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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.