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Annualized Functional Change in Alzheimer's Disease Participants and Normal Controls

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Abstract

The rate of functional change in persons with mild Alzheimer's disease (AD) was compared to that of cognitively normal elderly control subjects. A comparison of annualized rates of change on the Test of Everyday Functional Abilities (TEFA) was carried out, along with a brief measure of instrumental activities of daily living skills, in persons with mild AD (Mini-Mental State Exam score > 20) and cognitively normal elderly controls. Persons with AD (N = 30) showed an 8.5 % (3.5 point) annualized decline in TEFA scores over an average of 1.2 years; there was no decline in a group of elderly normal controls (N = 20) over an average of 1.5 years. Persons with mild AD showed functional changes over the course of a year on a direct measure of instrumental activities of daily living; a comparable group of normally aging persons did not.

Keywords

Alzheimer's disease; Direct measure; Functional abilities

Introduction

To date, the primary outcome measures in studies of drugs to treat Alzheimer's disease (AD) have been cognitive testing with the Alzheimer's Disease Assessment Scale (ADAS; Rosen, Mohs, & Davis, 1984), and the Clinician's Global Impression of Change (CIBIC; Schneider et al., 1997), but neither the ADAS nor the CIBIC involves significant direct assessment of patients' ability to perform instrumental activities of daily living.

The Test of Everyday Functional Abilities (TEFA) was created as a brief, ecologically valid, performance-based measure to directly assess functional ability in cognitively impaired persons. The TEFA is administered in a brief interview/assessment format over 15–20 minutes. In a recent study (Weiner, Gehrmann, Hynan, Saine, & Cullum, 2006), the total TEFA score was highly correlated— $r(25) = .892, p < .001$ —with the total score on the Independent Living Scale (Loeb, 1996), a longer standardized assessment instrument for overall functioning that is administered to caregivers. TEFA 1-month test–retest reliability is high ($r = .93$ for AD; $r = .53$ for normal elderly controls). The lower correlation for 1-month test–retest reliability found among controls was likely due to their narrower range of scores (TEFA = 36–51) as

compared with AD participants ($TFA = 2-44$). There is a 96% level of sensitivity and an overall correct classification rate of 80% for persons with AD. TEFA total scores correlate strongly with Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) scores ($r = .92$). While age was not associated with TEFA or MMSE scores in AD participants or elderly controls, higher education was associated with higher TEFA and MMSE scores ($r = .61$ and $r = .52$, respectively), but the correlation between TEFA and MMSE remained significant when controlling for education ($r = .89$) (Cullum et al., 2001). The TEFA has also shown sensitivity to medication treatment effects in AD patients. In a 1-year open-label study of 24 participants treated with a cholinesterase inhibitor, scores showed significant positive change after 1 and 3 months of treatment and a return to baseline values at 1-year follow-up, paralleling a rise and subsequent drop in MMSE scores (Saine et al., 2002). A previous study (Saine, Mayfield, Martin-Cook, Cullum, & Weiner, 1998) showed a moderate correlation between the TEFA and a popular caregiver-administered scale for global function, the Blessed Dementia Rating Scale (Blessed, Tomlinson, & Roth, 1968) ($r = -.51$).

Method

The data for this study were derived from the database of the University of Texas Southwestern Medical Center's Alzheimer's Disease Center (ADC). The ADC follows at yearly intervals cohorts of individuals with normal cognition (NC) and AD. At annual visits, interim medical history is reviewed, and participants receive physical and neurological examinations by behavioral neurologists or geriatric psychiatrists. Participants are also administered a standardized battery of neuropsychological tests, including the TEFA. All participants and/or their legally authorized representative have signed UT Southwestern IRB-approved informed consent to use participants' de-identified data for scientific purposes. To serve as controls, participants must have no memory complaints or CNS disorder, no history of recent mental illness, and must score within normal limits on a neuropsychological test battery that includes the CERAD Battery (Morris et al., 1989), the Logical Memory subtest of the Wechsler Memory Scale (1997) and the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987). AD is diagnosed by NINCDS-ADRDA criteria (McKhann et al., 1984). AD participants at our facility are designated as mild by MMSE scores ≥ 20 .

Instrument

The TEFA has a range of 0–54 points (higher is better), with five subscales:

- Dressing: Two tasks—put on coat and button correctly, and tie shoelaces on a tennis shoe (5 points maximum).
- Time: Seven items—tell time, calculate passage of time, set a clock, and read a calendar (17 points maximum).
- Money: Three tasks—count money, make change, and write out a check (12 points maximum).
- Communication: Five tasks—address an envelope, look up phone numbers, dial the phone, access emergency services, and make a snack (12 points maximum).
- Memory: Three items—remember a previously given instruction and information from tasks completed earlier (8 points maximum).

Statistical methods

Participants were included in the analysis if test scores were available for both MMSE and TEFA at two time points, with time between tests more than 9 months. This resulted in 27 AD participants and 20 NC. Pairs of participants from each group were selected using gender,

education, and age at initial evaluation as pairing criteria to reduce the effect of these factors. To use most of the 47 patients, 6 males were paired with females, the largest education difference was 5 years, and the largest age difference was 10 years.

Demographic characteristics for the AD and NC participants on the continuous measures (age and education) were compared using a two independent samples *t*-test and on the dichotomous measure (gender) using a χ^2 test. Annualized change scores were calculated for Total MMSE scores and Total TEFA scores using the formula [(Score at time 1 – Score at time 2)/Time between tests]. Two independent samples *t*-tests were used to compare the group on Total MMSE score at first and second visits, annualized MMSE scores, Total TEFA scores at first and second visits, annualized TEFA scores, and time between testing sessions.

Additional analyses were performed on these data. Three-way analyses of covariance (ANCOVA) were performed with two between-group factors (diagnosis group and gender) and one within-group factor (testing time 1 and 2), with covariates education and age at initial visit. Gender and the covariates were found to be non-significant in all analyses. Annualized MMSE and TEFA scores were also analyzed using two-way ANCOVA models with two between factors (gender and diagnosis) and covariates education and age at initial evaluation. Gender and the two covariates were again found to be non-significant in these models.

Correlations between the MMSE and TEFA measures were performed using Spearman Rank Order Correlations; the assumption of linearity for the Pearson Product Moment Correlation Coefficient was violated.

Assumptions for all tests were checked for violations; the two independent sample *t*-test assumption of equal group variances was violated and the unequal variance form of the *t*-test was used, where appropriate. All analyses were performed using SPSS V14. Statistical significance was set to $p < .05$.

Results

As shown in Table 1 there were 20 early AD participants and 20 cognitively normal controls; there were no significant differences in age or education. Gender distribution differed between groups ($p = .057$), but not significantly. The average follow-up time for both groups was 1.08 to 1.25 years. Both TEFA and MMSE total scores showed a significant annualized decline—3.1 points (8.5%) for TEFA vs 1.71 points (5.7%) for MMSE in persons with AD (Table 2). Neither scale declined in controls. The Spearman rank order correlation across all participants for MMSE and TEFA total scores was 0.72 ($df = 38, p < .001$) at visit 1 and 0.87 ($df = 38, p < .001$) at visit 2. The correlation for the Annualized Total scores for MMSE and TEFA was 0.46 ($df = 38, p = .003$).

Of the participants with AD, 19 (95%) were receiving a cholinesterase inhibitor (donepezil, galantamine, or rivastigmine) and 11 (55%) a cholinesterase inhibitor plus an NMDA antagonist (memantine). It was not possible to determine the length of time our participants had been on these drugs. Within the AD group, one person was regularly receiving anticholinergic agents (tolteridine and dicyclomine).

Discussion

This study shows that quantifiable changes in everyday functional abilities are detectable in patients in the early stages of AD using a brief, direct measure of abilities. Direct measurement of functional abilities could be a useful adjunct to the cognitive and global measures presently in use to monitor the progression of AD and its response to treatment, but more work needs to be done to establish the utility of the TEFA and other direct measures. Our findings may be

limited by sample bias. We are a tertiary care center and see individuals with relatively high levels of education and motivation for treatment. Our findings are limited by inclusion of a majority of participants taking anti-AD drugs who may have declined at a different rate than if they had been untreated, but it would not have been ethically possible to examine the progression rate of untreated AD. We also did not exclude the person receiving anticholinergic agents; a larger study would have allowed us to control for use of such drugs. The strong correlation between TEFA and MMSE scores is in agreement with previous findings (Cullum et al., 2001), but further suggests that the TEFA may show greater changes over time than the MMSE alone. The TEFA seems well suited as a functional outcome measure for treatment studies aiming to improve or stabilize “real-world” functioning in cognitively impaired persons. Its validity and reliability have been well demonstrated. It correlates well with a much longer functional measure, is sensitive to the effects of a cognitive enhancer, and shows decline over time in persons with AD. It will be important to examine TEFA scores over a period greater than 1 year as the rate of change in instrumental activities of daily living may differ with AD progression, as has been demonstrated with cognitive measures (Doody, Massman, & Dunn, 2001; Stern et al. 1994), which showed that clinical progression appears to be slower in early- and late-stage disease than mid-stage disease. At present, no stage-related information is available for direct measures of activities of daily living. A future study will evaluate the utility of the TEFA in persons with mild cognitive impairment.

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Table 1

Demographics of Alzheimer's disease participants and normal controls

	Alzheimer subjects (<i>N</i> = 20) Mean ± <i>SD</i>	Normal Controls (<i>N</i> = 20) Mean ± <i>SD</i>	Two sided <i>p</i> -value
Age	73.41 ± 8.76	73.89 ± 10.10	.873 ¹
Education (years)	15.45 ± 2.74	15.15 ± 1.90	.690 ¹
% Female	40%	70%	.057 ²

¹Two independent samples *t*-test, *df* = 38.² χ^2 test, *df* = 1.

Table 2
Test of everyday functional abilities and mini-mental state exam changes over time

Measure	AD		NC		t	df	2-tailed p-value
	Mean	SD	Mean	SD			
Interval between tests (years)	1.08	0.30	1.25	0.52	-1.25	30.34	.222
MMSE* score visit 1	25.45	2.76	29.35	0.75	-6.10	21.75	<.001
MMSE score visit 2	23.40	4.12	29.15	1.14	-6.01	21.87	<.001
Annualized MMSE change	1.71	2.28	0.22	1.18	2.60	28.43	.015
TEFA** score visit 1	38.20	6.27	48.30	3.25	-6.40	28.50	<.001
TEFA score visit 2	34.65	10.74	48.95	2.28	-5.83	20.71	<.001
Annualized TEFA change	3.10	7.37	-0.59	2.75	2.09	24.20	.047

* MMSE = Mini-Mental State Examination

** TEFA = Test of Everyday Functional Abilities.