Published in final edited form as:

Neurobiol Aging. 2012 July ; 33(7): 1148–1155. doi:10.1016/j.neurobiolaging.2010.09.026.

Midlife memory improvement predicts preservation of hippocampal volume in old age

Paul R. Borghesani^{1,2,6}, Kurt E. Weaver^{2,6}, Elizabeth H. Aylward⁴, Anne L. Richards¹, Tara M Madhyastha^{1,6}, Ali R. Kahn⁵, Olivia Liang^{2,6}, Rachel L. Ellenbogen³, M. Faisal Beg⁵, K. Warner Schaie¹, and Sherry L Willis¹

¹Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle WA, USA

²Department of Radiology, University of Washington School of Medicine, Seattle WA, USA

³Department of Neurological Surgery, University of Washington School of Medicine, Seattle WA, USA

⁴Center for Integrated Brain Research (CIBR), Seattle Children's Research Institute, Seattle WA, USA

⁵School of Engineering Sciences, Simon Fraser University, Burnaby BC, Canada

⁶Integrated Brain Imaging Center, University of Washington Medical Center, Seattle WA, USA

Abstract

This study examines whether midlife change in episodic memory predicts hippocampal volume in old-age. From the Seattle Longitudinal Study we retrospectively identified 84 healthy, cognitively normal individuals, age 52 to 87, whose episodic memory had reliably declined (n=33), improved (n=28) or remained stable (n=23) over a 14 year period in midlife (age 43–63). Midlife memory improvement was associated with 13% larger hippocampal volume ($p < 0.01$) in old-age (age 66–87), compared to old-age individuals whose midlife episodic memory had either declined or remained stable during midlife. Midlife memory change did not predict total hippocampal volume for those currently in late middle-age (age 52–65). The pattern of findings was not modified by gender, apolipoprotein $\epsilon 4$ status, education or current memory performance. Change in midlife memory scores over 14 years, but not any single assessment, predicted hippocampal volumes in old age, emphasizing the importance of longitudinal data in examining brain-cognition relationships. These findings suggest that improvement in memory in midlife is associated with sparing of hippocampal volume in later life.

Keywords

aging; hippocampus; longitudinal; memory; volumetry; delayed recall; midlife

© 2010 Elsevier Inc. All rights reserved

Corresponding author: Paul R. Borghesani Box 356560 1959 NE Pacific St Seattle, WA 98195-6565 Phone: 206 685-0491 FAX: 206-543-9520 paulrb@uw.edu. Alternate corresponding author: Sherry L. Willis 180 Nickerson, Suite 206, Seattle, WA 98109 Phone: 206-281-4050 FAX: 206-281-4380 oldage@uw.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DISCLOSURE STATEMENT: None of the authors have any known or potential conflicts of interest that might bias this work.

1. Introduction

Aging can lead to cognitive decline and brain atrophy which can be variably categorized as either normal or pathologic depending on the age of onset, the rate of decline, and the extent of change [Hedden and Gabrieli, 2004, Raz and Rodrigue, 2006]. The association between hippocampal volume and episodic memory and their salience in both the preclinical phase and diagnosis of dementia is well studied [Barnes et al., 2009]. Both age-related memory loss and Alzheimer's disease are associated with hippocampal volume loss [Backman, 2008, Braak and Braak, 1991] and the rate of hippocampal atrophy is predictive of transition from normal cognition to mild cognitive impairment (MCI) and to dementia [Mungas et al., 2005]. However, the level of cognitive performance during the years preceding the diagnosis of AD, i.e. preclinical deficits, cannot reliably differentiate lifelong lower cognition from preclinical disease [Backman et al., 2005]. Similarly, absolute hippocampal volume during midlife is poorly correlated with memory function and later cognitive decline [Van Petten, 2004]. Thus, while midlife is increasingly recognized as a critical period in the study of both healthy and pathological aging [Finch, 2009], it remains unclear how midlife cognitive abilities relate to cognitive decline and brain atrophy in old age.

Most aging research focuses on normative versus pathological aging leaving our knowledge of what constitutes optimal aging more limited. Cross-sectional studies suggest that memory, and other cognitive domains, decline throughout life beginning in early adulthood [Park and Reuter-Lorenz, 2009, Salthouse, 2009]. Longitudinal studies, including our own, suggest that many cognitive abilities remain relatively stable during midlife (defined as ages 40–60) only to decline later in old-age [Giambra et al., 1995, Hultsch et al., 1998, Nilsson et al., 2009, Schaie et al., 2005]. However, we have found that some individuals during midlife appear to improve or decline on various cognitive measures, including episodic memory (i.e., memory for time-related events and experiences) [Schaie et al., 2005]. Thus using longitudinal data, we sought to determine if level of memory performance in midlife or if differential change (stability, improvement, or decline) in midlife episodic memory predicts hippocampal volumes in non-demented adults in middle and old age.

In this study we have used longitudinal cognitive testing data from the Seattle Longitudinal Study (SLS; [Schaie et al., 2005]), to retrospectively identify subjects, age 52 to 87, whose episodic memory improved, declined or remained stable during midlife (age 43–63). Structural MRIs were then collected in 2006–2007 to determine: 1) if individual midlife memory scores predicted hippocampal volume in middle and old age, 2) if midlife memory decline would predict smaller hippocampal volumes in middle and old age, and, 3) if change in midlife memory as a predictor of hippocampal volume was moderated by factors such as gender, education, memory scores at the time of MRI, vascular risk factors, or apolipoprotein $\epsilon 4$ (APOE $\epsilon 4$) carrier status, a known risk factor for brain atrophy and dementia [Mahley et al., 2006].

2. Materials and Methods

2.1. Participants

The Seattle Longitudinal Study (SLS) is a cohort-sequential longitudinal study of the relationship between aging, health, cognition and life-style [Schaie et al., 2005]. In brief, cognitive and behavioral assessments have been conducted every 7 years starting in 1956 on a mixed age cohort (age 20–80) with follow-up and recruitment of new subjects every seven years (1956 through 2005). SLS members at recruitment represent a stratified-by-age and gender random sample of the membership of the Group Health Cooperative of Puget Sound, a large HMO in western Washington State. This study has been approved by the University

of Washington Medical Center and the Group Health Cooperative of Puget Sound Institutional Review Boards.

The present analysis involves 84 SLS participants who were selected to undergo MRI scanning in 2006–2007. This subset was selected from a larger group ($n=572$) and, i) had 2 to 3 assessments of episodic memory over a 14-year interval during midlife (ages ranged from 43 to 63 yrs), ii) participated in the 2005 SLS data collection and, iii) for the old age cohort, had at least one assessment in old age (> 64 yrs). For design purposes, participants were stratified into two birth cohorts; middle age (MA) d.o.b. 1941–1955, $N = 49$ and old age (OA) d.o.b. 1907–1941, $N = 35$. Beyond cognitive and imaging data, participants completed demographic questionnaires, health surveys to assess for vascular risk and disease, and provided blood samples for APOE genotyping (Northwest Lipid Research Laboratories, Seattle WA, USA). A vascular risk summary score (0 to 3) was assigned to each subject based on self-reported diagnoses of hypertension, diabetes or hyperlipidemia (each risk factor being given an equal weight of 1 point).

2.2. Assignment of midlife memory change

At 7-year intervals SLS participants were assessed on a broad battery of psychometric abilities in two, 2.5-hour sessions [Schaie, 2005, Schaie et al., 2004]. All subjects were cognitively normal based on neuropsychological assessment and consensus review by neuropsychologists. Episodic memory was assessed by both immediate and delayed recall measures [Zelinski et al., 1993, Zelinski and Kennison, 2007, Zelinski and Lewis, 2003]. For immediate recall, participants studied a 20-word list for 3.5 minutes followed by 3.5 minutes of free recall. Delayed recall involved free recall after 1-hour of interim activities (test-retest reliability $r = 0.72$ [Zelinski et al., 1993]). The same test version was used every 7 years during all SLS waves in order to permit assessment of the magnitude of retest/practice effects across waves [Schaie, 1977, Schaie, 1988, Schaie, 2009]. Longitudinal cognitive data are converted into T-scores to permit comparisons across measures with different metrics and assessment of the magnitude of longitudinal change [Schaie et al., 2005]. For the memory tests, the standardization base is the first occasion of measurement for all SLS subjects who have been administered the test ($N = 2039$). All longitudinal data for a given test are standardized to this standardization base ($X = 50$, $SD = 10$). Practice effects over 7 years are modest, on the order of 0.20 SD (dropping to 0.05 when adjusted for attrition, [Schaie, 2005]), compared to a standard error of change (approximately 0.50 SD in T-score) which was the criterion for assignment of decline/improve status during midlife (see below). Using the entire sample's initial assessment, regardless of age, as the basis for standardization maintains the meaning of longitudinal changes across the lifespan, i.e., increasing (or decreasing) T-scores with age reflect actual improvement (or decline) within a cognitive domain.

Midlife episodic memory change was characterized as declining, improving, or stable by examining each individual's immediate and delayed recall scores over two 7-year intervals in midlife (average age interval 46 to 53 yrs and 53 to 60 yrs). Improvement or decline was defined by: i) > 1 standard error (S.E.) of change over a 14-year interval in immediate and delayed recall [Dudek, 1979, Willis and Schaie, 1986, Willis et al., 2006], ii) consistent direction of memory change in each of the two 7-year intervals and, iii) concordant direction of change for immediate and for delayed recall. In the entire sample of SLS participants with midlife memory data ($n=572$), approximately 12% ($N = 67$) of individuals were identified as improving and 14% ($N = 78$) declining (Willis et al, submitted).

2.3. MRI protocol

Magnetization prepared rapid gradient echo (MPRAGE) imaging was performed on a Philips 3.0 T Achieva scanner using the following parameters; repetition time (TR) = 7 milliseconds (ms), echo time (TE) = 3.20 ms; flip angle = 8°; matrix size of 240×240 and with 160 sagittally collected slices and a slice thickness of 1 mm. Time of collection was approximately 20 minutes.

2.4. Volumetric analysis

MPRAGE scans were reconstructed into a 1×1×1 mm 3D volume using MRIcron software and dcm2nii (<http://www.sph.sc.edu/comd/rorden/mricron/dcm2nii.html>). All measurements were performed blinded on de-identified data. *Intra-cranial Volumes (ICV)*: The ICV for each individual was calculated using a stereologic Cavalieri technique [Barta et al., 1997] implemented through MEASURE software (<http://pni.med.jhu.edu/methods/morph.htm>) using the Gundersen formula [Gundersen et al., 1988]. This encompassed manually creating a 3D grid of points overlaying the intracranial cavity (including the cerebrum, cerebellum, sulcal and ventricular CSF, and brainstem superior to the foramen magnum) for each subject by a single rater (R.L.E.). *Whole brain volumes*. The brain (cerebrum, cerebellum, and brain stem) was skull stripped using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>) and manually reviewed. The FANTASM plugin for MIPAV (<http://medic.rad.jhu.edu/projects/fantasm/> and <http://mipav.cit.nih.gov/>) was used to segment the stripped brain image into gray matter, white matter, and cerebral spinal fluid; white and gray matter were added together for total volume. *Hippocampal volumes*. A FreeSurfer + LDDMM (large deformation diffeomorphic metric mapping [Beg et al., 2005]) pipeline as described by Khan et al [Khan et al., 2008] and Wang et al [Wang et al., 2009] was used. The atlas-based segmentation method performs non-linear registration between a labeled template image and a target image, and then transforms the template mask to the target image accordingly. In brief, the stripped brains were segmented into subcortical and neocortical structures using FreeSurfer 4.1.0 [Fischl et al., 2002] and these “bounding boxes” were used to limit LDDMM during the template-to-target transformations. Confidence maps from the FreeSurfer segmentations [Khan et al., 2009] were used to weight the influence of the initial segmentations in a simultaneous LDDMM registration. A single hippocampal template mask (both left and right) was generated by hand from one typical study subject by an expert rater (E.H.A.). Hippocampal masks created by LDDMM were visually inspected in every subject. Volumes obtained from hand tracings (n=17, E.H.A.) and LDDMM were highly correlated (0.85). Change in hippocampal volume was an a priori hypothesis and thus for this report only hippocampal and total brain volumes were assessed.

2.5 Statistical Methods

Data were analyzed with STATA 10 (www.stata.com). Group differences were tested using standard analyses of variance (ANOVA) and covariance (ANCOVA) methods with subsequent post-hoc comparisons adjusting for unequal n's. Dependent variables included hippocampal volume, total brain volume and the ratio of hippocampal volume to total brain volume as described below. Regression methods were used to correct hippocampal and brain volume for head size with the following formula: $adjusted_volume = raw_volume - \beta(ICV - mean_ICV)$. In this formula β is the slope of the regression of ICV to raw_volume and $mean_ICV$ is the average ICV from all 84 subjects [Rodrigue and Raz, 2004]. In our analyses midlife memory change (improve, decline or stable), gender, age/cohort (MA or OA), and APOE status (APOE $\epsilon 4$ +/- or -/-) were used as categorical variables. All subjects with an APOE $\epsilon 4$ allele were heterozygous for $\epsilon 4$. Continuous covariates included age at MRI (AGE_{MRI}), delayed recall (DR) scores, vascular risk score (0–3), and education (in years). To assess the effects of APOE $\epsilon 4$ heterozygosity, ordered logistic regressions

were performed with midlife memory status as the dependent variable in the order of decline < stable < improve.

3. Results

3.1 Study population

Table 1 summarizes the demographics and cognitive scores by midlife memory change status within age cohorts. Within their age cohorts (MA or OA), groups did not differ in regards to gender, education, or MMSE. Two thirds (67%) of subjects self-reported one or more vascular risk factors (history of smoking, hypertension, diabetes and/or hyperlipidemia) but the average vascular risk burden did not differ between midlife memory change status groups within cohorts (ordered logistic regression with the vascular risk score (0 – 3) as the dependant variable and midlife memory change as the predictor; for MA $\chi^2 = 0.18$ $p = 0.67$ and in OA $\chi^2 = 0.01$ $p = 0.92$) or between age cohorts (ordered logistic $\chi^2 = 0.81$ $p = 0.37$). Carriers of an APOE $\epsilon 4$ allele ($\epsilon 3/\epsilon 4$ heterozygotes) are more likely to be midlife memory decliners than improvers. Across the entire sample 59% of $\epsilon 4$ carriers are decliners, 23% are stable, 18% are improvers (ordered logistic regression with midlife memory status (declining < stable < improving) as the dependent variable and APOE $\epsilon 4$ (–/– or +/–) as the predictor: $\chi^2 = 5.5$ $p < 0.05$). However, within cohorts, differences in APOE $\epsilon 4$ status was not significantly associated with memory status (ordered logistic regression in MA: $\chi^2 = 2.8$ $p = 0.10$ and in OA: $\chi^2 = 2.5$ $p = 0.11$); possibly reflecting the small sample size and reduced power to detect a difference by memory status. The average age of OA decliners at the time of MRI (AGE_{MRI}) was greater ($p < 0.01$) than the other OA groups (Table 1). Delayed recall (DR) scores were lower in decliners than improvers at average age 60 in both cohorts (range 57–63) and onward in the OA cohort (Figure 1). DR scores did not differ for improvers and stables at any age (Table 2).

3.2. Hippocampal and brain volumes

The first objective of the study was to compare three measures of volume (hippocampal volume, total brain volume, hippocampal-to-brain ratio) in memory decliners, improvers and stables, within and across age cohorts. A 3 midlife memory change $\times$ 2 age cohort ANOVA with hippocampal volume as the dependent variable revealed significant main effects of midlife memory change status ($F_{2,78} = 4.4$ $p < 0.05$), age cohort ($F_{1,78} = 32.5$ $p < 0.001$), and the interaction of age cohort and midlife memory change ($F_{2,78} = 4.1$ $p < 0.05$). Post hoc comparisons for the age cohort main effect indicated that hippocampal volume was greater ($p < 0.01$) for MA than for OA age cohorts (in MA 7.32 ± 0.1 cm^3 and OA 6.6 ± 0.1 cm^3). Post hocs for the age cohort $\times$ midlife memory change status interaction indicated that (see Table 3), i) OA memory improvers had significantly ($p < 0.01$) larger hippocampal volume than OA decliners or stables, ii) hippocampal volume of OA decliners and stables did not differ and iii) there were no differences in hippocampal volume among MA gainers, decliners or stables. Overall, hippocampal volumes in OA improvers were ~13% larger than OA stables and decliners and did not differ from MA subjects.

Similar ANOVAs using total brain volume as the dependent variable revealed a significant main effect for age cohort ($F_{1,78} = 30.3$ $p < 0.001$) with the MA cohort having ~6% larger brains than OA cohort (Table 3). Finally, the ratio of hippocampal to whole brain volume was examined to confirm that midlife memory change affected hippocampal volume and not broader whole brain volume. Similar to findings above for hippocampal volume, ANOVA revealed main effects of cohort ($F_{1,78} = 6.9$ $p < 0.05$), midlife memory change ($F_{2,78} = 5.6$ $p < 0.01$) and the interaction of cohort and midlife memory change ($F_{2,78} = 5.1$ $p < 0.01$) on hippocampal-to-brain ratios. OA improvers had greater ($p < 0.01$) hippocampal-to-brain ratios than OA stables or decliners and did not differ from MA subjects (Table 3).

3.3. The effects of DR scores, gender, vascular risk factors and APOE

To confirm that the above findings regarding hippocampal volume were not accounted for by factors at the time of scan (memory score), by biomarkers (APOE status, vascular risk) or by demographics (gender, education), we performed a series of further analyses. A 3 memory change status $\times$ 2 age cohort $\times$ 2 gender ANCOVA with covariates of education, vascular risk and memory score at time of scan (DR_{MRI}) supported the same pattern of findings as reported above; the covariates were not significant; and the age cohort main effect ($F_{1,68} = 33.2$ $p < 0.01$) and the memory change $\times$ age cohort interaction remained significant ($F_{2,68} = 3.2$ $p < 0.05$). Neither the gender main effect ($F_{1,68} = 0.18$ $p = 0.67$) nor the interaction terms with gender were significant. Likewise, in regression analyses, the inclusion of gender did not substantially change the amount of variance accounted for by the model ($\text{adj}R^2 = 0.34$ with gender; $\text{adj}R^2 = 0.32$ without gender). With regard to the covariate of DR_{MRI} , regression analyses further demonstrated that neither DR_{MRI} nor DR scores 7 or 14 years prior (in either cohort) or 21 years prior (OA cohort only) significantly predicted hippocampal volume (data not shown). Given that a greater proportion of memory decliners had one APOE e4 allele, a 3 midlife memory change status $\times$ 2 age cohort $\times$ 2 APOE ANOVA was conducted. Neither the APOE main effect ($F_{1,65} = 2.2$ $p = 0.14$) nor the interactions with APOE were significant (cohort $\times$ APOE $F_{1,65} = 1.4$ $p = 0.24$; memory change $\times$ APOE $F_{2,65} = 0.5$ $p = 0.59$) while, as before, the midlife memory change $\times$ cohort interaction remained significant ($F_{2,65} = 3.5$ $p < 0.05$).

4. DISCUSSION

These findings confirm our a priori hypothesis that midlife memory change predicts hippocampal volumes. Midlife memory improvement was associated with larger hippocampal volumes in old-age (OA), in comparison to OA decliners or stablers. Although total brain volume was lower in OA, volumes were similar among the improvers, decliners, and stablers in both the middle-age (MA) and OA cohorts, suggesting that larger hippocampi in OA memory improvers was somewhat region-specific. Overall, hippocampal volumes in OA improvers were no different from MA subjects. In contrast, episodic memory scores at any single age during midlife did not predict hippocampal volumes (in either MA or OA) demonstrating that memory change, not scores from an individual assessment, are important for predicting future hippocampal volumes.

Hippocampal volume loss in older individuals has been estimated to be about ~1% annually [Resnick et al., 2003], may accelerate with age [Raz et al., 2004], and is associated with age-related episodic memory decline and cognitive impairment [Jack et al., 1999]. In contrast during middle-age the association between hippocampal volume and episodic memory is more ambiguous, with some research even suggesting a negative relationship between hippocampal volume and episodic memory [Van Petten, 2004]. Only a few papers have explored the longitudinal association between midlife cognitive changes and hippocampal volume [Persson et al., 2006, Raz et al., 2005]. Similar to our findings, Persson [28] reported that individuals whose cognitive abilities declined over a decade had reduced hippocampal volume, decreased white matter integrity and altered brain function.

Our findings can be considered in relation to cognitive and neural plasticity, specifically cognitive training and cognitive reserve. Short-term cognitive training in old age has been shown to significantly enhance cognitive performance and modify brain structure [Draganski et al., 2006] and function [Thomas et al., 2009]. Meta analysis of the cognitive training literature in healthy elders [Valenzuela and Sachdev, 2009] indicates that cognitive training can have lasting benefits after the cessation of training for at least 3 months. In the ACTIVE clinical trial [Ball et al., 2002, Willis et al., 2006] cognitive training effects were maintained for five years in comparison to a control. The effects of midlife memory

improvement in this study, which represented an average change of 0.75 standard deviations over a fourteen-year period in midlife, had long-term outcomes in old age, up to fourteen years after the end of midlife (age 60).

These effects cannot be accounted for by the traditional definition of cognitive reserve. Cognitive reserve as defined by Stern (2009) refers to preservation of cognitive performance in the face of neural deterioration. On average, OA improvers were functioning at a level higher than their performance level in early midlife (Figure 1) while their hippocampal volumes were the same as middle age subjects, suggesting little or no neural deterioration. In contrast, cognitive reserve could account for the finding that OA stablers maintained a high level of functioning in midlife and through mean age 67 in spite of their hippocampal volumes being comparable to OA decliners. It is important to note, however, that, similar to studies of cognitive intervention [Papp et al., 2009], episodic memory improvement was generally ability-specific. That is, memory improvers did not uniformly demonstrate comparable gains on other abilities during midlife, such as executive functioning [Willis and Schaie, 2005].

Neuroprotection and disease modification [Valenzuela et al., 2007] have been proposed to account for superior aging in some individuals and either process could be at work in this sample given that hippocampal volumes were similar in midlife and differed in old age. A major challenge for our future research is examining the specific lifestyle and activities of memory improvers, particularly in midlife, to identify factors associated with this sustained cognitive and neural enhancement. For instance, mental activity across the lifespan has been associated with decreased hippocampal atrophy in late life [Valenzuela et al., 2008].

Genetic and vascular risk factors have been found to impact both cognitive aging and hippocampal atrophy [Raz et al., 2008, Small et al., 2004]. Cognitive decline, particularly episodic memory and executive functioning, begins almost a decade earlier in carriers of the APOE $\epsilon 4$ allele, a genetic risk for MCI and AD [Mahley et al., 2006], as compared to normative samples [Small et al., 2004]. Likewise, beginning in midlife, APOE $\epsilon 4$ carriers are reported to have smaller hippocampal volume and a greater accumulation of senile plaques [Kok et al., 2009, Small et al., 2004]. In our sample, significantly more midlife memory decliners were APOE $\epsilon 4$ carriers (42%) in comparison to improvers (18%). Overall, 27% of our participants were APOE $\epsilon 4$ carriers, similar to the expected prevalence in community samples [Fullerton et al., 2000]. APOE $\epsilon 4$ status, however, did not account for significant additional variance in our models predicting hippocampal volume in either our MA or OA cohorts. This finding is in accord with prior research that although a significant factor in cognitive aging and dementia, APOE $\epsilon 4$ status per se accounts for relatively little variance in prediction models [Small et al., 2004]. Likewise, vascular risk has been found to exert a negative influence on age-sensitive cognitive abilities and to be related to hippocampal atrophy [Cohen et al., 2006, Gianaros et al., 2006, Rodrigue and Raz, 2004]. Of interest are the four improvers who were APOE $\epsilon 4$ carriers and reported no vascular risk factors. This is in accordance with findings that suggest the detrimental effects of APOE $\epsilon 4$ can be attenuated by monitoring of blood pressure and cholesterol [Kivipelto et al., 2002].

Limitations of this study include both sample and technological issues. Hippocampal volumes were evaluated cross-sectionally and thus although hippocampal volumes in the MA cohort did not differ with regard to midlife memory change we cannot establish whether this was true for the OA cohort in midlife. Our sample size is relatively small, generally well educated and racially homogeneous and thus the generalizability to lower socioeconomic groups who have increased risk for cognitive decline is unclear. Second, semi-automated volumetric techniques require careful monitoring and each hippocampal mask generated by

the LDDMM procedure was visually inspected and systematic errors were addressed by reprocessing the entire sample. How/if to correct hippocampal volumes for head size is debated. Uncorrected volumes, structure-of-interest to brain ratios, and covariance with ICV are all routinely employed and we chose to use regression methods to correct hippocampal and brain volumes for ICV. In fact, if gender is not a primary question or confound then the method of correction, or correcting at all, appears to make little difference when calculating age-related cerebral atrophy [Greenberg et al., 2008].

Practice or retest effects are components of all longitudinal cognitive studies and must be taken into account. Generally retest effects over a seven-year interval have been found to be on the order of 0.20 SD and are small compared to the age-related improvement of midlife gainers of 0.50 SD. Reciprocally, retest effects in midlife decliners may have caused an underestimate of the magnitude of decline that they experienced. Hence, retest effects cannot explain the differences in midlife memory change observed in memory improvers and decliners.

This study illustrates the significance of midlife memory change on future memory function and hippocampal volume. Although decline in midlife cognition and its implications for normal and pathological aging have been reported [Persson et al., 2006], this study is one of the first, to our knowledge, to examine the impact of midlife memory improvement on cognitive and brain aging. Little is known about the specifics of cognitive engagement and stimulation that are assumed to be associated with development of cognitive reserve. If midlife memory improvement is a marker for optimal hippocampal aging then interventions aimed at improving brain health, be they lifestyle or pharmacologic, should be begun during middle age.

Acknowledgments

We would like to thank the staff of the Seattle Longitudinal Study for coordinating the imaging sessions and neuropsychological assessments, and Dr. Paul Choi and Jenee O'Brian for MRI acquisition. As always, we are indebted to our study participants.

FUNDING: This work was supported by National Institute of Aging (grant number R37-AG024102) and PRB is a KL2 scholar supported by National Center for Research Resources (grant number 5KL2RR025015-02).

References

- Backman L. Memory and cognition in preclinical dementia: what we know and what we do not know. *Can J Psychiatry*. 2008; 53(6):354–60. [PubMed: 18616855]
- Backman L, Jones S, Berger AK, Laukka EJ, Small BJ. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology*. 2005; 19(4):520–31. [PubMed: 16060827]
- Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, Willis SL. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002; 288(18):2271–81. [PubMed: 12425704]
- Barnes J, Ourselin S, Fox NC. Clinical application measurement of hippocampal atrophy in degenerative dementias. *Hippocampus*. 2009; 19(6):510–6. [PubMed: 19405145]
- Barta PE, Dhingra L, Royall R, Schwartz E. Improving stereological estimates for the volume of structures identified in three-dimensional arrays of spatial data. *J Neurosci Methods*. 1997; 75(2): 111–8. [PubMed: 9288642]
- Beg MF, Miller MI, Troune A, Younes L. Computing large deformation metric mappings via geodesic flows of diffeomorphisms. *International Journal of Computer Vision*. 2005; 61(2):139–57.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991; 82(4):239–59. [PubMed: 1759558]

- Cohen RM, Szczepanik J, McManus M, Mirza N, Putnam K, Levy J, Sunderland T. Hippocampal atrophy in the healthy is initially linear and independent of age. *Neurobiol Aging*. 2006; 27(10): 1385–94. [PubMed: 16168525]
- Draganski B, Gaser C, Kempermann G, Kuhn HG, Winkler J, Buchel C, May A. Temporal and spatial dynamics of brain structure changes during extensive learning. *J Neurosci*. 2006; 26(23):6314–7. [PubMed: 16763039]
- Dudek FJ. The continuing misinterpretation of the standard error of measurement. *Psychological Bulletin*. 1979; 86:335–7.
- Finch CE. The neurobiology of middle-age has arrived. *Neurobiol Aging*. 2009; 30(4):515–20. discussion 30–33. [PubMed: 19231030]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33(3):341–55. [PubMed: 11832223]
- Fullerton SM, Clark AG, Weiss KM, Nickerson DA, Taylor SL, Stengard JH, Salomaa V, Vartiainen E, Perola M, Boerwinkle E, Sing CF. Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. *Am J Hum Genet*. 2000; 67(4):881–900. [PubMed: 10986041]
- Giambra LM, Arenberg D, Kawas C, Zonderman AB, Costa PT Jr. Adult life span changes in immediate visual memory and verbal intelligence. *Psychol Aging*. 1995; 10(1):123–39. [PubMed: 7779310]
- Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. *Neuroimage*. 2006; 31(2): 754–65. [PubMed: 16488626]
- Greenberg DL, Messer DF, Payne ME, Macfall JR, Provenzale JM, Steffens DC, Krishnan RR. Aging, gender, and the elderly adult brain: an examination of analytical strategies. *Neurobiol Aging*. 2008; 29(2):290–302. [PubMed: 17049410]
- Gundersen HJ, Bagger P, Bendtsen TF, Evans SM, Korbo L, Marcussen N, Moller A, Nielsen K, Nyengaard JR, Pakkenberg B. The new stereological tools: disector, fractionator, nucleator and point sampled intercepts and their use in pathological research and diagnosis. *APMIS*. 1988; 96(10):857–81. [PubMed: 3056461]
- Hedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci*. 2004; 5(2):87–96. [PubMed: 14735112]
- Hultsch, DF.; Herzog, C.; Dixon, RA.; Small, BJ. *Memory change in the aged*. Cambridge University Press; Cambridge, U.K.; New York: 1998.
- Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999; 52(7):1397–403. [PubMed: 10227624]
- Khan AR, Chung MK, Beg MF. Robust atlas-based brain segmentation using multi-structure confidence-weighted registration. *Proceedings of the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI)*. 2009; 5762:549–57.
- Khan AR, Wang L, Beg MF. FreeSurfer-initiated fully-automated subcortical brain segmentation in MRI using Large Deformation Diffeomorphic Metric Mapping. *Neuroimage*. 2008; 41(3):735–46. [PubMed: 18455931]
- Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Iivonen S, Mannermaa A, Tuomilehto J, Nissinen A, Soininen H. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med*. 2002; 137(3):149–55. [PubMed: 12160362]
- Kok E, Haikonen S, Luoto T, Huhtala H, Goebeler S, Haapasalo H, Karhunen PJ. Apolipoprotein E-dependent accumulation of Alzheimer disease-related lesions begins in middle age. *Ann Neurol*. 2009; 65(6):650–7. [PubMed: 19557866]
- Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2006; 103(15):5644–51. [PubMed: 16567625]

- Mungas D, Harvey D, Reed BR, Jagust WJ, DeCarli C, Beckett L, Mack WJ, Kramer JH, Weiner MW, Schuff N, Chui HC. Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology*. 2005; 65(4):565–71. [PubMed: 16116117]
- Nilsson LG, Sternang O, Ronnlund M, Nyberg L. Challenging the notion of an early-onset of cognitive decline. *Neurobiol Aging*. 2009; 30(4):521–4. discussion 30–3. [PubMed: 19285194]
- Papp KV, Walsh SJ, Snyder PJ. Immediate and delayed effects of cognitive interventions in healthy elderly: a review of current literature and future directions. *Alzheimers Dement*. 2009; 5(1):50–60. [PubMed: 19118809]
- Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol*. 2009; 60:173–96. [PubMed: 19035823]
- Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, Buckner RL. Structure-function correlates of cognitive decline in aging. *Cereb Cortex*. 2006; 16(7):907–15. [PubMed: 16162855]
- Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol Aging*. 2004; 25(3):377–96. [PubMed: 15123343]
- Raz N, Lindenberger U, Ghisletta P, Rodrigue KM, Kennedy KM, Acker JD. Neuroanatomical correlates of fluid intelligence in healthy adults and persons with vascular risk factors. *Cereb Cortex*. 2008; 18(3):718–26. [PubMed: 17615248]
- Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex*. 2005; 15(11):1676–89. [PubMed: 15703252]
- Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev*. 2006; 30(6):730–48. [PubMed: 16919333]
- Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci*. 2003; 23(8):3295–301. [PubMed: 12716936]
- Rodrigue KM, Raz N. Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *J Neurosci*. 2004; 24(4):956–63. [PubMed: 14749440]
- Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*. 2009; 30(4):507–14. [PubMed: 19231028]
- Schaie KW. Developmental influences on adult intelligence : the Seattle longitudinal study. Oxford University Press; Oxford; New York: 2005.
- Schaie KW. Toward a stage theory of adult cognitive development. *Int J Aging Hum Dev*. 1977; 8(2): 129–38. [PubMed: 892914]
- Schaie KW. Variability in cognitive function in the elderly: implications for societal participation. *Basic Life Sci*. 1988; 43:191–211. [PubMed: 3284520]
- Schaie KW. “When does age-related cognitive decline begin?” Salthouse again reifies the “cross-sectional fallacy”. *Neurobiol Aging*. 2009; 30(4):528–9. discussion 30–33. [PubMed: 19231029]
- Schaie KW, Willis SL, Caskie GI. The Seattle longitudinal study: relationship between personality and cognition. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2004; 11(2–3):304–24.
- Schaie KW, Willis SL, Pennak S. An Historical Framework for Cohort Differences in Intelligence. *Res Hum Dev*. 2005; 2(1–2):43–67. [PubMed: 16858496]
- Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging*. 2004; 19(4):592–600. [PubMed: 15584785]
- Thomas AG, Marrett S, Saad ZS, Ruff DA, Martin A, Bandettini PA. Functional but not structural changes associated with learning: an exploration of longitudinal voxel-based morphometry (VBM). *Neuroimage*. 2009; 48(1):117–25. [PubMed: 19520171]
- Valenzuela M, Sachdev P. Can Cognitive Exercise Prevent the Onset of Dementia? Systematic Review of Randomized Clinical Trials with Longitudinal Follow-up. *Am J Geriatr Psychiatry*. 2009; 17(3): 179–87. [PubMed: 19225276]
- Valenzuela MJ, Breakspear M, Sachdev P. Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. *Brain Res Rev*. 2007; 56(1):198–213. [PubMed: 17870176]

- Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS ONE*. 2008; 3(7):e2598. [PubMed: 18612379]
- Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*. 2004; 42(10):1394–413. [PubMed: 15193947]
- Wang L, Khan A, Csernansky JG, Fischl B, Miller MI, Morris JC, Beg MF. Fully-automated, multi-stage hippocampus mapping in very mild Alzheimer disease. *Hippocampus*. 2009; 19(6):541–8. [PubMed: 19405129]
- Willis, SL.; Schaie, KW. Cognitive trajectories in midlife and cognitive functioning in old age. In: Willis, SL.; Martin, M., editors. *Middle adulthood: A lifespan perspective*. Thousand Oaks; Sage: 2005. p. 243-76.
- Willis SL, Schaie KW. Training the elderly on the ability factors of spatial orientation and inductive reasoning. *Psychol Aging*. 1986; 1(3):239–47. [PubMed: 3267404]
- Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, Morris JN, Rebok GW, Unverzagt FW, Stoddard AM, Wright E. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*. 2006; 296(23):2805–14. [PubMed: 17179457]
- Zelinski EM, Gilewski MJ, Schaie KW. Individual differences in cross-sectional and 3-year longitudinal memory performance across the adult life span. *Psychol Aging*. 1993; 8(2):176–86. [PubMed: 8323722]
- Zelinski EM, Kennison RF. Not your parents' test scores: cohort reduces psychometric aging effects. *Psychol Aging*. 2007; 22(3):546–57. [PubMed: 17874953]
- Zelinski EM, Lewis KL. Adult age differences in multiple cognitive functions: differentiation, dedifferentiation, or process-specific change? *Psychol Aging*. 2003; 18(4):727–45. [PubMed: 14692860]

Figure 1.

Mean standardized delayed recall (DR) scores in decliners and improvers (decliners - light gray triangle; improvers - black circle; MA cohort - dashed line; OA cohort - solid line). After average age 60, decliners have lower DR scores than improvers. * mean DR scores for decliners < improvers, Bonferroni corrected t-tests $p < 0.01$. Error bars represent standard error of the mean.

Table 1

Sample Demographics

	MA Cohort			OA cohort		
	Decline	Improve	Stable	Decline	Improve	Stable
# of subjects	21	13	15	12	15	8
Age	60.3 (3.1)	61.2 (3.0)	61.9 (2.5)	78.6 (5.2) ^a	74.1 (3.9)	72.0 (4.7)
Age Range	53–65	55–65	59–65	68–87	66–79	66–79
Gender (F/M)	10/11	7/6	11/4	6/6	11/4	5/3
APOE +/-	44%	17%	27%	42%	14%	25%
Education	16.6 (2.4)	16.6 (2.6)	16.6 (1.4)	16.2 (3.3)	15.6 (3.1)	16.1 (2.4)
MMSE	29.3 (1.1)	29.3 (1.2)	29.2 (0.8)	28.8 (1.8)	29.0 (1.3)	29.4 (1.0)
DR _{mri}	46.5 (4.2) ^b	57.6 (9.2)	60.0 (6.8)	45.2 (5.8) ^b	54.7 (6.6)	55.3 (10.3)
Vascular Risk	0.9 (1.0)	0.9 (0.9)	0.9 (0.8)	1.2 (1.1)	1.1 (0.9)	1.1 (0.9)

Values are means ($\pm$ s.d), % or frequencies.

APOE = apolipoprotein; DR = delayed recall; DR_{mri} = DR at time of MRI, MA = middle age; MMSE = Mini-mental status exam; OA = old age

^aThe average age of the OA decliners is greater than other OA subjects, ANOVA $p < 0.01$.

^bAverage DR_{mri} for the decliners is less than other groups in both MA and OA subjects, (ANOVA $p < 0.05$)

Table 2

Mean standardized delayed recall scores in MA and OA cohorts

Mean Age	MA cohort			OA cohort		
	Decline	Improve	Stable	Decline	Improve	Stable
46	56.4 (5.5)	51.6 (6.9)	59.8 (6.5)	58.7 (6.4)	48.8 (9.2)	60 (8.8)
53	50.7 (7.3)	56.3 (5.9)	60.5 (6.2)	52.4 (5.6)	52.3 (7.2)	59.3 (9.0)
60	46.6 (4.3) ^{a,b}	57.9 (10.0)	60.0 (6.8)	45.3 (7.7) ^{a,b}	58.3 (7.2)	60.0 (8.7)
67	--	--	--	43.3 (10.5) ^{a,b}	55.3 (6.3)	56.8 (6.8)
74	--	--	--	42.1 (6.4) ^a	55.3 (6.9)	45.3 (11.0) ^c

^a mean scores for decliners < improvers, $p < 0.01$ for Bonferroni corrected t-tests at each age

^b mean scores for decliner < stables, $p < 0.01$ for Bonferroni corrected t-test at each age

^c data from 3 subjects

Table 3

Hippocampal and brain volumes in MA and OA cohorts

	MA cohort			OA cohort		
	Decline	Improve	Stable	Decline	Improve	Stable
Hippocampus	7.4 (0.5)	7.3 (0.7)	7.4 (0.7)	6.2 (0.8)	7.1 (0.4) ^a	6.6 (0.8)
Total brain	1126 (46)	1128 (45)	1129 (41)	1050 (88)	1068 (35)	1070 (52)
Hipp/brain (%)	0.65 (.04)	0.65 (.05)	0.65 (.05)	0.59 (.07)	0.66 (.03) ^b	0.62 (.06)

Volumes are in cm³ (SD) and have been corrected for ICV via regression (see methods).
see Table 1 for abbreviations.

^a 3 midlife memory status × 2 age cohort ANOVA; memory status × age cohort interaction (F_{2,78} = 4.1 p < 0.05), Bonferroni corrected t-tests: OA improve > OA decline p < 0.05, OA improve > OA stable p < 0.05. No significant differences within the MA cohort or between MA groups and OA improvers.

^b 3 midlife memory status × 2 age cohort ANOVA; memory status × age cohort interaction (F_{2,78} = 5.1 p < 0.01), Bonferroni corrected t-tests: OA improve > OA decline, p < 0.01, OA improve > OA stable, p < 0.01, No significant differences within the MA cohort or between MA groups and OA improvers.