Computerized Touch-panel Screening Tests for Detecting Mild Cognitive Impairment and Alzheimer’s Disease

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Abstract

Objective  The increasing population of elderly people in Japan has accelerated the demand for a simple screening test to detect cognitive and affective declines in mild cognitive impairment (MCI) and the early stage of dementia.

Methods  We compared the cognitive and affective functions, activities of daily living (ADLs) and the results of four computerized touch-panel screening tests in 41 MCI subjects, 124 patients with Alzheimer’s disease (AD) and 75 age- and gender-matched normal controls.

Results  All computerized touch-panel games were successfully used to discriminate the AD patients from the normal controls (** p<0.01). Although there were no differences in the findings of the conventional cognitive assessments, the results of the flipping cards game were significantly different (** p<0.01) between the normal controls (19.3±9.5 sec) and MCI subjects (30.9±18.4 sec). Three conventional affective assessments, the ADL score, Abe’s behavioral and psychological symptoms of dementia (ABS) (** p<0.01) and the apathy scale (AS) (* p<0.05), could be used to discriminate the MCI subjects (ABS, 0.9±1.5; AS, 12.8±5.9) from the normal controls (ABS, 0.1±0.4; AS, 8.9±5.3).

Conclusion  In the present study, all four touch-panel screening tests could be employed to discriminate AD patients from normal controls, whereas only the flipping cards game was effective for distinguishing MCI subjects from normal controls. Therefore, this novel touch-panel screening test may be a more sensitive tool for detecting MCI subjects among elderly patients.

Key words: Alzheimer’s disease, mild cognitive impairment, dementia, screening test, cognitive disorder, affective disorder

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Introduction

As the population of elderly people is growing in developed countries, the number of patients with dementia is also progressively increasing. In particular, Alzheimer’s disease (AD) is a representative disease causing cognitive and affective impairments. Mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia (1), and amnestic MCI is defined as a prodromal stage of AD (2). It is therefore necessary to develop a suitable screening test for MCI in order to avoid disease progression. Various conventional questionnaires are available to evaluate the cognitive and affective functions, such as the mini-mental state examination (MMSE), Hasegawa dementia scale-revised (HDS-R), geriatric depression scale (GDS) and apathy scale (AS). These conventional cognitive and affective assessments may be used to detect AD and other causes of dementia, although they do not focus on MCI subjects, making screening for MCI difficult.

We and other groups have reported the validity of computerized touch-panel screening tests as tools for detecting
AD (3-5), ischemic stroke (6), Parkinson’s disease (7) and amyotrophic lateral sclerosis (8). However, touch-panel tests have not been previously used to examine and detect patients with MCI.

The purpose of this study was therefore to examine the cognitive and affective ability in MCI subjects and AD patients using the above computerized touch-panel screening test. Obtaining an early diagnosis of MCI is important for preventing AD progression using disease-modifying therapies.

### Materials and Methods

Ethics approval for this study was given by the Ethics Committee on Epidemiological Studies of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (approval number 694), and informed consent was obtained from all participants.

#### Participants

A total of 41 MCI patients (16 men and 25 women; mean age: 75.3±6.5 years) and 124 AD patients (41 men and 83 women; mean age: 75.6±5.9 years) who consulted Okayama University Hospital and its affiliated hospitals between June 2010 and December 2013 were analyzed. The patients were evaluated based on the AD neuroimaging initiative (ADNI) criteria for MCI and AD (9). The general inclusion and exclusion criteria are summarized below. The MCI subjects had a MMSE score of ≥24, memory complaints, a clinical dementia rating (CDR) (10) of 0.5, the absence of significant impairment in other cognitive domains, essentially preserved activities of daily living (ADLs) and the absence of dementia. The AD patients had a MMSE score of ≥24 and CDR of ≥0.5. Seventy-five age- and gender-matched individuals with a MMSE score of ≥24, CDR of 0, non-MCI status and no symptoms of dementia were included as normal controls (26 men and 49 women; mean age: 75.1±6.1). The history of education in each group was not significantly different (normal controls: 11.9±2.3 years, MCI: 12.3±2.1, AD: 11.3±2.3). The clinical details for each group are shown in Table 1. We excluded patients diagnosed with ophthalmic diseases, parkinsonism, cerebral vascular disease and other central nervous system diseases.

### Touch-panel screening test

A touch-panel screening test for the early diagnosis of dementia (the Ryokansan, Ohtsu Computer, Ohtsu, Japan) was performed by all subjects according to the protocol described in our previous reports (6-8). The touch panel screen included a large monitor (39×33 cm) that was not tablet size. The test did not include tasks, such as writing, that require fine manual dexterity. The screening test consisted of four games: flipping cards, finding mistakes, arranging pictures and beating devils (Fig. 1). Among the participants who performed the tests several times, we adopted the records for the first examination at the time of diagnosis. In the flipping cards game (Fig. 1a), we measured the time taken (sec) and number of errors (times) to turn over all pairs of matching picture cards; there were three pairs of six picture cards. In the finding mistakes game (Fig. 1b), we measured the time taken (sec) to find all three mistakes between panels. In the arranging pictures game (Fig. 1c), we measured the time taken (sec) to arrange four scenes from a famous fairy tale in the correct order. The participants chose among four famous fairy tales understanding the content sufficiently (i.e., Momotaro, Issunboushi, Urashimataro, Kachikachiyama) and touched four scenes along in chronological order. We recorded the accuracy (percent correct) in the beating devils game (Fig. 1d). In the beating devils game, the patients were instructed to distinguish between the emergence of heroes and devils, and we measured their accuracy in exterminating only the devils during a 30-second period. The frequency of appearance of devils was 0.71±0.12 times/sec, versus 0.22±0.08 times/sec for heroes. Hence, devils appeared at a rate of 76.3±8.9% in total. Although the specific cognitive functions reflected by each task are unclear, in broad terms, the flipping card game reflects recent memory, the finding mistakes game reflects attention and discrimination, the arranging pictures game reflects processing and remote memory and the beating devil game reflects judgment (6, 7).

### Standard cognitive and affective assessments

The cognitive function was assessed using the MMSE and HDS-R. Affective functions, such as behavioral and psychological symptoms of dementia (BPSD), depression and apathy were assessed using the Abe’s BPSD (ABS), the 15-

### Table 1. Clinical Profiles in Normal Control, MCI, and AD

<table>
<thead>
<tr>
<th></th>
<th>normal control</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>75</td>
<td>41</td>
<td>124</td>
</tr>
<tr>
<td>Sex(male/female)</td>
<td>26/49</td>
<td>16/25</td>
<td>41/83</td>
</tr>
<tr>
<td>Male(%)</td>
<td>34.7</td>
<td>38.1</td>
<td>33.1</td>
</tr>
<tr>
<td>Mean Age ± SD</td>
<td>75.1 ± 6.1</td>
<td>75.3 ± 6.5</td>
<td>75.6 ± 5.9</td>
</tr>
<tr>
<td>Education(years)</td>
<td>11.9 ± 2.3</td>
<td>12.3 ± 2.1</td>
<td>11.3 ± 2.3</td>
</tr>
</tbody>
</table>

MCI: mild cognitive impairment, AD: Alzheimer’s disease
item GDS and the AS. In addition, we assessed the ADL scores using the AD Cooperative Study-Activities of Daily Living (ADCS-ADL). The MMSE evaluates seven aspects of cognition: orientation, registration, attention and calculation, recall, comprehension of spoken language (naming objects, four spoken language abilities, following commands), writing and construction drawing (11). The HDS-R evaluates orientation, immediate recall, serial subtraction, backward digit recitation, recall of three words, recall of five objects and verbal fluency (generating names of vegetables) (12). The ABS evaluates wandering, aberrant motor activity, delusions and hallucinations, abusiveness, sleep disorders, agitation, apathy, depression, violence and irritation. Therefore, the ABS gives scores to each BPSD item ranging from 0 to 9, resulting in a new BPSD score ranging from 0 to 44 [no BPSD (score 0) to full BPSD (score 44)]. There is a strong correlation between the scores for the ABS and neuropsychiatric inventory (NPI) (13). The GDS includes a screening questionnaire for depression and anxiety. The total scores range from 0 to 15, with higher scores indicating more severe symptoms of depression (14, 15). The AS scores range from 0 to 42, with higher scores indicating more severe apathy. A cutoff score exceeding 14 points implies “with apathy” (16). The ADL scores range from 0 to 30, with lower scores indicating worse functioning (17).

**Statistical analysis**

The statistical analyses were performed using a statistical software package (SPSS 22.0.0.0; IBM, Armonk, USA). After checking for normality, we performed the Kruskal-Wallis test to compare the findings of the touch-panel screening tests and cognitive and affective assessments between the normal controls, MCI subjects and AD patients. p values of less than 0.05 were considered to be significant. In order to examine the influence of the cognitive and affective functions and ADLs on the results of the computerized touch-panel screening tests, we performed Spearman’s rank correlation coefficient tests and a multiple regression analysis using the stepwise method among the normal controls and MCI subjects. Receiver-operator characteristic (ROC) curves were computed, and the cutoff levels were selected from the ROC curves based on optimum sensitivity and specificity.

**Results**

Table 1 presents a summary of the characteristics of the participants in this study. The number of participants differed in each group (normal controls: n=75, MCI: n=41, AD: n=124); however, the mean age and gender were well matched.
Figure 2. Touch-panel screening test results for the normal controls (open bars), MCI subjects (gray bars) and AD patients (black bars). Note that the flipping cards game significantly distinguished the MCI subjects from the normal controls. In addition, all four games discriminated the AD patients from the normal controls (*p<0.05, **p<0.01 vs. normal controls; #p<0.05, ##p<0.01 vs. MCI subjects).

**Touch-panel screening tests**

Fig. 2 shows the results of the touch-panel screening tests. In the flipping cards game, compared with the normal controls (19.3±9.5 sec), the MCI subjects (30.9±18.4 sec; ** p<0.01 vs. normal controls) and AD patients (44.0±28.9 sec; ** p<0.01 vs. normal controls) took longer to complete the game (Fig. 2, left end). In addition, compared with the normal controls (2.4±1.3 times), the MCI subjects (3.1±1.8 times; p=ns vs. normal controls) had more errors in completing the game. The AD patients also demonstrated significantly more errors (3.5±2.7 times) than the normal controls (** p<0.05).

In the finding mistakes game, compared with the normal controls (53.2±36.2 sec), the MCI subjects (62.3±35.2 sec; p=ns vs. normal controls) took more time to complete the game. Additionally, the AD patients required significantly more time to complete the game (83.3±39.4 sec) than the normal controls (** p<0.01) and MCI subjects (# p<0.05) (Fig. 2, center left).

In the arranging pictures game, compared with the normal controls (20.4±12.5 sec), the MCI subjects (29.5±20.0 sec; p=ns vs. normal controls) took longer to complete the game. Meanwhile, the AD patients required significantly more time to complete the game (49.6±30.1 sec) than the normal controls (** p<0.01) and MCI subjects (## p<0.01) (Fig. 2, center right).

In the beating devils game, compared with the normal controls (92.6±12.2%), the MCI subjects (88.7±11.5%; p=ns vs. normal controls) showed reduced accuracy. In contrast, the AD patients exhibited significantly reduced accuracy (65.6±31.0%) compared with the normal controls (** p<0.01) and MCI subjects (# # p<0.01).

**Standard cognitive and affective assessments**

The assessments of cognitive impairment revealed a mean MMSE score of 27.6±1.9 in the normal controls, 27.8±2.0 in the MCI subjects and 19.6±5.0 in the AD patients, while only the AD patients showed a significant reduction in the scores (** p<0.01 vs. normal controls, ## p<0.01 vs. MCI subjects) (Fig. 3, left end). Furthermore, the mean HDS-R scores displayed a similar pattern to the MMSE scores (27.9±1.7 in the normal controls, 26.6±3.2 in the MCI subjects and 17.9±5.8 in the AD patients; ** p<0.01 vs. normal controls, ## p<0.01 vs. MCI subjects) (Fig. 3, second from the left).

The assessments of affective impairment revealed a mean ABS score of 0.1±0.4 in the normal controls, 0.9±1.5 in the MCI subjects (** p<0.01 vs. normal controls) and 6.0±7.5 in the AD patients (** p<0.01 vs. normal controls, ## p<0.01 vs. MCI subjects) (Fig. 3, center left). In contrast, the mean GDS scores showed no significant differences between the three groups (3.2±3.5 in the normal controls, 4.5±3.2 in the MCI subjects and 4.6±4.2 in the AD patients) (Fig. 3, center right). The mean AS scores increased significantly in the following order: normal controls (8.9±5.3), MCI subjects
**Figure 3.** Scores for the standard cognitive and affective assessments in the normal controls (open bars), MCI subjects (gray bars) and AD patients (black bars). Note the lack of significant differences in the MMSE and HDS-R scores between the normal controls and MCI subjects. Both the ABS scores and AS scores were significantly different between the normal controls and MCI subjects (*p<0.05, **p<0.01 vs. normal controls; #p<0.05, ##p<0.01 vs. MCI subjects).

**Table 2.** Reference Chart of Correlation Coefficients

<table>
<thead>
<tr>
<th></th>
<th>Flipping cards(s)</th>
<th>AS</th>
<th>ABS</th>
</tr>
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<tr>
<td>Flipping cards(s)</td>
<td>1.000</td>
<td>0.234 **</td>
<td>0.142</td>
</tr>
<tr>
<td>AS</td>
<td>0.234 **</td>
<td>1.000</td>
<td>0.190 *</td>
</tr>
<tr>
<td>ABS</td>
<td>0.142</td>
<td>0.190 *</td>
<td>1.000</td>
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</tbody>
</table>

AS: apathy scale, ABS: Abe’s behavioral and psychological symptoms of dementia

(12.8±5.9; * p<0.05 vs. normal controls), AD patients (14.9±10.4; ** p<0.01 vs. normal controls) (Fig. 3, second from the right).

The ADL scores were similar in the normal controls (27.9±2.1) and MCI subjects (26.8±3.0) and decreased in the AD patients (19.2±6.8; ** p<0.01 vs. normal controls, # # p<0.01 vs. MCI subjects) (Fig. 3, right end).

**Correlation and regression analyses**

The analyses of the correlations among the scores for the flipping cards game, ABS and AS using Spearman’s rank correlation coefficient revealed little correlations between the three tests (Table 2). In order to evaluate the effects of the affective assessment on the flipping cards game, we performed a multiple regression analysis with the independent variables of ABS and AS. The AS was subsequently excluded as a variable. Although the ABS was adopted as a variable, the correlation between the results of the flipping cards game and the ABS was poor (standardized partial regression coefficient=0.23) and the predictive precision was low (R^2=0.055) (Table 3).

**ROC curve analysis**

ROC curves were computed to evaluate the diagnostic sensitivity and specificity of the touch-panel screening tests and affective assessments (AS and ABS) exhibiting significant differences according to the Kruskal-Wallis test. Fig. 4 shows the ROC curves for the flipping cards game, ABS and AS between the normal controls and MCI subjects (Fig. 4A) and the finding mistakes game, arranging pictures game and beating devils game between the MCI subjects and AD patients (Fig. 4B). When the cutoff value for the flipping cards game was set to 21.5, the sensitivity and specificity for distinguishing the normal controls from the MCI subjects were 76.9% and 70.7%, respectively. Similarly (cutoff: 8.5), the sensitivity and specificity were 84.6% and 52.0%, respectively, for AS and 42.3% and 97.3%, respectively, for ABS (cutoff: 0.5) (Fig. 4A). Meanwhile, the sensitivity and specificity of the finding mistakes game between the MCI subjects and AD subjects were 70.7% and 56.5%.
Table 3. Reference Chart of Multiple Regression Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>SPRC</th>
<th>P value</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>ABS</td>
<td>0.48</td>
<td>0.23</td>
<td>0.018</td>
<td>0.08-0.87</td>
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<tr>
<td>ABS</td>
<td>0.48</td>
<td>0.23</td>
<td>0.018</td>
<td>0.08-0.87</td>
</tr>
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</table>

\( R^2 = 0.055, \) ANOVA \( p < 0.01 \)

SPRC: standardized partial regression coefficient, PRC: partial regression coefficient, CI: confidence interval

Discussion

The present findings (Fig. 3, left) confirmed the difficulty of using conventional cognitive assessments (MMSE, HDS-R) to detect significant differences between normal controls and MCI subjects (18-20). A novel finding of the present study is that, among the computerized touch-panel tests, the flipping cards game (Fig. 1a) sensitively distinguished MCI subjects from normal controls (Fig. 2, left end). Of the three affective and ADL scores, the ABS and AS, as conventional assessments, discriminated MCI subjects from normal controls (Fig. 3, middle and right). In addition, there were weak correlations among the results of the flipping cards game, ABS and AS (Table 2, 3). As for the ability to discriminate between the normal controls and AD patients, most of the conventional assessments, including cognitive and affective assessments and the ADL scores, demonstrated significantly different findings, except for the GDS (Fig. 3). All four games also effectively discriminated the AD patients from the normal controls (Fig. 2).

As the population of elderly people increases, the number of individuals with dementia increases dramatically, thus accelerating the demand for a simple screening test to detect cognitive and affective declines in the setting of MCI and the early stage of dementia. A few computerized touch-panel screening tests have recently been used as possible diagnostic tools for assessing the severity of dementia (3), supplemental tests to the MMSE and HDS-R in order to examine the visuospatial memory function (4) and a possible substitution for the AD Assessment Scale-Cognitive scale (ADAS-Cog) (5). We previously reported that the present touch-panel screening test is useful for assessing cognitive dysfunction in patients with ischemic stroke (6), Parkinson’s disease (7) and amyotrophic lateral sclerosis (8). These results suggest that the results of the touch-panel screening test are significantly correlated with those of conventional tests.

There are various assessments for diagnosing dementia, including the questionnaire test (MMSE and HDS-R), imagining studies using computed tomography (CT) (21), magnetic resonance imaging (MRI) (22) and Pittsburgh compound B amyloid imaging positron emission tomography (PIB-PET) (23-25), as well as biomarkers, such as the cerebrospinal fluid beta-amyloid 42 (CSF Aβ42) and phosphorylated tau (p-tau) levels (26-28). Although imaging modalities and CSF biomarkers may be useful for identifying MCI subjects and AD patients, it is difficult to apply these assessments for screening due to their invasiveness and high costs. Detecting MCI using conventional cognitive assessments (MMSE, HDS-R) is also difficult, as these tests do not focus on de-

(cutoff: 78.5), respectively, compared 73.2% and 68.5% (cutoff: 31.5) for the arranging pictures game and 82.9% and 56.5% (cutoff: 79.5) for the beating devils game (Fig. 4B).

Figure 4. ROC curves for the flipping cards game and ABS and AS scores for the normal controls versus MCI subjects (A) and the finding mistakes game, arranging pictures game and beating devils game for the MCI subjects versus the AD patients (B).
testing MCI in particular. In fact, the present data showed no significant difference in the MMSE and HSD-R scores between the normal controls and MCI subjects (Fig. 3, left). In contrast, the touch-panel screening test detected a significant difference between the normal controls and MCI subjects (Fig. 2, left end). Of interest is that both the ABS and AS scores also showed significant differences between the normal controls and MCI subjects (Fig. 3, middle).

Among the computerized touch-panel tests, the flipping cards game demonstrated a significant difference between the normal controls and MCI subjects (Fig. 2, left end), regardless of the lack of differences on conventional cognitive assessments (MMSE, HDS-R, Fig. 3). The ROC curve analysis also showed the flipping cards game to be useful for discriminating MCI subjects from normal controls (Fig. 4A). The flipping cards game primarily requires recent memory versus remote memory (7), suggesting that this touch-panel screening test may be better suited for detecting amnestic MCI than conventional assessments. The characteristics of the other three games are as follows. The finding mistakes game primarily requires the skills of attention and discrimination, the picture arrangement game primarily requires long-term remote memory and cognition of construction and the beating devils game primarily requires quick judgment and inhibitory control (7). If it is difficult to introduce the “Ryokansan,” these games may be modified for use without a computer (i.e., six cards for the “concentration game”).

In summary, the present findings demonstrated that all four evaluated touch-panel screening tests can be used to discriminate AD patients from normal controls and that the flipping cards game sensitively distinguishes MCI subjects from normal controls. Hence, this novel touch-panel screening test may be a more sensitive tool for detecting MCI among elderly patients.

The authors state that they have no Conflict of Interest (COI).

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