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Supervisory experience at work is linked to low rate of hippocampal atrophy in late life

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ABSTRACT

Cultivation of an active cognitive lifestyle, including diverse and challenging educational, occupational and cognitively-loaded leisure activities may be protective against development of dementia but the mechanisms underlying this link are not clear. We used the *Lifetime Experiences Questionnaire* (LEQ) to assess the structural brain correlates of cognitive lifestyle in the Sydney Memory and Aging Study, a large population-based cohort of originally 1037 non-demented elderly aged over 70 years of age. After excluding those without structural Magnetic Resonance Image data or Mild Cognitive Impairment at their most recent assessment, 151 cognitively intact subjects were studied. Whole-brain voxel based morphometric analysis found that higher total *Lifetime Experiences Questionnaire* scores are linked with increased grey matter volume in the medial temporal lobe, especially in the hippocampus. Through a series of more specific analyses, we found that supervisory and managerial experience in midlife was the dominant contributor to this effect. Furthermore, in those with longitudinal neuroimaging data ($N=91$), we measured hippocampal structural changes over a 2–3 year period by gold-standard manual tracing. The rate of hippocampal atrophy in late-life in those with high level supervisory experience in midlife was five-times slower than those with no midlife supervisory experience ($p<0.001$). Individual differences in intracranial volume, age, gender, physical activity, depressive symptoms, or apolipoprotein ε4 genetic status could not explain these findings, nor could specific lifestyle patterns in late life. For the first time, we reveal that managerial and supervisory experience during our working life is connected to hippocampal integrity after retirement, some 20–30 years later. Our results stimulate several questions about the nature of work-related effects on longterm behaviour, structural neuroplasticity and neuroprotection, and may help explain differences in dementia-risk based on cognitive lifestyle.

Introduction

Maintaining an active cognitive lifestyle is by all accounts an important protective and modifiable risk factor in the development of dementia. Cognitive lifestyle, defined in relation to educational, occupational and cognitively-loaded leisure activities, has been linked to a reduced incidence of dementia in many long-term cohort studies (Valenzuela and Sachdev, 2006b), as well as a diminished rate of cognitive decline (Valenzuela and Sachdev, 2006a). Recently, we found that it is a combination of cognitive lifestyle factors across the lifespan, rather than any single factor, that is most protective against dementia (Valenzuela et al., 2011a).

Amongst cognitive lifestyle factors, studies of education have provided the least consistent results in terms of dementia risk and related brain changes. Whilst our meta-analysis showed that the odds ratio for incident dementia related to higher levels of education was 0.53, effects were highly variable between studies ($\chi^2=30.61$, indicative of significant heterogeneity across 15 studies) (Valenzuela and Sachdev, 2006b). Neuroimaging studies in non-demented older persons have been similarly inconsistent. Some studies have found that higher education is related to greater brain pathology, including brain atrophy (Coffey et al., 1999; Querbes et al., 2009) and larger volume of white matter hyperintensities (Brickman et al., 2011). By contrast, positive effects have also been reported between education and brain structure. For example, decreased hippocampal diffusion was found linked to higher education in healthy elderly (Piras et al.,

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2011) and a recent large study of non-demented individuals found that education was correlated with grey and white matter regional volumes (Foubert-Samier et al., 2012). Yet other studies have found no relationship (Christensen et al., 2009; Murray et al., 2011).

These contradictory findings may arise from the high degree of cognitive variability amongst aged non-demented individuals. For example, a positive correlation between education and medial temporal lobe white matter integrity in healthy older subjects was, in the same study, inverted in those with probable Alzheimer's Disease (AD) (Teipel et al., 2009). Heightened AD burden in those with greater educational attainment has also been found, but restricted to those with a MCI (Mild Cognitive Impairment)—no such relationship was reported in cognitively-intact elders in the same study (Garibotto et al., 2008; Seo et al., 2011). The relationship between cognitive lifestyle and brain structure is therefore likely to remain unclear in the absence of careful cognitive assessment to distinguish between normal cognition and MCI.

From a lifespan perspective, occupational complexity is the second major cognitive lifestyle factor after education and can be conceptually divided into a job's status as opposed to supervisory or managerial demands. Occupational status is often classified using nation-specific systems that take into account both a position's cognitive demands as well as socioeconomic profile. Greater occupational status is consistently linked to a reduced risk of dementia in cohort studies (meta-analysis odd ratio = 0.56, $\chi^2 = 18.95$ indicative of non-significant heterogeneity) (Valenzuela and Sachdev, 2006b), as well as a higher level of cognition in late life (Potter et al., 2008; Singh-Manoux et al., 2011). Schmand et al. (1997) compared the impact of occupational status in comparison to managerial experience, and found that being in charge of a number of people during one's working life was independently protective against dementia rather than job status per se. On the other hand, neuroimaging studies of occupation in older healthy individuals are quite limited. One study found higher occupational status linked with a reduction of glucose metabolism (Garibotto et al., 2008), another reported no significant correlation between occupation status and white matter hyperintensities or hippocampal atrophy (Murray et al., 2011). As far as we are aware, no study has to date investigated structural brain correlates of supervisory or managerial experience.

Diverse and mentally challenging day-to-day activities, hobbies, new learning and socialising are the third main factor in our conceptualisation of cognitive lifestyle. Long term cohort studies consistently link it to lower dementia incidence (meta-analysis odd ratio = 0.50, $\chi^2 = 4.98$ indicative of non-significant heterogeneity) (Valenzuela and Sachdev, 2006b). The neural correlates of late-life complex mental activity are yet to be investigated in isolation, but studies have combined this information with education and occupation to investigate cumulative cognitive lifestyle. Bartres-Faz and colleagues found that a more active cognitive lifestyle is associated with increased frontal lobe cortical thickness as well as overall larger brain volume in cognitive intact elderly, and observed the reverse in those with MCI (Bartres-Faz et al., 2009; Bosch et al., 2010; Sole-Padulles et al., 2009). Using our *Lifetime of Experiences Questionnaire* (LEQ) to assess cognitive lifestyle (Valenzuela and Sachdev, 2007), we found that higher LEQ scores were predictive of slower rates of hippocampal atrophy in non-demented elders (Valenzuela et al., 2008), but because this region was selected a priori, the long-term effect of cognitive lifestyle on other brain regions was not tested. Furthermore, our previous study and those of Bartres-Faz and colleagues relied on convenience or clinic-based samples, and so introduce potential bias and limit the generalizability of the findings.

Our interest was therefore to conduct the first longitudinal structural neuroimaging study of cognitive lifestyle within a large, population-based cognitively-intact ageing cohort. We carried out a series of consecutive analyses aimed at addressing increasingly more specific questions: (1) What is the link between overall cognitive lifestyle and grey matter volume? (2) Which lifestage, if any, contributes most strongly to this link? (3) Is there a specific type of complex mental activity at a specific time in life that drives the findings? (4) Are results robust to different structural MRI methodologies, and finally (5) Are the findings based on differential rates of atrophy as opposed to cross-sectional associations?

Methods

Subjects

Participants were drawn from the Wave II stage (first 2-year follow up assessment) of the Sydney Memory and Ageing Study (MAS), a prospective, population based study examining the predictors of cognitive decline in an elderly (70–90 years), originally non-demented, community dwelling sample (baseline N = 1037) (Sachdev et al., 2010). They were recruited randomly through the electoral roll from two electorates in eastern Sydney, Australia, where registration is compulsory. The Lifetime Experiences Questionnaire (LEQ) was administered by mail to all those enrolled in the study in July 2010 (N = 872). 555 completed forms were returned (return rate 64%). Individuals with MCI at the Wave II cognitive assessment have been removed from this dataset, leaving a sample of 302 cognitively intact individuals with LEQ data. Next, those subjects with a contemporaneous Wave II MRI brain scan (N = 151) formed the cross-sectional dataset. Amongst this sample, 138 subjects also had Wave I MRI data; 91 of these individuals had either the highest level of supervisory experience, or none, and constituted the longitudinal dataset. Fig. 1 shows the flow chart of subject recruitment. The study was approved by the human ethics committee of the University of New South Wales.

Lifetime of Experiences Questionnaire (LEQ)

LEQ booklets were mailed to all participants and returned using a prepaid envelope. Incomplete booklets were first screened out manually. An optical data scanner (OpScan iNSIGHT 4) was then used to scan and convert the LEQ responses into digital data. Finally, I.L. went through each questionnaire to verify the accuracy of the automated data entry process.

The basic structure of LEQ is shown in Fig. 2. Three life stages are defined: 1) Young Adult, ages 13–30 years; 2) Mid Life, ages 31–64; 3) Late Life, age 65 and above (Valenzuela and Sachdev, 2007). Furthermore, each life stage has two main sub-parts: A) Specific lifestage questions directed at the dominant cognitive lifestyle activity of each age range (and hence are different for each lifestage), and B) General mental activity questions that are identical and repeated for each lifestage. Total LEQ scores and subscores were calculated for each individual.

In addition, included within the LEQ booklet sent to all individuals were the following three physical exercise questions directed at each lifestage and analysed separately to the LEQ: i) How often did you take part in mildly energetic sports or physical activity (e.g. walking, carpentry, gardening, housework)? ii) How often did you take part in moderately energetic sports or physical activity (e.g. dancing, golf, lawn mowing, leisurely swim, easy bicycling)?, iii) How often did you take part in vigorous sports or physical activity (e.g. running, competitive tennis, squash, hard bicycling)? Each question had 6 response options (never, less than monthly, monthly, fortnightly, weekly, daily) and so each lifestage produced specific physical activity information (min 0–max 15) as well as a cumulative Physical Activity Score (PAS min 0–max 45).

Total LEQ and subtotals were treated as either a continuous or categorical variable. In the latter case, we split the whole sample into equal tertiles as in our previous studies (Valenzuela et al., 2008; Valenzuela et al., 2011a), and are referred to as low, medium or high LEQ groups.

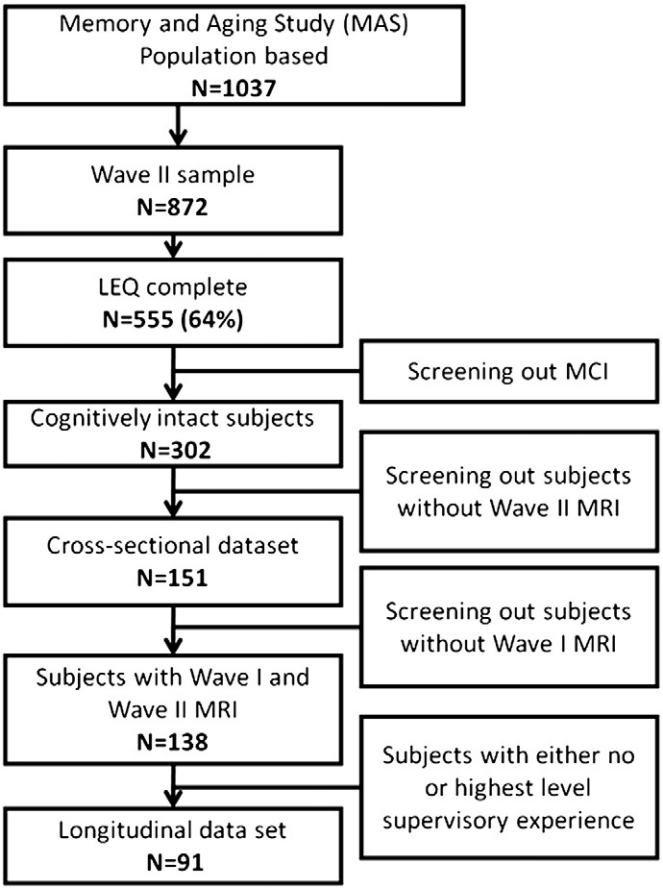

Fig. 1. Flow chart of subject recruitment.

MRI acquisition

All subjects were scanned on a Philips 3 T Achieva Quasar Dual scanner. Acquisition parameters for T1-weighted structural MRI scans were: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, 190 slices, and slice thickness = 1 mm without gap; yielding 1 × 1 × 1 mm^3 isotropic voxels. Analyses 1–4 analysed LEQ relationships with contemporaneous Wave II MRI scans acquired during 2008–2009. For the longitudinal-based Analysis 5, baseline Wave I MRI scans (2006–2007) taken two years prior to Wave II were used to calculate rates of hippocampal atrophy. All scans from Wave II were conducted on the same scanner; there were no major hardware upgrades during Wave II MRI collection.

Image processing

Preprocessing

We applied the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) method, available in the VBM toolbox (Ashburner, 2007). Processing procedures were implemented in SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) on MATLAB 7.6/R2008a (Math Works, Natick, MA, USA). Firstly, the original T1-weighted MRI scans were checked for obvious anatomical or positional abnormalities. Next, tissue segmentation was performed with Hidden Markov Random Field (HMRF) option to minimize the noise level using the segmentation function of SPM. The DARTEL toolbox was next utilized to generate a series of customized templates based on our whole sample (N = 151) to produce flow fields of GM and WM following iterative registration. Flow fields that parameterise the deformations of GM and WM were used to create the Jacobian modulated warped tissue class images. Spatial normalisation of GM to MNI space was achieved by using an affine transformation to the ICBM152 template. Finally, a 10-mm FWHM Gaussian kernel smoothing was performed and the smoothed modulated normalised GM data were ready for subsequent statistical analysis.

Voxel-Based Morphometry (VBM)

VBM analyses were performed using the second level analysis option in SPM. In Analyses 1 and 2, two sample t-tests were used to compare the high and low LEQ subgroups of interest after control for covariates. A core set of covariates was common to all analyses, namely age, gender, Physical Activity Score (PAS), Cardiovascular Risk Factor Scale (CRFS, based on aggregate cardiac and vascular risk factors as per; D'Agostino et al., 2008) and total intracranial volume (TIV). Additional covariates were added to analyses as required. Absolute

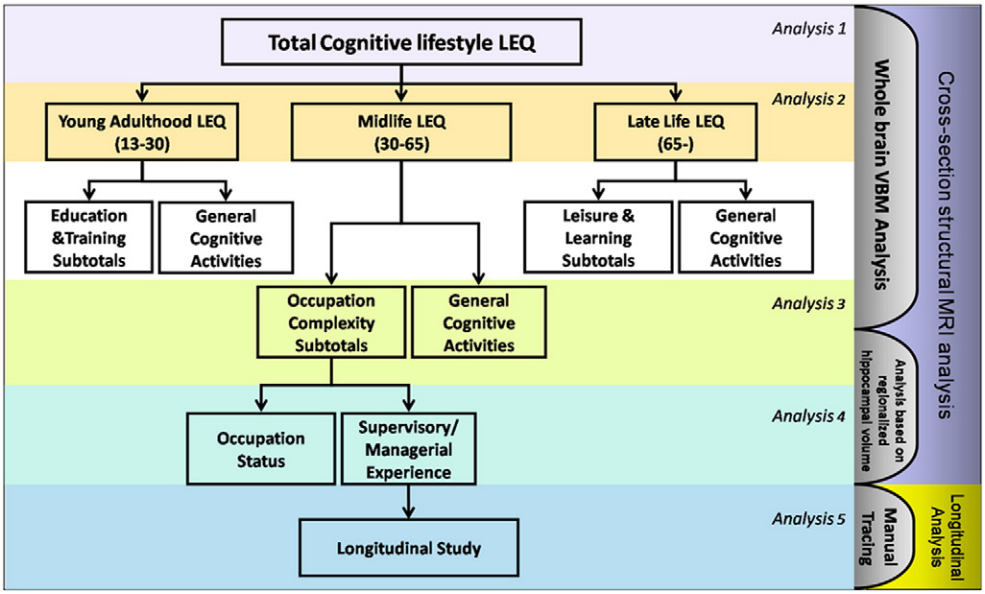

Fig. 2. Structure of the LEQ and overview of our analysis. Analyses 1 to 4 were cross-sectional studies examining the association between the indicated component of LEQ and brain structure. Analysis 5 was a longitudinal examination of Supervisory Experience and rate of hippocampal atrophy.

Table 1
General characteristics of the sample (N = 151).

	Mean	SD
Age	80.8	4.6
Sex (%female)	55.6	N/A
Education (years)	11.4	3.4
Mini Mental State Examination (MMSE)	29.2	1.1
Cardiovascular Risk Factor Scale (CRFS)	17.3	3.4
Geriatric Depression Scale (GDS)	2.1	2.2
Instrumental Activities of Daily Living (IADLs)	1.3	0.47
NART-r estimated premorbid IQ	109.9	9.9
Physical Activity Score (PAS)	13.2	2.5

threshold mask was set at 0.1. To correct for multiple comparison in VBM, areas with a p-value ≤ 0.05 following cluster-level Familywise Error (FWE) correction were considered significant, with an initial height threshold of $p \leq 0.005$ and the extent threshold to 50 contiguous voxels. Analysis 3 employed a multiple regression analysis to test for significant correlations between different aspects of midlife cognitive lifestyle and grey matter volume on a voxel-by-voxel basis. Identical thresholds were applied as above.

Regionalized hippocampal volume

In both Analysis 3 and Analysis 4, regional grey matter volumes were also acquired by applying an Anatomical Automatic Labeling (AAL) template on each individual's unsmoothed grey matter maps acquired by the same VBM preprocessing described above (Tzourio-Mazoyer et al., 2002). The AAL hippocampal mask was then used to extract regionalized hippocampal grey matter volumes.

Longitudinal hippocampal atrophy

Hippocampal volume was measured by manual tracing in those 91 individuals with high or nil supervisory experience and paired Wave I and Wave II MRI. To minimize error, we firstly pitch-rotated a standard template so that the long axis of the hippocampus was orientated horizontally on sagittal view. Then each subject's raw T1 image was rigid-body coregistered to this new template and coronally resliced. The left hippocampus was traced by CS from these coronal images using ANALYZE (version 10, Mayo Clinic) as published previously (Valenzuela et al., 2008). CS was blind to cognitive lifestyle and temporal information of the subjects for all measurements.

Statistical analysis

Statistical analysis of demographic information, LEQ scores, and regional GM volumes was performed using the PASW 18.0 statistical program (SPSS, Chicago, Illinois). Three models were used. Partial correlation was used to test the correlation between a continuous LEQ-derived variable and grey matter volumes. On the other, we used the General Linear Model (GLM) to test categorical effects between high and low cognitive life style groups on regionalized hippocampal volumes. Finally, we used a repeated measurement GLM to test for the interaction between TIME × GROUP (cognitive lifestyle) controlling for covariates as indicated.

Results

Characteristics of the sample

As seen in Table 1, our elderly sample was of above average estimated IQ, had minimal depressive symptoms and was cognitively normal. LEQ cognitive lifestyle information is shown in Table 2, including overall total, lifestage subtotals, and lifestage component subscores.

Potential bias in our LEQ-neuroimaging sample was evaluated by comparing the demographic, clinical and LEQ characteristics of those healthy subjects with Wave II MRI data (N = 151) and those without MRI (N = 151). Group tests found no differences on any variable. These results are available in Supplementary Table S2.

Analysis 1: whole-brain VBM analysis of total LEQ scores

Firstly, we found that total intracranial volume (TIV) was significantly correlated with total LEQ ($r = 0.2$, $p = 0.014$) and so TIV is included as a covariate for all analyses. Whole-brain VBM T-test comparison of high and low total LEQ groups revealed three significant regions (as part of one cluster), where individuals with higher LEQ scores had greater GM volume. One large significant cluster covered bilateral hippocampi and left amygdala (Fig. 3, Table 3).

Analysis 2: whole-brain VBM analysis of LEQ by lifestage

Two-group VBM analyses were conducted in order to determine which, if any, LEQ lifestage was most closely associated with preservation of grey matter volume. Comparison of high and low *Young Adulthood* LEQ groups produced no significant results or trends. Comparison based on *Late Life LEQ* also resulted in no significant differences in grey matter volume; however there were near-significant trends in the left parahippocampus in favour of the high Late Life LEQ group (see Supplementary Fig. S1 for further details).

However, when subjects were grouped on *Midlife LEQ*, those with higher midlife scores exhibited greater left hippocampal volume after FWE-correction and controlling for age, gender, CRFS, PAS and TIV (see Fig. 4, Table 4).

Table 2
Descriptive LEQ characteristics for the whole sample and comparisons between men and women.

	Total (N = 151)		Female (N = 84)		Male (N = 67)	
	Mean	SD	Mean	SD	Mean	SD
Total LEQ *	80.2	21.9	74.9	22.7	86.9	19.1
Subscores						
Young Adulthood LEQ (YA)	26.6	8.9	25.4	9.0	28.1	8.6
YA specific subtotal (Education & Training)*	12.7	7.1	11.0	6.9	14.8	6.8
YA General Cognitive Activities	18.4	4.0	18.9	4.3	17.7	3.4
Midlife LEQ (ML)*	31.8	11.7	28.3	12.3	36.3	9.0
ML specific subtotal (Occupational Complexity)*	14.5	7.7	11.0	7.5	19.0	5.6
ML General Cognitive Activities	14.2	3.9	14.1	4.2	14.2	3.4
Late Life LEQ (LL)	21.8	6.1	21.3	5.5	22.5	6.7
LL specific subtotal (Leisure & Learning)	9.3	2.6	9.2	2.4	9.4	2.8
LL General Cognitive Activities	16.3	4.5	15.9	4.1	16.9	5.0

* Significant difference between men and women, $p < 0.001$.

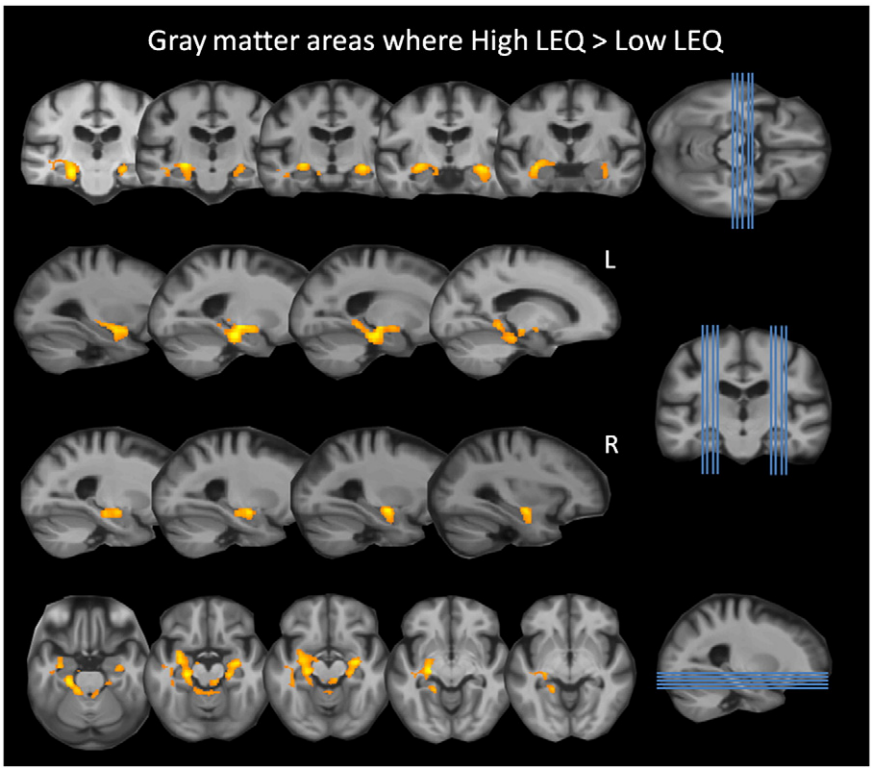

Fig. 3. Two group whole brain VBM showed that the high LEQ group has significantly less atrophy in one predominant cluster including the bilateral hippocampi and left amygdala (controlling for age, gender, cardiovascular risk factor score, physical activity score and total intracranial volume, whole brain cluster-level FWE correction).

Analysis 3: dissection of the midlife LEQ-hippocampal volume dependency

Midlife cognitive lifestyle was identified as salient to hippocampal grey matter volume in late life. We therefore carried out a further analytical step by comparing and contrasting the effect of the two subtotal components of Midlife LEQ (Occupational Complexity and General Cognitive Activities) on brain structure. Because we observed that Occupation Complexity subtotals were significantly higher in men than women (Table 2), we ran separate sex-specific analyses.

Firstly, using a voxel-based multiple regression analysis, we found a positive correlation between midlife *Occupational Complexity* and left hippocampal grey matter volume in men. In order to increase the specificity of this result, we expanded the list of covariates to include age, TIV, PAS, CRFS, *Young Adulthood LEQ subtotal*, *Late Life LEQ subtotal*, and *midlife General Cognitive Activities*; the result was conserved (Fig. 5, Table 5). No significant results were found in women. Corresponding analyses with *midlife General Cognitive Activities* as the independent variable (whilst controlling for *Occupational Status*) were non-significant in both men and women.

Next, to better demonstrate that these effects, we extracted each subjects' left and right hippocampus volumes using an AAL hippocampal template. As shown in Fig. 6, there was a significant partial correlation ($r = 0.375$, $p < 0.005$) between left hippocampal volume and Occupation Complexity subtotals for men, but not women, after controlling for the same covariates as above.

Table 3
Whole-brain VBM group analysis comparing high versus low LEQ.

Region	MNI coordinates			Peak t-value	Cluster size	$p_{FWE\ corrected}$
	X	Y	Z			
Left hippocampus	−21	−24	−15	4.15	2916	0.029
	−23	−19	−6	3.87		
Left amygdala	−30	−7	−14	3.67		
Right hippocampus	29	−12	−11	3.83		

Analysis 4: midlife occupation status vs. supervisory experience

We further deconstructed Occupational Complexity into occupational status and supervisory experience. The LEQ classifies an individual's history of major occupations according to the Australian Standard Classifications of Occupations (ASCO), with each job categorised into one of 10 hierarchical levels. Supervisory experience was measured as the maximum number of people that the individual had been in charge of or supervised, and was coded in one of four ategories: none, 1–5 people, 6–10 people and over 10 people.

Table 6 shows the results of partial correlation based on the whole sample and broken down by sex. Whilst midlife Occupation Complexity was significantly correlated with hippocampal volumes in the whole sample, this was clearly only the case in men and not women (Fig. 6). In men, both elevated Occupational Status and greater Supervisory Experience were positively associated with hippocampal volume in late life; in women only greater Supervisory Experience was predictive of greater hippocampal volume. Even after accounting for our full suite of covariates, plus the addition of Occupational Status into the model, high level Supervisory Experience was independently associated with enhanced hippocampal volume in late life in both men and women (Fig. 7).

Analysis 5: longterm effects of supervisory experience on rate of hippocampal atrophy

Finally, in order to cross-verify our AAL template-based results and disambiguate cross-sectional associations from possible long term effect on the rate of hippocampal atrophy, we carried out the gold-standard approach of manual tracing of the hippocampus at both the Wave II and I timepoints. AAL template-based hippocampal volumes

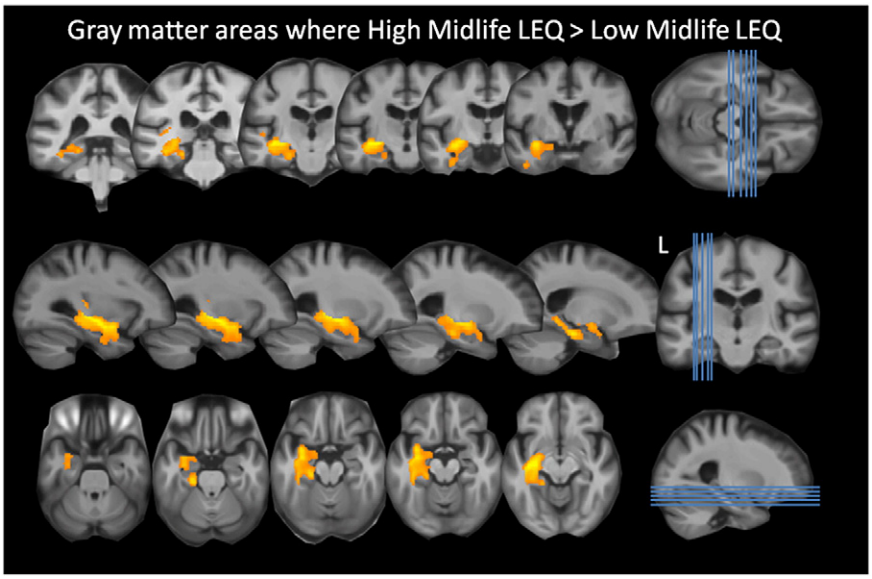

Fig. 4. Group VBM analysis showed that individuals with a high Midlife LEQ score had significantly more grey matter in the left hippocampus than those with a low score after control for age, gender, total intracranial volume, cardiovascular risk factor score, physical activity score (whole brain cluster-level FWE correction).

were highly correlated with traced volumes ($r = 0.71$, $p < 0.001$—see Supplementary Fig. S2) and so support our prior results.

Repeated measures analysis found a significant TIME × GROUP effect ($F = 55.2$, $df = 83$, $p < 0.001$), whereby those who had a high level of supervisory experience between the ages of 30–65 years ($n = 45$) had significantly less hippocampal atrophy over the 2–3 year follow-up period (in their 70s and 80s) compared to those with no experience ($n = 46$). On average, those with high supervisory experience had a 0.96% decline in hippocampal volume per year, whilst those with no such experience lost volume at a rate of 4.9% per year. There is no evidence of a differential effect between men and women, as the TIME × GROUP × SEX interaction was not significant.

In addition, we completed a longitudinal VBM analysis based on these 91 subjects. Results showed a trend for conserved volume in those with high managerial experience in the left hippocampal volume and in some other brain regions (see Supplementary results), however none reached significance after multiple comparison testing.

In order to potentially explain this finding, we tested for differences between the high and nil supervisory experience groups on sociodemographic, clinical and LEQ data (i.e., variables in Table 1). There were no differences between groups except that those with high levels of supervisory experience had significantly higher Young Adult LEQ subtotals (indicative of greater education and training experiences), a greater frequency of contact with family or friends in late life, and a trend towards a higher Late Life Leisure and Learning LEQ subtotal (see Table S1 Supplementary). In order to exclude these as possible confounding factors, we added these variables into our repeated measures GLM. After accounting for all variables in this comprehensive model (covariates: age, sex, total intracranial volume, cardiovascular risk factor score, physical activity score, young adulthood LEQ, late life LEQ) the interactive effect of midlife supervisory experience on rate of late life hippocampal atrophy remained highly significant ($F = 56.4$, $df = 78$, $p < 0.001$). Furthermore, this effect was largely unchanged ($F = 55.2$, $df = 72$, $p < 0.001$) after adding Apolipoprotein ε4 allele (APOE4) positivity, NART-IQ and the Geriatric Depression Scale as covariates (Fig. 8).

Finally, because of evidence of a trend towards a higher Late Life Leisure and Learning subtotal in those with high supervisory experience, we investigated whether any individual item moderated the link between management and hippocampal atrophy. Three statistical relationships were tested for each item: i) Did supervisory experience in midlife modify item responses in late life?; ii) Did the item covary with rate of hippocampal atrophy?; and iii) Did inclusion of the item in our comprehensive repeated measures GLM eliminate the connection between supervisory experience and hippocampal atrophy? As can be seen in Table S1 (Supplementary), no individual item satisfied these criteria. Frequency of contact with family and friends in late life was significantly higher in those with supervisory experience in midlife, and this item significantly correlated negatively with hippocampal atrophy rate. However addition of this item into our model did not eliminate the effect of supervisory experience on rate of hippocampal atrophy. This and other correlations or trends are reported in Table S1. Overall, we could not identify a specific sociodemographic, clinical or behavioural trait in experienced managers or supervisors that could explain their protection from hippocampal atrophy some 10–20 years after the end of their working life.

Table 4
Whole-brain VBM group analysis comparing high Midlife versus low Midlife LEQ.

Region	MNI coordinates			Peak t-value	Cluster size	$p_{FWE\ corrected}$
	X	Y	Z			
Left hippocampus	−27	−15	−8	3.88		
	−27	−25	−3	3.79	3545	0.006
	−21	−24	−17	3.76		

Discussion

Beginning with a broad interest in cognitive lifestyle and brain structure, progressively more specific analyses revealed a new, unexpected and independent link between supervisory experience in midlife and diminished rate of hippocampal atrophy in late life. This result was replicated using different types of volumetric methodologies and observed in a population-based cohort that had excluded preclinical dementia through rigorous neuropsychological evaluation. Our findings therefore extend our understanding of the link between cognitive lifestyle in middle-age and long-term neuroplasticity, particularly the potential role for complex mental stimulation during our working lives to shape hippocampal structure and integrity.

The nature of what we do for work and its influence on long term changes in cognition, brain structure and dementia risk are only beginning to be understood (Singh-Manoux et al., 2011; Staff et al.,

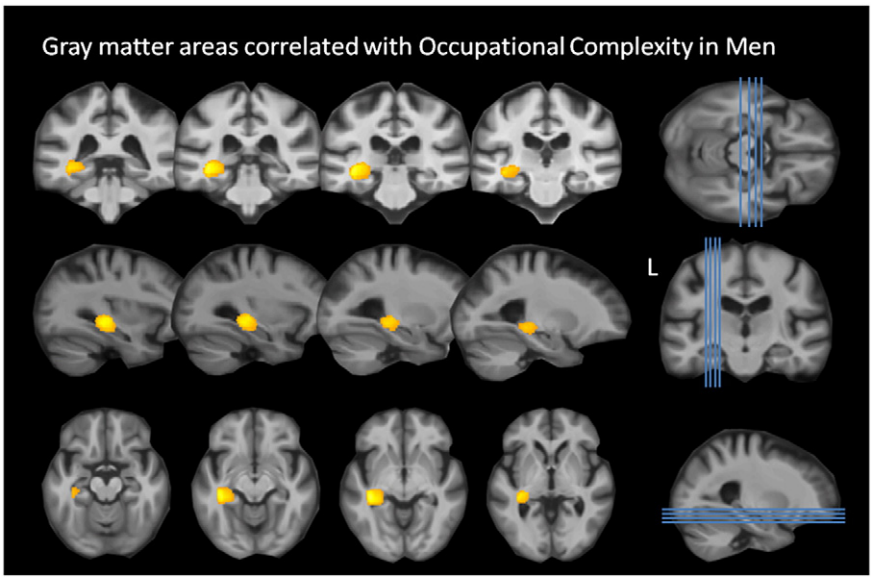

Fig. 5. Voxel-based multiple regression of midlife Occupation Complexity in men. There was a significant correlation with left hippocampal grey matter volume after controlling for age, TIV, cardiovascular risk factor score, physical activity score, Young Adult LEQ, Late Life LEQ, midlife General Cognitive Activities (whole brain cluster-level FWE correction).

2004; Woollett and Maguire, 2011). In women, a cohort study found an increased risk of dementia in those who had never been appointed to a leading position (Bickel and Kurz, 2009). In male veterans, intellectually demanding work that required complex communication or interpersonal interactions was independently associated with enhanced cognitive performance in late life (Potter et al., 2008). Schmand et al. (1997) specifically found that supervisory experience, but not occupational status, was related to incident dementia risk over and above variance in years of education or premorbid IQ. The interpersonal and cognitive demands of complex occupations may therefore be more important to long term dementia risk than education alone (Stern et al., 1995).

Midlife occupational complexity also had a stronger impact on grey matter integrity than educational achievements in young adulthood. We found that midlife supervisory experience—and not occupational status—was the specific cognitive lifestyle activity linked to attenuated hippocampal atrophy in men and women. This finding was independent of intracranial volume and so not likely to reflect innate or developmental differences in maximal brain size. This finding remained significant after accounting for differences in age, sex, depressive symptoms, physical exercise patterns, intracranial volume, APOE4 status, premorbid IQ, as well as other cognitive lifestyle activities in midlife and late life. Whole-brain VBM analysis also confirmed that this protective association was circumscribed to the hippocampus, and our results were replicated using both template-based analysis and gold-standard blinded manual tracing. Our findings therefore stimulate several questions about the long term influence of cognitive lifestyle on brain structure.

Managerial positions are characterised by brief and fragmentary interactions that rely heavily on verbal communication (Boatsman et al., 1983; Gioia and Sims, 1983; Gordon et al., 1975; Kalbfleisch and Davies, 1993; Penley et al., 1991; Simons, 1993). It has been estimated that leaders in corporate firms spend 85% of their time with other people and 60% of their working hours in meetings (Bandiera et al., 2011). Indeed, communication is the cornerstone of effective management (Bolton and Dewatripont, 1994; Christoffels et al., 2006; Davis, 1968; Garicano, 2000) as well as successful supervision (Noe, 1988). Linguistic competency, verbal comprehension and verbal memory may therefore represent key cognitive processes in high-level management and supervision. Given the long history of research implicating the left hippocampus in the mediation of verbal comprehension and memory (Davis and Johnsrude, 2003; Frisk and Milner, 1990; Kelley et al., 1998; Muriel Deutsch and Lezak, 2004; Smith and Milner, 1981), it is interesting that our findings were heavily localised to the left hippocampus. Moreover, the observed effects were strong: rates of left hippocampal atrophy in experienced supervisors were 5-times lower than in individuals with no such

Table 5
Whole-brain VBM regression analysis of midlife occupation complexity in men.

Regions	MNI coordinates			Peak t-value	Cluster size	$p_{FWE\ corrected}$
	X	Y	Z			
Left hippocampus	−36	−30	−5	5.25	902	0.046

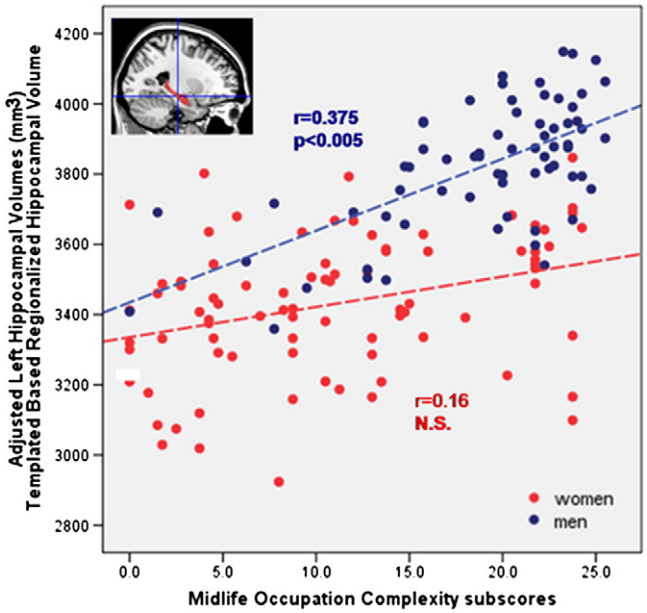

Fig. 6. Partial correlation between AAL-template based left hippocampal volume and midlife Occupational Complexity LEQ subtotal. Adjusted for age, TIV, cardiovascular risk factor score, physical activity score, Young Adult LEQ, Late Life LEQ, midlife General Cognitive Activities.

Table 6
Dependence of AAL-template based hippocampal volume in late life on midlife occupational status and supervisory experience.

Whole sample (N = 151)	Occupation complexity subtotal		=	Occupation status		+	Supervisory experience	
	Correlation[a]	p		Correlation[a]	p		Correlation[b]	p
Left hippocampus	**0.187**	**0.027**		0.071	0.402		**0.206**	**0.016**
Right hippocampus	**0.185**	**0.025**		0.095	0.234		**0.144**	**0.049**
Average	**0.193**	**0.013**		0.085	0.305		**0.172**	**0.045**
Women (N = 84)	Correlation[a]	p		Correlation[a]	p		Correlation[b]	p
Left hippocampus	0.016	0.896		0.013	0.933		**0.289**	**0.014**
Right hippocampus	0.053	0.654		0.025	0.416		**0.215**	**0.05**
Average	0.031	0.785		0.023	0.745		**0.242**	**0.04**
Men (N = 67)	Correlation[a]	p		Correlation[a]	p		Correlation[b]	p
Left hippocampus	**0.375**	**0.003**		0.297	**0.021**		**0.325**	**0.012**
Right hippocampus	**0.354**	**0.005**		0.296	**0.022**		**0.261**	**0.046**
Average	**0.365**	**0.004**		0.318	**0.016**		**0.307**	**0.018**

Bold indicates partial correlation p-value less than 0.05.
[a] Partial correlation test, controlling for age, gender (in total sample analysis only), total intracranial volumes, cardiovascular risk factor score, physical activity factor, young adulthood LEQ, late life LEQ, midlife general complex activity.
[b] Partial correlation test, controlling for age, gender (in total sample analysis only), total intracranial volumes, cardiovascular risk factor score, physical activity factor, young adulthood LEQ, late life LEQ, midlife general complex activity and occupation status.

experience. In fact, whilst the overall rate of atrophy in our participants (2.8%) was well in line with results from a meta-analysis (Barnes et al., 2009), by segregating subjects on the extent of supervision, we uncovered a below-average 0.96% pa atrophy rate in those with high level experience, compared to an elevated rate of 4.9% pa in those who were never in charge of another person, approaching atrophy rates seen in AD (Barnes et al., 2009).

Yet how might supervisory experience in midlife lead to diminished rates of hippocampal atrophy some 20–30 years later? Clearly, more resesearch is required but we suggest the possibility that repetitive and challenging verbal comprehension and memory demands inherent in supervising or managing large groups of individuals may set off a cascade of neuroplastic changes in the left hippocampus. Taxi-drivers, for example, not only have a larger hippocampus compared to non taxi-drivers (Maguire et al., 2000), but also undergo structural plasticity in the posterior tail of the hippocampus following successful completion of driver training (Woollett and Maguire, 2011). By contrast, our findings were evident throughout the head and body of the structure—a brain region selectively vulnerable to atrophy in early AD and a prognostic biomarker of risk for transition to dementia (Devanand et al., 2007; Gosche et al., 2002; Jack et al., 1999). It is possible that the relative protection from hippocampal atrophy afforded by high level supervision and management may be one mechanism by which an active cognitive lifestyle also lowers dementia risk.

At a cellular level, a recent population-based clinicopathological study found no evidence that a more active cognitive lifestyle increases hippocampal neuronal numbers or decreases AD pathology, however, this study examined the implications of occupational status rather than supervisory experience per se (Valenzuela et al., 2011b). Rather, our observed effects may potentially reflect neurotrophic changes on the synaptodendritic compartment, the dominant component of the neuropil (Bennett, 2011). Support for such a mechanism can be seen in animal studies of environmental enrichment that found both volumetric expansion of the hippocampus (Kempermann et al., 1997), as well as profound upregulation of synaptic density (Rampon et al., 2000; Moser et al., 1994; Nithianantharajah and Hannan, 2006; Olson et al., 2006). Whilst definitive human neurobiological data are lacking, similar mechanisms may be implicated in training-dependent increases in grey matter volume following motor training (Boyke et al., 2008) and cognitive brain training (Engvig et al., 2010; Suo and Valenzuela, 2012).

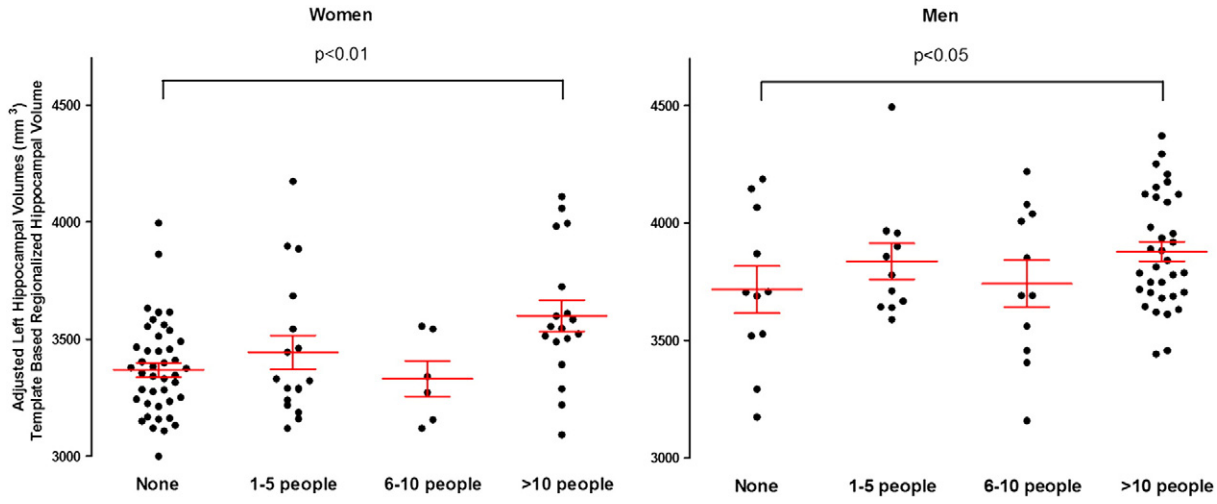

Fig. 7. Supervisory experience in midlife has a significant effect on hippocampal volume in late life in both men and women. Estimated marginal AAL template-based hippocampal means corrected for: age, total intracranial volumes, cardiovascular risk factor score, physical activities score, young adulthood LEQ, late life LEQ, midlife general cognitive activities, and midlife occupational status.

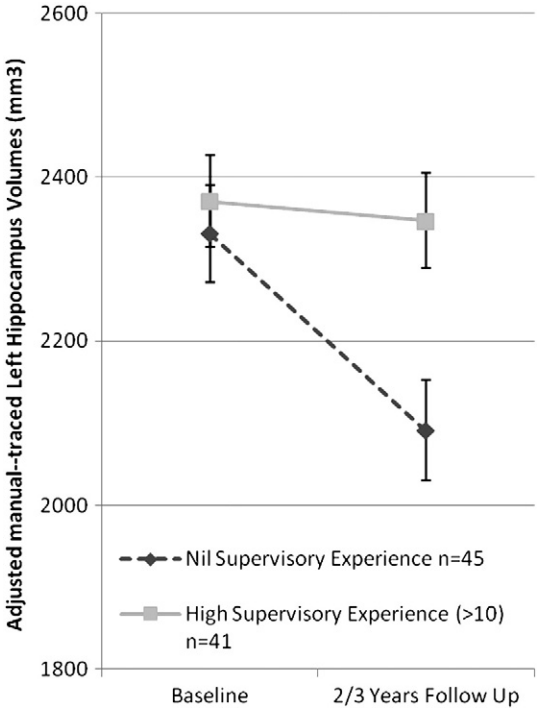

Fig. 8. Rate of hippocampal atrophy in late life is significantly lower in individuals with a high level of supervisory experience in midlife compared to those with no supervisory experience ($p<0.001$, controlling for age, gender and total intracranial volume, cardiovascular risk factor score, physical activity score, young adulthood LEQ, late life LEQ, Apolipoprotein ε4 allele positivity, premorbid IQ and the Geriatric Depression Scale, error bar = standard error).

At the behavioural level, we also found evidence that being in charge of others throughout one's working life may habituate a person towards seeking out a more active cognitive lifestyle after retirement. Indeed, we found a trend for higher late life LEQ subscores in experienced supervisors, and they made significantly more contact with their friends and family at the time of their brain imaging than those who had never been in charge of others (Table S1). Whilst late life social contact was also associated with a slower rate of hippocampal atrophy, inclusion of this potential mediating variable did not eliminate the protective link between supervisory experience in midlife and late life hippocampal atrophy (Table S1). Possible mediating effects of a range of other sociodemographic, clinical and individual cognitive lifestyle activities in late life were also tested, and whilst some trends were found, no one factor could explain our findings. Some residual cognitive lifestyle or behavioural factor that we did not measure may of course be implicated. For example, well known predictors of success in professional jobs that require workforce management include intelligence and personality (Holland, 1968). Also, we recognise that there are more dimensions to work other than managerial experience or occupational status. Work factors not measured by the LEQ may therefore have additional links with hippocampal volume. Inclusion of estimated premorbid IQ did not affect our results, but we did not measure more distal developmental characteristics such as extraversion or introversion, and so these personality factors may connect both a propensity to occupational supervision as well as social engagement after retirement. Further research is required to clarify long term behavioural antecedents and consequences of workforce management and its impact on the brain.

Finally, because of the evident differences in occupational history in men and women of this age, we split most of our analyses by sex and suffered a resultant decrease in power. Yet despite this, a link between supervisory experience and rates of hippocampal atrophy were conserved in men and women separately, suggestive of a generalised effect. Furthermore, this distribution of occupational experience matches that of the wider Australian population of this generation (Anker, 1997; Watts, 2003), and so underscores the benefit of starting with a population-based cohort.

In conclusion, we conducted the first whole-brain structural MRI investigation of cognitive lifestyle in a large, population-based healthy ageing cohort. VBM analysis confirmed that the influence of cognitive lifestyle was concentrated in the hippocampus. We then used a combination of VBM, template-based analysis and manual tracing to drill down on this result. Unexpectedly, supervisory experience in midlife was not only an independent predictor of hippocampal volume in late life, but also predictive of a five-fold decreased rate of hippocampal atrophy some 20–30 years later. We were able to exclude several possible alternate explanations, including lifespan changes in physical activity or differences in late-life mental activities, APOE genetic status, premorbid IQ or mood symptoms. Our findings stimulate several questions about the influence of cognitive lifestyle on brain structure, and suggest that complex and challenging supervisory experiences in midlife may set off a chain reaction of neuroplastic changes that continue well past retirement.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.08.015.

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