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RHEA,* a Nonpharmacological Cognitive Training Intervention in Patients With Mild Cognitive Impairment

A Pilot Study

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Objective: This study aimed to examine the effectiveness of RHEA, a cognitive training through kinetic exercises, on patients with mild cognitive impairment.

Subjects and Method: Participants, completing study, were 58 mild cognitive impairment patients with MMSE = 27.69, assigned to 2 groups of 29 each (experimental, 20-weekly RHEA sessions, and no-therapy control), matched for age, gender, education, cholinesterase inhibitors, cognitive abilities. Neuropsychological assessments were performed at baseline and after 5 months.

Results: Between groups difference to the benefit of the experimental group were demonstrated in attention ($P = .002$), language ($P = .015$), visual-spatial abilities ($P = .013$), MMSE ($P = .047$), and daily function ($P = .009$). Experimental participants improved cognitive and functional performances while control participants remained stable.

Key words: cognition, cognitive motion therapy, cognitive training, kinetic exercises, MCI, neural plasticity, nonpharmacological intervention, RHEA

The aging population is increasing and many elderly express subjective mild memory complaints often identified by neuropsychological assessment, even though their functional performance in activities of daily life (ADL) remains in the normal range. This condition is called mild cognitive impairment (MCI) and it does not fulfill the criteria for dementia[1]; however, it presents divergence from healthy aging[2] and indicates a possible need for medical care and treatment.[3]

The initial conception for MCI focused almost exclusively on memory deficits. To date, it is clear that MCI may entail symptoms in cognitive domains other than memory. This led to a classification for MCI comprising 4 subtypes: (a) MCI amnestic—single domain (sd MCIa), [AQ3] (b) MCI amnestic—multiple domains (md MCIa), (c) MCI nonamnestic—single domain (sd MCInon-a) and (d) MCI nonamnestic—multiple domains (md MCInon-a).[4,5] The identification of non–memory deficits depends on the sensitivity of the measurements used in related studies. This is crucial because measurements of mental speed, executive function, auditory attention, and verbal fluency have proved to be reliable markers for MCI's conversion to dementia.[6] There are also research data suggesting clinical impairment of attention and executive function in MCI patients.[7-10] Moreover, mild kinetic impairments are observed in MCI patients. Most of them have problems with joint function, balance,[11] walking,[12] position in space, posture, and praxis.[13] These problems may be due to aging or diseases of musculoskeletal systems, and/or to cognitive impairment.

There is evidence that a parallel approach of activation and interdependence of 2 cortical structures, such as the prefrontal cortex and the cerebellum, are related with cognitive and kinetic development, respectively. Recently it has been discovered that the prefrontal cortex and the cerebellum interact and exchange information on motor and cognition including involvement in language.[14,15] The lateral posterior prefrontal cortex supports cognitive[16] processes such as memory processing, inhibition of irrelevant stimuli and focusing of attention. All the above processes are important for skillful kinetic activity. Consequently, it is not surprising that kinetic and cognitive development are interdependent, as shown by the effect of focus of attention upon motor skill learning.[17] Further research suggested that kinetic and cognitive development are closely related[18] and that physical exercise stimulated a positive increase in executive control processes including planning, scheduling, working memory, inhibitory processes, and multitasking.[19] The mental and kinetic abilities interact through the

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* Rhea was the Titaness daughter of Uranus, the sky, and Gaia, the earth, in Greek mythology. She was known as "the mother of gods," mother of the Olympian gods and goddesses. The word RHEA means flow, discharge, and motion.

entire life span, as they mutually support or inhibit each other. Evidence for this interaction is further supported by lifestyle research indicating that kinetic abilities lead to improved physical and mental health throughout life.[20]

Many scientists consider MCI as a preclinical state of dementia.[21,22] Research has demonstrated that especially in the area of the hippocampus, there is neurogeneration throughout human life, even during older adult years.[23,24] Physical exercise has been shown to be a key facilitator of neurogenesis, in the hippocampus and elsewhere, and that the rate of neurogenesis is related to dose.[25,26]

Systematic and intense exercise that provides new experience can provoke alterations in the brain and contribute to cognitive rehabilitation.[24] A meta-analysis study compared outcomes of participation in strength and endurance training between cognitively impaired persons and cognitively intact persons and found that both groups showed similar improvements.[27] Another study demonstrated that a fitness and focused attention task helped human subjects to better ignore irrelevant stimuli.[28]

For many years, it was believed that rehabilitation was successful only for sensory and kinetic systems. Today, data suggest that cognitive rehabilitation is beneficial for attention,[29,30] memory,[31,32] and executive dysfunctions.[30] However, the interventions have to be structured according to the special needs and abilities of the patient. The therapist has to adjust the exercises to the mental age of the trainee[33] and must not demand tasks or activities that the trainee cannot perform.[34] It is also recommended that rehabilitation for persons with MCI include language and psychomotor activities to enhance cognitive skills and physical endurance.[3]

Building upon different sets of research and clinical findings regarding rehabilitation for both kinetic and cognitive systems, we designed a cognitive motion therapeutic program, named RHEA, for elderly persons with MCI of multiple domains. The program is a nonpharmacological therapy consisting of kinetic exercises that logically would enhance specific cognitive functions, particularly those commonly impaired in MCI (see Figure 1).

The cognitive abilities that the RHEA program is designed to practice and enhance through execution of motion instructions include visuospatial abilities, attentional abilities, executive functions, and language skills. We hypothesized that those abilities would be improved at the end of the intervention. We also hypothesized that the score in an ADL measure would be improved as well.[35,36] On the contrary, controls were expected to demonstrate mild deterioration of cognitive and functional performance. We arrived at these hypotheses because several studies showed that MCI patients with memory deficits plus deficits in other domains were more likely to convert to AD. ADL measures in fact are critical for dementia diagnosis.[37–39] [AQ4]

METHOD [AQ5]

Participants and sampling

Baseline characteristics of the participants are presented in Table 1. Participants were recruited from 242 patients visiting the two Hellenic Alzheimer association day centers to receive an assessment for cognitive concerns between April to July 2009. Patients visit these day centers voluntarily to receive neuropsychological assessment, neurological examination, and treatment. [AQ6]

Patients were diagnosed according to the criteria of Petersen et al[40] and Artero et al[41] for MCI, and the NINCDS-ADRDA[42] criteria for dementia, and were assessed for psychiatric symptoms (according to the Hellenic version of the Neuropsychological Inventory [NPI][43]). Neurological examination, neuropsychological assessment, medical/social history, neuroimaging examination (computerized tomography or magnetic resonance imaging) and blood tests were performed to establish a diagnosis. Of 124 persons who were either not eligible or not available, 106 did not fulfill the inclusion criteria, 14 lived in rural areas and it was not possible for them to attend the cognitive training program, and 4 died during this period. One hundred eighteen patients were approached for this study. All participants fulfilling the inclusion criteria were asked to participate in the RHEA program, but 30 of them refused. Finally, 88 patients were consented and included in the study. Participants who were willing to participate but not at this time were placed in the waitlist control group. The 88 initial participants were assigned to 2 groups. Forty-nine (49) patients were assigned to the experimental group and 39 to the control group. (see Figure 2). The groups of the study were matched in gender, age, education, MMSE, and cholinesterase inhibitor status, prior to any dropouts. (see Table 1). The participants and their family caregivers each signed a written consent of volunteer participation in the study. They were aware of the goals, the theoretical expectations of the treatment and the researchers' responsibility to keep their personal data confidential. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000 and with the principles of good clinical practice. The study was approved by Scientific and Ethics Committee of Hellenic Alzheimer Association.

Compliance and attrition

Twelve patients of the experimental group removed their consent and 8 withdrew because they missed 5 sessions. Ten patients of the control group removed their consent. The dropouts were mainly due to health and family problems. At the completion of the study, there were 29 patients (6 men, 23 women) in the experimental group and 29 patients (6 men, 23 women) in the control group, a total of 58 persons.

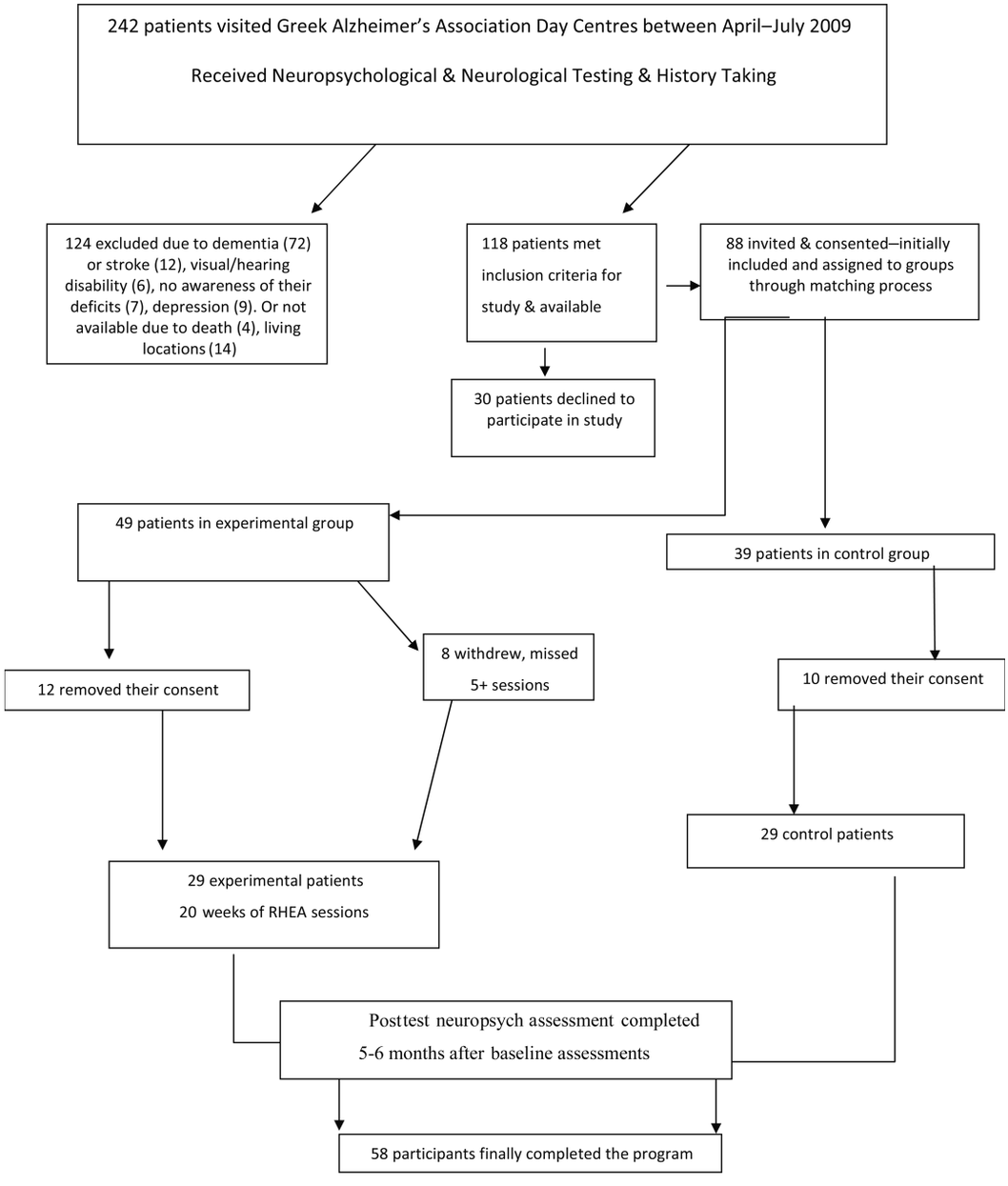

Figure 1. RHEA intervention: abilities practiced during each exercise. [AQ14]

INCLUSION AND EXCLUSION CRITERIA

To be eligible to participate in the study, people had to meet inclusion and exclusion criteria. The inclusion criteria were the following: a diagnosis of MCI in accordance with the criteria of Petersen et al[40] and Artero et al,[41] participants had insight of their deficits according to their initial evaluation, and they retained language skills as these were assessed during the baseline neuropsychological assessment. The evaluation of insight was achieved asking the patient (*a*) whether he/she knew why he/she visited the day center, (*b*) whether he/she knew that he/she forgets, and (*c*) whether these memory problems affected their everyday life. Potential participants were excluded if they were diagnosed at baseline, after neurological/psychiatric examination, with a diagnosis of dementia,[42] stroke or ischemic lesions, neuropsychiatric symptoms according to NPI, primary depression, and/or visual/hearing impairment or reading/writing disability, sufficient to interfere with participation in RHEA.

RHEA intervention

In the literature, there is confusion about labeling each nonpharmacological intervention. Although Clare et al[44] provided a clear, specific taxonomy of cognitive interventions,

TABLE 1 Participant Baseline Characteristics[a]

Variable	GROUP	
	Experimental	Control
Age, y	70.48 (7.52)	67.83 (7.29)
Gender (Male/Female)	6/23	6/23
Education, y	9.59 (4.77)	7.79 (3.79)
No inhibitor/with inhibitor	N22/W7	N25/W4
Outcome measure		
MMSE	28.03 (1.61)	27.34 (1.83)
FUCAS	44.93 (3.75)	44.90 (2.79)
WCST	11.74 (8.83)	8.87 (3.44)
1 min TEA	30.86 (11.64)	30.38 (11.76)
2 min TEA	50.07 (16.57)	50.19 (12.85)
Speed of Selective visual attention TEA	5.97 (3.10)	5.77 (1.78)
Switch of visual attention TEA	7.84 (2.41)	7.12 (1.94)
Verbal Learning RAVLT	4.76 (1.80)	5.07 (2.53)
Delayed verbal recall RAVLT	–3.45 (2.22)	–2.48 (1.55)
Delayed story recall RBMT	11.62 (3.63)	10.59 (4.60)
Figure recall and reproduction ROCFT	14.87 (5.94)	13.44 (7.58)
BNT, %	73.14 (19.31)	62.26 (13.98)
Verbal fluency FAS	10.16 (3.30)	8.87 (3.44)
Figure copy ROCFT-C	29.39 (6.78)	29.32 (7.37)
FRSSD	3.90 (1.67)	4.24 (2.21)

Abbreviations: BNT, Boston Naming Test; FAS, Verbal Fluency Test; FRSSD, Functional Rating Scale of Symptoms of Dementia; FUCAS, Executive Function: Functional Cognitive Assessment Scale; MMSE, mini-mental state examination; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioral Memory Test; ROCFT, Rey-Osterrieth Complex Figure Test; TEA, Test of Everyday Attention; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.

[a] Values represent mean (SD) unless otherwise indicated.

several similar interventions have been labeled as cognitive intervention or cognitive stimulation or cognitive rehabilitation. This limits the ability for meta-analysis and generalization of results. We labeled our intervention as cognitive training because of the use of structured tasks with different levels of difficulty focusing on specific cognitive abilities.

Based in part on the literature cited, RHEA was designed to directly enhance visual and auditory, selective attention, shifting and switching of attention, and dual task. Through consolidation of attention training and generalization, we expected improvement also in short-term and long-term memory. For example, the patient has to remember the instruction to complete the attentional task and to recall information concerning previous cognitive motor tasks at the end of the session. Selective attention is practiced, because the patients have to pay attention to the instruction and choose the correct response between several others. The shift of attention is practiced as the patient shifts attention from one instruction to another, or from one place to another in the room. Consequently, visuospatial abilities are also reinforced during the execution of the attentional tasks. The dual-task ability is enhanced when trainees are asked to carry out simultaneously a verbal and a kinetic task during the session.

In our cognitive training program, learning strategies were not taught directly,[45] but indirectly through the execution of each task, and patients were encouraged to use their own personal strategies to execute the tasks.

The RHEA intervention in this study comprised 90-minute, once-a-week sessions for 20 weeks. The program includes visuomotor, and verbal-kinetic tasks including visual and verbal kinetic stimuli, respectively. Figure 1 lists 5 types of kinetic exercises and cognitive abilities that

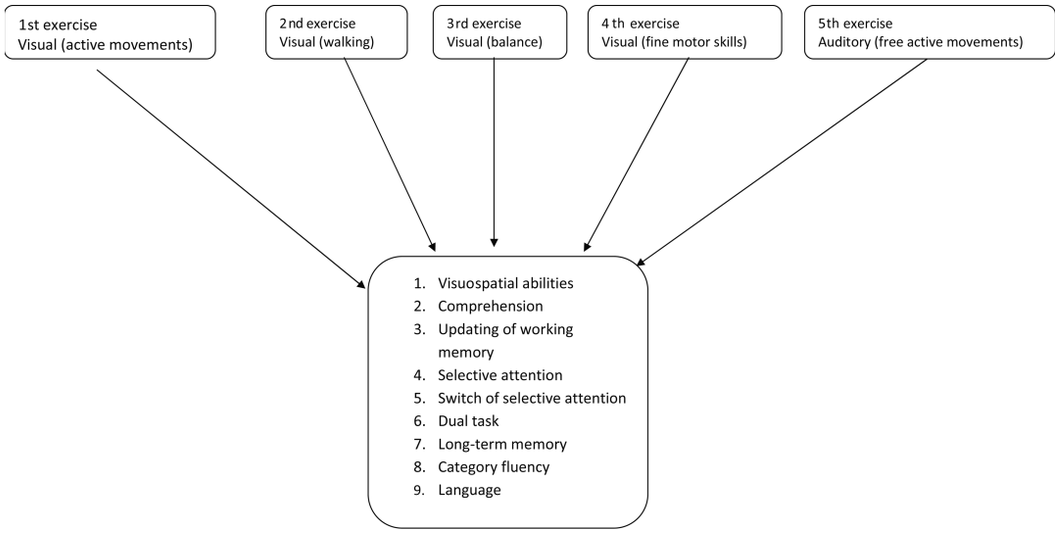

Figure 2. Participants and study design: recruitment, screening, assignments, and attrition.

the exercises are designed to practice or train. The tasks are ecological because they are recruited from the patient's daily life. The stimuli that we use are shapes, colors, sizes, and numbers. The technical materials include wreath, boards with letters, cards with colors, shapes and numbers, corridors with numbers, balls, wands, rings, and cones (see Figure 3). The session includes 5 exercises each lasting approximately 15 minutes.

The program has tasks with an increasing degree of difficulty varying according to the baseline cognitive and kinetic performance of the participants. Moreover, the content of the weekly sessions vary to maintain the patient's interest while the session structure remains stable. Thus, in each session, the instructions, the movements, and the stimuli are different, while maintaining the routine of all 5 types of exercises.

Testing

The effectiveness of the intervention was assessed by neuropsychological assessment performed at baseline (pretest) and after a period of 5 months (posttest), at the end of the therapy for the experimental participants. Psychometric tools included scales assessing general cognitive performance and specific cognitive skills: executive function, attention, visual and verbal memory, language (verbal fluency and naming), and visual-spatial constructional abilities. In addition, ADLs were assessed as a measure of independent functioning. The instruments used are listed in Table 2.

Practice bias in tests' performance due to familiarity did not occur because (a) there was an interval of 5 months between the repeated assessments, (b) we used different versions of tests wherever available (Rivermead Behavioral Memory Test [RBMT], Rey Auditory Verbal Learning Test [RAVLT], Test of Everyday Attention [TEA], Rey-Osterrieth Complex Figure Test [ROCFT]), and (c) test-retest reliability was high for all tests used in this study as shown in Table 2. Moreover, FRSSD is administered to the relatives, who give their subjective opinion, so there was no practice bias affecting the patients' performance. All participants, both experimental and controls, were examined at the same time and place and by the same psychologist. The psychologists were blinded as to the experimental status of the participants.

Intervention and wait list description

The participants assigned to the experimental group visited the Hellenic Alzheimer day center once a week and attended 20 sessions of 90 minutes. All of the participants in the experimental group attended RHEA under the same conditions, time, and exercise materials. The intervention was applied as a group therapy, with each group comprising 5 participants. The programs were administered by expert psychologists trained in cognitive rehabilitation. During the same time period, the control group was on a waiting list and did not take part in any kind of nonpharmacological therapy at the day center or anywhere else.

Data analyses

The statistical analysis of the neuropsychological data collected before and after the intervention was accomplished using a SPSS 17.0 software program (SPSS, Inc, Chicago, IL). Nonparametric tests were used because of the small sample size and the heterogeneity of cognitive performance. According to Kolmogorov-Smyrnov, the majority of variables in pre- and postassessments did not show regular

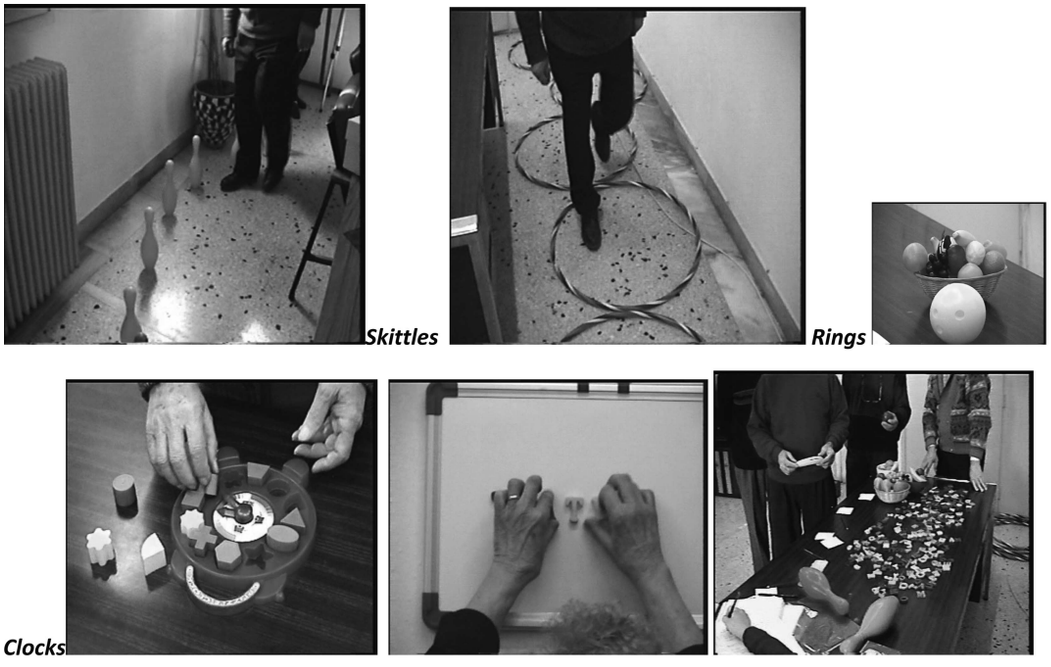

Figure 3. Materials for RHEA—examples of variety.

distribution of performance in a cumulative sample. Mann-Whitney test, for 2 independent samples (Monte Carlo method), and chi-square test were used to investigate significance in between-group differences. Comparisons between the two groups' performances, at the end of the 5-month period, concerned cognitive and functional abilities in which the two groups were found to be matched at baseline. Wilcoxon test for 2 related samples was used to examine within group differences with comparisons performed between the pretest and the posttest assessments, separately for each group. To lessen the number of false-positives, because we had multiple measures for some cognitive abilities, and many measures, we adjusted *P* levels required to reach statistical significance using Bonferroni's correction.[64] Thus for several outcome measures, *P* levels of .01 or .025 were required rather than the standard $P = .05$ to reach statistical significance. Some measures did not achieve statistical significance. We performed post hoc power analysis and showed low statistical power (0.08-0.36) with 95% confidence interval. Because of the extended neuropsychological battery used and the long time between the two assessments, 25% of participants did not participate during the follow-up examination in all tests of the battery and were lost to follow-up. As it was mentioned earlier, there were 8 experimental participants who missed more than 5 sessions (see Figure 2). These participants were not included in the baseline figures shown.

TABLE 2 Test-Retest Reliability of Outcome Measures

Outcome Measure	Reliability Coefficient
MMSE[46,47]	.83-.89[47]
FUCAS[48]	1.00[48]
WCST[49]	34 -.83[50]
TEA[51]	PV
TEA-Speed	PV
TEA-Switch	PV
WAIS-R[52]	.82-.88[53]
RAVLT[54]	.70[55]
RBMT[56,57]	.84-.80[56] PV
ROCFT[58]	.60-.76[59]
BNT[60]	.92[61]
FAS[62]	.70-.71[55]
ROCFT-C[58]	.60-.76[59]
FRSSD[63]	*

*Abbreviations: *, Administered to caregivers; ADL, activity of daily living; BNT, Boston Naming Test (using the 60 and 30 item versions, and recording percentage of correct responses); FAS, Verbal Fluency Test; FRSSD, Functional Rating Scale of Symptoms of Dementia; FUCAS, Executive Function: Functional Cognitive Assessment Scale; MMSE, mini-mental state examination; PV, Parallel versions; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioral Memory Test; ROCFT-C, Rey-Osterrieth Complex Figure Test-Copy; TEA, 1 min and 2 min Test of Everyday Attention; VSCA, Visual Spatial Constructive Abilities; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.*

RESULTS

At baseline, there were no significant differences in cognitive and functional performance between the two groups, after applying Bonferroni's correction. At the end of the therapy, significant differences were noticed between the two groups in favor of the experimental group, in cognitive abilities as well as in ADLs (see Table 3). The differences were observed in general cognitive performance (MMSE) ($P = .047$), speed of selective visual attention (TEA) ($P = .002$), visual spatial constructional (copying) abilities (ROCFT-C) ($P = .013$), verbal fluency (FAS) ($P = .015$), and ADLs using the FRSSD ($P = .009$).

Following the intervention period, the experimental participants showed improvement in ADLs (FRSSD) ($P = 0.004$), general cognitive performance (MMSE) ($P = 0.045$), verbal memory for both verbal learning and delayed story recall ($P \leq .001$), verbal fluency (FAS) ($P = 0.007$), attention (TEA) in both speed and switching ($P \leq .008$), and visual-spatial abilities (ROCFT-C) ($P = .003$) (Table 4). Experimental MCI patients benefited from 20 weeks of RHEA training in both cognitive and functional abilities.

In contrast, after the same 5-month time period, the control group showed stability of performance in ADLs as well as in all measures of cognitive function, except in naming ability, where control participants exhibited a significant improvement in BNT ($P = .016$) (Table 5).

DISCUSSION

Mild cognitive impairment is one of the most substantial risk factors for developing dementia. To date, there is no proven pharmaceutical therapy for MCI. Although there are studies showing that cognitive training or other cognitive interventions are effective for improving MCI patients' cognitive performance, there is little evidence that this benefit can be generalized to everyday life. In a previous study (Tsolaki et al, 2010),[65] we showed that a cognitive intervention of holistic approach, including cognitive training, cognitive stimulation, and psychotherapeutic techniques, improved MCI patients' cognitive performances and ADLs, compared to patients in the control group who experienced deterioration in ADLs. One question generated by that study was whether a single cognitive training

TABLE 3 Between Group Differences at Posttest[a]

Outcome Measure	Experimental Group	Control Group	*P*
MMSE	28.41 (1.40)	27.03 (2.74)	.047
FUCAS	44.31 (2.42)	46.45 (8.28)	NS
WCST	8.93 (5.75)	11.96 (9.15)	NS
1 min TEA	33.26 (12.23)	27.81 (10.20)	.039[b]
2 min TEA	51.19 (9.91)	48.04 (12.12)	NS
Speed of Selective visual attention TEA	4.62 (1.37)	6.19 (9.11)	.002
Switch of visual attention TEA	8.62 (1.92)	8.00 (1.77)	NS
WAIS-R	31.85 (13.74)	27.48 (14.30)	NS
Verbal Learning RAVLT	5.97 (1.91)	5.45 (2.70)	NS
Delayed verbal recall RAVLT	–3.17 (2.66)	–3.00 (2.03)	NS
Delayed story recall RBMT	13.14 (3.13)	11.00 (4.38)	.050[b]
Figure recall and reproduction ROCFT	15.51 (8.29)	13.58 (8.78)	NS
BNT	78.19 (14.33)	72.19 (14.44)	NS
Verbal fluency FAS	11.42 (3.63)	9.21 (3.54)	.015
Figure copy ROCFT-C	31.53 (4.79)	28.48 (6.69)	.013
FRSSD	3.24 (2.01)	4.57 (2.50)	.009

Abbreviations: BNT, Boston Naming Test (using the 60 and 30 item versions, and recording percentage of correct responses); FAS, Verbal Fluency Test; FRSSD, Functional Rating Scale of Symptoms of Dementia; FUCAS, Executive Function: Functional Cognitive Assessment Scale; MMSE, mini-mental state examination; NS, not statistically significant because >.05; PV, Parallel versions; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioral Memory Test; ROCFT-C, Rey-Osterrieth Complex Figure Test; TEA, Test of Everyday Attention; VSCA, Visual Spatial Constructive Abilities; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.

[a]*Values represent mean (SD) unless otherwise indicated.*

[b]*Not statistically significant because of Bonferroni's correction.*

TABLE 4 Experimental Group Change From Pre- to Posttest[a]

Outcome Measure	Pretest	Posttest	P
MMSE	28.03 (1.61)	28.41 (1.40)	.045
FUCAS	44.93 (3.75)	44.31 (2.42)	NS
WCST	11.74 (8.83)	8.93 (5.75)	.016[b]
1 min TEA	30.86 (11.64)	33.26 (12.23)	NS
2 min TEA	50.07 (16.57)	51.19 (9.91)	NS
Speed of Selective visual attention	5.97 (3.10)	4.62 (1.37)	.008
Switch of visual attention TEA	7.84 (2.41)	8.62 (1.92)	.002
WAIS-R	32.25 (18.93)	31.85 (13.74)	NS
Verbal Learning RAVLT	4.76 (1.80)	5.97 (1.91)	.001
Delayed verbal recall RAVLT	–3.45 (2.22)	–3.17 (2.66)	NS
Delayed story recall RBMT	11.62 (3.63)	13.14 (3.13)	.001
Figure recall and reproduction ROCFT	14.87 (5.94)	15.51 (8.29)	NS
BNT	73.14 (19.31)	78.19 (14.33)	.030[b]
Verbal fluency FAS	10.16 (3.30)	11.42 (3.63)	.007
Figure copy ROCFT-C	29.39 (6.78)	31.53 (4.79)	.003
FRSSD	3.90 (1.67)	3.24 (2.01)	.004

Abbreviations: BNT, Boston Naming Test (using the 60 and 30 item versions, and recording percentage of correct responses); FAS, Verbal Fluency Test; FRSSD, Functional Rating Scale of Symptoms of Dementia; FUCAS, Executive Function: Functional Cognitive Assessment Scale; MMSE, mini-mental state examination; NS, not statistically significant because >.05; PV, Parallel versions; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioral Memory Test; ROCFT-C, Rey-Osterrieth Complex Figure Test; TEA, Test of Everyday Attention; VSCA, Visual Spatial Constructive Abilities; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.

[a] Values represent mean (SD) unless otherwise indicated.

[b] Not statistically significant because of Bonferroni's correction.

program performed alone could provide benefit to MCI patients.

The aim of this study was to test the hypothesis that RHEA would enhance multiple cognitive abilities in addition to daily functioning, in persons with a diagnosis of multidomain MCI. In contrast, we hypothesized that controls would exhibit either decline or no change in cognitive and functional performance in the 5-month period. The results of this pilot study support these hypotheses. Pre- and postintervention comparison of experimental participants' performance showed improvement of their cognitive and functional performance, as this was expressed by themselves and their families (according to FRSSD).

Control participants exhibited no significant changes in almost all of the measures used for cognitive and functional performance. Possible reasons may include sample [AQ7] selection, or natural history of MCImd. Studies show that many MCI patients remain stable in a 1-year period.[66] The lone significant improvement in BNT could be due to "casually available information" as Henderson et al[67] have reported. The patient in repeated assessment of semantic memory may present a deviation of performance of 20% more or less, because the brain appears to have a reserve of information casually and variably available according to the patient's mood, psychological status, and the strategy used. The difference of naming in the control group represented 4.23% of the initial performance and is unlikely the result of new learning.

Effect of training on cognitive measures

For several of the cognitive abilities that the RHEA program was hypothesized to maintain or improve, our pilot study results provide support. For 4 cognitive measures, experimental participants, on average, showed statistically significant improvement and had posttest results that were significantly better than those of control participants. These measures are general cognitive performance (MMSE), *speed* of selective visual attention (TEA), visual spatial construction (copying) abilities (ROCFT), and 1 of 2 language skills tested verbal fluency (FAS). On 3 additional cognitive measures—verbal learning [RAVLT], de- [AQ8] layed story recall [RBMT], and attention *switching*—experimental participants showed significant improvement after the 20 week RHEA program, but the posttest results were not significantly better than those for the control participants:

TABLE 5 Control Group Changes From Pretest to Posttest[a]

Outcome Measure	Pretest	Posttest	*P*
MMSE	27.34 (1.83)	27.03 (2.74)	NS
FUCAS	44.90 (2.79)	46.45 (8.28)	NS
Perseverative responses WCST	8.87 (3.44)	11.96 (9.15)	.029[b]
1 min TEA	30.38 (11.76)	27.81 (10.20)	NS
2 min TEA	50.19 (12.85)	48.04 (12.12)	.040[b]
Speed of selective visual attention TEA	5.77 (1.78)	6.19 (9.11)	NS
Switch of visual attention TEA	7.12 (1.94)	8.00 (1.77)	NS
WAIS-R	26.19 (11.92)	27.48 (14.30)	NS
Verbal learning RAVLT	5.07 (2.53)	5.45 (2.70)	NS
Delayed verbal recall RAVLT	-2.48 (1.55)	-3.00 (2.03)	NS
Delayed story recall RBMT	10.59 (4.60)	11.00 (4.38)	NS
Figure recall and reproduction ROCFT	13.44 (7.58)	13.58 (8.78)	NS
BNT	62.26 (13.98)	72.19 (14.44)	.016
Verbal fluency FAS	8.87 (3.44)	9.21 (3.54)	NS
Figure copy ROCFT-C	29.32 (7.37)	28.48 (6.69)	NS
FRSSD	4.24 (2.21)	4.57 (2.50)	NS

Abbreviations: BNT, Boston Naming Test (using the 60 and 30 item versions, and recording percentage of correct responses); FAS, Verbal Fluency Test; FRSSD, Functional Rating Scale of Symptoms of Dementia; FUCAS, Executive Function: Functional Cognitive Assessment Scale; MMSE, mini-mental state examination; NS, not statistically significant because >.05; PV, Parallel versions; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioral Memory Test; ROCFT-C, Rey-Osterrieth Complex Figure Test; TEA, Test of Everyday Attention; VSCA, Visual Spatial Constructive Abilities; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.

[a] Values represent mean (SD) unless otherwise indicated.

[b] Not statistically significant because of Bonferroni's correction.

The primary training target of the study was the enhancement of attentional abilities and parameters of executive function. The results included improvement of the speed in attentional tasks and the switching of attention. These are abilities of executive attention,[68-70] so we can say that the primary target was accomplished. Furthermore, the delayed verbal recall, the verbal fluency, and the reproduction of the complex figure also include abilities of executive function (use of strategies) together with abilities of episodic and semantic memory. All of them share common neuronal networks with the speed and the switching of attention.[71] Thus, Wu et al[71] concluded that impairment in executive function affects coding and retrieval of information.

Effect of training on activities of daily living

We hypothesized that many functional skills would be improved both because of the general link between cognition and ADLs, and also because the RHEA exercises specifically involved practicing balance and movement of limbs and hands, eye-hand coordination, and vision related to movements.

Our results support our general hypothesis as we found robust statistically significant differences at posttest in favor of the experimental group ($P = .009$), as well as statistically significant improvement in the experimental group ($P = .004$) over the 20-week treatment period.

Our results can be compared with those of the studies by Belleville et al[72] and Kinsella et al,[73] which showed improvement in episodic memory, when MCI patients participated in a cognitive training program focusing on teaching episodic memory strategies. Unlike with our results, however, these interventions did not improve participants' ADLs. Perhaps we achieved better results in ADLs because our intervention was designed to primarily target the practice of attention and executive function with tasks recruited from daily life.

Most nonpharmacological interventions have not provided a benefit in ADLs.[74] This could be due to the studies' methodological constraints—that is, no ecological tasks—or the use of insensitive neuropsychological measures. Nevertheless, in our study, experimental patients and their families reported, through FRSSD, less memory or attention difficulties during ADLs.

More similar to our study is Londos et al's goal-oriented memory strategy training program,[36] which includes learning of practical strategies, and an educational presentation

about the brain and memory, and other factors that can influence memory, but no memory training per se. This program showed improvement in cognitive functioning as well as performance of ADLs in individuals with MCIa. However, this study[36] lacked any control group. Using another cognitive training program,[75] which involved ecological activities, Brum et al[75] found improvement for the experimental group in attention, time orientation, shopping skills, and dealing with finances (ADLs). Despite these encouraging results, the number of participants in this study was small (16 experimental/18 control), the study duration was short (only 8 sessions) and some participants were on treatment with antidepressants.

Clinical significance

The difference in MMSE of 1.5 points between the two groups at posttest may be clinically significant, primarily because the experimental group improved slightly while the control group declined slightly. But both ceiling effects and common fluctuations on this measure during a short time period caution against overinterpretation.

The difference in properties of attention may hold greater clinical significance. The speed is measured in seconds, so the posttest difference in speed of visual selective attention reflects a 25% improvement for the experimental group (which was slower than the control group at baseline). The change in the experimental group in the measure of accurate switching represents a 10% improvement. The experimental group's improvement in visual selective attention's speed and switching (TEA) together with the 2-point (7%) improvement in visual-spatial, visual-perceptive abilities (ROCFT) support the necessary skills for medication, bathing, orientation, and telephone communication. All these skills, as measured separately by FUCAS, appeared as a trend of improvement, although not statistically significant, possibly because of ceiling effects.

The improvement in FAS is consistent with the verbal performance of the participants in naming, as independently measured by a section of the FRSSD. Here also the improvement was only a trend perhaps because of a ceiling effect. Finally, the benefit noticed in RAVLT and RBMT (story) represents improvement in verbal learning and verbal logical memory. These functions support the skills for the memory of recent events, as reflected in another subsection of the FRSSD. This is important because a healthy older person needs to be aware of current social or political events, to actively participate in daily life.

The significant improvement of 0.65 of a point in FRSSD for the experimental group (while the control group deteriorated by 0.25 points or 5%) represents a 16% improvement in this score. Moreover, the improvements in daily function observed and reported by the families through the FRSSD were consistent with the patient's improvement on direct testing of relevant cognitive skills.

CONCLUSIONS

One potential important value of the RHEA therapy, compared with cognitive training methods that do not have a movement component, is that it is designed to, and appears to assist with, functioning in everyday life, tapping into the skills of kinetic memory, which are spared in MCI elderly people.

Furthermore, RHEA appeared to help delay further deterioration of cognitive symptoms in a group of people with diagnoses of multidomain MCI (including abnormal executive function), which the literature suggests are at greater risk to deteriorate and convert to Alzheimer compared to those with pure amnestic MCI.[37-39]

Limitations of the study and future directions

The primary limitation of this pilot study was that, given the logistics of the clinical setting, we were not able to randomly assign patients, nor provide an active control intervention so that participants were less aware of their experimental status. However, assessors were blinded as to experimental status of participants, a study strength. Even though we considered brain plasticity, it was not possible to obtain neuroimaging data to provide an objective measure of structural brain change. Another limitation of this study was the small sample size of this pilot proof of concept study.

One of our next goals will be to examine whether RHEA will be more effective when it is provided in combination with computer-based training, or paper and pencil, or oral tasks. Furthermore, RHEA might be combined with other promising nonpharmacological therapies such as brain healthy nutrition, weight-bearing and other physical exercises, and cognitive stimulation therapies, as well as state of the art medical management of comorbidities and the cognitive diagnosis.

This promising trial needs to be repeated using randomized assignment methods, and larger, well-characterized set of persons with multidomain MCI. In addition, this innovative therapy should be studied with persons with diagnoses of single domain MCI, mild to moderate Alzheimer disease, as well as in persons with other dementias.

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AUTHOR QUERIES

TITLE: RHEA,* a Nonpharmacological Cognitive Training Intervention in Patients With Mild Cognitive Impairment: A Pilot Study

AUTHORS: E Kounti; E Bakoglidou; C Agogiatou; NB Emerson Lombardo; LL Serper; M Tsolaki

[AQ1]: Please provide the full names and academic degrees of all the authors so that social titles be added to their surnames in the affiliations. Also check whether the affiliations are set well.

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