



## Midlife memory improvement predicts preservation of hippocampal volume in old age

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### 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 with 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.

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### 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 vol-

ume 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.

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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 nondemented 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. 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 7 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 years), ii) participated in the 2005 SLS data collection and, iii) for the old age cohort, had at least one assessment in old age ( $>64$  years). 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 three) was assigned to each subject based on self-reported diagnoses of hypertension, diabetes or hyperlipidemia (each risk factor being given an equal weight of one 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 et al., 2004; Schaie, 2005). 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 and Kennison, 2007; Zelinski and Lewis, 2003; Zelinski et al., 1993). 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 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 with 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 years and 53 to 60 years). Improvement or decline was defined by i)

>1 standard error (SE) 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 (msecond), 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 ([www.sph.sc.edu/comd/rorden/mricron/dcm2nii.html](http://www.sph.sc.edu/comd/rorden/mricron/dcm2nii.html)). All measurements were performed blinded on deidentified data. *Intracranial volumes (ICV)*: the ICV for each individual was calculated using a stereologic Cavalieri technique (Barta et al., 1997) implemented through MEASURE software ([pni.med.jhu.edu/methods/morph.htm](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 ([surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/)) and manually reviewed. The FANTASM plug in for MIPAV ([medic.rad.jhu.edu/projects/fantasm/](http://medic.rad.jhu.edu/projects/fantasm/) and [mipav.cit.nih.gov/](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 nonlinear 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](http://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  $\beta$  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

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) <sup>a</sup>	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 $\epsilon 4$ +/-	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 <sub>MRI</sub>	46.5 (4.2) <sup>b</sup>	57.6 (9.2)	60.0 (6.8)	45.2 (5.8) <sup>b</sup>	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<sub>MRI</sub>, DR at time of MRI; MA, middle age; MMSE, minimal status examination; OA, old age.

<sup>a</sup> The average age of the OA decliners is greater than other OA subjects, ANOVA  $p < 0.01$ .

<sup>b</sup> average DR<sub>MRI</sub> for the decliners is less than other groups in both MA and OA subjects, (ANOVA  $p < 0.05$ ).

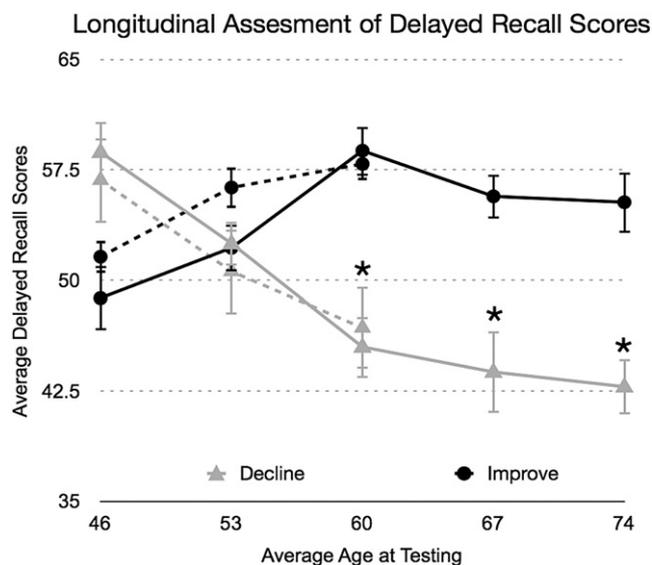


Fig. 1. Mean standardized DR scores in decliners and improvers (decliners – light gray triangle; improvers – black circle; MA cohort – dashed line; OA cohort – solid line). After average age 60, decliners have lower DR scores than improvers. \* mean DR scores for decliners < improvers, Bonferroni corrected  $t$ -tests  $p < 0.01$ . Error bars represent standard error of the mean.

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<sub>MRI</sub>) 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 (Fig. 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 three midlife memory change  $\times$  two 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  $7.32 \pm 0.1$  cm<sup>3</sup> and OA  $6.6 \pm 0.1$  cm<sup>3</sup>). Post hoc for the age cohort  $\times$  midlife memory change status interaction indicated that (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  $\sim 13\%$  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  $\sim 6\%$  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).

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) <sup>a,b</sup>	57.9 (10.0)	60.0 (6.8)	45.3 (7.7) <sup>a,b</sup>	58.3 (7.2)	60.0 (8.7)
67	—	—	—	43.3 (10.5) <sup>a,b</sup>	55.3 (6.3)	56.8 (6.8)
74	—	—	—	42.1 (6.4) <sup>a</sup>	55.3 (6.9)	45.3 (11.0) <sup>c</sup>

<sup>a</sup> mean scores for decliners < improvers,  $p < 0.01$  for Bonferroni corrected  $t$ -tests at each age.

<sup>b</sup> mean scores for decliner < stabler,  $p < 0.01$  for Bonferroni corrected  $t$ -test at each age.

<sup>c</sup> data from three 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) <sup>a</sup>	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) <sup>b</sup>	0.62 (.06)

Volumes are in  $\text{cm}^3$  (SD) and have been corrected for ICV via regression (see methods).

See Table 1 for abbreviations.

<sup>a</sup> Three midlife memory status x two age cohort ANOVA; memory status x 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.

<sup>b</sup> Three midlife memory status x two age cohort ANOVA; memory status x 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.

### 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 three memory change status x two age cohort x two 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 x 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  $\epsilon 4$  allele, a three midlife memory change status x two age cohort x two APOE status ( $\epsilon 4$  -/- or -/+) ANOVA was conducted. Neither the APOE main effect ( $F_{1,65} = 2.2$   $p =$

0.14) nor the interactions with APOE were significant (cohort x APOE  $F_{1,65} = 1.4$   $p = 0.24$ ; memory change x APOE  $F_{2,65} = 0.5$   $p = 0.59$ ) while, as before, the midlife memory change x 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 OA, in comparison with OA decliners or stabler. Although total brain volume was lower in OA, volumes were similar among the improvers, decliners, and stabler in both the 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  $\sim 1\%$  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 et al., (2006) 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 5 years in comparison with a control. The effects of midlife memory improvement in this study, which represented an average change of 0.75 standard deviations over a 14-year period in midlife, had long-term outcomes in old age, up to 14 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 (Fig. 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 despite 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), compared with 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 with 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, semiautomated 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 7-year interval have been found to be approximately 0.20 SD and are small compared with 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.

## Disclosure Statement

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

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