.0 (1–13)	13.0 (7–13)	9.0 (1–13)	<0.001
Cognitive scores				
SDMT ^c	39.7 ± 16.1 (0–74)	48.9 ± 11.8 (17–74)	29.8 ± 14.2 (0–63)	<0.001
Stroop color ^c	58.5 ± 18.4 (16–100)	67.8 ± 15.0 (33–100)	48.6 ± 16.5 (16–83)	<0.001
Stroop word ^c	78.2 ± 22.9 (26–135)	90.0 ± 17.1 (46–135)	65.6 ± 21.5 (26–117)	<0.001
Stroop interference ^c	34.5 ± 12.6 (3–67)	41.1 ± 10.0 (14–67)	27.5 ± 11.2 (3–56)	<0.001
TMT-B ^d	94.9 ± 67.6 (23–240)	62.8 ± 41.9 (23–240)	129.5 ± 73.0 (28–240)	<0.001
Neuropsychiatric^e				
Depression score	4.9 ± 5.8 (0–28)	4.7 ± 5.3 (0–22)	5.2 ± 6.4 (0–28)	0.531
Irritability score	2.6 ± 3.5 (0–18)	2.1 ± 2.8 (0–12)	3.2 ± 4.0 (0–18)	0.019
Apathy score	1.4 ± 2.9 (0–16)	0.75 ± 1.9 (0–9)	2.2 ± 3.6 (0–16)	<0.001
Psychotic score	0.1 ± 1.2 (0–18)	0.0 ± 0.1 (0–1)	0.2 ± 1.8 (0–16)	0.326
Executive functioning score	1.5 ± 3.3 (0–18)	0.6 ± 2.1 (0–16)	2.5 ± 4.1 (0–18)	<0.001

^aData are mean ± SD (median; range), median (range) for UHDRS-TFC, and number (%) for gender and job demands. Independent sample t-tests were performed for all variables except gender (chi-square test), and UHDRS-TFC (Mann-Whitney U test) to investigate group differences between employed and unemployed individuals. Significant differences ($p < 0.05$) are shown in bold. Abbreviations: CAG = Cytosine-Adenine-Guanine; NA = Not Applicable; UHDRS-TFC = Unified Huntington's Disease Rating Scale Total Functional Capacity; UHDRS-TMS = Unified Huntington's Disease Rating Scale Total Motor Score; SDMT = Symbol Digit Modalities Test; TMT-B: Trail Making Test part B

^bData represent only unemployed participants for whom the year of retirement was available (N=105)

^cHigher scores indicate better performances

^dCompletion time is in seconds, with higher scores indicating worse performances

^eHigher scores indicate increased neuropsychiatric disturbances

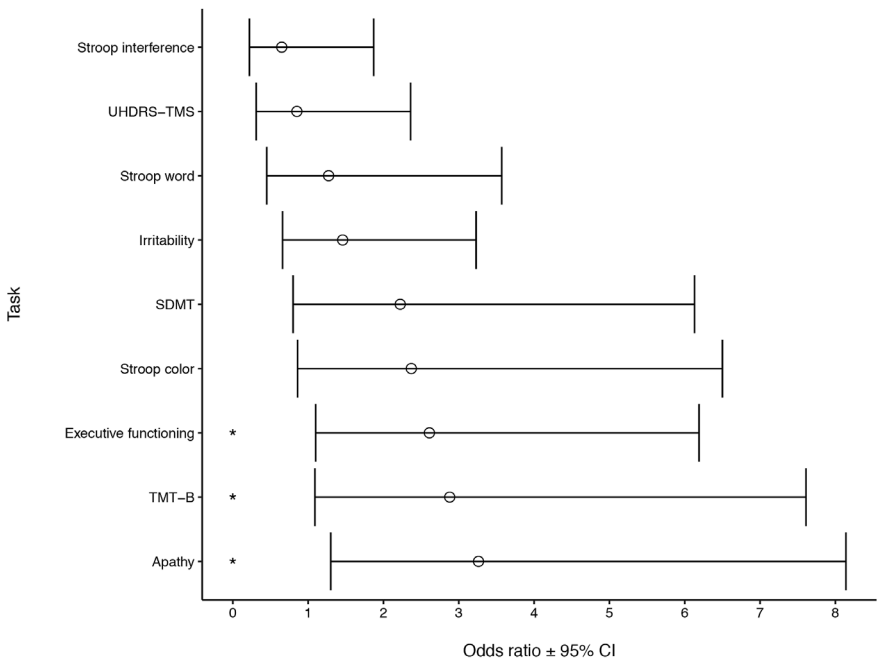
The univariate logistic regression analyses showed that after adjusting for age and gender, the UHDRS-TMS, SDMT, Stroop test, TMT-B, and irritability, apathy, and executive functioning scores were predictive of unemployment (Table 2). Scores on the SDMT were the strongest predictor (odds ratio [OR] = 8.09, 95% confidence interval [CI] = 4.18–15.64, $p < 0.001$), meaning that HD mutation carriers with a total score of less than 42 on the SDMT are 8.09 times more likely of being unemployed than are HD mutation carriers with higher scores (Table 2). Depression and psychotic scores on the PBA-s were not significantly related to unemployment. The multivariate logistic regression analysis, including all significant predictors in one fully adjusted model, revealed that scores on the TMT-B, apathy, and executive functioning domains were significantly related to unemployment (Table 2; Figure 1). Here, apathy was the most significant predictor, with HD mutation carriers who showed signs of apathy having 3.26 times more chance of being unemployed than would HD mutation carriers without apathy (OR = 3.26 [1.30 – 8.14], $p = 0.011$). All other independent variables were no longer associated with unemployment in this adjusted model.

TABLE 2 Clinical correlates of unemployment in HD mutation carriers

	Employed (N=114)		Unemployed (N=106)		Univariate logistic regression		Multivariate logistic regression			
	N	%	N	%	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
UHDRS-TMS > 15	32	28	78	74	5.20	2.66 – 10.18	<0.001	0.85	0.31 – 2.36	0.756
SDMT score < 42	28	25	83	78	8.09	4.18 – 15.64	<0.001	2.22	0.80 – 6.13	0.125
Stroop color score < 60	32	28	81	76	6.24	3.30 – 11.81	<0.001	2.37	0.86 – 6.50	0.095
Stroop word score < 80	31	27	79	75	5.50	2.88 – 10.53	<0.001	1.27	0.45 – 3.57	0.656
Stroop interference score < 36	31	27	79	75	6.04	3.22 – 11.36	<0.001	0.65	0.22 – 1.87	0.421
TMT-B score > 66	28	25	82	77	8.07	4.20 – 15.50	<0.001	2.88	1.09 – 7.61	0.033
Depression score > 2	59	52	52	49	0.88	0.49 – 1.57	0.668			
Irritability score > 1	43	38	59	56	2.40	1.32 – 4.37	0.004	1.46	0.66 – 3.23	0.353
Apathy score > 0	24	21	45	43	3.52	1.80 – 6.88	<0.001	3.26	1.30 – 8.14	0.011
Psychotic score > 0	2	2	2	2	0.75	0.10 – 5.87	0.786			
Executive functioning score > 0	22	19	42	40	3.12	1.60 – 6.11	0.001	2.61	1.10 – 6.19	0.029

Data are presented as n (%). Univariate logistic regression was performed separately for age and gender with working status as dependent variable. For all other variables, the univariate logistic regression was adjusted for age and gender. Scores on the independent variables were split at the median. All significant predictors from the univariate regression analysis were entered in a fully adjusted model using multivariate regression analysis. Multivariate logistic regression analysis was corrected for age, gender, group and years of education. Statistically significant p-values ($p < 0.05$) are displayed in bold SDMT = Symbol Digit Modalities Test; TMT-B = Trail Making Test part B; UHDRS-TMS = Unified Huntington's Disease Rating Scale - Total Motor Score

FIGURE 1 Predictors of unemployment in Huntington’s disease (HD) mutation carriers^a



^a Odds ratios and 95% confidence intervals (CIs) are based on the multivariate logistic regression analysis. Abbreviations: SDMT = Symbol Digit Modalities Test; TMT-B = Trail Making Test Part B; UHDRS-TMS = Unified Huntington’s Disease Rating Scale-Total Motor Score.

* $p < 0.05$

DISCUSSION

This study identified significant predictors of unemployment in HD mutation carriers. Our results showed that worse performances on cognitive tasks reflecting speed of processing and cognitive flexibility are independent determinants of unemployment. Additionally, apathy and executive functioning, evaluated using the PBA-s, are also predictors of unemployment. Motor functioning was not a significant independent predictor of unemployment. This suggests that although motor functioning is considered the clinical hallmark of HD, impairments in cognitive and psychiatric domains are more important to assess when discussing occupational changes. The association between motor functioning and unemployment diminished in the multivariate analysis because of the stronger influence of cognition. However, the cognitive task that was significantly related to unemployment (i.e., TMT-B) also includes a motor component, and this should be considered when interpreting the results.

Not being able to work affects a patients' quality of life, so it is important to consider potential working cessation carefully and try to postpone unemployment if possible. Adjusting or restructuring the work responsibilities to cognitively less demanding tasks might result in longer job participation. This will not be applicable to all professions, and not all employers may be willing to change the working environment. Patients should be advised about other possible activities that they can undertake, such as volunteer work, to prevent social isolation.

Cognitive functioning is increasingly being considered when forming the clinical HD diagnosis.⁹ Our results strengthen the ideas that regular evaluation of cognitive and behavioral functioning is necessary, because these factors influence daily life activities, in particular work abilities. Apathy is very common and progressive in HD mutation carriers, even in early stages of the disease.^{5,6,28-30} It has also been related to a decline in general functioning.¹⁷ Our study showed that apathy is specifically related to unemployment, which is often incorporated in measures of general functioning. Cognitive functioning and psychiatric behavior, in particular apathy, are also significantly related.^{29,31} Cognitive apathy has been defined as poor planning and organizational skills, and lower cognitive flexibility.²⁸ This might explain our results showing that both cognitive functioning and apathy are predictive of unemployment. However, the TMT, and apathy scores remained significant predictors in the fully adjusted model. Thus, taken this correlation between apathy and cognition into consideration, these constructs are still independent determinants of unemployment. Interestingly, depression was not a predictor of unemployment in both analyses,

while depression has been strongly linked to quality of life, and up to 50% of the HD patients report depressive symptoms at some point during the disease.^{5,17,28} In our study, half of the HD mutation carriers reported depressive symptoms, but this was comparable for both the employed and unemployed participants (52% and 49%, respectively). One explanation might be that depressive symptoms are more manageable with psychotropic medication than are other psychiatric symptoms and therefore interfere less with daily life activities. The progression of depressive symptoms is also nonlinear, and the severity decreases over time.^{6,28} The lack of a relationship between psychotic scores and unemployment might be explained by the low presence of psychotic behavior in our cohort. In general, psychotic behavior has a relatively low prevalence in HD (3%-11%) and is often reported in later disease stages.^{5,9}

When we categorized the professions of the unemployed in our cohort into physical and nonphysical demanding jobs, unemployed individuals mostly worked in nonphysical jobs (50.9% versus 49.1%). This suggests that physical activity alone might not be a reason to quit working, which is in line with our results that cognitive impairment is more predictive of work cessation than motor function. However, this distinction remains arbitrary and the influence of different job demands should be further explored. In addition, only unemployed participants, and no participants who reduced their working capacity, were included in this study. Further, patients with more cognitive and psychiatric symptoms might not participate in research, resulting in a potential bias. Our study still revealed significant determinants of unemployment, suggesting that cognitive and psychiatric signs influence the ability to work. Most manifest HD participants in the studied cohort were classified in disease stage 1 and 2 (80.4%), so evaluating cognitive and psychiatric symptoms that might affect work is already important at an early stage of the disease. Longitudinal studies are needed to determine how disease progression is related to changes in work ability. To reduce potential cultural influences, we only included participants from one study site. The cohort contained more than 200 participants, which is considered large enough to investigate group differences. Still, more specific information regarding job types and classifications is necessary to thoroughly explore differences between professions and cultures. Asking participants to categorize their own job as either physical or nonphysical has previously been studied and could also be an interesting approach for future studies in HD.³²

To our knowledge, this study is a first effort to determine strong predictors of unemployment in HD mutation carriers and to provide results for all types of professions. In conclusion, our study shows that cognitive impairments, especially in

the executive domain, and apathy are independent determinants of unemployment in HD mutation carriers. Motor disturbances, the clinical hallmark of HD, do not seem to be the most important predictor for work cessation. This should be taken into consideration in the clinical practice when evaluating the ability to work.

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Driving with a neurodegenerative disorder: an overview of the current literature

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ABSTRACT

Driving is important for employment, social activities, and for the feeling of independence. The decision to cease driving affects the quality of life and has been associated with reduced mobility, social isolation, and sadness. Patients with neurodegenerative disorders can experience difficulties while driving due to their cognitive, motor, and behavioral impairments. The aim of this review is to summarize the available literature on changes in driving competence and behavior in patients with neurodegenerative disorders, with a particular focus on Huntington's (HD), Parkinson's (PD) and Alzheimer's disease (AD). A systematic literature search was conducted in the PubMed/Medline database. Studies using on-road or simulated driving assessments were examined in this review. In addition, studies investigating the association between cognitive functioning and driving were included. The review identified 70 studies. Only a few publications were available on HD ($N = 7$) compared to PD ($N = 32$) and AD ($N = 31$). This review revealed that driving is impaired in patients with neurodegenerative disorders on all levels of driving competence. The errors most commonly committed were on the tactical level including lane maintenance and lane changing. Deficits in executive functioning, attention, and visuospatial abilities can partially predict driving competence, and the performance on neuropsychological tests might be useful when discussing potential driving cessation. Currently, there is no gold standard to assess driving ability using clinical measures such as neuropsychological assessments, so more studies are necessary to detect valid screening tools and develop useful and reliable evidence-based guidelines.

INTRODUCTION

Progressive neurodegenerative diseases can result in a loss of motor and cognitive functioning, which interfere with daily activities such as the ability to drive a car.¹ Many individuals rely on their car for employment, social activities, and independency.²⁻⁴ Therefore, the decision to cease driving affects the quality of life. Driving cessation has been associated with negative outcomes such as social isolation, reduced mobility, and sadness.⁵ A difficult question that clinicians face in everyday practice is when to advise patients with early disease to abstain from driving. In most European countries, neurologists evaluate driving competence in patients with neurodegenerative disorders, based on their clinical examination.⁶ Depending on the outcome of this evaluation, patients can be advised to contact an official national driving evaluation center. However, the evaluations of neurologists are often an overestimation of the actual driving capacities and inconsistent with on-road performances.³ In the Netherlands, a neurologist has to evaluate if a patient should perform a formal driving test.⁷ However, the decision to inform the national driving evaluation center relies on the self-report of patients. If a patient passes the formal driving test, the driver license can be renewed with a maximum of five years. Within this 5-year period, patients have no obligation to perform a retest. This can potentially be unsafe with the progressive character of neurodegenerative diseases, especially since changes in cognitive and daily functioning can already occur within five years.^{8,9}

The aim of this review is to provide an overview of the available literature on changes in driving competence in patients with neurodegenerative disorders and to identify potential gaps in the literature that should be further investigated, with particular interest for Huntington's disease (HD), Parkinson's disease (PD), and Alzheimer's disease (AD). We focused on these neurodegenerative disorders, since they are comparable in cognitive, psychiatric, and motor symptoms. A comprehensive review incorporating all three diseases has not been published before. Furthermore, we evaluate if specific cognitive tests have been identified that are predictive of driving ability and if these tests can be implemented in the clinical practice. Since simulators are increasingly being used in driving research and might be a proper screening tool to assess driving in patients with neurodegenerative diseases, we also included available literature on driving simulators.

METHODS

An electronic database search in PubMed/MEDLINE was performed to identify the available literature. The last database search was performed on 27th October 2016. The following search terms were used individually and in combination: "driving" "driving ability" "neurodegeneration", "Huntington's disease", "Huntington", "Parkinson's disease", "Parkinson", "Alzheimer's disease", "Alzheimer", "dementia" "cognition" "cognitive functioning", and "simulator". In addition, references and reviews were checked in search of relevant studies. In the initial search only papers written in English were considered and selected for further review. Only original articles and full communications were included (e.g., no letters to editors, editorial comments, or reviews). Articles were deemed relevant if they directly investigated driving-related issues using formal driving assessments (i.e., on-road or simulator) in diagnosed patients with HD, PD, or AD.

RESULTS

Search results

The database search yielded 240 articles that were selected for further review based on title. The abstract of each article was reviewed and the inclusion/exclusion criteria were checked. From these 240 articles, 70 studies met the inclusion criteria of the current review (7 HD, 32 PD, and 31 AD studies). The majority of the studies described on-road driving performances ($N = 45$), 21 studies involved driving simulation, and 51 articles investigated the relationship between cognitive performances and driving outcomes. A summary of the included literature and the methods that were used is given per group in Tables 1, 2, and 3. When applicable, we will use the driving model of Michon et al. (1989).¹⁰ According to this model, driving errors can be sorted in three categories: (a) strategic errors that occur before actual driving, such as route planning; (b) tactical errors consisting of errors in speed adaptations, changing lanes, and keeping distance; (c) operational errors such as incorrect responses to changing driving environments and vehicle control.^{11, 12} An overview of the committed driving errors by patient group per category is given in Table 4.

Driving and Huntington's disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by choreatic movements, cognitive dysfunction, and psychiatric symptoms.¹³ It is caused by a gene mutation located on chromosome 4.¹⁴ The mean age at onset is between 30 and 50 years, with a mean disease duration of 17-20 years.¹³ The earliest cognitive symptoms are characterized by executive dysfunctions, such as difficulties in planning, cognitive inflexibility, and lack of awareness.^{13, 15} The cognitive symptoms gradually worsen and eventually result in dementia. Due to the progressive nature of the disease, patients become more dependent in their daily life activities. With the onset of HD during midlife, a lot of patients rely on their car for work and social activities so patients might find it difficult to decide when to stop driving. However, concern about driving safely is one of the first issues reported by HD patients (33.5%) and has been associated with motor, cognitive, and depressive symptoms.^{16, 17} The influence of other psychiatric symptoms, such as aggression and impulsivity, has not yet been investigated.

Only seven studies were found that investigated driving in HD patients.¹⁶⁻²² Four of these studies used formal driving assessments, either on-road or simulated, to investigate driving competence.^{18, 20-22} Due to the limited amount of studies available on HD and driving, the studies that did not investigate driving with formal driving assessments but with questionnaires or retrospective data analyses are also discussed.^{16, 17, 19} An observational study investigating the association between different disease aspects of HD with functional changes showed that motor functioning and the Stroop task, measuring cognitive flexibility and information processing, were significantly associated with driving safety.¹⁶ Increased motor impairment was related to a lower likelihood of being able to drive safely as rated by a professional. This study did not include a formal driving assessment. During a semi-structured interview, 11 out of 16 HD participants reported changes in their driving behavior.¹⁷ They reported lower reaction times, had concerns about their safety, and had difficulties multi-tasking. A study that investigated clinical predictors of driving by retrospective patient file reviews showed that cognitive impairment, especially a reduction of psychomotor speed and attention, is a strong risk factor for driving cessation in HD.¹⁹ Increased motor impairments were also associated with not driving a car, but were not a risk factor affecting the decision to cease driving.¹⁹ An early study investigating driving in HD with a driving simulator showed that HD patients committed errors on the operational and tactical level.¹⁸ They were less accurate and had longer reaction times compared to controls.¹⁸ HD patients also had higher error rates in signaling, steering, braking, maintaining speed, and accelerator use.

They were more likely to be involved in accidents compared to healthy individuals (58% and 11% respectively).¹⁸ Still, most of the HD patients in this study continued driving after onset of the disease (53/73). In addition, half of the HD patients that still drive failed an on-road driving assessment.²⁰ This confirms a limited insight regarding their own driving skills and emphasizes the importance of early evaluation.^{23–25} In one study, 14 of the 30 HD patients (47%) failed the on-road driving test.²¹ HD patients committed most errors on the operational and tactical levels, including errors in lane positioning, speed adaptations, keeping distance, turning left, and lane changing.²¹ They also made more errors in perception of road signs, reflecting errors on the strategic level. Selective attention and disease stage were highly correlated with on-road driving failure in manifest HD.²¹ A combination of neuropsychological tasks measuring visual processing speed, visual scanning, and attentional shifting best predicted the pass/fail rate of an on-road driving assessment, instead of a model that also included motor functioning.²⁰ More recently, it has been reported that some neuropsychological assessments focusing on speed of processing, cognitive flexibility, and visual attentional control seem to be good predictors for driving competence in manifest HD.²²

The results of the reviewed studies showed that driving competence is impaired in patients with HD and that concerns about driving safely are one of the earliest symptoms reported by both patients and families. Especially executive functioning and visuospatial abilities have been related to driving competence in HD. However, due to the limited amount of data, no conclusions can be drawn regarding which cognitive battery is most predictive of driving impairment in HD. None of the studies to date have focused on evaluating driving competency in the earliest stages of HD or in gene mutation carriers without a clinical diagnosis (i.e., premanifest gene carriers), while they often have questions for their physician regarding their driving skills and are most likely in need of a driving evaluation in the near future. Furthermore, no longitudinal studies have been performed investigating driving in HD, so there are no results available about the potential decline in driving competence during the course of the disease. Follow-up measurements are important to determine when driving-related issues become apparent and when to discuss potential driving cessation. It also provides an opportunity to monitor driving from early to more advanced stages of the disease.

TABLE 1 Study details of included studies on Huntington's disease

Authors (year)	Number of participants (N) HD/controls (C)	Age (years) mean ± SD HD/controls (C)	Driving assessment	Cognitive/motor assessments	Main findings
Beglinger et al. (2010)	265 HD at risk/no C	44.5 ± 12.4	Questionnaire	UHDRS-TMS, TFC, FAS, Stroop, Verbal fluency, SDMT	1. 33.5% (86/265) reported inability to drive safely 2. Motor functioning and Stroop test were significantly associated with driving safety item of a questionnaire
Beglinger et al. (2012)	74 HD/no C	48.2 ± 12.3	Driving status determined by chart review	UHDRS-TMS, TFC, Verbal fluency, SDMT, Stroop, RBANS, TMT, WAIS-III information, letter-number sequencing, similarities	1. Motor, cognitive, and functional decline were associated with driving 2. Cognitive impairment was the most strongest risk factor for driving cessation
Devos et al. (2012)	30 HD/30 C	HD: 50.2 ± 12.4/C: 50.3 ± 12.6	On-road and simulator	UHDRS-TMS, TFC, Verbal fluency, Stroop, SDMT, TMT, MMSE	1. 50% of HD patients failed the on-road evaluation (controls did not perform on-road assessment) 2. Pass/fail scores of the on-road assessment were best predicted by a combination of the SDMT, Stroop word, and TMT-B tasks (sensitivity/specificity = 87%)
Devos et al. (2014)	30 HD/30 C	HD: 50.2 ± 12.4/C: 50.3 ± 12.6	On-road	UHDRS-TMS, Verbal fluency, Stroop, SDMT, TMT, UFOV, Visual scanning, Divided attention	1. 47% of the HD patients (14/30) failed the on-road evaluation versus none of the controls 2. HD patients scored worse than controls on all items of the road test 3. Selective attention was the only predictor that correlated with all clusters of the on-road score
Hennig et al. (2014)	52 HD/no C	HD (referred to DMV): 47.3 ± 11.0 / HD (not referred to DMV): 45.0 ± 12.3	On-road	RBANS coding, TMT part B, Stroop, CalCAP sequential reaction time	1. 31/52 HD patients were referred to DMV for a driving evaluation 2. Association between neuropsychological assessments and driving competence
Rebok et al. (1995)	73 HD 29 HD/16 C for simulator study	HD: 43.8 ± 11.9 Not reported for simulator study	Simulator	MMSE, WAIS-R vocabulary, block design, VMI, FAS, BTA, HVLT, TMT, Stroop, WCST, WMS-R logical memory, visual reproduction, Motor-free VPT, Spatial recognition test, Reaction time task	1. 53/73 (72%) continued driving after disease onset 2. HD patients had higher error rates on the driving simulator outcomes and lower cognitive scores compared to healthy individuals
Williams et al. (2011)	16 HD/no C	65.6 ± 10.0	Semi-structured interview	-	1. Driving was the most common endorsed item (11/16) 2. HD patients reported lower reaction times, difficulties multi-tasking, and concerns about safety

C = Controls; CalCAP = California Computerized Assessment Package; DMV = Department of Motor Vehicles; FAS = Oral Word Association Test; HD = Huntington's Disease; HVLT = Hopkins Verbal Learning Test; MMSE = Mini-Mental State Examination; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SDMT = Symbol Digit Modalities Test; TFC = Total Functional Capacity; TMT = Trail Making Test; UFOV = Useful Field of View; UHDRS-TMS = Unified Huntington's Disease Rating Scale – Total Motor Score; VMI = Visual Motor Integration; VPT = Visual Perception Test; WAIS-III = Wechsler Adult Intelligence Scale-III; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test; WMS-R = Wechsler Memory Scale-Revised; WMS-III = Wechsler Memory Scale-Third edition

Driving and Parkinson's and Alzheimer's disease

Contrary to driving studies in HD, a large number of studies have been performed evaluating driving competence in Parkinson's disease (PD; $N = 32$) and Alzheimer's disease (AD; $N = 31$). Three studies compared the driving competence of patients with PD and AD. In the following sections we will discuss the on-road driving studies first, followed by the studies using driving simulators, and last the studies that also incorporated cognitive functioning in relation to driving performance.

Parkinson's disease

Studies using on-road driving assessments ($N = 22$) to evaluate driving competence showed that 12–56% of the PD patients failed an on-road driving test.^{1, 26–34} PD patients had a higher number of total driving safety errors compared to control participants. Studies that focused on identifying specific driving errors showed that PD patients are most likely to make errors on a tactical level including difficulties with yielding at intersections²⁹ and lane changing.¹ They were less likely to check their blind spot, and used their rear view and side mirrors less frequently than controls.^{1, 35} Patients with PD also showed a decreased awareness of others, hesitated longer before making a turn, did not accelerate to a proper speed, and were less concentrated.²⁶ They made more errors in adjusting to different driving situations compared to controls²⁹ and showed difficulties driving in traffic flow.³ PD patients made more errors in reversing and car parking.¹ Drivers with PD also had more difficulties with road positioning and driving on roundabouts compared to controls.³³ Most of the errors were present while driving in an urban environment.³ Errors in the lateral position on the road at low speed and turning left³ were the best predictors of overall pass/fail driving outcome.³² Overall, PD patients had an unsteady car speed and tended to drive slower,^{35–37} especially during distraction.³⁸ However, it has also been reported that they drove faster on highways compared to controls,³⁷ and had more difficulties adapting their speed at a higher speed.³² They also identified fewer traffic signs and landmarks compared to controls.³⁹

On the operational level, PD patients made more incorrect turns and did not signal appropriately compared to controls.^{26, 35, 36} They also made more errors in lane maintenance.^{1, 29, 40} Strategically, PD patients made fewer driving trips,^{37, 41} drove less distance, and shorter durations^{1, 41} compared to controls. PD patients had a higher preference for driving with a passenger,^{1, 37} reported less nighttime driving^{29, 37} and more often used alternative transportation.²⁹ Driving simulator studies ($N = 12$) showed that patients with PD had lower reaction times,^{42, 43} missed more red lights,

and showed impaired accuracy compared to control subjects.⁴² Furthermore, they had a higher number of traffic offences,⁴³ more accidents,^{43, 44} and a worse overall simulator score compared to controls.⁴³ Patients who passed an on-road driving assessment also performed better on the simulator tests compared to patients who failed the on-road assessment.³¹ Patients with PD tended to drive faster than controls and had poorer vehicle control, especially during low contrast visibility conditions.⁴⁵ PD patients were found to brake later during incongruent driving conditions.⁴⁶ They waited for external cues before they responded, while control subjects initiated a response prior to the cue. This result is similar to another study which found that PD patients relied more on external than internal cues to regulate their driving behavior.⁴⁷

A number of studies have incorporated cognitive assessments in an attempt to determine which test performances are associated with the driving competence of patients with PD. Most studies reported an association between cognitive functioning and driving competence.^{3, 12, 26–28, 31, 32, 36, 38–40, 43, 46, 48–52} However, some studies also reported no associations between cognition and driving in PD patients,^{1, 33, 53} so results are inconsistent. Driving errors were particularly associated with lower performances in cognitive flexibility,^{26, 27, 38, 39, 49, 52} visuoconstructional abilities,^{26, 36, 39} attention,^{12, 27, 32, 36, 40, 46} psychomotor speed,^{46, 51} working memory,^{12, 49} set shifting,^{12, 48} information processing,^{12, 49} contrast sensitivity,^{27, 31, 43, 48, 51} visual scanning,³² visual acuity,^{32, 40} speed of visual processing,^{3, 27, 28, 40} and visual memory.^{3, 36}

TABLE 2 Study details of included studies on Parkinson's disease

Authors (year)	Number of participants (N) PD/controls (C)	Age (years) mean ± SD PD/controls (C)	Driving assessment	Cognitive/motor assessments	Main findings
Amick et al. (2007)	25 PD/no C	PD (safe): 62.9 ± 8.9 PD (marginal): 66.1 ± 6.5	On-road	UPDRS motor, Contrast sensitivity, ROCF, TMT, UFOV, Backwards visual masking, FACT, Pelli-Robson	1. 11/25 (44%) PD patients had marginal or unsafe rating on the road test 2. Composite measure of executive functioning and visuospatial abilities correctly classified 71.4% of safe drivers and 72.7% of marginal unsafe drivers
Classen et al. (2009)	19 PD/104 C	PD: 74.8 ± 6.1/C: 75.4 ± 6.4	On-road	UPDRS, UFOV, MMSE, TMT part B, Contrast sensitivity tests	1. 8/19 (42%) PD patients failed the on-road assessment versus 21.2% controls (22/104) 2. UFOV scores showed strongest correlation with on-road performance 3. UFOV risk index: cut-off = 3, sensitivity = 87%, specificity = 82%; UFOV divided attention: cut-off = 223 ms, sensitivity = 87.5%, specificity = 81.8%; UFOV selected attention: cut-off = 273 ms, sensitivity = 75%, specificity = 72.7%
Classen et al. (2011)	41 PD/41 C	PD: 73.1 ± 6.0/C: 73.0 ± 5.2	On-road	UPDRS, Rapid pace walk, MMSE, UFOV, Contrast sensitivity tests	1. 56% of PD patients failed the on-road assessment versus 12.2% of controls 2. Model with UFOV divided attention and Rapid pace walk accurately classified 80.5% of PD subjects in pass/fail category (sensitivity = 82.6%, specificity = 77.8%)
Classen et al. (2014)	101 PD/138 C	PD: 69.4 ± 7.4/C: 71.8 ± 5.1	On-road	-	1. 41% of PD patients failed the on-road assessment versus 9% of controls 2. Errors in visual scanning, signaling, vehicle positioning and speed regulation were most predictive of overall pass/fail scores
Classen et al. (2015)	99 PD/no C	Not reported (range: 35 – 89)	On-road	UPDRS motor, TMT part B, FNT, Rapid pace walk, Contrast sensitivity	1. Poorer performance on the clinical variables was associated with more driving errors. Contrast sensitivity, TMT part B, and FNT were predictors of on-road performance
Cordell et al. (2008)	53 PD/129 C	PD: 69.3 ± 8.3/C: 72.9 ± 7.1	On-road	-	1. Control group performed better on all driving tasks 2. Most common errors by PD patients were failing to check blind spot, unsteady car speed, and inappropriate signaling at roundabouts
Crizzle et al. (2013)	27 PD/20 C	PD: 71.6 ± 6.6/C: 70.6 ± 7.9	On-road	UPDRS motor, Pelli-Robson, MoCA	1. PD patients had lower reaction times and worse cognitive scores compared to controls. Reaction time was negatively associated with night driving
Crizzle et al. (2013)	27 PD/20 C	PD: 71.6 ± 6.6/C: 70.6 ± 7.9	On-road	-	1. PD patients had a more restricted driving pattern compared to controls with less driving at night and during bad weather
Crizzle et al. (2013)	55 PD/no C	71.0 ± 7.0	On-road	UPDRS motor, Rapid pace walk, Modified Hoehn and Yahr	1. 28/55 (51%) of PD patients failed the road test 2. Combined scores of Rapid pace walk and Modified Hoehn and Yahr best predictor of safe driving

TABLE 2 Study details of included studies on Parkinson's disease

Authors (year)	Number of participants (N) PD/controls (C)	Age (years) mean ± SD PD/controls (C)	Driving assessment	Cognitive/motor assessments	Main findings
Devos et al. (2007)	40 PD/40 C	PD: 61.6 ± 9.4/C: 62.8 ± 7.6	On-road and simulator	UPDRS motor, UPDRS ADL, CDR, Pelli-Robson, ROCF, UFOV, Visual scanning tests, Attention tasks	3. MHY score of ≥2.5: sensitivity = 61%, specificity = 78%; RPW score of ≥6.22: sensitivity = 68%, specificity = 89% 1. 11/40 (27.5%) of PD patients failed the on-road test (controls did not perform on-road assessment) 2. PD patients performed worse on the driving simulator score and made more traffic offences compared to controls 3. Adding a driving simulator to screening battery increased accurate classification from 90% to 97.5% (sensitivity = 91%, specificity = 100%)
Devos et al. (2013)	60 PD/no C	PD (pass): 62.7 ± 9.7/PD (fail): 71.1 ± 7.1	On-road and simulator	UPDRS motor, Pelli-Robson, CDR	1. 40% of PD patients failed the on-road assessment 2. Predictive model accurately classified 46 drivers in pass/fail category (sensitivity = 96%, specificity = 94%)
Devos et al. (2013)	104 PD/no C	66.0 ± not reported	On-road	Binocular acuity, Kinetic vision, Pelli-Robson, UPDRS motor, UFOV, ROCF, Attention tasks, Visual scanning tests	1.35% of PD patients failed the on-road assessment 2. The fail group performed worse on all other clinical tasks compared to pass group
Heikkilä et al. (1998)	20 PD/20 C	PD: 59.0 ± 11.0/C: 55.0 ± 6.0	On-road	Visual memory, Perception, Vigilance, Choice reactions, Information processing	1. PD patients had most difficulties driving in an urban area and committed more errors than controls 2. Neurologist overestimated driving ability of PD patients
Madeley et al. (1990)	10 PD/10 C	PD: 54.6 ± not reported/C: 55.9 ± not reported	Simulator	-	1. Driving reaction time and steering accuracy were impaired in the PD patients
Radford et al. (2004)	51 PD/no C	64.4 ± 9.1	On-road	Webster's rating scale, UPDRS motor, SDSA, AMIPB, Stroop, PASAT, Tapping task	1. 6/49 (12%) PD patients were classified as unsafe drivers 2. Unsafe drivers drove worse on roundabouts and had poorer road positioning. No differences in cognitive performance between safe and unsafe drivers with PD
Ranchet et al. (2011)	25 PD/25 C	PD: 65.4 ± 5.2/C: 66.7 ± 4.4	Simulator	UPDRS motor, MMSE, Stroop, TMT, BVRT, Digit span, PMT, N-back, Mental flexibility, Three tasks during driving simulator assessment	1. Updating information was impaired in PD patients compared to controls 2. TMT was the best predictor of driving simulator outcome (explained 40.7% of variance on simulator test)
Ranchet et al. (2013)	19 PD/21 C	PD: 66.1 ± 5.1/C: 69.1 ± 3.9	On-road	UPDRS motor, MMSE, Stroop, TMT, BVRT, Digit span, PMT, N-back, Mental flexibility	1. Driving performance was poorer in PD patients compared to controls 2. Combination of cognitive measures discriminated between at-risk and safe drivers (sensitivity = 93.8%, specificity = 85.7%)

TABLE 2 Study details of included studies on Parkinson's disease

Authors (year)	Number of participants (N) PD/controls (C)	Age (years) mean ± SD PD/controls (C)	Driving assessment	Cognitive/motor assessments	Main findings
Ranchet et al. (2016)	25 PD (16 at follow-up)/25 C (21 at follow-up)	PD: 65.4 ± 5.2/C: 66.7 ± 4.4	Simulator	UPDRS motor, MMSE, Stroop test, TMT, BVRT, Digit span, PMT, N-back, Mental flexibility, Three tasks during driving simulator assessment	1. At follow-up, PD patients performed worse compared to controls on updating information during the simulator
Scally et al. (2011)	19 PD/19 C	PD: 68.7 ± 6.7/C: 68.05 ± 7.2	Simulator	UPDRS motor, MMSE, WMS-III digit span, WMS-III mental control, TMT	1. PD patients showed delayed initiation in braking response 2. Slower psychomotor speed and poorer attention was associated with earlier braking in the PD group
Singh et al. (2007)	154 PD/no C	67.6 ± not reported	On-road	-	1. 50/154 (32.5%) of PD patients were unsuitable to drive
Stolwyk et al. (2005)	18 PD/18 C	PD: 67.6 ± 6.5/C: 67.1 ± 6.5	Simulator	UPDRS motor, MMSE	1. PD patients relied more on external than internal cues to regulate driving compared to controls
Stolwyk et al. (2006)	18 PD/18 C	PD: 67.6 ± 6.5/C: 67.1 ± 6.5	Simulator	UPDRS motor, MMSE	1. PD patients drove more cautious than controls
Stolwyk et al. (2006)	18 PD/18 C	PD: 67.6 ± 6.5/C: 67.1 ± 6.5	Simulator	UPDRS motor, MMSE, Up-and-Go test, TMT, SDMT, Reaction time tests, Brixton test, WAIS-III picture completion, WAIS-III digit span, WAIS-III block design, JLO	1. Correlations between specific neuropsychological tests and driving outcome variables 2. TMT-B, Brixton test, and Block design correlated with tactical errors; SDMT, Picture completion, and JLO correlated with operational errors
Uc et al. (2006)	79 PD/151 C	PD: 65.9 ± 8.6/C: 65.3 ± 11.5	On-road	UFOV, Pelli-Robson, Visual acuity, UPDRS, JLO, MMSE, CFT, BVRT, TMT, AVLT, COWA, Blocks, Structure from Motion test	1. PD patients committed more safety errors and identified fewer traffic signs compared to controls and landmarks 2. Specific neuropsychological tests (TMT, UFOV, CFT) correlated with driving outcome
Uc et al. (2006)	71 PD/147 C	PD: 66.0 ± 8.6/C: not reported	On-road	UFOV, Pelli-Robson, Visual acuity, UPDRS, JLO, MMSE, CFT, BVRT, TMT, AVLT, COWA, WAIS-R block design, PASAT	1. Driving safety decreased in PD group during distraction 2. Cognitive and motor functioning predicted effects of distraction in the PD group
Uc et al. (2007)	77 PD/152 C	PD: 65.9 ± 8.6/C: 65.3 ± 11.5	On-road	UFOV, Pelli-Robson, Visual acuity, UPDRS, JLO, MMSE, CFT, BVRT, TMT, AVLT, COWA, WAIS-R block design	1. PD patients made more incorrect turns, safety errors, and got lost more often than controls. 2. Poor performance on CFT and UFOV was predictive of driving errors
Uc et al. (2009)	84 PD/182 C	PD: 67.3 ± 7.8/C: 67.6 ± 7.5	On-road	UFOV, Pelli-Robson, Visual acuity, UPDRS, JLO, MMSE, CFT, BVRT, TMT, AVLT, COWA, WAIS-R block design	1. PD patients committed more total safety errors compared to controls (41.6 versus 32.9); lane violations were the most common error 2. Visual processing speed, attention, and visual acuity were predictive of total number of errors

TABLE 2 Study details of included studies on Parkinson's disease

Authors (year)	Number of participants (N) PD/controls (C)	Age (years) mean ± SD PD/controls (C)	Driving assessment	Cognitive/motor assessments	Main findings
Uc et al. (2009)	67 PD/51 C	PD: 66.2 ± 9.0/C: 64.0 ± 7.2	Simulator	UFOV, Pelli-Robson, Visual acuity, UPDRS, JLO, MMSE, CFT, BVRT, TMT, AVLT, COWA, WAIS-R block design	1. PD patients had higher SDLP and lane violations during fog conditions compared to controls
Vardaki et al. (2016)	10 PD/10 C	PD: 62.2 ± 8.4/C: 57.6 ± 5.1	Simulator	MMSE, FAB, SDMT, UFOV, HVLT-R, TMT, WMS letter number sequencing, spatial span task, Spatial addition test, Driving scenes test	1. No differences between PD patients and controls in sign recall after driving 2. PD patients performed worse on the neuropsychological tests compared to controls
Wood et al. (2005)	25 PD/21 C	PD: 63.7 ± 6.8/C: 65.2 ± 8.6	On-road	UPDRS motor	1. 14/25 (56%) PD patients failed the on-road driving test versus 5/21 (24%) controls 2. PD patients made more safety errors compared to controls (e.g. lane keeping, reversing, parking)
Worringham et al. (2006)	25 PD/21 C	PD: 63.7 ± 6.8/C: 65.2 ± 8.6	On-road	UPDRS motor, MMSE, UFOV, Visual acuity, Pelli-Robson, Motion sensitivity, SDMT, TMT, Stroop, Purdue Pegboard, Reaction time task	1. Motor performance (Purdue pegboard), contrast sensitivity (Pelli-Robson) and cognitive function (SDMT) predicted pass/fail category in PD group (sensitivity = 72.7%, specificity = 64.3%)
Zesiewicz et al. (2002)	39 PD/25 C	PD: 63.8 ± 11.5/C: 65.6 ± 10.3	Simulator	UPDRS motor	1. PD patients had more total collisions compared to controls 2. Motor functioning was associated with total number of collisions

ADL = Activities of Daily Living; AMIPB = Adult Memory and Information Processing Battery; AVLT = Auditory Verbal Learning Test; BVRT = Benton Visual Retention Test; C = Controls; CDR = Clinical Dementia Rating scale; CFT = Complex Figure Test; COWA = Controlled Oral Word Association; FAB = Frontal Assessment Battery; FACT = Functional acuity contrast test; FNT = Finger to Nose Test; HVLT = Hopkins Verbal Learning Test; JLO = Judgement of Line Orientation test; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PASAT = Paced Auditory Serial Addition Task; PD = Parkinson's Disease; PMT = Plus Minus Task; ROCF = Rey-Osterrieth Complex Figure; SDLP = Standard Deviation of Lateral Position; SDMT = Symbol Digit Modalities Test; SDSA = Stroke Drivers Screening Assessment; TMT = Trail Making Test; UFOV = Useful Field of View; UPDRS = Unified Parkinson's Disease Rating Scale; WAIS-III = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale Revised; WMS-III = Wechsler Memory Scale-Third edition

Alzheimer's disease

Twenty-three studies were included in this review that investigated driving competence in AD using on-road driving tests. Between 15% and 65% of the AD patients failed an on-road driving assessment.^{54–64} They had lower overall driving performance scores compared to controls and committed more overall driving errors,^{62, 65–71} even in situations that were not considered challenging.⁵⁴ Driving performance scores tended to decrease with increasing dementia.^{57, 63, 72} The largest decline in driving performance was reported in mild AD patients.⁵⁷ On a tactical level, AD patients committed more errors compared to controls in lane positioning,^{54, 67, 73} lane changing,^{57, 74} checking their blind spot,⁷⁴ and they tended to drive slower.^{68, 75} They also had a higher inability to stop the vehicle appropriately,^{54, 76} and more difficulties avoiding potential collisions compared to controls.⁷⁶ Errors in turning,^{54, 70, 73, 75, 77} signaling,^{57, 74} and lane maintenance^{54, 67, 73} were the most reported errors on the operational level. In contrast, some studies showed no differences between AD patients and healthy individuals in vehicle control.^{54, 70} Strategic errors included less attention while driving, slower decision-making, and difficulties with road rules compared to controls.⁵⁴ AD patients also had more planning difficulties,⁷⁵ identified fewer landmarks and traffic signs compared to controls,⁷¹ and showed more problems with route following.⁷⁰

Comparing driving competence of patients with PD and AD using on-road driving assessments showed that both patient groups committed more overall driving errors compared to controls.⁷³ These driving errors increased when a concurrent task was included.⁷³ There are also differences reported between both groups in types of driving errors.⁷⁴ Both AD and PD patients committed most errors on the tactical level, but patients with AD also made errors on the operational and strategic levels. Patients with PD committed relatively few operational and strategic errors compared to AD patients.⁷⁴ AD patients reported fewer driving trips and drove less miles compared to patients with PD and controls.^{62, 74} Contrary, minimal differences between both groups have also been reported.^{53, 73}

The nine simulator studies reviewed showed that AD patients committed more errors in lane keeping (i.e., more lane deviations),^{64, 78–81} turning left,⁷⁸ and vehicle control⁸⁰ compared to controls. AD patients also tended to drive slower,^{64, 78, 80} took longer to complete the driving tests,^{78, 79} had less brake pressure,⁷⁸ and made more judgmental errors (e.g., accidents, collisions).⁸⁰ They failed to stop at traffic lights^{80, 81} and exceeded the speed limit more often than controls.⁸¹ Six out of 18 AD patients crashed during a simulator test.⁸² Cognitive and visual tests were predictive of the number of crashes.^{81–83} Contrary, no differences in number of crashes between AD

patients and controls have also been reported.⁸³ AD patients performed best when single, simple auditory-only driving navigation instructions were used compared to visual plus audio or visual-only instructions.⁸⁴

Drivers with increased cognitive impairments were more likely to be unsafe drivers compared to control subjects.⁷⁴ AD patients who failed an on-road assessment performed worse on neuropsychological tasks compared to AD patients who passed the on-road test.⁶⁴ Decreased performances on cognitive tests measuring speed of processing,^{62, 67, 73, 85} executive functioning,^{56, 74} attention,^{56, 70–72, 76} memory,^{67, 68, 70, 71, 73, 76} set shifting,^{62, 71, 73} visuoconstructional and visuospatial abilities,^{56, 67, 70, 71, 73, 74, 76} visual searching,^{56, 67, 72} and visual tracking⁶⁸ have been associated with worse scores on driving outcome variables and increased error rates in patients with AD. A composite battery of tests was more predictive of driving than individual tests,^{60, 67} and cognitive performance was more predictive of driving ability than AD diagnosis alone.⁸⁵ However, no correlations between neuropsychological outcome measures and on-road evaluations have also been reported.^{58, 77}

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TABLE 3 Study details of included studies on Alzheimer's disease

Authors (year)	Number of participants (N) AD/controls (C)	Age (years) mean $\pm$ SD AD / controls (C)	Driving assessment	Cognitive/motor assessments	MMSE mean $\pm$ SD for AD/controls (C)	Main findings
Barco et al. (2015)	60 AD/32 C	AD: 74.2 $\pm$ 8.5/C: 70.7 $\pm$ 8.1	On-road	AD8, SBT, Clock drawing, TMT, Maze test, UFOV, Visual closure test	-	1. 62% of AD patients failed the on-road test versus 3% of controls 2. AD patients who failed made more errors in driving straight and turning compared to pass group
Bhalla et al. (2007)	84 AD/44 C	AD (safe): 75.3 $\pm$ 7.2/AD (unsafe): 77.3 $\pm$ 5.7/C: 73.6 $\pm$ 9.1	On-road	-	-	1. 19% of AD patients were classified as unsafe drivers versus none of the controls
Bieliauskas et al. (1998)	9 AD/9 C	AD: 70.4 $\pm$ 6.0/C: 71.7 $\pm$ 4.6	On-road	MMSE, Visual search test, Reaction time test, Figure-ground perception test, WCST, SILS	AD: 19.4 $\pm$ 3.1/ C: 27.9 $\pm$ 1.5	1. AD patients made more total driving errors compared to controls 2. Errors in turning were the most frequent
Bixby et al. (2015)	75 AD/no C	76.6 $\pm$ 6.3	On-road	-	-	1. Ratings by clinicians and spouses were poorly associated with driving performance. Ratings by adult children were most related to driving
Brown et al. (2005)	31 AD/24 C	AD: 76.9 $\pm$ 5.4/C: 72.0 $\pm$ 10.3	On-road	-	AD: 25.1 $\pm$ 3.6/ C: 29.1 $\pm$ 1.2	1. AD patients performed worse compared to controls on the road test
Brown et al. (2005)	50 AD/25 C	AD (mild): 73.2 $\pm$ 8.3/AD (very mild): 77.1 $\pm$ 5.3/C: 72.4 $\pm$ 10.2	On-road	-	AD (mild): 21.5 $\pm$ 3.9/ AD (very mild): 24.9 $\pm$ 3.6/C: 29.1 $\pm$ 1.2	1. AD patients had worse overall driving scores compared to controls 2. 9/50 (18%) were classified unsafe by driving instructor versus none of the controls 3. rediction by physician was associated with driving test
Carr et al. (2011)	99 AD/no C	74.2 $\pm$ 9.0	On-road	AD8, Visual acuity, Pelli-Robson, SBT, Clock drawing, TMT, Digit span, UFOV, Visual perceptual test, SMT, Rapid pace walk, 9-hole peg test	-	1. 65% of AD patients failed the on-road test 2. Combination of clinical tests was able to accurately classify safe/unsafe drivers(AD8, CDT, TMT-A, SMT; sensitivity = 67%, specificity = 94%)
Cox et al. (1998)	29 AD/21 C	AD: 72.0 $\pm$ 8.6/C: 70.1 $\pm$ 10.0	Simulator	MMSE	AD: 21.2 $\pm$ 4.6/ C: 28.7 $\pm$ 9.6	1. AD patients more often drove off the road, drove slower, had less brake pressure, and had more difficulty turning left compared to controls

TABLE 3 Study details of included studies on Alzheimer's disease

Authors (year)	Number of participants (N) AD/ controls (C)	Age (years) mean ± SD AD / controls (C)	Driving assessment	Cognitive/motor assessments	MMSE mean ± SD for AD/controls (C)	Main findings
Dawson et al. (2009)	40 AD/115 C	AD: 75.1 ± 7.7/C: 69.4 ± 7.0	On-road	MMSE, CFT, WAIS-R block design, BVRT, TMT, ALVT, JLO, COWA, UFOV, Pelli-Robson, Visual acuity, SFM, Get-up-and-Go	AD: 26.5 ± 2.9/ C: not reported	1. AD patients made more total driving errors compared to controls 2. Lane violations were the most common error
Duchek et al. (1998)	78 AD/58 C	Not reported	On-road	BNT, WMS, BVRT, WFT, WAIS information, block design, digit symbol, Visual search task, Visual monitoring task, UFOV	-	1. Error rate and reaction time during visual search were the best predictors of driving performance
Duchek et al. (2003)	50 AD/58 C	AD (mild): 74.2 ± 7.8/AD (very mild): 73.7 ± 7.0/C: 77.0 ± 8.6	On-road	-	-	1. 41% of mild AD and 14% of very mild AD patients were rated as unsafe drivers. Lane changing and signaling were more impaired with increasing dementia severity
Fitten et al. (1995)	13 AD/24 C	AD: 70.0 ± 7.4/C: 71.8 ± 6.8	On-road	MMSE, Clock drawing, Visual tracking, Vigilance, Divided attention, Short-term memory task	AD: 23.2 ± 2.6/ C: 29.2 ± 0.9	1. AD patients drove slower, had lower driving scores and committed more errors than controls
Fox et al. (1997)	19AD/no C	74.3 ± 6.4	On-road	MMSE, JLO, BVRT, TMT, VFDT, WAIS-R picture completion, block design, digit symbol substitution	21.3 ± 2.8	1. 63% of AD patients failed the on-road test 2. Neuropsychological tests were not associated with total driving score
Frittelli et al. (2009)	20 AD/19 C	AD: 72.0 ± 5.5/C: 68.9 ± 6.3	Simulator	MMSE, Visual reaction task	AD: 22.3 ± 3.8/ C: 29.1 ± 1.5	1. AD patients had worse simulated driving performance compared to controls
Hunt et al. (1997)	65 AD/58 C	AD: 73.7 ± 7.8/C: 76.8 ± 8.6	On-road	-	-	1. 29% of AD patients were classified as unsafe drivers versus 3% of controls

TABLE 3 Study details of included studies on Alzheimer's disease

Authors (year)	Number of participants (N) AD/controls (C)	Age (years) mean $\pm$ SD AD/controls (C)	Driving assessment	Cognitive/motor assessments	MMSE mean $\pm$ SD for AD/controls (C)	Main findings
Lafont et al. (2010)	20 AD/56 C	AD: 73.3 $\pm$ 4.9/C: not reported for total sample	On-road	MMSE, BVRT, Semantic fluency, Cancellation test, DSST, Go/No go test, Stroop, Stop signal, Finger tapping, Reaction time task	AD: 26.4 $\pm$ 2.2/ C: 29.0 $\pm$ 1.1	1. 1/20 (30%) AD patients versus 1/56 (2%) controls were judged unsafe drivers 2. Cognitive functioning (e.g. speed of processing) was associated with an increased risk of unsafe driving (DSST cut-off <25, sensitivity = 75%, specificity = 92%)
Lincoln et al. (2006)	42 AD/33 C	AD: 71.0 $\pm$ 8.9/C: 68.5 $\pm$ 5.7	On-road	MMSE, SDSA, SORT, Stroop, TEA, VOSP, Letters and Cube, BADS, AMIPB, Balloons test	AD (median): 23/ C (median): 29	1. 27% of AD patients were judged as unsafe drivers versus none of the controls 2. Composite battery of cognitive tests was predictive of driving safety (cut-off = 5, sensitivity = 67%, specificity = 100%)
Manning et al. (2014)	75 AD/47 C	AD: 76.7 $\pm$ 6.2/C: 71.9 $\pm$ 7.8	On-road	MMSE, Clock drawing	AD: 25.1 $\pm$ 2.8/ C: 29.5 $\pm$ 0.7	1. AD patients had a higher error rate on the road test compared to controls (54.7% versus 14.9%) 2. Clock drawing had low predictive value of driving performance
Ott et al. (2005)	50 AD/no C	75.7 $\pm$ 6.6	On-road	-	23.7 $\pm$ 4.0	1. 18% of AD patients were classified as unsafe drivers
Ott et al. (2008)	84 AD/128 C	AD: 75.7 $\pm$ 7.0/C: 73.5 $\pm$ 9.1	On-road	-	AD: 24.1 $\pm$ 3.6/ C: 29.1 $\pm$ 1.1	1. 15% of AD patients failed the on-road test versus none of the controls
Ott et al. (2008)	88 AD/45 C	AD: 75.8 $\pm$ 6.9 /C: 73.6 $\pm$ 9.0	On-road	MMSE, Maze task, CFT, TMT, Finger tapping task, HVLT	AD: 24.0 $\pm$ 3.5/ C: 29.1 $\pm$ 1.1	1. 19% of AD patients were unsafe drivers versus 2% of controls 2. Road navigation was associated with maze navigation 3. Composite battery with maze task, HVLT and TMT-A correctly classified 78.2% of all subjects as safe/unsafe

TABLE 3 Study details of included studies on Alzheimer's disease

Authors (year)	Number of participants (N) AD/ controls (C)	Age (years) mean $\pm$ SD AD / controls (C)	Driving assessment	Cognitive/motor assessments	MMSE mean $\pm$ SD for AD/controls (C)	Main findings
Paire-Ficout et al. (2016)	18 AD/18 C	AD: 72.7 $\pm$ 4.8/C: 74.5 $\pm$ 5.4	On-road	MMSE, Verbal fluency, BVRT, Cancellation test, Digit symbol substitution, Go/No go test, Stroop, Stop signal, Finger tapping, Reaction time task, Rotation task	AD: 26.7 $\pm$ 1.9 / C: 29.3 $\pm$ 0.9	1. AD patients showed planning difficulties during left turns and were slower compared to controls
Piersma et al. (2016)	81 AD/45 C	AD: 72.3 $\pm$ 9.4/C: 76.3 $\pm$ 4.7	On-road and Simulator	MMSE, TMT, Clock drawing, Cube drawing, Maze test, ATAVT, Traffic test, Reaction time, Hazard perception test	AD: 23.2 $\pm$ 3.7/ C: 28.8 $\pm$ 1.1	1. 50.6% of AD patients failed the on-road assessment versus 4.4% of controls 2. AD patients had worse lane keeping on the driving simulator compared to controls
Rizzo et al. (1997)	21 AD/18 C	AD: 71.5 $\pm$ 8.5/C: 71.9 $\pm$ 5.5	Simulator	RCFT, TMT, WAIS-R block design, WAIS-R information, WAIS-R digit span, BVRT, COWA, Pelli-Robson, UFOV	-	1. No difference between AD patients and controls in number of crashes 2. Cognitive and visual tests were predictive of crashes

TABLE 3 Study details of included studies on Alzheimer's disease

Authors (year)	Number of participants (N) AD/ controls (C)	Age (years) mean $\pm$ SD AD / controls (C)	Driving assessment	Cognitive/motor assessments	MMSE mean $\pm$ SD for AD/controls (C)	Main findings
Rizzo et al. (2001)	18 AD/12 C	AD: 73.0 $\pm$ 7.0/C: 70.0 $\pm$ 4.7	Simulator	RCFT, BVRT, TMT, COWA, WAIS-R block design, WAIS-R information, WAIS-R digit span, Facial Recognition, Pelli-Robson, UFOV	-	1. Six of 18 AD patients crashed during simulator test versus none of the controls 2. Cognitive tests were predictive of crashes
Stein et al. (2011)	17 AD/63 C	AD (mild): 71.2 $\pm$ 8.7/AD (very mild): 74.3 $\pm$ 12.2/C: 73.5 $\pm$ 6.9	Simulator	-	-	1. AD patients had impaired vehicle control, difficulties lane keeping, drove slower and made more judgmental errors compared to controls
Uc et al. (2004)	32 AD/136 C	AD: 75.9 $\pm$ 6.2/C: 64.0 $\pm$ 11.4	On-road	MMSE, COGSTAT, AVLT, BVRT, RCFT, JLO, WAIS-R block design, TMT part B, COWA, UFOV, SFM, Visual acuity, Contrast sensitivity	AD: 26.3 $\pm$ 2.9/ C: not reported	1. AD patients performed worse on a route following task compared to controls 2. Safety errors could be predicted by verbal memory, attention and visuospatial abilities
Uc et al. (2005)	33 AD/137 C	AD: 76.1 $\pm$ 6.3/C: 64.3 $\pm$ 11.4	On-road	MMSE, COGSTAT, AVLT, BVRT, RCFT, JLO, WAIS-R block design, TMT part B, COWA, UFOV, SFM, Visual acuity, Contrast sensitivity	AD: 26.1 $\pm$ 3.0/ C: not reported	1. AD patients identified fewer landmark and traffic signs compared to controls and committed more safety errors

TABLE 3 Study details of included studies on Alzheimer's disease

Authors (year)	Number of participants (N) AD/ controls (C)	Age (years) mean $\pm$ SD AD/ controls (C)	Driving assessment	Cognitive/motor assessments	MMSE mean $\pm$ SD for AD/controls (C)	Main findings
Uc et al. (2006)	61 AD/115 C	AD: 73.5 $\pm$ 8.5/C: 69.4 $\pm$ 6.7	Simulator	AVLT, RCFT, WAIS-R block design, BVRT, JLO, TMT part B, COWA, COGSTAT, UFOV, Contrast sensitivity, Visual acuity	AD: 25.6 $\pm$ 3.8/ C: not reported	1. No differences in crash rates between AD patients and controls 2. AD patients slowed down more abruptly compared to controls
Yamin et al. (2016)	20 AD/21 C	AD: 78.5 $\pm$ 7.2/C: 77.0 $\pm$ 5.9	Simulator	MMSE, DRS-2, VOSP, TEA, UFOV	AD: 24.0 $\pm$ 4.9/ C: 29.0 $\pm$ 1.3	1. AD patients performed poorer on almost all driving outcome measures compared to controls
Yi et al. (2015)	28 AD/no C	65.6 $\pm$ not reported	Simulator	MMSE, DPT, TMT part B, RFMT	24.1 $\pm$ 2.4	1. AD patients performed best using single, simple auditory driving navigation instructions

AD = Alzheimer's Disease; AD8 = Assessing Dementia-8 screening interview; ADL = Activities of Daily Living; AMIPB = Adult Memory and Information Processing Battery; ATAVT = Adaptive Tachistoscopic Traffic Perception Test; AVLT = Auditory Verbal Learning Test; BADS = Behavioral Assessment of the Dysexecutive Syndrome; BNT = Boston Naming Test; BVRT = Benton Visual Retention Test; C = Controls; CDR = Clinical Dementia Rating scale; CFT = Complex Figure Test; COGSTAT = Composite Measure of Cognitive Impairment; COWA = Controlled Oral Word Association; DPT = Benton Visual Retention Test; DRS = Dementia Rating Scale; DSST = Digit Symbol Substitution Test; HVLIT = Hopkins Verbal Learning Test; JLO = Judgement of Line Orientation test; MMSE = Mini-Mental State Examination; SBT = Short Blessed Test; SDSA = Stroke Drivers Screening Assessment; SFM = Structure from Motion; SILS = Shipley Institute of Living Scale; SMT = Snellgrove Maze Test; SORT = Salford Objective Recognition Test; TEA = Test of Everyday Attention; TMT = Trail Making Test; UFOV = Useful Field of View; VOSP = Visual Object and Space Perception battery; WAIS-III = Wechsler Adult Intelligence Scale-III; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test; WFT = Word Fluency Test; WMS = Wechsler Memory Scale

Self-assessment of driving performances

In addition to differences in driving performances, there are also differences reported in the evaluation of driving ability performed by patients, caregivers, and physicians. One study reported that PD patients rated their own driving performances lower than controls.⁵⁰ Contrary results showed that about 20% of the PD and AD patients misjudged their own driving ability.^{3, 43} In addition, the rating performed by a neurologist ($M = 8.0$) was more optimistic compared to the rating performed by a driving instructor ($M = 5.1$) and psychologist ($M = 5.7$).³ Spouses tended to overestimate the driving ability of AD patients.⁸⁶ Ratings performed by an adult child were more related to driving outcome variables than ratings performed by spouses.⁸⁶ Self-ratings of driving ability performed by AD patients and ratings by spouses were significantly higher than ratings by an independent evaluator and physician.^{65, 87} Ratings by a clinician were poorly associated with an on-road driving test, but not with naturalistic driving.⁸⁶ However, these clinician ratings were still more associated with driving performance compared to the self-evaluation by patients and the evaluation by spouses.⁶⁵ Caregivers did acknowledge general problems with driving, but still rated the AD patients driving competence significantly higher than an independent rater.⁸⁷

Driving simulator use

Since on-road driving assessments in patients with neurodegenerative disorders might be unsafe, an alternative is to evaluate driving competence with a simulator. Driving simulators provide the opportunity to present challenging situations and events in a standardized setting, with a high reproducibility compared to on-road driving assessments where situations cannot be manipulated.⁸⁸ Simulators are also used to train novice drivers before they start their on-road driving lessons.⁸⁹ Results of a concurrent and discriminant validity study comparing an on-road driving assessment with driving simulator tasks revealed that a driving simulator is a valid measure of driving performance for research purposes.⁹⁰ The driving simulator outcomes were able to discriminate between drivers with different levels of experience. In a study with elderly drivers, over 65% of the variability in the on-road assessments could be explained by driving simulator outcomes.⁹¹ Adding a driving simulator increased the total variance explained by a potential screening battery to 60 and 94%,^{31, 43} suggesting that a driving simulator might be a useful screening tool to evaluate driving fitness. Studies that described the use of simulators for rehabilitation and training purposes in various disorders showed promising results, with more patients passing an on-road assessment after training with a simulator.⁹²

The lower ecological validity of a simulator, however, could be a disadvantage, because participants may prefer driving a real vehicle. It is also important to keep in mind that a reduction of driving performance measured with a simulator might reflect the adaptation to the simulator itself and not actual driving ability. Therefore, it is necessary to further investigate the differences between disease groups and healthy individuals to minimize the effects of simulator use. In addition, the relationship between on-road performances and simulator driving should be further explored to determine whether simulator outcome measures are, indeed, consistent with on-road driving performance.

A common issue in simulator research is the existence of simulator sickness, which is comparable to motion sickness.^{93, 94} It includes dizziness, nausea, vomiting, and sweating. The symptoms of simulator sickness are typically less severe than motion sickness and tend to decrease with multiple exposure and time.^{94, 95} Dropouts in simulator studies have been related to simulator sickness, with up to one-third of the participants experiencing signs of simulator sickness.^{64, 84, 91} The duration and configuration of driving scenario influence this dropout rate.⁹⁶ For example, scenarios including more turns and sudden stops increase the risk for simulator sickness. Older age, female gender, and prior history of motion sickness have also been associated with higher susceptibility of experiencing simulator sickness.^{97, 98} However, dropouts are not necessarily those subjects with the poorest performances.^{98, 99} Several theories have been proposed to explain the occurrence of simulator sickness.⁹⁴ A conflict between structures within the sensory and vestibular systems has been the most widely excepted theory.^{94, 100} When using a simulator to evaluate driving competence, this side-effect should be taken into consideration by excluding patients who experience simulator sickness or by screening beforehand. However, this might result in selection bias that should be accounted for. For more information regarding the topic of simulator sickness, we refer to the systematic review by Classen et al. (2011).⁹⁷

TABLE 4 Types of driving errors categorized by group

Error level	Type of driving error	HD	PD	AD
Tactical	Lane changing	X	X	X
	Speed adaptations	X	X	X
	Unsteady car speed	NR	X	X
	Yielding at intersections	NR	X	NR
	Keeping distance	X	X	NR
	Checking blind spot	NR	X	X
	Longer reaction times	X	X	X
Operational	Road positioning	X	X	X
	Lane maintenance	X	X	X
	Signaling	NR	X	X
	Steering	NR	X	NR
	Incorrect turning	X	X	X
Strategic	Difficulties with road rules	X	X	X
	Inattention while driving	NR	NR	X
	Fewer driving trips	NR	X	X
	Driving less distance	NR	X	NR
	Driving shorter durations	NR	X	X
	Less night time driving	NR	X	NR

Types of driving errors are based on the model by Michon et al.¹⁰

X = driving error is reported for this patient group;

NR = not reported in reviewed literature; AD = Alzheimer's disease; HD =Huntington's disease;

PD = Parkinson's disease

DISCUSSION

The majority of studies investigated driving competence of patients with a neurodegenerative disorder with on-road driving assessments, and this is considered the gold standard. Results showed worse driving performances in patients compared to controls, although there is a large variability in types of driving errors. Most errors are committed in lane changing, lane maintenance, lower reaction times, and larger variabilities in speed. Inconsistencies in results might be attributable to different methods and outcome measures. In addition, there is a large heterogeneity in the patient population and sample sizes (range $N = 16\text{--}266$). Specific types of driving errors are often not investigated and only global pass/fail ratings are reported. For research purposes, it is important to determine which types of driving errors are most common and if these errors also pose a safety hazard for the patient and environment. Some errors might be manageable and do not necessarily mean that the patient should cease driving. For example, errors on the strategic level, such as difficulties with planning a route, are less dangerous and more manageable than errors concerning reacting to other road users and vehicle control. Adaptations to the vehicle might also increase the time that a patient is still able to drive safely. PD patients were better drivers when they used an automatic car compared to a manually operated car.³⁴ Driving simulators have the potential to assist in investigating driving competence, but there are still limited results available. Additionally, there is the phenomenon of simulator sickness that should be considered when using a simulator.⁹⁷ There is also variability in types of driving simulators (i.e., manufacturers) and scenarios that are used. Driving simulator studies often use motorway scenarios, because they are less susceptible to simulator sickness. These scenarios are useful to investigate reaction times and speed adaptations, but might not properly reflect the driving ability on the road in an environment with more distractors. Driving scenarios including rural or urban areas, with more traffic, different speeding zones, and sudden events, might be more difficult due to the higher demand on cognitive functioning. The utility of a driving simulator to predict on-road driving behavior in both research and clinical practice has to be further explored.

In most studies, more than half of the patients with a neurodegenerative disorder were classified as safe drivers. This suggests that a majority of the patients can still drive safely. Therefore, professionals should not base their recommendations about potential driving cessation solely on the presence of a clinical diagnosis.⁸⁵ Individual evaluations are important and changes in driving performance should be monitored

regularly, preferable every year. Due to the progressive nature of neurodegenerative disorders, formal retesting of driving skills is recommended even if the driver license has been renewed for an extended period of time. Although this is not a review on driving competence in the normal elderly population, the influence of aging should be taken into consideration. However, the mean ages in the reviewed studies were relatively young (HD = 43.1 years, PD = 66.4 years, AD = 74.0 years), and most analyses were corrected for the effects of age. This suggests that older age alone is not a criterion to continue or cease driving.

Overall, the findings reported in the reviewed studies suggest that cognitive functioning is associated with safely operating a vehicle. The current literature suggests some consensus on which cognitive domains are associated with decreased driving competence. Diminished functioning in the visuoconstructional, visuospatial, executive, and attentional domains has consistently been associated with impaired driving. Specific neuropsychological assessments are partially predictive of driving outcomes, but there is currently no valid screening battery that can accurately be used in the clinical practice. There are limited cut-off scores available, so it is still difficult to translate performances on neuropsychological tests to clinical recommendations. The most promising screening batteries, with sensitivity and specificity ranging between 61% and 94%, included the Trail Making Test (TMT), Useful Field of View (UFOV), Pelli-Robson, and Symbol Digit Modalities Test (SDMT). Baseline and follow-up assessments are necessary to further validate the usefulness of these tests. Recently, it has been reported that a combination of assessments (i.e., clinical interviews, neuropsychological assessments, and driving simulator outcomes) best predicted fitness to drive in patients with AD.⁶⁴ Furthermore, composite neuropsychological test batteries have been more predictive of driving performances than separate tests.^{26, 31, 32, 40, 50, 60, 67} This suggests that a composite battery including multiple cognitive domains might be a reliable predictor of driving performance. However, this approach should be further validated before the practical application of such a screening battery can be determined.

Our review showed that there is still a gap in the current driving literature. Only a limited amount of longitudinal studies have been performed in AD and PD but none in HD. Follow-up is important for early intervention and to monitor changes over time. Moreover, there is a large discrepancy in the amount of studies available regarding driving in HD compared to PD and AD. Since the etiology of HD is known, this disorder could potentially be a good prototype to investigate changes in driving competency and the association with cognitive decline. Furthermore, there is the opportunity to investigate both symptomatic and asymptomatic gene carriers in

an attempt to detect at which point in the disease driving-related issues become apparent. This is particularly useful for the clinical practice and to establish guidelines for patients, families, and caregivers. An important factor differentiating HD from PD and AD is the age at onset. HD typically occurs during midlife with a mean age at onset between 30 and 50 years, while signs and symptoms of PD and AD are most often developed later in life.^{13, 101, 102} With this relatively young age at onset of HD, most patients still rely on their car for employment and social activities. Therefore, discussing driving ability is important at an early stage of the disease. Furthermore, no studies have been performed regarding the association between psychiatric symptoms (e.g., irritability and apathy) and driving. These are important signs of HD that can already be present at early stages of the disease and might influence driving behavior.¹⁵

Both HD and PD can be distinguished from AD by the presence of motor disturbances, but the nature of cognitive deficits also differs. The cognitive impairments observed in AD can be considered a cortical dementia, whereas HD and PD are mainly characterized by subcortical changes.^{103, 104} In HD and PD, problems in the executive domain are most commonly observed, while in AD, memory impairments are more pronounced.^{105, 106} This different expression of cognitive profiles might also affect driving in distinctive ways. In addition, specific subtypes of motor signs in PD (i.e. tremor versus dyskinesia) potentially influence the ability to operate a car. Differences between these specific subtypes in fitness to drive have not been studied to date. However, it has been reported that patients with postural instability and gait disorder PD subtype failed an on-road driving assessment more often than patients with the tremor dominant subtype of PD (46% versus 7%).³² Different motor subtypes can also be distinguished in HD (chorea versus hypokinesia-rigidity) and these subtypes have been associated with different cognitive profiles.^{107, 108} These differences in symptomatology should be further investigated in relation with driving performance to increase knowledge about important individual differences.

An important issue to keep in mind is the limited insight of patients with neurodegenerative disorders into their own disabilities. We believe that it is important to discuss driving in the outpatient clinic in the presence of spouses or relatives to ascertain a more objective point of view. However, some partners might find it difficult to express their concerns with the patient there. The role of the physicians is important to start the discussion at the right time and to provide the necessary referrals. On the same note, it is interesting to further explore the patient's perspective regarding driving cessation, since some studies did report that there are

patients who modify their driving behavior.^{109, 110}

In general, there are numerous difficulties in performing driving research in neurodegenerative disorders that should be considered when developing study protocols. An important issue is the presence of potential selection bias. Patients might fear that their license will be revoked and, therefore, do not want to participate in driving-related studies.¹¹¹ Patients who are less confident about their driving ability might be less willing to participate. In addition, there are safety concerns when evaluating driving performances. Other issues are the relatively small sample sizes, lack of control groups, and differences in methodology.

CONCLUSIONS

Based on the current available literature, it is not possible to draw one final conclusion if and when patients with neurodegenerative disorders should be restricted in their driving. Driving requires optimal cognitive functioning and lower performances on neuropsychological assessments might serve as a first indicator of driving incompetence. However, there is currently no validated screening battery available. Some patients with neurodegenerative disorders are still able to drive safely, so a restriction of driving solely based on a clinical diagnosis is unwarranted. None of the studies to date have resulted in practical guidelines that can be implemented in clinical settings. We are of the opinion that formal retesting should be mandatory due to the progressive nature of neurodegenerative diseases. Longitudinal studies are, therefore, necessary to determine when driving-related issues become apparent and to investigate the progression rate of driving incompetence. Future studies focusing on establishing specific evidence-based guidelines that take differences between disorders into consideration are needed. The lack of patient insight into their own driving competence should be further explored and emphasizes the need to quantify driving status.

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Altered driving performance of symptomatic Huntington's disease gene carriers in simulated road conditions

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ABSTRACT

Objective

In clinical practice, patients with Huntington's disease (HD) often decide to solely drive in their own familiar neighborhoods and not on a motorway or in an unknown area. The aim of the study was to identify differences in driving performances between HD gene carriers and healthy individuals in simulated urban and motorway environments.

Methods

This cross-sectional study included 87 participants (28 premanifest HD, 30 manifest HD, 29 controls). All participants were active drivers and were assessed using a driving simulator, a driving history questionnaire, and the Unified Huntington's Disease Rating Scale. The driving simulator session included urban and motorway scenarios. Analysis of Variance and Kruskal-Wallis tests were used to compare urban and motorway driving across all three groups.

Results

Manifest HD drove slower compared to controls and premanifest HD when speed limits increased (80 and 100 km/h) and they had a less steady speed compared to premanifest HD on the motorway and in a 30 km/h zone. Manifest HD also had a larger standard deviation of the lateral position (i.e., more weaving of the car/less vehicle control) compared to controls and premanifest HD on the motorway.

Conclusions

Manifest HD drive more cautious in a driving simulator when speed limits increase compared to premanifest HD and controls and they have less vehicle control on the motorway. The driving simulator parameters are able to discriminate between manifest HD and healthy individuals, so a driving simulator seems a feasible tool to use when investigating changes in driving in manifest HD.

INTRODUCTION

The ability to drive a car is important for practical reasons and adds to an individual's independence. As the disease progresses, patients with Huntington's disease (HD) become increasingly dependent in their daily life activities, and, for most patients, it can be difficult to quit driving.¹ HD is an inherited neurodegenerative disorder characterized by a triad of symptoms including motor disturbances, cognitive dysfunction and psychiatric symptoms.² Disease onset typically occurs during mid-life (mean age between 30 and 50 years), which is a period where carriers of the HD gene are fully participating in work and social life.^{2,3} The clinical hallmark of HD is the presence of chorea, which are unwanted, involuntary jerky movements of different body parts.² Cognitive impairments, such as executive dysfunction and slower psychomotor speed, are already present in early stages of HD and can compromise the ability to drive safely.^{4,5} Due to the heterogeneity and individual variability in symptoms it can be difficult to determine how HD affects driving. However, the fact that HD is a genetic disorder with a known etiology provides an opportunity to investigate driving impairments in gene carriers without clinical symptoms and, thus, attempt to assess which and when changes in driving first occur.

To date, only four studies investigated driving competence in HD using either on-road or simulated driving assessments.⁶⁻¹⁰ One early study using a driving simulator showed that patients with HD were more likely to be involved in accidents compared to controls (58% versus 11%, respectively).⁶ They were also less accurate, had longer reaction times, and committed more overall errors compared to healthy controls during simulated driving.⁶ Still, 72% of the HD patients in this study continued driving after disease onset.⁶ Studies using on-road driving assessments showed that half of the patients with early stage HD that still drove failed the driving assessment compared to none of the age-matched controls.^{7,8} In particular, errors in lane positioning, speed adaptations, keeping distance, turning left, and lane changing were observed.⁸ General functional capacity was lower in patients who failed the on-road test compared to those who passed. Based on their results, the authors also suggested that driving competence might already be affected in HD gene carriers without a clinical diagnosis, because two patients with maximum functional capacity scores also failed the on-road test.⁸ This emphasizes the need to evaluate driving skills at an early stage of the disease.

Poor performance on cognitive assessments and decreased motor functioning have been associated with impaired driving in patients with HD.⁷⁻⁹ A recent study showed that specific assessments are necessary when evaluating driving competence

in different types of dementia.¹¹ Patients with HD who failed the on-road driving assessment also performed worse on driving simulator evaluations.⁷ Using a driving simulator has the advantage that different driving situations (e.g., low or high traffic density) can be assessed in a safe and standardized environment. Between 39% and 79% of the variability in on-road tests can be explained by simulator assessments, suggesting that a simulator provides information about real-world driving skills.^{12–14} Currently, no study has focused on driving performance in the early asymptomatic stage of HD. Different road conditions, such as urban and motorway, have also not been studied in HD; in clinical practice, patients often decide to only drive in their own familiar neighborhoods and not on the motorway anymore. The aim of our study was to compare driving patterns in simulated urban and motorway environments between patients in different HD stages and healthy individuals. Further, we wanted to investigate the feasibility of using a driving simulator in HD research.

METHODS

Participants

Participants were recruited via the outpatient clinic of the Leiden University Medical Center and per magazine advertisement from June 2016 through July 2017. All participants were at least 18 years of age, possessed a valid Dutch driver's license, and drove at least 300 kilometers in the previous 12 months before inclusion. All HD participants had a confirmed Cytosine-Adenine-Guanine (CAG) expansion of ≥ 36 in the *HTT* gene. Exclusion criteria were major comorbidities unrelated to HD (e.g., other neurological disorder, ophthalmic disorders), drug use in the past 4 weeks prior to the study visit, alcohol abuse, and current participation in intervention trials. Alcohol use was not allowed 24 hours prior to the study visit. The study was approved by the local ethics committee of the Leiden University Medical Center and all participants signed written informed consent.

Demographic and clinical data

Demographic and clinical data were recorded for gender, date of birth, age, medical history, current medication use, and number of CAG repeats (HD gene carriers only). A questionnaire regarding the participant's driving history was administered to record data on driving experience. This included questions on type of driver's license (i.e., car, motor, truck, other), year the participant obtained his or her car license, average number of kilometers driven per year, average number of car use per week,

number of driving tickets/accidents in the past 12 months, whether the participant restricted him- or herself in driving (e.g., only driving in the own neighborhood), whether the participant's partner restricted his or her driving, and whether the participant considered quitting driving. Participants were also asked to grade their own driving ability, with 0 being the lowest and 10 being the highest score. The Unified Huntington's Disease Rating Scale (UHDRS) was administered to assess motor functioning (TMS) and functional capacity (TFC).¹⁵ The UHDRS-TMS reflects motor impairments that are common in HD, including eye movements/oculomotor function, chorea, dystonia, tongue protrusion, gait, and bradykinesia. The score ranges from 0 to 124, with higher scores indicating increased motor dysfunction. The TFC was used to measure the amount of functional disability in daily life. The TFC includes the capacity to work, ability to manage finances, and ability to carry out domestic chores. The score ranges from 0 to 13, with lower scores reflecting more impairments. The TFC was also used to categorize the manifest HD into disease stages (1 – 5).¹⁶ Stage 1 represents the earliest symptomatic stage of HD and stage 5 represents the last stage.

Driving simulator

The GreenDino DriveMaster LT driving simulator manufactured by GreenDino B.V. from Wageningen, the Netherlands, was used to assess driving capacity. The simulator consisted of three 24-inch flat-panel monitors; a steering wheel; gas, brake, and clutch pedals; and gearshifts (Figure 1). The dashboard, side mirrors, and rear view mirror were displayed on the screens.

The total duration of the driving session was approximately 45 minutes. Participants started with a practice session for eight minutes to familiarize themselves with operating the simulator. Then, the simulator assessment started. The driving session was administered in a standardized sequence, with an urban scenario followed by a motorway scenario. Participants drove each scenario once. Navigation instructions were provided both verbally and on the simulator screen. Participants were asked to obey the general Dutch traffic rules and instructed to drive as they normally would. The first part of the driving session was driven in the urban environment, which included different speed zones (i.e., 30, 50 and 80 km/h). Additionally, other traffic was added to reflect distractions that also occur during regular urban driving, such as other cars and bicycles. A pedestrian crossing and emergency stop were included to measure reaction time. The sequence of the events was standardized for all participants. The second part of the driving session was a motorway scenario and had a duration of approximately 30 minutes, with a maximum allowed speed of 100

km/h. Participants were allowed to overtake other vehicles. In the final 10 minutes of the motorway scenario, driving lanes were closed by showing a red cross above the particular lane. Participants then had to switch lanes.

If the participants were feeling any discomfort during the driving session they were instructed to report this to the investigators. Participants were advised to take a short break or abort the simulator assessment if their symptoms continued.

Outcome measures for the urban scenario were mean speed per speed zone, speed variability per speed zone, distance keeping in meters, reaction time to an emergency stop (seconds), and reaction time to a pedestrian crossing (seconds). The outcome measures for the motorway scenario were mean speed, speed variability, distance keeping in meters, reaction time to lane closures (seconds), and standard deviation of the lateral position (SDLP). Crashes with static objects or other road users were counted in both scenarios.

Statistical analyses

Differences between groups in demographic and clinical data were analyzed using Analysis of Variance (ANOVA), chi-square test, and Kruskal-Wallis test for continuous, categorical and skewed data respectively. Kolmogorov-Smirnov test was used to screen simulator outcome parameters for normality. ANOVA and Kruskal-Wallis tests were conducted to compare driving simulator performances in the two road conditions (urban and motorway) among the three groups of premanifest HD, manifest HD, and controls. If a significant main effect of group was observed, a generalized linear model was used to further quantify the results. Differences between groups in total number of crashes were analyzed using chi-square tests. Exploratory correlational analysis, using Pearson's r or Spearman's ρ when applicable, was performed in HD gene carriers between age, CAG repeat length, UHDRS-TMS, UHDRS-TFC and the driving simulator measures. Data analyses were performed using SPSS version 23.0. Statistical significant threshold was set at $p < .05$.

FIGURE 1 Driving simulator and example of the scenarios



A) Driving Simulator



B) Urban scenario



C) Motorway scenario

Note: Examples of the scenarios correspond with what is displayed on the middle screen.

RESULTS

Demographic and clinical characteristics

A total of 87 participants (58 HD gene carriers and 29 controls) were included in the study. The UHDRS-TMS was used to divide the HD gene carriers in manifest HD (TMS >5) and premanifest HD (TMS ≤5), resulting in 28 premanifest and 30 manifest HD participants. A TMS of 5 or less indicates no substantial motor signs related to HD.¹⁷ All manifest HD were in the early stages of the disease (1 – 2), except for one participant (disease stage 3).

Three participants could not perform any of the driving simulator assessments due to significant symptoms of simulator sickness during the practice session, so no data were available for the driving simulator analyses. This resulted in a final dataset of 84 participants. An additional 12 participants (14.3%) experienced symptoms of simulator sickness to some degree during the assessments. This resulted in missing data on certain outcome measures, because participants were not able to finish the entire simulator session. All available driving simulator data were included in the analyses, following an intention-to-treat approach. An overview of missing data per outcome measure is provided in Table A1.

There was a significant difference between the groups in age, UHDRS-TMS, UHDRS-TFC, years of driving experience, average number of kilometers driven per year, total number of driving restrictions, and total number of driving restrictions by partner (Table 1). There were no significant differences in gender, CAG repeat length, car use per week, car type (i.e., manual or automated), and total number of fines and accidents. Premanifest HD graded their own driving ability with a mean score of 7.5, manifest HD with a mean of 7.1, and controls with a mean of 7.8. Sixteen family members or spouses also graded the average driving performance of the manifest HD participants, with a mean of 6.4. This grade did not significantly differ from the grade the corresponding participant graded their own driving, $t(15) = 0.92$, $p = 0.306$. Thirty-eight percent of the manifest HD and 14% of the premanifest HD reported restrictions in their driving. Self-reported driving restrictions were, for example, not driving long distances, only driving in the own neighborhoods, not driving with children in the car, and decreased nighttime driving. Only one manifest HD participant had considered quitting driving before the study visit.

TABLE 1 Demographic and clinical characteristics.^a

Parameter	Controls	Premanifest HD	Manifest HD	p-value
N	29	28	30	
Age	48.7 ± 11.0	38.4 ± 8.3	52.8 ± 10.5	<.001
Gender m/f (%m)	11/18 (37.9%)	15/13 (53.6%)	16/14 (53.3%)	.394
CAG repeat length	NA	41.6 ± 2.4	42.5 ± 2.5	.204
UHDRS TMS	1.8 ± 1.4	2.5 ± 1.3	22.1 ± 12.6	<.001
UHDRS TFC	13.0 (11 – 13)	13.0 (8 – 13)	10.0 (5 – 13)	<.001
Disease stage	NA	NA	2.0 (1 – 3)	NA
Driving experience, years	27.6 ± 11.7 ⁽⁻¹⁾	18.1 ± 9.3	32.5 ± 11.4	<.001
Car use days/week	4 (0 – 7)	5 (0 – 7)	3 (1 – 7) ⁽⁻¹⁾	.855
Kilometers driven/year ^b	1 (1 – 3) ⁽⁻¹⁾	2 (1 – 4) ⁽⁻¹⁾	2 (1 – 4) ⁽⁻²⁾	.009
Car type manual/automated	23 / 6	26 / 2	27 / 3	.265
Driving grade (0 – 10)	7.8 ± 0.8	7.5 ± 0.8	7.1 ± 0.9	.008
Number of fines (12 months): yes (%)	7 (24%)	6 (21%)	6 (21%) ⁽⁻¹⁾	.946
Number of accidents (12 months): yes (%)	2 (7%)	4 (14%)	5 (17%) ⁽⁻¹⁾	.478
Self-restrictions: yes (%)	2 (7%)	4 (14%)	11 (38%) ⁽⁻¹⁾	.008
Partner-restrictions: yes (%)	2 (7%)	0 (0%)	9 (31%) ⁽⁻¹⁾	.001

^a Data are mean ± SD for age, CAG repeat length, UHDRS-TMS, and driving experience. Median (range) are reported for UHDRS-TFC, disease stage, car use, and kilometers driven. Analysis of Variance was performed for age, UHDRS-TMS, CAG repeat length, driving grade, and driving experience. Chi-square test was used for gender, car type, number of fines, number of accidents, self-restrictions, and partner-restrictions. Kruskal-Wallis test was used for UHDRS TFC, car use, and kilometers driven. (-n) indicates total number of missing values per parameter/per group.

^b 1 = more than 10.000 km; 2 = between 5000 and 10.000 km; 3 = between 1000 and 5000 km; 4 = less than 1000 km

Significant p- values (p <.05) are in bold.

Urban scenario

One control participant, one premanifest HD, and 6 manifest HD crashed during the urban scenario ($\chi^2 = 6.91$, $p = 0.032$). Significant main group differences were observed for mean speed in the 80 km/h zone and speed variability in the 30 km/h zone (Table 2). Manifest HD drove significantly slower in the 80 km/h zone compared to both controls ($\beta = -4.78$, $p = 0.005$) and premanifest HD ($\beta = -4.94$; $p = 0.004$). In addition, manifest HD had more variability in their speed while driving in the 30 km/h zone compared to premanifest HD ($\beta = 0.80$, $p = 0.002$; Table 3).

There were no other significant differences between the groups in the urban road condition (Table 2). The strongest correlation observed in the urban scenario was between the UHDRS-TMS and speed variability in the 50 km/h zone ($r = 0.36$, $p < 0.001$). All significant correlations are reported in Table A2.

TABLE 2 Group differences in driving performance in the urban scenario.^a

Parameter	Controls	Premanifest HD	Manifest HD	<i>p-value</i>
Speed 30 km/h zone	29.3 ± 3.0	30.1 ± 3.2	29.7 ± 3.3	.628 ^b
Speed 50 km/h zone	47.7 ± 3.6	47.3 ± 3.7	47.1 ± 5.1	.851 ^b
Speed 80 km/h zone	66.7 (63.5 – 69.5)	67.2 (64.3 – 70.7)	63.0 (54.5 – 69.5)	.049^c
Speed variability (30 km/h)	3.4 (3.0 – 3.9)	3.2 (2.8 – 3.5)	3.7 (3.0 – 4.9)	.039^c
Speed variability (50 km/h)	5.5 ± 1.0	5.0 ± 1.2	5.8 ± 1.7	.079 ^b
Speed variability (80 km/h)	9.5 (8.0 – 10.8)	9.3 (7.7 – 10.9)	7.9 (4.2 – 10.5)	.086 ^c
Distance keeping (meters)	54.5 (45.4 – 69.3)	45.0 (23.8 – 66.1)	57.0 (38.4 – 86.7)	.136 ^c
Reaction time – emergency stop (seconds)	1.6 (1.4 – 1.9)	1.7 (1.5 – 2.0)	1.7 (1.5 – 2.0)	.441 ^c
Reaction time – pedestrian crossing (seconds)	1.7 ± 0.8	1.9 ± 0.5	1.7 ± 0.8	.404 ^b

^a Data are mean ± SD or median (interquartile range) when appropriate.

^b ANOVA.

^c Kruskal-Wallis test.

Statistically significant *p*-values ($p < .05$) are in bold.

Motorway scenario

Two manifest HD participants crashed on the motorway compared to none of the controls and premanifest HD. Mean speed, variability in speed, and SDLP were significantly different between the three groups (Table 4). Manifest HD drove significantly slower on the motorway than controls ($\beta = -2.75$, $p = 0.016$) and premanifest HD ($\beta = -2.32$, $p = 0.047$; Table 3). They also had a larger variability in their speed compared to premanifest HD ($\beta = 2.35$, $p = 0.007$). The SDLP of the manifest HD was significantly larger compared to both controls ($\beta = 6.68$, $p = 0.034$) and premanifest HD ($\beta = 10.47$, $p = 0.001$).

The UHDRS-TMS had a moderate correlation with speed variability ($p = 0.47$, $p < 0.01$) and the SDLP ($r = 0.59$, $p < 0.01$), which were the strongest correlations observed in the motorway scenario (Table A2). All significant correlations are reported in Table A2.

Because a relationship between speed and speed variability on the motorway has also been reported in previous studies¹⁸, we performed additional correlation analysis between these simulator parameters. Correlation analysis showed that, in our study, mean speed and SD of speed were negatively related ($r = -0.31$, $p = 0.005$), meaning that a lower speed is related with higher variability in speed. This correlation was stronger ($r = -0.53$, $p = 0.006$) in manifest HD only.

TABLE 3 Differences between the groups in the urban and motorway scenario according to generalized linear models.

Parameter	Premanifest HD vs. Controls		Manifest HD vs. Controls		Manifest HD vs. Premanifest HD	
	β (95% confidence interval)	<i>p</i> -value	β (95% confidence interval)	<i>p</i> -value	β (95% confidence interval)	<i>p</i> -value
Speed 80 km/h	0.16 (-3.18; 3.50)	.925	-4.78 (-8.12; -1.44)	.005	-4.94 (-8.31; -1.57)	.004
Speed variability 30 km/h	-0.25 (-0.76; 0.26)	.337	0.55 (0.04; 1.06)	.035	0.80 (0.28; 1.32)	.002
Speed 100 km/h	-0.43 (-2.63; 1.78)	.705	-2.75 (-4.50; -0.52)	.016	-2.32 (-4.61; -0.03)	.047
Speed variability 100 km/h	-1.39 (-3.03; 0.26)	.100	0.97 (-0.70; 2.63)	.255	2.35 (0.64; 4.07)	.007
SDLP	-3.78 (-9.89; 2.32)	.225	6.68 (0.51; 12.9)	.034	10.47 (4.13; 16.81)	.001

Statistically significant *P* values (*P* < .05) are in bold.

TABLE 4 Group differences in driving performance in the motorway scenario.^a

Parameter	Controls	Premanifest HD	Manifest HD	<i>p</i> -value
Speed (100 km/h)	99.2 ± 4.3	98.8 ± 2.7	96.3 ± 5.1	.031^b
Speed variability	4.5 (3.4 – 6.3)	3.7 (2.6 – 5.0)	4.7 (3.8 – 7.7)	.028^c
Distance keeping (meters)	40.6 ± 7.4	44.0 ± 8.9	41.0 ± 10.5	.342 ^b
Reaction time (seconds) ^d	-14.1 ± 11.1	-15.2 ± 10.9	-8.3 ± 12.3	.121 ^b
SDLP	35.9 ± 7.3	32.1 ± 6.8	42.6 ± 17.9	.008^b

^a Data are mean ± SD or median (interquartile range) when appropriate.

^b ANOVA.

^c Kruskal-Wallis test.

^d More negative indicates earlier response to lane closure.

Statistically significant *P* values (*P* < .05) are in bold.

DISCUSSION

The current study showed that manifest HD negatively affects driving performance in a simulated environment. The driving simulator outcome measures were able to differentiate between manifest HD and healthy individuals and between premanifest and manifest HD, despite the fact that all participants were active drivers. To our knowledge, this is the first study in HD to differentiate between driving in urban and motorway environments and to compare both road conditions. In clinical practice, patients with HD often decide to only drive in their own familiar urban neighborhoods and not on the motorway or highway due to the higher speed. Our results seem to confirm this suggestion, because we mainly observed differences between the groups in road conditions with higher speed limits (i.e., 80 km/h and 100 km/h). This finding suggests that patients with HD might be more cautious when driving in higher speed zones, resulting in lowering their speed as compensatory behavior. Lowering speed and increased weaving of the car are adaptations and errors on the tactical and operational levels.¹⁹ These levels include errors in operating the car (e.g., vehicle control, lane positioning) and adapting to traffic situations (e.g., speed adjustments, distance keeping). Previous findings also showed that patients with HD commit most errors on these levels.^{6,8} In addition, manifest HD showed more variability in their speed when driving on the motorway and in the 30 km/h zone in the urban scenario, implying that they had more difficulties maintaining a steady speed while driving at both higher and lower speeds.

Our results are in line with previous findings that SDLP is a sensitive measure for vehicle control.^{20–23} The fact that we observed group differences in a relatively straightforward motorway scenario suggests that SDLP can discriminate between HD and controls in a simple scenario. This is an interesting finding, because we expected that the urban driving scenario would be more challenging and that, therefore, manifest HD would show greater deficits in this type of setting compared to premanifest HD and controls. Urban driving is more complex and might require more focus, attention, and alertness, because unexpected events, such as sudden stops, different speed zones, and other traffic participants (e.g., pedestrians, bikers) more often occur during urban driving.²⁴ Both low- and high-demand situations can result in too much mental workload and affect driving performance.²⁴ A recent study, however, observed limited effects of age and driving experience in simulated urban driving.²⁵ The authors suggested that urban driving increases mental workload and that this effect is similar for experienced and inexperienced drivers. This could also explain why we observed limited group differences on the parameters measured

in the urban driving scenario. If driving in the urban scenario increased the mental workload in all groups, then subtle differences might not be detected. However, manifest HD had a higher variability in their speed while driving in the 30 km/h zone, which was the speed zone with most distractions and events. This could suggest that a more unsteady car speed can be observed when the mental workload is high. Another explanation for the limited differences might be that the urban driving session was too short (mean duration was 7.1 minutes). This is important to keep in mind when comparing results and defining new study protocols. Motorway driving often involves less distractions, but requires high levels of sustained attention and vigilance due to the more monotonous nature. Our results demonstrate that a motorway scenario is feasible to use in studies investigating differences in simulated driving. Different scenarios should be further explored to identify the most sensitive scenario to use in simulator studies and optimize outcome measures

We did not observe any differences between premanifest HD and controls on any of the driving parameters. This implies that there were no changes in driving competence in the premanifest HD gene carriers who participated in our study. The observed correlations between the UHDRS-TMS, UHDRS-TFC and simulator outcomes also indicate that symptoms of HD are related to driving performance. However, subtle alterations in driving ability might already occur in premanifest HD, but the measurements used in our study are perhaps not sensitive enough to detect these changes. It is well known that deterioration in HD-related signs, such as cognitive functioning, can already be present before clinical diagnosis, which is usually based on motor signs.⁵ In addition, concerns about driving safety are one of the earliest reported functional disabilities.^{26,27} Including HD gene carriers in the earliest stage of the disease is important in an attempt to detect when alterations in driving first occur.

In our study, 14% of the premanifest HD reported driving restrictions, indicating that self-induced changes in driving are already present before the clinical motor diagnosis of HD. These results are in line with previous studies reporting comparable driving adaptations in manifest HD.⁷ This finding further emphasizes the need for early discussion with patients regarding driving ability and possible cessation, in particular, because driving cessation negatively affects independence and social activities.²⁸ We did not observe a difference between patient and companion ratings of driving competence. This is contrary to other studies reporting that patients with a neurodegenerative disease have the tendency to overestimate their own driving capacities.^{7,29,30} Previous findings showed that patients with HD are unaware of their own functional impairments.^{31,32} In clinical practice, spouses and other family

members are often the first to express concerns about the driving competence of HD patients.²⁶ Investigating the opinions of spouses regarding driving safety could be of interest to further explore the possible limited insight of patients. Only grading driving competence on a scale from one to ten, as in our study, might be less sufficient to document the actual concerns of spouses compared to more extensive questionnaires or interviews.

Results of driving simulator studies have previously been compared with on-road performances, but the ecological validity and generalizability to a real vehicle might be somewhat limited.^{7,13,33} Nevertheless, the results from our study contribute to the existing literature and showed that a driving simulator is a valid tool to use when examining group differences. A driving simulator also provides a standardized and safe environment for research purposes. Previous findings suggested that a driving simulator can increase the prediction of on-road test results.¹⁴ In particular, driving assessment items related to operational tasks, such as vehicle control, have been highly correlated with on-road driving in HD, confirming the concurrent validity of a driving simulator.³⁴ An examination with a driving simulator cannot replace an on-road driving test, but it might be complementary and useful as a first screening to determine which patients might need a referral for a driving test.

The occurrence of simulator sickness is common in simulator research and can pose a risk for drop-out.³⁵ In our study, 17% of the participants (3 premanifest HD, 8 manifest HD, 4 controls) were not able to complete all driving simulator assessments due to symptoms of simulator sickness. However, studies also showed that the presence of simulator sickness does not have to influence the outcome measures.³⁶ In addition, symptoms of simulator sickness are not always restricted to the group of participants with the worst performances or related to cognitive impairments.^{37,38} Our simulator was a static simulator, and a motion-based simulator might decrease the susceptibility to simulator sickness, but there are also studies that report symptoms in motion-based simulators.³⁹ Another limitation is the possibility of participation bias. More impaired patients might be less willing to participate in driving research because they are concerned that their license could be revoked. To reduce this in our study, we explicitly stated in the informed consent form that there would be no consequences for their driver's license based on the simulator results. Further, longitudinal studies are necessary to monitor potential declines in driving competence and to investigate the sensitivity of a driving simulator. The relationship between simulator driving performances and on-road tests should be further examined in HD to determine the usefulness of driving simulators to monitor driving ability.

To conclude, our study showed that manifest HD drive more cautiously with increasing speed and have less vehicle control in a driving simulator compared to premanifest HD and controls. Changes in driving ability were not detected in the earliest premanifest stage of the disease, although some self-imposed driving restrictions were reported. A driving simulator is able to detect differences in driving performance between manifest HD and healthy individuals. Further studies are necessary to determine if a driving simulator can be used to monitor longitudinal changes in fitness to drive.

5

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SUPPLEMENTARY TABLE 1 Overview of missing data per outcome measure

Outcome measure	Controls (N=28)	Premanifest HD (N=28)	Manifest HD (N=28)
Urban scenario			
Speed 30 km/h zone	0 (0%)	1 (4%)	0 (0%)
Speed 50 km/h zone	0 (0%)	0 (0%)	0 (0%)
Speed 80 km/h zone	0 (0%)	1 (4%)	0 (0%)
Speed variability (30 km/h)	0 (0%)	1 (4%)	0 (0%)
Speed variability (50 km/h)	0 (0%)	0 (0%)	0 (0%)
Speed variability (80 km/h)	0 (0%)	1 (4%)	0 (0%)
Distance keeping (meters)	0 (0%)	2 (7%)	1 (4%)
Reaction time – emergency stop	1 (4%)	2 (7%)	4 (14%)
Reaction time – pedestrian crossing	0 (0%)	0 (0%)	1 (4%)
Motorway scenario			
Speed 100 km/h	0 (0%)	3 (11%)	3 (11%)
Speed variability (100 km/h)	0 (0%)	3 (11%)	3 (11%)
Distance keeping (meters)	0 (0%)	3 (11%)	3 (11%)
Reaction time lane closure	5 (18%)	3 (11%)	9 (32%)
SDLP	3 (11%)	4 (14%)	3 (11%)

Number of missing data (%) per outcome measure. HD = Huntington’s disease;
SDLP = Standard Deviation of Lateral Position

SUPPLEMENTARY TABLE 2 Significant correlations between clinical variables and driving simulator measures

	Urban scenario				Motorway scenario				
Clinical variable	Speed (80 km/h)	Speed variability (30 km/h)	Speed variability (50 km/h)	Speed variability (80 km/h)	Speed (100 km/h)	Speed variability (100 km/h)	Reaction time (seconds)	SDLP	
Age	-0.35** †			-0.30* †		0.35* †			
CAG repeat length					-0.33*		0.39*		
UHDRS-TMS	-0.28* †	0.33* †	0.36**			0.47** †		0.59**	
UHDRS-TFC						-0.38* †		-0.38**	

Note: only significant Pearson *r* and Spearman rho correlations between clinical variables and driving simulator outcome measures are reported. None of the clinical variables had a significant correlation with Mean speed in the 30 and 50 km/h zones, distance keeping (meters), and Reaction Times to pedestrian crossing and emergency stop
**= *p* < 0.01; * = *p* < 0.05
† = Spearman rho coefficient

CAG = Cytosine Adenine Guanine; SDLP = Standard Deviation of the Lateral Position; UHDRS-TFC = Unified Huntington’s Disease Rating Scale – Total Functional Capacity; UHDRS-TMS = Unified Huntington’s Disease Rating Scale –Total Motor Score

[illegible]

Predictors of simulated driving performance in Huntington's disease

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ABSTRACT

Background

As the disease progresses, patients with Huntington's disease (HD), an inherited neurodegenerative disorder, become less independent in their daily life activities and have to consider if they can still drive a car. For most patients, the decision to quit driving is difficult and affects their independence and social activities.

Objective

To investigate if cognitive, motor, or psychiatric symptoms can predict driving performance in HD gene carriers using a simulator situation.

Methods

Twenty-nine controls, 28 premanifest HD, and 30 manifest HD participated in this observational, cross-sectional study and underwent neuropsychological, motor, and psychiatric evaluations. All participants drove a motorway scenario in a driving simulator to evaluate driving performance. Group differences were analyzed using Analysis of Covariance and stepwise forward linear regression analysis was used to investigate which clinical assessments were predictors of driving simulator outcomes.

Results

Manifest HD drove slower and had less vehicle control in the driving simulator compared to controls and premanifest HD. They also performed worse on all clinical assessments compared to controls. Postural sway and slower speed of information processing were predictors of the driving simulator outcome measures. Psychiatric symptoms were unrelated to simulated driving. There were no significant differences between premanifest HD and controls.

Conclusions

Increased postural sway and slower speed of processing are predictive of driving simulator performance in manifest HD. Worse performance on these clinical tasks might be useful as a first screening and could assist clinicians in their referral for an official on-road driving test.

INTRODUCTION

Although on-road driving tests remain the gold standard to evaluate driving ability, simulators are increasingly being used to investigate fitness to drive. Driving simulators have the advantage that challenging situations can be presented in a standardized setting, with a high reproducibility and without any risks for other traffic participants.¹ Further, driving simulator performances correlate with on-road driving assessments.²⁻⁴ Currently, only two studies used a driving simulator to investigate driving competence in Huntington's disease (HD).^{5,6} HD is an autosomal dominant neurodegenerative disorder caused by a gene mutation located on chromosome 4.⁷ The disease is clinically characterized by motor impairments, cognitive decline, and behavioral changes.⁸ The symptoms gradually progress, resulting in increased functional disabilities and less independence.⁸ These two simulator studies showed that patients with HD had slower reaction times and committed more overall errors compared to healthy controls.^{5,6} HD patients who failed an on-road driving test also performed worse on a driving simulator assessment.⁶ In addition, worse performances on neuropsychological assessments have been related to unsafe road performances in HD and might assist when deciding to cease driving.⁹ Cognitive impairments were also more sensitive to discriminate between on-road pass/fail scores than motor disturbances.⁶ However, it is not known if these neuropsychological tests are also able to predict driving simulator performances in HD using continuous simulator outcome measures. In addition, possible alterations in driving performance have not been studied in asymptomatic HD gene carriers. The aim of this current study was to determine motor, cognitive and behavioral predictors of simulated driving performances in HD gene carriers compared to healthy individuals.

METHODS

Participants

Fifty-eight HD gene carriers (28 premanifest HD, 30 manifest HD) and 29 controls participated in this cross-sectional observational study. All participants were at least 18 years of age, had a valid Dutch driver's license, and drove at least 300 kilometers in the previous 12 months. All HD participants had a confirmed CAG expansion of ≥ 36 in the *HTT* gene. Based on the Total Motor Score of the Unified Huntington's Disease Rating Scale (UHDRS-TMS), HD gene carriers were divided in manifest

(TMS > 5) and premanifest HD (TMS ≤ 5).¹⁰ Exclusion criteria were major comorbidities unrelated to HD (e.g., other neurological disorders or ophthalmic disorders), drug use in the four weeks prior to the study visit, alcohol abuse, and current participation in intervention trials. Alcohol was not allowed 24 hours before the study visit. The study was approved by the local ethics committee of the Leiden University Medical Center and all participants signed written informed consent.

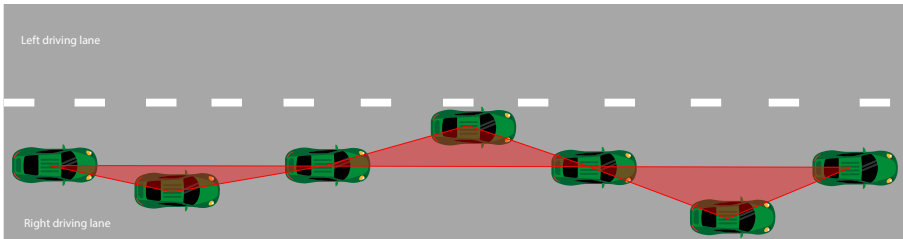
Demographic and clinical characteristics

Participants were asked if they restricted themselves in their driving behavior (e.g., not driving long distances), to gather information about self-reported adaptations or concerns about driving ability. The UHDRS was administered to assess the degree of motor disturbances (TMS) and functional capacity (TFC).¹⁰ The UHDRS-TMS (range 0 – 124) reflects motor impairments that are common in HD, including oculomotor function, chorea, dystonia, tongue protrusion, gait, and bradykinesia. Higher scores indicate increased motor dysfunction. The UHDRS-TFC (range 0 – 13) includes items on the capacity to work, manage finances, and the ability to carry out domestic chores. Lower scores indicate more functional disability.

Driving simulator

The driving simulator (DriveMaster LT, GreenDino B.V., Wageningen, the Netherlands) consisted of three 24-inch flat panel monitors, a steering wheel, gas-, brake-, and clutch pedals, and gearshifts. The dashboard, side mirrors and rear-view mirror were displayed on the screens. Instructions were provided both verbally and on the simulator screen. For the current study, a selection of measures was used from a comprehensive study that included both urban and motorway driving scenarios. A motorway scenario was selected for this study since this type of scenario has been proven sensitive to detect driving impairments.¹¹ Participants started with a practice trial to get familiarized with operating the simulator, after which the simulator assessment started. The motorway scenario had a duration of 30 minutes with a maximum allowed speed of 100 km/h. Participants were allowed to overtake other vehicles. In the final ten minutes of the motorway session, lane closings were marked by a red cross above the road, indicating that the participant needed to switch lanes. The time in seconds that the participant switched lanes before the lane closure was recorded as reaction time. The primary outcome variable was the standard deviation of the lateral position in centimeters (SDLP), which is a validated outcome measure in driving simulator studies.¹¹ It is a measure of vehicle control, with more weaving of the car resulting in higher SDLP values (Figure 1). Secondary outcome measures were.

FIGURE 1 Standard Deviation of the Lateral Position



Note: Example of the Standard Deviation of the Lateral Position. More deviation from the center of the driving lane results in higher deviation scores.

Quantitative motor assessments

Saccadic eye movements and smooth pursuit were measured by following a horizontal moving light on a computer screen. Three electrodes were placed (one on the forehead and one on either side of the lateral canthi of both eyes) for the registration of electro-oculographic signals. Saccadic inaccuracy (%) and average percentage of time that the eyes were in smooth pursuit of the target light (%) were used as outcome variables.¹²

Postural sway was assessed with a string potentiometer, which assesses body movements in a single plane. A string was attached to the waist (e.g., on the belt or pants), and participants were requested to stand still with their feet 20 centimeters apart and their eyes closed for 2 minutes. The total anterior-posterior body sway path in millimeters was the outcome measure.¹²

Motor activation and fluency was measured with a finger tapping task.¹² Participants were instructed to tap the space bar of a keyboard as quickly as possible with the index finger of their dominant hand. The task consisted of five trials of 10 seconds each. The mean tapping rate was used as outcome variable.

Cognitive assessments

The cognitive battery comprised of both paper-pencil and computerized assessments. The paper-pencil cognitive scores included the total number of correct responses on the written Symbol Digit Modalities Test (SDMT),¹³ which measures psychomotor speed and visual attention, the correct responses on the Stroop test (color, word, and interference),¹⁴ measuring speed of processing and executive functions, and the completion time in seconds of the Trail Making Test part B

(TMT-B),¹⁵ which was used to assess cognitive flexibility and executive functions.

Lower total scores on the SDMT and Stroop test indicated worse performances.

Lower completion times on the TMT-B indicated better performances.

The computerized cognitive assessments consisted of the Sustained Attention to Response Task (SART)¹⁶ and an adaptive tracking task.¹² The SART was used to measure attentional control and vigilance. Participants needed to press the spacebar of a keyboard as quickly and accurately as possible when the digits 1 – 9 randomly appeared on the computer screen, except when the number three (3) appeared. The digits were presented for 250 milliseconds and followed by a screen with a cross inside a circle that appeared for 900 milliseconds (i.e., mask stimulus). Each SART contained of 225 trials (200 go and 25 no-go digits). The total number of commission errors (i.e., participant pressed the spacebar when the number three appeared) was the outcome measure.

During the adaptive tracking task,¹² measuring visuo-motor control and vigilance, participants were instructed to keep a dot inside a moving circle using a joystick for 3.5 minutes. The joystick was operated with the dominant hand. This task was adaptive to the participants' performance, meaning that the speed of the moving circle increased when a participants' effort was successful. The speed of the moving circle reduced if the participant was not able to keep the dot inside the circle. The outcome variable was the average percentage of time (%) that the dot was inside the circle.

Neuropsychiatric assessments

The short version of the Problem Behavior Assessment-short (PBA-s)¹⁷ is a semi-structured interview that was used to assess the following symptoms: depression, suicidal ideation, anxiety, irritability, aggressive behavior, apathy, perseveration, obsessive-compulsive behavior, paranoid thinking, hallucinations, and disorientation. Severity and frequency scores are rated for each item on a 5-point scale (range 0 – 4), with a score of zero meaning that the symptom is absent and a score of four indicates that the symptom is causing severe problems in daily life. The total score is obtained by adding all sub-scores (range 0 – 176), with higher scores indicating more psychiatric and behavioral problems.

Two self-report questionnaires were administered that focus on self-evaluation of neuropsychiatric symptoms. The Frontal System Behavior Scale (FrSBe) is a 46-item questionnaire that assesses behavior that is associated with damage to frontal regions of the brain.^{18,19} Each item is rated on a 5-point scale (1 – 5). The total score ranges from 46 – 230, and this score was used in this study as outcome measure. The

Hospital Anxiety Depression Scale – Snaith Irritability Scale (HADS-SIS)^{20–22} was used to measure self-reported symptoms of anxiety, depression, and irritability. It contains 22 items, each scored on a 4-point scale (0 – 3), with a total score that ranges from 0 – 66.

Statistical analyses

Group differences on motor, cognitive, and neuropsychiatric assessments were analyzed using Analysis of Covariance (ANCOVA), corrected for age. The analyses on neuropsychiatric assessments were also corrected for gender. Analyses on cognitive assessments were additionally corrected for years of education. Simple contrasts (controls as reference group) were used to detect differences between premanifest and manifest HD versus controls. Contrasts were only interpreted if the ANCOVA revealed a significant main effect of group. Group differences on driving outcome measures were analyzed using Analysis of Variance or Kruskal-Wallis test when applicable.

Bivariate correlations were calculated between driving simulator parameters and clinical assessments that were significantly different between HD gene carriers and controls. Subsequently, stepwise forward linear regression analyses were performed to determine the prediction model of these simulator parameters. Only significant correlations were entered into the regression model.

All analyses were performed with the Statistical Package for Social Sciences (SPSS) for Windows version 23.0.

6

RESULTS

Three participants could not perform any of the driving simulator assessments due to symptoms of simulator sickness during the practice session. Twelve participants (14.3%) experienced symptoms of simulator sickness during the driving assessment, resulting in missing data on certain simulator outcome measures. Six manifest HD participants were unable to complete all computerized cognitive assessments due to disease severity. One control participant could not complete the computerized assessments due to time constraints. All available data for all assessments were included in the analyses, following an intention-to-treat approach. An overview of missing data per outcome measure is provided in Table S1. Demographics of all participants are reported in Table 1.

TABLE 1 Demographics

	Controls	Premanifest HD	Manifest HD
N	29	28	30
Age (years)	48.7 ± 11.0	38.4 ± 8.3	52.8 ± 10.5
Gender m/f (%m)	11/18 (38%)	15/13 (54%)	16/14 (53%)
CAG repeat length	NA	41.6 ± 2.4	42.5 ± 2.5
Years of education	15.6 ± 3.4	17.4 ± 3.0	16.4 ± 3.2
UHDRS-TFC	13.0 (11 – 13)	13.0 (8 – 13)	10 (5 – 13)
Simulator sickness yes/no (%yes)	3/26 (10%)	3/25 (11%)	9/21 (30%)

Data are mean ± SD, except for gender (total number)
CAG = Cytosine-Adenine-Guanine; NA = not applicable; UHDRS-TFC = Unified Huntington's Disease Rating Scale-Total Functional Capacity

Manifest HD performed worse on all motor, cognitive, and neuropsychiatric assessments compared to controls, except for the smooth pursuit variable (Table 2). In addition, manifest HD had higher scores on the SDLP and drove slower in the driving simulator compared to controls (Table 2). There were no significant differences between premanifest HD and controls on the clinical assessments and driving simulator outcomes. Bivariate correlations, using Pearson *r*, were calculated between SDLP, mean speed, and clinical assessments. Correlations between these parameters were only calculated for the manifest HD group since we did not observe any differences between premanifest HD and controls. Thus, we were only interested in correlations between driving simulator outcomes and clinical assessments in the manifest HD group.

TABLE 2 Group comparisons on clinical measures and driving simulator

	Controls (N=29)	Premanifest HD (N=28)	Manifest HD (N=30)	Premanifest HD vs Controls	Manifest HD vs Controls
Motor function					
UHDRS-TMS ^b	1.8 ± 1.4	2.5 ± 1.3	22.1 ± 12.6	<i>p</i> = 0.848	<i>p</i> < 0.001
Finger tapping ^a	61.0 ± 8.5	62.7 ± 6.9	51.3 ± 12.3	<i>p</i> = 0.812	<i>p</i> < 0.001
Saccadic inaccuracy (%) ^b	5.4 ± 1.5	5.6 ± 2.3	7.4 ± 2.1	<i>p</i> = 0.430	<i>p</i> = 0.001
Smooth pursuit (%) ^a	39.7 ± 8.1	40.6 ± 9.6	37.7 ± 6.7	NS	NS
Body sway (mm) ^a	293.0 ± 133.9	310.8 ± 223.8	1013.3 ± 1411.3	<i>p</i> = 0.933	<i>p</i> = 0.002
Cognition					
SDMT ^a	56.2 ± 11.1	56.7 ± 10.8	40.9 ± 11.7	<i>p</i> = 0.233	<i>p</i> < 0.001
Stroop – color ^a	81.1 ± 13.8	80.6 ± 12.9	58.9 ± 15.2	<i>p</i> = 0.501	<i>p</i> < 0.001
Stroop – word ^a	106.6 ± 17.3	102.9 ± 14.3	75.0 ± 16.2	<i>p</i> = 0.103	<i>p</i> < 0.001
Stroop – interference ^a	48.5 ± 9.8	49.8 ± 10.6	37.0 ± 12.7	<i>p</i> = 0.610	<i>p</i> < 0.001
TMT – B ^b	42.2 ± 15.7	37.2 ± 12.0	78.7 ± 45.7	<i>p</i> = 0.773	<i>p</i> < 0.001
Adaptive Tracking ^a	28.8 ± 5.7	30.4 ± 5.4	20.3 ± 7.9	<i>p</i> = 0.402	<i>p</i> < 0.001
SART ^b	7.8 ± 4.9	8.6 ± 5.7	10.6 ± 5.3	<i>p</i> = 0.673	<i>p</i> = 0.014
Neuropsychiatry					
PBA-s (total score) ^b	4.9 ± 6.4	4.6 ± 5.0	15.9 ± 13.7	<i>p</i> = 0.716	<i>p</i> < 0.001
HADS-SIS (total score) ^b	11.3 ± 7.2	8.9 ± 5.8	16.4 ± 9.9	<i>p</i> = 0.233	<i>p</i> = 0.016
FrSBe (total score) ^b	75.2 ± 17.7	74.5 ± 12.4	97.8 ± 25.3	<i>p</i> = 0.848	<i>p</i> < 0.001
Driving simulator					
SDLP ^b	35.9 ± 7.3	32.1 ± 6.8	42.6 ± 17.9	<i>p</i> = 0.238	<i>p</i> = 0.041
Mean speed	99.2 ± 4.3	98.8 ± 2.7	96.3 ± 5.1	<i>p</i> = 0.711	<i>p</i> = 0.013
SD of mean speed ^b	4.5 (3.4 – 6.3)	3.7 (2.6 – 5.0)	4.7 (3.8 – 7.7)	NS	NS
Distance to preceding car	40.6 ± 7.4	44.0 ± 8.9	41.0 ± 10.5	NS	NS
Reaction Time ^c	-14.1 ± 11.1	-15.2 ± 10.9	-8.3 ± 12.3	NS	NS

Data are mean ± SD, except for SD of mean speed (median with IQR). Univariate ANCOVA with simple contrasts was used for motor, cognitive, and neuropsychiatric variables (controls as reference group). All these analyses were corrected for age. The analyses on neuropsychiatric assessments were also corrected for gender. Analyses on cognitive assessments were additionally corrected for years of education. ANOVA and Kruskal-Wallis test were performed for driving simulator outcome measures. Significant *p*-values (*p* < 0.05) are printed in bold. If no significant group effect was observed then this is indicated with NS.

FrSBe = Frontal Systems Behavior Scale; HADS-SIS = Hospital Anxiety and Depression Scale – Snaith Irritability Scale; NS = Not Significant; PBA-s = Problem Behavior Assessment short; SART = Sustained Attention to Response Task; SDLP = Standard Deviation of the Lateral Position; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test; UHDRS-TMS = Unified Huntington’s Disease Rating Scale – Total Motor Score

^a = higher scores represent better performances
^b = higher scores represent worse performances
^c = more negative values indicate earlier reaction to events

Significant correlations, in order of strength, were observed between the SDLP and body sway, finger tapping, UHDRS-TMS, adaptive tracker, Stroop interference, TMT-B, Stroop word, and Stroop color (Table 3). Scores on the SDMT and TMT-B were significantly correlated with mean speed (Table 3). Stepwise forward regression analyses, entering all significant correlations, showed that the body sway parameter was the only significant predictor for the SDLP, whereas the SDMT was the only significant predictor for mean speed. The prediction equation for the SDLP was: $SDLP = 32.02 + (0.011061 * \text{body sway (mm)})$. The prediction equation for mean speed was: $\text{Mean speed} = 87.2 + (0.223093 * \text{SDMT})$. Additional exploratory correlation analysis revealed a significant correlation in manifest HD between if the patient restricted him/herself in driving and the SDLP ($r = 0.52, p = 0.010$).

TABLE 3 Correlations between clinical assessments and driving simulator parameters in manifest HD

Task	SDLP	Mean Speed
UHDRS-TMS	0.57**	-0.02
Finger tapping	-0.58**	0.24
Saccadic inaccuracy	0.16	-0.26
Smooth pursuit	-0.20	-0.35
Body sway	0.64**	-0.11
SDMT	-0.38	0.52**
TMT – B	0.49*	-0.43*
Stroop – color	-0.44*	0.15
Stroop – word	-0.47*	0.16
Stroop – interference	-0.51*	0.17
SART	0.07	-0.05
Adaptive tracker	-0.55**	0.17
PBA-s – total score	0.04	-0.33
HADS-SIS – total score	0.06	-0.25
FrSBe – total score	0.05	-0.13

Pearson r with significant correlations printed in bold ** = $p < 0.01$; * = $p < 0.05$
FrSBe = Frontal Systems Behavior Scale; HADS-SIS = Hospital Anxiety Depression Scale – Snaith Irritability Scale; PBA-s = Problem Behavior Assessment short; SART = Sustained Attention to Response Test; SDMT = Symbol Digit Modalities Test; UHDRS-TMS = Unified Huntington's Disease Rating Scale Total Motor Score

DISCUSSION

The results of our study showed that manifest HD have less vehicle control compared to both controls and premanifest HD. Patients with HD also tended to drive slower compared to controls, indicating a certain level of cautiousness. Less vehicle control and slower driving speed can be considered errors on the operational and tactical level, which are the first two levels of the model by Michon (1989).²³ Our results are in line with previous findings showing that patients with HD commit most errors on these levels during on-road assessments.⁹ This could indicate that patients with HD have difficulties with the operation of a car and adaptation to traffic situations. Adaptations on the third strategic level, such as no nighttime driving or no long-distance driving, can be managed before actual driving and might therefore be more difficult to detect with a simulator. Personal concerns and adaptations in driving behavior were, however, associated with decreased vehicle control.

We expected that manifest HD would have slower reaction times compared to controls and premanifest HD, since this was also reported in a previous simulator study.⁵ In addition, slower speed of processing and inattention are one of the first cognitive deteriorations in HD.²⁴ In our study, manifest HD had the slowest reaction time to lane closures, but this was not significantly different from controls. This might be explained by the fact that patients with HD also drove slower compared to controls, which could indicate compensatory behavior and, therefore, they might have enough time to detect the lane closures. Another explanation could be that the reaction time to lane switching, as was used in our study, was not sensitive enough to detect possible slowing. More sudden and unexpected events are perhaps a more accurate measure of the reaction time and slower speed of processing.

Patients with HD performed worse on all clinical assessments compared to controls, except for smooth eye movements, which is in line with other studies reporting cognitive deterioration in manifest HD.^{24,25} Previous studies have suggested that a cognitive evaluation is important in determining driving performance.^{6,26} We observed that less vehicle control, measured with the SDLP, was highly correlated with almost all cognitive assessments. The amount of postural sway, was a predictor for the level of vehicle control and weaving of the car, indicating that specific motor disturbances such as balance and postural sway are associated with driving errors on the operational level. It is possible that, in case of HD, this assessment reflects the amount of truncal choreiform movements and not only balance or gait. This might also explain the association with the SDLP, since increased movement of the upper body could result in more swaying of the car. Previous studies only used the

total motor score of the UHDRS instead of specific motor evaluations, which could explain the discrepancy in results.⁹ While the UHDRS-TMS was significantly correlated with vehicle control, it was not retained in the regression as a significant predictor. This result is in line with a previous finding where the TMS was also not predictive of driving performance.⁹ Slower speed of processing, measured with the SDMT, was predictive of a slower driving speed in the driving simulator, suggesting that mental slowing also induces slower driving. Previous studies also included the SDMT, or a comparable task, in their prediction models which indicates that this test is a strong and robust predictor in multiple study designs.^{6,27}

Worse performances on both the body sway test and SDMT could assist physicians in advising the patient about potential alterations in driving. The body sway test and SDMT can both be administered within five minutes, making these assessments relatively easy to use in the clinical practice. We feel that a clinical evaluation of driving ability should not only be based on the neurologists medical judgement, which is currently the national guideline in most European countries, but should also include a neuropsychological test battery.²⁸ HD is a heterogeneous disorder with deterioration on several domains and the onset of symptoms can vary per individual. Currently, there is no consensus on which neuropsychological assessments can predict driving ability in HD. We recommend to use clinical tests, such as the body sway and SDMT, as a first screening tool to determine the degree of deterioration due to HD. If the patient scores below a predefined cut-off score, then a formal driving assessment might be necessary. Some patients may already decide to quit driving by themselves when they acknowledge that the symptoms of HD are interfering with their functional capacity. Results on the screening battery could assist the treating clinicians in the discussion with the patient about potential driving cessation. At the moment, cut-off scores have not been determined, so it is important to establish these in future studies.

Neuropsychiatric behavior did not correlate with any of the driving simulator outcomes. In our study, only mild psychiatric disturbances were reported, so this might explain why we did not observe a significant correlation. However, it could also indicate that decreased driving performances already occur before the onset of severe psychiatric symptoms.

We did not observe any differences between premanifest HD and controls on the clinical and driving simulator assessments. This implies that alterations in driving performances are not yet present in this stage of HD and that they drive similar to healthy individuals when using the type of driving measures from our study. The distinction between HD stages is important in an attempt to examine when

alterations in driving first occur. It is known that cognitive symptoms can already be present years before the clinical motor diagnosis,²⁹ but it is still unclear when deteriorations in driving become overt. We are of the opinion that it is important to determine who is still able to drive safely instead of focusing on who is no longer fit to drive, since this might prolong the time a patient can be independent. A genetic confirmation of carrying the elongated CAG repeat alone should not be decisive for which individuals should cease driving. Clinical symptoms of the disease have to be present and individual evaluation is recommended. Our results showed that differences between HD patients and controls can be detected in a relatively easy and straightforward driving scenario. Using this type of motorway scenario has useful implications for future research, especially when investigating errors on the operational and tactical levels. Future studies are necessary to validate if the tests that emerged from our results are appropriate as a first screening tool and if they could be included in a clinical test battery. Although dropout due to simulator sickness occurred in our study, previous findings showed that symptoms of simulator sickness do not influence the outcome of simulator studies, and it are not necessarily the worst drivers who experience symptoms of sickness.^{30,31} Another limitation of our study is that we cannot compare our findings to on-road evaluations, which is currently the gold standard. Still, our study revealed that increased postural sway and slower speed of processing are predictive of driving simulator performance in manifest HD. This highlights the importance of discussing driving and cognitive functioning for those treating patients with HD. Worse performances on clinical screening tasks might assist clinicians in their referral for an official on-road driving test.

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SUPPLEMENTARY TABLE 1 Missing data on all outcome measures

	Controls (N=29)	Premanifest HD (N=28)	Manifest HD (N=30)
Motor functioning			
UHDRS-TMS	0 (0%)	0 (0%)	0 (0%)
Finger tapping	1 (3%)	0 (0%)	0 (0%)
Saccadic inaccuracy (%)	1 (3%)	0 (0%)	4 (13%)
Smooth pursuit (%)	1 (3%)	0 (0%)	3 (10%)
Body sway	2 (7%)	0 (0%)	2 (7%)
Cognition			
SDMT	0 (0%)	0 (0%)	0 (0%)
Stroop – color	0 (0%)	0 (0%)	0 (0%)
Stroop – word	0 (0%)	0 (0%)	0 (0%)
Stroop – interference	0 (0%)	0 (0%)	0 (0%)
TMT – B	0 (0%)	0 (0%)	0 (0%)
Adaptive Tracker	1 (3%)	0 (0%)	2 (7%)
SART	1 (3%)	0 (0%)	1 (3%)
Neuropsychiatry			
PBA-s (total score)	0 (0%)	0 (0%)	0 (0%)
HADS-SIS (total score)	0 (0%)	1 (4%)	0 (0%)
FrSBe (total score)	0 (0%)	0 (0%)	0 (0%)
Driving simulator			
SDLP	1 (3%)	3 (11%)	5 (17%)
Mean speed (100 km/h)	1 (3%)	3 (11%)	5 (17%)
SD speed (100 km/h)	1 (3%)	3 (11%)	5 (17%)
Distance keeping	1 (3%)	3 (11%)	5 (17%)
Reaction time	6 (21%)	3 (11%)	11 (37%)

Reported are total number of missing data (%) per variable and per group

FrSBe = Frontal Systems Behavior Scale; HADS-SIS = Hospital Anxiety and Depression Scale – Snaith Irritability Scale; PBA = Problem Behavior Assessment short; SART = Sustained Attention to Response Task; SDLP = Standard Deviation of the Lateral Position; SDMT = Symbol Digit Modalities Test; TMT-B = Trail Making Test; UHDRS-TMS = Unified Huntington's Disease Rating Scale Total Motor Score

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Comparable rates of simulator sickness in Huntington's disease and healthy individuals

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ABSTRACT

Objective

Investigating driving competence with a simulator provides a controlled setting and has a high reproducibility. In addition, there is less risk of physical harm compared to on-road tests. A disadvantage of using simulators is the occurrence of simulator sickness which is comparable to symptoms of motion sickness.

The aim of this study was to examine whether patients with Huntington's disease (HD) are more susceptible to develop simulator sickness compared to healthy individuals. Further, we investigated if the clinical symptoms of HD, such as motor disabilities and cognitive deterioration, might increase the occurrence of simulator sickness.

Methods

Eighty-three participants (54 HD, 29 controls) drove in a driving simulator that included urban and motorway scenarios. All participants were still active drivers. Motor, cognitive, and oculomotor assessments were administered. Participants completed a questionnaire after the driving session to report possible symptoms of simulator sickness.

Results

Fifty-eight (70%) participants completed the driving session, while 25 (30%) participants dropped out due to simulator sickness. The most reported symptoms of simulator sickness by dropouts were difficulties concentrating, dizziness, nausea, sweating, and vomiting. Dropouts were significantly older and more often female compared to completers. Decreased smooth ocular pursuit was predictive of dropout due to simulator sickness. The number of HD participants and controls in the dropout group was comparable. There was no significant difference in cognitive performance and motor functioning between completers and dropouts.

Conclusions

HD participants did not have a higher chance of developing simulator sickness while driving in a simulator compared to controls. Female gender, older age, and smooth ocular pursuit were associated with increased simulator sickness, whereas cognitive and motor functioning were unrelated to dropout due to simulator sickness.

INTRODUCTION

Revocation of a driver's license has a negative impact on an individual's quality of life, especially when you are dependent on the ability to drive in order to maintain a job or for social activities.^{1,2} It has been reported that driving competence decreases with increasing age and that older adults have a higher risk of crashing.³ This decline in fitness to drive is greater in patients with dementia and other neurodegenerative disorders compared to healthy older adults.⁴ In Huntington's disease (HD), an inherited neurodegenerative disorder caused by a gene mutation located on chromosome 4, decreased driving competence has also been reported.⁵⁻⁷ HD is clinically characterized by motor disturbances, cognitive decline, and psychiatric symptoms.⁸ The onset of symptoms typically occurs between 30 and 50 years. The symptoms gradually progress and, as a result, affect daily life activities such as driving at a relatively young age.⁹ Mainly cognitive impairments have been related to early alterations in fitness to drive in patients with HD.⁵ However, more than half of the HD patients continued driving after the onset of the disease, despite failing an on-road driving assessment.⁵

Studies showed that driving simulators have a high concurrent and discriminant validity as a measurement of on-road driving capability in healthy older adults.^{10,11} Simulators are also regularly used in studies investigating driving ability in patients with neurodegenerative disorders.⁴ The simulated environment provides a controlled setting that integrates the visual system, cognition, and motor capabilities of driving, with little risk of physical harm.¹²⁻¹⁴ However, a regularly encountered side-effect when operating a driving simulator is simulator sickness.^{12,15} The symptoms of simulator sickness are comparable to motion sickness and include sweating, dizziness, and nausea.¹² The symptoms are usually temporary and often decrease within one to two hours.¹⁶ The most accepted theory to explain simulator sickness is the sensory conflict theory, which states that an incompatibility of different sensory information, such as visual, auditory, and motion, occurs at the same time.¹⁷ The estimated prevalence of simulator sickness varies greatly among studies. In 5 to 30% of the cases, simulator sickness symptoms can lead to discontinuation of participation in research.^{16,18} Older age and female gender, as well as type of scenario and a longer duration of simulator driving, have been related to the occurrence of simulator sickness.^{12,18}

We conducted a driving performance study in HD and healthy individuals using a driving simulator. To determine potential causes of simulator sickness in our cohort, we wanted to explore whether patients with HD are more susceptible to simulator sickness compared to healthy individuals and if the cognitive and motor symptoms

that are related to HD potentially increase the risk of developing simulator sickness and, eventually, lead to dropout.

MATERIALS AND METHODS

Participants

Data of 83 participants (54 HD, 29 healthy controls), who were recruited from the outpatient Neurology clinic of the Leiden University Medical Center (LUMC) to participate in a driving simulator study, were used in this study. All participants were active drivers. All HD participants had a genetically confirmed diagnosis with a CAG repeat of more than 36 on the larger allele. With an expansion of more than 36 CAG repeats in the *HTT* gene a person will develop HD. Longer CAG repeats are associated with earlier clinical disease onset.¹⁹ The HD participants were divided into participants with a clinical diagnosis (i.e., manifest HD) and without a clinical diagnosis (i.e., premanifest HD). This division was based on the total motor score of the Unified Huntington's Disease Rating scale (UHDRS-TMS)²⁰; premanifest HD = TMS ≤ 5 and manifest HD = TMS > 5. This resulted in 27 premanifest HD and 27 manifest HD participants. Participants who were unable to complete the entire driving simulator session due to symptoms of simulator sickness were categorized as dropouts. Completers are all participants who completed the entire driving session. The study was approved by the local ethics committee of the Leiden University Medical Center and all participants signed a written informed consent.

Assessments

All assessments were performed during a single visit on the same day. The simulator (GreenDino DriveMaster LT) that was used to assess driving competence consisted of three 24-inch flat panel monitors, a steering wheel, gas-, brake-, and clutch pedals, and gearshifts. The lights in the room were dimmed and the room temperature was regulated with climate control. There was also a fan available for the participants. The total duration of the driving session was approximately 45 minutes. Participants started with an 8-minute practice trial to get familiarized with operating the simulator. Instructions were provided both verbally and on the simulator screen. Participants were asked to obey the general Dutch traffic rules and instructed to drive as they normally would. The first part of the driving session was conducted in an urban environment that included different speed zones (i.e., 30, 50 and 80 km/h) and multiple events (e.g., pedestrian crossing, emergency stop). This part had a duration

of approximately 8 minutes. The second part of the driving session was driven on a motorway and had a duration of approximately 30 minutes, with a maximum allowed speed of 100 km/h. Thereafter, participants drove the same urban scenario for a second time.

Participants were asked to fill in a questionnaire to assess the presence of symptoms related to simulator sickness after completing the driving session or after dropout. The questionnaire included the following items: less concentration, dizziness, fatigue, difficulty focusing, headache, nausea, stomach ache, sweating, and urge to vomit. Each item had to be rated on a four-point scale, with '1' meaning that the symptom was not present at all, and '4' meaning that the symptom was severely present. The UHDRS-TMS reflects the degree of motor disturbances that are common in HD, including eye movements and oculomotor function, chorea, dystonia, tongue protrusion, gait, and bradykinesia.²⁰ The scale ranges from 0 – 124, with higher scores indicating increased motor dysfunction. The cognitive battery included the total number of correct responses on the written Symbol Digit Modalities Test (SDMT),²¹ which was used to measure psychomotor speed and visual attention, the correct responses on the Stroop test (color, word, and interference),²² measuring speed of processing and executive functions, and the completion time in seconds of the Trail Making Test part B (TMT-B),²³ which was used to assess cognitive flexibility and executive functions. Lower total scores on the SDMT and Stroop test indicated worse performances. Lower completion times on the TMT-B indicated better performances. Oculomotor dysfunction was measured with saccadic eye movements and smooth pursuit. Three electrodes were applied (forehead and beside the lateral canthi of both eyes) for the registration of the electro-oculographic signals. Participants had to follow a horizontal moving light on a computer screen. Saccadic inaccuracy (%) and average percentage of time that the eyes were in smooth pursuit of the target light (%) were used as outcome variables.^{24,25}

Statistical analyses

Group comparisons in age, gender, education and UHDRS-TMS between completers and dropouts were performed using independent sample t-test, χ^2 -test, or Mann-Whitney *U* test for continuous, categorical and skewed data respectively. Analysis of Covariance (ANCOVA), corrected for age and gender, was used to compare the two groups on cognitive and oculomotor assessments. To analyze if the number of dropouts differed between premanifest HD, manifest HD and controls, Kruskal-Wallis test was used. Mann-Whitney *U* test was conducted to analyze which symptoms of simulator sickness, as reported on the questionnaire, differed between the completers

and dropouts. Correlation analysis was conducted between the questionnaire items and cognitive and oculomotor assessments. Multivariate logistic regression analysis was performed to investigate the association between gender, age, cognition, oculomotor function and dropout. All analyses were conducted using SPSS version 23.0 for Windows.

RESULTS

Thirty-nine males and 44 females were included, with a mean age of 47 years (SD = 11.6). Fifty-eight participants (69.9%) completed the entire driving session and 25 (30.1%) participants discontinued due to reported symptoms of simulator sickness (7 premanifest HD, 9 manifest HD, and 9 controls). The number of dropouts per group did not significantly differ ($H(2) = 0.365, p = 0.833$). In addition, there was no significant correlation between participant group and dropout ($r_s = 0.044, p = 0.692$). Dropouts were more often female and were significantly older compared to participants who completed the driving simulator session (Table 1). No significant differences were observed between the dropouts and completers in total years of education and UHDRS-TMS (Table 1).

TABLE 1 Demographic and clinical characteristics

	Completers (N=58)	Dropouts (N=25)	p-value
Controls, N (%)	20 (69%)	9 (31%)	NA
Premanifest HD, N (%)	20 (74%)	7 (26%)	NA
Manifest HD, N (%)	18 (67%)	9 (33%)	NA
Gender male / female (%male)	32 / 26 (55%)	7 / 18 (28%)	0.023
Age	45.0 ± 11.1	51.4 ± 11.6	0.020
Education, years	16.8 ± 3.2	15.7 ± 3.6	0.168
UHDRS-TMS	8.0 ± 11.0	9.1 ± 12.0	0.701

Data are mean ± SD for gender (total number and %). Independent sample t-tests were used for age, years of education, and UHDRS-TMS. χ^2 -test was used for gender. Statistically significant differences are printed in bold ($p < 0.05$)
HD = Huntington's disease; UHDRS-TMS = Unified Huntington's Disease Rating Scale – Total Motor Score

Of the 25 dropouts, three participants dropped out after the practice trial, 6 dropped out after the first urban part of the driving session, there were 14 dropouts after the motorway session, and 2 additional dropouts during the final part of the driving session. The 14 participants that dropped out after the motorway chose not to start the second urban session due to previously experienced symptoms of simulator sickness during the first urban session. No significant differences were observed between completers and dropouts on cognitive assessments and oculomotor function (Table 2).

The questionnaire containing items on simulator sickness was filled in by 57 participants (39 completers, 18 dropouts). Dropouts reported that they had significantly more difficulties with the ability to concentrate, had more feelings of dizziness, nausea, sweating, and vomiting compared to participants who completed the driving session (Table 3). Additional analyses per questionnaire item, using Kruskal-Wallis tests, revealed that there were no differences between premanifest HD, manifest HD and controls on what symptoms were reported on the questionnaire. The total score on the questionnaire also did not differ between the premanifest HD, manifest HD and controls ($F(2) = 1.197, p = 0.310$).

TABLE 2 Differences between completers and dropouts on cognitive and oculomotor assessments

Task	Completers (N=58)		Dropouts (N=25)		F (df)	p-value
	Mean	SD	Mean	SD		
SDMT ^a	52.1	12.3	50.6	14.6	0.31 (1, 79)	0.580
TMT – B ^b	49.5	28.4	58.8	45.5	0.09 (1, 79)	0.761
Stroop – word ^a	96.8	21.4	92.5	19.1	0.01 (1, 79)	0.937
Stroop – color ^a	74.6	16.0	72.7	18.4	0.05 (1, 79)	0.829
Stroop – interference ^a	45.3	11.3	46.0	14.2	1.64 (1, 79)	0.204
Saccadic inaccuracy ^b	6.2	2.4	5.8	1.8	0.73 (1, 74)	0.397
Smooth pursuit ^a	40.5	9.1	36.0	5.2	3.14 (1, 74)	0.081

Data are mean ± SD for completers and dropouts. Analysis of Covariance, corrected for age and gender, was used to investigate group differences on all assessments. Statistically significant threshold was set at $p<0.05$
SDMT = Symbol Digit Modalities Test; TMT-B = Trail Making Test part B

^a higher scores indicate better performances

^b lower scores indicate better performances

TABLE 3 Group differences between completers and dropouts in reported symptoms of simulator sickness

Questionnaire item	Completers (N=39)		Dropouts (N=18)		U	p-value
	Mean	SD	Mean	SD		
Concentration	1.7	0.7	2.2	0.7	230.0	0.026
Dizziness	1.7	0.9	3.1	1.1	122.0	<0.001
Fatigue	1.9	0.8	1.7	0.8	302.0	0.369
Focusing	1.8	0.7	2.1	0.9	289.5	0.258
Headache	1.3	0.6	1.7	0.9	274.5	0.115
Nausea	1.6	0.9	3.7	0.5	42.0	<0.001
Stomach ache	1.1	0.3	1.5	1.0	285.5	0.076
Sweating	1.2	0.6	2.3	1.2	188.5	0.001
Vomiting	1.1	0.7	3.3	0.9	55.0	<0.001

N = 57; missing data (N = 26) because some participants did not fill in the questionnaire.
Mann-Whitney U test was used to analyze differences between groups. Statistically significant
p-values are printed in bold ($p < 0.05$)

TABLE 4 Significant correlations between cognitive and ocular function and symptoms of simulator sickness

Task	Concentration	Focusing	Nausea	Vomiting
TMT – B		0.29*		
Stroop – word		-0.27*		
Saccadic inaccuracy	0.27*			
Smooth pursuit	-0.29*		-0.35**	-0.36*

Statistically significant Spearman's rho correlations are reported
* = $p < 0.05$
** = $p < 0.01$

Spearman's rho correlations revealed a significant relation between TMT-B, Stroop word, saccadic inaccuracy and smooth pursuit and the focusing, concentration, nausea and vomiting items of the simulator sickness questionnaire (Table 4). Decreased smooth pursuit (OR [95% CI] = 0.88 [0.80 – 0.97], $p = 0.01$) and female gender (OR [95% CI] = 0.10 [0.02 – 0.46], $p = 0.003$) were the only predictors for the chance of dropout due to simulator sickness.

DISCUSSION

In this study, we examined whether patients with Huntington's disease (HD) are more susceptible to simulator sickness and more often dropout compared to healthy individuals. In our study, 30% of the participants dropped out due to simulator sickness, which is comparable to other studies that reported a dropout rate between 5 and 30% in simulator studies.¹⁶ The number of dropouts in our study was evenly distributed across participants with HD and controls and there was no correlation between participant group and dropout. In addition, there was no difference between the dropouts and completers in UHDRS-TMS, indicating that patients with increased motor symptoms were not more likely to dropout. Cognitive and oculomotor functioning did not differ between completers and dropouts, confirming previously reported results.¹⁶ Therefore, we conclude that in our study, HD patients did not have a higher risk of experiencing symptoms of simulator sickness. This is promising for future studies, since it indicates that individuals who might drive poorly due to their cognitive impairments are able to undergo simulator assessments. It also reduces the chance of attrition bias and provides an opportunity to monitor decreased driving performances due to cognitive decline, without cognitive status influencing dropout rates. Our study showed that female participants more often develop symptoms of simulator sickness. In addition, older age was associated with an increased dropout risk. It has been reported that females are more likely to suffer from any form of visually-induced motion sickness compared to men, which could also explain the higher rate of female dropout in our study.^{18,26,27} Symptoms related with older age, such as increased dizziness and problems with balance, could be an explanation for the fact that age is associated with simulator sickness.¹⁵ Another explanation might be that younger participants are more comfortable with operating a simulator because they are more familiar with videogames and virtual reality. Decreased smooth ocular pursuit was associated with an increased chance of dropout, which could correspond with the sensory conflict theory that simulator sickness results from an incompatibility of different sensory information, such as visual and motion.¹⁷ This theory states that there is a mismatch between the visual motion a person sees and the motion that they experience, calledvection.²⁸ If there is a decrease in how smooth the eyes perceive the visual input, resulting in a more distorted and choppy image, then the discrepancy between visual information and motion might further increase. This, in turn, may result in higher levels of simulator sickness.

Most participants dropped out after driving the urban scenario or did not want to drive the urban session for a second time due to previously experienced simulator sickness. The urban scenario included more curves and sudden stops, so it is expected that most dropout would occur during this type of scenario.^{29,30} However, in our opinion, investigating urban scenarios is also necessary, since this resembles an important part of daily driving with more complex situations and increases the mental workload.³¹ Shorter sessions or more breaks might reduce the dropout rate during these types of scenarios. Adaptation to the simulator before the actual driving test could reduce the dropout due to simulator sickness. Previous studies showed that multiple exposures and more time between the practice session and the actual driving simulator test can decrease the occurrence of simulator sickness.³² A suggestion here is to perform the practice trials and actual assessments on separate occasions, but this might not be feasible for all participants.

In conclusion, our study confirmed that female gender, older age, and smooth ocular pursuit are risk factors for the occurrence of simulator sickness. Around one third of the participants dropped out as a result of simulator sickness and these symptoms seem to be unrelated to HD. To reduce the risk of dropout, we recommend to start the simulator assessment with scenarios that are less visually demanding (e.g., motorway scenarios and straight roads) before continuing to more complex and detailed scenarios with curves and sudden stops (e.g., urban scenarios). This way, participants can become better adapted to the simulated environment. The configuration of detailed scenarios should be optimized, in particular the refresh rates of the visual information on the screen. Future studies are necessary to determine the impact of HD symptomatology on driving using both simulators and on-road driving tests, before the clinical usefulness of a simulator can be determined. Researchers should be aware of the simulator sickness phenomenon and the potential dropout rate when designing simulator studies. They should consider screening potential participants for previous motion sickness and eligibility before participants start driving in the simulator.

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General discussion

The primary aim of this thesis was to study employment and driving ability in gene carriers with Huntington's disease (HD). We aimed to investigate predictors of work cessation and examine the influence of different symptoms and signs of HD on driving performance.

Employment and Huntington's disease

Work stress and employment changes are frequently mentioned by premanifest HD gene carriers when asked if they experience difficulties in daily life.¹ Most patients reduce their amount of work and this reduction is often perceived as a negative change as a result of disease.² However, contrary results have shown that it remains unclear whether HD gene carriers attribute these employment changes to signs of HD.³

Our findings showed that problems with concentration and multi-tasking, and slower reactions influenced the decision to stop working (**chapter 2**). Working in a physically demanding job might not be a reason to stop working prematurely, since half of the gene carriers who were no longer working had jobs with non-physical work demands (**chapter 3**). The first cognitive changes in HD are characterized by problems in executive functions including planning, organization, cognitive flexibility and attention, which might be more crucial in nonphysical occupations that require higher levels of cognition. Further, we found that worse cognitive functioning, in particular slower speed of processing and cognitive inflexibility, and apathy are predictors of work cessation in HD gene carriers (**chapter 3**). Thus, cognitive and behavioral changes interfere more with the ability to work than the characteristic motor signs of HD. HD gene carriers retired more than a decade before the general retirement age, confirming that work cessation occurs during mid-adulthood and that signs of HD are associated with stopping work (**chapter 2** and **chapter 3**). This is similar in patients with Parkinson's disease, who generally also retire before the official retirement age because of the impact of the disease on their ability to work.⁴ However, the number of studies focusing on work and HD is still very limited. No longer being able to work can result in psychological distress. In order to adjust to a new lifestyle, patients must develop active coping strategies. More than 50% of the HD gene carriers expressed concerns about genetic discrimination in the workplace.⁵ Better mental health has been associated with less work-related disability in premanifest HD.⁶ Counseling about possible career choices and evaluating the concerns of patients and families in the presymptomatic phase of the disease is, therefore, recommended. Patients in disease stages 1 and 2 experience the most changes in their health due to the progression of HD symptoms and show an increasing dependency on others in

activities of daily life.⁷ This group also reports that they experience a discrepancy between the care they need and the care they actually receive. Patients in disease stages 1 and 2 should be the main focus of psychoeducation, as well as gene carriers who do not yet experience any symptoms. Patients report that it can be frustrating that healthcare professionals lack knowledge about HD.⁸ Specialized and educated professionals are needed in the care system for HD patients.

Driving and Huntington's disease

It is presumed that the decision to stop driving is a dynamic stepwise process rather than an overnight decision.⁹ This process starts with increasing self-imposed driving restrictions, eventually resulting in complete cessation of driving. The fact that presymptomatic HD gene carriers reported that they adapt their driving behavior, for example with less nighttime driving, no motorway driving, and driving shorter distances, further supports this suggestion (**chapter 5**). In addition, it confirms that the capability to drive a car is a topic of interest and concern in gene carriers with HD. This emphasizes the need to start the discussion about driving in the early stages of HD and reexamine it regularly. The possibility of stopping driving should be included as a discussion topic in the clinic, because the inability to drive a car affects the independence and quality of life of patients. Healthcare professionals and driver's licensing authorities have the obligation to inform patients about the process of driving cessation, the risks of continuing driving, and must provide proper guidance. HD gene carriers who stopped driving were significantly older and more often female compared to active drivers (**chapter 2**). In general, women also tend to stop driving at a younger age compared to men, so this finding seems to be unrelated to HD.¹⁰ However, men and women differed in their primary reasons for stopping driving (**chapter 2**). Most males stated difficulties concentrating as their reason for stopping driving, whereas females reported feelings of anxiety as their primary reason. It is well known that patients with HD can have limited insight into their own functional decline.^{11,12} However, in our study, patients and spouses gave the driving performance of HD patients similar grades, suggesting a certain level of awareness in these HD patients (**chapter 5**). Spousal opinions often provide a more objective point of view, although they might give socially accepted answers because they rely on the patient being able to drive, or want to avoid an argument.^{13,14} Children of an affected parent might provide the most accurate and reliable answers about whether driving is still safe.¹⁵ To our knowledge, our study was the first to investigate the hypothesis that changes in driving performance already start in the early presymptomatic phase of HD. We found that the way presymptomatic gene carriers drove was comparable

to that of controls, while the performance of symptomatic gene carriers was worse (**chapter 5**). These results suggest that a genetic confirmation of HD should not be decisive for the recommendation to stop driving, but that individual symptoms have to be evaluated. In our opinion, the goal should be to let HD gene carriers drive for as long as this is still safe and not advise revoking the driver's license based on genetic confirmation alone.

Predicting driving performance

The findings of our study confirm that deteriorated cognition influences driving performance more than motor dysfunction (**chapter 6**). Especially slower speed of information processing and postural sway and instability are associated with alterations in driving. The SDMT and Body Sway tests emerged as significant predictors of driving performance in our study (**chapter 6**). These are both relatively short tests that can easily be administered with a low burden for the patient. In previous studies, the SDMT has been identified as a sensitive biomarker to detect early cognitive deterioration, and decreased psychomotor speed is one of the earliest cognitive changes observed in patients with HD.^{16–18} The fact that the SDMT was also a suitable predictor of driving competence in previous studies suggests that this test is a robust predictor of changes in driving and we would recommend including it in a screening assessment (**chapter 4**). Neuropsychological screening batteries could provide a better estimation of who should be referred for an official on-road driving test than a medical examination alone. Since HD is a heterogeneous disorder, where cognitive impairments can be more debilitating compared to the characteristic motor signs, a multidisciplinary approach seems mandatory when assessing driving ability. Specialists from disciplines other than neurology, such as psychologists or occupational therapists, should be involved in the evaluation of fitness to drive. Cognitive tests should, therefore, be embedded in the standard clinical driving evaluation. Using guidelines that have been proposed for other neurodegenerative disorders, such as Alzheimer's (AD) and Parkinson's disease (PD), seems unwarranted. Prediction models established for AD cannot necessarily be used in HD due to the different etiology and clinical expression,¹⁹ emphasizing the need for specialized consensus guidelines limited to HD. Multiple neuropsychological tests have been proposed to predict driving errors, but there is currently no validated standardized battery that can be used.^{20,21} To embed cognitive tests in the clinic, cut-off scores are necessary and these are currently still lacking. The use of one single test is not recommended and composite test batteries have been suggested to better discriminate between safe and unsafe drivers.²² We propose at

least including the SDMT in the yet to be developed HD specific clinical screening battery.

In contrast to cognitive impairment, psychiatric behavior was unrelated to driving performances (**chapter 6**). It is possible that psychiatric symptoms are more manageable with medication and, therefore, have less influence on driving skills. Furthermore, depressed mood, apathy, and anxiety might result in the patient deciding to stop driving voluntarily. Thus, psychiatric symptoms could influence driving behavior, but probably at a different level than the actual driving performance. In patients with PD, higher levels of anxiety were associated with their decision to stop driving.²³ Anxiety and feelings of insecurity were also among the primary reasons reported by HD gene carriers (**chapter 2**). Being overcautious may be a compensation for anxiousness, which could explain the fact that patients with HD tend to drive more slowly and below the speed limit compared to controls (**chapter 5**). The total motor score of the Unified Huntington's Disease Rating Scale did not contribute to the prediction of driving skills, while this score is the most frequently used rating scale in HD, as well as the primary outcome measure in most clinical trials (**chapter 6**). Previous findings also showed that motor functioning, measured with this scale, was not predictive of driving performance.²⁰ For the clinical screening of driving fitness, the total motor score would be insufficient.

Driving simulator

We chose to use a driving simulator in our study, because it provides the opportunity to test driving skills in a standardized and reproducible environment. In addition, it is safer to test certain conditions with a simulator rather than putting the participants in potentially hazardous and uncontrollable situations on the road. Although on-road evaluations are the gold standard and reflect real world circumstances, they lack generalizability and the challenges differ from individual to individual. In addition, there is variability in routes and vehicles.^{24,25} A validation study in HD showed that simulators have a good concurrent validity when compared to on-road tests, especially for the measurement of operational driving skills, such as vehicle control.²⁶ At the moment, in our opinion, it is not sufficient to use only a driving simulator when a definite decision about driving cessation has to be made, but it can complement the clinical evaluation of driving competence. In the Netherlands, novice drivers are trained with a driving simulator before their first on-road experience. Better test results in the simulator have been related to higher chances of passing the driving test the first time.²⁷ The results of one study indicated that simulator training is potentially useful in drivers with PD, showing improved scores on an on-road test

after simulator training.²⁸ In addition, PD patients who failed the on-road driving test before the training, passed the test post-training.²⁹ Thus, in the future, it might be effective to use a driving simulator as a training tool in HD. Since our study revealed that patients with HD have most difficulties operating a car and with adapting to certain road situations (**chapter 5**), training these driving skills could potentially increase the on-road driving capabilities.

A disadvantage of using simulators is the occurrence of simulator sickness, which is comparable to the symptoms of motion sickness. Although our findings illustrated that patients with HD were not more susceptible to developing symptoms of simulator sickness than controls, the occurrence of this phenomenon limits the usage of a driving simulator (**chapter 7**). Female gender and older age were associated with increased simulator sickness, whereas cognitive and motor functioning were unrelated to dropout due to simulator sickness. Symptoms of simulator sickness mostly occurred during the urban driving scenario, which is characterized by sharper turns and more sudden stops (**chapter 7**). However, we are of the opinion that these types of scenarios should be further optimized to properly test situations that require a high mental workload. Reducing the duration of the simulator assessments or taking more breaks in between sessions could alleviate the symptoms of simulator sickness.³⁰

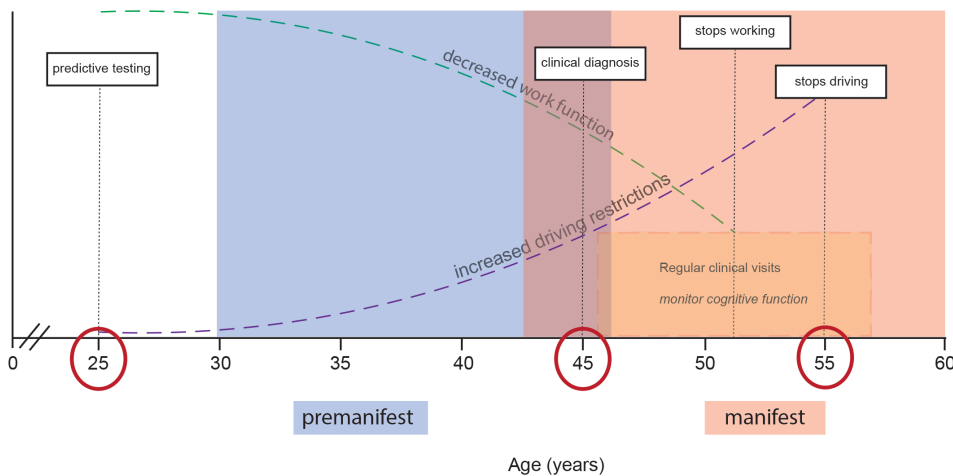
Recommendations and future perspectives

More studies are necessary to validate our findings and compare the simulator results with on-road assessments. Because of the progressive nature of HD, longitudinal studies should be performed to establish a reasonable follow-up period for retesting driving ability. The current lack of cut-off scores for cognitive tests has to be tackled. Investigating driving in a naturalistic driving setting, using a dashcam, could provide an opportunity to examine driving behavior during multiple occasions and in the patient's own car.²⁴

Since there is currently no cure for HD, the focus of treatment is on improving quality of life and providing the necessary support to patients and families. Maintaining independence through employment and driving, for as long and as safely as possible, has a substantial influence on a patient's own general functioning and their family. Because the symptomatic onset of HD mostly occurs during midlife, the disease can affect various activities of daily life, such as work, driving, and social relationships, at a relatively young age. Based on the main findings of this thesis, a proposed schematic timeline for when, during the course of HD, to discuss working and driving in the clinic, is shown in Figure 1. During the earliest phase of HD,

shortly after predictive testing, gene carriers should be informed about how the signs of HD can affect the capability to work and drive a car. This could be done via a brochure that describes the possible issues that patients with HD may be confronted with in daily life as the disease progresses. When the clinical diagnosis is established, physicians (e.g., neurologists) and other healthcare professionals, such as psychologists and occupational therapists, should again inform the patient and their spouses about the influence of HD on employment and driving ability. Psychoeducation will increase the awareness about what changes might occur in work and driving, how these relate to signs of HD, and the safety of themselves and others. Regarding work adjustments, lowering the work demands or reducing the number of hours might be a first solution. Discussing alternative options of transportation is important to help patients adjust to the loss of independence when they decide to stop driving. In general, during the earliest manifest stages, driving performance will not yet be altered and patients might be able to compensate for changes in driving by increasing the number of restrictions or adapting their car. For example, they can decide not to drive during rush hour, not to drive during nighttime, or to change to a car with automated transmission. For patients who visit the outpatient clinic, annual monitoring of cognitive decline is recommended. At the moment, a longitudinal, international, observational study is collecting data on demographics, motor, cognitive, and neuropsychiatric signs to improve the understanding and monitor the progression of HD (Enroll-HD).^{31,32} The neuropsychological test battery included in this study has the potential to be used as a screening tool to monitor changes in cognition related to work and driving. If cognitive function further deteriorates, patients should be advised to stop driving voluntarily, for their own safety and that of others. Voluntarily deciding to stop driving gives a feeling of autonomy, contrary to a forced revocation of a driver's license when a formal driving test is performed.

FIGURE 1



Hypothetical schematic timeline for the discussion of working and driving in the clinic. The influence of Huntington's disease on employment and driving should be discussed regularly, starting at an early stage, shortly after predictive testing, again after the clinical diagnosis has been given and during follow-up visits. Cognitive function should be monitored with a standardized assessment battery. Specialists from multiple disciplines, such as neurologists, psychologists and/or occupational therapists, should be included in the examination of fitness to work and drive.

CONCLUSIONS

This thesis addresses the topics working and driving ability as being relevant in HD. Our results consistently showed that the cognitive and behavioral changes in HD are more debilitating in daily life than the characteristic motor signs. Healthcare professionals should be educated about the different stages of HD, to allow them to provide appropriate information to patients and families when discussing possible changes in work and driving as a result of the disease. The driving performance of presymptomatic HD gene carriers and controls was comparable, suggesting that individual evaluation is warranted and that the decision to stop driving should not solely be based on disease stage or a genetic confirmation. Multidisciplinary screening, using a HD-specific test battery, is recommended and should be embedded in the clinic.

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8

Summary

**Nederlandse
samenvatting**

Dankwoord

List of publications

Curriculum Vitae

SUMMARY

The aim of this thesis is to examine employment and driving ability in gene carriers with Huntington's disease (HD). HD is an autosomal-dominant inherited neurodegenerative disorder, caused by a cytosine-adenine-guanine (CAG) repeat expansion on chromosome four of the Huntingtin gene, and manifests during mid-adulthood. The disease is clinically characterized by motor disturbances, cognitive decline and behavioral changes. The symptoms of HD gradually progress, resulting in increased functional disabilities and less independence. HD gene carriers can be divided into individuals with a genetic and clinical diagnosis (manifest HD), and those without clinical motor symptoms (premanifest HD).

The introduction of this thesis (**chapter 1**) illustrates that cognitive and behavioral changes are the most debilitating symptoms for patients with HD. Cognitive deterioration and psychiatric symptoms are associated with limitations in work, driving, managing finances, and a reduction in quality of life. Unemployment negatively affects psychological well-being and financial stability, and requires adaptation of daily routines. Cognitive and motor functioning have both been associated with work disability in HD. However, the influence of HD symptoms on the ability to work still remains relatively unknown. Safe driving requires the integration of complex cognitive, motor, behavioral and visual functions, which can be impaired in patients with HD. While studies on driving competence in HD are still scarce, it has been observed that driving performance decreases in HD patients. Although previous studies have hinted at diminished driving performance in premanifest gene carriers, this hypothesis has not been tested. The primary objective of this thesis was to study employment and driving ability in gene carriers with HD. We aimed to investigate predictors of work cessation and examine the influence of different symptoms and signs of HD on driving performance.

To explore reasons for work and driving cessation in HD, we used questionnaire responses from HD gene carriers ($N = 191$) who visited the outpatient Neurology clinic of the Leiden University Medical Center between 2016 and 2018 (**chapter 2**). HD gene carriers retired at a mean age of 51 years, which is well before the general retirement age. Our study further illustrates that difficulties with concentration interferes with both the decision to stop working and driving. Internal reasons, which are reasons within the individual, such as declining health or psychological factors (e.g., anxiety), were the most frequently mentioned reasons to stop driving. Men and

women stated different reasons for driving cessation, with men reporting difficulties concentrating and women feelings of anxiety and insecurity as their primary reason to stop driving. Based on our results, we recommend an individual approach to discuss changes in work and driving, acknowledging the differences between male and female perspectives. Early discussion of future work and driving cessation allows the patient to anticipate to functional changes due to HD.

HD gene carriers can become unable to work in their usual profession at a relatively young age and this affects their quality of life. In **chapter 3**, we investigated which clinical signs of HD are predictive of unemployment. Data of employed ($N = 114$) and unemployed ($N = 106$) HD gene carriers were used. Impairments in executive functioning, in particular cognitive inflexibility and attention, and apathy were predictors of unemployment in HD gene carriers. HD gene carriers with lower cognitive performances and more signs of apathy were more likely to be unemployed compared to HD gene carriers with higher cognitive scores and no signs of apathy. This confirms that cognitive and psychiatric impairments are more important to assess when discussing occupational changes than motor dysfunction.

Chapter 4 presents a literature study summarizing the findings of simulator and on-road driving studies in patients with HD, Parkinson (PD) and Alzheimer's disease (AD). The current available literature is not conclusive on if and when patients with a neurodegenerative disorder should be restricted in their driving. None of the studies to date have resulted in practical guidelines that can be implemented in clinical settings. There is a large discrepancy in the amount of studies available regarding driving in HD, compared to PD and AD. Since the etiology of HD is known, this provides the opportunity to investigate both symptomatic and presymptomatic gene carriers in an attempt to detect at which point in the disease driving-related issues become apparent. In most studies, more than half of the patients with a neurodegenerative disorder were classified as safe drivers. Thus, a recommendation regarding driving cessation solely based on a clinical or genetic diagnosis seems unwarranted. Individual evaluations are important and changes in driving performance should be monitored regularly, preferable every year. Due to the progressive nature of neurodegenerative disorders, formal retesting of driving skills is recommended even if the driver's license has been renewed for an extended period of time. The role of the physician is important to start the discussion about potential driving cessation at the right time and to provide the necessary referrals. Previous studies suggested a deterioration in driving performance in the premanifest

phase of HD, but this hypothesis had not yet been sufficiently tested. Therefore, the aim of the study described in **chapter 5** was to compare driving performance in simulated urban and motorway environments between different HD stages and healthy individuals. Further, we wanted to investigate the feasibility of using a driving simulator in HD research. Different simulated traffic situations were used, as well as a comprehensive clinical test battery to determine if performances on these assessments can predict simulator driving. This observational, cross-sectional study was conducted at the Leiden University Medical Center and the Centre for Human Drug Research, and included 29 control participants, 28 premanifest HD, and 30 manifest HD. We found that manifest HD gene carriers drove more cautious when speed limits increased and that they had less vehicle control on the motorway compared to premanifest HD and controls (**chapter 5**). This suggests that patients with HD commit most driving errors on the operational and tactical levels. Premanifest HD gene carriers reported some self-imposed driving restrictions, but alterations in driving performance were not detected in the driving assessment. The driving simulator parameters were able to discriminate between manifest HD and healthy individuals, confirming that a driving simulator is a feasible tool to use when investigating changes in driving in manifest HD. Future studies are necessary to determine if a driving simulator can be used to monitor longitudinal changes in fitness to drive.

Results on clinical tests, such as neuropsychological test batteries, might support health professionals when discussing possible changes in driving with patients and families. We investigated if cognitive, motor, or psychiatric symptoms that are common in HD can predict driving performance (**chapter 6**). Manifest HD performed worse on all clinical assessments compared to controls. There were no significant differences between premanifest HD and controls. Increased postural sway and slower speed of information processing were predictors of driving performance in manifest HD. Although motor functioning was related to driving performance, it was not retained as a predictor. This is in line with previous studies suggesting that cognitive decline is a more suitable predictor of driving than motor impairment. Psychiatric symptoms were unrelated to simulated driving. Worse performance on clinical screening tasks could assist clinicians in their referral for an official on-road driving test.

To determine potential causes of simulator sickness in our cohort, we wanted to examine whether patients with HD are more susceptible to simulator sickness

compared to healthy individuals (**chapter 7**). Further, we explored if the cognitive and motor symptoms that are related to HD potentially increase the risk of developing simulator sickness and, eventually, lead to dropout (**chapter 7**). Up to 30% of the participants in our study dropped out due to symptoms of simulator sickness. The most reported symptoms of simulator sickness by dropouts were difficulties concentrating, dizziness, nausea, sweating, and vomiting. HD gene carriers did not have a significantly higher chance of developing symptoms of simulator sickness while driving in a simulator compared to controls. Our findings confirmed previous results that female gender and older age were associated with increased simulator sickness. In addition, decreased smooth ocular pursuit was a predictor of dropout, whereas cognitive function did not increase the susceptibility to simulator sickness. Researchers should be aware of the simulator sickness phenomenon and the potential dropout rate when designing simulator studies.

The main findings and clinical implications of this thesis are discussed in **chapter 8**. Since there is currently no cure for HD, the focus of treatment is on improving quality of life and providing the necessary support to patients and families. Maintaining independence through employment and driving, for as long and as safely as possible, has a substantial influence on a patient's general functioning. This thesis addresses the topics working and driving ability as being relevant in HD. Our results consistently showed that the cognitive and behavioral changes of HD are more debilitating in daily life than the characteristic motor signs, and are associated with employment and driving a car. Healthcare professionals should be educated about HD to allow them to provide appropriate information to patients and families when discussing possible changes in working and driving as a result of HD. Individual evaluation of driving ability is warranted and the recommendation to stop driving should not solely be based on disease stage or a genetic confirmation. Multidisciplinary screening, using a HD-specific test battery, is recommended and should be embedded in the clinic.

NEDERLANDSE SAMENVATTING

Dit proefschrift beschrijft de resultaten van onderzoek dat wij hebben uitgevoerd naar werken en autorijden met de ziekte van Huntington (HD). HD is een zeldzame, autosomale dominante erfelijke, neurodegeneratieve ziekte die ontstaat door een gen mutatie op chromosoom 4. De ziekte manifesteert zich tussen het 30^e en 50^e levensjaar en heeft een gemiddelde ziekteduur van 17 tot 20 jaar. De ziekte wordt klinisch gekenmerkt door een achteruitgang in de motoriek, cognitieve veranderingen en psychiatrische symptomen, met als gevolg dat patiënten geleidelijk aan worden beperkt in hun dagelijkse activiteiten en dat de kwaliteit van leven verslechtert. De aard en ernst van de symptomen kunnen verschillen per individu. Momenteel is er enkel symptomatische behandeling beschikbaar en geen genezing. Gendragers met HD kunnen worden onderverdeeld in gendragers met een klinische motorische diagnose (manifest) en gendragers zonder klinische diagnose (premanifest).

In de introductie van dit proefschrift (**hoofdstuk 1**) wordt de impact van HD op het dagelijks functioneren van patiënten belicht. Gedurende het ziekteproces neemt de onafhankelijkheid van patiënten met HD geleidelijk af. Cognitieve achteruitgang en gedragsveranderingen zijn over het algemeen ingrijpender voor patiënten met HD en hun familie dan de motorische symptomen. Beperkingen in werk, autorijden, beheren van financiën en een afname in kwaliteit van leven zijn gerelateerd aan afwijkingen in het cognitief functioneren en psychiatrische symptomen. Echter, de invloed van HD symptomen op werkgeschiktheid is nog relatief onbekend. Een afname in de rijvaardigheid is een van de eerstgenoemde veranderingen die HD gendragers rapporteren. Veilig autorijden vraagt om de integratie van complexe motorische, cognitieve, visuele functies en gedrag. Dit zijn factoren die aangedaan kunnen zijn bij patiënten met HD. Onderzoeken naar autorijden met HD zijn schaars, maar eerdere resultaten laten zien dat de rijvaardigheid afneemt in patiënten met HD. Ondanks dat eerder onderzoek suggereert dat er ook in de eerste presymptomatische fase van HD veranderingen in de rijvaardigheid kunnen optreden, is deze hypothese niet eerder onderzocht.

Het primaire doel van dit proefschrift was om werken en rijvaardigheid te onderzoeken in gendragers met HD. We hebben onderzocht welke symptomen van HD voorspellend zijn voor werken en de rijvaardigheid van premanifest en manifest HD vergeleken met controle deelnemers.

We hebben vragenlijst onderzoek uitgevoerd in gendragers met HD ($N = 191$) om redenen voor stoppen met werken en autorijden te bestuderen (**hoofdstuk 2**). Dit onderzoek is uitgevoerd tussen 2016 en 2018 bij de polikliniek Neurologie van het Leids Universitair Medisch Centrum. Gendragers met HD waren gemiddeld 51 jaar oud wanneer zij stopten met werken en dit is aanzienlijk eerder dan de algemene pensioensleeftijd van 65-67 jaar. Daarnaast liet ons onderzoek zien dat een verminderde concentratie van invloed was op zowel de beslissing om te stoppen met werken als de beslissing om te stoppen met autorijden. Interne redenen om te stoppen met autorijden, zoals een slechtere gezondheid en psychologische factoren (e.g., angst) waren de meest genoemde redenen om te stoppen met autorijden. Mannen en vrouwen rapporteerden verschillende redenen om te stoppen met autorijden. Voor mannen bleek een verminderde concentratie de belangrijkste reden, terwijl vrouwen angst en onzekerheid als hun voornaamste reden opgaven om te stoppen. Op basis van deze resultaten adviseren wij een individuele aanpak bij het bespreken van veranderingen in werk en autorijden, waarbij men rekening moet houden met verschillen tussen mannen en vrouwen. Het tijdig bespreekbaar maken van toekomstige aanpassingen in werk en autorijden geeft de patiënten de mogelijkheid om zich voor te bereiden op deze praktische beperkingen als gevolg van HD.

Gendragers met HD kunnen al op relatief jonge leeftijd onbekwaam worden om hun werk voldoende uit te voeren en dit heeft een negatieve invloed op hun kwaliteit van leven. In **hoofdstuk 3** hebben we onderzocht welke klinische symptomen van HD voorspellend zijn voor stoppen met werken. Gegevens van werkende ($N = 114$) en niet werkende ($N = 106$) HD gendragers zijn onderzocht. Achteruitgang in executief functioneren en apathie waren voorspellend voor niet werken in HD gendragers. HD gendragers met een slechter cognitief functioneren en apathie hadden een grotere kans om niet werkzaam te zijn dan gendragers zonder apathie en met een beter cognitief functioneren. Deze resultaten bevestigen dat cognitieve en psychiatrische symptomen belangrijker zijn om te onderzoeken dan de karakteristieke motor symptomen van HD wanneer er sprake is van veranderingen in werk.

Hoofdstuk 4 omvat de resultaten van een literatuuronderzoek waarbij de bevindingen van onderzoeken met een simulator en rijtesten op de weg bij patiënten met HD, Parkinson (PD) en Alzheimer (AD) zijn samengevat. Op basis van de beschreven literatuur is het niet mogelijk om een conclusie te trekken of en wanneer patiënten met een neurodegeneratieve aandoening moeten stoppen met autorijden.

Tot dusver hebben de resultaten van de onderzoeken niet geleid tot richtlijnen die geïmplementeerd kunnen worden in de klinische praktijk. Er zijn veel minder onderzoeken naar autorijden met HD vergeleken met het aantal onderzoeken in PD en AD. Aangezien de etiologie van HD bekend is geeft dit de mogelijkheid om zowel presymptomatische als symptomatische gendragers te onderzoeken, zodat men kan proberen te bepalen wanneer in het ziekteproces veranderingen in de rijvaardigheid optreden. In de meeste onderzoeken werd meer dan de helft van de patiënten met een neurodegeneratieve aandoening geclassificeerd als veilige rijder. Dit suggereert dat een advies om te stoppen met autorijden niet enkel gebaseerd moet worden op een klinische of genetische diagnose. Individuele beoordeling is van belang en veranderingen in de rijvaardigheid moeten, idealiter elk jaar, worden getoetst. Ook als het rijbewijs eerder met een langere periode is verlengd, wordt her-testen aanbevolen vanwege het progressieve karakter van neurodegeneratieve stoornissen. De rol van de behandelaar is essentieel om een gesprek over potentieel stoppen met autorijden op het juiste moment te starten en de patiënt en zijn familie te voorzien van de juiste verwijzingen en informatie.

In eerder onderzoek werd gesuggereerd dat een verslechtering in de rijvaardigheid reeds zou kunnen optreden in de vroege, presymptomatische fase van HD. Echter, deze hypothese was nog niet eerder onderzocht. Het doel van het onderzoek beschreven in **hoofdstuk 5** en **hoofdstuk 6** was om de rijvaardigheid in verschillende verkeerssituaties (i.e., stad en snelweg) te vergelijken tussen verschillende stadia van HD en gezonde controles. Dit observationele, cross-sectionele onderzoek is uitgevoerd in het Leids Universitair Medisch Centrum en het Centre for Human Drug Research in Leiden. Er zijn 29 controle deelnemers, 28 premanifest HD en 30 manifest HD geïnccludeerd. De rijvaardigheid werd getest met behulp van een rijsimulator en er werd een uitgebreide neuropsychologische testbatterij afgenomen om te bepalen of de uitkomsten van deze taken voorspellend zijn voor autorijden.

Onze resultaten lieten zien dat manifest HD de neiging hebben om voorzichtiger te rijden in een rijsimulator wanneer de snelheidslimiet hoger is en dat zij minder controle hebben over het voertuig op de snelweg vergeleken met premanifest HD en controles (**hoofdstuk 5**). Dit suggereert dat patiënten met HD met name fouten maken op operationeel en tactisch niveau. Premanifest HD gendragers rapporteerden een aantal zelf opgelegde restricties in hun rijgedrag, maar er werden geen veranderingen in de rijvaardigheid in de rijsimulator geobserveerd. Met de gebruikte parameters kon er onderscheid worden gemaakt tussen manifest HD en controles, wat het gebruik van een rijsimulator als maat voor rijvaardigheid in

onderzoek verder ondersteunt. Toekomstig onderzoek is nodig om te bepalen of een simulator ook gebruikt kan worden om veranderingen in de rijvaardigheid te meten over een langere periode (i.e., longitudinaal).

Uitslagen van klinische testen, zoals neuropsychologisch onderzoek, kunnen ondersteunend zijn voor behandelaren wanneer zij eventuele veranderingen in de rijvaardigheid bespreken met patiënten en hun families. Wij hebben onderzocht of de cognitieve, motorische of gedragsveranderingen die voorkomen bij HD voorspellend zijn voor rijvaardigheid (**hoofdstuk 6**). Manifest HD scoorden slechter op alle klinische testen vergeleken met controles. Er waren geen significante verschillen tussen premanifest HD en controles. Een instabieler lichaamshouding en vertraagde verwerkingsnelheid bleken voorspellers voor rijvaardigheid in manifest HD. Motorisch functioneren bleek gerelateerd aan de rijprestaties, maar was geen voorspeller. Dit is vergelijkbaar met voorgaand onderzoek waaruit bleek dat cognitieve achteruitgang een betere voorspeller is voor rijvaardigheid dan motorische beperkingen. Psychiatrische symptomen waren niet gerelateerd aan rijvaardigheid. Slechtere prestaties op klinische screeningstaken kunnen behandelaren ondersteunen in hun verwijzing voor een officiële rijtest op de weg. Een HD specifieke testbatterij die gevalideerd is en waarin cut-off scores zijn gedefinieerd is momenteel nog niet ontwikkeld. Dit is noodzakelijk alvorens een dergelijke testbatterij kan worden geïmplementeerd in de klinische praktijk.

Simulator ziekte is een bijwerking die voorkomt in onderzoek met simulatoren. De symptomen van simulator ziekte zijn vergelijkbaar met wagenziekte, zoals transpireren, duizeligheid en misselijkheid. In onze studie hebben wij vergeleken of gendragers met HD gevoeliger zijn voor het ontwikkelen van simulator ziekte dan controle deelnemers, om de potentiële oorzaken van simulator ziekte in kaart te brengen (**hoofdstuk 7**). Daarnaast hebben we onderzocht of de cognitieve en motorische symptomen van HD het risico op het ontstaan van simulator ziekte verhogen. Hierdoor zou de kans op uitval door simulator ziekte ook kunnen toenemen. Rond de 30% van de deelnemers in onze studie viel uit als gevolg van simulator ziekte. De meest gerapporteerde symptomen van simulator ziekte waren moeite met concentreren, duizeligheid, misselijkheid, transpireren en de neiging tot overgeven. Wij concludeerden dat HD gendragers geen significant hogere kans hadden om simulator ziekte te ontwikkelen dan controle deelnemers. Onze resultaten bevestigden de bevindingen uit voorgaande studies dat een hogere leeftijd en vrouwelijk geslacht geassocieerd zijn met het ontstaan van simulator ziekte. Daarnaast bleek dat een vertraging in de oogbewegingen voorspellend was

voor uitval, terwijl verminderd cognitief functioneren niet voor een hoger risico op simulator ziekte zorgde. Onderzoekers moeten zich bewust zijn van het voorkomen van simulator ziekte bij het ontwikkelen van studieprotocollen. Meer training in de simulator en aanpassingen in de scenario's zouden het ontstaan van simulator ziekte wellicht kunnen verminderen.

Tot slot worden de belangrijkste bevindingen van dit proefschrift samengevat in **hoofdstuk 8**. De klinische implicaties worden besproken en er worden suggesties gedaan voor nader onderzoek. Momenteel is er geen genezing voor HD en ligt de focus van behandeling op het behouden van kwaliteit van leven en het ondersteunen van patiënten en hun families. Het behoud van onafhankelijkheid door middel van werk en autorijden, voor zolang mogelijk en veilig, heeft een substantiële impact op het algemeen functioneren van patiënten met HD. De resultaten van dit proefschrift laten zien dat stoppen met werken en autorijden belangrijke onderwerpen zijn voor gendragers met HD. Behandelaren moeten worden voorgelicht over de impact van stoppen met werken en autorijden, zodat zij in staat zijn om patiënten van de juiste informatie te voorzien. Daarnaast is individuele beoordeling van de rijvaardigheid noodzakelijk en de aanbeveling om te stoppen met rijden zou niet alleen gebaseerd moeten worden op de genetische aanwezigheid van HD of ziektestadium. Multidisciplinaire screening met een HD specifieke testbatterij wordt aanbevolen en moet worden geïmplementeerd in de klinische praktijk.

Appendix

DANKWOORD

Allereerst wil ik graag alle deelnemers bedanken voor hun bijdrage aan dit onderzoek. Zonder hen was dit proefschrift er evident niet geweest.

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Mijn paranimfen Emma en Anne: ik ga het missen om zo intensief met jullie samen te werken!

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Appendix

LIST OF PUBLICATIONS

Coppen EM, **Jacobs M**, van der Zwaan KF, Middelkoop HAM, Roos RAC. Visual object perception in premanifest and early manifest Huntington's disease. Archives of Clinical Neuropsychology. 2019 [e-pub ahead of print]

Jacobs M, van der Zwaan KF, Hart EP, Groeneveld G, Roos RAC. Comparable rates of simulator sickness in Huntington's disease and healthy individuals. Transportation Research Part F: Traffic Psychology and Behaviour. 2019; 60:499-504

Jacobs M, Hart EP, Mejia Miranda Y, Groeneveld G, van Gerven JMA, Roos RAC. Predictors of simulated driving performance in Huntington's disease gene carriers. Parkinsonism and Related Disorders. 2018 [e-pub ahead of print]

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* Both authors contributed equally to the manuscript

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Jacobs M, Coppen EM, Roos RAC. Reasons why Huntington's disease gene carriers decide to stop working or driving. – *submitted*

CURRICULUM VITAE

Milou Essink-Jacobs was born on 19 September 1990 in Oldenzaal. After completing her pre-university education, Milou started her study in Psychology at the University of Groningen in 2008. In 2012, she transferred to the University of Amsterdam and obtained her Master's degree in Clinical Health Psychology, with the specialization Clinical Neuropsychology, with distinction in 2014. During her study, she gained experience as a student assistant working on multiple research projects within the University of Amsterdam and the Academic Medical Center of Amsterdam.

Milou finished her clinical internship at the Neuropsychology section of the department of Neurology of the Leiden University Medical Center, where she also had her first introduction with patients with Huntington's disease. After her internship, she worked as a research assistant for the TRACK-HD study before starting her PhD in 2015 under supervision of Prof. dr. R.A.C. Roos, of which this thesis is the result. For her thesis project, she collaborated with the Centre for Human Drug Research in Leiden.

During her PhD, Milou was an active member of the Driving Task Force of the European Huntington's Disease Network. She also coordinated multiple clinical trials and presented her research at several conferences.

Milou lives in Haarlem and is married to Hugo. She is currently working as a Clinical Research Associate at the Amsterdam University Medical Center.

