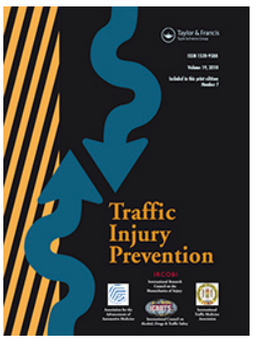

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# Altered driving performance of symptomatic Huntington's disease gene carriers in simulated road conditions

Milou Jacobs[a], Ellen P. Hart[b], Yuri Mejia Miranda[c], Geert Jan Groeneveld[b], Joop M. A. van Gerven[b], and Raymund A. C. Roos[a]

[a]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands; [b]Centre for Human Drug Research, Leiden, The Netherlands; [c]Department of Statistics, Centre for Human Drug Research, Leiden, The Netherlands

**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 performance 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 3 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.

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**KEYWORDS**
Driving behavior; driving simulator; Huntington's disease; SDLP

## 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 (Helder et al. 2001). HD is an inherited neurodegenerative disorder characterized by a triad of symptoms, including motor disturbances, cognitive dysfunction, and psychiatric symptoms (Roos 2010). 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 (Bates et al. 2015; Roos 2010). The clinical hallmark of HD is the presence of chorea, which are unwanted, involuntary jerky movements of different body parts (Roos 2010). 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 (Beglinger et al. 2012; Paulsen et al. 2008). 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 4 studies have investigated driving competence in HD using either on-road or simulated driving assessments (Devos et al. 2012, 2014; Hennig et al. 2014; Jacobs et al. 2017; Rebok et al. 1995). 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; Rebok et al. 1995). They were also less accurate, had longer reaction times, and committed more overall errors compared to healthy controls during simulated driving (Rebok et al. 1995). Still, 72% of the HD patients in this study continued driving after disease onset (Rebok et al. 1995). Studies using on-road driving

CONTACT Milou Jacobs m.jacobs@lumc.nl Department of Neurology Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands.
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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 (Devos et al. 2012, 2014). In particular, errors in lane positioning, speed adaptations, keeping distance, turning left, and lane changing were observed (Devos et al. 2014). 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 2 patients with maximum functional capacity scores also failed the on-road test (Devos et al. 2014). 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 (Devos et al. 2012, 2014; Hennig et al. 2014). A recent study showed that specific assessments are necessary when evaluating driving competence in different types of dementia (Piersma et al. 2018). Patients with HD who failed the on-road driving assessment also performed worse on driving simulator evaluations (Devos et al. 2012). 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 (Devos, Vandenberghe et al. 2013; Lee et al. 2007; Mayhew et al. 2011).

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 km in the previous 12 months before inclusion. All HD participants had a confirmed cytosine–adenine–guanine (CAG) expansion of $\geq$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 h 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 participant's 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 score 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; Huntington Study Group 1996). 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; Shoulson and Fahn 1979). 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-in. flat-panel monitors; a steering wheel; gas, brake, and clutch pedals; and gearshifts (Figure 1). The dashboard, side mirrors, and rearview mirror were displayed on the screens.

The total duration of the driving session was approximately 45 min. Participants started with a practice session for 8 min 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.

(A) Driving Simulator

(B) Urban scenario

(C) Motorway scenario

**Figure 1.** Driving simulator and example of the scenarios. Examples of the scenarios correspond with what is displayed on the middle screen.

The sequence of events was standardized for all participants. The second part of the driving session was a motorway scenario and had a duration of approximately 30 min, with a maximum allowed speed of 100 km/h. Participants were allowed to overtake other vehicles. In the final 10 min 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 2 road conditions (urban and motorway) among the 3 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 rho 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 Ver. 23.0. Statistical significant was set at $P < .05$.

## 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 (Tabrizi et al. 2009). 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 data set 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 (see online supplement).

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, $t(15) = 0.92$, $P = .306$. 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 their 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.

### Urban scenario

One control participant, one premanifest HD, and 6 manifest HD crashed during the urban scenario ($\chi^2 = 6.91$, $P = .032$). 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 ($\beta = -4.78$, $P = .005$) and premanifest HD ($\beta = -4.94$; $P = .004$). In addition, manifest HD had more variability in their speed while driving in the 30 km/h zone compared to premanifest HD ($\beta = 0.80$, $P = .002$; 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 ($r = 0.36$, $P < .001$). All significant correlations are reported in Table A2 (see online supplement).

### 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 3 groups (Table 4). Manifest HD drove significantly slower on the motorway than controls ($\beta = -2.75$, $P = .016$) and premanifest HD ($\beta = -2.32$, $P = .047$; Table 3). They also had a larger variability in their speed compared to premanifest HD ($\beta = 2.35$, $P = .007$). The SDLP of the manifest HD was significantly larger compared to both controls ($\beta = 6.68$, $P = .034$) and premanifest HD ($\beta = 10.47$, $P = .001$).

The UHDRS-TMS had a moderate correlation with speed variability ($\rho = 0.47$, $P < .01$) and SDLP ($r = 0.59$, $P < .01$),

**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 male/female (% male) | 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) 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 5,000 and 10,000 km; 3 = between 1,000 and 5,000 km; 4 = less than 1,000 km.
Significant P values (P < .05) are in bold.

**Table 2.** Group differences in driving performance in the urban scenario.[a]

| Parameter | Controls | Premanifest HD | Manifest HD | *P* value |
|---|---|---|---|---|
| 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 (m) | 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.

**Table 3.** Differences between the groups in the urban and motorway scenarios according to generalized linear models.

| | Premanifest HD vs. controls | | Manifest HD vs. controls | | Manifest HD vs. premanifest HD | |
|---|---|---|---|---|---|---|
| Parameter | β (95% confidence interval) | *P* value | β (95% confidence interval) | *P* value | β (95% confidence interval) | *P* 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 | *P* 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 (m) | 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.

which were the strongest correlations observed on 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 studies (Ranchet et al. 2011), 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 ($r = -0.31$, $P = .005$), meaning that a lower speed is related with higher variability in speed. This correlation was stronger ($r = -0.53$, $P = .006$) in manifest HD only.

## 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 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 (Michon 1989). 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 (Devos et al. 2014; Rebok et al. 1995). 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 difficulty 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 (Brookhuis et al. 2003; Piersma et al. 2016; Uc and Dastrup 2009; Verster and Roth 2011). 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 (Paxion et al. 2014). Both low- and high-demand situations can result in too much mental workload and affect driving performance (Paxion et al. 2014). A recent study, however, observed limited effects of age and driving experience in simulated urban driving (Michaels et al. 2017). 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 7.1 min). This is important to keep in mind when comparing results and defining new study protocols. Motorway driving often involves fewer 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 (Paulsen et al. 2008). In addition, concerns about driving safety are one of the earliest reported functional disabilities (Beglinger et al. 2010; Williams et al. 2011). 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 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 (Devos et al. 2012). 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 (Liddle et al. 2016). 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 (Devos et al. 2012; Heikkilä et al. 1998; Wild and Cotrell 2003). Previous findings showed that patients with HD are unaware of their own functional impairments (Ho et al. 2006; Hoth et al. 2007). In clinical practice, spouses and other family members are often the first to express concerns about the driving competence of HD patients (Beglinger et al. 2010). 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 1 to 10, 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 performance, but the ecological validity and generalizability to a real vehicle might be somewhat limited (Aksan et al. 2016; Devos et al. 2012; Mayhew et al. 2011). 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 (Devos, Vandenberghe et al. 2013). 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 (Devos, Nieuwboer et al. 2013). 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 dropout (Classen et al. 2011). 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 (Helland et al. 2016). In addition, symptoms of simulator sickness are not always restricted to the group of participants with the worst performance or related to cognitive impairments (Matas et al. 2015; Mullen et al. 2010). 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 (Pavlou et al. 2017). 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 whether a driving simulator can be used to monitor longitudinal changes in fitness to drive.

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