Cognitive Rehabilitation of Mildly Impaired Alzheimer Disease Patients on Cholinesterase Inhibitors

David A. Loewenstein, Ph.D., Amarilis Acevedo, Ph.D.
Sara J. Czaja, Ph.D., Ranjan Duara, M.D.

Objective: *The authors evaluated the efficacy of a new cognitive rehabilitation program on memory and functional performance of mildly impaired Alzheimer disease (AD) patients receiving a cholinesterase inhibitor.* **Methods:** *Twenty-five participants in the Cognitive Rehabilitation (CR) condition participated in two 45-minute sessions twice per week for 24 total sessions. CR training included face–name association tasks, object recall training, functional tasks (e.g., making change, paying bills), orientation to time and place, visuo-motor speed of processing , and the use of a memory notebook. Nineteen participants in the Mental Stimulation (MS) condition had equivalent therapist contact and number of sessions, which consisted of interactive computer games involving memory, concentration, and problem-solving skills.* **Results:** *Compared with the MS condition, participants in CR demonstrated improved performance on tasks that were similar to those used in training. Gains in recall of face–name associations, orientation, cognitive processing speed, and specific functional tasks were present post-intervention and at a 3-month follow-up.* **Conclusion:** *A systematic program of cognitive rehabilitation can result in maintained improvement in performance on specific cognitive and functional tasks in mildly impaired AD patients.* (Am J Geriatr Psychiatry 2004; 12:395–402)

Cognitive rehabilitation (CR) has been shown to be effective in improving the performance on memory and other cognitive measures among individuals who have suffered traumatic brain injury and stroke.[1,2] Although there are no empirically validated cognitive treatment programs for Alzheimer disease (AD) at present, three techniques, known as spaced retrieval, dual cognitive support, and procedural memory training have demonstrated promise in their ability to enhance learning in AD patients. The spaced-retrieval technique (SRT)[3,4] involves learning trials where a specific stimulus (e.g., a face) and a specific association (e.g., a name) are presented. Learning trials are separated by progressively longer time intervals filled with conversation or mental tracking tasks to prevent rehearsal of the to-be-re-

Received September 9, 2003; revised December 23, 2003; accepted February 3, 2004. From the Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL (DAL,AA,RD), and the Department of Psychiatry and Behavioral Sciences and Center on Aging, University of Miami School of Medicine, Miami, FL (DAL,AA,SJC). Send correspondence to David A. Loewenstein, Ph.D., University of Miami Department of Psychiatry, 2nd Floor, MRI Building, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, FL 33140. e-mail: dloewenstein@worldnet.att.net

membered information. If an error occurs on retrieval (e.g., incorrect retrieval of a name when a face is presented), corrective feedback is provided, and the interval between stimulus presentation and recall is decreased to the previous interval in which recall was correct. It has been postulated that SRT works by engaging implicit memory processes, by tapping procedural systems and by decreasing reliance on semantic or declarative mechanisms.[5]

Dual cognitive support involves the provision of cues and the enhancement of the saliency and organization of the to-be-remembered information at both acquisition and retrieval of the information. Such support has been associated with improved learning, as in verbal episodic memory tasks,[6–8] in AD.

Procedural memory training requires the activation of the motor system. In AD, motor learning has been shown in paradigms that require the self-selection of movements.[9–11] This training has also been used to improve performance on activities of daily living in AD, but these improvements seem to be short-lived.[12]

Thus, it appears that specific cognitive functions can be trained in mild and more moderately impaired AD patients, although no one paradigm has been developed that incorporates SRT, dual cognitive support, and functional procedural skills training as part of an integrated treatment package. Moreover, few studies have included adequate control groups or have equalized therapist contact and level of cognitive activity of the training tasks. The current investigation incorporates all of the aforementioned elements and is the first evaluation of a systematically applied CR program with AD patients who are on a stable dose of a cholinesterase inhibitor. We hypothesized that the use of specific cognitive and functional tasks in training would result in sustained improvement in cognitive and functional tasks that were similar, yet not identical, to the trained tasks.

METHODS

Forty-four subjects who participated in the study were diagnosed with probable AD or possible AD by NINCDS-ADRDA criteria[13] by an experienced neurologist after a thorough neurocognitive evaluation, blood tests, and MRI of the brain. Those patients with probable AD met DSM-IV criteria for dementia[14] and those subjects with possible AD evidenced, at minimum, a significant progressive deficit in memory, but did not have sufficient impairment social/occupational functioning, as required by DSM-IV criteria, for a dementia-syndrome diagnosis. Morris et al.[15] have demonstrated that clinically diagnosed patients with the latter characteristics typically represent early AD that ultimately progresses to dementia over time.

The sample consisted of 44 subjects, all of whom had been on a stable dose of a cholinesterase inhibitor for at least 8 weeks. Of the 41 subjects on donepezil, 32 subjects were taking 10 mg, 3 were taking 7.5 mg, 5 were taking 5 mg, and 1 was taking 15 mg. Three additional subjects were on either rivastigmine or galantamine. Subjects were randomly assigned to either CR or MS training, with a similar distribution of dosages and types of the cholinesterase inhibitors between the groups. All subjects completed a neuropsychological battery before the initiation of the intervention (i.e., baseline), at 1–2 weeks post-intervention, and at 3-month follow-up. All subjects were required to participate in 24 individual training sessions, each lasting 45 minutes, which typically took place twice per week, during a period of 12–16 weeks. A family member or friend assisted the patient in completing homework assignments. Results are provided for 25 of the 28 patients in CR (89%) and for 19 of the 21 patients in MS (90%) who completed all the required sessions. Of the total sample, 30 patients (68%) were English speakers, and 14 (32%) were Spanish speakers, with all components of the program (i.e., sessions, homework assignments, neuropsychological battery) conducted in the patient's primary language. Approximately 80% of Spanish speakers were of Cuban origin. As depicted in Table 1, there were no significant differences between the CR and MS groups with regard to age, gender, primary language, educational attainment, and baseline scores on the Mini-Mental State Exam (MMSE).[16]

Procedures

Subjects in the CR and MS conditions were assigned to one of two experienced neuropsychologists (DAL or AA). An equivalent number of subjects in each condition were seen by each neuropsychologist. The administration of the neuropsychological outcome battery at baseline, 1–2 weeks post-intervention, and at the 3-month follow-up was conducted by a psychometrist blinded to the subjects' treatment condition. All tests included in the neuropsychological outcome battery were translated and back-translated into Spanish according to standardized procedures.[17] The neuropsychological outcome battery included measures that were related (e.g., Face–Name Association Test) or unrelated (e.g., confrontation naming task) to the exercises used as part of the CR training. For the tasks that were related to the CR training, the items included in the neuropsychological outcome battery were different from those used in the training sessions. For example, practice items used in the training of making change for a purchase were different from those used in the Making Change for a Purchase Task included in the neuropsychological outcome battery. Likewise, items that were part of the Procedural Object-Memory Test were not used in the training sessions using procedural memory to remember objects. The only exception to this rule was the inclusion in the CR training sessions of 5 of the 10 faces that comprise the Face–Name Association Test, a measure that was created for the present project.

Cognitive Rehabilitation (CR) Training

The CR training was administered individually and focused on 1) learning face–name associations by using SRT and dual cognitive support (e.g., encouraging the subject to associate the target name with the name of a familiar person, to use first-letter cues, or facial cues); 2) practicing time-and-place orientation through in-session rehearsal and use of the calendar and personal information sections of the memory notebook in session and at home; 3) activating procedural and motor memory by asking patients to manipulate the objects as though they were using them; 4) sustaining attention and activating visuomotor processing by asking subjects to press the mouse button in response to yellow boxes that appeared at variable intervals across the computer screen or to selectively respond with right or left presses, depending on the specific letter contained within the box; 5) training to make change for a purchase from a $20-bill, using different amounts; and 6) balancing a checkbook by hand and with a calculator after paying three actual utility bills (i.e., telephone, electric, and water bills). All subjects were encouraged to work on their memory notebooks and to practice the aforementioned tasks at home with the assistance of a family member or friend as mentioned above.

The tasks and evaluations associated with this training were the following:

The Face–Name Association Task (Acevedo A, Loewenstein DA: unpublished manuscript, University of Miami School of Medicine, 2001). This reliable and valid task involves the presentation of 10 faces, each with a corresponding name. After each of the three learning trials, where faces are presented in a different order, recall is assessed by presenting the face to the subject, asking the subject to provide the correct name, and providing corrective feedback on incorrectly named faces. A 30-minute delayed-recall trial is also administered.

Orientation Task. This task included the time-and-place orientation items of the MMSE.[16]

The Continuous Performance Test.[18] This widely used attention and vigilance test requires the subject to hit a key or withhold a response when specific targets are presented on a computer screen. Omission errors, commission errors, and total processing/reaction time were used as outcome variables.

Procedural Object-Memory Evaluation (Loewenstein D, Acevedo A: The Procedural Object Memory Test [POM]. Administration and Scoring Manual, unpub-

TABLE 1. Demographic characteristics of patients in the Cognitive Rehabilitation (CR) and Mental Stimulation (MS) conditions, mean (standard deviation)

	CR (N = 25)	MS (N = 19)	F or χ^2
Age, years	78.12 (4.3)	74.74 (7.5)	3.56
Education, years	13.08 (4.1)	14.37 (3.0)	1.32
Baseline Mini-Mental State Exam score	23.40 (2.9)	24.53 (4.5)	1.01
Post-intervention, weeks from baseline	18.56 (2.8)	18.16 (3.0)	0.21
Follow-up from post-intervention to 3-month follow-up, weeks	13.67 (1.2)	12.79 (1.1)	5.92*
Men/Women	15/10	11/8	0.02
English-speaking/Spanish-speaking	16/9	14/5	0.47

Note: *$p < 0.05$; df for F tests: 1, 42 and for χ^2 tests: 1.

lished manuscript, University of Miami School of Medicine, 2001). This is test in which 12 common objects are placed in front of the subject, one at a time, for 10 seconds, and the patient is asked to recall them across three learning trials and after a 30-minute delay.

Modified Making-Change-For-A-Purchase Task (based on the Direct Assessment of Functional Status, [DAFS]).[19] This modified subtest of the DAFS requires the subject to make change for different amounts from a $20-dollar bill. Two points are awarded for correct responses to each of the five trials.

Bill-Paying: Balancing-A-Checkbook Task (based on the DAFS).[19] This modified subtest of the DAFS requires the subject to calculate by hand, and with the aid of a calculator, the remaining balances after paying each of three actual utility bills (i.e., electric, telephone, and water).

Mental Stimulation (MS) Training

The MS condition was administered individually; it focused on 1) commercially available computer games that required the subject to match pairs of letters, numbers, or designs from memory; 2) exercises such as "hangman," where the patient selected specific letters and then attempted to identify specific words and proverbs; 3) tasks that required the subject to find words distributed in an array of letters or to re-arrange sets of letters to generate as many words as possible using only those letters; 4) "topic of the day," where patients had to remember information from the recent or remote past (e.g., what they did the day before, their neighborhood when growing up; and 5) review and discussion of the homework that had been assigned for the session.

Neuropsychological outcome measures not related to tasks used in CR training were the following:

- List-Learning Task from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[20]
- Logical Memory test from the Wechsler Memory Scale, 3rd Edition (WMS-III)[21]
- Digit Span from the Wechsler Adult Intelligence Scale, 3rd Edition, (WAIS-III)[22]
- Trailmaking Test[23]
- Category Fluency Test[24]

Patient self-report and informant measures: 1) the Revised Memory and Behavior Problems Checklist (RMBPC);[25] 2) the Bayer Activities of Daily Living Scale (B-ADLS);[26] 3) the Center for Epidemiological Studies–Depression Scale (CES–D);[27] and 4) the Informant Questionnaire of the Cognitive Decline in the Elderly scale (IQCODE)[28]

On the IQCODE, the form used for baseline was modified by using the previous year (i.e., not the past 10 years) as the period against which the informant was asked to compare memory changes in the patient. A patient self-report version was also generated. At post-intervention and at the 3-month follow-up, the time period used to assess changes in memory was the previous 3 months.

RESULTS

We conducted a series of 2 × 3 Group (CR or MS) by Time (Baseline, Post-Intervention, 3-Month Follow-Up) repeated measures mixed model analysis of variance (ANOVA) models (Table 2). Primary language was also examined but was not associated with any of the outcome variables and is therefore not presented.

There were significant Group × Time Interactions for the three-trial ($F_{[2, 84]} = 5.89$; $p < 0.005$), delayed recall on the Face–Name Association Task ($F_{[2, 84]} = 15.16$; $p < 0.0001$), Orientation ($F_{[2, 84]} = 5.53$; $p < 0.01$), Making Change For A Purchase ($F_{[2, 84]} = 4.24$; $p < 0.05$), MMSE ($F_{[2, 84]} = 3.69$; $p < 0.05$), CPT commission errors ($F_{[2, 66]} = 5.29$; $p < 0.05$, and CPT reaction time ($F_{[2, 66]} = 8.24$; $p = 0.001$.

Table 3 shows the different means associated with statistically significant Group × Time interactions. Persons in the CR group tended to achieve higher scores on the Face–Name Association Test, Orientation, Making Change For A Purchase Test, and CPT time relative to baseline, at post-intervention, and at the 3-month follow-up. Relative to baseline, performance in the MS group was higher on the three-trial Face–Name Association recall and lower for Orientation at the 3-month follow-up. With the exception of lower commission errors on the CPT at post-intervention, there were no other differences between baseline and follow-up performance for the MS group.

TABLE 2. Differences in performance ($F_{[df]}$) among groups on trained and untrained tasks

	Group $_{[1, 42]}$	Time $_{[2, 84]}$	Group × Time $_{[2, 84]}$
		Trained Tasks	
Face–Name Association three-trial learning	2.05	24.70****	5.89**
Face–Name Association delay	0.49	15.30****	15.16****
Orientation	2.23	2.28	5.53**
Object-Memory three-trial learning	0.04	2.26	1.28
Object-Memory delayed recall	0.23	0.70	0.70
Change-For-Purchase test	0.48	0.27	4.24*
Balancing-A-Checkbook (hand)	2.38	0.12	0.23
Balancing-A-Checkbook (calculator)	2.80	1.25	1.74
CPT Omission Errors	0.14	0.12	0.21
CPT Commission Errors	16.36****	0.10	5.29*
CPT reaction time	1.15	4.73*	8.24***
		Untrained Tasks	
CERAD List Learning	0.13	6.28***	1.57
CERAD List Delay	0.01	2.95	1.26
Digit Span (WAIS-III)	3.25	0.39	0.43
Category Fluency	0.91	0.68	0.87
Folstein Mini-Mental State Exam	0.00	2.07	3.69*
Trails A	2.47	1.67	1.83
Trails B	0.09	0.32	1.37
Logical Memory (WMS-III), Immediate	0.19	0.51	0.47
Logical Memory (WMS-III), Delayed	0.74	1.20	0.88

Note: CPT: Continuous Performance Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; WAIS: Wechsler Adult Intelligence Scale; WMS: Wechsler Memory Scale.

CPT Time effect and interaction term df is [2, 66].

*p <0.05; **p <0.01; ***p ≤0.001; ****p <0.0001.

TABLE 3. Performance on trained skills of subjects with Alzheimer disease in Cognitive Rehabilitation (CR) and Mental Stimulation (MS) conditions, mean (standard deviation)

Trained Skills	Group	Baseline	Post-Intervention	3-Month Follow-Up	p (Group × Time Interaction)
Face–Name Association three-trial learning	CR	7.32 (5.5)	14.64 (7.5)***	13.75 (8.4)***	0.004
	MS	7.47 (5.5)	9.63 (7.9)	10.21 (7.9)*	
Face–Name Association delayed recall	CR	2.44 (2.3)	5.28 (3.0)***	4.88 (3.3)***	<0.001
	MS	3.68 (2.5)	3.84 (3.3)	3.42 (3.1)	
Orientation	CR	7.40 (1.9)	8.36 (1.3)**	8.04 (1.7)*	0.006
	MS	7.47 (2.3)	7.26 (2.3)	6.63 (2.5)*	
Object-Memory three-trial learning	CR	19.84 (5.5)	19.92 (7.5)	21.76 (7.2)	0.285
	MS	20.68 (6.6)	21.0 (7.7)	21.11 (8.2)	
Object-Memory delayed recall	CR	5.16 (3.4)	5.12 (3.6)	5.44 (3.9)	0.500
	MS	5.47 (3.4)	6.00 (3.8)	5.79 (3.9)	
Change-For-A-Purchase	CR	4.72 (3.6)	6.24 (3.4)*	5.76 (3.3)*	0.018
	MS	5.37 (4.0)	4.32 (4.2)	4.95 (3.9)	
Balancing Checkbook (by hand)	CR	2.33 (1.6)	2.25 (1.6)	2.25 (1.7)	0.789
	MS	1.47 (1.5)	1.53 (1.5)	1.78 (1.4)	
Balancing Checkbook (with calculator)	CR	2.63 (1.6)	3.38 (1.4)	3.33 (1.2)	0.182
	MS	2.50 (1.8)	2.26 (1.7)	2.61 (1.7)	
CPT Omission Errors	CR	21.58 (25.0)	19.43 (32.8)	23.85 (43.7)	0.811
	MS	20.12 (20.5)	20.00 (22.8)	19.28 (26.2)	
CPT Commission Errors	CR	13.29 (5.4)	17.05 (7.6)*	15.70 (8.4)	0.007
	MS	9.88 (6.6)	6.35 (4.3)*	7.56 (5.2)	
CPT Reaction Time	CR	525.80 (160.1)	427.68 (67.7)**	471.23 (142.9)**	0.001
	MS	509.08 (60.8)	523.24 (77.1)	514.64 (76.2)	

Note: CPT: Continuous Performance Test.

Mean performance at follow-up and 3-month evaluations for a specific group with a statistically significant interaction term are significantly different from baseline at *p <0.05; **p <0.01; ***p <0.001. The df for the interaction term is [2, 84].

The self-report of memory changes on the IQCODE showed a significant Time effect ($F_{[2,\ 82]} = 14.2$; $p < 0.01$), and the Group × Time Interaction approached significance ($F_{[2,\ 82]} = 2.94$; $p < 0.06$). Similarly, there was a significant Time effect ($F_{[2, 72]} = 7.76$; $p < 0.001$), and a significant Group × Time interaction ($F_{[2, 72]} = 3.58$; $p < 0.04$) on the informants' reports of memory changes in the patients.

As shown in Table 4, patients in both CR and MS groups reported significant improvements in memory from baseline on the IQCODE. However, informants of patients in the CR condition noted a significant improvement in memory function at post-intervention that was not reported by informants of patients in the MS condition. There was also a significant Time effect for CES–D scores of patients ($F_{[1, 82]} = 5.19$; $p < 0.01$), indicating that subjects in both CR and MS groups experienced less depression post-intervention. There was no association between reported depression and performance on neuropsychological outcome measures for any of the interventions. Furthermore, there was no statistically significant difference between the groups on the reports of the patients' informants on the RMBPC or BADLS.

DISCUSSION

To our knowledge, this study represents the first attempt to combine specific cognitive techniques (i.e., spaced retrieval, dual cognitive support, procedural-memory activation, visuo-motor processing activation, functional skills training) into a single cognitive-rehabilitation package for mildly impaired AD patients. This study is also novel in its inclusion of a comparison condition (i.e., mental stimulation) that allowed the examination of the impact of nonspecific variables (e.g., cognitive activation, therapist contact, familiarity with tests in follow-up assessments) on outcome variables. The current findings indicate that mildly impaired AD patients on a stable dose of cholinesterase inhibitors can benefit from a cognitive-rehabilitation intervention, demonstrating improvements in measures that assess orientation, learning of face–name associations, speed of processing, and specific functional abilities (i.e., making change for a purchase). It should be underscored that, with the exception of the Face–Name Association Test, where 5 of 10 items were used in CR training, items on the neuropsychological outcome battery were similar but not identical to those used in CR training. Furthermore, these training effects were maintained over the 3-month post-intervention follow-up period without any further training or maintenance sessions.

The ability to learn face–name associations by use of SRT and to maintain these gains over time is consistent with other studies demonstrating the efficacy of this procedure on AD patients.[3,4,29] The improvement in orientation among the CR group was most likely related to the orientation training in the office as well as the use of the memory notebook at home during the intervention. A number of subjects continued to use their memory notebooks post-intervention, possibly accounting for their consistent performance on the orientation measure at 3-month follow-up. This is impressive, given that patients in the MS intervention showed continued deterioration on orientation at 3-month follow-up. AD patients in the CR condition evidenced increased cognitive processing speed on the CPT at post-intervention and 3-month follow-up. There was also an increase in commission errors, but post-hoc analyses did indicate a relationship between the number of such errors and speed of cognitive processing. Although cognitive exercises have been shown to increase processing speed in cognitively normal adults,[30] the present study is the first to show such effects in mildly impaired AD patients. The finding that subjects in the CR condition improved their performance on the Making-Change-For-A-Purchase Test suggests that functional training can have a positive impact on real-world behaviors, potentially improving the quality of life of AD patients and/or their caregivers. Recent work by Farina et al.[12] has demonstrated improvement on certain instrumental activities of daily living in AD patients after procedural memory training. Also, an intervention based on SRT and errorless-learning training was shown to be effective in teaching two AD patients to use a mobile phone.[31] The present results indicate that functional training can facilitate performance on some functional tasks, but it is likely that maintenance or booster sessions will be required in order to maintain this performance level over time.

In the current study, there was no apparent learning effect for CR subjects on the Bill-Paying: Balancing-A-Checkbook Task when done by hand or when using a calculator. This may have stemmed from ceiling effects, because many CR and MS participants had achieved perfect scores on this task at baseline.

Also, there was no facilitation of recall for objects by having subjects manipulate and use the objects that they were later asked to recall, but it appeared that many CR patients did not spontaneously manipulate the objects at post-intervention assessment despite being trained to do so during CR. Although subjects in the CR condition performed better on outcome measures related to the trained tasks, there was no improvement on performance on neuropsychological tests that were seemingly unrelated to the trained tasks. This is consistent with the general CR literature indicating that outcome measures most similar to training tasks usually demonstrate the most improvement.[1,2] This finding suggests that the focus of CR programs in AD should specifically target the training of applied real-world tasks (e.g., making change for a purchase), rather than merely targeting broad theoretical cognitive constructs (e.g., memory).

The finding that CR enhanced performance on a number of measures and that these gains could be maintained over time among AD patients on cholinesterase inhibitors could help in the future development of cognitive interventions that may supplement the cognitive impact of pharmacological agents currently under study.

Several limitations of the present study should be addressed. Given the integrated nature of the CR intervention, it is possible that, rather than stemming from procedural training, the improved performance on functional tests such as Making-Change-For-A-Purchase was due to other components of the training program (e.g., visuo-motor processing training). A potential area of future research is to attempt to disentangle these effects by comparing the effects of a cognitive training program, a functional training program, and a combined cognitive/functional program. Further research is also required to determine whether the face–name association paradigm used in the present study could be used to facilitate the acquisition and retention of face–name associations for people in the patient's real life. Further development of ecologically valid CR paradigms is needed to assist the patients and their families with real-world tasks. Development of relevant outcome measures is also needed to assess the effectiveness of future cognitive and/or functional interventions across multiple assessments along the disease continuum.

In conclusion, this investigation supports the notion that AD patients can learn and maintain cognitive and functional gains. The extent to which post-termination maintenance sessions could prolong cognitive and functional gains in AD remains an empirical question. Further development of CR paradigms holds promise in the promotion of ecologically-valid cognitive and

TABLE 4. Scores on questionnaires of patients in the Cognitive Rehabilitation (CR) and Mental Stimulation (MS) groups and their caregivers, mean (standard deviation)

Measure	Group	Baseline	Post-Intervention	3-Month Follow-Up	p (Group × Time Interaction)
IQCODE Patient	CR	76.04 (12.7)	60.20 (18.2)***	61.00 (22.1)	0.059
	MS	71.37 (13.8)	59.90 (17.1)***	68.32 (17.1)	
IQCODE Informant	CR	80.00 (20.9)	64.05 (22.3)**	73.86 (18.9)****	0.033
	MS	81.17 (12.3)	77.44 (16.8)	75.67 (19.9)	
CES–D Patient	CR	9.48 (8.6)	8.52 (10.1)	6.28 (6.8)	0.149
	MS	12.79 (10.7)	8.42 (8.7)	9.84 (10.8)	
CES–D Informant	CR	10.33 (9.3)	9.14 (7.4)	10.76 (8.0)	0.456
	MS	11.22 (10.4)	11.89 (9.8)	11.17 (10.2)	
B-ADLS	CR	3.2 (1.7)	3.8 (2.1)	4.0 (2.0)	0.837
	MS	2.8 (1.6)	3.3 (1.8)	3.9 (2.3)	
RMBPC Total Number of Problem Behaviors	CR	10.82 (5.9)	9.12 (5.0)	10.12 (4.5)	0.094
	MS	8.39 (4.7)	9.28 (4.0)	9.76 (4.8)	
RMBPC Total Frequency of Problem Behaviors	CR	21.88 (13.3)	17.06 (10.7)	24.13 (14.6)	0.237
	MS	20.94 (20.4)	19.29 (12.2)	20.41 (13.1)	
RMBPC Total Informant Reaction score	CR	14.63 (15.6)	14.00 (13.0)	15.81 (15.1)	0.777
	MS	9.89 (11.2)	8.06 (8.3)	9.12 (11.3)	

Note: IQCODE: Informant Questionnaire of Cognitive Decline in the Elderly; CES–D: Center for Epidemiological Studies–Depression Scale; B-ADLS: Bayer Activities of Daily Living Scale; RMBPC: Revised Memory and Behavior Problems Checklist.

Mean performance at follow-up and 3-month evaluations for a specific group are significantly different from baseline at *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$. The df for the interaction term is [2, 84].

functional gains and, potentially, in complementing the impact of new pharmacological agents that are developed.

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