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Symbol digit modalities test predicts decline of off-road driving ability in Japanese patients with multiple sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic progressing neurological disease with exacerbations and remissions. Patients with MS can show a variety of neurological symptoms. Cognitive decline is noticed as one of them and is related with deterioration of daily life quality in a clinical practice. Driving a car is one of the common activities required in daily life and is also an important issue in MS patients.

Methods: To clarify the relationship between cognitive function and driving ability in MS patients, the symbol digit modalities test (SDMT) and a driving simulator were evaluated. We enrolled 24 patients with MS (5 males, 19 females, 39.04 ± 8.27 years old) and age- and sex-matched 24 healthy controls (5 males, 19 females, 40.54 ± 9.78 years old) in this study. They underwent the SDMT and also used a driving simulator to measure a total of 12 response values related to driving ability. In order to evaluate the relationship between SDMT and driving ability, MS patients were divided into two groups according to the median SDMT score: group A (SDMT 51 or more) and group B (SDMT less than 51). The data were statistically analyzed among control group, MS group A, and MS group B using Jonkheere-Terpstra trend test and Bonferroni's multiple comparison test.

Results: The group with higher scores on the SDMT tended to have significantly higher driving performance. Multiple comparison analysis among three groups showed that the reaction values for speed of response behavior were significantly higher in MS group B than control group.

Conclusion: This study revealed a relationship between driving abilities and SDMT scores. Clinical evaluation using the SDMT may help to detect cognitive decline and to make a decision on driving a car in patients with MS.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system clinically characterized by dissemination of the plaques in time and space. It causes a variety of neurological symptoms, including cranial nerve symptoms, pyramidal tract symptoms, cerebellar symptoms, and cognitive function. It is well-known that MS occurs mainly in young adults. However, in more than half of patients, cognitive decline is observed in the early phase from the onset, even when motor symptoms are minimal (Rocca et al., 2015). Especially, attention deficits and slowed information processing are characteristic and frequent (Chiaravalloti and Deluca, 2008; Rao et al., 1991a).

The brief repeatable battery of neuropsychological test (BRB-N) is widely used in Europe and the United States as a test battery to evaluate cognitive functions in MS patients. BRB-N consists of seven subtests, including the symbol digit modalities test (SDMT), which reflects visual attention and information processing speed, and the paced auditory serial addition test (PASAT), which reflects auditory attention and information processing speed. BRB-N can detect cognitive decline in MS patients with a sensitivity of 71% and a specificity of 94% (Rao et al., 1991b). A study conducted using the Japanese version of the BRB-N reported that MS patients scored significantly lower than healthy controls on all subtests, with the SDMT and the PASAT being particularly useful in assessing cognitive decline in MS (Niino et al., 2014). Another study reported that SDMT is the most sensitive method to assess

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cognitive decline in MS (Benedict and Zivadinov, 2011).

One of the most important issues in daily life is driving a car. Drivers require advanced cognitive functions such as processing various traffic information on the road and have to pay attention to pedestrians (Michon, 1985). Among neurological conditions, driving issues have been discussed in dementias and movement disorders (Grace et al., 2005). However, an association between cognitive function and driving issues still remains unclear in patients with MS. In a study, accidents and concentration problems during driving were more common in MS patients than in healthy controls (Kotterba et al., 2003). The number of motor vehicle accidents requiring emergency treatment was 3.4 times higher when MS patients drove a car (Lings, 2002). Furthermore, in the other study, comparing MS patients with cognitive decline with MS patients without cognitive decline, the incidence of motor vehicle crashes was higher in the group with cognitive decline (Schultheis et al., 2001). In the real world, 23% of patients diagnosed with MS have quit driving (Ryan et al., 2009).

A driving simulator is a useful tool for objectively and quantitatively evaluating automobile driving ability (Jacobs et al., 2017). However, very few studies have evaluated off-road driving ability using a driving simulator in MS, and almost no studies have examined the relationship between off-road driving ability and cognitive function (Harand et al., 2018). In addition, although some studies have shown a significant correlation between the PASAT and accident rates on driving simulators (Kotterba et al., 2003), the relationship between the SDMT and driving ability has not yet been investigated. The SDMT is reported as an optimal test battery to assess cognitive function in MS patients (Benedict and Zivadinov, 2011; Benedict et al., 2017). Therefore, we aimed to clarify the relationship between the SDMT and driving ability in MS patients in this study.

2. Methods

2.1. Subjects

We recruited patients with a diagnosis of MS according to the McDonald (2010) criteria (Polman et al., 2011) and satisfied the inclusion criteria of this study from December 2020 to September 2021, which include the following items; (i) having no or mild motor impairment with an expanded disability status scale (EDSS) (Kurtzke et al., 1983) of 4.5 or less, (ii) obtaining a driver's license, and (iii) driving a car on a daily basis. Patients with the mini-mental state examination (MMSE) score of less than 23 and obvious cognitive impairment or those with moderate or severe systemic diseases were excluded. The control group consisted of healthy subjects with no history of neurological diseases. The EDSS was evaluated by an experienced board-certified neurologist. The MMSE and the SDMT were performed by two experienced clinical neuropsychologists. We also determined a history of traffic accidents with driving fault within the last 5 years using with a self-administered questionnaire.

The protocol for this research project has been approved by the ethics committee of the institution (MH2020-156, 030121-03) and it conforms to the provisions of the declaration of Helsinki. Written informed consents were obtained from the all participants in this study.

2.2. Driving ability test

MS patients and controls underwent a driving ability test using a driving simulator system coupled with personal computer installed a software packed virtual driving courses and automatic evaluation tools of driving abilities (Honda Safety Navi®, Honda Motor Co., Ltd., Tokyo, Japan), which is commonly used in Japan to evaluate driving ability for the purposes of both clinical practice in patients under rehabilitation and clinical research (Nakagawa et al., 2019; Okuma et al., 2020; Takehara et al., 2016; Ooba et al., 2017).

The simulator consists of a monitor, a steering wheel, an accelerator pedal, and a brake pedal. Driving response tests were conducted on a sitting position in front of monitors, in which participants performed specified driving actions in response to instructions displayed on monitors. There were four types of tests; the simple response test (SR1) using only the accelerator pedal, the selective response test (SR2) using the accelerator pedal and the brake pedal, the steering wheel test (SW) using only the steering wheel, and the attention distribution and multiple tasks test (MT) using all of the steering wheel, the accelerator pedal, and the brake pedal. All tests begin when a driver presses the accelerator pedal with the right foot. In SR1, when the blue light appears on the monitor, a driver takes the foot off the accelerator pedal and immediately steps on the accelerator pedal, repeating this action 35 times. In SR2, a driver performs three types of actions randomly for a total of 50 times: when the red light appears on the monitor, a driver steps on the brake pedal with the right foot and immediately presses the accelerator pedal; when the yellow light appears, a driver takes the foot off the accelerator pedal and immediately presses the accelerator pedal; when the blue light appears, a driver continues to press the accelerator pedal. In SW, when two pylons appear on either side of the monitor, a driver quickly moves into the lane between the pylons by operating the steering wheel, repeating this action 36 times. In MT, a driver performs not only the same accelerating and braking operations as in SR2, but also turns the steering wheel quickly in the direction of the arrow when it appears on the monitor, for a total of 96 times. A total of 12 reaction values related to driving ability were measured, with speed of response behavior, unevenness in response behavior, false response, accuracy of operation evaluated, and left-right balance in each test. The speed of response behavior is a value (seconds) calculated as the average time from the instructions displayed on the monitor until the specified reaction, in which the smaller value indicates the faster the speed to response. Unevenness in response behavior is a value (seconds) expressing the degree of dispersion relative to the average time from the instructions displayed on the monitor until the specified reaction, expressed as a standard deviation value, in which the smaller value indicates less dispersion in response speed. False response is the total number of times that a given action is wrong in response to the instructions displayed on the monitor, in which the smaller value indicates fewer errors. Accuracy of operation is a percentage of the failed number of times to move into the lane correctly in the SW, in which the smaller value indicates more accurate operation. Left-right balance is a ratio (%) of the time taken to move to the left side to the right side in SW, in which the smaller value indicates that there is no difference in the speed of movement between the left and right sides. These driving reaction values were also evaluated as five grades of excellent (A), good (B), normal (C), cautious (D), and anxious (E), compared to the average of the same generation, referring to the age-specific reference values in this drive simulator. If it is equivalent to the same generation average, it is rated as grade C. The grade D and grade E mean that the driving reaction response is lower than the standard response. To reduce measurement variability according to the individual habituation, subjects practiced the entire process at once and took a second measurement within two weeks. We used the results of the second measurement for our analysis.

2.3. Statistical analysis

The mean values of each response of the driving simulator, the total number of grade D and grade E, and the number of grade E were compared between the two groups of MS and controls by using with Mann-Whitney's U test.

In order to evaluate the relationship between the SDMT and driving ability, we divided MS patients into two groups by the median SDMT score to avoid as much selection bias as possible, which were group A with SDMT 51 or more and group B with SDMT less than 51. Each response value of the driving simulator, the total number of grade D and grade E, and the number of grade E were obtained, and the linear trend of the mean values among controls, group A, and group B was analyzed using with the Jonkheere-Terpstra trend test. Comparison among three groups was also analyzed using with Bonferroni's multiple comparison test.

SPSS version 25 (IBM Japan, Tokyo, Japan) was used for all statistical analysis. Significance level is defined as $p < 0.05$.

3. Results

3.1. Clinical characteristics

A total of 24 patients with MS (5 males, 19 females, 39.04 ± 8.27 years old) and age- and sex-matched 24 healthy controls (5 males, 19 females, 40.54 ± 9.78 years old) were enrolled in the study (Table 1). Years of education were shorter in the MS group (13.46 ± 1.47 years) than the control group (15.22 ± 2.07 years) with a statistical significance ($p = 0.02$). In patients with MS, EDSS was 1.0 (0 - 2.0), and duration of illness was 8.29 ± 6.61 years. Their MMSE score was 29.58 ± 0.58. There was no significant correlation between their years of education and the SDMT scores ($p = 0.13$). The SDMT score was significantly lower in the MS group than the control group ($p < 0.001$) which were 48.67 ± 10.70 and 63.42 ± 7.60, respectively. EDSS is shown as median and interquartile range (IQR) and other values are shown as mean ± standard deviation.

3.2. History of traffic accidents

Within the last 5 years, 4 traffic accidents with driving fault have occurred in 4 patients with MS and 1 traffic accident in 1 control subject. We could not obtain information about traffic accident from 1 subject in control. The rates of subjects experienced any traffic accidents were 16.67% in the MS group and 4.35% in the control group. There was not significantly difference between two groups ($p = 0.348$).

3.3. Difference of driving ability between MS patients and controls

The detailed results of the driving simulator for control group and MS group are shown in Table 2. MS group showed significantly higher values of speed of response behavior in all tests and unevenness in response behavior in SR2 than control group. On the automatic grading tool of driving abilities, total number of grade D and grade E was 2.21 ± 1.79 in the control group and 3.79 ± 2.36 in the MS group, which was significantly higher in the MS group than in the control group ($p = 0.018$). The number of grade E was 0.29 ± 0.62 in the control group and 1.33 ± 1.37 in the MS group, which was also significantly higher in the MS group than in the control group ($p = 0.001$). Nobody complained of evident simulator sickness (Classen et al., 2011) in subjects of this study.

Table 1
Clinical characteristics.

	Controls(n = 24)	MS patients(n = 24)	P value
Age, mean ± SD, range (years)	40.54 ± 9.78, 21–59	39.04 ± 8.27, 25–56	0.403
Sex, M/F	5/19	5/19	> 0.999
Education, mean ± SD, range (years)	15.22 ± 2.07, 12–21	13.46 ± 1.47, 12-16	0.02
MMSE, mean ± SD, range	-	29.58 ± 0.58, 28–30	-
EDSS, median (IQR)	-	1.0 (0–2.0)	-
Duration of illness, mean ± SD, range (years)	-	8.29 ± 6.61, 0–27	-
SDMT, range	63.42 ± 7.60, 43–78	48.67 ± 10.7, 24–65	< 0.001
Subjects rate having traffic accidents for 5 years (%)	4.35	16.67	0.348

MS, multiple sclerosis; SD, standard deviation; IQR, interquartile range; MMSE, mini-mental state examination; EDSS, expanded disability status scale; SDMT, symbol digit modalities test.

Table 2
Difference of driving ability between MS patients and controls.

Simulation tests	Reaction values on driving ability	Controls(n = 24)	MS patients (n = 24)	P value
Simple response test	Speed of response behavior (mean sec)	0.35 ± 0.02	0.37 ± 0.04	0.006
	Unevenness in response behavior (SD sec)	0.04 ± 0.02	0.04 ± 0.01	0.934
Selective response test	Speed of response behavior (mean sec)	0.63 ± 0.06	0.70 ± 0.09	0.001
	Unevenness in response behavior (SD sec)	0.08 ± 0.02	0.11 ± 0.04	0.009
	False response (times)	2.75 ± 2.79	3.17 ± 3.56	0.744
	Speed of decision (mean sec)	0.19 ± 0.06	0.23 ± 0.09	0.112
Steering wheel test	Speed of response behavior (mean sec)	1.93 ± 0.17	2.22 ± 0.53	< 0.001
	Accuracy of operation (winning rate, %)	15.4 ± 18.2	22.1 ± 21.0	0.157
	Left-right balance (%)	11.7 ± 8.50	14.6 ± 19.3	0.797
Multiple tasks test	Speed of response behavior (mean sec)	0.73 ± 0.07	0.82 ± 0.07	0.001
	Unevenness in response behavior (SD sec)	0.13 ± 0.04	0.81 ± 0.07	0.062
	False response (times)	1.71 ± 1.65	2.46 ± 2.91	0.555

MS, multiple sclerosis; SD, standard deviation. All values are shown as mean ± SD.

3.4. Reaction values on driving ability among controls, MS group A, and MS group B

The detailed results of the driving simulator for control group, MS group A, and MS group B are shown in Table 3. The group with higher scores on the SDMT tended to have significantly higher driving performance in the reaction values for speed of response behavior in all tests and unevenness in response behavior in SR2 and MT ($p < 0.05$). The total number of grade D and grade E was 2.21 ± 1.79 in the control group, 3.64 ± 1.86 in the MS group A and 3.92 ± 2.78 in the MS group B, which showed significant increasing trend ($p = 0.024$). The number of grade E was 0.29 ± 0.62 in the control group, 1.64 ± 1.36 in the MS group A and 1.08 ± 1.38 in the MS group B, which also showed significant increasing trend ($p = 0.010$).

Multiple comparison among three groups showed that the reaction values for speed of response behavior in driving response tests (Fig. 1) and unevenness in response behavior in MT were significantly higher in the MS group B than the control group (Fig. 2). The reaction values for speed of response behavior in SW was also significantly higher in the MS group A (Fig. 1). The number of grade E was 1.64 ± 1.36 in the MS group A and 1.08 ± 1.38 in the MS group B, which in the MS group A was significantly higher ($p < 0.01$) than in the control group (0.29 ± 0.62).

4. Discussion

4.1. Practical significance of the SDMT in drivers with MS

Impaired cognitive function is a factor deteriorating driving ability. Although some studies have assessed the ability of MS patients to drive a car on-road (Morrow et al., 2018; Marcotte et al., 2008), very few studies have quantitatively assessed it using a car driving simulator. The driving ability of MS patients was evaluated using with a driving simulator and the SDMT in this study. The SDMT is a cognitive function test battery to

Table 3
Trend of mean reaction values on driving ability among controls, MS group A, and MS group B.

Simulation tests	Reaction values on driving ability	Controls ($n = 24$)	MS patients		P values for trend
			group A ($n = 11$)	group B ($n = 13$)	
Simple response test	Speed of response behavior (mean sec)	0.35 ± 0.02	0.36 ± 0.03	0.39 ± 0.04	0.001
	Unevenness in response behavior (SD sec)	0.04 ± 0.02	0.04 ± 0.02	0.05 ± 0.01	0.567
Selective response test	Speed of response behavior (mean sec)	0.63 ± 0.06	0.70 ± 0.11	0.71 ± 0.07	0.002
	Unevenness in response behavior (SD sec)	0.08 ± 0.02	0.11 ± 0.04	0.11 ± 0.04	0.016
	False response (times)	2.75 ± 2.79	2.55 ± 2.91	3.69 ± 4.07	0.641
	Speed of decision (mean sec)	0.19 ± 0.06	0.26 ± 0.10	0.21 ± 0.07	0.317
Steering wheel test	Speed of response behavior (mean sec)	1.93 ± 0.17	2.38 ± 0.75	2.08 ± 0.13	0.002
	Accuracy of operation (winning rate, %)	15.4 ± 18.2	21.9 ± 18.4	22.3 ± 23.8	0.239
	Left-right balance (%)	11.7 ± 8.50	11.0 ± 5.7	17.7 ± 25.8	0.749
Multiple tasks test	Speed of response behavior (mean sec)	0.73 ± 0.07	0.80 ± 0.09	0.82 ± 0.04	< 0.001
	Unevenness in response behavior (SD sec)	0.13 ± 0.04	0.13 ± 0.02	0.16 ± 0.03	0.008
	False response (times)	1.71 ± 1.65	1.91 ± 1.76	2.92 ± 3.64	0.512

MS, multiple sclerosis; SDMT, symbol digit modalities test; SD, standard deviation. All values are shown as mean ± SD.

be able to evaluate attention and information processing speed (Parmenter et al., 2007). This study showed that the SDMT scores were significantly lower in MS patients who had normal range of MMSE scores than in healthy controls. The results support the previous evidence which reported that attention and concentration were frequently observed as cognitive decline in MS patients (Chiaravalloti and Deluca, 2008). Furthermore, it was also shown that the SDMT could more closely reflect cognitive decline in MS patients (Mckay et al., 2022; Lopez-Gongora et al., 2015). The number of traffic accidents was not higher compared to healthy controls. However, off-road assessment using driving simulator could reveal significantly impaired driving responses more than healthy controls. The automatic grading tool of driving abilities could also detect more low-grade scores in MS patients than healthy controls. MS patients with lower SDMT scores also had impaired driving responses compared with MS patients with better SDMT scores. These our results suggest that the SDMT is useful to evaluate driving ability in MS patients with mild cognitive decline. Because driving a car requires a higher level of cognitive function, it is important to use a more appropriate test battery when evaluating driving ability. Therefore, this study provided valuable evidence contributing to the practical evaluation of driving ability in MS patients.

4.2. Driving ability features for MS

Patients with MS who participated in this study had a lower EDSS with a median of 1.0 (IQR: 0 - 2.0), which was much less physically restrictive than previous studies (Kotterba et al., 2003). Nonetheless, there were several items in which the MS group performed worse than the control group in the driving simulator. These results suggest that there are factors other than physical factors that contribute to the decline in driving ability. As for the items of the driving simulator, speed of response was significantly increase in all tests, while false response and accuracy of operation were not significantly increase. Some features of driving ability have been reported in neurological conditions. In patients with dementias such as Alzheimer's disease, not only reduced attention but also judgment errors (Stein and Dubinsky, 2011) are strongly related to reduced driving ability. In patients with Parkinson's disease, reduced executive function and visuospatial function (Devos et al., 2013) are reported as features of cognitive decline. Our study suggested that less operational errors despite reduced reaction speed are shown as characteristic features of driving ability in patients with MS.

4.3. Cognitive function needed for drivers with MS

The cognitive function for driving a car is composed of a three-tiered structure (Michon, 1985). There are three levels as followings: the strategic level, which is concerned with planning before and during driving; the tactical level, which is concerned with maintaining relationships with the surroundings while driving, such as speed and distance between vehicles; and the operational level, which is concerned with basic driving operations, such as accelerating and steering. Our study revealed that response speed was related to driving ability in MS patients, which is related to the tactical and operational levels of cognitive function for driving a car. However, it is difficult to clinically evaluate the strategic levels on a driving simulator. In order to clarify the cognitive function required for driving a car, it is necessary to conduct a prospective study using the actual accident history as an outcome, because it is not possible to make a decision based on the SDMT score alone whether or not a patient with MS can safely drive a car.

4.4. Driving simulator for clinical assessment

We used a simple car driving simulator called Honda Safety Navi®. Honda is one of the most famous automobile manufacturers and also a company providing educational equipment and programs for road safety, drawing on its experience in promoting safe driving. In Japan, this driving simulator has been used at driving schools and rehabilitation hospitals since 2012, which plays a practical role in preventing automobile accidents. Some clinical studies have been conducted in Japan using this simulator to evaluate whether or not a person with brain injury can resume driving (Okuma et al., 2020; Takehara et al., 2016; Ooba et al., 2017), and it is considered to be useful as a method of evaluating driving ability (Nakagawa et al., 2019; Okuma et al., 2020). We applied this driving simulator in this study, because it has been adopted into the clinical research purpose as well.

4.5. Limitations in this study

This study has some limitations. The number of cases may be small. Recall bias may have occurred. Because there are essential differences in individual driving skills, it may be necessary to stratify MS patients by age, gender, and so on. The educational levels were different between the MS group and the control group. Although it is unclear whether educational levels have had any impact on this study because there was no significant correlation between their educational levels and SDMT, the levels may need to be matched in future research.

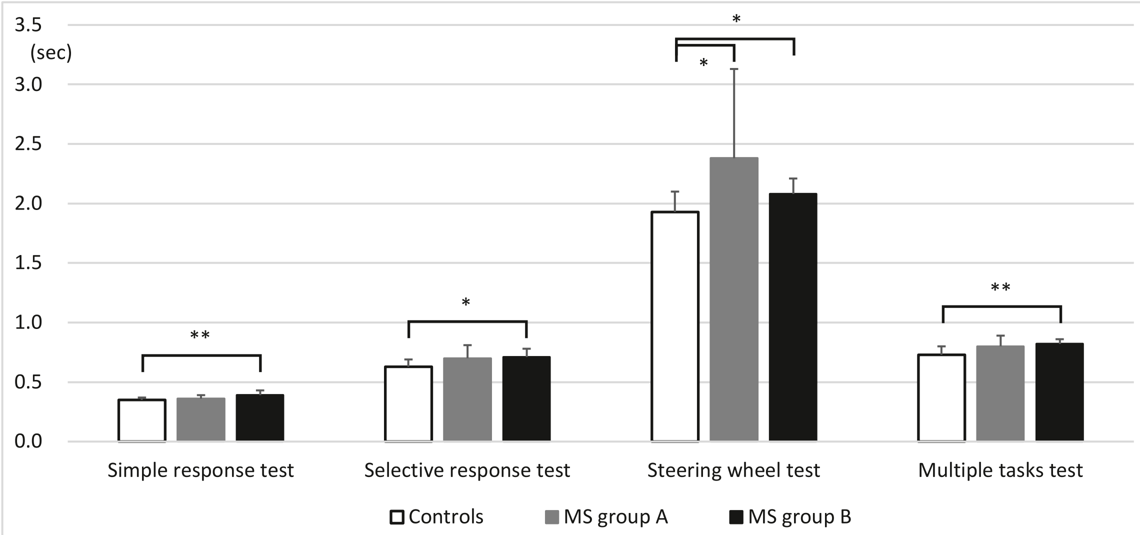

Fig. 1. Speed of response behavior in driving response tests among controls, MS group A, and B. Speed of response behavior was significantly higher in the MS group B than controls in all driving response tests, which was also significantly higher in the MS group A than controls in steering wheel test. MS, multiple sclerosis; *, $p < 0.05$; **, $p < 0.001$.

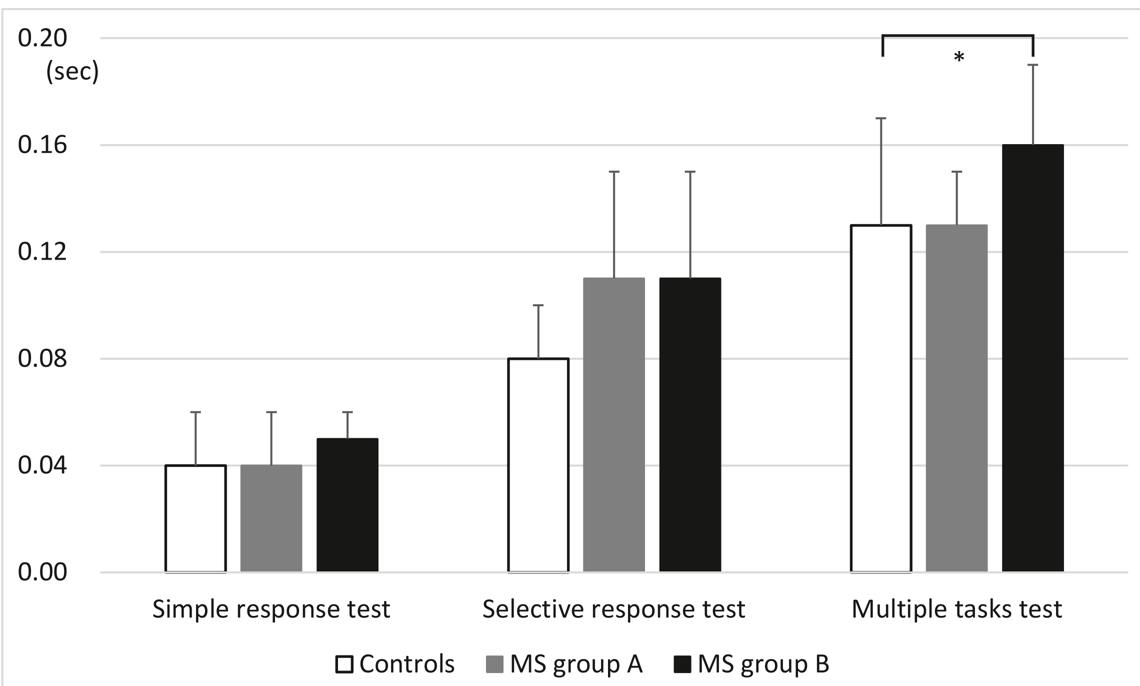

Fig. 2. Unevenness in response behavior in driving response tests among controls, MS group A, and B. Unevenness in response behavior was significantly higher in the MS group B than controls in multiple tasks test. MS, multiple sclerosis; *, $p < 0.05$; **, $p < 0.001$.

5. Conclusion

The driving ability of MS patients was evaluated using with a driving simulator and the SDMT in this study. MS patients are associated with cognitive decline even when motor disability is mild. The SDMT could detect cognitive decline in MS patients performed well on the MMSE which are characterized as deteriorations of attention and information processing speed. This study revealed a relationship between driving abilities and SDMT scores. Clinical evaluation using the SDMT may help to detect cognitive decline and to make a decision on driving a car in patients with MS.

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CRediT authorship contribution statement

Manami Maeta: Data curation, Formal analysis, Project administration, Writing – original draft. **Masanori Mizuno:** Conceptualization, Methodology, Project administration. **Satoru Okubo:** Data curation, Investigation. **Miku Ogasawara:** Data curation, Investigation. **Takahiro Terauchi:** Investigation. **Masako Suzuki:** Investigation. **Hiroshi**

Akasaka: Data curation, Formal analysis. **Yoshitomo Sato:** Investigation. **Kiyohumi Ohi:** Supervision. **Tetsuya Maeda:** Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

None.

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