Published in final edited form as:
Neuropsychology. 2012 May ; 26(3): 385–399. doi:10.1037/a0027545.

Mnemonic strategy training improves memory for object location associations in both healthy elderly and patients with amnestic mild cognitive impairment: a randomized, single-blind study

Benjamin M. Hampstead, Ph.D.[a,b], **K. Sathian, M.D., Ph.D.**[a,b,c,d], **Pamela A. Phillips, Psy.D.**[b,e], **Akshay Amaraneni, B.S.**[b], **William R. Delaune, Ph.D.**[a], and **Anthony Y. Stringer, Ph.D.**[b,d]

[a]Rehabilitation R&D Center of Excellence, Atlanta VAMC, Decatur, Georgia

[b]Department of Rehabilitation Medicine, Emory University, Atlanta, Georgia

[c]Department of Neurology, Emory University, Atlanta, Georgia

[d]Department of Psychology, Emory University, Atlanta, Georgia

[e]Neuropsychology Section, Department of Neurology, Indiana University, Indianapolis, Indiana

Abstract

Objectives—To evaluate the efficacy of mnemonic strategy training versus a matched-exposure control condition and also to examine the relationship between training-related gains, neuropsychological abilities, and medial temporal lobe volumetrics in patients with amnestic mild cognitive impairment (aMCI) and age-matched healthy controls.

Methods—Twenty-three of 45 screened healthy controls and 29 of 42 screened aMCI were randomized to mnemonic strategy or matched-exposure groups. Groups were run in parallel, with participants blind to the other intervention. All participants completed five sessions within two weeks. Memory testing for object-location associations was performed during sessions one and five and at a one-month follow-up. During sessions 2–4, participants received either mnemonic strategy training or a matched number of exposures with corrective feedback for a total of 45 object-location associations. Structural MRI was performed in most participants and medial temporal lobe volumetrics were acquired.

Corresponding Author: Benjamin M. Hampstead, Ph.D., 1441 Clifton Rd NE Room 150, Atlanta, GA 30087, 404-712-5667 (office), 404-712-1652 (fax), bhampst@emory.edu.

The contents of this manuscript do not represent the views of the Department of Veterans Affairs or the United States Government. Portions of this work were presented at the annual meetings of the International Neuropsychological Society (2010) and the American Academy of Clinical Neuropsychology (2011).

Conflicts of Interest
There are no conflicts of interest.

Author Contributions
Each author provided significant intellectual contribution to warrant authorship and declares that he/she has seen and approved this manuscript. Dr. Benjamin M. Hampstead had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results—Twenty-one healthy controls and 28 aMCI patients were included in data analysis. Mnemonic strategy training was significantly more beneficial than matched-exposure immediately after training, p =.006, $p\eta^2$ = .16, and at one month, p<.001, $p\eta^2$ = .35, regardless of diagnostic group (healthy controls or aMCI). Although aMCI patients demonstrated gains comparable to the healthy control groups, their overall performance generally remained reduced. Mnemonic strategy-related improvement was positively correlated with baseline memory and executive functioning and negatively with inferior lateral ventricle volume in aMCI patients; no significant relationships were evident in matched-exposure patients.

Conclusions—Mnemonic strategies effectively improve memory for specific content for at least one month in aMCI.

Keywords

cognitive rehabilitation; associative memory; MRI; hippocampal volume; aging

Introduction

Approximately 9.5 percent of individuals over age 70 have Alzheimer's disease (AD) in the United States (Brookmeyer et al., 2011). This figure is expected to increase dramatically over the next few decades (Ferri et al., 2005). An additional 8 percent of this aged population is believed to be in the prodromal stage of AD (Brookmeyer et al., 2011). The diagnosis of amnestic mild cognitive impairment (aMCI) is widely used to represent this prodromal phase (Petersen, 2004), although some degree of caution is warranted since 10–18 percent of patients demonstrate cognitive improvement at follow-up (Ganguli et al., 2011) and other subtypes of MCI can ultimately develop AD. Substantial financial savings and improved quality of life could be realized if these at-risk patients were able to function independently for a longer period of time. Although cholinesterase inhibitors are the most frequently prescribed medications for AD, they have not consistently altered the pattern of cognitive decline (Daviglus et al., 2010).

Cognitive rehabilitation is considered a standard of practice for some neurologically impaired populations (Cicerone et al., 2005; Cicerone et al., 2011); however, its use is a topic of contention in both healthy elderly and patients with aMCI as some results have been favorable (Acevedo & Loewenstein, 2007; Jean, Bergeron, Thivierge, & Simard, 2010; Li et al., 2011; Stott & Spector, 2011; Willis et al., 2006) whereas others have not (Clare & Woods, 2004; Martin, Clare, Altgassen, Cameron, & Zehnder, 2011). Cognitive rehabilitation typically employs a wide variety of strategies that are designed to improve an individual patient's everyday functioning. Study-related variables, such as the techniques employed, outcome measures, treatment format (group vs. individual), and length of treatment vary widely. This lack of standardization likely contributes to the discrepant findings noted above and makes it difficult to reach a general conclusion. As a result, it may be more fruitful to consider the efficacy of specific techniques within these populations and the conditions under which such techniques are effective. Once established, the empirically supported techniques could be selected and combined to meet the needs of each individual patient.

The current study focuses on mnemonic strategies, which include techniques like semantic organization, semantic elaboration, and mental imagery. Mnemonic strategies are frequently included in comprehensive cognitive rehabilitation programs; however, it is unclear whether they are effective in, or appropriate for, patients with aMCI. The available evidence suggests that healthy older adults benefit from mnemonic strategy use significantly more than from other types of training (Verhaeghen, Marcoen, & Goossens, 1992). These findings have

been supported by a number of large-scale studies that included mnemonic strategies within more comprehensive memory rehabilitation programs (Craik et al., 2007; Oswald, Rupprecht, Cunzelmann, & Tritt, 1996; Willis et al., 2006). Within the aMCI literature, nearly half of the studies included in a recent review taught mnemonic strategies either alone or in combination with other techniques (Jean et al., 2010). Only a few of these studies demonstrated statistically significant improvement despite effect sizes that were generally medium to large. Thus, it is unclear whether the strategies contributed to the overall efficacy of the training programs. Further, most of the studies cited by Jean and colleagues (2010) taught patients a number of mnemonic strategies, thereby requiring them to select and employ the most appropriate one(s) when encountering different types of information. This is potentially significant since a previous study found aMCI patients were able to learn a number of strategies but became confused when required to use them (Rapp, Brenes, & Marsh, 2002). As a result, we suggested that a single approach applied to multiple types of information might be more appropriate for neurologically impaired populations (Hampstead, Sathian, Moore, Nalisnick, & Stringer, 2008; Stringer, 2007).

To address some of the weaknesses noted above, we have adopted a hierarchical approach for establishing the efficacy of mnemonic strategies and clearly identifying the conditions under which they are effective in aMCI. At a basic level (addressed in the current study), the mnemonic strategies should improve memory for specific information. Negative results would suggest that these strategies are ineffective and should not be included within cognitive rehabilitation programs. Efforts could then focus on other promising techniques. Positive findings would lead to the next step, which would assess patients' ability to independently learn and apply the strategies to novel information that is similar to the conditions used during training. Negative results at this stage would mean that family or caregivers would need to help patients learn information using the strategies. The highest level would require patients to independently implement and then generalize the trained techniques within their everyday life. Negative results at this stage would suggest that training should focus only on a select number of areas that are causing the greatest difficulty in everyday life.

The current study was designed to build on our preliminary findings (Hampstead et al., 2008) and provide support for the use of mnemonic strategies at the basic (i.e., content specific) level using a randomized, controlled design. We included both healthy older controls and aMCI patients in order to clarify whether the presence and severity of cognitive impairment affected the efficacy of mnemonic strategies. This issue has rarely been studied in the literature as we found only three studies that directly compared healthy older adults and aMCI patients. In one study, patients and healthy older adults demonstrated comparable improvement (and effect sizes) on some objective outcome measures (Belleville et al., 2006). Further, aMCI post-training performances were comparable to healthy older adults pre-training performances, whereas untrained aMCI patients declined over the same time period. Subsequent work by this group led to similar findings (Belleville et al., 2011). In the final study, aMCI showed gains on objective outcome measures that were at least comparable to "normal" older adults (Wenisch et al., 2007). Thus, it appears that the magnitude of training-related gains is comparable between aMCI patients and healthy controls; however, this conclusion rests on a small body of evidence and clearly requires substantiation. It is also unclear whether performance in aMCI patients remains reduced or if it improves to "normal" levels relative to healthy older controls.

We have developed and used associative memory paradigms to assess training efficacy because they are dependent on medial temporal lobe functioning (Mayes, Montaldi, & Migo, 2007). Medial temporal atrophy is a characteristic structural change in aMCI and AD (Apostolova, Mosconi, et al., 2010; Apostolova, Thompson, et al., 2010; Fjell et al., 2009)

and is generally believed to be primarily responsible for the learning and memory deficits these patients experience. Other groups have posited that aMCI patients may not benefit from mnemonic strategies due to medial temporal lobe dysfunction and atrophy (Unverzagt et al., 2007). To our knowledge, however, no studies have directly assessed the relationship between atrophy in this region and training efficacy.

The current report details the behavioral results of a randomized, controlled, single-blind study wherein healthy controls and patients with aMCI were assigned to either mnemonic strategy training or an exposure-matched control condition. All groups learned a total of 45 object-location associations (OLAs) during three training sessions (15 OLAs per session). We previously reported that, at baseline, healthy controls remembered significantly more of these associations and demonstrated increased activity within brain regions associated with object processing (ventral visual stream), spatial processing (dorsal visual stream), and the binding of objects and locations (hippocampus and other medial temporal structures) relative to aMCI patients (Hampstead, Stringer, Stilla, Amaraneni, & Sathian, 2011b). These regions are posited as critical for memory of OLAs (Postma, Kessels, & van Asselen, 2008). Further, memory test performance correlated with activity within each of these regions in the healthy controls whereas performance correlated with regions associated with sensorimotor processing in aMCI patients (Hampstead et al., 2011b). These findings suggest that aMCI patients may have been approaching the task in a more rudimentary manner by focusing on the physical properties of the objects as opposed to the relevant relationship between the object and its location. Using this OLA paradigm, our primary aims were to examine (1) whether mnemonic strategy training was more beneficial than an exposure-matched control condition, both immediately post-training and at a one month follow-up time point; (2) whether mnemonic strategies “normalized” performance in aMCI to levels comparable with healthy controls; and (3) examine the relationship between individual characteristics (standardized neuropsychological measures and medial temporal lobe volumetrics) and training-related improvement.

Methods

Participants

Patients with aMCI were recruited from the Atlanta Veterans Affairs Medical Center and Emory University, including the Emory University Alzheimer’s Disease Research Center (ADRC). Each patient had been diagnosed with aMCI according to Petersen’s criteria (Petersen, 2004) at a consensus conference that included neurologists, neuropsychologists, geriatricians, or other key clinical staff. All relevant clinical data were considered during this consensus conference including neuropsychological results, structural neuroimaging (MRI or CT), laboratory results, and any other relevant medical information. To be diagnosed with aMCI, there was a subjective report of cognitive decline (provided by the patient or an informant) and evidence of objective memory impairment within the context of generally preserved global cognitive functioning. Patients were also required to be largely independent in activities of daily living based on informant report. Healthy controls came from the ADRC longitudinal registry or the general Atlanta area, were free of subjective and objective memory impairments, and were independent in activities of daily living. General exclusion criteria included a history of neurologic injury/disease (e.g., dementia, stroke, epilepsy, traumatic brain injury), psychiatric disorders (e.g., severe depression, bipolar disorder, schizophrenia), and current or past alcohol or drug abuse. There were no changes to the eligibility criteria once the study began. The study was approved by the Institutional Review Board of Emory University and the Research and Development Committee of the Atlanta VAMC. All participants gave written informed consent. All study-related procedures were performed at Emory University.

Although all patients had been previously diagnosed with aMCI, both aMCI patients and healthy controls completed a brief neuropsychological screening protocol within approximately one month before taking part in this study. This protocol allowed us to ensure that (1) aMCI patients had not progressed to dementia or reverted to normal and (2) the healthy controls did not demonstrate significant memory deficits. The protocol consisted of the Mini-Mental Status Exam (MMSE) (Folstein, 1975), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, 1998), the Trail Making Test, the Geriatric Depression Scale (GDS) (Yesavage et al., 1983), and the Functional Activities Questionnaire (FAQ) (Pfeffer, Harrah, Chance, & Filos, 1982).

Following Petersen's (2004) criteria, we required that patients' memory (i.e., performance on the RBANS Delayed Memory Index) was below expectations based on their background/premorbid status. We did not employ any specific cut-off criteria for several reasons. First, patients had already been diagnosed with aMCI. Second, we selected the RBANS because it was not used in the referring clinics and, as a result, provided an independent measure of memory functioning. However, Duff et al. (2008) found that RBANS performances 1 to 1.5 standard deviations below the mean successfully differentiated patients with AD from healthy older adults. Using these performances as cut-offs could result in a sample that was more biased toward AD. Excluding those who are closer to the "healthy" end of the spectrum may minimize the efficacy of rehabilitative techniques. Nonetheless, only four of our 28 patients were within one standard deviation of the mean, two of whom fell just short (z-scores of −0.87 and −0.93). Using available clinical records, we gathered follow-up data on the aMCI patients in our study as of June 2011 (1–2 years after participating in the study). Six patients were lost to follow-up after the initial diagnosis that led to inclusion in our study (3 mnemonic strategy, 3 exposure), 15 were still diagnosed with MCI (7 mnemonic strategy, 8 exposure), and 7 had converted to AD (4 mnemonic strategy, 3 exposure).

Stimuli

As previously described (Hampstead et al., 2011b), our paradigm is similar to one used by Kessels and colleagues (Kessel, Feijen, & Postma, 2005). Because many patients report difficulty remembering where they have placed objects, we designed our OLA paradigm to be as ecologically relevant as possible within the confines of a neuroimaging environment. To create the stimuli, we used a computerized three-dimensional design program (www.Plan3d.com) to create two lists of nine rooms that consisted of a bathroom, bedroom, dining room, garage, kitchen, laundry room, living room, office, and recreational room. Within each of these rooms, we identified five locations that were reasonably spaced from one another and spread the entire width and, to the extent possible, height of each room (e.g., floor, shelves, tables, cabinets).

We selected 90 objects that could feasibly be found in at least two rooms within the home from a larger group identified via an online database (http://www.psy.uwa.edu.au/mrcdatabase/mrc2.html). These 90 objects were then divided into two lists of 45 that were very similar in terms of concreteness (List A: $M = 586.2$, $SD = 34.9$; List B: $M = 590.5$, $SD = 38.1$; $t(81) = 0.54$, $p = .59$), familiarity (List A: $M = 556.8$, $SD = 43.3$; List B: $M = 543.9$, $SD = 50.9$; $t(81) = 1.24$, $p = .22$), and imageability (List A: $M = 581.9$, $SD = 31.8$; List B: $M = 570.6$, $SD = 45.1$; $t(81) = 1.33$, $p = .19$). Additionally, the frequency (per million words) with which the object names appear in American English was also similar between these lists (List A: $M = 37.74$, $SD = 111.8$; List B: $M = 25.36$, $SD = 49.6$; $t(87) = 0.68$, $p = .5$; http://subtlexus.lexique.org; Brysbaert & New, 2009).

We then assigned five objects to each room, taking care to match each object to a room in which it was likely to be found. Importantly, however, each object was pseudo-randomly

placed into one of the locations within each room such that any object could have reasonably appeared in any of the five target locations in that room. This method limited the influence of implicit or semantic associations on these specific OLAs. Examples of our stimuli can be seen in Figure 1.

Group randomization and training procedures

All participants were informed during the consent process that we were examining the efficacy of various cognitive rehabilitation techniques. Participants were given information about their specific treatment only after they had been randomized (on a 1:1 ratio) to either mnemonic strategy training or a matched-exposure group (see treatment details below). At no point were participants given information about the methods used in the other training group. The randomization schedule was created before the study began, with separate lists for the healthy controls and aMCI groups (via the list randomizer option on www.random.org). A research assistant administered the neuropsychological screening protocol and a neuropsychologist (BMH or AYS) reviewed the results to determine eligibility. After a participant was deemed eligible, the research assistant assigned him or her to the next open space in the randomization schedule. Thus, the neuropsychologist was unaware of the group to which each participant would be assigned.

Following this process, a total of four groups were created (healthy control mnemonic strategy, healthy control exposure, aMCI mnemonic strategy, aMCI exposure). All treatment sessions were individually administered (i.e., just the trainer and the participant) and all groups were run in parallel. Each participant completed the initial screening session to determine eligibility. Once enrolled, participants completed five sessions within a two-week period of time as well as a one-month follow-up session (Figure 2). This same design was used in our previous study (Hampstead et al., 2008).

Sessions One and Five (pre- and post-training)

The procedures were divided into encoding and retrieval phases and were generally administered during fMRI scanning (fMRI results will be reported separately). During the encoding phase, participants were instructed to remember the location of each object. Each of the 90 OLAs (List A + List B) was presented for a total of 6 seconds: just the object for the first 2 seconds, followed immediately by the object in its location during the next 4 seconds. The retrieval phase began after a 1-hour delay and participants were instructed to identify the location of the object from among three possible choices. Again, objects were presented for 2 seconds and then participants had 4 seconds to select the correct location. Importantly, each of these choices was a target location of one of the five objects within the particular room. We implemented this design in order to minimize the possible contribution of familiarity-based judgments in favor of recollective memories. OLA accuracy was the primary dependent variable of interest. The same procedures were used during both Session One (pre-training) and Session Five (post-training).

A subset of participants could not undergo fMRI and completed these phases in a quiet office setting. During Session One, seven participants were seen in our office. Importantly, the number of participants was comparable across the aMCI (mnemonic strategies n=1, exposure n=1) and healthy control groups (mnemonic strategies n=3, exposure n=2). Three additional aMCI patients completed Session Five in our office because they either did not tolerate the fMRI scanning (n=1) or there were technical errors in pre-training data acquisition that eliminated the need for post-training fMRI (n=2). However, the number of participants seen within our office remained comparable between the aMCI groups during Session Five (mnemonic strategies n=3, exposure n=2). Importantly, there were no

significant differences between participants who underwent fMRI vs. office-based exposure during Session One, $t(47) = 1.7$, $p = .09$, or Session Five, $t(47) = 0.99$, $p = .33$.

Following the Session Five retrieval phase, participants were asked to complete a brief questionnaire that focused on the perceived usefulness of the training and quality of their interactions with the examiners. Participants returned one month after Session Five and completed the exact same memory test within our office so that we could assess their long-term retention of information. Importantly, patients had not seen any of the stimuli during this month. OLA accuracy was again the key variable of interest.

Training sessions

The overall training approach and sample sizes were based on our previous work with face-name associations (Hampstead et al., 2011a). Within each treatment group, participants were randomly assigned to be trained on either List A or B on a 1:1 ratio (referred to hereafter as the trained list, the other being the untrained list). Thus, half of the participants in the study were trained on each list, which avoids any stimulus-specific confounds. Each of the three individual training sessions (Sessions 2–4) lasted approximately 60–90 minutes. The same general approach was used for all groups (Figure 2). During each session, participants were trained on 15 OLAs in three successive sets of five for three trials each. After the third set of five OLAs, all 15 were reviewed as a single set for an additional three trials (same-day review). The next session began with a three-trial review of the 15 OLAs learned during the previous session (delayed review). If necessary, corrective feedback was provided immediately after each trial in all groups. Accuracy during each of these three periods was a secondary outcome variable.

Mnemonic strategy groups—The mnemonic strategies used with these groups are analogous to those in our earlier study (Hampstead et al., 2008) and stem from a comprehensive cognitive rehabilitation program (Stringer, 2007). Because we are systematically examining the conditions under which mnemonic training is effective in these populations, we provided specific cues for each OLA. This was deemed critical at this stage of the research program since it standardized the procedures across participants. For each OLA, we first introduced a salient feature within the room that was near the location of the object and then provided a verbally-based reason that linked the object to the specific feature. Participants were encouraged to close their eyes and create a detailed mental image (or "movie") of the object, feature, and reason. Examples of the cues are provided in Figure 1. This initial introduction took approximately 15–20 seconds per OLA. On each subsequent trial, participants were required to recall, in order, the feature, the reason, and then the location of the object within the room from among the five choices. This process was designed to promote a specific series of steps that participants could use with OLAs in general.

Exposure groups—As noted above, participants in these groups received the exact same procedures (i.e., number of trials and sessions, corrective feedback) as the mnemonic strategy groups, except that the mnemonic strategies were omitted. During an initial introduction, participants were allowed as much time as necessary to learn the location of each object. To be consistent with the mnemonic strategy groups, a minimum of about 15 seconds was given even if the participant indicated readiness to proceed before this time had expired. During each subsequent trial, participants were shown an object and asked to identify its location from among the five possible choices within the associated room.

Structural MRI and volumetric measurements

We acquired structural MRI scans on the majority of the participants (26 aMCI: 13 in each group; 16 healthy controls: 8 in each group) in order to examine the relationship between medial temporal lobe volume and efficacy of training since this has not been empirically addressed to date. MR scans were performed on a Siemens Trio 3T MRI scanner (Siemens Medical Solutions, Malvern, PA), using a 12-channel head coil. High-resolution anatomic images were acquired using a 3D MPRAGE sequence (TR 2300 ms, TE 3.9 ms, TI 1100 ms, FA 8°) consisting of 176 sagittal slices of 1 mm thickness (FOV 256 mm, in-plane resolution 1×1 mm, in-plane matrix 256×256). As in our previous study (Hampstead et al., 2011b), volumetric measurements were acquired using an FDA-approved, commercially available program (NeuroQuant®). This program was previously validated against a computer-aided manual segmentation procedure and was found to be sensitive to volumetric changes in mild AD (Brewer, Magda, Airriess, & Smith, 2009). We used the percentage of intracranial volume values for each region since this method reduces measurement variability more than other techniques (Gold & Squire, 2005). Previous work has revealed substantial and comparable atrophic changes within the hippocampus and the amygdala as well as marked increases in the size of the inferior lateral ventricles over one to two years in both healthy controls and AD patients (Fjell et al., 2009). Volumes of the hippocampus, amygdala and inferior lateral ventricle are provided by NeuroQuant and were included in the analyses below.

Statistical methods

Between-group differences on demographic variables and baseline neuropsychological data were assessed with 2 (between-subjects factors: healthy controls vs. aMCI) × 2 (between-subjects factors: mnemonic strategies vs. exposure) multivariate analysis of variance (MANOVA) with Bonferroni post-hoc tests as appropriate.

Treatment efficacy was calculated using a modified change score that provided the percent of improvement relative to that possible after accounting for pre-training (Session One) performances. Two scores were calculated for both the trained and untrained stimuli. Immediate improvement was calculated as follows: ((Session Five % correct – Session One % correct) / (100 – Session One % correct))*100. Long-term improvement was calculated as follows: ((1-month % correct – Session One % correct) / (100 – Session One % correct)) * 100. These formulas provided a standard metric that was not as limited by ceiling effects as the raw change scores and that could be directly compared across all groups.

Aim 1 was to examine the efficacy of mnemonic strategies vs. exposure for the trained stimuli; therefore, we performed a 2 (between-subjects factors: healthy controls vs. aMCI) × 2 (between-subjects factors: mnemonic strategies vs. exposure) analysis of variance (ANOVA), separately for the immediate and the long-term improvement scores. These separate analyses made full use of our sample since patients who were lost at one month were still included in the immediate improvement analysis. Although our study was not designed to specifically assess generalization, we conducted these same analyses for the untrained stimuli.

During training, participants completed three different training tasks that consisted of different set sizes (small sets of five stimuli for three trials each vs. reviews of 15 stimuli for three trials each) and delay requirements (small sets < same day review < delayed review). We compared performances (in percent correct) during the three training sessions by examining the overall accuracy during each training task using a 2 (between-subjects factors: healthy control vs. aMCI) × 2 (between-subjects factors: mnemonic strategies vs.

exposure) × 3 (within-subjects factors: small set; same day review; delayed review) repeated measures ANOVA.

Aim 2 was to examine whether mnemonic strategy training normalized aMCI behavioral performance. Therefore, we compared the "raw" accuracy for the trained stimuli during Sessions One and Five and at 1-month between the aMCI mnemonic strategy group and the two healthy control groups using separate one-way ANOVAs.

Aim 3 was to examine the relationship between training-related improvement (using the modified change score described above), medial temporal lobe volumetrics, and standardized neuropsychological measures. This aim was accomplished using correlation analyses (Spearman's rho). We considered a number of previous findings when selecting the measures for this aim. Other groups have suggested a relationship between medial temporal lobe atrophy and training-related gains (Unverzagt et al., 2007). So, we included the volumes of the hippocampus, amygdala, and inferior lateral ventricles, which are the three medial temporal regions available via NeuroQuant®. If this relationship exists, it should also be reflected by standardized memory tests (here, the RBANS Delayed Memory Index – DMI). The prefrontal cortex is generally viewed as critical for organizing and structuring information. Lezak, Howieson, and Loring (2004 p.35) note that preserved executive functioning can allow individuals to remain functionally independent even when they experience significant impairment in other cognitive domains. Additionally, several previous fMRI studies demonstrated increased activity within the prefrontal cortex after mnemonic strategy training (Hampstead et al., 2011a; Kondo et al., 2005; Miotto et al., 2006). Therefore, we posited that executive abilities might be critical to the success of mnemonic strategies and included Trails B as a result. However, we calculated the Trails B/A ratio using the demographically corrected T-scores in order to obtain a purer measure of executive functioning that controls for psychomotor processing speed (Strauss, Sherman, & Spreen, 2006, p. 663). We first performed the correlations within the combined intervention group (healthy control + aMCI) in order to capture the variability across the spectrum from healthy through aMCI. We repeated these same correlations within each of the four groups separately in order to examine whether the same relationships persisted.

All analyses were performed using SPSS 18.0 and results were considered significant at $p<.05$, with Bonferroni corrected post-hoc tests performed as appropriate.

Results

Group demographics and baseline neuropsychological functioning

The flow of participants in both diagnostic groups can be seen in 0Figures 3 and 4. Based on the results of our previous study (Hampstead et al., 2008; Hampstead et al., 2011a), our goal was to have at least eight right-handed participants complete the fMRI portion of the study in each of the four groups and we continued recruiting until this target was fulfilled. All data were collected between June 2008 and January 2010. Within the aMCI groups, a total of 29 patients were randomized and completed through Session Five; 25 patients returned at 1 month (86% retention rate). Three of the four patients lost to follow up were in the exposure group; however, there did not appear to be any systematic bias since they failed to return due to a sudden family tragedy (n=1) and scheduling problems associated with leisure travel (n=2). The lost mnemonic strategy patient simply could not be contacted. The age, $t(26) = 0.99$, $p=.33$, education $t(26) = 1.58$, $p=.13$, and neuropsychological functioning (p-values for tests in Table 1 ranged from .13 to .94) of these lost patients were not significantly different from the remainder of the patients. One additional mnemonic strategy patient was excluded because he was diagnosed with AD within 1 month of completing the study. Overall then, 14 mnemonic strategy and 14 exposure aMCI patients were included in data analyses

through Session Five and 13 mnemonic strategy and 11 exposure aMCI patients were included at 1 month.

Of the 23 healthy controls who were randomized, 22 completed the study (including the one month follow-up) (95% retention rate). The remaining participant withdrew after being randomized but before the pre-training session. One participant from the mnemonic strategy group was subsequently excluded because she disclosed her ongoing treatment with chemotherapy (for breast cancer) midway through the study. This resulted in 11 participants in the mnemonic strategy and 10 in the exposure group at both time points.

There were no significant differences between the treatment groups (mnemonic strategies vs. exposure) within the diagnostic groups (healthy controls or aMCI patients), as can be seen in Table 1. As expected, aMCI demonstrated significantly lower scores on the MMSE in addition to learning and memory deficits on the RBANS. There was also a significant difference between the diagnostic groups on the Language Index of the RBANS. The aMCI patients had more difficulty in daily functioning than the healthy controls, but their scores on the FAQ were within the range typical of aMCI patients as opposed to those with dementia (Steenland et al., 2008). Such mild "inconveniences" in daily functioning are described in Petersen's diagnostic criteria and are likely related to the ramifications of memory impairment (Petersen, 2004). Significant differences were also evident in the volume of all medial temporal lobe structures, especially between the hippocampal volumes of the two mnemonic strategy groups (aMCI < healthy controls). However, overall cortical gray matter and size of the lateral ventricles were not significantly different between groups. Thus, the overall neurocognitive profile and pattern of atrophy within our aMCI patients are consistent with individuals who are at increased risk of converting to AD (Petersen, 2004).

No significant differences were observed on the post-training questionnaire that examined the subjective benefits of training and participants' interaction with our research team (Table 2).

Intervention results

Are mnemonic strategies more effective than matched-exposure?—Table 3 shows the average raw performances within each group as well as the modified change scores used in the analyses. For the immediate improvements, there was a main effect of intervention group, where mnemonic strategies resulted in significantly greater improvement than exposure, $F(1,45) = 8.5$, $p = .006$, $p\eta^2 = .16$. There was no overlap between the 95% confidence intervals (mnemonic strategy groups: [76.85, 90.41]; exposure: [62.58, 76.51]). There was also a significant main effect of diagnostic group as healthy controls outperformed aMCI, $F(1,45) = 25.6$, $p<.001$, $p\eta^2 = .36$. The intervention by diagnostic group interaction was not significant, $F(1,45) = 1.1$, $p= .3$, $p\eta^2 = .02$.

The same general pattern of results emerged for the long-term improvements where mnemonic strategies were again superior to exposure (main effect of intervention: $F(1,41) = 21.8$, $p <.001$, $p\eta^2 = .35$), with no overlap between the 95% confidence intervals (mnemonic strategies: [44.17, 68.97]; exposure: [1.43, 27.88]). The main effect of diagnostic group failed to reach significance, $F(1,41) = 3.9$, $p =.056$, $p\eta^2 = .09$. The interaction was not significant, $F(1,41) = 1.1$, $p = .3$, $p\eta^2 = .03$.

During the training sessions, participants in the mnemonic strategy groups outperformed those in the exposure groups (main effect of intervention), $F(1,45) = 7.981$, $p = .007$, $p\eta^2 = .151$, and healthy controls outperformed aMCI (main effect of diagnostic group), $F(1,45) = 13.744$, $p = .001$, $p\eta^2 = .234$. There was a significant main effect of training task, $F(2,90) = 11.866$, $p <.001$, $p\eta^2 = .209$, and a significant intervention group by training task interaction,

$F(2,90) = 5.922$, $p = .004$, $p\eta^2 = .116$. This interaction was driven by stable performances across training tasks in the mnemonic strategy groups, $F(2,48) = 1.427$, $p = .250$, $p\eta^2 = .056$, but significantly different performances across training tasks in the exposure groups, $F(2,46) = 13.897$, $p < .001$, $p\eta^2 = .377$. The exposure groups performed significantly better on the small sets (90.74%) than during the same day (83.46%; $p = .001$) or delayed reviews (79.66%; $p = .001$). Their performances on the review sets were not significantly different ($p = .188$). No other interactions reached statistical significance, intervention × diagnostic group: $F(1,45) = 0.886$, $p = .352$, $p\eta^2 = .019$; training task × diagnostic group: $F(2,90) = 1.459$, $p = .238$, $p\eta^2 = .031$; training task × intervention group × diagnostic group: $F(2,90) = 0.265$, $p = .768$, $p\eta^2 = .006$.

For the untrained stimuli, the healthy controls showed significantly greater immediate improvement compared to the aMCI patients, $F(1,45) = 31.6$, $p < .001$, $p\eta^2 = .413$. Neither the main effect of treatment, $F(1,45) = .014$, $p = .714$, $p\eta^2 = .003$, nor the interaction were significant, $F(1,45) = 2.14$, $p = .150$, $p\eta^2 = .045$. There were no significant long-term improvements for the untrained stimuli, diagnosis: $F(1,41) = 1.699$, $p = .200$, $p\eta^2 = .040$; intervention: $F(1,41) = 0.34$, $p = .563$, $p\eta^2 = .008$; diagnosis × intervention interaction: $F(1,41) = 0.03$, $p = .864$, $p\eta^2 = .001$.

Does mnemonic strategy training normalize aMCI performance?

While the above analyses examined the amount of improvement after training, here we examine whether mnemonic strategies allowed aMCI patients to perform at levels comparable to the healthy control groups by analyzing the raw performances at each time point. During Session One, there were significant differences between these groups, $F(2,32) = 4.80$, $p = .015$, $p\eta^2 = .231$, due to better performance in the healthy control mnemonic strategy group relative the aMCI group, $p = .016$. Although differences between the aMCI mnemonic strategy group and healthy control exposure group were not significant, $p = .158$, there was a large effect size favoring the healthy controls, *Cohen's d* = .76. The same results emerged during Session Five, $F(2,32) = 6.40$, $p = .005$, $p\eta^2 = .286$, where the aMCI group's performance was worse than the healthy control mnemonic strategy group, $p = .004$, but not significantly different than the healthy control exposure group, $p = .10$, despite a large effect size, *Cohen's d* = .83. At one month, the overall ANOVA was again significant, $F(2,31) = 7.79$, $p = .002$, $p\eta^2 = .334$, and the aMCI mnemonic strategy group performed significantly below the healthy elderly mnemonic strategy group, $p = .006$. The aMCI mnemonic strategy group again performed comparably with the healthy control exposure group, $p = 1.0$, but now a nominal effect size favored the aMCI, *Cohen's d* = .11.

Relationships of performance gains to neuropsychological tests and volumetrics

In the participants receiving mnemonic strategies (healthy controls & aMCI), the immediate gains were significantly positively correlated with the RBANS DMI and amygdala volume and significantly negatively correlated with the volume of the inferior lateral ventricles (Table 4). Within the aMCI group, this pattern changed slightly as immediate gains were significantly positively correlated with the RBANS DMI and the Trails B/A ratio and significantly negatively correlated with the volume of the inferior lateral ventricles. Although a positive relationship existed between immediate improvement and amygdala volume, it fell just short of statistical significance, $p = .051$. Importantly, the RBANS DMI and the Trails B/A ratio were not significantly correlated, $r_s = .27$, $p = .35$, which suggests these variables contributed relatively independently of one another and that our findings are not easily accounted for by general disease severity.

In those receiving exposure (healthy controls & aMCI), immediate gains were related to only the RBANS DMI (Table 4). Interestingly, none of these variables correlated with improvement in the healthy control or the aMCI groups by themselves.

Discussion

This randomized, controlled, single-blind study used an OLA memory paradigm in order to establish basic efficacy for the use of mnemonic strategies in healthy controls and aMCI. Specifically, we examined whether the use of mnemonic strategies is more effective than repeated exposure for specific content. Within each diagnostic group (healthy controls, aMCI), the treatment groups were comparable in regards to demographics, neuropsychological test performances, and even brain volumetrics. Overall our results indicate that mnemonic strategies are superior to exposure, with benefits that persist for at least one month after training. These findings reinforce our earlier report using face-name associations (Hampstead et al., 2008). Importantly, unintentional experimenter bias cannot account for our findings since there were no significant differences between the groups in terms of the subjective benefits of training or the manner in which they were treated by our research team.

Mnemonic strategies are superior to matched-exposure

Aim 1 was to examine the efficacy of mnemonic strategies versus exposure and our results clearly demonstrated that information learned using mnemonic strategies is remembered significantly better than with exposure regardless of diagnostic status (i.e., healthy controls or aMCI). There was no overlap in the 95% confidence intervals for the intervention group means at either time point, which reinforces the robustness of these primary results. Interestingly, the benefits of the mnemonic strategies actually appeared to increase over time, as indicated by the larger long-term ($p\eta^2$ = .35) than immediate effect sizes ($p\eta^2$ = .16). This finding may initially seem counterintuitive; however, it reflects the fact that we were assessing memory for trained content. In essence, participants who used mnemonic strategies during encoding showed less degradation in memory over the course of one month compared those who used repeated exposure. These effects cannot easily be explained by extraneous factors like the test, since all groups completed the exact same test at each time point so any practice or familiarity effects should have been comparable between the groups. Similarly, attrition is unlikely to have biased our findings since we had a 91.8% overall retention rate at one month. We cannot rule out the possibility that participants in the mnemonic strategy groups practiced using these techniques during the one-month period; however, it is unclear why they would be any more likely to rehearse the trained stimuli than those in the exposure groups.

The benefits of the strategies were first evident during the training sessions, where those receiving mnemonic strategies maintained a stable level of performance both within and across sessions whereas exposure participants declined. The plateau after the first three trials suggests that participants rapidly encode information using mnemonic strategies and that extensive repetition is not needed to achieve improved memory for the targeted material. Additional work is needed, however, to determine the dosage at which mnemonic strategies result in the long-term benefits reported above.

Overall then, these primary and secondary results provide clear evidence that mnemonic strategies are effective at the basic (i.e., content specific) level of our hierarchy discussed above. Our findings have particular importance in light of a recent Cochrane review that found memory training (broadly defined) and “control” (non-memory) interventions to be equally effective in healthy controls and aMCI (Martin et al., 2011). As previously discussed, several factors could account for these findings and the systematic study of

individual cognitive rehabilitation techniques may ultimately lead to more effective and patient-centered treatments.

There are likely several reasons that mnemonic strategies were effective in the current study, with level (depth) of processing probably being the most relevant factor (Craik & Lockhard, 1972). This classic literature has demonstrated that increased attention, personal meaning, and semantic elaboration improve subsequent memory (Craik, 2002). Here, requiring participants to focus on a feature within the room likely increased their attention to and processing of the location, which appeared to be deficient in aMCI during Session One (Hampstead et al., 2011b). The verbal "reasons" (i.e., rationale linking the object & feature) provided a detail-rich context that utilized existing semantic, and possibly personal, knowledge. Such a process was shown to improve memory nearly 35 years ago (Craik, 2002; Moscovitch & Craik, 1976). Finally, we encouraged patients to use mental imagery on the initial learning trial, which is effective in a number of neurologically impaired populations (Kaschel et al., 2002; Wilson, 2009). In fact, a recent study found increased cortical thickness in healthy older adults after mental imagery training (Engvig et al., 2010). An intriguing question is whether (and the extent to which) the mnemonic strategies allowed aMCI patients to re-engage dysfunctional brain regions (i.e., "restorative" changes) and/or recruit novel regions (i.e., "compensatory" changes). Further analysis of our fMRI data may offer some insight into this question and is currently underway.

What remains unclear is the extent to which healthy controls and aMCI patients can independently apply mnemonic strategies to novel information, which represents the next step of our hierarchy and the focus of our ongoing studies. We did not find any evidence that participants generalized the strategies to the untrained stimuli in the current study, which is not necessarily surprising for several reasons. First, we focused on using the strategies to teach specific content rather than on teaching patients to independently use the techniques. Second, participants were only given four seconds to integrate the object and the location, which is unlikely to be sufficient for even healthy young individuals. Interestingly, however, our previous fMRI results suggest that participants alter their approach to learning these untrained stimuli as reflected by increased lateral prefrontal and inferior parietal activity (Hampstead et al., 2011a). Initial results of the fMRI data from the current study appear to support this conclusion as do findings from an independent group (Belleville et al., 2011). Regardless, future studies should consider assessing generalization using tasks that provide sufficient time for any strategies to be implemented. Recently developed tests, such as the Ecologic Memory Simulations (Stringer, 2011), may be helpful for this purpose as well as for assessing generalization to tasks that are likely to be encountered in everyday life.

In regard to the transient improvements shown by the exposure groups, we provided a single learning trial and then multiple test trials that included corrective feedback. Roediger and colleagues have examined this "testing effect" extensively within an educational setting (Larsen, Butler, & Roediger, 2009) and, more recently, in elderly individuals (Tse, Balota, & Roediger, 2010). While such studies provide support for the efficacy of repeated testing (as opposed to repeated study), our results suggest that this method may be appropriate if information needs to be retained for a relatively short period of time. However, the exposure-related improvement does not appear to be dependent on the integrity of cognitive functioning or medial temporal lobe structures, which suggests that rehearsal-based approaches could continue to be effective in more advanced patients (i.e., those closer to AD). Such methods may be useful in helping patients acclimate to new environments (or people) with relatively little effort. Additional "booster" trials would likely be needed to maintain any behavioral improvements over the long-term.

Mnemonic strategies do not clearly normalize performance in aMCI

The magnitude of improvement in our aMCI mnemonic strategy group was comparable to that of healthy controls, which is encouraging given the severity of their baseline memory deficits. This finding is consistent with several previous studies (Belleville et al., 2006; Belleville et al., 2011; Wenisch et al., 2007). However, there was limited evidence suggesting that the mnemonic strategies "normalized" memory test performance. Specifically, the healthy control mnemonic strategy group significantly outperformed the corresponding aMCI group at all time points. A more ambiguous picture emerged when these aMCI patients were compared to the healthy controls in the exposure group since there were no significant differences at any time point, even pre-training. We suspect that our relatively small groups affected these results since the medium – large effect sizes favored the healthy controls pre- and immediately post-training. However, the nominal effect size at one month favored the aMCI patients. Thus, it appears that the magnitude of improvement may be comparable but that aMCI patients do not necessarily "catch" up to healthy individuals in terms of memory functioning.

Neuropsychological and neuroanatomical correlates of change

Almost by definition, aMCI encompasses a rather heterogeneous population, with patients ranging from virtually normal to almost indistinguishable from AD. Therefore, identifying factors that affect the efficacy of mnemonic strategies is critical if an intervention is to be effective within a clinical setting. Across all mnemonic strategy participants (healthy controls & aMCI), immediate improvement was related to the functional (RBANS DMI) and structural (volumetrics) integrity of the medial temporal lobes. This pattern, and an additional relationship with executive functioning (Trails B/A ratio), was also seen in the aMCI group alone. However, no significant relationships persisted in the healthy controls. Together, these findings suggest that the mnemonic strategies trained in the current study engage compensatory, prefrontally-mediated mechanisms. This relationship is also consistent with our previous findings of increased activity within both the medial and lateral prefrontal cortex after training with these strategies (Hampstead et al., 2011a). Thus, factors that negatively impact executive functioning, such as extensive white matter disease (Hampstead et al., 2010; Ramos-Estebanez et al., 2011) may potentially decrease the effectiveness of these and possibly other mnemonic strategies.

The implications of the lack of a relationship between hippocampal volume and immediate improvement are unclear at this point. The anterior hippocampus experiences the earliest changes in aMCI and AD (Apostolova, Mosconi et al., 2010; Apostolova, Thompson et al., 2010) and is important for associative memory (Chua et al., 2007). The amygdala abuts the anterior hippocampus and the distinction between the two can be challenging, especially in diseased brains. We are uncertain how accurately NeuroQuant® is able to differentiate between these structures. Another possible interpretation is that mnemonic strategies help facilitate the process through which memories become independent of the hippocampus, which may explain the marked increase in activity within the "semantic memory network" (Binder, Desai, Graves, & Conant, 2009) (i.e., medial frontal and parietal cortices) after mnemonic strategy training (Hampstead et al., 2011a). Regardless, our results suggest that the volume of the inferior lateral ventricles is related to mnemonic strategy-based improvement and likely represents the widespread medial temporal atrophy known to occur during the early stages of AD (Fjell et al., 2009). Practically then, alternative techniques should be employed in patients with memory and executive dysfunction and who demonstrate significant medial temporal lobe atrophy. As previously noted (Section 4.1), repeated exposure (i.e., the "testing effect") appears to be an appropriate method for inducing time-limited improvement in such patients given the apparent independence between improvement and the assessed cognitive and volumetric variables.

Other Limitations

In addition to those discussed above, we believe it is important to clearly define the limitations of the current study. Our findings demonstrate that mnemonic strategies effectively improve memory for specific content, with comparable improvements in healthy controls and aMCI patients. At a minimum, this means that family, friends, or caregivers could help patients use the strategies to remember information that is important to them, such as the names of people at church or the location of infrequently used objects. Our ongoing studies are examining whether patients can independently use and generalize the strategies, which may require a substantially larger "dose" of training than provided in the current study. It will be important for future studies to demonstrate persistent gains using longer follow-up periods. We selected a one-month time frame because of our focus on memory for specific content. By virtually any definition, memories retained for one-month can be considered "long-term." Although tightly controlled, the current study had relatively small sample sizes so the results may not generalize to all patients with aMCI (or other MCI subtypes). Finally, it is possible that some methodological aspects (e.g., ceiling effects during testing) affected the gains in healthy controls. For this reason, future studies should assess gains using novel stimuli and measures that are not subject to ceiling effects. It is important to note, however, that ceiling effects would not have affected performance at one month, which is when the benefits of mnemonic strategies were greatest (especially in healthy controls). Despite these limitations, the current study represents a well-controlled and encouraging first-step to establishing the efficacy of mnemonic strategies in patients with aMCI.

Conclusion

The current randomized, controlled, single-blind study revealed that mnemonic strategies are superior to a matched-exposure condition both immediately after training and over the long-term (one month) regardless of whether they were administered to healthy controls or aMCI patients. Although the overall magnitude of improvement was comparable in healthy controls and aMCI patients, the mnemonic strategies did not clearly "normalize" memory test performance in aMCI patients. The severity of memory impairment and executive dysfunction as well as the size of the inferior lateral ventricles (and possibly the amygdala) may be important for determining the success of mnemonic strategies in aMCI patients. None of these factors were related to repeated-exposure based improvement for aMCI patients. Thus, it may be appropriate to employ mnemonic strategies in "mild" aMCI patients (i.e., those closer to "normal") but rehearsal-based techniques in more advanced aMCI patients (i.e., those closer to AD). We are currently examining whether patients are able to independently apply the strategies and generalize the techniques to novel material, which would be the optimal method for improving their everyday functioning.

Acknowledgments

This material is based upon work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and Rehabilitation Research and Development Service through grants B4602H & B6366W to BMH and VA Merit B6662R to KS. This work was also funded through the Emory Alzheimer's Disease Research Center (NIA: 2P50AG025688) and support to KS from the National Institutes of Health (NIH) grant K24 EY017332. This study was registered with the National Clinical Trials database (NCT00714571).

Works Cited

Acevedo A, Loewenstein DA. Nonpharmacological cognitive interventions in aging and dementia. Journal of Geriatric Psychiatry and Neurology. 2007; 20:239–249. [PubMed: 18004010]

Apostolova LG, Mosconi L, Thompson PM, Green AE, Hwang KS, Ramirez A, de Leon MJ. Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal. Neurobiology of Aging. 2010; 31(7):1077–1088. [PubMed: 18814937]

Apostolova LG, Thompson PM, Green AE, Hwang KS, Zoumalan C, Jack CR, DeCarli CS. 3D Comparison of Low Intermediate, and Advanced Hippocampal Atrophy in MCI. Human Brain Mapping. 2010; 31(5):786–797. [PubMed: 20143386]

Belleville S, Gilbert B, Fontaine F, Gagnon L, Menard E, Gauthier S. Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: Evidence from a cognitive intervention program. Dementia and Geriatric Cognitive Disorders. 2006; 22(5–6):486–499. [PubMed: 17050952]

Belleville S, Clement F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain. 2011; 134:1623–1634. [PubMed: 21427462]

Binder JR, Desai RH, Graves WW, Conant LL. Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies. Cerebral Cortex. 2009; 19(12):2767–2796. [PubMed: 19329570]

Brewer JB, Magda S, Airriess C, Smith ME. Fully-automated quantification of regional brain volumes for improved detection of focal atrophy in Alzheimer's disease. American Journal of Neuroradiology. 2009; 30:578–580. [PubMed: 19112065]

Brookmeyer R, Evans DA, Hebert L, Langa KM, Heeringa SG, Plassman BL, Kukull WA. National estimates of the prevalence of Alzheimer's disease in the United States. Alzheimers & Dementia. 2011; 7(1):61–73.

Brysbaert M, New B. Moving beyond Kucera and Francis: A critical evaluation of current word frequency norms and the introduction of a new and improved word frequency measure for American English. Behavior Research Methods. 2009; 41(4):977–990. [PubMed: 19897807]

Chua EF, Schacter DL, Rand-Giovannetti E, Sperling RA. Evidence for a specific role of the anterior hippocampal region in successful associative encoding. Hippocampus. 2007; 17:1071–1080. [PubMed: 17604351]

Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, Catanese J. Evidence-based cognitive rehabilitation: Update review of literature from 1998 through 2002. Archives of Physical Medicine and Rehabilitation. 2005; 86:1681–1692. [PubMed: 16084827]

Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, Ashman T. Evidence-Based Cognitive Rehabilitation: Updated Review of the Literature From 2003 Through 2008. Archives of Physical Medicine and Rehabilitation. 2011; 92(4):519–530. [PubMed: 21440699]

Clare L, Woods RT. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: A review. Neuropsychological Rehabilitation. 2004; 14(4):385–401.

Craik FIM. Levels of processing: Past, present…and future? Memory. 2002; 10(5/6):305–318. [PubMed: 12396643]

Craik FIM, Lockhart RS. Levels of processing: A framework for memory research. Journal of Verbal Learning and Verbal Behavior. 1972; 11:671–684.

Craik FIM, Winocur G, Palmer H, Binns MA, Edwards M, Bridges K, Stuss DT. Cognitive rehabilitation in the elderly: Effects on memory. Journal of the International Neuropsychological Society. 2007; 13:132–142. [PubMed: 17166312]

Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES, Cox NJ, Trevisan M. National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer's Disease and Cognitive Decline. NIH Consens State Sci Statements. 2010; 27(4):1–30.

Duff K, Humphreys JD, O'Bryant SE, Mold JW, Schiffer RB, Sutker PB. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. Archives of Clinical Neuropsychology. 2008; 23:603–612. [PubMed: 18639437]

Engvig A, Fjell AM, Westlye LT, Moberget T, Sundseth O, Larsen VA, Walhovd KB. Effects of memory training on cortical thickness in the elderly. Neuroimage. 2010; 52(4):1667–1676. [PubMed: 20580844]

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Scazufca M. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005; 366(9503):2112–2117. [PubMed: 16360788]

Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Dale AM. One-Year Brain Atrophy Evident in Healthy Aging. Journal of Neuroscience. 2009; 29(48):15223–15231. [PubMed: 19955375]

Folstein M, Folstein SE, McHugh PR. Mini-Mental State: A practical method for grading the cognitive status of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. [PubMed: 1202204]

Ganguli M, Snitz BE, Saxton JA, Chang CCH, Lee CW, Vander Bilt J, Petersen RC. Outcomes of mild cognitive impairment by definition. Archives of Neurology. 2011; 68(6):761–767. [PubMed: 21670400]

Gold JJ, Squire L. Quantifying medial temporal lobe damage in memory-impaired patients. Hippocampus. 2005; 15:79–85. [PubMed: 15390163]

Hampstead BM, Sathian K, Moore AB, Nalisnick C, Stringer AY. Explicit memory training leads to improved memory for face-name pairs in patients with mild cognitive impairment: Results of a pilot investigation. Journal of the International Neuropsychological Society. 2008; 14(5):883–889. [PubMed: 18764984]

Hampstead BM, Libon DJ, Moelter ST, Swirsky-Sacchetti T, Scheffer L, Platek SM, Chute D. Temporal order memory differences in Alzheimer's disease and vascular dementia. Journal of Clinical and Experimental Neuropsychology. 2010; 32(6):645–654. [PubMed: 20087810]

Hampstead BM, Stringer AY, Stilla RF, Deshpande G, Hu XP, Moore AB, Sathian K. Activation and Effective Connectivity Changes Following Explicit-Memory Training for Face-Name Pairs in Patients With Mild Cognitive Impairment: A Pilot Study. Neurorehabilitation and Neural Repair. 2011a; 25(3):210–222. [PubMed: 20935339]

Hampstead BM, Stringer AY, Stilla RF, Amaraneni A, Sathian K. Where did I put that? Patients with amnestic mild cognitive impairment demonstrate widespread reductions in activity during the encoding of ecologically relevant object-location associations. Neuropsychologia. 2011b; 49:2349–2361. [PubMed: 21530556]

Jean L, Bergeron ME, Thivierge S, Simard M. Cognitive Intervention Programs for Individuals With Mild Cognitive Impairment: Systematic Review of the Literature. American Journal of Geriatric Psychiatry. 2010; 18(4):281–296. [PubMed: 20220584]

Kaschel R, Della Sala S, Cantagallo A, Fahlbock A, Laaksonen R, Kazen M. Imagery mnemonics for the rehabilitation of memory: A randomised group controlled trial. Neuropsychological Rehabilitation. 2002; 12(2):127–153.

Kessels RPC, Feijen J, Postma A. Implicit and explicit memory for spatial information in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2005; 20(2–3):184–191. [PubMed: 16088143]

Kondo Y, Suzuki M, Mugikura S, Abe N, Takahashi S, Iijima T, Fujii T. Changes in brain activation associated with use of a memory strategy: A functional MRI study. Neuroimage. 2005; 24:1154–1163. [PubMed: 15670693]

Larsen DP, Butler AC, Roediger HL. Repeated testing improves long-term retention relative to repeated study: a randomised controlled trial. Medical Education. 2009; 43(12):1174–1181. [PubMed: 19930508]

Lezak, MD.; Howieson, DB.; Loring, DW. Neuropsychological Assessment. 4th ed.. New York, NY: Oxford University Press; 2004.

Li HJ, Li JA, Li NX, Li B, Wang PY, Zhou T. Cognitive intervention for persons with mild cognitive impairment: A meta-analysis. Ageing Research Reviews. 2011; 10(2):285–296. [PubMed: 21130185]

Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. Cochrane Databaase of Systematic Reviews. 2011; (1) Art. No.: CD006220.

Mayes A, Montaldi D, Migo E. Associative memory and the medial temporal lobes. TRENDS in Cognitive Sciences. 2007; 11(3):126–135. [PubMed: 17270487]

Miotto EC, Savage CR, Evans JJ, Wilson BA, Martins MGM, Iaki S, Amaro E. Bilateral activation of the prefrontal cortex after strategic semantic cognitive training. Human Brain Mapping. 2006; 27:288–295. [PubMed: 16082657]

Moscovitch M, Craik FIM. Depth of processing, retrieval cues, and uniqueness of encoding as factors in recall. Journal of Verbal Learning and Verbal Behavior. 1976; 15:447–458.

Oswald WD, Rupprecht R, Cunzelmann T, Tritt K. The SIMA-project: Effects of 1 year cognitive and psychomotor training on cognitive abilities of the elderly. Behavioural Brain Research. 1996; 78:67–72. [PubMed: 8793039]

Petersen RC. Mild cognitive impairment as a diagnostic entity. Journal of International Medicine. 2004; 256:183–194.

Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. Journal of Gerontology. 1982; 37:323–329. [PubMed: 7069156]

Postma A, Kessels RPC, van Asselen M. How the brain remembers and forgets where things are: The neurocognition of object-location memory. Neuroscience and Biobehavioral Reviews. 2008; 32(8):1339–1345. [PubMed: 18562002]

Ramos-Estebanez C, Moral-Arce I, Gonzalez-Mandly A, Dhagubatti V, Gonzalez- Macias J, Munoz R, Hernandez-Hernandez JL. Vascular cognitive impairment in small vessel disease: clinical and neuropsychological features of lacunar state and Binswanger's disease. Age and Ageing. 2011; 40(2):175–180. [PubMed: 21239411]

Randolph, C. Repeatable battery for the assessment of neuropsychological status manual. San Antonio: The Psychological Corporation; 1998.

Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging & Mental Health. 2002; 6(1):5–11. [PubMed: 11827617]

Steenland NK, Auman CM, Patel PM, Bartell SM, Goldstein FC, Levey AI, Lah JJ. Development of a rapid screening instrument for mild cognitive impairment and undiagnosed dementia. Journal of Alzheimer's Disease. 2008; 15(3):419–427.

Strauss, E.; Sherman, EMS.; Spreen, O. A Compendium of Neuropsychological Tests (3rd ed.). New York, NY: Oxford University Press; 2006.

Stringer, AY. Ecologically-oriented Neurorehabilitation of Memory Therapist Manual. Los Angeles, CA: Western Psychological Services; 2007.

Stringer AY. Ecologically-oriented neurorehabilitation of memory: Robustness of outcome across diagnosis and severity. Brain Injury. 2011; 25(2):169–178. [PubMed: 21219089]

Stott J, Spector A. A review of the effectiveness of memory interventions in mild cognitive impairment (MCI). International Psychogeriatrics. 2011; 23(4):526–538. [PubMed: 20946704]

Tse CS, Balota DA, Roediger HL. The benefits and costs of repeated testing on the learning of face-name pairs in healthy older adults. Psychology and Aging. 2010; 25(4):833–845. [PubMed: 20718541]

Unverzagt FW, Kasten L, Johnson KE, Rebok GW, Marsiske M, Koepke KM, Tennstedt SL. Effect of memory impairment on training outcomes in ACTIVE. Journal of the International Neuropsychological Society. 2007; 13(6):953–960. [PubMed: 17942013]

Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training - a meta-analytic study. Psychology and Aging. 1992; 7(2):242–251. [PubMed: 1535198]

Wenisch E, Cantegreil-Kallen I, DeRotrou J, Garrigue P, Moulin F, Batouche F, Rigaud AS. Cognitive stimulation intervention for elders with mild cognitive impairment compared with normal aged subjects: preliminary results. Aging Clinical and Experimental Research. 2007; 19:316–322. [PubMed: 17726363]

Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, Wright E. Long-term effects of cognitive training on everyday functional outcomes in older adults. Journal of the American Medical Association. 2006; 296(23):2805–2814. [PubMed: 17179457]

Wilson, BA. Memory Rehabilitation Integrating Theory and Practice. New York: The Guilford Press; 2009.

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale - A preliminary report. Journal of Psychiatric Research. 1983; 17(1):37–49. [PubMed: 7183759]

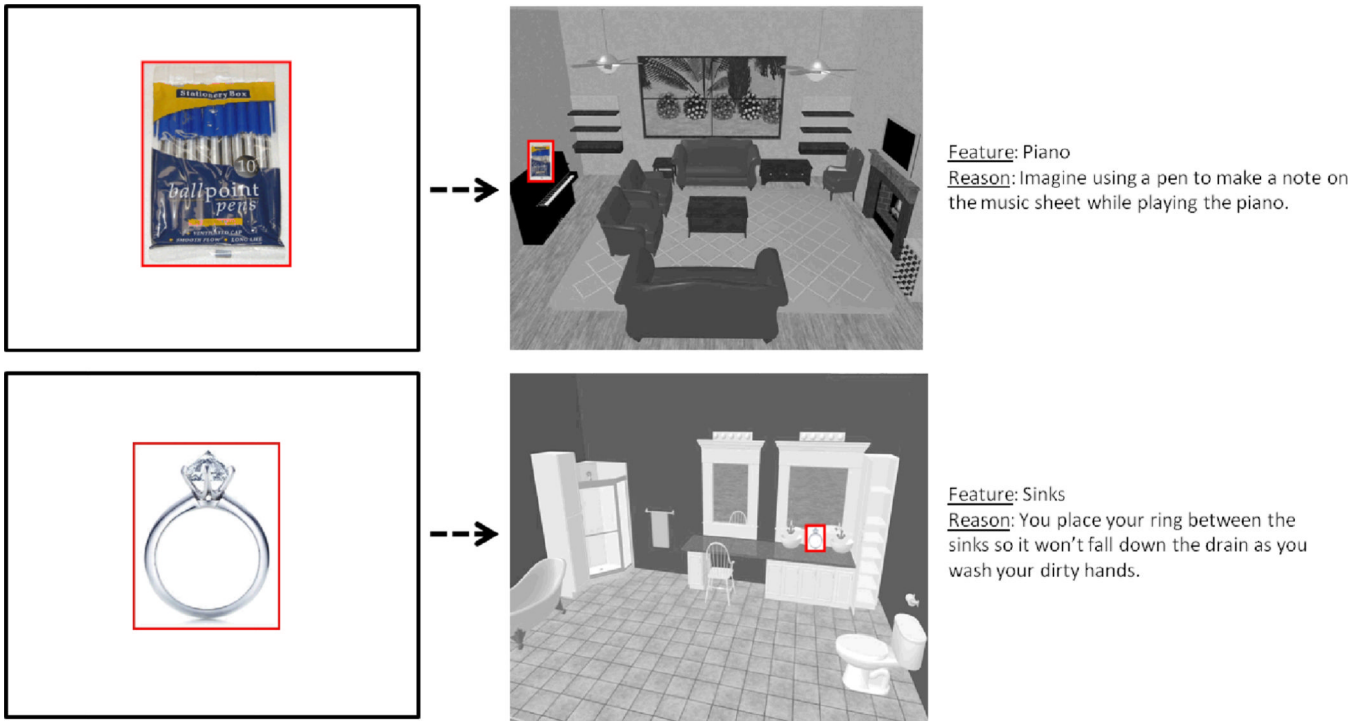

Figure 1.
Examples of stimuli and the mnemonic cues. Participants in the exposure group learned the same stimuli, but did not receive the mnemonic cues.

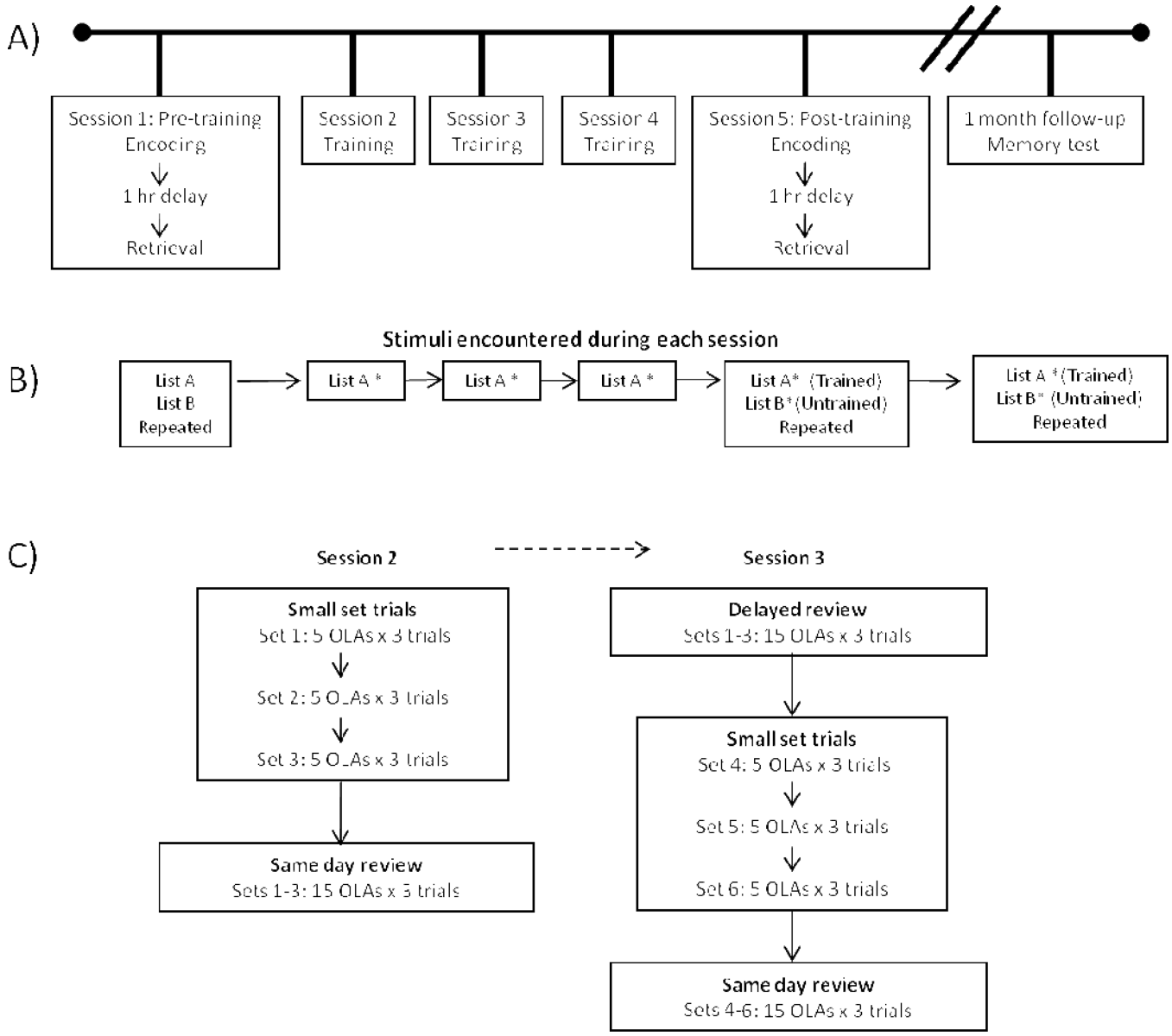

Figure 2.

(A) Basic study design. Sessions 1–5 were completed within a 2 week period of time. In general, 2–3 days elapsed between each of these 5 sessions. Training occurred during sessions 2–4, each of which was approximately 60–90 minutes long. (B) Stimulus lists seen during each session. In this example, List A was the "trained list" and list B was the "untrained list". * denotes that the trained list was counterbalanced across participants. (C) The 45 OLAs in Lists A and B were subdivided into 9 sets of 5. Patients learned a total of 15 novel OLAs each session, initially as small sets (3 trials each), then reviewed the stimuli during the same day review (3 trials). They began the next session with a review of stimuli from the previous session (delayed review; 3 trials).

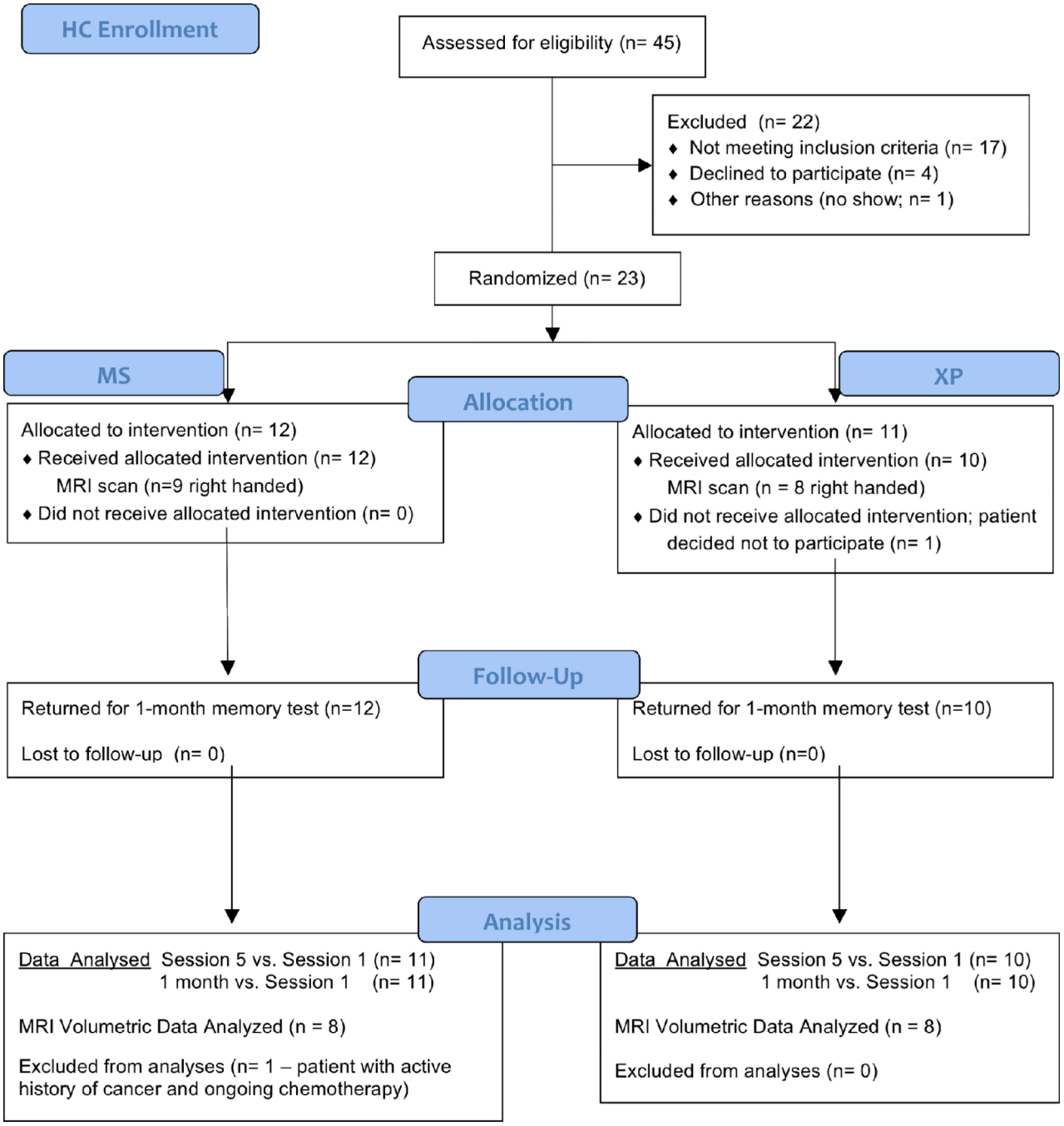

Figure 3.
CONSORT flow chart for the healthy control (HC) groups.

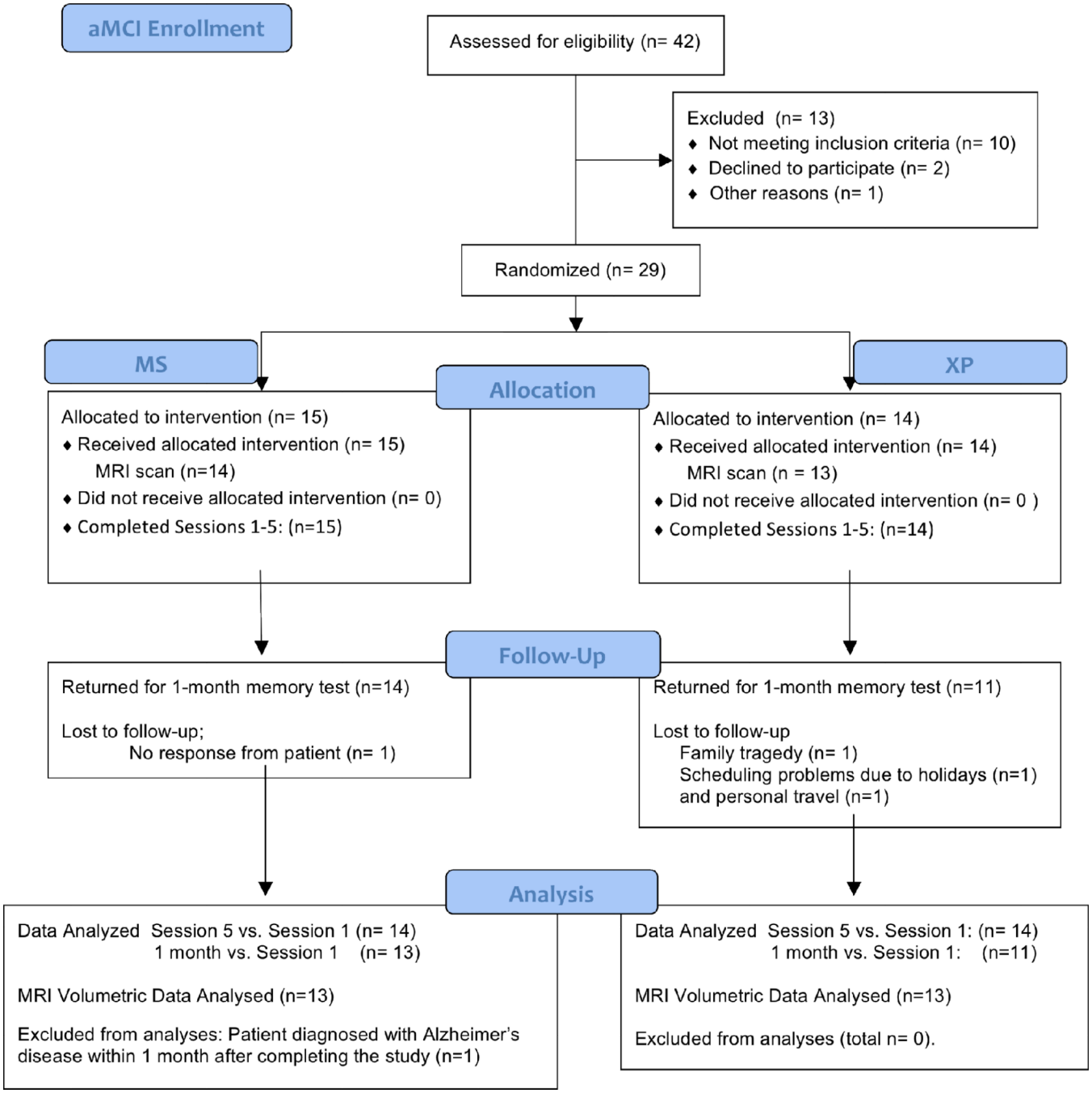

Figure 4.
CONSORT flow chart for the aMCI groups.

Table 1

Demographic, baseline neuropsychological test results, and volumetric analyses for the healthy control and aMCI groups.

	Healthy Controls		aMCI		Main Effect of Diagnosis	Main Effect of Intervention	Diagnosis × Intervention	Post-hoc Contrasts
	MS (n=11) *M (SD)*	XP (n=10) *M (SD)*	MS (n=14) *M (SD)*	XP (n=14) *M (SD)*	*F*(1,45)=	*F*(1,45)=	*F*(1,45)=	
Age (years)	73.2 (7.7)	72.5 (6.8)	73.5 (10.1)	70.5 (5.8)	0.14, *p*=.712	0.66, *p* =.420	0.26, *p*=.611	
Education (years)	16.1 (3.4)	16.4 (2.0)	17.2 (2.2)	16.1 (2.4)	0.34, *p* =.563	0.26, *p* =.610	0.86, *p* =.358	
MMSE (raw score)	28.2 (1.5)	27.7 (2.2)	26.9 (1.8)	26.1 (2.1)	**6.62, *p* = .013**	1.14, *p*=.291	0.04, *p* =.837	
RBANS Indices (Standard Scores)								
Immediate Memory	103.4 (12.9)	107.3 (13.8)	85.7 (12.3)	81.6 (16.8)	**28.01, *p* <.001**	0.00, *p* = .987	0.96, *p* =.333	
Visuospatial/construction	94.1 (13.7)	104.4 (13.3)	94.8 (18.5)	90.3 (12.5)	2.44, *p*=.126	0.46, *p*=.503	2.97, *p* =.092	
Language	103.2 (12.8)	103.3 (17.6)	95.3 (7.9)	91.5 (6.2)	**9.11, *p* = .004**	0.32, *p*= .577	0.36, *p* =.553	
Attention	107.8 (13.0)	109.5 (11.5)	103.1 (15.3)	102.1 (14.7)	2.23, *p*=.143	0.01, *p*=.933	0.11, *p*=.741	
Delayed Memory	103.5 (8.8)	104.9 (10.0)	72.1 (16.6)	70.4 (15.0)	**71.66, *p* <. 001**	0.00, *p*=.971	0.15, *p* =.702	
Total Score	103.0 (12.8)	108.8 (15.2)	87.1 (13.9)	82.8 (10.1)	**31.26, *p* <. 001**	0.37, *p*=.848	1.84, *p*=.182	
Trails A (T-scores)	48.7 (9.0)	48.8 (7.6)	41.8 (7.2)	46.2 (14.4)	2.56, *p*=.115	0.58, *p* =.452	0.54, *p* =.467	
Trails B (T-scores)	45.7 (12.8)	50.5 (8.5)	48.2 (7.8)	43.2 (8.3)	0.78, *p* =.382	0.00, *p* =.967	3.23, *p* =.079	
GDS (raw scores)	1.6 (2.1)	0.7 (1.3)	1.7 (2.0)	2.3 (2.0)	2.27, *p*=.139	0.11, *p*=.743	1.87, *p*=.179	
FAQ (raw scores)	0.5 (0.8)	0.0 (0)	3.1 (3.7)	4.4 (3.8)	**17.97, *p* < .001**	0.26, *p* =.616	1.12, *p*=.296	
Brain Volume (% ICV)	(n=8)	(n=8)	(n=13)	(n=13)	*F*(1,38)=	*F*(1,38)=	*F*(1,38)=	
Cortical gray matter	29.6 (2.17)	30.6 (2.0)	28.9 (1.74)	29.1 (1.89)	3.29, *p* =.078	0.93, *p*=.341	0.40, *p* =.531	
Lateral ventricles	2.06 (0.69)	2.34 (0.83)	2.81 (1.15)	2.80 (0.94)	3.92, *p* =.055	0.18, *p*=.671	0.28, *p* =.603	
Inferior lateral ventricles	0.15 (0.04)	0.17 (0.05)	0.22 (0.08)	0.19 (0.05)	**4.90, *p* = .033**	0.34, *p* =.566	1.66, *p* =.205	
Hippocampus	0.50 (0.06)	0.48 (0.05)	0.43 (0.06)	0.48 (0.04)	**4.25, *p* = .046**	0.35, *p* =.560	**4.11, *p* = .050**	#l, *p*=.038
Amygdala	0.23 (0.02)	0.23 (0.03)	0.19 (0.05)	0.22 (0.03)	**4.43, *p* = .042**	1.73, *p*=.197	3.05, *p*=.089	

Brain volumetrics are provided in percent of intracranial volume (% ICV). Post-hoc contrasts (Bonferroni corrected): #1 = healthy control MS > aMCI MS. MS = Mnemonic strategy group; XP = Exposure group; MMSE = mini-mental state exam; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GDS = Geriatric Depression Scale; FAQ = Functional Activities Questionnaire.

Table 2

Group averages for the post-training questionnaire that used a visual analogue scale where 0 = not at all, 5 = somewhat, 10 = extremely.

	HC MS *M (SD)*	**HC XP** *M (SD)*	**aMCI MS** *M (SD)*	**aMCI XP** *M (SD)*	$F_{3,42}$	**p-value**
1) How useful was the training?	8.4 (1.9)	6.8 (2.8)	8.3 (1.9)	7.9 (2.2)	1.0	.39
2) How much do you feel the training improved your memory?	8.1 (1.6)	6.5 (2.1)	7.3 (2.4)	6.9 (2.4)	0.9	.46
3) How likely are you to use these strategies in your everyday life?	8.6 (2.1)	6.1 (2.5)	7.2 (2.9)	7.8 (2.1)	1.7	.17
4) How likely would you be to do a similar study?	9.4 (1.2)	7.3 (3.0)	7.6 (3.2)	8.5 (1.9)	1.3	.30
5) How likely would you be to refer a friend or family member for this study?	9.8 (0.7)	8.1 (1.5)	8.5 (2.2)	8.8 (1.5)	1.6	.21
6) How friendly was our staff (How well did we treat you)?	10 (0)	9.9 (0.3)	9.9 (0.3)	10 (0)	0.6	.62
7) How would you rate your overall experience in the study?	10 (0)	8.4 (2.6)	9.2 (2.2)	9.2 (0.9)	1.2	.34

Note: HC = healthy control; MS = Mnemonic strategy group; XP = Exposure group

Table 3

Primary and secondary outcome variables by training group.

	HC MS *M (SD)*	HC XP *M (SD)*	aMCI MS *M (SD)*	aMCI XP *M (SD)*
Trained List				
Accuracy (percent correct)				
Pre-training	53.9 (10.2)	48.9 (14.5)	37.6 (15.0)	37.3 (8.7)
Post-training	97.0 (4.0)	92.0 (6.9)	82.5 (14.7)	71.4 (13.2)
1 month	85.3 (10.1)	63.3 (13.7)	65.1 (17.8)	45.8 (8.3)
Immediate Improvement	93.3 (10.25)	84.3 (11.58)	74.0 (21.22)	54.8 (18.53)
95% confidence interval	[83.13, 103.44]	[73.66, 94.95]	[64.97, 82.97]	[45.79, 63.78]
Long-term Improvement	70.1 (15.74)	18.73 (49.71)	43.0 (27.90)	10.6 (16.68)
95% confidence interval	[51.87, 88.37]	[−0.42, 37.87]	[26.24, 59.81]	[−7.68, 28.83]
Untrained List				
Accuracy (percent correct)				
Pre-training	54.9 (13.7)	48.9 (14.7)	37.0 (10.4)	33.7 (9.3)
Post-training	77.8 (19.1)	71.3 (14.0)	43.3 (16.2)	45.4 (11.6)
1 month	51.3 (12.3)	45.3 (8.4)	33.9 (8.0)	33.3 (4.7)
Immediate Improvement	57.0 (31.86)	45.02 (18.77)	10.7 (23.40)	17.9 (14.00)
95% confidence interval	[43.25, 70.70]	[30.63, 59.42]	[−1.46, 22.87]	[5.69, 30.02]
Long-term Improvement	−16.4 (50.42)	−12.8 (27.37)	−6.5 (12.62)	0.1 (10.47)
95% confidence interval	[−34.28, 1.39]	[−31.55, 5.87]	[−22.93, 9.87]	[−17.73, 17.94]
Training Session Accuracy				
Small sets (of 5)	100 (0)	95.5 (6.1)	89.5 (16.7)	78.0 (14.5)
Same day review	99.9 (0.3)	92.4 (10.9)	89.0 (19.3)	77.0 (16.3)
Delayed review	99.9 (0.2)	90.3 (11.9)	90.0 (14.0)	72.1 (17.4)

Note: HC = healthy control; MS = Mnemonic strategy group; XP = Exposure group

Table 4

Correlation results between Immediate improvement and neuropsychological variables and medial temporal lobe volumetrics.

	All MS (HC & aMCI)	HC MS	aMCI MS	All XP (HC & aMCI)	HC XP	aMCI XP
RBANS DMI	**.68 (<.001)**	.44 (.18)	**.67 (.009)**	**.68 (<.001)**	.41 (.24)	.14 (.65)
Trails B/A	.07 (.74)	−.02 (.96)	**.57 (.03)**	−.04 (.85)	−.08 (.83)	−.22 (.45)
ILV	**−.75 (<.001)**	−.4 (.33)	**−.81 (.001)**	−.28 (.22)	−.64 (.09)	.16 (.6)
Hippocampus	.35 (.12)	.02 (.97)	.25 (.42)	.26 (.26)	.57 (.14)	.2 (.5)
Amygdala	**.54 (.01)**	.04 (.93)	*.55 (.051)*	.12 (.61)	.66 (.07)	−.19 (.54)

Spearman's rho correlations with p-values in parentheses. HC = healthy control; MS = Mnemonic strategy group; XP = Exposure group ILV = inferior lateral ventricles.