Cognition and the Middle-Aged Brain

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The neural correlates of memory encoding in young and middle-aged males: Age and performance-dependent differences

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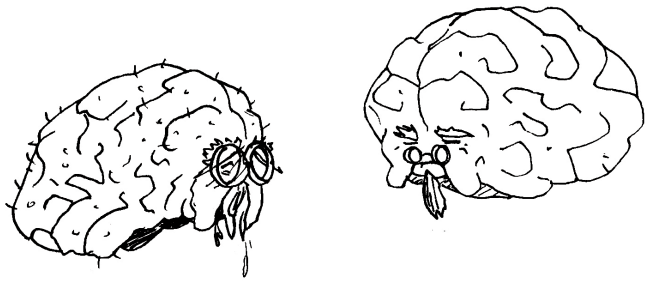


ABSTRACT

Cognition declines across the adult lifespan. Yet, ageing studies primarily utilise comparisons between young and old (60+) adults. Hence, little is known about age-related changes in middle-aged adults. Age-related cognitive decline in middle age may have implications for workplace performance and satisfaction, and thus affect a large proportion of the workforce. Therefore, we examined age-related differences in episodic memory encoding performance and brain activation between young (25-35 years) and middle-aged (40-61 years) professionals using functional magnetic resonance imaging. Furthermore, we investigated differences within the middle-aged group between a low-performing subgroup and a high-performing subgroup. An event-related analysis was used to examine encoding activation on the basis of performance on a subsequent recognition task; encoding task words were categorised according to whether they were subsequently remembered or forgotten. Results are in accordance with findings from previous studies comparing young and old adults. Middle-aged adults showed greater recruitment of the bilateral dorsolateral prefrontal cortex (DLPFC) during subsequently remembered words than young adults, with the age-related increase in activation in the right DLPFC evident to a greater extent in low than in high-performing middle-aged adults. These findings contribute to ongoing discussion regarding the nature of age-related prefrontal over-recruitment; findings corroborate the suggestion that over-recruitment of the right DLPFC does not serve a compensatory function in the support of a higher level of performance in ageing adults and may instead represent an age-related decline in neural efficiency.

* This chapter is based on data from fMRI study 1 (control session) and study 2 (placebo session).

INTRODUCTION

Healthy cognitive ageing is thought to impact most heavily on episodic long-term memory (Reuter-Lorenz and Park, 2010), with cross-sectional neuropsychological studies showing a decline in episodic memory across the adult lifespan (Park et al., 2002; Van der Elst et al., 2005; Verhaeghen and Salthouse, 1997). Insights into the neural correlates of this decline, however, are primarily provided by imaging studies comparing young and old (60+ years) adults. Hence, little is known about brain activation underlying episodic memory changes in middle age (40 to 60 years). In the present functional magnetic resonance imaging (fMRI) study, we investigate age-related differences in activation during successful episodic memory encoding in healthy young and middle-aged males.

Changes in episodic memory prior to the age of 60 are more controversial than changes in older adults (Salthouse, 2010). For example, in contrast to cross-sectional ageing studies, a longitudinal analysis indicated that episodic memory decrements only appear after the age of 60 (Ronnlund et al., 2005). However, cognitive decline already present in middle age may not yet manifest robustly in behavioural measures due to the action of neural compensation processes that preserve performance at the behavioural level. Therefore, fMRI can provide valuable insights into age-related changes present in middle age, as compensatory brain activation processes can be detected using fMRI even when task performance is equivalent (Park and Reuter-Lorenz, 2009).

Functional MRI has been used to investigate successful memory encoding activation using the subsequent memory paradigm (Paller and Wagner, 2002). In this paradigm, items studied during an encoding task are classified according to performance on a subsequent recognition task as subsequently remembered or subsequently forgotten. Functional MRI studies examining activation related to successful encoding in young and old adults have primarily reported age group differences in the prefrontal cortex (PFC) and medial temporal lobes (MTL). Studies have reported increased left dorsolateral PFC (DLPFC) recruitment coupled with decreased (left or bilateral) MTL function during successful encoding in old compared to younger adults (Dennis et al., 2007; Gutchess et al., 2005). These findings led to the suggestion that DLPFC activation functionally compensates for an age-related reduction in MTL function. A study by Morcom et al. (2003) reported that activation related to successful encoding was distributed more bilaterally in the PFC in older adults than in younger adults (in whom activation was primarily left lateralised), but did not differ in MTL. This pattern of PFC activation is consistent with the 'Hemispheric Asymmetry Reduction in Older Adults' (HAROLD) account of cognitive ageing proposed by Cabeza (2002). Although bilateral PFC activation in older adults may also represent neural compensation, an alternative explanation attributes this activation pattern to cortical dedifferentiation (Buckner and Logan, 2002; Logan et al., 2002). The cortical dedifferentiation account suggests that ageing is associated with a decrease in processing efficiency in the brain, whereby older adults consequentially fail to allocate resources in a selective manner. Therefore, the neural compensation and cortical dedifferentiation accounts make contrasting predictions regarding the relationship between brain activation and performance: neural compensatory activation can be expected to support a high level of task performance, whereas cortical dedifferentiation can be expected in relation to

poorer performance.

Recently, a number of fMRI studies have examined the relationship between age-related activation differences and successful encoding performance. These studies demonstrated that greater bilateral PFC activation is primarily apparent in poorer performing older (58 – 82 years) adults (Duverne et al., 2009; Miller et al., 2008). This finding is consistent with the suggestion that increased recruitment of the right PFC is deleterious, rather than beneficial, to performance (Rajah and D'Esposito, 2005; Spreng et al., 2010). As such, these results do not support the neural compensation account and are instead more consistent with cortical dedifferentiation. However, the investigators note that findings do not necessarily mean that increased right PFC activation does not benefit performance, as this pattern of activation may reflect an adaptation in poorer performing older adults in response to greater cognitive decline.

In the present study, we aimed to determine differences in successful encoding activation between 1) young and middle-aged males, and 2) between low- and high-performing middle-aged males. Based on previous studies, we expected to find age-related activation differences in the PFC and MTL, and expected that middle-aged adults would show increased and more bilateral PFC activation than young adults. Furthermore, we expected that increased right PFC recruitment in middle-aged adults would be greater in low performers than in high performers. Findings provide insight into activation differences underlying age-related episodic memory decline in middle age and take a step towards arbitrating between neural compensation and cortical dedifferentiation accounts of these age-related differences.

MATERIALS AND METHODS

Participants

Fourteen young (25 - 35 years) and 39 middle-aged (40 – 61 years), right-handed males took part in the study. Inclusion criteria specified a high level of education and fulltime employment in a white-collar profession, increasing population homogeneity. Volunteers were screened for significant past or present physical or psychiatric illness, medication use (other than antihypertensives in two middle-aged participants), alcohol or drug abuse, nicotine use, and MRI contraindications. The study was approved by the medical ethical committee at Maastricht University academic hospital. Participants gave informed consent prior to their paid participation.

Design

In the present analysis we made use of data from the control session of two separate intervention studies in which the same tasks were administered in two similar randomised, controlled, crossover designs. In both studies the control session followed the same procedure; participants completed pre-scan subjective rating scales, were scanned during the encoding and recognition tasks, and then completed the same subjective rating scales post-scan. Neuropsychological tests were administered in a separate session 1-2 weeks before the fMRI session, at which time the encoding and recognition tasks were also

practiced in a dummy scanner to familiarise participants with the scanning environment and minimise practice effects.

Neuropsychological testing

Tests known to show an age-related increase or decrease in performance were administered to provide an indication of the cognitive characteristics of our sample. General cognitive functioning (information processing speed) was tested using the Letter Digit Substitution Test (LDST) (van der Elst et al., 2006). The Dutch version of the National Adult Reading test (DART) (Nelson, 1991) was administered as a measure of mental ability (intelligence) based on vocabulary.

fMRI paradigm

During the encoding (6 min) and recognition (16 min) tasks, 100 words were presented one-by-one on the screen in pseudorandom order such that the proximity of highly semantically or phonetically similar words was minimised. Words were divided equally into four semantic categories: food (F), animals (A), utensils/tools (U) and landscape features (L). During encoding, participants were instructed to indicate the category to which a word belonged by pressing the appropriate button, using the left- and right-hand middle and index fingers. The categories were displayed at the bottom of the screen as each word was presented (as: F A U L). Participants were aware that they would subsequently be required to remember the encoding task words. During recognition, the same 100 'old' words were presented, plus an additional 100 'new' words. Participants were instructed to indicate with a button-press response whether they judged each word to be old or new, and how confident they were about this judgment. Response options therefore included: definitely old, probably old, probably new, and definitely new (displayed at the bottom of the screen as: Old 1 2 3 4 New). Encoding and recognition tasks were separated by a period of about 15 min, during which participants completed an unrelated task (involving letters only, making interference with the present task unlikely).

Encoding task words were presented in blocks of 8 stimuli followed by three null trials (consisting of a fixation point). Words were displayed in the center of the screen for 2500 ms, followed by a jittered inter-trial interval (500 - 1250 ms). The tasks were practiced with 200 words from the categories sport, country, city and occupation.

Subjective rating scales

The neural compensation account is commonly described in relation to cognitive effort, where compensatory activation is suggested to reflect the exertion of increased cognitive effort in order to maintain performance despite cognitive impairment. However, the sustained exertion of cognitive effort is associated with increased subsequent feelings of task-related fatigue (DeLuca, 2005; Lorist, 2008) and may lead to an experience of greater task-related workload. Hence, we included subjective fatigue and workload ratings as complementary information in the interpretation of encoding performance and brain activation differences.

The Dutch short visual analogue scale version of the Profile of Mood States (POMS)

(Wald and Mellenbergh, 1990) was administered before (time 0) and after (time 1) MRI scanning. The POMS fatigue (6 items: 0 = low fatigue, 100 = high fatigue) and vigour (5 items: 0 = low vigour, 100 = high vigour) scales are recommended measures of the mood of energy and fatigue in investigations that are short in duration (O'Connor, 2006).

The NASA Task Load Index (NASA TLX: Hart and Staveland, 1988) was administered at time 1 to measure the subjective experience of workload during the scanning session. The NASA TLX workload score is calculated based on subscales targeting mental demand, physical demand, frustration, effort, performance and time pressure, and provides an indication of the costs of maintaining task performance.

MRI acquisition

30 participants' (aged 25 – 61) scans were acquired in a 3 Tesla Philips whole body scanner (Philips Achieva, Philips Medical Systems, Best, the Netherlands). A body coil was used for RF transmission and an 8-element SENSE head coil (SENSE-factor 2) for signal detection. During the encoding task, approximately 180 EPI scans were made (TR = 2000 ms, TE = 35 ms, number of slices = 32, image matrix = 64 x 64, voxel size = 4 x 4 x 3.5 mm). A T1-weighted anatomical scan was also acquired for anatomical reference (image matrix = 256 x 256, number of slices = 150, voxel size = 1 x 1 x 1 mm).

23 participants' (aged 40 – 61) scans were acquired in a 3 Tesla Siemens head scanner (Siemens MAGNETOM Allegra, Siemens Medical systems, Erlangen, Germany) with an 8-channel head coil. Again, approximately 180 EPI scans were made during the encoding task (TR = 2000 ms, TE = 30 ms, number of slices = 32, image matrix = 64 x 64, voxel size = 3.5 x 3.5 x 3.5 mm). A T1 weighted anatomical (ADNI) scan was also acquired for anatomical reference (image matrix = 256 x 256, number of slices = 192, voxel size = 1 x 1 x 1 mm).

fMRI analysis

SPM8 (Statistical Parametric Mapping: Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London) was used to preprocess and analyse the fMRI data. Preprocessing steps included: slice time correction, realign and unwarp, coregistration, spatial normalisation (MNI space using individual spatial normalisation parameters obtained during structural image segmentation), and smoothing (FWHM 6 mm). Functional MRI data were analysed in an event-related analysis in which activity related to the various event types was modeled by convolving a vector of the onset times with the canonical hemodynamic response function within the context of the general linear model. Incorrectly categorised words during the encoding task were modeled separately as errors while correctly categorised words were modeled based on subsequent memory performance during the recognition task as: (1) subsequently remembered (with high confidence) and (2) subsequently forgotten (including subsequently recognised with low confidence and subsequent misses, i.e. old items incorrectly judged new with low or high confidence) (Dennis et al., 2008; Duverne et al., 2009; Morcom et al., 2003).

Activation contrasts were computed for each participant using the successful encoding contrast (subsequently remembered minus subsequently forgotten events) and for

subsequently remembered and forgotten events separately (subsequently remembered and subsequently forgotten events were contrasted with null events). We included subsequently remembered and forgotten contrasts separately in our analysis as previous studies have shown small effects and a lack of correlation with performance using the successful encoding contrast even when measures were taken to boost robustness (e.g., Duverne et al., 2009). Individual successful encoding, subsequently remembered and subsequently forgotten activation contrasts were entered into separate one-sample t-tests in SPM8 to examine task-related activation and into independent samples t-tests to identify age-related activation differences between young and middle-aged adults (with scanner as a covariate in the model to account for data collection in two different MRI scanners). Activation differences between young adults, low-performing middle-aged and high-performing middle-aged adults were firstly examined by entering individual successful encoding, subsequently remembered and subsequently forgotten activation contrasts into separate Full Factorial models (again with scanner as a covariate). Activation was examined at p(uncorrected) < .001 with a cluster size threshold > 10, with reported peak activation significant at $p < .05$ family wise error (FWE) corrected for multiple comparisons following small volume correction for the PFC and MTL (using AAL regions defined using the SPM8 wfupickatlas toolbox: Maldjian et al., 2004; Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). Secondly, activation differences between young, low- and high-performing middle-aged adults were examined within regions that showed a significant main effect of age group using region of interest (ROI) analyses. ROIs were constructed by making 5 mm spheres around peak activation coordinates from clusters showing a significant main effect of age in the previous t-test (and masking to ensure inclusion of gray matter only). ROI analyses were conducted using the MarsBaR toolbox for SPM (Brett et al., 2002).

Behavioural statistics

All behavioural analyses were carried out using PASWstatistics (version 18.0). Analysis of variance (ANOVA) was used to compare young adults and low- and high-performing middle-aged adults on the neuropsychological tests, subjective rating scales and memory task accuracy and reaction time (RT). Memory task accuracy was examined in terms of the number of correctly categorised words during the encoding task, and the number of subsequently remembered and subsequently forgotten words on the recognition task as well as corrected recognition scores (the number of remembered words minus the number of false alarms). The corrected recognition score corrects for differences in the response criterion (participants who have a greater tendency to identify words as 'old' with high confidence during the recognition task will show more correctly judged 'old' words, but also more false alarms i.e. 'new' words incorrectly judged to be 'old'). Encoding task RT was examined in terms of RT to subsequently remembered and subsequently forgotten words.

RESULTS

Low- and high-performing subgroups of the middle-aged adults were segregated using a median split based on corrected recognition scores, resulting in 20 low-performing and 19 high-performing middle-aged adults. NASA TLX scores from one low- and one high-

performing middle-aged participant were missing due to a procedural error.

Neuropsychological results

Scores on the LDST and DART are shown in Table 1. No significant differences between young, low- or high-performing middle-aged adults were evident on the LDST. A main effect of group was found on the DART ($F(2, 50) = 6.22$, $p = .004$), with follow-up t-tests showing higher scores in both low-performing ($t(32) = 3.08$, $p = .004$) and high-performing ($t(31) = 2.98$, $p = .006$) middle-aged adults than in young adults.

Table 1 | Age, Neuropsychological test performance, Encoding task performance and subjective ratings.

		Young	Low-performing Middle-aged	High-performing Middle-aged
Age		30.9 (3.0)	50.3 (5.4)	52.1 (6.3)
Neuropsychological test performance				
LDST		57.00 (8.11)	53.10 (7.72)	58.00 (8.37)
DART * [a, b]		80.86 (7.78)	87.90 (5.58)	88.52 (6.96)
Encoding task performance				
Categorisation accuracy		93.21 (3.93)	92.50 (4.74)	94.94 (2.54)
Subsequently remembered words * [a,c]		54.79 (15.10)	37.55 (21.83)	59.05 (9.8)
RT during subsequently remembered		1106 (149)	1133 (145)	1144 (152)
Corrected recognition scores * [a,c]		41.14 (13.10)	24.95 (10.34)	48.95 (9.21)
Subjective ratings				
Fatigue	Time 0	26.37 (13.35)	23.74 (12.76)	24.96 (17.70)
	Time 1	32.89 (19.21)	33.63 (15.05)	31.94 (20.86)
Vigour	Time 0	69.46 (15.81)	75.89 (16.75)	77.96 (13.84)
	Time 1	65.14 (23.22)	66.35 (17.53)	69.52 (17.59)
Workload	Time 1	50.05 (17.80)	53.67 (14.35)	41.81 (18.84)

Mean (standard deviation) scores. * shows a significant difference with [a] denoting a difference between young and low-performing, [b] a difference between young and high-performing and [c] a difference between low- and high-performing middle-aged adults.

fMRI task behavioural performance

Mean accuracy and RT are shown in Table 1. Young, low- and high-performing middle-aged adults did not differ with regard to categorisation accuracy on the encoding task. A significant main effect of group was found on corrected recognition scores ($F(2, 50) = 25.11$, $p < .001$) and the number of subsequently remembered words ($F(2, 50) = 9.05$, $p < .001$) on the recognition task, whereas no effect was evident on encoding task RT during subsequently remembered or forgotten words. Follow-up t-tests showed significantly lower corrected recognition scores ($t(32) = 4.02$, $p < .001$; $t(37) = 7.64$, $p < .001$) and less

subsequently remembered words (t(32) = 2.55, p = .016; t(37) = 3.93, p < .001) in low-performers than in young adults or high-performers.

fMRI results

Task-related successful encoding activation across all participants was found in the bilateral anterior cingulate cortex (ACC: peak coordinates -9, 27, 36 and 9, 33, 39; t = 4.92; cluster size = 31), with additional activation evident at the uncorrected level (p < .001) in the left ventrolateral (VLPFC)/orbitofrontal cortex (OFC) (peak coordinates -48, 30, 3 and -51, 15, 27 and -42, 33, -6; t = 4.29; cluster size = 28) and bilateral dorsomedial PFC (DMPFC) extending to left DLPFC (peak coordinates -12, 48, 24 and 0, 51, 27 and -15, 48, 36; t = 3.88; cluster size = 23). However, the comparison of young and middle-aged adults using the successful encoding contrast showed no age-related activation differences. Therefore, this activation contrast was not investigated further.

Task-related activation associated with subsequently remembered and subsequently forgotten words alone is shown in Table 2. The comparison between young and middle-aged adults revealed a significant difference in activation to subsequently remembered words, but not in activation to subsequently forgotten words. Middle-aged adults showed significantly greater activation than young adults during subsequently remembered words in the right DLPFC (peak coordinates 21, 36, 27; t = 5.39; cluster size = 19), with homotopic activation evident in the left DLPFC (peak coordinates -21, 36, 27; t = 3.88; cluster size = 30), although the left DLPFC activation difference was significant only at the uncorrected level (p < .001) (Figure 1a).

The investigation of differences in activation during subsequently remembered words between young, low- and high-performing middle-aged adults (Figure 1b) showed significantly greater activation in low-performers than in young adults in the right DLPFC (peak coordinates 21, 36, 27; t = 5.83; cluster size = 16; with the left DLPFC activation difference again evident at the uncorrected level: peak coordinates -24, 39, 30; t = 3.82; cluster size = 17) and greater activation in high-performers than in young adults in the right DLPFC (peak coordinates 18, 39, 24; t = 5.18; cluster size = 11), but no other activation differences.

We then investigated differences in activation during subsequently remembered words between young, low- and high-performing middle-aged adults within left (MNI coordinates: -21, 36, 27) and right (MNI coordinates: 21, 36, 27) DLPFC ROIs constructed based on the age-related differences between young and middle-aged adults (Figure 1b). The ROI analysis showed greater activation in the left and right DLPFC in low-performers than in young adults (t = 3.61, p < .001; t = 5.09, p < .001) and in high-performers than in young adults (t = 3.39, p = .001; t = 3.91, p < .001). The comparison of low- and high-performing middle-aged adults showed greater activation in the right DLPFC in low-performers than in high-performers (t = 1.71, p = .047), whereas there was no activation difference in the left DLPFC.

In addition to the group-wise comparisons described above, we computed across subject correlations to examine the relationship between activation in the left and right DLPFC ROIs and corrected recognition scores. We found a significant negative correlation across

all young and middle-aged participants in the right DLPFC (t = 1.70, p = .047), but not the left, confirming increased right DLPFC activation in relation to poorer subsequent recognition performance across all participants.

Table 2 | Task-related activation during subsequently remembered and forgotten words.

Region		BA	MNI coordinates			t-value	Cluster size (voxels)
			X	Y	Z		
Subsequently remembered							
Ventrolateral PFC	L	48	-42	9	24	11.28	959
	L	*44*	*-51*	*9*	*30*	*10.38*	
	L	*45*	*-45*	*36*	*15*	*6.46*	
Orbitofrontal cortex	*L*	*47*	*-30*	*27*	*0*	*10.86*	
Premotor cortex	*L*	*6*	*-39*	*-6*	*54*	*9.34*	
	L	*6*	*-27*	*0*	*54*	*8.42*	
Anterior cingulate	*L*	*32*	*-6*	*15*	*42*	*8.03*	
Premotor cortex	R	6	30	0	48	8.83	328
Ventrolateral PFC	*R*	*44*	*45*	*6*	*33*	*8.13*	
	R	*6*	*36*	*3*	*36*	*7.98*	
Insula	*R*	*47*	*36*	*24*	*-3*	*6.87*	
Hippocampus	L	27	-21	-30	-6	6.97	7
Fusiform gyrus	L	19	-30	-69	-6	10.06	12
	R	19	30	-63	-6	6.13	7
Subsequently forgotten							
Premotor cortex	L	6	-36	0	45	9.04	546
	L	*6*	*-24*	*3*	*57*	*8.18*	
	L	*6*	*-45*	*6*	*42*	*7.62*	
Ventrolateral PFC	L	6	-57	9	18	6.57	
	L	*44*	*-54*	*9*	*27*	*7.95*	
	L	*45*	*-48*	*33*	*18*	*6.04*	
Anterior cingulate	L	32	-6	15	42	6.08	18
Premotor cortex	R	6	42	-6	54	8.81	294
	R	*6*	*27*	*0*	*51*	*7.54*	
	R	*6*	*33*	*-3*	*57*	*7.24*	
Ventrolateral PFC	*R*	*44*	*48*	*9*	*33*	*7.63*	
Insula	L	47	-30	27	0	7.88	91
	R	47	33	27	-3	5.80	5
Hippocampus	L	27	-21	-30	-6	5.82	2
Fusiform gyrus	L	19	-30	-69	-6	9.38	10
	R	19	30	-63	-6	7.36	11

* Peak activation examined at p(FWE) < .05, within the prefrontal cortex (PFC) and medial temporal lobe (small volume corrected). Italics indicate additional activation peaks within a cluster.

Subjective ratings

No significant differences were found in fatigue, vigour or workload ratings at time 0 or time 1 (Table 1). However, workload ratings were somewhat higher in low-performers than in high-performers ($t(35) = 2.16$, $p = .038$), although this effect did not survive Bonferroni correction.

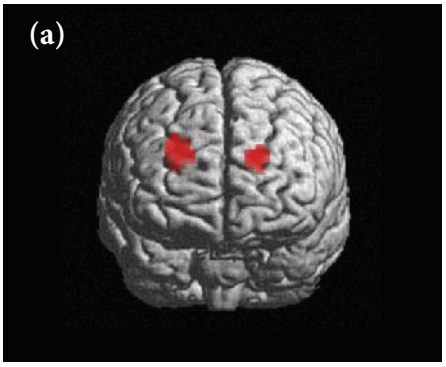
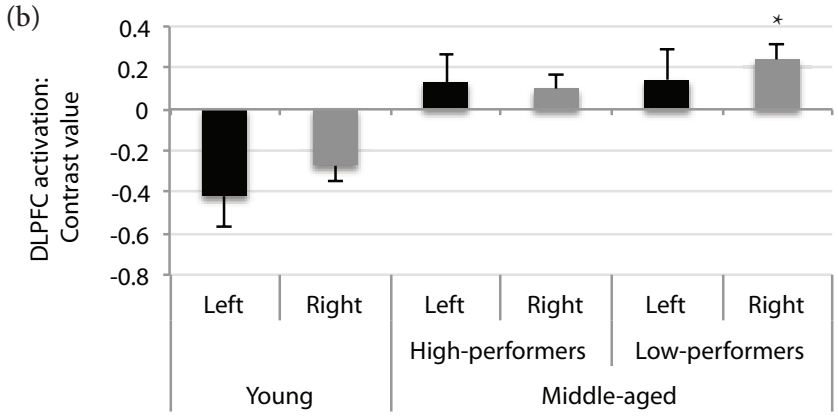


Figure 1 |
a) Dorsolateral prefrontal cortex (DLPFC) areas showing greater activation in middle-aged than in young adults during encoding.

b) Activation within the right and left DLPFC regions in young, low-performing and high-performing middle-aged adults. * Indicates significantly greater DLPFC activation in low-performing middle-aged adults than in both high-performers and young adults.



DISCUSSION

Findings from the present study demonstrate encoding activation differences between young and middle-aged adults. Namely, middle-aged adults showed increased and more bilateral PFC activation than young adults. These activation differences were consistent with findings from previous studies in older adults (Duverne et al., 2009; Morcom et al., 2003). To date, studies investigating cognitive ageing have primarily relied on comparisons between young and older adults (60+ years). As such, our study is one of few to provide insight into neural mechanisms underlying cognitive ageing in middle age.

The investigation of brain activation underlying memory performance differences within the middle-aged group revealed greater right PFC recruitment in the low than in the high-performing subgroup. This finding was again consistent with results from previous studies in older adults (Duverne et al., 2009; Miller et al., 2008) and contributes to ongoing discussion regarding the nature of age-related neural over-recruitment. Specifically, our

results corroborate the suggestion that over-recruitment of the right DLPFC does not act in a 'compensatory' manner to support a higher level of cognitive performance in ageing adults.

Young and middle-aged participants were well matched with regard to education level and employment in a white-collar profession. Both low and high-performing middle-aged subgroups showed higher scores on the DART than young adults, consistent with an age-related increase in crystallised verbal intelligence. On the other hand, cognitive decline was evident in episodic memory recognition accuracy and to a lesser extent in general processing speed (LDST) in low, but not high-performing middle-aged adults compared to young adults. Hence, at the behavioural level, an age-related decline in performance was evident only in low-performing middle-aged adults.

The most robust age-related increase in encoding activation was evident in the right DLPFC. Since overall task-related activation in the DLPFC was primarily left lateralised, increased right DLPFC recruitment with age is consistent with the HAROLD model of an age-related reduction in hemispheric asymmetry (Cabeza, 2002). The DLPFC is generally considered to play a central role in top-down attentional and cognitive control processes (Toro et al., 2008). Blumenfeld and Ranganath (2007) suggest that the DLPFC is particularly involved in organisational processing during memory encoding, such as building associations between to-be-remembered items. Hence, increased recruitment of this area may be expected to result in better memory performance. However, in the present study we found that recruitment of the right DLPFC was evident to a greater extent in low rather than high-performing middle-aged adults compared to young adults. This finding is consistent with the suggestion that an age-related increase in right PFC activation is deleterious, rather than beneficial, to performance (Rajah and D'Esposito, 2005; Spreng et al., 2010), and with previous studies similarly showing greater right PFC activation during memory encoding in poorer performing older (58 – 82 years) adults (Duverne et al., 2009; Miller et al., 2008). Hence, our findings do not substantiate the 'neural compensation' hypothesis in the sense that over-recruitment of the right PFC in middle-aged adults did not support a higher level of performance in this age group (Cabeza et al., 2002; Rosen et al., 2002).

However, over-recruitment of the right PFC in low-performers may not necessarily be detrimental to performance. As suggested in previous studies in older adults, over-recruitment may be an adaptive response to functional decline (Duverne et al., 2009; Miller et al., 2008; Persson et al., 2006). As such, greater cognitive decline in low-performers may have meant that the encoding task was experienced as more demanding and therefore required increased allocation of neural resources to attentional and cognitive control or organisational processes. This suggestion is supported by the somewhat greater subsequent workload ratings in the low-performing subgroup, indicating that the task my have necessitated the exertion of greater cognitive effort by low-performers. Increased neural recruitment or effort in low-performers during the encoding task appears to have successfully fulfilled a 'compensatory' function with respect to the relatively simple categorisation performance requirements on the encoding task, as categorisation performance did not differ between low-performing middle-aged adults and young adults or high-performing middle-aged adults. However, over-recruitment in low-performers

appears to have been insufficient with respect to the support of processes involved in successfully encoding words for subsequent memory recognition.

Alternatively, in line with the cortical dedifferentiation hypothesis, greater recruitment of the right DLPFC in low-performers may reflect the deleterious effects of decreased processing efficiency in relation to cognitive ageing (Buckner and Logan, 2002; Logan et al., 2002). In this case, greater subsequent workload ratings may still indicate the increased exertion of cognitive effort in low-performers, albeit in an inefficient manner. Although fMRI provides insight into the mechanisms underlying cognitive ageing, insight from other techniques may be necessary in order to properly arbitrate between 'compensation' and 'dedifferentiation' accounts of cognitive ageing. For example, transcranial magnetic stimulation (TMS) may be used to examine the effects of selective inhibition or excitation of the left or right DLPFC in low- or high-performers during memory encoding (Manenti et al., 2011; Rossi et al., 2004; Turriziani et al., 2012).

A strength of the present study is that cognitive ageing was investigated in a homogeneous population of working adults, rather than using the typical comparison between young university students and retired older adults, often utilised in ageing studies. Although the recruitment of professionals employed fulltime is considerably more difficult than the more commonly studied populations, such studies are important to our understanding of cognitive decline across the lifespan. Furthermore, in ageing societies, cognitive ageing effects in middle-aged adults are of relevance to an increasingly greater proportion of the working population. Thus, knowledge of age-related cognitive decline in middle age provides an important basis for the development of strategies to combat these ageing effects and thereby attempt to maximise workplace performance in this extensive working population. Furthermore, age-related cognitive decline in the context of high workplace demands may be a contributor to work-related stress and/or fatigue type complaints, possibly in relation to an inability to meet expectations. Therefore, such knowledge may also be used to improve workplace satisfaction and quality of life in middle age.

On the other hand, while restricting the sample population in the present study to highly educated males increased sample homogeneity (and therefore improved functional localisation, increasing the reliability of our findings and therefore the ability to detect differences despite a less extreme age-group comparison), it does limit the generalisability of the findings. There is no reason to expect different results in females, however we may expect greater cognitive decline in middle-aged individuals with a lower education level, due to the proposed association between education level and cognitive reserve (Stern, 2009). Hence, future studies may consider examining this relationship in other population groups.

In conclusion, we demonstrate that age-related differences in encoding activation are present in a group of highly educated, professionally high-performing middle-aged males. Furthermore, we demonstrate that an age-related over-activation of the right DLPFC is evident to a greater extent in low-performing than in high-performing middle-aged adults, indicating that over-recruitment does not serve a compensatory function in the support of a higher level of performance in ageing adults and may instead represent an age-related decline in neural efficiency.

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