Cognitive training and practice effects

Protocol Summary

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Sponsor:	NIH NATIONAL INSTITUTE ON AGING
Principal Investigator:	Kevin Duff
Internal Staff and Sub-Investigators:	Taylor Atkinson Bonnie Dalley Tom Greene Dustin Hammers Bernie LaSalle Karen Mara Sydney Schaefer Kayla Suhrie Jian Ying
External Sub-Investigators:	Fred Wolinsky

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Background and Introduction

Cognitive impairments, including those affecting processing speed and memory, are common in older adults. Recently, multiple cognitive training programs have been validated to improve cognitive functioning in older adults (1 - 4). However, two weaknesses remain in this literature. First, most cognitive training programs have examined cognitively healthy elders, whereas their benefits in individuals with current cognitive impairments are less clear. Second, there have been few attempts to identify, a priori, individuals who are likely to benefit from these training programs. The current proposal seeks to build on these weaknesses by examining the effectiveness of a computerized cognitive training program in individuals with milder cognitive impairments and using practice effects as a means to identify responders.

Practice effects are improvements in scores on cognitive tests due to repeated exposure to the tests (5). Traditionally, practice effects have been viewed as a source of error that needs to be minimized. However, we and others have recently reported that practice effects might have clinical value in patients with mild cognitive impairments. For example, older adults with mild cognitive difficulties who do benefit from practice remained stable across one year, whereas those who do not show the expected practice effects tended to significantly decline over this same period (6, 7). In a small pilot study of older adults, practice effects were predictive of response to a memory training course (8). Practice effects in elders have also been linked to amyloid deposition on brain imaging (9). Taken together, practice effects have the potential to identify subjects who are more likely to benefit from cognitive training programs.

Purpose and Objectives

The current proposal seeks to examine the effectiveness of a computerized cognitive training program in individuals with mild cognitive impairments and use practice effects as a means to identify responders.

The specific aims of this project are:

1. Examine short- and long-term efficacy of a computerized cognitive training program in older adults with Mild Cognitive Impairment. It is hypothesized that individuals in the cognitive training group will show greater cognitive improvement (both immediately after completing the training and after 12 months) compared to individuals in a control group.

2. Assess moderating variables of treatment response, including pre-training practice effects, demographic variables, clinical variables, and amount of training. It is hypothesized that larger practice effects will be associated with better outcomes following the training. It is further hypothesized that younger, better educated, and more cognitively intact subjects will do better following training. Lastly, those subjects that do more training are expected to improve more across time.

Study Population

Age of Participants: 65+

Sample Size:

At Utah:	300
All Centers:	300

Inclusion Criteria:

1. Classified as Mild Cognitive Impairment (i.e., subjective memory complaints, objective memory deficits, largely intact cognition otherwise, no significant functional impairments), through a clinical diagnosis or a total score of >= 20 and immediate and delayed recall scores of < = 8 on the Modified Telephone Interview for Cognitive Status
2. 65 years of age or older
3. Availability of a collateral source (e.g. spouse, adult child, caregiver) who will be able to comment on the cognitive abilities and daily functioning of the subject
4. Access to a computer with audio device like speakers or headphones and the internet. This access could be at home, work, community center, or public library.
5. Adequate vision, hearing, and motor abilities to participate in training.

Exclusion Criteria:

1. History of major neurological illness (e.g. stroke, head injury with loss of consciousness of >30 minutes) or other neurological disorder or systemic illness that would likely affect cognition (e.g., seizure disorder, demyelinating disorder, etc.)
2. Current or past major psychiatric illness (e.g., schizophrenia, bipolar affective disorder) that would likely affect cognition
3. History of substance abuse.
4. Current use of antipsychotic or anticonvulsant medications.
5. Currently residing in a nursing home or other skilled nursing facility.
6. Current depression as identified by a score of >=15 on the 30-item Geriatric Depression Scale.

Design

Survey/Questionnaire Research
Interviews and Focus Groups
Prospective Clinical Research
Placebo Controlled

Randomized

Study Procedures

Recruitment/Participant Identification Process:
Several methods will be used to identify/recruit participants for this study.

1. **Database/participant pool. Participants from prior study (**IRB_00039496) will be contacted via a letter (attached) to ask if they are interested in participating in the current study. In the former study, participants received many of the same cognitive measures that will be given in the current study. However, the prior study was observational, whereas the current study also offers an intervention. In the consent document from the prior study, participants could indicate that they would be willing to be contacted about participating in future studies. Only those individuals who noted that they would like to be contacted will be sent the letter. Additionally, potential participants may be identified through research participant registries such as the Center on Aging Research Participant Registry and ResearchMatch.org.
2. **Referrals. Providers from the** Cognitive Disorders Clinic at the University of Utah (including Drs. Foster, Zamrini, and King [neurologists], Drs. Chelune, Duff, and Hammers (neuropsychologists), Troy Anderson [social worker], and Liz Garcia-Leavitt [health educator]) may refer their patients who might qualify for this study. Referrals could come from other clinics at the University of Utah (e.g., Geriatrics, Primary Care) or from other institutions (e.g., St. Mark's, Intermountain Healthcare). Referred individuals will be sent a letter (same as noted above) about the study. It should be noted that Drs. Duff and Zamrini are both providers and part of the Research Team on this study.
3. **Records review.** Potential participants may be identified from the Cognitive Disorders Clinic database at the University of Utah. During clinical visits, patients are asked if they would like to be contacted about research opportunities. Those current patients who have expressed an interest in research and are diagnosed with Mild Cognitive Impairment will be contacted via a letter (same as noted above).
4. **Educational presentations. We will conduct educational presentations in the community to inform individuals about this study. In the past, we have successfully used these presentations to recruit for other, similar studies. These presentations will be conducted at senior centers, independent living facilities, and other community forums (e.g., health fairs). Site permission will be obtained before the presentation is conducted. Although most of the content of these presentations is not related to this specific study, a copy of the slides that are directly related to this research project is attached.**
5. **Brochures. In addition to the letter, we have developed a brochure (attached) to describe the study. This brochure can be distributed at our educational presentation.**

Informed Consent:

Description of location(s) where consent will be obtained:

Imaging & Neurosciences Center; Center for Alzheimer's Care, Imaging, & Research; participants' homes

Description of the consent process(es), including the timing of consent:

Typically, consent is obtained during the first visit; however, some potential participants may have a consent form mailed to them before considering participation. All consenting will be done in person. All potential participants can have as much time as they want to consider participation.

Procedures:

Participants who have indicated that they would like to be contacted for other research opportunities during previous studies or who express interest in the study to their clinicians at the Cognitive Disorders Clinic will be sent a letter and subsequently called. Participants who indicate interest at community events will be asked for contact information and will subsequently be called.

Potential participants will be screened over the telephone for inclusion and exclusion criteria, including the 15-item Geriatric Depression Scale (GDS) and for those without a clinical diagnosis of mild cognitive impairment, the Modified Telephone Interview for Cognitive Status.

Participants who are identified as being eligible for the study will provide informed consent. Following consent of participants, four visits will be completed.

1. During this pre-treatment visit, participants will complete multiple measures of cognition and daily functioning. Participants will complete a demographics questionnaire and measure their dominant hand by completing the Edinburgh Handedness Inventory (EHI). The Geriatric Depression Scale (GDS) will also be administered to assess mood. This visit should take approximately 3.5 hours.

    a. Cognition will be assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This individually administered, 30-minute battery yields information about overall cognition, immediate and delayed memory, attention, visuospatial functioning, and language. It will serve as one of the outcome measures in this study. We will also complete the Reading subtest of the Wide Range Achievement Test – IV, which will assess premorbid intellect. Additionally, the participant and informant will be asked a series of questions to evaluate current subjective cognitive complaints.
    b. To assess practice effects, the six tests in the Table will be administered. We have successfully used these measures in the past to quantify the amount of learning/practice in patients with Mild Cognitive Impairment.
    c. Daily functioning will be assessed in two ways. First, the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory that has been adapted for MCI (ADCS-ADL MCI) will be administered to the participant and a knowledgeable informant. This subjective rating scale uses standardized questions about the ability of the participant to perform basic and instrumental activities of daily living over the past four weeks Second, several subscales of the Independent Living Scale (ILS),a direct measure of functional abilities will be utilized. The ILS is a performance-based measure of everyday activities. Participants will complete the Managing Money, Managing Home and Transportation, and Health and

Safety subscales.

Table. Practice effects battery.

Measure	Assesses
Hopkins Verbal Learning Test-Revised (HVLT-R)	Verbal memory
Brief Visuospatial Memory Test -Revised (BVMT-R)	Visual memory
Symbol Digit Modalities Test (SDMT)	Processing speed
Trail Making Test (TMT), Part A	Processing speed
TMT, Part B	Processing speed
Simulated feeding task	Motor learning

2. Participants will return approximately one week after completing the pre-treatment visit and repeat the measures in Table. The change on these measures between the first two visits will be used to quantify practice effects. This visit should take approximately 1.5 hours to complete. Participants will be randomized to either the experimental or control group and trained on the use of the Cognitive Training program at this visit.

3. Approximately 13 weeks after randomization, participants will return for their post-treatment testing, which will include the following measures: RBANS, ADCS-ADL MCI, and ILS. The Cognitive Failures Questionnaire, subjective cognitive functioning questions, and the GDS will also be administered. A post-treatment questionnaire will be administered to measure the effectiveness of blinding. The practice effects tests will not be repeated at this visit. This visit should take approximately 2 hours.

4. Approximately 12 months after the post-treatment visit, the measures of cognition, daily functioning, and practice effects will be repeated for all participants. The Cognitive Failures Questionnaire, subjective cognitive functioning questions, and the GDS will also be administered, along with a post-treatment questionnaire to measure the effectiveness of blinding. This visit should take approximately 3.5 hours.

Three additional measures will be collected at visits 1 and 4 to assess medical comorbities.

- Charlson Comorbidity Index, which asks about conditions like diabetes, cerebrovascular disease, and cancer, will be used to rate level of medical comorbidity. This will allow us to characterize the physical health of the participants.
- Chronic Disease Score is calculated from names of prescription medications and has been correlated with disease severity, healthcare utilization, and mortality. We will ask participants to bring their medications to visits to calculate this score, which could be considered as a moderating variable in cognitive outcomes following training.

- Modified Hachinski scale, which is a widely used measure of stroke risk factors.

Randomization

Participants will be randomly assigned to either the experimental or control groups with the use of a computer-generated schedule. Randomization will occur at the conclusion of the PE visit. To minimize the risk of predicting the treatment assignment of the next eligible participant and to balance participant numbers assigned to the two groups, randomization will be performed in permuted blocks of four with random variation of the blocking number. The group membership will be coded and blinded to the statistician performing the data analysis until the analyses are complete.

Blinding

Participants will be told that the intervention involves "cognitive exercises," so both the experimental and control groups (described below) will have face validity and should blind participants to group assignment. The effectiveness of participant blinding will be evaluated via a post-tx questionnaire on self-reported perception of change in cognitive function. We will also compare the proportions of voluntarily withdrawals from each group. The use of multiple examiners is also crucial for maintaining the blind.

Computerized Cognitive Training

All participants will receive a unique username and password, but a single web address. Once logged into the main website, the username will determine the web content that each participant can access. For example, those randomly assigned to the experimental group will only be able to access the experimental tasks; those assigned to the control group will only be able to access control tasks. Logging in and out of the main website will allow us to track the amount of time each participant spends at the site, which is one of the potential moderating variables in Specific Aim #2b.

Experimental group. Participants randomly assigned to this group will be directed to the Plasticity-based Cognitive Remediation (PACR) system from Brain Plasticity, Inc. This web-based application consists of 6 computerized exercises designed to improve the speed and accuracy of information processing, as well as memory and reasoning. Exercises continually adjust difficulty level to user performance to maintain approximately 85% correct rate, which challenges the participant and maintains engagement. Both auditory and visual stimuli are used. Exercises include: discrimination of confusing syllables, matching pairs of confusing syllables, and identification of details in verbally presented scenarios. Initial trials are exaggerated (e.g., presented slower and louder) to maximize engagement with the task, but later trials get progressively more difficult (e.g., presented faster and softer) to maximize the challenge. Participants will complete 40 hours of training over approximately 13 weeks. Each day they will be presented with 3 of the 6 exercises for 15 minutes each, to complete a 45-minute training session, 4-5 days per week. The PACR system tracks exercises completed and progress within exercises. All

of this information is immediately available for download by the PI.

All PACR data is regularly backed-up on two remote servers in distinct physical and geographical locations, and Brain Plasticity Inc. employs Risk Assessment and Management Procedures compliant with the US Food and Drug Administration requirements. In compliance with current HIPAA requirements, all user data is encrypted during transmission and storage to ensure security. PACR users must have authorized usernames and passwords to access the system (which will be the same as their initial usernames and passwords), and industry-standard safeguards are in place to detect and prevent unauthorized use. In multiple studies with healthy elderly and patients with schizophrenia, no serious adverse events have occurred.

Control group. This study will utilize an active control condition. When participants randomly assigned to this group log into the main website, they will be presented with 3 out of 6 alternating cognitively stimulating activities (e.g., crossword puzzles, card games, word searches). Although these activities are cognitively engaging, they have not been empirically validated to improve processing speed and memory, like the exercises in the experimental group. These exercises will be presented in the same format, with the same schedule as the experimental exercises. Therefore, the control condition should have some face validity and help maintain the blinding of the participants.

Following the 12-month visit, all participants in the control group will be offered the experimental treatment for at least 40 sessions. That is, once control participants complete their 12-month testing, they will be offered an individual account to the PACR system for up to 40 sessions. Of course, they can decline to participate in this "open-label extension" and no additional testing will be completed on either group.

To increase compliance, a local telephone helpline and email address will be provided for all participants, which will assist with those who have trouble logging onto the PACR system, the control websites, or accessing the Internet. Personnel at the University of Utah who have considerable experience with the PACR system will staff this helpline.

Retention Strategy

Despite relatively low attrition, the following retention strategies will be used across this 1-year longitudinal study. First, most subjects enrolled in this study will be patients at the University of Utah's Cognitive Disorders Clinic, followed by the PI and one of the Co-Is. Their routine clinic visits will put them in regular contact with the research team, which should improve retention. Second, we will send enrolled participants, with their permission, a copy of a bi-annual newsletter that informs them about our study progress (e.g., overview of the study, number of subjects currently enrolled, preliminary results). We have used these newsletters in other studies to minimize attrition. Third, with subject permission, we will send participants a New Year's card wishing them well from the research team. Fourth, home visits for data collection will be offered if transportation or other obstacles are noted. Fifth, we will request permission to contact participants on a

weekly basis to check on their training progress, troubleshoot any obstacles, and answer any questions. Participants will be asked to provide a preferred method (e.g., email, telephone number) and time of contact. Finally, participants will have access to our helpline to call with questions. All of these strategies have been shown to be effective in improving retention.

Procedures performed for research purposes only:

Statistical Methods, Data Analysis and Interpretation

The specific aims of the research project are:

1. Examine short- and long-term efficacy of training in improving cognition in older adults with Mild Cognitive Impairment.

1. Short-term efficacy will be examined immediately after completion of the training.
2. Long-term efficacy will be examined 12 months after training.

1. Assess moderating variables of treatment response.

1. Determine if short-term practice effects can identify those who respond to the intervention.
2. Examine other possible moderating variables of treatment response (e.g., demographics, clinical variables, and amount of training).

Measurements of practice effects and cognition will be normalized using our existing data from an observational study of practice effects and cognitive change. Normalizing this data with an external reference sample should make the findings more generalizable.

The primary cognitive outcome measure will be the Auditory Memory/ Attention Index from the RBANS, as the intervention focuses on improving auditory processing. Secondary outcomes will include the ADCS-ADL MCI, ILS, and NAT, as well as other cognitive scores.

Aim 1: The treatment effect on the primary outcome of the Auditory Memory/ Attention Index will be estimated under a mixed effects model relating the outcome's values at the post-tx and 12-month visits to the randomized treatment assignment, while assuming equal mean levels of the baseline outcome variable in the two treatment groups. An unstructured covariance model will be used to account for serial correlations of the outcome within the same patients. Linear contrasts will be constructed to estimate each of the following:

1. The treatment effect on the change in Auditory Memory/ Attention Index from pre-tx to the post-tx visit,

2. The treatment effect on the change in Auditory Memory/ Attention Index from pre-tx to the 12-month visit,
3. The average of the treatment effect estimates in (a) and (b) above, and
4. The difference between the treatment effects at 12-month and the post-tx visit.

Power for Aim 1: We expect that we will complete the post-tx and 12-month follow-up visits for 92.5% and 85% of the 230 randomized subjects, respectively. With these sample sizes, we will have 80% power with a 2-sided $\alpha = 0.05$ to detect differences of 0.47 and 0.49 of one standard deviation at the post-tx and 12-month visits, respectively.

Aim 2a: The mixed effects model described for Aim 1 will be extended by the addition of a pairwise interaction term between an indicator variable for treatment assignment and baseline primary practice effects score as a continuous variable. This extended model will be used to test if the treatment effect estimates on Auditory Memory/ Attention Index from Aim 1 differ between patients with lower and higher practice effects.

Aim 2b: The extension of the mixed effects analysis described for Aim 2a will be repeated for other potential effect modulators, including age, education, baseline cognition, and amount of training time.

Power for Aim 2: Statistical power for Aim 2a is most simply expressed for the model where the practice effects score is categorized as above or below the median level. For the post-tx assessment, the trial design will have approximately 80% power with a 2-sided $\alpha = 0.05$ to detect a difference in the treatment effect on the change in Auditory Memory/ Attention Index between patients with practice effects above the median vs. patients with practice effects below the median if the treatment effect for those with practice effects above the median is at least 0.94 of one standard deviation greater than the treatment effect for those with practice effects below the median. The corresponding minimum detectable difference in treatment effects on the 12-month Auditory Memory/ Attention Index between patients with practice effects above the median vs. patients with practice effects below the median is 0.98 of one standard deviation.

Missing Data. The results of the primary mixed effects analyses will remain valid as long as missing data satisfy the missing at random [MAR] condition. Sensitivity analyses will be performed using multiple imputation to impute baseline or follow-up values for the cognitive measurements when these are missing (68). An imputation model will be developed incorporating baseline cognitive measures as well as additional baseline and follow-up variables which are expected to be predictive of follow-up variables and/or risk of loss to follow-up. The imputation will be carried out using a Monte-Carlo Markov Chain algorithm under multivariate normal models.