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Research article

Cognitive screening test for rehabilitation using spatiotemporal data extracted from a digital trail making test part-A

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ABSTRACT

We investigated a newly developed digitized Trail Making Test using an iPad (iTMT) as a brief cognitive function screening test. We found that the iTMT part-A (iTMT-A) can estimate generalized cognitive function in rehabilitation inpatients examined using the Mini-Mental State Examination (MMSE). Forty-two hospitalized participants undergoing rehabilitation (rehab participants), 30 of whom had cerebral infarction/hemorrhage (stroke participants), performed the iTMT five times (first three times: iTMT-A; fourth: paper version of TMT-A; fifth: the inverse version of iTMT-A) and the MMSE once. Each iTMT-A trial's completion time was divided into the move and dwell times. A linear mixed model following post-hoc tests revealed that the completion time of the third and fourth iTMT-A was faster compared to that of the first iTMT-A, suggesting the presence of a learning effect. In the partial least squares (PLS) regression analysis, the coefficient of determination for estimating the MMSE score was increased by using the dwell and move times extracted from the repeated iTMT-A and the availability of TMT-B, even for subjects with low MMSE scores. These findings indicate that the dwell time of iTMT-A may be important for estimating cognitive function. The iTMT-A extracts significant factors temporally and spatially, and by incorporating the learning effect of repeated trials, it may be possible to screen cognitive and physical functions for rehabilitation patients.

1. Introduction

Patients who require rehabilitation for brain damage due to stroke or brain trauma, as well as older adults, may have various brain function disorders coexisting with cognitive/executive dysfunctions [1]. For such patients, in communicating with therapists and caregivers and achieving the desired training effect, it is crucial to identify and quantify the specific impairments, residual capacity,

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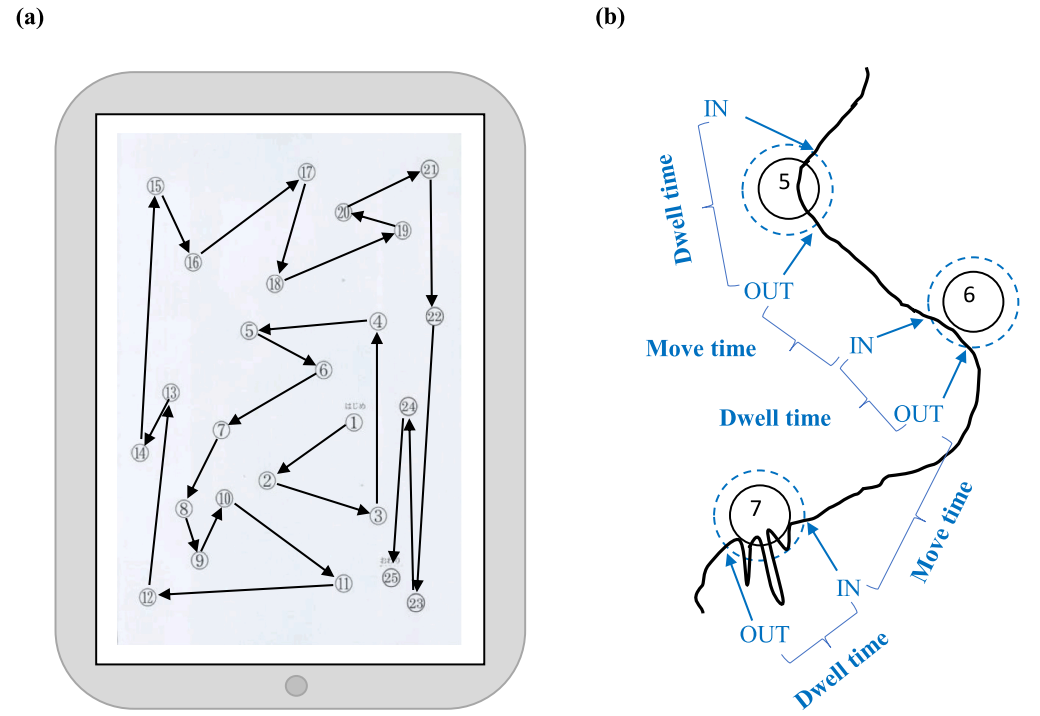
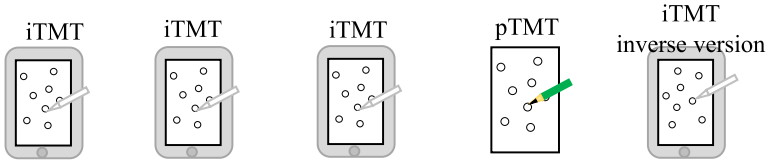
and subtle changes in mental and cognitive functions at the beginning of rehabilitation [1]. Because it is impossible to comprehensively test every brain function for all patients from the start of rehabilitation, many cognitive screening tests have been developed. The Mini-Mental State Examination (MMSE), which measures cognitive aspects of mental status, is a widely used cognitive screening test for rehabilitation [1–5]. It is biased toward orientation, memory, and language tasks and has limited capability to detect deterioration of the executive function and complex visuospatial processing [6,7], which is widely considered to diminish the effect of rehabilitation [8–10].

The Trail Making Test (TMT) is a commonly used pencil-and-paper test in neuropsychology [11–14]. This test comprises two parts: part-A (TMT-A) and part-B (TMT-B). In the TMT-A, the objective is to connect circled numbers presented on paper in ascending order from 1 to 25 by drawing a line with a pen or pencil (Fig. 1(a)). In the TMT-B, the objective is to connect circled numbers and letters (the



(c) Study design



Extracted data	TMT-A trial				
	1st	2nd	3rd	4th	5th
Completion time	○	○	○	○	○
Dwell time	○	○	○		
Move time	○	○	○		

Fig. 1. Schema of a Trail Making Test (TMT) part-A trial. (a) Displayed iPad screen image of a digitized trial of the TMT part-A. The arrows indicate the directions of the lines drawn between circles. (b) Calculation of the dwell and move times, with the conditions for entering (IN) and exiting (OUT) circles represented by blue dashed lines. (c) Overview of the study protocol using data extracted from five repeated TMT trials. The data that could be extracted at each time instance in a TMT are marked with circles.

Japanese version uses Japanese syllabary characters, or “kana,” instead of letters) alternately with lines in ascending order (i.e., 1–A–2–B– …). The TMT is usually evaluated in terms of the completion time, and the TMT-B typically takes longer to complete [12]. Many previous researchers have calculated the TMT completion time as the TMT-B–TMT-A difference or the TMT-B/TMT-A ratio, which might provide a variety of cognitive elements from the TMT-B [12,15. Thus, TMT-A and -B results have robust correlation with overall measures of intelligence and are sensitive indicators of neurological impairments [15].

Digitization of a brief screening test for cognitive function can benefit busy clinical settings by reducing the time associated with test administration, scoring, conversion of raw scores via normative data, and result entry into an electronic medical record [16]. Moreover, the increase in wearable devices and cloud-based innovations in Internet-of-things technology potentially facilitates the digitization of classic face-to-face neuropsychological tests [16–21]. The recent COVID-19 pandemic also forced a reduction in face-to-face care and accelerated the trend toward digitization [19]. Recently, digital TMT versions that use tablets and computers have been developed, and their benefits have been reported [11,14,22–24]. The use of a digital TMT reduces the influence of the examiner and automatically corrects errors. Moreover, a digital TMT can be used to extract several variables besides the start and completion times, and it can enable segmental analysis based on the dwell time (the time to find the next target through visual search and attention) or the move time (the time to move the pencil) and on the number of errors. On the other hand, these digital TMT versions introduce challenges that are not found in the paper version, such as difficulty for the subject to operate the digital device (i.e., a keyboard and mouse for a computer, or a finger tap or pen for a tablet), varying familiarity with digital devices, and friction on the display and writing surface [23]. While digitized neuropsychological assessment is still perceived as problematic in replacing traditional paper-and-pencil assessment, its advantages in busy clinical settings are clear [25]. This is particularly the case when digitized assessments can be used for initial screening of subjects and identification of those who should proceed to a detailed, face-to-face examination [16].

The purpose of this study is to verify the possibility of developing a brief, digitized screening test for rehabilitation patients. As assumed in this study, many of these patients have suffered stroke or are older adults. We think a suitable screening test should be able to measure many brain functions with a small number of tests by extracting many factors from as simple a task as possible. In particular, if the MMSE score could be estimated using a large amount of data extracted from a digitized TMT-A, we could conduct a single test to simultaneously estimate executive function/visuospatial processing, which the TMT-A captures well, and cognitive aspects of mental status, which the MMSE captures well.

2. Materials and methods

2.1. Study design

The ethics committees of Hiroshima University (E−1554-2; July 3, 2020) and Hibino Hospital approved this study. Written informed consent was obtained from all patients prior to participation. Further, the study complied with the relevant guidelines and regulations of the Declaration of Helsinki.

Previous studies have suggested that the learning effect in the TMT reaches a plateau in two to three sessions [11]. Thus, to account for the learning effect, we performed five consecutive trials of the iTMT-A and B. As shown in Fig. 1(c), the first three used the iTMT, the fourth used the paper version (pTMT), and the fifth used an inverse version of the iTMT, which mirrored the up–down and right–left directions and enabled us to verify the effect of remembering the target positions. Then, we examined the equivalence between the iTMT and pTMT in comparison with the completion times for the TMT-A repeated five times sequentially. We also examined the correlation between the dwell or move time and the physical disability, or the side where a cerebral lesion exists, for both the rehab participants and the hospitalized participants with cerebral infarction/hemorrhage (stroke participants). The TMT-B has been reported to have a correlation with the MMSE, while the MMSE’s relationship with the TMT-A is said to be weaker than that with the TMT-B [26–29]. Hence, to obtain a factor that could be evaluated through digitization, we divided the iTMT completion time into the dwell and move times, as illustrated in Fig. 1(b). In addition, repeated TMT trials lead to motor skill learning, which a number of previous studies have shown to be an important cognitive function that is linked with neural multi-circuits [30]. Because rehabilitation patients with stroke and older adults generally have decreased ability for motor skill learning, we also examined the effects of motor skill learning by analyzing the TMT data from three trials. Finally, we examined the possibility that the general cognitive function evaluated by the MMSE can be assessed by analyzing many factors extracted from the iTMT-A.

2.2. Subjects

Participants were selected from a consecutive series of individuals who were admitted for rehabilitation at Hibino Hospital for less than three months. The exclusion criteria were (1) any history of major psychiatric illness, and (2) any medical illness, physical disability, or speech impediment that would preclude completion of the TMT (i.e., being unable to hold a sitting position, to reach and write, or to respond to instructions) and cognitive function testing.

Forty-seven patients could perform the MMSE. Among them, five patients (10.6 %) could not complete the TMT-A, and 21 patients (44.7 %) could not complete the TMT-B test, as shown in the Supplementary Fig. S1 for the TMT-A (a-c) and the TMT-B (d-f). Forty-two hospitalized participants undergoing rehabilitation, who completed the iTMT-A and MMSE, were included as "rehab participants" in this study. Among these 42 rehab participants, 30 who had suffered from cerebral infarction/hemorrhage were included as "stroke participants," because cerebral infarction or hemorrhage presents with focal neurological symptoms. All participants’ dominant hand was the right hand (i.e., none of the participants was left-handed), but three stroke participants used their left hand because their

writing function with the right hand was problematic without aphasia.

2.3. Stroke severity

We estimated the disability severity of the rehab and stroke participants by using the Functional Independence Measure (FIM), version 3.0, which contains 18 items (13 motor and five cognitive items). These participants were assessed through observation by using the sum of items on a seven-point rating scale that evaluates disability in terms of dependency, where a lower score indicates a greater disability [31]. Table 1 lists the motor (maximum 91), cognitive (maximum 35), and total FIM scores (maximum 126) on admission and discharge of the participants.

In addition, physical disabilities of the upper-limb performance were estimated in terms of the presence or absence of paralysis and/or ataxia. Lastly, the side (right or left) of cerebral lesions due to infarction or hemorrhage was assessed using magnetic resonance imaging (MRI) or computed tomography (CT).

2.4. Brief cognitive screening test

We evaluated the cognitive function of the rehab participants by using the MMSE, as described above [4,32].

Table 1
Basic characteristics of subjects who could perform the iTMT-A.

	Rehab participants (n = 42)	Stroke participants (n = 30)
Age	69.7 ± 13.5	68.5 ± 12.0
Gender (male; female)	31; 11	25; 5
Type of disease		
Infarction	23 (54.8 %)	23 (76.7 %)
Hemorrhage	7 (16.7 %)	7 (23.3 %)
Subarachnoid hemorrhage	1 (2.4 %)	0
Head injury	5 (11.9 %)	0
Other	6 (14.3 %)	0
Laterality of hand with pen (right; left)	39; 3	27; 3
Physical disability of performance hand	16 (38.1 %)	14 (46.7 %)
Aphasia	5 (11.9 %)	4 (13.3 %)
Laterality of cerebral lesion (new)		
Rt	14 (33.3 %)	13 (43.3 %)
Lt	11 (26.2 %)	9 (30.0 %)
MMSE score	27 (24, 29.3)	28 (25.3, 27.9)
Total FIM on admission	77.8 ± 23.9	78.6 ± 24.2
Motor FIM on admission	53.0 ± 19.0	53.9 ± 19.4
Cognitive FIM on admission	27 (20.8, 30.3)	27 (20.8, 30.0)
Total FIM at discharge	113 (101.75, 119)	117 (103, 119.25)
Motor FIM at discharge	82.5 (71, 87.25)	84 (72.5, 88)
Cognitive FIM at discharge	31 (29, 35)	31.5 (29.75, 35)
Completion time (sec)		
1st TMT-A	49.5 (36.75, 78.25)	46.5 (35.5, 73.25)
2nd TMT-A	50 (39.75, 67.25)	50.0 (38.75, 65.5)
3rd TMT-A	46.5 (33.75, 58.75)	45 (32.75, 54.25)
4th TMT	43.575 (30.71, 57.0625)	41.09 (30.71, 54.57)
5th TMT	44.5 (33, 62.25)	41.5 (32.5, 59.75)
Dwell time		
1st TMT-A	37.92 (23.90, 62.44)	35.92 (22.54, 54.10)
2nd TMT-A	37.56 (25.68, 53.53)	37.56 (24.80, 47.72)
3rd TMT-A	32.12 (20.02, 42.75)	31.35 (19.79, 41.12)
Move time		
1st TMT-A	10.63 (8.85, 14.62)	9.91 (8.85, 14.62)
2nd TMT-A	10.56 (8.90, 14.02)	10.56 (8.97, 12.99)
3rd TMT-A	10.80 (8.78, 12.90)	10.80 (8.70, 14.40)

Physical disability of the performance hand entails paresis and/or ataxia. The normality assumptions for each value were analyzed using the Shapiro-Wilk test. Values are listed as the mean ± standard deviation (normal distribution), the median (interquartile range, non-normal distribution), or n (%, categorial values).

Via the FIM, subjects were assessed on each item with a seven-point scale having values of 1 (total assistance), 2 (maximal assistance), 3 (moderate assistance), 4 (minimal assistance), 5 (supervision), 6 (modified independence), and 7 (complete independence). The table lists the summed rating scale results for the motor (maximum 91), cognitive (maximum 35), and total scores (maximum 126) of the FIM on admission and discharge of the subjects.

iTMT-A: iPad version of the Trail Making Test part-A. MMSE: Mini-Mental State Examination. FIM: Functional Independence Measure.

2.5. Measurements using iPad TMT

We adopted the pTMT as described previously [33–36] and administered it according to the standard protocol. Because the iTMT was smaller overall than the pTMT, their results were compared after correcting the pTMT results for size. Specifically, the length of a line in the iTMT was 0.83 times shorter than the corresponding line in the pTMT; thus, the pTMT results were multiplied by 0.83 to make them comparable to the iTMT results.

For the digital TMT (iTMT), we used an iPad Pro (12.9-inch, version 10.2.1, Apple Inc., CA, USA), and lines were drawn using an Apple Pencil. The numbers displayed on the iTMT screen and the iTMT procedure were both the same as those of the traditional paper version of the TMT (pTMT), consisting of structured practice and test trials, as described previously [12,15,33–36].

For a practice trial, the participants performed a shortened version that required drawing a line only from the first to the tenth target (with part-A using only search numbers and part-B alternating search numbers and kana). Next, the participants performed a test trial, in which they were required to draw a continuous line on the screen as quickly as possible without lifting the pen from the test screen. When a participant made a mistake (e.g., erroneous line connection) during the test and did not correct it, the study investigator immediately corrected the participant orally. The completion time to connect all 25 items on both screens was measured, including the extra time required for the administrator to correct for errors.

The specifications of the iTMT used in this study were as follows. (1) The operating system (OS) was iOS (not open source). (2) The sampling frequency was higher than 100 Hz. (3) The display was a Retina display with a viewing angle of 178°. (4) The display size was 220.6 mm (width) × 305.7 mm (height). (5) The pick-up area for pressure from the Apple Pencil was 1024 points (width) × 1366 points (height) with 0.5-point increments. (6) The diameter of the actual target (circle) was 14 mm (64 points). (7) The start signal was "Touch the bottom of the screen." (8) The operation from the start signal to the actual start was represented by a paper-flipping animation. (9) The end signal was the time of entering the judgment area (referred to as the 1.5-circle, as explained below) of the last target (see the supplementary video).

The participants were urged to connect the circles as quickly as possible without lifting the Apple Pencil from the screen. The supplementary video shows the operation of the iTMT-A software, which involved the following steps: (1) display the explanation screen; (2) display the screen for selecting a practice or test trial; (3) touch the practice trial key; (4) touch the start key and begin; (5) display the practice result screen; (6) touch the test trial key; (7) touch the start key and begin; (8) display the test result screen. To make the conditions the same as for the paper version and reduce the differences between participants, the examiner explained the procedure and touched the screen keys for the participants.

In previous reports on using a digital TMT, the number of circles was changed after passing through the correct circle, and parts outside a circle's circumference were ignored [11]. Moreover, errors classified as passes through incorrect circles caused those circles to flash certain colors [11]. The iTMT used here allowed selection of whether to color a target when the Apple Pencil passes through it. In our study, however, the circles did not change color, irrespective of whether a circle was passed through correctly or incorrectly. When a participant made a mistake (erroneous line connection) during the test and did not correct it, the study investigator immediately corrected them orally, as with the pTMT test.

To incorporate alternate versions, we created three mirrored patterns (right–left, up–down, and both) of the numbers displayed on the iTMT screen. In this study, to verify the effect of remembering the target positions, we used both the right–left and up–down mirror versions as alternate versions for the fifth TMT trial.

2.6. Data collection from iTMT

In addition to the completion time, we measured the move time and dwell time on a segment-by-segment basis [11]. The move time was the time required to move the Apple Pencil. The dwell time was the time required to look for the next target number, which was calculated by subtracting the move time from each segment time. However, the participants constantly moved the Apple Pencil, and it was not possible to clearly distinguish when the pencil was moving and when it was stationary. Accordingly, as shown in Fig. 1(b), we defined a virtual circle that was 1.5 times larger than the actual circle; we refer to this as a "1.5-circle." Then, the dwell time was defined as the time from entering the 1.5-circle to the time of the final exit from the 1.5-circle (regardless of passing in and out of it before the final exit). The move time was defined as the time from the end of the dwell time to the time of entry to the next 1.5-circle.

Because the distance of each segment was different, it was corrected by the ratio of time (sec)/distance (cm) for each segment.

2.7. Statistical analysis

The Shapiro-Wilk test was used to examine whether the data fit a normal distribution. As summarized in Table 1, variables that were considered normally distributed were described by the mean (95 % confidence interval: CI); otherwise, variables were described by the median (interquartile range).

For the stroke participants, we used the Mann–Whitney *U* test to investigate the effect of physical disabilities (presence or absence of paralysis and/or ataxia). We also used a Kruskal–Wallis one-way analysis of variance to investigate the effect of the side of cerebral lesions (none, right, or left, as no study participants had cerebral lesions on both sides) on the dwell or move times extracted from three repeated iTMT-A trials. We also examined the differences in the completion times of the five repeated measurements (first to fifth) in the same subjects using linear mixed-effects models with the effect of the repeated testing and differences in individual subjects allowing for input of both within-subject and between-subject effects, followed by Dunnett post-hoc tests for the rehab participants.

Completion time ~ session + (1 | participant),

where "session" is represented by a nominal variable indicating the first to fifth sessions of the TMT.

For the rehab participants, we also applied the partial least squares (PLS) regression method to investigate the relationships between each factor extracted from the iTMT and the MMSE scores. PLS, which is a dimension reduction approach based on basic latent component decomposition [37] and coupled with a regression model, is known to be robust to high collinearity among independent variables [38]. The independent effects of predictor variables on the MMSE score were evaluated using the nonlinear iterative partial least squares (NIPALS) method.

These predictor variables include the age, sex, laterality of the performing hand, and disease type (brain infarction/hemorrhage, or other). In the analysis of the relationship between only the iTMT completion time and MMSE, these variables include the completion time of iTMT-A and -B from the first to third times.

In the analysis of the relationship between the many data extracted from iTMT-A and MMSE, we included the following variables as predictor variables: dwell and move times of the first to third iTMT-A, the amount by which the dwell and move times of iTMT-A changed from the first to second trial and from the first to third trail, and whether or not iTMT-B was completed. The model's prediction performance was evaluated through a leave-one-patient-out cross-validation: one participant was used for evaluation while all other participants were used for model training (parameter value estimation), and all such combinations were evaluated [39].

To compare the performance of each model, we calculated two metrics between the actual MMSE and the predicted MMSE obtained from all iterations: the squared correlation coefficient (R^2) and the root-mean-square error (RMSE). Except for the power analysis of the model, all statistical analyses were performed using JMP 16.0 (SAS Institute Inc., Cary, NC). The power analysis for the PLS model was calculated using the power analysis method for multiple regression analysis provided by G*Power (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower), as described previously [40–42].

3. Results

3.1. Baseline data of rehab and stroke participants

The baseline characteristics of the rehab participants (n = 42) and stroke participants (n = 30) are listed in Table 1. The average motor FIM was 53 on admission and 82.5 at discharge; the averages for each sub-item were 4.1 and 6.3, respectively. The averages correspond to a participant who required minimal assistance (modified dependence) on admission but improved to modified

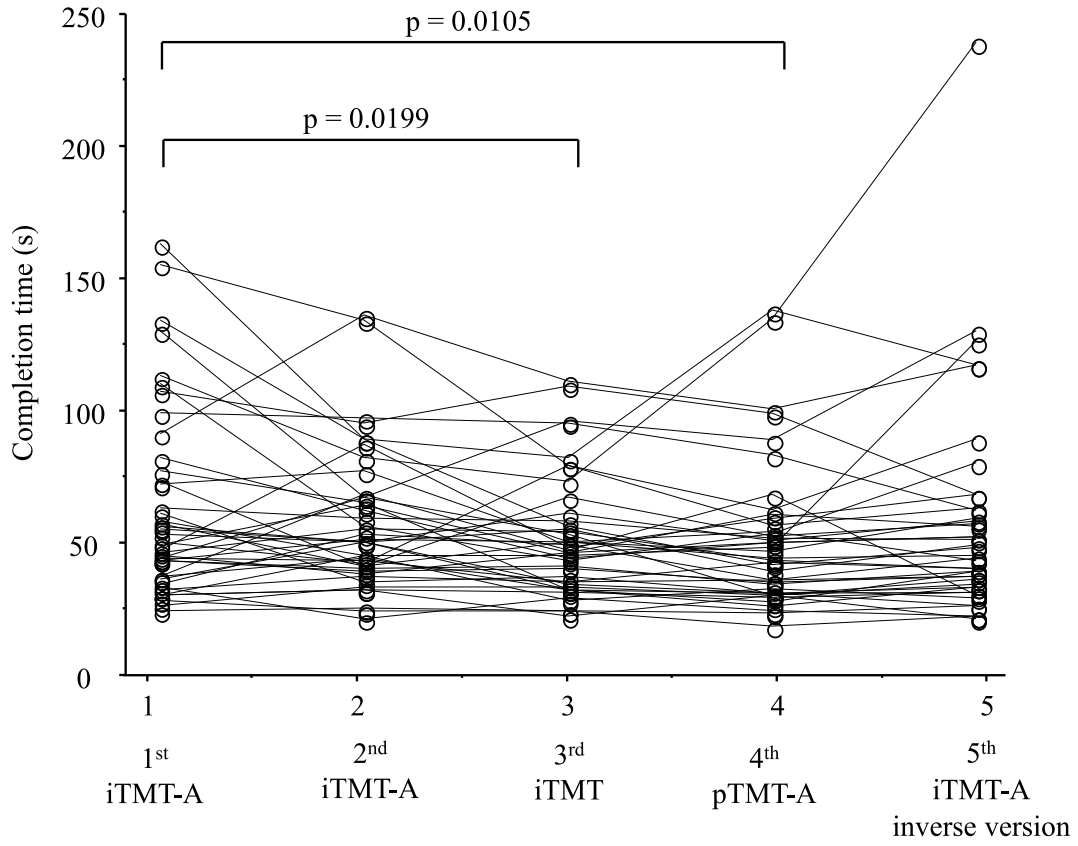


Fig. 2. Scatter plots with line of the completion time differences in five sequential TMT-A trials. Each circle represents a rehab participant. P value indicates statistical significance using Dunnett post-hoc test.

independence at the time of discharge. The average cognitive FIM was 27 on admission and 31 at discharge, and the averages for each sub-item were 5.4 and 6.2, respectively. There was little or no cognitive decline that required assistance in daily life from the time of admission.

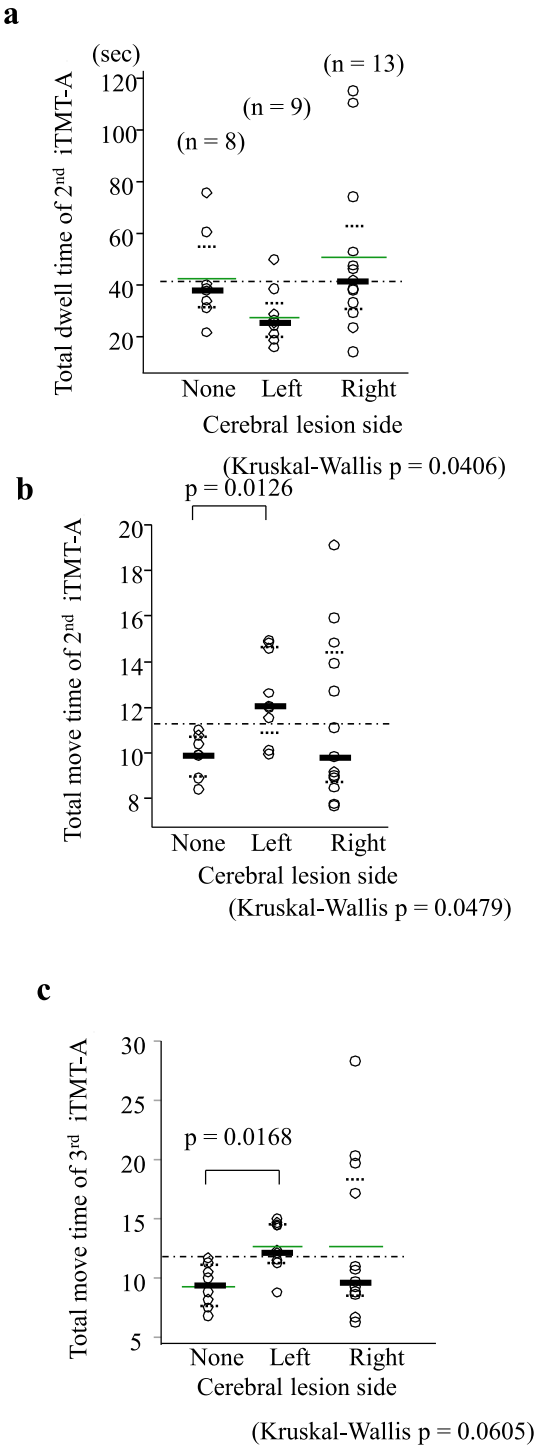


Fig. 3. Dot plots of the differences between the cerebral lesion side (left or right) and (a) the total dwell time of the 2nd iTMT-A, (b) the total move time of the 2nd iTMT-A, (c) the total move time of the 3rd iTMT-A. These differences were statistically examined using the Kruskal-Wallis test followed by a post-hoc test for the cerebral lesion side; the figure shows the p-values.

3.2. Equivalence between iTMT-A and pTMT-A in rehab participants

The results of the linear mixed model show that the completion time of the third and fourth iTMT-A was faster compared to that of the first iTMT-A, suggesting the presence of a learning effect (Fig. 2). However, there was no difference between the third iTMT-A and fourth pTMT-A. Thus, the learning effect was observed by repeating the test three times, but there was no significant difference between the paper version and the iPad version of TMT-A.

3.3. Detection of disability in stroke participants, via effect of physical disability or cerebral lesion site on dwell or move time

To examine whether the many factors extracted from the repeated iTMT-A trials were meaningful in explaining brain disorders and physical dysfunction, we investigated whether the physical dysfunction or the cerebral lesion site affected the dwell or move time. The results are shown in Fig. 3. The total dwell time was significantly longer when the new cerebral lesion was on the right side, while the move time was significantly longer (slower) when the new cerebral lesion was on the left. On the other hand, there was no significant difference between the physical disability and the dwell or move times.

3.4. Detection of cognitive dysfunction in rehab participants via partial least squares (PLS) multiple regression analysis

In the partial least squares (PLS) regression analysis of the relationship between the iTMT completion time and MMSE, there was one latent component, and the cumulative R^2 value was 0.4499 (Table 2). The completion times of iTMT-A and -B from the first to third trial and the change of completion time from the first to second or first to third iTMT-A were all highly important factors, with VIP >0.8 (Fig. 4(a), Sup Fig. S2(a)).

In the analysis of the relationship between the many data extracted from iTMT-A and MMSE, there was seven latent components, and the cumulative R^2 value was 0.7170 (Table 2). The dwell and move times, the amount of change in the dwell and move times, and the availability of TMT-B were all important factors (VIP >0.8) (Fig. 4(c)). For the latent component 1, which explained 41.6 % of MMSE, the dwell time (first to third iTMT-A) and availability of iTMT-B were shown to be highly important variables, suggesting that the dwell time of iTMT-A and the availability of TMT-B are important for estimating cognitive function.

Fig. 4 (b)(d) show scatter plots comparing the actual and predicted MMSE values of the three trials for two types of PLS regression analysis (completion time of the iTMT-A and iTMT-B, and dwell/move times and availability of iTMT-B in the iTMT-A). It is difficult to estimate the MMSE scores of participants with low MMSE scores through analysis using the completion times of both the iTMT-A and iTMT-B (Fig. 4(b)). However, analysis using the dwell/move times in the iTMT-A and availability of iTMT-B enables MMSE score estimation for such participants (Fig. 4(d)). These two models themselves showed high power of over 0.9 (Table 2).

4. Discussion

In the present study, to predict MMSE using the TMT, both iTMT-A and iTMT-B were important as explanatory variables in PLS regression analysis, even if iTMT-B was not completed. In previous reports, cognitive functions were mainly correlated with the TMT-B rather than the TMT-A, as the TMT-B requires more executive functions than the TMT-A does [29,43]. In our study, the TMT-A could be completed even by rehab participants with an MMSE score below 20, but the TMT-B was difficult for rehab participants with a score below 25. The proportions of older adults and inpatients in the rehabilitation ward with stroke were high, and the proportion of patients with cognitive decline was also high. The TMT-A is considered to have a wider range of indications than the TMT-B for cognitive function screening of rehabilitation inpatients. Thus, we examined whether a digitized TMT-A, rather than the TMT-B, could be used in the same way as a brief screening test for various disabilities in elderly participants and in rehab participants with stroke. However, even if the TMT-B cannot be completed, the ability to estimate the MMSE will be affected by whether or not the TMT-B was completed, so the availability of TMT-B was used for explanatory variables for the MMSE prediction of the PLS regression analysis.

We compared the completion times between the iTMT and the pTMT. According to previous reports, the digital TMT and pTMT are different in terms of their operation methods, arrangement of numbers, habituation of operations, and slippage on digital surfaces [44,45]. In this study, the same versions of the iPad and Apple Pencil were used, and the test display used the same number arrangement as the pTMT. However, the simple transition from a paper version to a digital version cannot be compared in the same way as previously described [20]. In this study, the iTMT or pTMT test was performed after administrating practice trials to teach the participants how to

Table 2
Model comparison summary in PLS for each fitted model predicting MMSE score.

Variables for model	Number of factors	Percent variation explained for cumulative X	Percent variation explained for cumulative Y (cumulative R2 value (%))	Number of VIP >0.8	Power
Completion time of TMT-A and TMT-B	1	38.668519	44.99329	8	0.90488
Dwell and move times of iTMT-A	7	82.931327	71.699674	13	0.99996

VIP: Variable importance for projection. X: Explanatory variables. Y: Response variable. TMT-A: Trail making test part A. TMT-B: Trail making test part B. MMSE: Mini-Mental State Examination.

PLS model using completion time of TMT-A and TMT-B

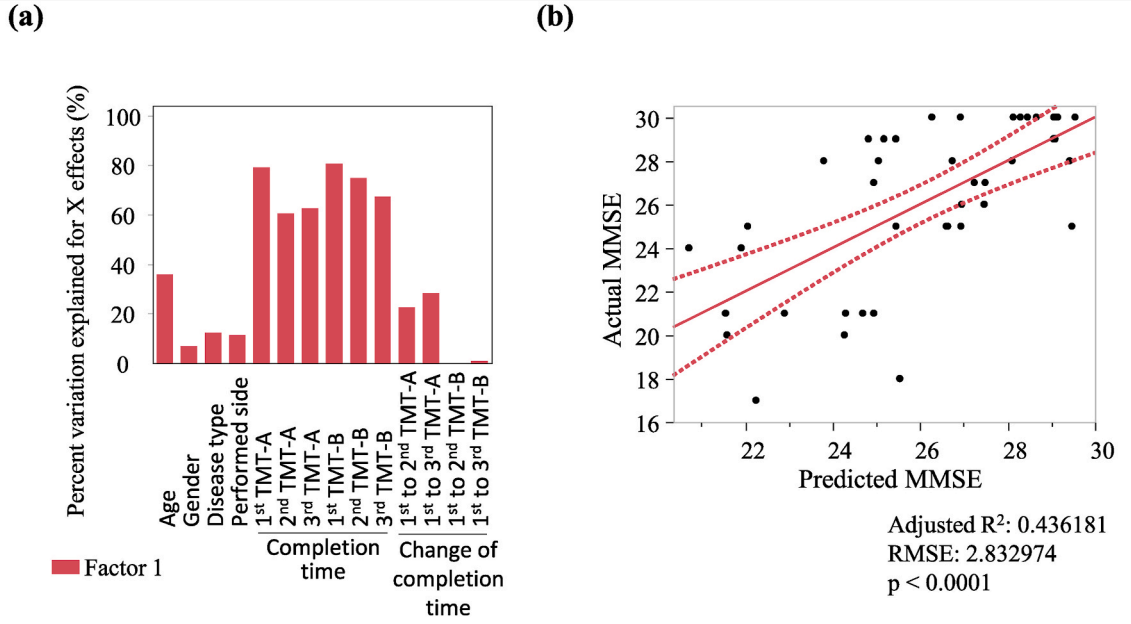
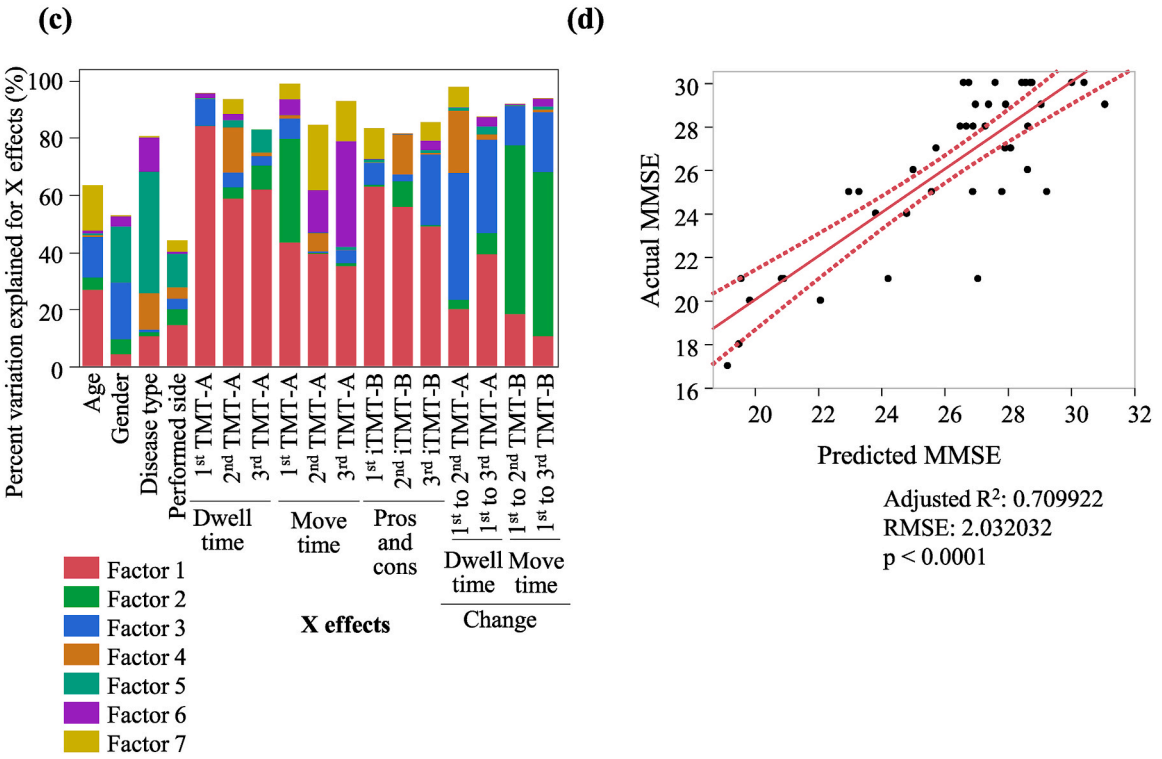


Figure shows stacked bar charts representing the percent variation explained by extracted factor for the Xs.

PLS model using dwell and move times from 3 repeated iTMT-A



(caption on next page)

Fig. 4. Partial least squares (PLS) regression method to investigate the relationships between MMSE scores and each factor extracted from the iTMT. (a), (b) Completion times of iTMT-A and iTMT-B. (c), (d) Dwell/move times and availability of iTMT-B. In (a), (c), stacked bar charts represent the percent variation explained by extracted factor for the Xs. In (b), (d), scatter plots of the predicted MMSE vs. actual MMSE for the two prediction models are shown. The solid lines represent simple linear regression lines between the actual and predicted MMSE scores. The dashed line indicates the 95 % confidence interval of each regression line. Each model's prediction performance is shown by the adjusted coefficient of determination (R^2), with values calculated by leave-one-subject-out cross-validation (shown in parentheses).

operate the digital test and thus reduce their potential anxiety or difficulty with new technologies [25]. It has also been postulated that pretest computer training might reduce or eliminate the differences in test performance across different levels of computer familiarity [46]. Moreover, the pTMT completion time was calculated after size correction, and the 3rd TMT trial (iTMT-A) could not be shown to have any statistical significance with respect to the 4th TMT trial (pTMT-A).

Although the MMSE is one of the most commonly used screening tests for cognitive function, it is not thought to be an effective screening test for monitoring cognitive decline in aging [6,7]. Indeed, while the MMSE cannot support diagnostic responsibility alone [4], it can demonstrate deterioration or improvement in the cognitive state over time and with treatment. Therefore, it is considered to have high clinical significance for simple use as an initial cognitive screening test or for follow-up observation during treatment or rehabilitation. In addition, the MMSE shows no or little correlation with the TMT-A but little or high correlation with the TMT-B [26–29]. In this study, we found that the TMT-A could gain a stronger relationship with the MMSE score though digitization, and this may have been caused by differences in the range of cognitive domains measured by the digitized TMT-A. A more detailed PLS regression analysis to predict the MMSE score was performed using the dwell and move times of three repeated iTMT-A trials. In this analysis, the iTMT-A showed greater predictive ability than analysis using the completion times of both iTMT-A and iTMT-B trials. This finding is consistent with our study's purpose, which is to develop a simple cognitive screening test for rehabilitation patients, including many older adults and stroke patients. In this study, the ability to predict the MMSE score was improved by adding the availability of the TMT-B. In the future, it will be necessary to conduct research on how to enable TMT to be used for estimating brain function even if it cannot be completed.

Specifically, the dwell time is assumed to reflect the time to search for the next target and plan the upper-limb movement [47]. Moreover, bivariate analysis results also showed that the total dwell times were significantly slower when a new cerebral lesion was on the right. Our previous study demonstrated that right hemisphere damage was thought to influence regulation of speed and accuracy for performing tasks (i.e., a speed-accuracy trade-off) [48]. From these observations, the dwell time is related to various cognitive functions (i.e., visual information processing and attentional failure) that are influenced by cerebral lesion locations.

The move time in this study reflected the line-drawing motion using an Apple Pencil to connect two targets. In the bivariate analysis, the delay in move time when the cerebral lesion was on the left was related to the fact that most participants performed with their right hand, which would have been affected by such a lesion. Moreover, our present results of the five repeated TMT trials suggest that the line-drawing motion involves repetition, which may be associated with cognitive functions such as motor skill learning, and motor skill learning is acquired to balance the speed and accuracy of gaze-anchoring and reaching movements [30]. Given this, we believe that the participants' cognitive function was influenced by the learning effect. Even for simple tasks like connecting numbers with lines in the TMT-A, we have shown the possibility of measuring various physical and cognitive functions by extracting and analyzing many digitized factors.

5. Study limitations

First, this research aimed to show the possibility of easily measuring various brain functions with a small number of tests by extracting many factors at once through digitized tests. Many factors obtained by the iTMT-A were considered to be involved in many different cognitive functions. To improve the iTMT-A's prediction ability for cognitive function, it will be necessary to compare it with other brain function tests besides the MMSE. For example, regarding the MMSE's application to dementia screening tests, it is necessary to investigate its correlation with MoCA or ACE-IV, which have been considered more sensitive to MCI than the MMSE is.

Second, this study used a small number of participants, and we cannot conclude anything definitive about the clinical significance of the many factors used here for each disease. The power of our present study did not reflect the uncertainties in future studies, so the sample size for future experiments should evaluated separately. Future studies will thus need to incorporate many subjects with varying diseases and to adjust the inspection methods to determine normal values and improve the diagnostic ability.

Third, in our present study, we have repeated measurements (first to third) on the same participants for the MMSE prediction model. Therefore, we also conducted a linear mixed model with session as a random effect. However, if session is used as a random effect, it becomes impossible to define the variation between sessions as an explanatory variable, which creates a contradiction in that it becomes impossible to consider the variation between sessions as proposed in this paper. This is why we decided to use the PLS regression. Future studies are needed for building a prediction model that allows putting both between and within factors in one model.

The fourth limitation is that the simple transition from a paper version to a digital version entails various problems i.e., the user's level of technical experience, device familiarity, or touchscreen literacy that will need to be solved in future studies [25].

Fifth, patients with cognitive decline often could not complete either the TMT-A or the TMT-B, and the study included few patients with low MMSE scores. Further studies will be needed to assess cognitive function without requiring completion of the TMT-A or TMT-B.

A final limitation is that none of the participants in this study were left-handed, while three participants performed TMT with their non-dominant hand. In the previous study targeting Japanese people, no clear differences were observed between the dominant and non-dominant hands on which the pTMT was performed [49]. However, it might be difficult to apply this previous study to our present work, as our study uses dwell and move times extracted from the iPad version. In this study, only three participants performed the TMT with their non-dominant hand, making statistical analysis difficult. Thus, future studies will be needed to analyze the effect of handedness.

6. Conclusions

By extracting the move and dwell times, and by analyzing the learning effect via repeated iTMT-A trials, we found a significant correlation of the iTMT-A result with the MMSE score. By attempting to estimate the results of neuropsychological tests other than the MMSE by using data extracted from a digitized TMT-A, it might become possible to estimate more brain functions with a single test in the future. This research is positioned as the first step in that direction. In daily clinical practice and in using the TMT's paper version, it is difficult, if not impossible, to obtain and analyze the dwell and move times separately. In contrast, the digitized version makes this easy and practical, and use of the iTMT-A instead of the traditional paper TMT could be a highly advantageous and promising technique for clinical practice.

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Data availability statement

The datasets generated and/or analyzed in this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Kouki Kubo: Writing – original draft, Investigation. **Seiji Hama:** Writing – original draft, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Akira Furui:** Visualization, Methodology, Formal analysis. **Tomohiko Mizuguchi:** Software, Resources. **Zu Soh:** Formal analysis. **Akiko Yanagawa:** Investigation. **Akihiko Kandori:** Validation, Supervision, Methodology. **Hiroto Sakai:** Methodology, Formal analysis. **Yutaro Morisako:** Investigation. **Yuki Orino:** Investigation. **Maho Hamai:** Investigation. **Kasumi Fujita:** Investigation. **Shigeto Yamawaki:** Validation, Supervision, Methodology. **Toshio Tsuji:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tomohiko Mizuguchi reports a relationship with Maxell, Ltd., Tokyo, Japan that includes: employment. Akihiko Kandori reports a relationship with Hitachi Ltd., Tokyo, Japan that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33135.

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