The IMPACT Study: A Randomized Controlled Trial of a Brain Plasticity-Based Training Program for Age-Related Cognitive Decline

Elizabeth M. Zelinski[1], Kristine Yaffe[2,3], Ronald M. Ruff[2,4], Robert K. Kennison[5] & Glenn E. Smith[6] Corresponding Author: Elizabeth M. Zelinski, email: Zelinski@USC.edu

Affiliations
1. University of Southern California
2. University of California, San Francisco
3. San Francisco Veterans Affairs Medical Center
4. San Francisco Clinical Neuroscience
5. California State University, Los Angeles
6. Mayo Clinic Foundation

Abstract

Introduction: Previous interventions for normal age-related cognitive declines have shown limited generalizability beyond the skills directly trained.

Purpose: We report results from a large-scale randomized controlled clinical trial designed to evaluate whether improvements from training can extend to untrained measures of memory performance and to self-perceived everyday cognition.

Method: The IMPACT Study was a multi-site double-blind trial in adults >65 with normal cognition (MMSE >26) of the Posit Science Brain Fitness Program (BFP). Using an intensive series of adaptive computerized exercises, BFP targets the speed/accuracy of auditory and language processes, and neuromodulatory systems associated with learning and memory. 468 individuals were randomized to 1) the BFP (intervention), or 2) a structured computer-based learning program matched for novelty/intensity (control). Predefined endpoints distinct in design/content from training exercises included standardized neuropsychological assessments of memory and participant-reported outcome (PRO) assessments measuring perceptions of everyday cognition.

Results: The participants' mean age was: 75.1 (6.4), education: 15.7 (2.6), estimated IQ: 113.9 (8.0). After 10 weeks of training, significant group by time interactions ($p < 0.05$) favoring the experimental group were seen on the primary endpoint measure (RBANS Auditory Memory) and multiple within-modality (RAVLT trials 1–5, RAVLT delayed, WMS-III digits backwards, WMS-III letter-number) but not cross-modality (RBANS Visual Memory) secondary endpoint measures. PRO measures of everyday cognitive function were significant on pre-post ($p<0.002$) and post-only ($p<0.003$) assessments.

Conclusion: These results demonstrate the training program studied produces significantly superior improvements in generalized measures of memory and perception of cognitive performance in everyday life, compared to a treatment-as-usual control.

Background

- Normally aging older adults may experience declines in memory and other cognitive abilities, including information processing, executive function and perception.
- Prevalence of memory complaints in community-based samples of older adults varies between 25% and 50% (Jonker, Geerlings & Schmand, 2000).
- Predictors of negative frequency of forgetting ratings include: higher depression, lower conscientiousness, poorer performance on list recall, female gender, and increased age (Zelinski & Gilewski, 2004).

Problem

Numerous interventions for improving cognitive and memory performance are available. However, the effectiveness of most interventions has not been empirically verified, especially in regard to the generalizability of improvements beyond directly trained skills (but see Wolinsky et al., 2006; Willis et al., 2006).

Objective

To evaluate whether improvements from a training program based on brain plasticity extend to untrained measures of memory performance and self-perceived everyday cognition.

Methods

Participants

Recruitment: Direct mail, radio, newspaper ads, flyers, presentations

Inclusion criteria:
- Age 65+
- Mini-Mental Status Examination (MMSE) score >26
- Able to read 14 point type
- Adequate hearing capacity
- Willing commit to 6-month time requirement of the study period

References

Jonker, C., Geerlings, M.I., & Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population-based studies. International Journal of Geriatric Psychiatry, 15, 983-991.

Mahncke, H.W., Bronstone, A. & Merzenich, M.M. (2006). Brain plasticity and functional losses in the aged: Scientific bases for a novel intervention. In A. Moler, S. Chapman, & S. Lomber (eds.) Reprogramming the Brain (pp. 81-110). Amsterdam: Elsevier.

Wolinski, F.D., Unverzagt, F.W., Smith, D.M., Jones, R., Stoddard, A. & Tennstedt, S.L.. (2006a). The ACTIVE cognitive training trial and health-related quality of life: Protection that lasts for 5 years. Journals of Gerontology: Medical Sciences, 61A, 1324-1329.

Willis, S.L. et al. (2006) Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA, 296, 2805-2814 (2006).

Zelinski, E.M. & Gilewski, M.J. (2004). A 10-item Rasch modeled memory self-efficacy scale. Aging & Mental Health, 8, 293-306.

Methods (continued)

Procedure

- Multi-site double-blind randomized clinical trial using test re-test treatment controlled design
- Participants randomized into experimental treatment (ET) and active control (AC) groups
- Clinicians administering neuropsychological evaluations blinded as to randomization
- Follow-up on all outcome measures at conclusion of intervention

Outcome Measures

Primary: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Global Auditory Memory Score, derived from six sub-tests (list learning, story memory, digit span forward, delayed free list recall, delayed list recognition, delayed free story recall)

Secondary:
- Rey Auditory Verbal Learning Test (RAVLT): Trials 1–5 and Delayed Recall
- Wechsler Memory Scale (WMS-III): Digit Span Backwards and Letter-Number Sequencing
- Rivermead Behavioral Memory Test (RBMT): Story Memory Immediate and Story Memory Delayed

RBANS: Visual Function Score, derived from four sub-tests (figure copy, line orientation, coding, figure recall)

Participant Reported Outcome (PRO) assessments:
- Cognitive Self-Report Questionnaire: CSRQ-25
- CSRQ-64

Analysis Groups

- Intent to Treat (ITT)
  Participants randomized into the study
- Fully Evaluable
  Participants who completed the study
- Fully Trained
  ET Participants who completed 85% of training on principal exercise

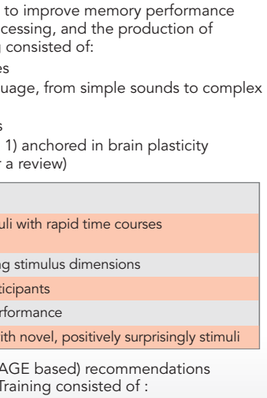
IMPACT Study Algorithm
Review of Participant Flow

Intent to Treat (n = 468)
- ET n = 232
- AC n = 236

Fully Evaluable at V2 (n = 422)
- ET n = 214
- AC n = 208

Drop or Withdrawal (n = 46)
- ET n = 18
- AC n = 28

Fully Trained (n = 389)
- ET n = 181
- AC n = 208



Interventions

ET: The Brain Fitness Program (BFP, Posit Science) is intended to improve memory performance by increasing the speed and accuracy of aural information processing, and the production of neuromodulators important for learning and memory. Training consisted of:
- Six adaptive, challenging computerized listening exercises
- Stimuli span acoustic and organizational structure of language, from simple sounds to complex manipulations of speech
- Minimum of 60 minutes/day, 5 days/week for 8–10 weeks
- ET designed around a model for effective learning (Table 1) anchored in brain plasticity research (see Mahncke, Bronstone & Merzenich, 2006 for a review)

Table 1. SAAGE Model for Effective Learning

Speed	Require participants to make judgments on stimuli with rapid time courses over brief periods
Accuracy	Drive participants to accurately discriminate along stimulus dimensions
Adaptivity	Individually adapt to continuously challenge participants
Generalizability	Increasingly resemble demands of real-world performance
Engagement	Repeatedly engage neuromodulatory systems with novel, positively surprisingly stimuli

AC: Program simulating physician treatment-as-usual (non-SAAGE based) recommendations for memory complaints, matched to ET for novelty/intensity. Training consisted of :
- DVD-based educational training on computer
- Paper and pencil quizzes probing memory and comprehension of content
- Minimum of 60 minutes/day, 5 days/week, for 8–10 weeks

Analyses

Individual linear mixed effects models developed for each outcome measure
- Parameters estimated: training group (ET, AC), time, gender, site, and training group X time interaction
- Training group X time interaction represented effect of cognitive training

Results

Table 2. Baseline Characteristics (ITT)

	Experimental Training (ET) Mean	ET SD	Active Control (AC) Mean	AC SD	p value
Age	75.3	6.6	74.9	6.3	n.s.
Education	15.7	2.6	15.7	2.6	n.s.
MMSE	29.1	1.1	29.1	1.1	n.s.
GDS	1.2	1.6	1.3	1.7	n.s.
Predicted IQ	114.0	7.7	113.8	8.2	n.s.
Gender	42.2%	(male)	52.5%	(male)	< 0.05

- No baseline group differences distinguished ET (n=232) and AC (n=236) groups (Table 2) with the exception of gender
- ET (18, 7.8%) and AC (28, 11.9%) participants withdrew during training
- No differences identified by group, but overall those withdrawing scored significantly lower on MMSE ($p<0.01$) and RBANS Total ($p<0.001$)

Table 3. Mean Change in Scores (ITT)

	ET Baseline	ET Post-Training	AC Baseline	AC Post-Training	p value (group X time interaction)
RBANS Auditory Memory Score	95.4 (1.44)	99.2 (1.45)	95.6 (1.45)	97.3 (1.45)	< 0.02
Overall Memory Composite	97.1 (2.14)	101.4 (2.15)	96.9 (2.14)	97.9 (2.15)	< 0.01
RBANS Visual Functioning Score	98.5 (0.94)	102.6 (0.95)	97.9 (0.94)	100.8 (0.95)	n.s.
RAVLT Trials 1–5	39.3 (1.32)	40.6 (1.33)	40.2 (1.32)	39.2 (1.33)	< 0.01
RAVLT Delayed Recall	6.3 (0.42)	6.9 (0.43)	6.6 (0.42)	6.6 (0.43)	< 0.05
WMS-III Digit Span Backwards	7.3 (0.21)	7.9 (0.21)	7.1 (0.21)	7.3 (0.21)	< 0.02
WMS-III Letter-Number Sequencing	9.5 (0.29)	10.2 (0.29)	9.4 (0.29)	9.5 (0.29)	< 0.02
RBMT Story Memory Immediate	7.8 (0.36)	8.4 (0.37)	7.6 (0.36)	8.1 (0.37)	n.s.
RBMT Story Memory Delayed	6.3 (0.35)	7.1 (0.35)	6.4 (0.35)	6.9 (0.36)	n.s.
Speed of Processing	116.2 (7.73)	50.8 (7.84)	120.2 (7.34)	113.4 (7.82)	< 0.001

Numbers in Parentheses Designate Standard Error

- Significant group X time interactions ($p<0.02$) favoring ET group found on primary endpoint measure (Table 3) and on multiple within-modality secondary endpoint measures ($p<0.05$). Effect sizes in generalized measures of memory ranged from 0.20 and 0.43
- No significant interactions were found for two within-modality (RBMT Story Memory Immediate and Delayed) and one cross-modality (RBANS Visual Functioning) measures
- PRO measures of everyday cognitive function were significant on pre-post ($p<0.002$) and post-only ($p<0.003$) assessments

Table 4. ITT Versus Fully Trained Effect Sizes (Cohen's *d*)

	ITT (N = 468)	FT (N = 389)
RBANS Auditory Memory	0.24	0.28
Overall Memory Composite	0.30	0.43

Discussion

Compared to a treatment-as-usual control, the experimental treatment yielded significantly superior results in:
- Speed of processing
- Generalized measures of memory
- Self-reported cognitive benefits

UNIVERSITY OF SOUTHERN CALIFORNIA

This study was funded by grants from Posit Science Corporation to the University of Southern California (E. M. Zelinski, PI) and to the Mayo Clinic Foundation (G. Smith, PI).