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Klaassen, E.B.

2012

document version
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Link to publication in VU Research Portal

citation for published version (APA)
Klaassen, E. B. (2012). *Cognition and the Middle-Aged Brain: Functional MRI studies examining demand, fatigue and caffeine effects*.

Chapter 2

Working memory in middle-aged males: age-related brain activation changes and cognitive fatigue effects

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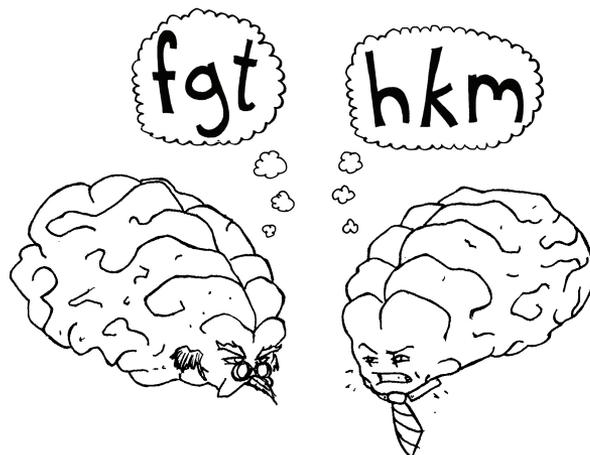[c] Centre for Learning Sciences and Technologies (CELSTEC), Open University, The Netherlands
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ABSTRACT

We examined the effects of ageing and induced cognitive fatigue on brain activation during encoding and maintenance phases of a working memory (WM) task using functional magnetic resonance imaging. Effects were investigated in 13 young and 16 middle-aged male school teachers. Cognitive fatigue was induced by the sustained performance of cognitively demanding tasks (compared to a control condition). Greater encoding activation in middle-aged than young adults in the left dorsolateral prefrontal cortex and superior parietal cortex, regardless of WM load or fatigue condition, appeared to fulfil a neural compensatory function, supporting a higher level of performance. An interaction effect in the dorsomedial prefrontal cortex reflected greater load-dependent activation in middle-aged than young adults in the control condition, but a lack of difference between the age groups in the fatigue condition due to increased activation in the young group. This age and fatigue-related increase in DMPFC recruitment in middle-aged and young adults respectively, appeared to reflect less effortful, neurally inefficient processing.

* This chapter is based on data from fMRI study 1.

INTRODUCTION

Performance on working memory (WM) maintenance tasks declines across the adult lifespan (e.g., Bopp and Verhaeghen, 2005; Myerson et al., 2003; Park et al., 2002). Studies using functional magnetic resonance imaging (fMRI) have provided insight into the nature of this decline in old age (60+ years) by identifying underlying neural activation changes (Cappell et al., 2010; Nagel et al., 2009; Rypma et al., 2002; Schneider-Garces et al., 2010; Zarahn et al., 2007). However, although an age-related decline in WM maintenance is also present in middle age (40 - 60 years) (Bopp and Verhaeghen, 2005; Myerson et al., 2003; Park et al., 2002), little is known about the nature of the changes, or the associated neural activation, at this stage of life. This relative dearth of fMRI studies including middle-aged adults represents somewhat of a gap in our understanding of the cognitive ageing process as a whole.

In the current study, we used fMRI to examine brain activation during a WM maintenance task (Sternberg task) in middle-aged compared to young adults. Furthermore, we examined the effect of induced cognitive fatigue on differences between these two age groups. Young and middle-aged adults were therefore examined in a control condition and in an induced fatigue condition where fatigue was induced by the sustained performance of cognitively demanding tasks (Boksem et al., 2006; Kato et al., 2009; Lorist, 2008; Lorist et al., 2005; van der Linden et al., 2003). In this paradigm, fatigue is conceptualised as resulting from the continuous exertion of a high level of cognitive effort (DeLuca, 2005a). The arising induced fatigue state is associated with performance impairments and increased subjective feelings of fatigue (Boksem et al., 2006; Kato et al., 2009; Lorist, 2008; Lorist et al., 2005; van der Linden et al., 2003). Although fatigue-inducing situations are commonly encountered in daily life, the effect of cognitive fatigue on age-related differences is largely unknown. The investigation of age-related differences in the context of factors encountered during daily life, such as varying fatigue states, is an important step towards a better, more ecologically valid understanding of the effects of cognitive ageing.

Studies comparing young and old adults on verbal WM maintenance tasks have demonstrated differential age effects as a result of varying WM load and task demand. In a behavioral study, Gazzaley et al. (2007) reported equivalent performance between young and old adults at low WM load, but the appearance of performance decrements in old adults when high WM load was combined with a manipulation that increased task demands, namely distraction (but see Hale et al., 2011). Functional MRI studies have reported increased recruitment of fronto-parietal network areas in older compared to younger adults when WM load was low, despite equivalent behavioural performance (Cabeza et al., 2004), but relatively decreased activation in older adults and an associated performance decline when WM load was high (Cappell et al., 2010; Nagel et al., 2009; Schneider-Garces et al., 2010). These findings have been taken as support for the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz and Cappell, 2008). The CRUNCH hypothesis suggests that while the over-recruitment of neural resources supports the maintenance of a high level of performance in older adults at relatively low levels of task load, it is associated with a cost. This cost, or 'crunch' point, takes the form of the exhaustion of limited neural resources at higher task

loads and an associated decline in performance. As age-related cognitive decline is less advanced in middle-aged than in old adults, we expected that middle-aged participants in the control condition of the current study would maintain a similar level of behavioural performance on the WM task to young adults. However, in line with previous studies in old adults, we hypothesised that age-related differences in brain activation would underlie this equivalent performance and that brain activation differences between the two age groups would be modulated by WM load. Specifically, we hypothesised that WM load-related activation in fronto-parietal network areas would be greater in middle-aged than in young adults.

Park and Reuter Lorenz (2009) proposed that the increased recruitment of neural resources in an attempt to maintain performance is not restricted to older adults, but is a normal response of the brain to challenge, regardless of whether the challenge is extrinsic (WM load) or intrinsic (cognitive impairment). Thus, the level of challenge is greater at higher levels of WM load and further increases when it is also necessary to 'compensate' for age-related cognitive decline. We expected that the necessity to perform demanding cognitive tasks for a prolonged period of time would further add to the level of challenge experienced during the WM task. Furthermore, we expected that temporary resource depletion arising from the prolonged exertion of cognitive effort (Persson et al., 2007; Smit et al., 2004) in the fatigue condition would result in an earlier 'crunch' point (i.e. resource exhaustion at a lower level of WM load) in middle-aged adults. Studies utilising the induced fatigue paradigm (in which elicited fatigue falls under the construct of 'primary fatigue' proposed by DeLuca, 2005b) have shown that higher-level cognitive control functions are particularly sensitive to detrimental induced fatigue effects (Lorist et al., 2005; Lorist et al., 2000; van der Linden et al., 2003). Furthermore, sustained task performance has been shown to elicit a lasting decrease in cerebral blood flow in the fronto-parietal attention network in association with a fatigue-related reduction in performance (Lim et al., 2009). Therefore, we hypothesised that middle-aged adults would show a reduction in load-related activation and an associated performance decrement resulting from the exhaustion of cognitive resources in this age group, particularly in areas related to cognitive control. Young adults, on the other hand, were expected to respond to the increased challenge posed by the fatigue condition by increasing WM load-related activation compared to the control condition.

We investigated age and fatigue condition effects during WM encoding (presentation of a target for memorisation) and WM maintenance (retention/maintenance of the target over a delay period) within fronto-parietal network areas involved in top-down cognitive control and WM. These areas included the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC), anterior insula cortex and lateral parietal cortex (Fox et al., 2005; Seeley et al., 2007; Toro et al., 2008). Our aim was to determine the effects of age (young vs. middle-aged adults) and induced fatigue (control vs. fatigue condition) on WM performance, WM load-dependent brain activation (high vs. low WM load) and WM load-independent activation (activation across WM load levels). To our knowledge this is the first study to examine the interaction between age and induced fatigue effects in groups of young and middle-aged adults during a WM maintenance task using fMRI. Effects were investigated in a population of male school

teachers, providing a homogeneous sample in terms of gender, education level and daily cognitive workload.

MATERIALS AND METHODS

Participants

Healthy, right handed, young (14 participants aged 25-35) and middle-aged (18 participants aged 50-61) male school teachers were recruited via advertisements placed in school bulletins, fliers distributed at schools or short information sessions for teachers. Men who suffered significant past or present physical or psychiatric illness, received medication (other than antihypertensives in two middle aged participants), or had MRI contraindications, were not included. Females were not included due to increased fluctuation of cognition, mood and fatigue in this population in relation to the menstrual cycle (Farage et al., 2008). Thus, in light of the relatively small sample groups and the less extreme age-group comparison in the present study than in most aging studies, we elected to minimise variance between repeated measures and age groups (in relation to brain activation, minimising functional localisation differences between age groups) by only testing males. The homogeneous education level and daily cognitive workload within the school teacher sample was considered important due to the effects of education level on age-related brain activation (Springer et al., 2005), and the possible effect of occupation-related experience with cognitively demanding tasks on the effects of the fatigue manipulation, cognitive performance and brain activation. The study was approved by the local medical ethical committee at Maastricht University academic hospital. Participants gave informed consent prior to their (paid) voluntary participation.

Procedure

Young and middle-aged participants were compared in a to-the-tester blind, randomised crossover study design. Each participant completed a training session and two test sessions. Therefore, one practice and two test versions of the fMRI WM task were constructed. The training session was completed in the week prior to the first test session. During the training session, participants completed a battery of neuropsychological tests and practiced the WM task in the dummy MRI scanner to become familiarised with the scanning environment and minimise practice effects during the test sessions.

During the test sessions, participants spent the first 1.5 h completing the fatigue manipulation outside the MRI scanner. Participants were scanned while performing the WM task twice: once following the completion of a highly cognitively demanding fatigue condition and once following a low demand control condition. Test sessions took place during the weekend, starting at 0900, 1100 or 1300 h (with both test sessions completed at the same time of day). The order of the test sessions (control or fatigue condition, and WM task version) was randomised. Subjective rating scales targeting fatigue and effort were completed three times during the test session: upon arrival at the test session (time 0), between the manipulation and the scanning session (time 1), and at the end of the scanning session (time 2). An additional cognitive task and resting state measure were also completed, the results of which will be reported elsewhere. The researcher operating the

MRI scanner and providing instructions during scanning was blind to the manipulation type the participants had just completed.

Neuropsychological testing

A battery of standardised neuropsychological tests was administered to assess memory processes investigated in our fMRI tasks, other cognitive functions known to decline or remain stable with age, and the intelligence characteristics of the sample. The visual verbal Word Learning Test (WLT) (Van der Elst et al., 2005) was administered as a measure of immediate and delayed memory recall and recognition, while the Digit span (forward and backward) was administered as a test of short-term/WM capacity (Lezak et al., 2004). General cognitive functions were tested using the Letter digit substitution test (LDST) (van der Elst et al., 2006a) and the Letter verbal fluency test (Van der Elst et al., 2006b). Finally, the Dutch version of the National Adult Reading test (Nelson, 1991) was administered as a measure of mental ability (intelligence) in adults based on vocabulary.

Fatigue manipulation

During the fatigue condition, participants performed the following tasks: 2 and 3 N-back task (3 x 10 min), Stroop task with additional simultaneous auditory presentation of incongruent color words (2 x 10 min), mental arithmetic (20 min), and brain teasers/puzzles (20 min). These tasks were selected to fatigue executive functions including cognitive control and WM processes subsequently required during the scanning tasks. During the control condition, participants watched a documentary style DVD and/or read a magazine (e.g., the National Geographic) at their leisure.

Subjective rating scales

The fatigue subscale of the Dutch visual analogue scale (VAS) version of the Profile of Mood States (POMS) was administered (Wald and Mellenbergh, 1990) at time 0, 1 and 2. The POMS fatigue subscale is a recommended measure of subjective fatigue in investigations that are short in duration (e.g., a few hours; O'Connor, 2006). The fatigue subscale examines the 'mood of fatigue' described as "feelings of having a reduced capacity to complete mental or physical activities" (O'Connor, 2004, pp S7). The NASA Task Load Index (NASA TLX: Hart and Staveland, 1988) was administered at time 1 and 2 to obtain effort ratings. The NASA TLX targets the subjective experience of workload and provides an indication of the costs of maintaining task performance. An additional independent VAS item requiring participants to rate how interested/engaged, versus uninterested/bored, they were was also administered at time 1 and 2.

Working memory task fMRI paradigm

During scanning, participants performed a parametric version (letter strings consisting of 3, 4, 5 or 6 letters) of the letter Sternberg task. The task consisted of 144 trials (36 for each letter string length) organised in a fast event-related design and presented in a fixed pseudorandom order (stimulus letters, but not trial order, varied per task version). Experimental trials consisted of an encoding phase, a maintenance phase and a retrieval phase. Participants were instructed to memorise the letter string (lower case consonants)

presented on the screen (for 4 s) during the encoding phase. The maintenance phase followed, consisting of a fixation cross in the centre of the screen (for a jittered interval of 3 to 6 s). Finally, in the retrieval phase, participants responded to the probe letter by pressing a button to indicate whether the probe letter was part of the previous letter string (right button press) or not (left button press). Trials were separated by a 3 s pause (during which time three asterisks were shown in the centre of the screen). In addition to jittering, partial trials were also included to reduce the problem of multicolinearity (arising from the delayed nature of the blood oxygenation level-dependent (BOLD) response) inherent to tasks, such as the Sternberg task, with a fixed stimulus event order (Dale, 1999; Miezin et al., 2000; Ollinger et al., 2001a; Ollinger et al., 2001b; Serences, 2004). The partial trial technique allows the unique estimation of the different trial phases and has been shown to be more effective than jittering or slow event-related designs for the detection of cue-related activity in the prefrontal cortex (PFC) (Goghari and MacDonald, 2008). Fifty percent of all trials consisted of the encoding and maintenance phases only and a further 17% consisted of the encoding phase only. Participants were therefore not required to respond to these incomplete trials, but were required to encode and maintain, or encode only, respectively. The task was administered in three blocks of approximately 11 min each and 48 trials per block.

MRI data acquisition

Scans were made 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. In total, during each of the three task blocks, approximately 330 EPI scans were made (TR = 2.0 s, 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 and coregistration of the two test sessions (image matrix = 256 x 256, number of slices = 150, voxel size = 1 x 1 x 1 mm).

MRI data analysis

SPM8 (Statistical Parametric Mapping: Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London) was used to preprocess the fMRI scans. Preprocessing steps included: slice time correction, realign and unwarp, coregistration (session 2 scans were coregistered to session 1), spatial normalisation (MNI space, EPI template), and smoothing (FWHM 8 mm). Data were analysed using the general linear model, using boxcar regressors convolved with the canonical hemodynamic response function to model activation during each event type (regardless of partial trial status). Encoding phase events were modeled as 4 s blocks. Maintenance phase events were modeled as blocks with the duration dependent on jittering time. Additionally, motion parameters were included to correct for motion-related activation.

We adopted an fMRI analysis congruous to the non-linear RT findings on the WM task in the present study. Specifically, activation to the letter strings was grouped into low load (3 + 4 letter string) and high load (5 + 6 letter string). This distinction is also consistent with the 'magic number four' proposal by Cowan (2000) that the memorisation of four

or less items engages a capacity-limited WM system, whereas more than about four items engage executive mechanisms that facilitate 'chunking' of information. Both the effect of WM load on RT found in the present study (RT increased significantly from four to five letters only) and post-testing reports by participants indicating the engagement of strategy use (such as chunking) primarily for letter strings greater than four letters, support this distinction.

Individual low and high WM load activation contrasts (WM load versus the implicit baseline within the fMRI task, provided primarily by the inter-trial pause) were created for each participant for the encoding and maintenance phases in the control and fatigue conditions. Activation contrasts were then entered into two second-level Full Factorial models (one for encoding phase activation and one for maintenance phase activation) to assess the effects of age group (young vs. middle-aged adults) and fatigue condition (control vs. fatigue condition) on WM load-dependent (high load > low load) and load-independent (low load + high load) activation in each of the task phases. Age group and fatigue condition effects were investigated within the fronto-parietal network by small volume correcting (reducing the risk of false positives) using a mask constructed in the SPM8 WFUpickatlas toolbox (Maldjian et al., 2004; Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002) consisting of the following AAL areas: middle frontal gyrus, inferior frontal gyrus, superior frontal gyrus, precentral gyrus, SMA, insula, inferior and superior parietal cortex. Comparisons were also masked inclusively (at $p < .05$) with the appropriate task-related activation to restrict the search for effects to those voxels showing a main effect of task and were examined following correction at the voxel level for multiple comparisons using the family-wise error (FWE) rate correction at p(FWE) $< .05$.

Analysis of neuropsychological tests, subjective rating scales and working memory task behavioural data

All analyses were carried out using PASWStatistics (version 18.0). One-way between subjects analyses of variance (ANOVA) were used to compare scores on the neuropsychological tests in young and middle-aged participants. The subjective rating scales were analysed using mixed design repeated measures ANOVAs with age group as the between subjects factor and within-subjects factors of fatigue condition (2 levels) and time point (NASA TLX: 2 levels, POMS: 3 levels). Mixed design repeated measures ANOVAs with age group as the between subjects factor and within-subjects factors of fatigue condition (2 levels) and WM load (4 levels) were used to examine the number of errors made during the WM task and the reaction time (RT).

RESULTS

One young and two middle-aged participants were excluded from the analysis due to excessive movement, intervening panic and incorrect task execution respectively, leaving 13 young (mean age = 30.92) and 16 middle-aged (mean age = 55.31) participants for group analysis.

Neuropsychological testing

Mean scores on each of the tests in the young and middle-aged groups are shown in Table 1. No significant differences were found between the two age groups on the Digit span forward or backwards. Scores were significantly lower in middle-aged than young adults on the WLT immediate free recall test (t(27) = 2.05, p = .05), but did not differ on the WLT delayed free recall or cued recognition. Scores on the LDST were lower in middle-aged than young participants (t(27) = 2.27, p = .031). Middle-aged adults showed higher scores on the Dutch adult reading test (t(27) = 2.77, p = .01) and there was a near-significant effect for higher scores in middle-aged than young adults on the letter fluency test (t(27) = 2.04, p = .052).

Table 1 | Neuropsychological testing

	Young			Middle age		
	Mean	SD	Range	Mean	SD	Range
WLT immediate free recall *	12.5	2.0	9 – 15	10.9	2.2	7 – 14
WLT delayed free recall	10.8	3.3	5 – 15	9.9	2.4	6 – 14
WLT delayed cued recognition	14.3	0.8	13 – 15	14.3	1.1	12 – 15
Forward digit span	9.8	1.7	7 – 13	9.1	2.2	6 – 12
Backward digit span	7.7	2.1	4 – 13	7.3	2.3	4 – 12
LDST *	58.2	7.1	47 – 70	52.1	7.1	37 – 66
Letter fluency	13.8	3.1	8 – 18	16.9	4.7	9 – 23
Dutch adult reading test **	81.9	7.1	65 – 90	88.3	5.3	78 – 96

Significant age-group differences: * p < .05; ** p < .01.

Subjective rating scales

Ratings on the fatigue and effort subscales are presented in Figure 1. A main effect of fatigue condition was found on the POMS fatigue subscale (F(1,27) = 15.45, p = .001) and the NASA TLX effort subscale (F(1, 27) = 39.63, p < .001), as well as an interaction between fatigue condition and time point on each subscale respectively (F(2, 54) = 4.08, p = .023; F(1, 27) = 8.63, p = .007). Follow-up t-tests showed that fatigue and effort ratings were higher in the fatigue than the control condition at time 1 (t(1, 28) = 2.78, p = .010; t(1, 28) = 5.59, p < .001) and time 2 (t(1, 28) = 5.14, p < .001; t(1, 28) = 3.26, p = .003). A repeated measures ANOVA of the interest/engagement VAS showed no effect of fatigue condition or age group. Mean interest/engagement ratings were all 80 or higher throughout the test sessions regardless of age group or fatigue condition (with 100 indicating completely interested/engaged).
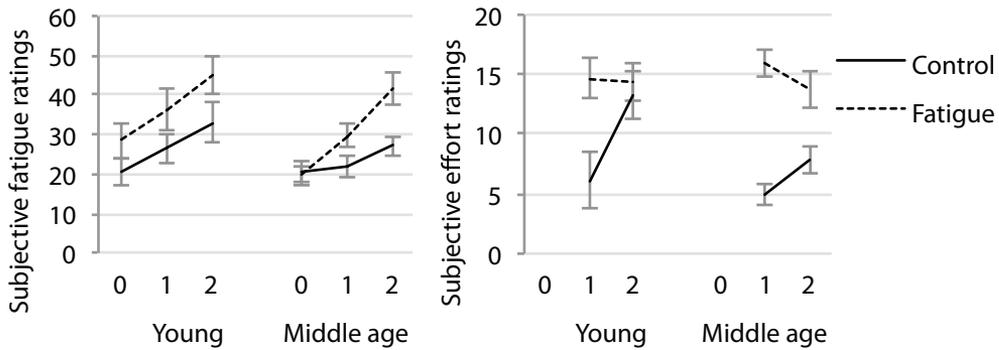
Figure 1 | Mean ratings (with error bars showing standard error) on the subjective fatigue and effort subscales before the fatigue manipulation (time 0), between the manipulation and the MRI scanning session (time 1), and after the scanning session (time 2).

Working memory task behavioural results

Mean percentage accuracy and RT are presented in Figure 2a and 2b respectively. A significant main effect of WM load was found on the number of errors ($F(3, 81) = 5.76$, $p = .002$) and on RT ($F(3, 81) = 16.98$, $p < .001$). Follow-up tests indicated that significantly more errors were made during six letter trials than during five letter trials ($F(1, 27) = 7.77$, $p = .010$) and that RT increased significantly between four and five letter trials ($F(1, 27) = 24.05$, $p < .001$).

There was no effect of age group on the number of errors, whereas a significant effect of age was apparent on RT. Reaction time (regardless of WM load level) was significantly slower in middle-aged than in young participants ($F(1, 27) = 6.11$, $p = .020$). Fatigue condition significantly affected the number of errors, with more errors made in the fatigue than in the control condition ($F(1, 27) = 20.72$, $p < .001$), but did not affect RT.
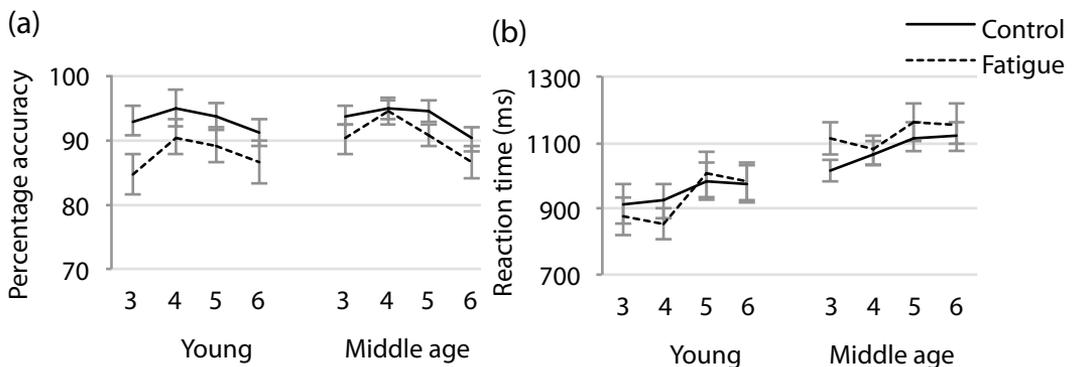

Figure 2 | Mean (with error bars showing standard error) percentage accuracy (a) and reaction time (b) presented for each letter string length of the working memory task.

Working memory task fMRI results

Task-related activation (significant at p(FWE) < .05) during encoding and maintenance phases in the control condition is shown in Table 2. Activated areas were similar to previous fMRI findings using the Sternberg task to examine WM load-related activation during encoding and maintenance separately (e.g., Cairo et al., 2004; Veltman et al., 2003; Woodward et al., 2006).

A main effect of age group was found on load-independent encoding phase activation in the left DLPFC (MNI coordinates x = -39, y = 36, z = 36; t-value = 4.41; p = .049) and the left superior parietal cortex (coordinates x = -39, y = -66, z = 54; t-value = 4.84; p = .011), reflecting greater load-independent activation in these areas in middle-aged than in young adults regardless of fatigue condition (Figure 3a). There were no further effects of age group or fatigue condition on load-independent activation in either the encoding or maintenance phases.

There was no main effect of age group or fatigue condition on WM load-dependent activation in the encoding or maintenance phases. However, a significant interaction between the effects of age group and fatigue condition on WM load-dependent activation in the encoding phase was evident in the DMPFC (coordinates x = -9, y = 3, z = 72; t-value = 5.12; p = .004) (Figure 3b). Follow-up comparisons revealed significantly greater DMPFC activation in middle-aged than young adults in the control condition (t-value = 4.49, p = .037), but a lack of difference between the age groups in the fatigue condition. Furthermore, young adults showed an increase in load-related DMPFC activation in the fatigue compared to the control condition (t-value = 4.94, p = .008), whereas middle-aged adults did not show a significant change in activation in this area.
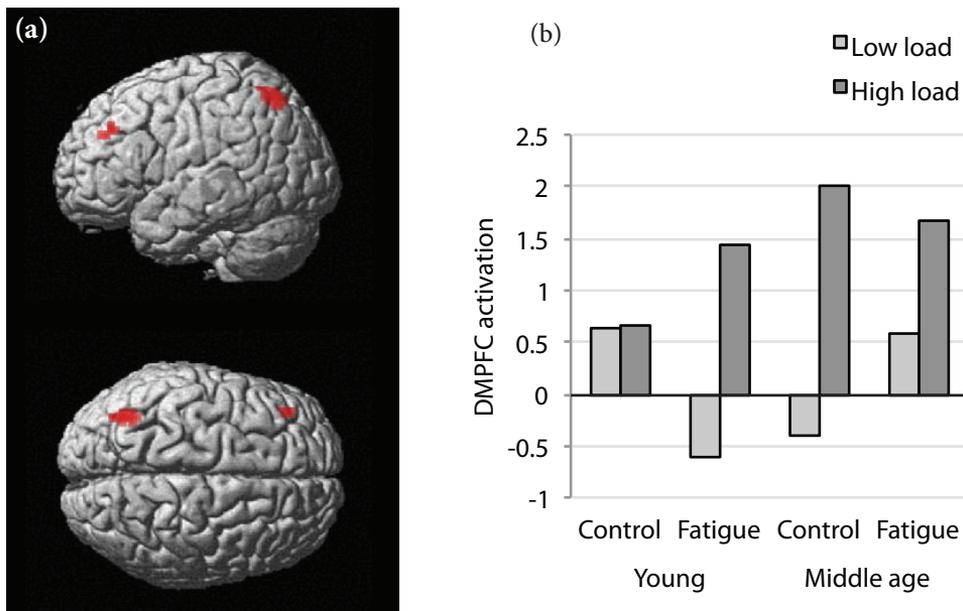

Figure 3 | (a) Main effect of age: greater load-independent activation in middle-aged than in young adults in the left dorsolateral prefrontal cortex and left superior parietal cortex during encoding. (b) Interaction effect: load-related encoding activation in the dorsomedial prefrontal cortex.

Table 2 | Task-related load-dependent activation (high WM load > low WM load)

Region		BA	MNI coordinates			t-value	Cluster size
			x	y	z		
Encoding phase activation							
Dorsomedial PFC	L	6	-3	3	69	8.62	567
	L	6	-3	9	54	8.58	
	R	6	9	15	51	7.46	
Insula	R	48	36	18	0	5.91	37
Premotor cortex	L	6	-48	-3	45	9.42	557
	L	6	-54	6	18	6.55	
	L	6	-27	-3	51	6.26	
	R	6	33	0	45	6.85	257
	R	6	57	3	33	5.77	
Occipital	L	17	-12	-87	-3	13.96	5383
	R	17	12	-84	0	13.26	
Superior parietal	L	7	-21	-66	54	9.04	
	R	7	24	-63	60	8.32	
Putamen	L	-	-18	9	0	6.67	134
Thalamus	L	-	-12	-15	6	5.02	
Maintenance phase activation							
Dorsolateral PFC	L	45	-42	36	27	4.09	19^
	L	46	-42	45	24	3.99	
	R	46	42	51	21	5.01	4
	R	45	42	33	33	3.98	
Premotor cortex	L	6	-48	0	54	6.07	49
Insula	L	48	-45	12	-3	5.30	44

Significant at p(FWE) < .05. ^ indicates clusters significant at p(FWE) < .01 at the cluster level only. Italics are used to indicate additional activation peaks within a cluster.

Post-hoc correlations

In order to assist with the interpretation of our results, we examined the relationship between activation (in the DMPFC, left DLPFC and left superior parietal cortex) and behavioural performance (WM task accuracy and RT, neuropsychological task scores and subjective fatigue and effort ratings). The relationship between activation in each of these areas and the various behavioural measures was investigated (at a more lenient p < .1 in order to gain a more complete impression of the relationship between activation and performance in our relatively small sample) using regression analyses in SPM within

regions of interest (ROIs) created around peak activation coordinates (10mm sphere masked with a grey matter mask) in each of the activation areas. ROI analyses were conducted using the MarsBaR toolbox for SPM (Brett et al., 2002).

In the control condition, load-dependent activation in the DMPFC showed a significant negative relationship with effort ratings (t-value = 1.98, p = .029). Furthermore, the change in activation from the control to the fatigue condition in the young group showed a negative correlation with the change in effort ratings (t-vale = 2.23, p = .024). In the fatigue condition, load-dependent activation in the DMPFC showed a significant negative relationship with scores on the digit span (total of forward and backward scores) (t-value = 1.40, p = .086) and LDST (t-value = 2.56, p = .008). Hence, increased DMPFC activation was associated with lower effort ratings and poorer behavioural performance.

In the control condition, load-independent activation in the left DLPFC showed a positive relationship with accuracy on the fMRI WM task (t-value = 1.45, p = .079). In the fatigue condition, load-independent activation showed a positive relationship with scores on the digit span and the LDST in both the left DLPFC (t-value = 1.38, p = .089; t-value = 2.59, p = .007) and the left superior parietal cortex (t-value = 1.39, p = .088; t-value = 2.59, p = .007). Thus, increased activation in the left DLPFC and superior parietal cortex was associated with better behavioural performance.

In light of the age range of the middle-aged sample in the current study, we also investigated the possibility that this group consisted of a group of 'young' higher performing middle-aged adults and a group of 'old' poorer performing middle-aged adults. We examined correlations within both the young and middle-aged groups between age and neuropsychological task performance, fMRI task performance and brain activation. Within-group differences in fMRI activation as a function of age were examined at low and high memory load separately, and in the control and fatigue conditions using regression analyses (masked with task-related activation, small-volume corrected with fronto-parietal network areas and examined at p(FWE) < .1). No correlations were found between age and any of the outcome measures within either age group, suggesting that the young and middle-aged groups did not consist of dichotomous sub-groups.

DISCUSSION

The current study resulted in two major findings. Firstly, middle-aged adults showed greater activation during WM encoding in the left DLPFC and left superior parietal cortex than young adults regardless of WM load or fatigue condition. Secondly, a significant interaction was found between the effect of age group and fatigue condition on encoding phase activation in the DMPFC. Specifically, middle-aged adults showed greater WM load-dependent encoding activation in the DMPFC than young adults in the control condition, whereas activation did not differ between the two groups in the fatigue condition. This lack of activation difference in the fatigue condition was due to an increase in load-dependent activation from the control to fatigue condition in young adults, but a lack of significant change in activation in middle-aged adults. Results are discussed below in the context of theories of cognitive ageing and fatigue.

Performance accuracy on the Digit span test and the fMRI WM task was statistically equivalent in young and middle-aged participants. Therefore, age-related WM impairment in middle-aged compared to young adults was not detected at the behavioural level. However, performance on the WLT did show age group differences reflecting the typical pattern of ageing effects on memory, with middle-aged adults showing poorer memory recall scores, but unaffected delayed recognition scores. Furthermore, poorer performance on the LDST and slower RTs on the fMRI WM task in middle-aged than in young adults are consistent with a slowing of processing speed with increasing age (Park et al., 2002). Hence, subtle age-related cognitive decline was evident in our population of middle-aged adults.

Functional MRI revealed age-related differences in brain activation in the fronto-parietal network underlying equivalent performance accuracy on the WM task. The maintenance of an equivalently high level of performance appeared to necessitate increased recruitment of the left DLPFC and superior parietal cortex during encoding in middle-aged compared to young adults. These areas are consistent with areas showing age-related activation differences between young and older adults in previous studies (Cappell, et al., 2010; Schneider-Garces, et al., 2009; Nagel, et al., 2009). According to the CRUNCH model, this increased neural recruitment in older adults results from an age-related decline in neural efficiency (Reuter-Lorenz & Cappell, 2008). However, age-related over-activations, particularly in PFC regions, have typically been interpreted as representing functional compensation in response to cognitive decline, especially when the compensation is 'successful' (i.e. associated with equivalent performance to a young group) (Cabeza et al., 2000; Reuter-Lorenz & Park, 2010). Correlations between brain activation and performance can be examined in relation to these interpretations of age-related brain activation changes as increased activation in relation to neural compensation may be expected to show a positive association with performance. In the present study, activation in the left DLPFC and superior parietal cortex indeed showed a positive relationship with WM behavioural performance (on the fMRI WM task and the Digit span neuropsychological test) and general speed of processing (in relation to LDST performance). Hence, we suggest that the age-related increase in activation in these areas fulfilled a compensatory role.

We had expected that age-related differences in the DLPFC and superior parietal cortex would be modulated by WM load and fatigue. However, we found a main effect of age in these areas (but no interaction with WM load or fatigue) indicating similarly increased activation in middle-aged than in young adults regardless of WM load level or fatigue condition. Hence, even the low WM load level necessitated increased recruitment of the DLPFC and superior parietal cortex in middle-aged compared to young adults, but recruitment did not increase further with the additional challenges posed by the high WM load level or fatigue condition. This finding is somewhat consistent with studies in older adults demonstrating a plateauing of load-related activation after about 4 or 5 items (Cappell, et al., 2010; Schneider-Garces, et al., 2009; Nagel, et al., 2009) and may indicate that activation recruitment in these areas reached its limit. Activation differences in the DMPFC, on the other hand, were more in accordance with our hypotheses. Middle-aged adults showed greater load-dependent activation than young adults in the control condition, and the fatigue condition was associated with a change in these activation

differences. However, although young adults showed a fatigue induced increase in load-dependent DMPFC activation, middle-aged adults did not show a significant fatigue-related decrease in load-related activation. Therefore, despite the combined challenge of a high WM demand and induced fatigue in aging adults, neural recruitment did not appear to reach a 'crunch' point (Reuter-Lorenz & Cappell, 2009) in either the DMPFC, DLPFC or superior parietal cortex. Hence, we suggest that future studies investigating the CRUNCH hypothesis in middle-aged adults should include higher levels of WM load in order to facilitate the investigation of this hypothesis.

Unlike activation in the DLPFC and superior parietal cortex, greater activation in the DMPFC was associated with poorer behavioural performance (on the Digit span and LDST). Hence, we suggest that greater activation in this area more likely reflects neural inefficiency than neural compensation. Inefficient recruitment of this area was evident in middle-aged compared to young adults in the control condition and was elicited in young adults in the fatigue compared to control condition. Although, fatigue and effort ratings increased as expected from the control to the fatigue condition, DMPFC activation also showed a negative relationship with effort ratings. As such, middle-aged adults showed somewhat lower effort ratings than young adults in the control condition and the increase in DMPFC activation in young adults in the fatigue compared to control condition was associated with lower effort ratings. Therefore, we suggest that increased recruitment of the DMPFC may have been related to the adoption of a less effortful, neurally inefficient approach to the task.

In contrast to findings in the encoding phase, age group and fatigue condition effects were not found in the maintenance phase. Cappell et al. (2010), on the other hand, reported over-activations in the right PFC in old compared to young adults during WM maintenance, but not during encoding. However, the timing of the encoding and maintenance phases in the study by Cappell et al. (2010) differed greatly from those used in the present study; Cappell et al. (2010) displayed the encoding stimulus for a considerably shorter period (1.5 s), while the maintenance phase was considerably longer (4 – 10 s). These timing differences, as well as the use of partial trials in the present study to improve signal deconvolution, may account for the difference in results between our study and the study by Cappell et al. (2010). With regard to our finding of ageing effects in the encoding phase, but not in the maintenance phase, several previous studies have also reported differences in the effects of ageing across the encoding, maintenance and retrieval phases of WM tasks, indicating that age-related activation changes can vary depending on the cognitive process engaged (Carp et al., 2010; Holtzer et al., 2009; Rypma and D'Esposito, 2000; Zarahn et al., 2007).

Interestingly, despite equivalent education level and employment type in the two age groups, middle-aged adults were characterised by significantly higher letter fluency and Dutch adult reading test scores. This finding is indicative of higher verbal intelligence in the middle-aged group, as letter fluency in particular has been shown to decline with age (Van der Elst et al., 2006b). However, since letter fluency and reading test scores did not correlate with performance on the fMRI task, we consider it unlikely that this difference between the two age groups significantly influenced fMRI findings.

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 aging studies. This homogeneous population of school teachers was also advantageous in relation to the investigation of induced cognitive fatigue effects, providing homogeneity in relation to experience with cognitively demanding tasks and education level. However, the recruitment of professionals employed fulltime is considerably more difficult than the more commonly studied populations (especially for fMRI studies requiring a significant time investment) and thus resulted in smaller sample sizes. Nevertheless, such studies are important to our understanding of cognitive decline across the lifespan. In aging societies, the interaction between cognitive aging and fatigue effects in middle-aged adults is of relevance to an increasingly greater proportion of the working population. Knowledge of age-related cognitive impairment and impairment-exacerbating factors in middle age may provide an important basis for the development of strategies to combat detrimental aging effects and maximise workplace performance in this extensive working population. This knowledge is particularly relevant to professional populations faced with highly demanding workdays, such as the school teachers examined in the present study.

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.

The present study was also limited with regard to the ecological validity of the findings by the use of a battery of cognitive tasks in a laboratory setting to induce cognitive fatigue. Although the fatigue condition in the current study provides greater insight into age-related differences by examining them in different contexts, future studies may extend this investigation to more real-world conditions, such as fatigue induced by a real-life workday.

Although not a limitation to the present study, it should also be noted that we did not find the monotonic increase in RT with increasing WM load commonly found on traditional Sternberg tasks. Instead, we found a significant RT difference between low (3 + 4 letter strings) and high (5 + 6 letter strings) WM load levels (but no significant differences within these levels). This division between low and high WM load is congruous to the proposal by Cowan (2000) that the capacity limited WM system can hold around four items, and that executive mechanisms facilitating 'chunking' are required for more than four items. Further support for this distinction in the current study was provided by participants' reports during debriefing indicating that strategy use (such as chunking) was primarily engaged in response to high WM loads. In addition, it can be argued that the use of partial trials, while advantageous for proper modeling of the BOLD response, may have introduced decreased motivation and response readiness due to the lower response frequency. However, subjective ratings indicated that participants felt a high level of

interest/engagement during the scan session and response accuracy was high, arguing against low task motivation and/or task disengagement.

In summary, the current study demonstrated that age-related changes in brain activation in the fronto-parietal network during a WM maintenance task are already present in middle age. Increased recruitment of the left DLPFC and left superior parietal cortex appeared to fulfil a neural compensatory function in middle-aged adults. On the other hand, the age and fatigue-related increase in DMPFC recruitment in middle-aged and young adults respectively, appeared to reflect less effortful, neurally inefficient processing.

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