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Benchmarking a Test of Temporal Orientation with Data from American and Taiwanese Persons with Alzheimer's Disease and American Normal Elderly

Rochelle E. Tractenberg^a, Maxine Weinstein^b, Myron F. Weiner^c, Paul S. Aisen^d, Jong-Ling Fuh^e, Noreen Goldman^f, and Yi-Li Chuang^g

^aDepartment of Biomathematics and Biostatistics, Georgetown University School of Medicine, Georgetown University, Washington, D.C.

^bCenter for Population and Health, Georgetown University, Washington, D.C.

^cDepartment of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Tex.

^dDepartment of Neurology, Georgetown University School of Medicine, Washington, D.C., USA

^e The Neurological Institute, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan

^fOffice of Population Research, Princeton University, Princeton, N.J., USA

^g National Institute of Family Planning, Taichung, Taiwan

Abstract

Orientation questions are readily incorporated into longitudinal population surveys, but their value as a screening tool for cognitive impairment is uncertain. We evaluated the screening value of four orientation-to-time items (TTO) from the Mini-Mental State Examination (MMSE) by determining their association with full-scale MMSE scores. Data collected under protocols with strict eligibility criteria in the US (64 normal elderly, 242 persons with probable Alzheimer's disease) and Taiwan (241 persons with probable Alzheimer's disease) were analyzed. The TTO and full-scale MMSE scores were significantly correlated ($p < 0.05$) in persons with a Clinical Dementia Rating (CDR) score of 0 or 1; this was not significant in persons with a CDR of >1 ($p > 0.05$). Both TTO and MMSE were significantly associated with education in persons with 0–7 years of education; some MMSE items, but none of the TTO items, were associated with education in persons with more than 7 years of education. TTO may be a useful component of cognitive screening efforts.

Keywords

Alzheimer's disease; Orientation; Dementia; longitudinal

Introduction

This study was undertaken to estimate the utility of cognition-related items that are currently part of national survey efforts, such as the Longitudinal Study on Aging (LSOA, National Center for Health Statistics) and the Survey of Health and Living Status of the Elderly in Taiwan [1]. Our efforts were focused on persons diagnosed with Alzheimer's disease (AD), a disorder affecting cognition and in which the Mini-Mental State Examination (MMSE) [2] is sensitive to change in early stages [3]. We sought to determine if the TTO scores have descriptive power for general cognitive function by ascertaining whether they are significantly correlated with full-scale MMSE scores in two independent cohorts of AD patients and a control (cognitively normal) cohort, hypothesizing that the TTO scores would show significant correlation with full-scale MMSE scores in each group.

The MMSE, originally intended to be a brief evaluation of cognitive status [2], has been used worldwide as a screening tool to identify individuals for more in-depth testing for dementia or diagnosable cognitive impairment [4-11]. Tierney et al. [12] found that each of the MMSE items tended to be associated to the same extent with neuropsychological tests specifically designed to assess particular cognitive domains (e.g., orientation, attention, recent memory). Tierney et al. [12] concluded that the MMSE is actually a general indicator of cognitive function because each item is associated with several cognitive domains. Temporal disorientation is rare in persons with intact cognition [3, 12], so a test of temporal orientation (TTO) should have high specificity for cognitive impairment.

It is well known that MMSE performance is strongly influenced by education [10, 13, 14]. Not only the MMSE score (high vs. low) but also its interpretation (cognitive impairment/no cognitive impairment) can be affected by the respondent's education level [15]. Education-based adjustments to full-scale MMSE performance, for purposes of identifying individuals with, or at risk of, cognitive impairment, have been developed with American subjects [13, 16]. Whether adjustments [17] or cutoff scores [13] are employed, it is certain that these methods are based on the performance of persons who have had some level of formal education; typically completion of some high school education. The elderly in Taiwan, particularly women, are more likely to have had little or no education [18], making adjustments or norms difficult to implement [15]. Thus, it was also important to document the influence of education on all of the MMSE items for comparison with the four items incorporated into the TTO score and particularly for persons with educational achievement in the none-to-7th grade range. This was a secondary objective for this study.

We evaluated the association between a correct answer on each MMSE item and education in the TAD patients; particularly those with 0–7 years of education to determine if the items in the TTO score represent a score less biased against individuals with little or no education than the full-scale MMSE. We also explored the influence of sex on TTO.

Methods

Subjects

American Normal Elderly (ANE)—A cohort of 64 elderly Americans with no clinical evidence of dementia or AD (all Clinical Dementia Ratings (CDR) [19] = 0, no dementia) was recruited at AD clinics [20] across the United States for a 1-year study of the utility of new instruments for the study of AD [21].

American NINCDS-ADRDA-Diagnosed Probable Alzheimer's Disease (AAD)—A cohort of 242 elderly Americans recruited at AD clinics [20] across the United States for a 1-year study of the utility of new instruments for the study of AD [21] constituted the AAD group. These participants had a National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnosis of probable AD [22]. Roughly 50 individuals were recruited to each of five AD severity levels based on baseline full-scale MMSE: 21+ (mild), 16–20, 10–15, 5–9, and 0–4 (severe). Their CDRs ranged from 1 (mild) to 3 (severe). These American clinical cohorts have been extensively described elsewhere [21].

Taiwanese DSM-Diagnosed Probable Alzheimer's Disease (TAD)—A cohort of AD patients from Taiwan (TAD) was comprised of 241 outpatients with DSM-III-R [23] diagnoses of AD and dementia severity (by CDR) ranging from mild to severe. This cohort, seen in a VA hospital, was of particular interest for this analysis because it included many individuals with low (1–7 years) levels of or no formal education.

Instruments

CDR—Dementia severity was staged with the CDR scale [19]. This is based on semi-structured interviews with the patient and a knowledgeable informant [24]. Patients are rated on six domains: judgment and problem solving, memory, community affairs, home and hobbies, personal care and orientation. The domain ratings are 0 (no impairment), 0.5 (questionable impairment), 1, 2 or 3 (mild, moderate or severe impairment). The personal care domain has no 0.5 rating possible. The CDR global rating, which represents the dementia severity, is based on a weighted combination of these domain scores [24].

MMSE—Full-scale MMSE scores are calculated as the sum of 1/0 correct/incorrect answers to 30 questions, so scores range from 0 to 30 (worst to best). Scores at every point on this range were observed in the reference cohorts (ANE range 22–30). The MMSE was administered as part of the screening visit according to the study protocols; the Taiwanese patients were tested using a validated Chinese version of the MMSE [15]. The TTO score was based on four items that are a part of both the Chinese and English versions: date, month, year, and day of week; ranging from 0 to 4 (worst to best). Because temporal disorientation is so rare in persons without cognitive impairment [3, 12], we also dichotomized the TTO score to reflect 'normal' performance (TTO = 4) and 'not normal' performance (TTO = 0–3).

Statistical Methods

After TTO scores (0–4) were computed, Spearman's rank correlations (ρ) between MMSE and TTO (adjusted as described below) were calculated. The educational bias of each of the MMSE items and performance on TTO were explored by independent samples t tests or Wilcoxon rank sum tests comparing mean educational achievement across individuals in the TAD cohort answering correctly and incorrectly (MMSE items) and across individuals with TTO scores of 4 (100% correct) or 0–3 (0–75% correct). We compared educational attainment in ANE and AAD participants with TTO = 4 vs. those with TTO 0–3 and examined the association between TTO = 4 or TTO = 0–3 with sex. Tests were carried out separately for the three cohorts.

In the TAD cohort, we compared years of education in individuals who succeeded or failed to answer each of the full-scale MMSE items correctly. If the TTO score has less of a relationship with education than full-scale MMSE does, then we would find that at least some of the MMSE items excluded to form the TTO have significant association with education after adjustment for multiple (26^1) comparisons [25]. These comparisons were carried out for the full TAD cohort and replicated for individuals with 0–7 years of education. We also compared educational attainment in TAD participants with TTO = 4 vs. those with TTO 0–3 and examined the association between TTO = 4 or TTO = 0–3 with sex.

Correlations—There would be some correlation between TTO and full-scale MMSE, even if no real association existed, simply because the former is part of the latter whole [26]. Thus, the correlation between MMSE and TTO is inflated due to their relationship. This inflated correlation was corrected by subtracting the correlation between TTO and (MMSE-TTO) [27]. Therefore, we analyzed the adjusted coefficient, i.e., $r_{(\text{MMSE}/\text{TTO})} - r_{(\text{TTO}/(\text{MMSE}-\text{TTO}))}$ rather than the 'raw' value ($r_{(\text{MMSE}/\text{TTO})}$) to determine significance [28].

Inflation of type-I error rates was corrected for multiple comparisons according to the method of Holm [25]; adjusted p values of <0.05 were considered significant. All analyses were carried out using SPSS 11.5 (SPSS, 2002) for the PC.

Results

Descriptive Statistics

The descriptive statistics for the three cohorts are shown in table 1. The two American cohorts were younger and better educated than the Taiwanese AD cohort, and had roughly 50% more women. The average degree of cognitive impairment (MMSE) and dementia severity (CDR) were worse for the AAD than for the TAD. Performance on the TTO was much better in the TAD than the AAD, probably a reflection of the greater level of dementia in the AAD.

¹There were only 26 items in these analyses of the TAD cohort because in place of one of the MMSE items, 'world' spelled backwards, the clinician used either serial sevens or a five-word Chinese proverb (instead of 'world') backwards, whichever one the patient did better on. In all samples, full-scale MMSE score ranged from 0 to 30, but for these item-level t tests, a score of 0–3 was rescored as 0 and a score of 4–5 was rescored as 1.

In table 1 it can be seen that only 1.2% of the AAD cohort and no member of the ANE cohort had fewer than 7 years of education, compared with 52.7% of the TAD. Table 1 also shows that the dementia severity (indicated by CDR) was greater in the AAD (median rating = moderate severity) than in the TAD (median rating = mild severity). The TAD cohort shows clearly that worse MMSE and TTO performance corresponds to less education, and although only 3 individuals in the AAD cohort had 1–6 years of formal education, the patterns suggest that worse MMSE and TTO performance were also observed in these individuals.

TTO and MMSE

TTO scores were calculated from baseline visit MMSE item level responses and full-scale MMSE and TTO scores were correlated as described above. Spearman's correlation coefficient for MMSE and TTO in the ANE was 0.41, and after adjusting for shared elements, this was significant ($t(62) = 2.12$, $p = 0.025$). The correlation coefficient for MMSE and TTO in the AAD was 0.71, but after adjusting for shared elements, this failed to reach significance ($t(240) = 1.24$, $p > 0.10$). The TTO and full-scale MMSE scores in the TAD were strongly and positively correlated (Spearman's $\rho = 0.768$) to a degree similar to that observed in the AAD cohort. After correcting for shared components, the correlation was significant ($t(232) = 2.56$, $p < 0.01$).

TTO, MMSE, Education and Sex

We dichotomized TTO as described above (4 correct = 1, else = 0) and evaluated its association with MMSE, education and sex separately for each group. As shown in table 2, full-scale MMSE scores were significantly higher for those with four correct (ANE: $t(62) = -2.1$, $p < 0.05$; AAD: $t(16.4) = -9.3$, $p < 0.001$; TAD: $t(79.6) = -11.1$, $p < 0.001$).

Education was not associated with the dichotomized TTO variable for ANE (Wilcoxon rank-sum test: $W = 186.5$, $p = 0.32$) or for AAD ($t(13.04) = -1.58$, $p = 0.14$).

In the Taiwanese cohort, education was significantly associated with getting all four TTO items correct ($t(47.9) = -7.5$, $p < 0.001$); the latter finding also reached significance when education was categorized as 0, 1–6 or 7+ years (Kendall's $\tau_b = 0.235$, $p < 0.001$).

The association between the dichotomized TTO variable and sex was marginally not significant for ANE (all four correct: men 97.5%, women 83.3%, $p = 0.061$) and virtually the same proportion of men and women in the AAD cohort had all four correct (men 5.4%, women 5.3%; $p = 1.0$). However, more than twice as many men (20.1 %) as women (8.8%) in the TAD cohort were able to answer all four correctly ($\chi^2 = 6.6$, $p = 0.01$).

TAD: Education and Item Responses

Independent samples t tests were carried out to compare the mean educational level attained by TAD participants who were correct or wrong on each of the 26 (see footnote 1) full-scale MMSE items. These 26 analyses were corrected for multiple comparisons [25]. Table 3 presents the mean educational attainment for individuals who responded correctly or incorrectly to each of the full-scale MMSE items.

Table 3 shows that significantly lower education was associated with incorrect responses on 46% of the full-scale MMSE items. Of the four items included in the TTO score, significantly lower education was observed for those answering two of these incorrectly (today's date and the year). Significantly lower educational attainment was also observed in persons with incorrect responses to ten other MMSE items (all adjusted $p = 0.05$). We then limited the TAD cohort to only those with 0–7 years of formal education ($n = 92$), and repeated the 26 t tests comparing the mean level of education in respondents who were right and wrong for each item (data not shown). None of the TTO items and four of the twelve where significantly greater education was associated with correct answers in the full sample (what city are we in; what hospital are we in; serial 7 s/'world' spelled backwards, and following the command to close your eyes) were associated with more education in those with 0–7 years of education (all adjusted $p < 0.05$). When the analyses were replicated including only those with more than 7 years of education, no differences were observed (all adjusted $p > 0.05$).

TTO and Dementia

ANE ($CDR = 0$) and the two AD cohorts were stratified by dementia severity level (CDR) and their performances on MMSE (0–30), TTO (0–4) and on the dichotomous TTO variable (% with all 4 correct) are shown in table 4. All four items on the TTO were correct in 92.2% of ANE and 5.4% of AAD, while 15% of TAD had correct answers on all four orientation items, nearly three times the proportion observed in the AAD cohort.

The means and ranges for both MMSE and TTO decreased as dementia severity (CDR) increased. Correlation coefficients were calculated for MMSE and TTO for the stratified samples. Only the coefficient for individuals with $CDR = 1$ was significant (AAD: $\rho = 0.558$, $p < 0.005$; TAD: $\rho = 0.597$, $p < 0.001$; all other ρ ranged from 0.160 to 0.488, all other $p > 0.05$). The correlations weakened linearly with dementia severity (data not shown).

Discussion

The TTO score correlated strongly and positively with full-scale MMSE for each clinical sample. Of particular importance to screening for incident dementia is the finding that the association between MMSE and TTO was strongest (and significant) in individuals with $CDR = 0$, and in individuals with $CDR = 1$ in both AAD and TAD. While the diagnoses for each cohort were based on different criteria (i.e., NINCDS-ADRDA for AAD and DSM-III-R for TAD), dementia severity in both groups was staged using the same instrument (CDR), reinforcing the applicability of the TTO.

In a group of Taiwanese persons with AD, significant differences in education were observed between individuals with correct and incorrect answers on 12 of 26 MMSE items; correct answers on two of the four items making up the TTO were associated with significantly more education in this cohort. Thus, both scores were sensitive to education, with roughly 50% of items associated with this variable. In contrast to previous findings with general cognitive scores [29], we found that when analyses were limited to individuals with 0–7 years of education, the association was more limited: just 4 of 26 MMSE items and none of the TTO items were associated with education.

The finding of an association between education and orientation (TTO and dichotomous TTO) replicates earlier work [14, 30] and extends these earlier results to a non-Western cohort. In the Taiwanese cohort (45% female), more men than women were correct on all four orientation items; by contrast, the American cohorts were mostly female (over 60%) and six times as many men as women in the cognitively normal cohort missed at least one orientation item. In the AAD group, men and women did equally poorly. Evidence for an association between respondent sex and TTO performance is thus equivocal.

We hope to capitalize on this benchmarking exercise in future analyses of relationships between social factors, biomarkers and cognition in survey data. Moreover, in the analysis of survey data, it may be desirable to adjust or control for ‘cognitive function’ or ‘cognition’; we propose that scoring 1 00% on the four elements of the orientation score (TTO) might be utilized to identify individuals as having ‘intact orientation’ [31]. A change in this status over time in longitudinal social or epidemio-logic surveys can be used to identify a significant change in cognition [11].

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Table 1Descriptive statistics by cohort: mean $\pm$ SD/median or percent: overall and by education

	ANE (n = 64)	AAD (n = 242)	TAD (n = 241 ^b)
Education, years	13.8 (2.9)	13.1 (2.9)	8.7 (5.4)
Age, years			
Overall	70.3 $\pm$ 8.8	72.3 $\pm$ 9.0	76.6 $\pm$ 7.1
No formal education	(n = 0)	(n = 0)	79.2 $\pm$ 7.2 (n = 33)
1–6 years education	(n = 0)	87.0 $\pm$ 5.3 (n = 3)	74.7 $\pm$ 7.3 (n = 59)
7+ years education	70.3 $\pm$ 8.8 (n = 64)	72.1 $\pm$ 8.9 (n = 239)	76.6 $\pm$ 6.8 (n = 114)
Gender, % female			
Overall	63	61	45
No formal education	–	–	79
1–6 years education	–	67 (n = 3)	64
7+ years education	63	61	28
CDR (dementia severity)			
Overall	0	1.7 $\pm$ 0.6	1.5 $\pm$ 0.7/median 1
No formal education	–	–	1.7 $\pm$ 0.7/median 2
1–6 years education	–	2.3 $\pm$ 0.6/median 2	1.5 $\pm$ 0.7/median 1
7+ years education	0	1.7 $\pm$ 0.6/median 2	1.4 $\pm$ 0.6/median 1
MMSE (full-scale) ^a			
Overall	29.3 $\pm$ 1.3	12.8 $\pm$ 7.9	16.9 $\pm$ 6.9
No formal education	–	–	10.9 $\pm$ 4.8
1–6 years education	–	8.0 $\pm$ 5.6	15.5 $\pm$ 6.5
7+ years education	29.3 $\pm$ 1.3	12.9 $\pm$ 7.9	19.3 $\pm$ 6.2
TTO ^a			
Overall	3.9 $\pm$ 0.3	0.8 $\pm$ 1.2	1.5 $\pm$ 1.5
No formal education	–	–	0.8 $\pm$ 1.2
1–6 years education	–	0.0 $\pm$ 0	1.2 $\pm$ 1.5
7+ years education	3.9 $\pm$ 0.3	0.8 $\pm$ 1.2	1.9 $\pm$ 1.5

TAD = Taiwanese DSM-diagnosed probable Alzheimer's disease; AAD = American NINCDS-ADRDA-diagnosed probable Alzheimer's disease; ANE = American normal elderly (controls); CDR = Clinical Dementia Rating, global.

^a Full scale MMSE (0–30, 30 = best) and TTO (0–4, 4 = best) from first/intake visit.

^b Education values missing for 33 subjects.

Table 2Mean ($\pm$ SD) of MMSE and education for TTO = 4 vs. TTO = 0–3 by cohort

TTO score	ANE		AAD		TAD ^a	
	MMSE	education	MMSE	education	MMSE	education
4 correct	29.4 $\pm$ 1.3 *	13.7 $\pm$ 2.9	24.2 $\pm$ 4.3 **	14.5 $\pm$ 3.3	24.1 $\pm$ 3.6 **	11.9 $\pm$ 4.4 **
0–3 correct	28.2 $\pm$ 0.8	15.0 $\pm$ 3.2	12.2 $\pm$ 7.6	13.1 $\pm$ 2.8	15.6 $\pm$ 6.6	8.1 $\pm$ 5.4

TAD = Taiwanese DSM-diagnosed probable Alzheimer's disease; AAD = American NINCDS-ADRDA-diagnosed probable Alzheimer's disease; ANE = American normal elderly (controls).

* Significantly higher than for individuals in the cohort scoring 0–3: $p < 0.05$.

** Significantly higher than for individuals in the cohort scoring 0–3: $p < 0.001$.

^a Education values missing for 33 subjects.

Table 3

Taiwan Alzheimer's disease patients (TAD): proportion with correct response per item and mean (SD) education for correct/incorrect responses on MMSE items

Item	% correct	Mean education	
		correct	incorrect
1 Today's date ^a	26.0	11.0 (4.8)	7.9 (5.4)
2 Year ^a	42.3	10.9 (4.9)	7.0 (5.3)
3 Month	46.3	9.8 (5.2)	7.7 (5.5)
4 Day of week	37.3	9.8 (5.2)	8.0 (5.5)
5 Season	36.8	9.3 (5.4)	7.6 (5.4)
6 Name of hospital ^{a,c}	71.6	9.7 (5.3)	6.2 (5.1)
7 Floor we're on ^a	37.3	10.6 (5.2)	7.5 (5.3)
8 City we're in ^{a,c}	64.2	9.9 (5.0)	6.5 (5.6)
9 Department ^a	51.7	10.0 (4.9)	7.3 (5.7)
10 Room we're in ^a	17.4	11.6 (4.6)	8.1 (5.4)
11 Immediate recall 1	93.5	8.8 (5.5)	7.7 (5.7)
12 Immediate recall 2 ^b	93.0	8.6 (5.5)	9.3 (4.2)
13 Immediate recall 3 ^b	85.1	8.6 (5.4)	9.3 (5.6)
14–18 'World'/serial 7 s ^a	41.3	11.4 (4.2)	6.8 (5.5)
19 Delayed recall 1	27.3	9.8 (5.7)	8.3 (5.3)
20 Delayed recall 2	23.9	9.8 (5.4)	8.4 (5.5)
21 Delayed recall 3	19.9	10.1 (5.2)	8.3 (5.5)
22 Name item 1 ^b	95.5	8.7 (5.5)	9.1 (3.8)
23 Name item 2	95.5	8.8 (5.4)	5.3 (5.1)
24 Repeat phrase	78.0	9.0 (5.4)	7.7 (5.4)
25 Obey directions: right hand	72.6	9.2 (5.2)	7.4 (6.0)
26 Obey directions: fold paper	57.2	9.1 (5.3)	8.1 (5.7)
27 Obey directions: floor ^d	51.7	9.8 (5.0)	7.5 (5.6)
28 Close eyes ^a	72.3	11.1 (4.2)	6.2 (5.0)
29 Write sentence ^a	52.9	11.4 (4.1)	7.8 (5.3)
30 Pentagons ^a	61.7	10.2 (4.9)	6.4 (5.4)

Items shown in bold type are included in the TTO score, t tests comparing educational attainment in persons answering correctly vs. education in those answering incorrectly.

^a Holm-adjusted p value of < 0.05.

^b Higher mean education in people with incorrect response.

^c Majority of group had correct response *and* a Holm-adjusted p value of < 0.05.

^d Adjusted p = 0.05.

Table 4Mean $\pm$ SD and range for MMSE and TTO, and percent with TTO = 4 by group and CDR

Group	n	MMSE		TTO		TTO = 4 %
		mean $\pm$ SD	range	mean $\pm$ SD	range	
ANE (CDR = 0) ^a	64	29.3 $\pm$ 1.3	22–30	3.9 $\pm$ 0.3	3–4	92.2
AAD overall	242	12.8 $\pm$ 7.9	0–30	0.8 $\pm$ 1.2	0–4	5.4
AAD CDR = 1 ^a	91	20.5 $\pm$ 4.5	8–30	1.8 $\pm$ 1.4	0–4	14.3
AAD CDR = 2	126	9.2 $\pm$ 5.4	0–19	0.3 $\pm$ 0.5	0–2	0
AAD CDR = 3	25	2.8 $\pm$ 2.3	0–9	0.04 $\pm$ 0.2	0–1	0
TAD overall ^a	234 ^b	16.9 $\pm$ 6.9	1–30	1.5 $\pm$ 1.5	0–4	15.5
TAD CDR = 1 ^a	137	21.0 $\pm$ 4.9	7–30	2.3 $\pm$ 1.4	0–4	25.6
TAD CDR = 2	78	12.4 $\pm$ 4.5	2–23	0.6 $\pm$ 0.9	0–3	0
TAD CDR = 3	19	5.9 $\pm$ 3.3	1–12	0.05 $\pm$ 0.2	0–1	0

MMSE = Mini-Mental State Examination; TTO = Test of Temporal Orientation; ANE = American normal elderly; AAD = American persons with Alzheimer's disease; TAD = Taiwanese persons with Alzheimer's disease.

^a After adjusting, the correlation between TTO and MMSE was significant: $p < 0.05$ (see text).

^b The number represents individuals with both MMSE and TTO scores.