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Depressive Symptoms and Memory Performance among Older Adults: Results from the ACTIVE Memory Training Intervention

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Abstract

Background—Cognitive performance benefits from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study may differ for individuals who exhibit a greater number of depressive symptoms.

Methods—Using data from ACTIVE memory training and control conditions, we evaluated the effect of depressive symptomatology on memory scores across a five-year period. Of 1,401 participants, 210 had elevated depressive symptoms at baseline, as measured by a 12-item version of the Center for Epidemiological Studies-Depression Scale (CES-D).

Results—Participants with elevated depressive symptoms scored significantly lower at baseline and had faster decline in memory performance than those exhibiting fewer depressive symptoms. Memory score differences among depressive symptom categories did not differ between training conditions.

Discussion—Findings suggest that elevated depressive symptoms may predict declines in memory ability over time, but do not attenuate gains from training. Training provides a potential method of improving memory which is robust to effects of depression.

Keywords

depressive symptoms; memory; memory training; aging

Introduction

Normal aging is associated with decline in a number of cognitive ability domains including memory, abstract reasoning, and processing speed (Hedden & Gabrieli, 2004). Memory in particular is vulnerable to aging. Both healthy aging and pathologic aging are associated with decline in some but not all aspects of memory. For instance, episodic and working memory abilities may show steep declines with age, whereas semantic and other memory abilities can remain relatively unimpaired (Craik, 2008). Differences suggest that memory ability is not a singular cognitive phenomenon but a group of inter-related diverse processes.

Likewise, memory ability is related with and dependent on other cognitive abilities such as attention and executive functions which are vulnerable to decline in late life (Craik, 2008).

In addition, cognitive impairments in older adults – including memory deficits – are associated with elevated levels of depressive symptoms as seen in major depressive disorder. Numerous studies have demonstrated that major depression and elevated depressive symptoms are risk factors for dementia, cognitive decline, and specifically memory loss, but the mechanisms driving this association are unclear (Burt, Zembar, & Niederehe, 1995; Jorm, 2000, 2001). Depression may be a reaction to early signs of cognitive decline, a prodrome of dementia, a causal factor in the progression and onset of cognitive decline, or a factor influencing the diagnosis of cognitive decline (Gabryelewicz et al., 2007; Jorm, 2000). Furthermore, as it is thought that depressive symptoms most associated with risk of dementia might be ‘motivational symptoms’ such as lack of interest, loss of energy, and concentration difficulties, the relationship between depression and cognitive decline may be reinforced by differential ability to access or learn compensatory cognitive strategies (Jorm, 2001).

The proportion of older adults in the population is expected to grow significantly, and with this growth the prevalence of dementia and milder forms of cognitive impairment will also increase (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). This growth will create significant social and economic strain in terms of care-giving (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007) as well as considerable impact on quality of life (Alexopoulos, 2005). Interventions which can produce even modest delays in the onset of dementia can reduce the prevalence and thus the social burden of dementia.

Cognitive training is a non-pharmacologic intervention that is being studied as a means of altering cognitive and functional trajectories to improve quality of life for older adults. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study randomized community-dwelling, older adults to receive training in one of three separate cognitive capacities (memory, reasoning and processing speed), or to a control condition, to evaluate the effect of cognitive training on declines in these domains, and to delay or prevent associated functional deficits (Ball et al., 2002; Jobe et al., 2001). Prior analyses from ACTIVE provide evidence for beneficial effects of cognitive training. ACTIVE participants trained in mnemonic strategies, reasoning, and processing speed performed better in those respective areas (Ball et al., 2002), and those trained in reasoning showed significantly less difficulty in instrumental activities of daily living (IADL) (Willis et al., 2006).

Previous research suggests individuals respond in different ways to cognitive training within the ACTIVE memory training program, but these studies have focused on demographic and cognitive predictors of treatment response, showing for instance that memory-impaired individuals respond less to memory training (Langbaum, Rebok, Bandeen-Roche, & Carlson, 2009; Unverzagt et al., 2007). Prior research has not investigated how elevated depressive symptoms might predict memory ability or responsiveness to training programs.

The current study had two main objectives: (1) to determine whether elevated depressive symptoms at baseline are associated with decreased memory ability and longitudinal memory trajectories, confirming prior studies; and (2) to ascertain whether elevated depressive symptoms influence responsiveness to memory training. The a priori hypotheses were that participants with elevated depressive symptoms have lower baseline memory scores and benefit less from memory training than those without elevated symptoms, suggesting a moderating effect of depression on training gains and memory scores over time. We expected to find that depressed participants overall would have lower baseline

memory scores and steeper temporal declines, and that the memory differences between those with and without elevated symptoms of depression would be greater among memory-trained individuals than among controls.

Methods

Design and Participants

The ACTIVE study is a randomized, controlled, single-blind trial of cognitive training among community-dwelling older adults (Ball et al., 2002; Jobe et al., 2001). Detailed inclusion criteria and recruitment procedures for ACTIVE are described elsewhere (Jobe et al., 2001). Briefly, the study population at baseline consisted of 2,802 participants aged 65 to 94 years (mean 73.6 years) selected from six university-based sites across the United States. As described previously, participants were recruited using different methods and from different sources for each ACTIVE study site (Jobe et al., 2001). Participants were eligible for inclusion if they were at least 65 years old, had no serious cognitive deficits (characterized by a Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score below 23), and had no self-reported functional declines and no medical conditions predictive of imminent functional or physical decline.

The present study used data from participants randomized to the memory training ($n = 703$) and no-contact control ($n = 698$) groups. Memory training consisted of ten 60- to 75-minute instructor-led sessions offered over a 6-week period. Participants in the memory training group were taught mnemonic strategies, including categorization, visualization, association, and the method of loci to improve episodic memory. They received verbal feedback on their performance and practice tests of episodic memory ability at the end of each training session.

Measures

Memory variables at six time points were analyzed: baseline, immediate post-training, and four follow-up assessment waves (1, 2, 3, and 5 years post-training). Measures from two memory tests were considered: the Hopkins Verbal Learning Test (HVLT) (Brandt, 1991) and the Rey Auditory Verbal Learning Test (AVLT) (Rey, 1941). The basic design and administration of both tests are similar: respondents are read lists of words from an audiotape with a two-second pause between words, and in a modification for group administration, are then allowed two minutes to write down as many words as they could recall. This process was repeated across three (HVLT) or five (AVLT) recall trials. The HVLT and AVLT total recall scores were the sum of three recall trials and five recall trials, respectively. Recognition tasks are also similar between the HVLT and AVLT in that participants are asked to identify target words presented during the recall trials among distracting words. Recognition discrimination scores are the difference between the number of true positive recognitions (i.e., correctly identifying target words) and the number of false positive recognitions (i.e., incorrectly identifying distractor words). Both the HVLT and AVLT contain separate recall and recognition trials as well as alternate test forms, making them optimal for longitudinal research. Because alternate but nonequivalent forms were used at each time point, scores for each of these tests were adjusted using an equipercentile equating procedure (Kolen & Brennan, 1995).

Self-reported depressive symptoms were measured using the 12-item version of the Center for Epidemiological Studies-Depression scale (CES-D) (Ross, Mirowsky, & Huber, 1983). The CESD-12 asks respondents to rate levels of depressive symptoms on a four-level ordinal scale: *rarely or none of the time*, *some of the time*, *much of the time*, and *most or all of the time*. The distribution of CESD-12 total scores could range from 0 (no depressive

symptoms) to 36 (most or all of the time for all items). The CESD-12 was designed to assess depressive symptomatology, and is not a substitute for clinical diagnosis of major depression. A baseline CES-D cutoff score of 9 or more points was used to indicate elevated depressive symptoms. We used this criterion based on prior studies which found it to be comparable to cutoff scores in longer versions of the CES-D which agreed well with interview assessment of depression (Beekman et al., 1995; Kohout, Berkman, Evans, & Cornoni-Huntley, 1993). Furthermore, as others have noted, a CESD-12 score of 9 represents approximately 26% of the maximum symptom score, similar to the better-validated criterion used in the longer, 20-item CES-D versions (Wolinsky et al., 2009).

Analysis

For analysis, 703 participants in the memory-trained group and 698 participants in the control group were categorized by level of depressive symptoms (CESD-12 score < 9 vs. 9) at baseline. Baseline demographic characteristics of the memory and control groups by depressive symptom status are shown in Table 1. Participants who had elevated depressive symptoms were considered the 'depressed' group in the study analysis although this categorization is not meant to indicate a clinical diagnosis of major depression.

To evaluate the hypothesis of a depression effect on memory scores, longitudinal random-effects regression models were fit to data from memory-trained and control groups accounting for correlations between memory scores measured on the same individuals over multiple time points (Laird & Ware, 1982). Mixed-effects models use all available information from subjects, not only those who completed all follow-up measurements. Estimates from mixed-effects models are robust to missing data assuming that missing data depends only on covariates included in the model or that the likelihood of dropout depends only on past values of the outcome (Gibbons, Hedeker, & DuToit, 2010). The outcomes of interest in each model were mean HVLT and AVLT recall and recognition discrimination scores. Along with main effects for time, depressive symptom score, and interactions between depressive symptom score and each time point, the model was adjusted for age (years), sex, race (White/non-White), education (years), and global cognition measured by the MMSE (Folstein et al., 1975). Interaction terms between depression and time were used to determine whether cognitive outcomes differed as a function of depression and transition between measurement time points. Three-way interactions of measurement time, depressive symptom score, and treatment group were also fit in the model to assess whether the association between depressive symptoms and memory over time differed between memory training and control groups. All analyses were repeated separately by ACTIVE recruitment site.

Results

Approximately one quarter of memory-trained and control participants had CES-D scores greater than or equal to 9 at baseline, corresponding to moderate or severe levels of depressive symptoms (Table 1). Compared to participants without elevated depressive symptoms, individuals with elevated symptoms were significantly older, less educated, and had lower MMSE scores in both the memory-trained and control groups. Overall, participants had an average of 4.4 memory measurements from the maximum of six. Those with elevated depressive symptoms at baseline were more likely to be lost to follow-up. For instance, approximately 30% of participants with elevated depressive symptoms at baseline were lost to follow-up by the first annual measurement compared to 22% of those without elevated symptoms. The difference in attrition between depressive symptom groups was consistent across all follow-up waves. Among control group participants, those with elevated symptoms of depression were significantly more likely to be females. Control

group participants did not differ significantly from memory-trained participants in terms of age, sex, race, education, global cognition (MMSE), or depression status.

Longitudinal associations between depressive symptoms and recall memory

Figure 1 displays mean HVLT and AVLT recall scores among memory-trained and control participants with ($n = 146$) and without ($n = 557$) elevated depressive symptoms over six visits. Regression coefficients from covariate-adjusted and unadjusted random-effects models are provided in Table 2. Combining memory-trained and control participants, those with elevated depressive symptoms performed significantly lower on HVLT recall at the baseline visit, with a mean score 1.18 points ($p < .001$) lower than non-depressed participants when adjusted for age, sex, race, education, and global cognition (Table 2). There were also significant main effects at certain measurement points on mean HVLT scores. At the immediate post-test measurement, the mean score coefficient was slightly positive ($\beta = 0.35$, $p = .008$), but there was a significant negative coefficient for the fifth annual assessment ($\beta = -1.20$, $p < .001$), suggesting that, compared to baseline, overall scores increased just after training and then declined at later measurements. For the HVLT recall score, only the interaction from the third annual measurement time was significant ($\beta = -1.11$, $p = .007$; Table 2), suggesting lower memory in the elevated depressive symptoms group compared to non-depressed participants at this time point. Differences in HVLT sum of recall between depression categories were also significant when considering memory-trained and control groups separately (Figure 1).

For AVLT sum of recall scores, the effect of elevated depressive symptoms was similar to HVLT. The baseline deficit of recall scores for those with elevated depressive symptoms was evident among both memory-trained and control participants (Figure 1). Combining participants from both training conditions, those with elevated depressive symptoms had a mean score 2.37 points below participants without elevated symptoms ($p = .001$) when adjusted for covariates. Furthermore, there were significant main effects for all but the third assessment time, indicating a trend of increasing scores immediately after training followed by decreasing mean scores at annual assessments, also similar to HVLT. Coefficient estimates of interactions between depressive symptom level and measurement time were significant at the first annual ($\beta = -1.69$, $p = .004$) and fifth annual ($\beta = -1.65$, $p = .036$) follow-up times, indicating that mean memory scores for participants with elevated depressive symptoms decreased more relative to baseline at these times than scores for participants without elevated symptoms. Interaction terms at the second and third annual measurement times were also marginally significant ($\beta = -1.21$, $p = .055$ and $\beta = -1.21$, $p = .081$, respectively), suggesting a trend of lower recall sum scores over time in the group with elevated depressive symptoms. As with the HVLT recall sum totals, each interaction term was negative, implying steeper declines in memory scores over time among individuals with elevated depressive symptoms.

Although comparisons of mean trajectories by training and depressive symptom group in Figure 1 indicate that the relationship between recall memory and depression differs between training conditions, three-way interaction terms between depression category, measurement time, and training group were not statistically significant and so do not confirm this inference (Table 4).

Longitudinal associations between depressive symptoms and recognition memory

Results of the longitudinal regression of recognition discrimination scores from the HVLT are shown in Figure 2. Coefficient estimates from adjusted and unadjusted models are provided in Table 3. Combined across both memory-trained and control group participants, there were significant differences between depression categories in HVLT recognition

discrimination memory. At baseline, those with elevated depressive symptoms scored 0.18 points ($\beta = 0.18$, $p = .039$) below those without elevated symptoms. The fifth annual time by depressive level interaction term was significant ($\beta = -0.39$, $p = .020$); and marginally significant at the first ($\beta = -0.22$, $p = .069$) and third ($\beta = -0.23$, $p = .095$) annual assessments. Similar to recall memory scores, interaction terms between time and depressive status for HVLTL discrimination were consistently negative, indicating steeper declines in discrimination scores among those with elevated depressive symptoms.

Model results using AVLT recognition discrimination memory scores were different than those using the HVLTL. Combining memory-trained and control groups, participants with elevated depressive symptoms scored significantly lower at baseline than non-depressed participants, 1.19 points ($p < .001$) lower on average. Unlike results from the HVLTL, interaction terms for depression and measurement time were not consistent in their effect direction at all time-points (Table 3).

Interactions between depressive symptom level, measurement time indicators, and training group were not significant for HVLTL recognition memory scores; however, there was a trend in the negative direction for all measurement point coefficients in the adjusted model (Table 4), indicating faster decline in mean discrimination among participants in the memory training group with higher depressive symptom scores, relative to those with lower depressive symptom scores. With regard to AVLT discrimination scores, two interaction terms corresponding with the first annual ($\beta = -2.07$, $p = .003$) and fifth annual ($\beta = -1.58$, $p = .052$) measurements were significant or marginally significant. The significant terms indicate that at these time points relative to baseline, the negative difference between those with elevated symptoms of depression and those without was greater among the memory-trained participants than among the control participants.

To assess the potential influence of different recruitment procedures among ACTIVE study sites, all analyses were repeated separately by site. Compared to overall results, there were no substantial differences in the direction and magnitude of associations between depressive symptoms and memory over time.

Discussion

The present study investigated the effect of depressive symptoms on memory and memory training in independently living older adults. We found that baseline verbal recall memory was significantly lower among individuals with clinically significant depressive symptoms (CES-D ≥ 9), after adjustment for demographic characteristics. The magnitude of this association was similar for AVLT and HVLTL sum of recall measures. Furthermore, the differences between depressive symptom groups appeared to increase over time, as individuals with elevated depressive symptoms scored significantly lower at certain annual measurements relative to baseline than those without elevated depressive symptoms. However, despite a clear association between depressive symptoms and recall memory, we found that depressive symptoms were not significantly associated with the effect of memory training. In other words, both those with and without elevated depressive symptoms appear to benefit to the same extent from memory training.

A notable conclusion from these data regards the longitudinal relationship between memory, memory training, and depression. Interaction terms between these characteristics inform whether training results differ between depression categories. Interaction coefficients between depression, training (memory-training vs. control), and time for both AVLT and HVLTL recall sum scores were not statistically significant. This means that differences in recall between those with and without elevated depressive symptoms in the memory-trained

group did not differ relative to the same differences between depressive symptom categorizations in the control group at any study visit. In addition to memory, depression is associated with deficits in attention, processing speed, and executive control processes which are also important in learning new things, especially among older adults (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008; Reppermund, Ising, Lucae, & Zihl, 2009). So, if depressive symptoms at baseline prevented participants from learning memory strategies as a result of inattentiveness, processing, or some other mechanism, the memory score difference between those with and without elevated depressive symptoms would likely be greater among memory-trained than control individuals after training. Instead, participants from the present study with elevated depressive symptoms benefited to similar extents from memory training, implying that the depressive symptoms do not attenuate the effect of training. In light of these findings, it is evident that cognitive training benefits are not differential with respect to depressive category at the time of training, and can thus be an important preventative measure regardless of depressive symptomology. In fact, given the association of elevated depressive symptoms with decreased recall memory, cognitive training might be especially important for those *with* elevated depressive symptoms or depression.

The overall deficit in recall memory among individuals with elevated depressive symptoms found in this study is also consistent with previous research showing impaired recall among older adults with clinical depression (Burt et al., 1995). Furthermore, our results suggest that elevated depressive symptoms are associated with a higher rate of memory loss and perhaps a more general process of underlying decline as has been suggested by other studies (Gabryelewicz et al., 2007; Jorm, 2000; Reppermund et al., 2009). Memory deficits at baseline might therefore reflect declines which occurred in depressed participants prior to the ACTIVE study; however, the current data demonstrate that decline in memory scores cannot be explained entirely by effects prior to training, because recall scores among participants with elevated depressive symptoms continued to decline more during the study period relative to those without elevated symptoms.

From a theoretical standpoint, results are not consistent with the hypothesis of a differential effect of depression on recall and recognition memory. HVLT and AVLT recognition discrimination was significantly lower among depressed participants, indicating the association between depressive symptoms and memory deficits is not unique to recall memory as hypothesized. One explanation for these results is that scores from the HVLT and AVLT are not calibrated to detect differences between recall and recognition memory. The HVLT, designed to be a relatively brief instrument to administer, could be limited in range of response (Benedict, Schretlen, Groninger, & Brandt, 1999; Gross, Rebok, Unverzagt, Willis, & Brandt, 2011a, 2011b). For instance, 33% of participants from ACTIVE, a cognitively healthy sample, scored perfectly on the HVLT recognition discrimination task at baseline. Alternatively, the AVLT has a larger range and might therefore be more sensitive to memory differences between depression categories. To our knowledge, this hypothesis has not been empirically tested and is speculative; however, qualitative features suggest the AVLT is more difficult than the HVLT because it contains a longer list of words and more trials (Brandt, 1991; Rey, 1941).

Our findings have several important implications for research and theory of cognitive training. First, depression appears to attenuate participants' performance on recall memory tasks. Because verbal memory tests like the HVLT can predict changes in everyday functional status (Gross et al., 2011a, 2011b) and dementia (Hogervorst et al., 2002) and because screening tools for global cognition incorporate recall memory tasks (Folstein et al., 1975) depression is an important consideration for a dementia diagnosis. This problem, in which the cognitive deficits of dementia are imitated by depressive states, has been

previously described (Alexopoulos, 2003; Solfrizzi, Nard, Panza, Mastroianni, & Capurso, 1996). By not accounting for the association of depression and memory, projections of cognitive decline can be misleading. That is, some cognitive deficits are likely attributable in part to depression, a treatable condition. Since, the underlying condition and not the symptoms deserves focus in terms of theory and treatment, continued effort should be taken to help distinguish cognitive deficits based on etiology. The effect of depression on baseline memory is consistent across multiple memory tests and types of memory tasks, underscoring the importance of this concern.

The present study's findings suggest that memory training attenuates memory decline but that depressive symptoms do not moderate this relationship. Thus, it appears that memory training is beneficial despite depressive symptoms, but other mechanisms that explain these results are possible. For instance, the recall improvement may be the result of more general benefits of social enrichment provided by cognitive training. Other intervention studies propose that social home visit and activity programs improve mood and quality of life among older adults (Kerse et al., 2010). An improvement of mood may in turn lead to improvements in cognitive testing results. However, previous studies of depressive symptoms in ACTIVE found no effect of cognitive training on recovery from depressive symptoms (Wolinsky et al., 2009), and the present study detected no differences among depression symptom categories between training groups. Other cognitive processes vulnerable to both depression and aging cannot be excluded as potential mediators and include executive functions (Alexopoulos, 2005), motor activity, attention/effort (Backman, Nyberg, Lindenberger, Li, & Farde, 2006; Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982), motivation (Austin, Mitchell, & Goodwin, 2001), or the biological/genetic factors which might underlie these cognitive and psychiatric constructs (McEwen, 2000; Salat et al., 2004; Terry, Buccafusco, & Wilson, 2008).

This study has noteworthy strengths. The ACTIVE cohort is a large sample of older adults randomized to cognitive training groups, allowing suitable size for analysis and control of confounding at baseline. The use of longitudinal data analysis methods allows for the appropriate consideration of variation within and between individuals over time. Potential limitations include poor generalizability, attrition bias, and method of depressive symptom measurement. Though the generalizability of results from the ACTIVE study are limited by selection of healthier, older adult volunteers, longitudinal relationships of memory scores and depressive symptoms did not differ by study site, indicating that bias from differential recruitment procedures and volunteerism was minimal. A prior study of ACTIVE data also found that loss to follow-up did not differ substantially by training condition, but was more likely among those who were older, male, had less education and had lower cognitive scores at baseline (Willis et al., 2006). The same study found that multiple imputation of missing data did not influence estimates of training effects on cognitive measures. In the current study, attrition was more likely among those with elevated depressive symptoms; however, because attrition was also more likely among those with lower baseline cognitive test scores (Willis et al., 2006), this loss would likely bias our findings toward the null. An additional potential limitation to this analysis is that only baseline CES-D scores were used to measure depression because it is unsafe to assume that depression ratings do not change over time (Beekman, Copeland, & Prince, 1999; Hybels & Blazer, 2003). Levels of depression may even change as a function of the socializing effects of memory training. Associating recovery of depression with concurrent changes in memory would strengthen the temporal evidence of a possible causal relationship between depression and memory decline. Lastly, because major depression is relatively rare in elderly populations (Beekman et al., 1999; Hybels & Blazer, 2003), the CES-D better reflects moderate to severe symptom levels, rather than clinical diagnosis. Misclassification of depressive categories from use of the CES-D may dilute differences in memory scores between training groups.

The personal and social impact of cognitive and functional decline among older adults is destructive and pervasive, so it is imperative to properly inform methods such as cognitive training that can prevent such decline. Evidence presented in this study indicates that elevated depressive symptoms are associated with memory deficits in old age and precede memory decline over time. The nature of this decline indicates that depression and memory ability may be linked through cumulative biological stresses or other unknown processes of general mental decline. Therefore, research on the efficacy and development of cognitive intervention programs must account for these and other concepts to more accurately describe the interrelation of cognitive mechanisms and more effectively prevent decline. Further elucidation of the factors involved in cognitive decline will lead to better methods to improve cognitive profiles of aging.

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References

- Alexopoulos G. Clinical and biological interactions in affective and cognitive geriatric syndromes. *The American Journal of Psychiatry*. 2003; 160(5):811–814. [PubMed: 12727680]
- Alexopoulos GS. Depression in the elderly. *Lancet*. 2005; 365(9475):1961–1970. [PubMed: 15936426]
- Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: Possible implications for functional neuropathology. *The British Journal of Psychiatry*. 2001; 178(3):200–206. [PubMed: 11230029]
- Backman L, Nyberg L, Lindenberger U, Li SC, Farde L. The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Methodological and Conceptual Advances in the Study of Brain-Behavior Dynamics: A Multivariate Lifespan Perspective*. 2006; 30(6):791–807.
- Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: A randomized controlled trial. *Journal of the American Medical Association*. 2002; 288(18):2271–2281. [PubMed: 12425704]
- Beekman A, Deeg D, vanTilburg T, Smit J, Hooijer C, vanTilburg W. Major and minor depression in later life: A study of prevalence and risk factors. *Journal of affective disorders*. 1995; 36(1–2):65. [PubMed: 8988267]
- Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *The British Journal of Psychiatry*. 1999; 174(4):307–311. [PubMed: 10533549]
- Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test - Revised normative data and analysis of inter-form and test retest reliability. *The Clinical Neuropsychologist*. 1999; 12(1):43–55.
- Brandt J. The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. *Clinical Neuropsychologist*. 1991; 5(2):125–142.
- Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimer's and Dementia*. 2007; 3(3):186–191.

- Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. *Psychological bulletin*. 1995; 117(2):285–305. [PubMed: 7724692]
- Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lonnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of affective disorders*. 2008; 106(1–2):1–27. [PubMed: 17707915]
- Cohen RM, Weingartner H, Smallberg SA, Pickar D, Murphy DL. Effort and cognition in depression. *Arch Gen Psychiatry*. 1982; 39(5):593–597. [PubMed: 7092490]
- Craik FI. Memory changes in normal and pathological aging. *Can J Psychiatry*. 2008; 53(6):343–345. [PubMed: 18616853]
- Folstein MF, Folstein SE, McHugh PR. “Mini-mental state” : A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975; 12(3):189–198. [PubMed: 1202204]
- Gabryelewicz T, Styczynska M, Luczywek E, Barczak A, Pfeffer A, Androsiuk W, et al. The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. *International Journal of Geriatric Psychiatry*. 2007; 22(6):563–567. [PubMed: 17136705]
- Gibbons R, Hedeker D, DuToit S. Advances in analysis of longitudinal data. *Annual Review of Clinical Psychology*. 2010; 6:79–107.10.1146/annurev.clinpsy.032408.153550
- Gross AL, Rebok GW, Unverzagt FW, Willis SL, Brandt J. Word list memory predicts everyday function and problem-solving in the elderly: results from the ACTIVE cognitive intervention trial. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2011a; 18(2):129–146. [PubMed: 21069610]
- Gross AL, Rebok GW, Unverzagt FW, Willis SL, Brandt J. Cognitive predictors of everyday functioning in older adults: results from the ACTIVE cognitive intervention trial. *J Gerontol B Psychol Sci Soc Sci*. 2011b; 66(5):557–566. [PubMed: 21558167]
- Hebert L, Scherr P, Bienias J, Bennett D, Evans D. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology*. 2003; 60(8):1119–1122. [PubMed: 12925369]
- Hedden T, Gabrieli JDE. Insights into the ageing mind: A view from cognitive neuroscience. *Nature reviews Neuroscience*. 2004; 5(2):87–96.
- Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M. The Hopkins Verbal Learning Test and screening for Dementia. *Dementia and Geriatric Cognitive Disorders*. 2002; 13(1):13–20. [PubMed: 11731710]
- Hybels CF, Blazer DG. Epidemiology of late-life mental disorders. *Clinics in Geriatric Medicine*. 2003; 19(4):663–696. [PubMed: 15024807]
- Jobe JB, Smith DM, Ball K, Tennstedt SL, Marsiske M, Willis SL, et al. ACTIVE: A cognitive intervention trial to promote independence in older adults. *Controlled clinical trials*. 2001; 22(4):453–479. [PubMed: 11514044]
- Jorm AF. Is depression a risk factor for Dementia or cognitive decline? *Gerontology*. 2000; 46(4):219–227. [PubMed: 10859462]
- Jorm AF. History of depression as a risk factor for dementia: An updated review. *Australian and New Zealand Journal of Psychiatry*. 2001; 35(6):776–781. [PubMed: 11990888]
- Kerse N, Hayman K, Moyes S, Peri K, Robinson E, Dowell A, et al. Home-based activity program for older people with depressive symptoms: DeLLITE--A randomized controlled trial. *Annals of Family Medicine*. 2010; 8(3):214–223. [PubMed: 20458104]
- Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D Depression Symptoms Index. *Journal of Aging and Health*. 1993; 5(2):179–193. [PubMed: 10125443]
- Kolen, M.; Brennan, R. Test equating: Methods and Practices. New York: Springer; 1995.
- Laird NM, Ware JH. Random effects models for longitudinal data: An overview of recent results. *Biometrics*. 1982; 38:963–974. [PubMed: 7168798]
- Langbaum JBS, Rebok GW, Bandeen-Roche K, Carlson MC. Predicting memory training response patterns: Results from ACTIVE. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2009; 64B(1):14–23.

- McEwen BS. Allostasis, allostatic load, and the aging nervous system: Role of excitatory amino acids and excitotoxicity. *Neurochemical Research*. 2000; 25(9):1219–1231. [PubMed: 11059796]
- Reppermund S, Ising M, Lucae S, Zihl J. Cognitive impairment in unipolar depression is persistent and non-specific: Further evidence for the final common pathway disorder hypothesis. *Psychological Medicine*. 2009; 39(04):603–614. [PubMed: 18667101]
- Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie*. 1941; 28:215–285.
- Ross C, Mirowsky J, Huber J. Dividing work, sharing work, and in-between: Marriage patterns and depression. *American Sociological Review*. 1983; 48(6):809–823.10.2307/2095327 [PubMed: 6666885]
- Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RSR, Busa E, et al. Thinning of the cerebral cortex in aging. *Cerebral Cortex*. 2004; 14(7):721–730. [PubMed: 15054051]
- Solfrizzi V, Nard GA, Panza F, Mastroianni F, Capurso A. Impact of aging on the relationships between impairment of “orientation” and “recall” items of MMSE and mild to moderate mood disorders. *Archives of Gerontology and Geriatrics*. 1996; 22(Suppl 1):69–72. [PubMed: 18653011]
- Terry AV, Buccafusco JJ, Wilson C. Cognitive dysfunction in neuropsychiatric disorders: Selected serotonin receptor subtypes as therapeutic targets. *Serotonin and Cognition: Mechanisms and Applications*. 2008; 195(1):30–38.
- Unverzagt F, Kasten L, Johnson K, Rebok G, Marsiske M, Koepke K, et al. Effect of memory impairment on training outcomes in ACTIVE. *Journal of the International Neuropsychological Society*. 2007; 13(6):953–960. [PubMed: 17942013]
- Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*. 2006; 296(23):2805–2814. [PubMed: 17179457]
- Wolinsky FD, Mahncke HW, Weg MWV, Martin R, Unverzagt FW, Ball KK, et al. The ACTIVE cognitive training interventions and the onset of and recovery from suspected clinical depression. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2009; 64B(5): 577–585.

Figure 1. Mean trajectories of HVL and AVL Recall by Training and Depressive Symptom Level Group: Results from ACTIVE (N = 1,401)

Figure 2. Mean trajectories of HVL and AVL Recognition Discrimination by Training and Depressive Symptom Level Group: Results from ACTIVE (N = 1,401)

Baseline Characteristics by Depressive Symptom Status

Characteristics	Memory-training Group Participants				Control Group Participants			
	Total (N=703)	Non-Elevated Depressive Symptoms (N= 557; CES-D<9)	Elevated Depressive Symptoms (N=146; CES-D ≥ 9)	p-value ^a	Total (N=698)	Non-Elevated Depressive Symptoms (N= 534; CES-D<9)	Elevated Depressive Symptoms (N=164; CES-D ≥ 9)	p-value ^a
Age, mean (SD)	73.5 (6.0)	73.1 (5.8)	75.3 (6.5)	< 0.001	74.0 (6.0)	73.8 (5.9)	75.0 (6.5)	0.03
Race, N (%)				0.65				0.38
White	524 (74.5%)	416 (74.7%)	108 (74.0%)		503 (72.1%)	390 (73.0%)	113 (68.9%)	
African American	176 (25.0%)	138 (24.8%)	38 (26.0%)		187 (26.8%)	137 (25.7%)	50 (30.5%)	
Other	3 (5%)	3 (5%)	0 (0%)		8 (1.1%)	7 (1.3%)	1 (0.61%)	
Sex, N (% female)	537 (76.4%)	422 (75.8%)	115 (78.8%)	0.45	514 (73.6%)	374 (70.0%)	140 (85.4%)	< 0.001
Education, mean (SD)	13.6 (2.7)	13.8 (2.7)	12.8 (2.9)	< 0.001	13.4 (2.7)	13.7 (2.7)	12.3 (2.5)	< 0.001
MMSE score, mean (SD)	27.3 (2.0)	27.5 (2.0)	26.7 (2.2)	< 0.001	27.3 (2.1)	27.5 (1.9)	26.5 (2.1)	< 0.001

^a p-values comparing depressed and non-depressed participants obtained by chi-square and t-test comparisons

Table 2

Adjusted and Unadjusted Random-Effects Models – Recall Memory Total Scores: Results from ACTIVE (N = 1,401)

	HVLt recall sum				AVLT recall sum			
	Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a	
	β	95% CI ^b	β	95% CI ^b	β	95% CI ^b	β	95% CI ^b
Main effects								
Depressive symptom category (1 = elevated)	-2.58 *	(-3.22, -1.94)	-1.18 *	(-1.68, -0.84)	-4.67 *	(-5.91, -3.42)	-2.37 *	(-3.38, -1.35)
Post-training assessment	0.36 *	(0.10, 0.62)	0.35 *	(0.09, 0.61)	0.70 *	(0.27, 1.13)	0.65 *	(0.22, 1.08)
1 st annual assessment	0.03	(-0.26, 0.31)	-0.02	(-0.31, 0.26)	0.13	(-0.34, 0.60)	0.07	(-0.40, 0.53)
2 nd annual assessment	0.14	(-0.16, 0.44)	0.11	(-0.18, 0.41)	-0.44	(-0.94, 0.06)	-0.50 *	(-1.00, -0.01)
3 rd annual assessment	-0.15	(-0.47, 0.18)	-0.17	(-0.49, 0.16)	-1.14 *	(-1.69, -0.58)	-1.17 *	(-1.71, -0.63)
5 th annual assessment	-1.19 *	(-1.56, -0.83)	-1.20 *	(-1.56, -0.84)	-3.32 *	(-3.95, -2.69)	-3.31 *	(-3.93, -2.70)
Depressive symptom level $\times$ time interactions								
Depression $\times$ Post-training	-0.30	(-0.94, 0.33)	-0.37	(-1.01, 0.26)	-0.17	(-1.21, 0.86)	-0.32	(-2.85, 0.72)
Depression $\times$ 1 st annual	-0.46	(-1.16, 0.24)	-0.57	(-1.27, 0.12)	-1.57 *	(-2.73, -0.41)	-1.69 *	(-2.85, -0.53)
Depression $\times$ 2 nd annual	-0.52	(-1.26, 0.22)	-0.59	(-1.32, 0.14)	-1.07	(-2.31, 0.18)	-1.21	(-2.44, 0.02)
Depression $\times$ 3 rd annual	-1.04 *	(-1.86, -0.22)	-1.11 *	(-1.91, -0.30)	-1.13	(-2.52, 0.27)	-1.21	(-2.58, 0.15)
Depression $\times$ 5 th annual	-0.52	(-1.45, 0.40)	-0.59	(-1.50, 0.32)	-1.59 *	(-3.18, 0.00)	-1.65 *	(-3.19, -0.10)
Demographic characteristics								
Age	-		-0.27 *	(-0.30, -0.23)	-		-0.58 *	(-0.65, -0.51)
Education (years)	-		0.29 *	(0.21, 0.38)	-		0.53 *	(0.37, 0.69)
MMSE	-		0.95 *	(0.85, 1.06)	-		1.49 *	(1.27, 1.71)
Ethnicity (White)	-		1.87 *	(1.39, 2.35)	-		2.78 *	(1.82, 3.74)
Sex (Female)	-		3.23 *	(2.75, 3.71)	-		7.17 *	(6.20, 8.13)

*
p < 0.05^a Adjusted for age, sex, ethnicity, education, and MMSE^b 95% CI: 95% confidence interval

Table 3

Adjusted and Unadjusted Random-Effects Models – Recognition Discrimination Scores: Results from ACTIVE (N = 1,401)

	HVLT recognition discrimination				AVLT recognition discrimination			
	Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a	
	β	95% CI ^b	β	95% CI ^b	β	95% CI ^b	β	95% CI ^b
Main effects								
Depressive symptom category (1 = elevated)	-0.46 *	(-0.65, -0.28)	-0.18 *	(-0.34, -0.01)	-2.48 *	(-3.01, -1.89)	-1.19 *	(-1.70, -0.69)
Post-training assessment	-0.42 *	(-0.52, -0.32)	-0.43 *	(-0.53, -0.33)	1.52 *	(1.27, 1.77)	1.49 *	(1.24, 1.74)
1 st annual assessment	0.74 *	(0.64, 0.85)	0.73 *	(0.62, 0.83)	1.52 *	(1.25, 1.79)	1.49 *	(1.21, 1.76)
2 nd annual assessment	-0.19 *	(-0.30, -0.08)	-0.20 *	(-0.31, -0.10)	1.81 *	(1.53, 2.10)	1.79 *	(1.49, 2.06)
3 rd annual assessment	-0.03	(-0.15, 0.09)	-0.04	(-0.16, 0.07)	0.83 *	(0.52, 1.14)	0.81 *	(0.50, 1.11)
5 th annual assessment	-0.98 *	(-1.11, -0.84)	-1.00 *	(-1.11, -0.85)	0.84 *	(0.50, 1.19)	0.82 *	(0.48, 1.16)
Depressive symptom level $\times$ time interactions								
Depression $\times$ Post-training	-0.21	(-0.44, .02)	-0.22	(-0.46, 0.02)	0.03	(-0.58, 0.63)	-0.06	(-0.67, 0.55)
Depression $\times$ 1 st annual	-0.02	(-0.28, 0.24)	-0.03	(-0.29, 0.23)	0.69 *	(0.01, 1.36)	0.65	(-0.02, 1.32)
Depression $\times$ 2 nd annual	-0.21	(-0.49, 0.06)	-0.23	(-0.50, 0.04)	0.35	(-0.35, 1.06)	0.29	(-0.42, 0.99)
Depression $\times$ 3 rd annual	-0.15	(-0.45, 0.15)	-0.16	(-0.46, 0.13)	0.27	(-0.50, 1.05)	0.21	(-0.56, 0.98)
Depression $\times$ 5 th annual	-0.39 *	(-0.72, -0.05)	-0.39 *	(-0.72, -0.06)	-0.71	(-1.58, 0.15)	-0.76	(-1.62, 0.10)
Demographic characteristics								
Age	-		-0.07 *	(-0.08, -0.06)	-		-0.27 *	(-0.30, -0.24)
Education (years)	-		0.04 *	(0.01, 0.07)	-		0.31 *	(0.23, 0.39)
MMSE	-		0.21 *	(0.18, 0.25)	-		0.67 *	(0.56, 0.77)
Ethnicity (White)	-		0.26 *	(0.11, 0.42)	-		1.66 *	(1.19, 2.14)
Sex (Female)	-		0.69 *	(0.53, 0.85)	-		1.66 *	(1.18, 2.13)

*
p < 0.05^a Adjusted for age, sex, ethnicity, education, and MMSE^b 95% CI: 95% confidence interval

Table 4

Adjusted Random-Effects Model – Depressive Symptoms Modification of Treatment Over Time: Results from ACTIVE (N = 1,401)

	HVL T				AVLT			
	Recall sum ^a		Recognition discrimination ^a		Recall sum ^a		Recognition discrimination ^a	
	β	95% CI ^b	β	95% CI ^b	β	95% CI ^b	β	95% CI ^b
Depressive symptom level $\times$ treatment interactions								
Post-training assessment	-0.24	(-1.54, 1.07)	-0.24	(-0.73, 0.24)	1.22	(-0.95, 3.39)	0.50	(-0.75, 1.76)
1 st annual assessment time	0.18	(-1.22, 1.58)	-0.26	(-0.78, 0.27)	-0.35	(-2.70, 2.01)	-2.07*	(-3.44, -0.71)
2 nd annual assessment time	0.05	(-1.38, 1.48)	-0.12	(-0.65, 0.42)	2.11	(-0.32, 4.53)	-0.33	(-1.73, 1.07)
3 rd annual assessment time	0.72	(-0.80, 2.24)	-0.45	(-1.02, 0.11)	1.38	(-1.18, 3.94)	-0.12	(-1.60, 1.35)
5 th annual assessment time	0.30	(-1.34, 1.93)	-0.50	(-1.11, 0.11)	0.01	(-2.74, 2.77)	-1.58	(-3.17, 0.10)

* p < 0.05

^a Adjusted for age, sex, ethnicity, education, and MMSE

^b 95% CI: 95% confidence interval