A 5-Year Retrospective Examination of Cognitive Screening Test Stages in Normal Older Adults and Patients With Alzheimer’s Disease: The Tajiri Project

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One conception of aging and cognitive deterioration is that cognitive decline becomes common with age, and dementia may be regarded as one extreme of the continuum. An alternative conception is that the cognitive process is spared by the aging process itself and that cognitive functioning of normal older adults and those with slight cognitive impairment, a CDR (Clinical Dementia Rating) score of 0.5 (suspected dementia), should be different. We examined changes in the screening test performances of 170 older adults over a 5-year period and found the following: (a) The CDR 0 (normal) participants did not show remarkable changes even in the older groups and (b) the subitems of orientation, memory, and so forth were useful for distinguishing normal older adults from early Alzheimer’s disease patients. The results support the idea that dementia is better conceptualized as an age-related than as an “aging-related” disorder and that a CDR score of 0.5 should be considered very mild Alzheimer’s disease.

It is well known that subtle cognitive impairment can be present for several years before the clinical diagnosis of probable Alzheimer’s disease (AD; Bayles & Kasznia, 1987). For assessing cognitive functions, the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) has been widely used (Bassett & Folstein, 1991; Tombough & McIntyre, 1992). It provides a structured approach to mental status that screens for intellectual impairment and allows comparison of performance across time and among patients (Abraham et al., 1994; Galasko et al., 1990). The MMSE score has been found to be related to age and educational level (Callahan et al., 1996; Launer, Dingkreve, Jonker, Hooijer, & Lindeboom, 1993; O’Connor, Pollitt, Treasure, Brook, & Reiss, 1989). Crum, Anthony, Bassett, and Folstein (1993) noted the distribution of the MMSE scores of 18,056 participants by age and education at five sites in the United States. They reported that there were two normative influences on MMSE scores, namely, age and education.

Cross-sectional studies, however, make it difficult to distinguish among aging and cohort effects. Longitudinal studies are clearly more appropriate for the examination of aging and cohort effects. Brayne, Gill, Paykel, Huppert, and O’Connor (1995) followed 1,111 cognitively normal elderly people for 28 months to examine normal aging and mental deterioration. They demonstrated that the normal distribution of change in MMSE score included a decline of 1.3 points. Adding a group of individuals with dementia did not alter the normal distribution. They thus concluded that cognitive decline became increasingly common with advancing age, suggesting that dementia may be regarded as one extreme of the continuum of cognitive decline.

Jacqmin-Gadda, Fabrigoule, Commenges, and Dartigues (1997) conducted a 5-year longitudinal study of MMSE scores in a sample of 2,537 nondemented older adults. Jacqmin-Gadda and associates found that MMSE score declined very slightly, suggesting that cognitive decline as measured by the MMSE was spared by the aging process.

These two conceptualizations of aging and mental deterioration are important. According to a meta-analysis of epidemiological studies (Ritchie & Kildea, 1995), senile dementia is better conceptualized as an age-related disorder, more common within a specific age range, than as an aging-related disorder, caused by the aging process itself.

According to Hughes, Berg, Danziger, Coben, and Martin (1982), even older adults with “questionable” dementia who have a Clinical Dementia Rating (CDR) score of 0.5 suffered pathologic changes indicative of AD and impaired neuropsychological performance (Morris & Fulling, 1988; Morris et al., 1991). These findings demonstrate that even slight cognitive impairment should be distinguished from the aging process itself.

The MMSE and Dementia Screening Test (DST; Otsuka et al., 1988) were administered as part of the Tohoku University and Tajiri Project of Stroke, Dementia, and Bed Confinement Prevention (Tajiri Project). We previously reported the MMSE scores of older adults in relation to their age and educational levels (Ishizaki et al., 1998). Building on the previous study, this current study examines changes in MMSE and DST scores over a 5-year period among normal older adults (CDR 0) and older adults with diagnosis of suspected dementia (CDR 0.5) and AD (CDRs 1 and 2).
To investigate the alternative possibilities of age-related versus aging-related changes, two specific questions are considered: (a) Do normal adults with a CDR score of 0 show MMSE changes over time within different age groups and (b) do specific subitems in the MMSE and DST tests delineate early AD patients from normal older adults?

**METHODS**

Participants and MMSE and DST Interviews in the Tajiri Project

As part of the Tajiri Project, medical and social questionnaires were administered to older adults in the town of Tajiri, which is located in Miyagi Prefecture in the northern part of Japan. The total population was 14,707 in 1991, the time the original baseline study was conducted.

We first targeted all 2,516 residents older than 65 years of age in the town. A total of 2,352 respondents completed the interview, and 88% of them completed both the MMSE and DST tests (MMSE1 and DST1). The DST was originally developed in Japan to facilitate differentiation between patients with dementia and normal adults. It assesses semantic characteristics of cognitive abilities more thoroughly than the MMSE. Both tests were performed by trained public health nurses and psychologists under the direction of neurologists and a psychiatrist. Previously, we reported community-based data of MMSE scores in relation to the effects of age and educational level (Ishizaki et al., 1998).

Subsequently, based on age and sex, 240 older adults we refer to as “magnetic resonance imaging (MRI)-listed participants” were randomly selected from the first survey population (n = 2,352) and requested to undergo MRI examinations: 200 individuals (83%) underwent MRI (Yokokawa MRVetra 0.5 T scanner, Japan) in 1992. The remaining 40 participants were predominately aged 80 years and older, and were unable to undergo MRI due to physical weakness, sudden illness, and so forth.

Third, neuropsychological and psychiatric interviews were planned in 1996 for all 200 MRI-administered participants. We were able to interview 170 participants (85%). The MMSE and DST were again performed (MMSE2 and DST2) by trained public health nurses and psychologists, and the CDR scales were determined at a joint meeting of a psychiatrist, neurologists, psychologists, and public health nurses. Participants were classified into three groups on the basis of CDR ratings: CDR 0 (normal; n = 99), CDR 0.5 (suspected dementia; n = 55), and CDR 1 and 2 groups (dementia; n = 16). For the diagnosis of dementia, 16 participants in the CDR 1 and 2 groups met the criteria of probable AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (McKhann et al., 1984). The two distribution patterns of the first survey population and the 200 MRI-administered participants were similar with the exception of the differing distribution of participants age 80 years and older. Written informed consent was obtained from all participants in this study.

Table 1 shows the demographics of the final study population (n = 170). There were significant CDR group effects for age, F(2, 168) = 5.38, p < .01, and education, F(2, 168) = 3.98, p < .05, and those in the CDR 1 and 2 groups were older and had fewer years of education.

**RESULTS**

Figure 1 illustrates changes in MMSE and DST scores for each CDR group over the 5-year period. For the MMSE, there were significant effects of group, F(2, 165) = 28.89, p < .001, and education, F(1, 165) = 14.38, p < .001, and a Time × Group interaction, F(2, 165) = 9.40, p < .001. Post hoc tests showed that the MMSE2 of each group was significantly different (p < .001). For the DST, there were significant effects of group, F(2, 165) = 22.32, p < .001, and education, F(1, 165) = 18.63, p < .001, and a Time × Group interaction, F(2, 165) = 12.68, p < .001. Post hoc tests showed that the DST2 of each group was significantly different (p < .001).

We examined MMSE scores over the 5-year period for each age group. The 65–69-year-old group contained only 1

![Figure 1. Changes in Mini-Mental State Exam (MMSE) and Dementia Screening Test (DST) scores for each Clinical Dementia Rating (CDR) group over the 5-year period.](http://psy.chasegerontology.oxfordjournals.org/)

**Table 1. Demographics of the Study Population**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male/Female</th>
<th>Age (years) M</th>
<th>Age (years) SD</th>
<th>Education (years) M</th>
<th>Education (years) SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR 0</td>
<td>99</td>
<td>40/59</td>
<td>72.4</td>
<td>5.1</td>
<td>8.1</td>
<td>1.8</td>
</tr>
<tr>
<td>CDR 0.5</td>
<td>55</td>
<td>30/25</td>
<td>74.0</td>
<td>5.5</td>
<td>7.7</td>
<td>2.3</td>
</tr>
<tr>
<td>CDR 1 &amp; 2</td>
<td>16</td>
<td>9/7</td>
<td>76.7</td>
<td>5.4</td>
<td>6.6</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Notes: There were significant group effects for age and educational years, those of the CDR 1 and 2 group being older and lower. CDR = Clinical Dementia Rating.
For the 70–74-year-old group, there were significant effects of CDR group and time (nearly significant for the DST; see Table 2) and a Time × CDR group interaction, we performed a MANOVA for the MMSE subitems for this group.

Table 3 shows the changes in the MMSE and DST subitems over the 5-year period for the 75–79-year old group. For the MMSE subitems, there were significant CDR group effects for time and place orientation, registration, calculation, and figure copying, and there were time effects for time and place orientation and short-term memory. Regarding the DST subitems, there were significant CDR group effects for time orientation, Semantic Knowledge 1 and 2, direction knowledge, calculation, and digit span forward and backward. There were significant time effects for calculation and digit span backward.

**DISCUSSION**

In this study, we examined changes in the MMSE and DST scores of older adults over a 5-year period and found the following:

1. Sixteen participants with CDR 1 and 2 were diagnosed as probable AD.

### Table 2. Multivariate Analysis of Variance Results of the MMSE and DST Interval Changes for Each Age Group

<table>
<thead>
<tr>
<th>Test</th>
<th>Age Group</th>
<th>n</th>
<th>CDR Effect</th>
<th>Education</th>
<th>Time Effect</th>
<th>CDR × Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>65–69</td>
<td>47</td>
<td>2.54</td>
<td>2.13</td>
<td>0.27</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>70–74</td>
<td>56</td>
<td>6.11**</td>
<td>4.27*</td>
<td>0.06</td>
<td>7.16**</td>
</tr>
<tr>
<td></td>
<td>75–79</td>
<td>47</td>
<td>11.38**</td>
<td>8.05**</td>
<td>11.15**</td>
<td>3.27*</td>
</tr>
<tr>
<td></td>
<td>80–89</td>
<td>20</td>
<td>9.90**</td>
<td>0.22</td>
<td>3.16</td>
<td>5.37*</td>
</tr>
<tr>
<td>DST</td>
<td>65–69</td>
<td>47</td>
<td>0.40</td>
<td>7.37</td>
<td>1.88</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>70–74</td>
<td>56</td>
<td>8.55**</td>
<td>4.28*</td>
<td>0.01</td>
<td>2.01</td>
</tr>
<tr>
<td></td>
<td>75–79</td>
<td>47</td>
<td>14.31**</td>
<td>4.80*</td>
<td>3.56</td>
<td>4.78*</td>
</tr>
<tr>
<td></td>
<td>80–89</td>
<td>20</td>
<td>5.30*</td>
<td>4.81*</td>
<td>0.49</td>
<td>6.04*</td>
</tr>
</tbody>
</table>

**Notes:** Multivariate analysis of variance with the covariate of education years with two repeated conditions (time) was performed. MMSE = Mini-Mental State Exam; DST = Dementia Screening Test; CDR = Clinical Dementia Rating.

\( ^{1}p < .10; ^{*}p < .05; ^{**}p < .01. \)

patient in the CDR 1 group and 2 groups. There were no significant effects of CDR group, education, or time. However, the small cell sizes preclude confidence in the findings.

For the 70–74-year-old group, there were significant effects of CDR group, \( F(2, 52) = 6.11, p < .004 \), and education, \( F(1, 52) = 4.27, p < .05 \), and a Time × CDR Group interaction, \( F(2, 52) = 7.16, p < .002 \). There was no significant time effect. For the 75–79-year-old group, there were significant effects of CDR group, \( F(2, 43) = 11.38, p < .001 \); education, \( F(1, 43) = 8.05, p < .009 \); and Time, \( F(1, 43) = 11.15, p < .002 \), and a Time × CDR Group interaction, \( F(2, 43) = 3.27, p < .05 \). For the 80 years and older group, there was a significant CDR group effect, \( F(2, 15) = 9.90, p < .002 \), and a Time × CDR Group interaction, \( F(2, 15) = 5.37, p < .02 \). There were no significant changes in scores over the 5-year period for the CDR 0 participants.

Similar patterns were found for the DST scores, and Table 2 summarizes the MANOVA results of the MMSE and DST changes over the 5-year period for each age group. Because only the 75–79-year old group showed significant effects of CDR group and time (nearly significant for the DST; see Table 2) and a Time × CDR group interaction, we performed a MANOVA for the MMSE subitems for this group.

Table 3 shows the changes in the MMSE and DST subitems over the 5-year period for the 75–79-year old group. For the MMSE subitems, there were significant CDR group effects for time and place orientation, registration, calculation, and figure copying, and there were time effects for time and place orientation and short-term memory. Regarding the DST subitems, there were significant CDR group effects for time orientation, Semantic Knowledge 1 and 2, direction knowledge, calculation, and digit span forward and backward. There were significant time effects for calculation and digit span backward.

### Table 3. Changes of the MMSE and DST Subitems Over the 5-Year Period for the Age 75–79-Year Group (n = 47)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Subitem</th>
<th>Maximum Score</th>
<th>CDR Effect</th>
<th>Education</th>
<th>Time</th>
<th>CDR × Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>1</td>
<td>Time orientation</td>
<td>5</td>
<td>11.86**</td>
<td>0.33</td>
<td>6.13*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Place orientation</td>
<td>5</td>
<td>8.75**</td>
<td>10.54**</td>
<td>4.05*</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Registration</td>
<td>3</td>
<td>3.62*</td>
<td>2.99</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Calculation</td>
<td>5</td>
<td>4.37*</td>
<td>0.50</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Short-term memory</td>
<td>3</td>
<td>2.21</td>
<td>3.13</td>
<td>13.31**</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Naming</td>
<td>2</td>
<td>0.10</td>
<td>1.14</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Sentence repetition</td>
<td>1</td>
<td>0.51</td>
<td>2.66</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Following commands</td>
<td>3</td>
<td>1.20</td>
<td>0.24</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Reading</td>
<td>1</td>
<td>1.15</td>
<td>2.30</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Writing</td>
<td>1</td>
<td>0.06</td>
<td>6.34*</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Figure copying</td>
<td>1</td>
<td>4.70*</td>
<td>8.57**</td>
<td>0.23</td>
</tr>
<tr>
<td>DST</td>
<td>1</td>
<td>Birthday</td>
<td>2</td>
<td>0.59</td>
<td>0.24</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Time orientation</td>
<td>3</td>
<td>5.22**</td>
<td>5.17*</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Semantic knowledge 1</td>
<td>2</td>
<td>3.43*</td>
<td>4.26*</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Semantic knowledge 2</td>
<td>3</td>
<td>13.70**</td>
<td>0.36</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Direction knowledge</td>
<td>3</td>
<td>7.96**</td>
<td>5.97*</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Calculation</td>
<td>2</td>
<td>5.79**</td>
<td>3.70*</td>
<td>6.84*</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Sentence repetition</td>
<td>1</td>
<td>0.21</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Digit span forward</td>
<td>1</td>
<td>3.52*</td>
<td>5.93*</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Digit span backward</td>
<td>3</td>
<td>8.43**</td>
<td>7.19*</td>
<td>6.01*</td>
</tr>
</tbody>
</table>

**Notes:** Multivariate analysis of variance with the covariate of education years with two repeated conditions (time) were performed. MMSE = Mini-Mental State Exam; DST = Dementia Screening Test; CDR = Clinical Dementia Rating.

\( ^{1}p < .10; ^{*}p < .05; ^{**}p < .01. \)
2. Both MMSE and DST scores were affected by CDR group education as a covariate.
3. Most of the age groups showed a CDR effect, and the CDR 0 participants did not show remarkable changes even in the older groups. That is, normal older adults did not show mental deterioration in the 5-year period.
4. Examination of the MMSE and DST subitems indicated that there was a significant time effect in orientation, short-term memory, calculation, and digit span backward. There was also a significant CDR \times Time interaction in time orientation, semantic knowledge, and calculation. These subitems are likely to be useful for distinguishing normal older adults from early AD patients.

Results from the current study suggest that the best conceptualization of senile dementia is as an age-related disorder that occurs within a specific age range rather than as an aging-related disorder that is caused by the aging process itself. Results also support the conceptualization of CDR 0.5 as very mild AD.

Limitations of the Study
Before discussing the results, we should mention some limitations of the study. With regard to sample size, a large sample size would clearly offer many advantages for this kind of research. However, after the first wave of the large sample, MRI examinations were planned as part of the Tajiri Project. Because the MRI fees were paid by the town, the sample size was limited by economic constraints. As described above, the demographic patterns of the first survey population and the MRI-administered participants were similar except for the older respondents. However, as shown in Table 2, there were relatively few participants aged 60–69 compared with other age groups. Most people in the town of Tajiri are farmers who also work at private companies. Many of those age 65–69 were unable to participate in the interview because they were unable to take time off during the day. Presumably they were not demented, and thus we concluded that the data of the CDR 0 group in this study were not overestimated. However, we should note that the results from analyses with small samples should be viewed with extreme caution.

The Aging Process and Mental Deterioration
All of the age groups except for the 65–69 group showed the CDR group effect (and there was only 1 participant in the CDR 1 and 2 group between ages 65 and 69). Although Figure 1 indicates that people 80 years and older appeared to show an effect of time, this is probably due to the small sample size. The significant time effect seen in the 75–79 group was due to a sharper decline in the CDR, with a crossover of the CDR 0.5 and CDR 1 and 2, as indicated by the significant CDR \times Time Group interaction. Among the CDR 0 participants, we believe it is important to note that there were no MMSE or DST changes during the 5-year interval for any age group. This supports the hypothesis that normal older adults do not show mental deterioration simply as a result of the aging process itself.

As noted previously, there have been two primary conceptualizations concerning the association between the aging process and cognitive deterioration. One is the idea that cognitive decline becomes increasingly common with advancing age and that dementia may be regarded as one extreme of the continuum of cognitive decline. However, our findings support the alternative conceptualization, namely that the cognitive process is not synonymous with the aging process itself (Ritchie & Kildea, 1995). The data reported here suggest that the state of normal older adults, even those with slight cognitive impairment (i.e., a CDR score of 0.5), is different from dementia. The conceptualization of the cognitive state of older adults with a CDR score of 0.5 as nondemented is a delicate point; although these older adults have only slight cognitive impairment, we suggest that this slight impairment is not related to the aging process itself. Rather, our results suggest that a CDR score of 0.5 is indicative of very mild AD. This distinction offers support for智商-Gadda and associates (1997) and Ritchie and Kildea’s (1995) proposal that senile dementia is better conceptualized as an age-related disorder, occurring within a specific age range, than as an aging-related disorder, caused by the aging process itself.

Neuropsychological Findings of Early Dementia
Analyzing the MMSE and DST subitems for the 75–79-year-old group indicated that there was a significant time effect for orientation, short-term memory, calculation, and digit span backward. There was a significant CDR \times Time interaction for time orientation, semantic knowledge, and calculation. These subitems are likely to be useful for distinguishing normal older adults from early AD patients.

The preclinical phase of AD has been defined as the period between disease onset and subsequent clinical diagnosis of AD (Linn et al., 1995). Linn and colleagues (1995) suggested that as the length of the preclinical phase is unknown, a fundamental question faces clinicians and researchers alike: When does AD begin? Addressing this question, Linn and associates performed a longitudinal follow-up study using 1,045 normal older adults for up to 13 years. They suggested that cognitive decline can be detected a minimum of 7 years before clinical diagnosis of AD, supporting the contention (Aronson et al., 1990) that a preclinical phase of cognitive deficits is present for many years before actual diagnosis. The concept of a preclinical phase of AD was supported by the recent MMSE follow-up study (Small, Fratiglioni, Vittanen, Winblad, & Backman, 2000) and the 22-year prospective study (Elias et al., 2000) following the Linn and colleagues study.

Our results showed a tendency (not significant) for the CDR 0.5 participants to already have lower MMSE and DST scores compared with the CDR 0 participants (see Figure 1), and the subitems of orientation, memory, and calculation were found to distinguish normal older adults from early AD patients. Detailed analysis of neuropsychological examinations is needed as cognitive screening tests were developed to assess global cognitive functions.

Our findings also support the applicability of CDR assessment. According to Morris and colleagues (Morris & Fulling, 1988; Morris et al., 1991), even older adults who had “questionable” dementia with a CDR score of 0.5 had the same AD pathology, such as senile plaque, neurofibril-
lary tangles, and impaired neuropsychological performance. Older adults with a CDR score of 0.5 should be considered to have very mild AD (Morrison & Fulling, 1988; Morrison et al., 1991).

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