Impact of Huntington's disease on working and driving

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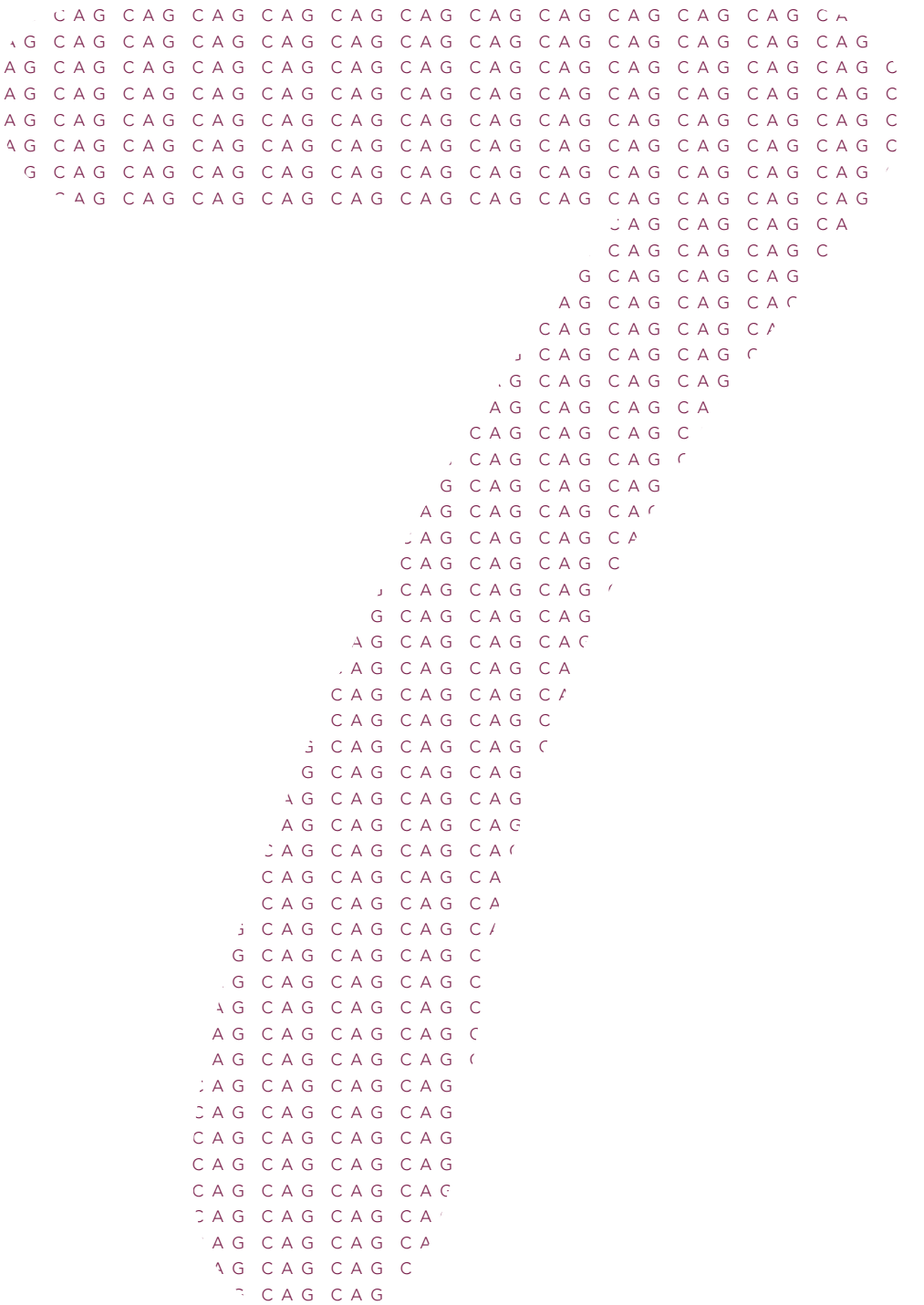

Comparable rates of simulator sickness in Huntington's disease and healthy individuals

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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

	Completers (N=58)		Dropouts (N=25)			
Task	Mean	SD	Mean	SD	*F* (df)	*p*-value
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

	Completers (*N*=39)		Dropouts (*N*=18)			
Questionnaire item	Mean	SD	Mean	SD	U	*p*-value
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 here is a mismatch between the visual motion a person sees and the motion that they experience, called vection.[28] If there is a decrease in how smooth the eyes perceive the visual input, resulting in a more distorted and choppier 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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