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

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\textbf{A B S T R A C T}

We examined the effects of aging and cognitive fatigue on working memory (WM) related brain activation using functional magnetic resonance imaging. Age-related differences were investigated in 13 young and 16 middle-aged male school teachers. Cognitive fatigue was induced by sustained performance on cognitively demanding tasks (compared to a control condition). Results showed a main effect of age on left dorsolateral prefrontal and superior parietal cortex activation during WM encoding; greater activation was evident in middle-aged than young adults regardless of WM load or fatigue condition. An interaction effect was found in the dorsomedial prefrontal cortex (DMPFC); WM load–dependent activation was elevated in middle-aged compared to young in the control condition, but did not differ in the fatigue condition due to a reduction in activation in middle-aged in contrast to an increase in activation in the young group. These findings demonstrate age-related activation differences and differential effects of fatigue on activation in young and middle-aged adults.

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\section{1. Introduction}

Performance on working memory (WM) maintenance tasks declines across the adult lifespan (e.g. Bopp & Verhaeghen, 2005; Myerson, Emery, White, & Hale, 2003; Park et al., 2002). Studies using functional magnetic resonance imaging (fMRI) have provided insight into the nature of this decline in old age (older than 60 years) by identifying underlying neural activation changes (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Nagel et al., 2009; Rypma, Berger, & D’Esposito, 2002; Schneider–Garcés et al., 2010; Zaranh, Rakitin, Abela, Flynn, & Stern, 2007). However, although an age-related decline in WM maintenance is also present in middle age (between the ages of 40 and 60 years) (Bopp & 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 aging 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. 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, such as varying fatigue states, encountered during daily life is an important step toward a better, more ecologically valid understanding of the effects of cognitive aging.

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, Meijman, & Lorist, 2006; Kato, Endo, & Kizuka, 2009; Lorist, Boksem, & Ridderinkhof, 2005; Lorist, 2008; Van der Linden, Frese, & Meijman, 2003). In this paradigm, fatigue is conceptualized 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

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subjective feelings of fatigue (Boksem et al., 2006; Kato et al., 2009; Lorist et al., 2005; Lorist, 2008; Van der Linden et al., 2003).

We based our hypotheses regarding age-related differences in the control condition on previous studies comparing young and older adults on verbal WM maintenance tasks. These studies demonstrated differential age effects as a result of varying WM load and task demand. In a behavioral study, Gazzaley, Sheridan, Cooney, and D’Esposito (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 behavioral 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-Garcés et al., 2010). These findings have been taken as support for the Compensation-Related Utilization of Neuronal Circuits Hypothesis (CRUNCH) (Reuter-Lorenz & 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 behavioral performance on the WM task to young adults at both low and high levels of WM load. However, in line with previous studies in old adults, we hypothesized that age-related differences in brain activation would underlie this equivalent performance, depending on the level of WM load. Specifically, we hypothesized that middle-aged adults would show a greater increase in activation from low to high WM load levels than young adults. As such, we expected that the over-activations seen in older adults at lower levels of WM load would similarly be evident in middle-aged adults, but in association with the maintenance of a high level of performance at higher WM load, rather than at lower levels of WM load. Therefore, we expected that WM load-related activation (low load < high load) 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, Welsh, Jonides, & Reuter-Lorenz, 2007; Smit, Eling, & Coenen, 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 utilizing 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., 2000, 2005; 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., 2010). Therefore, we hypothesized middle-aged adults would show a reduction in load-related activation and an associated performance decrement (primarily at high levels of WM load) resulting from the exhaustion of cognitive resources in this age group at high levels of WM load, particularly in areas related to cognitive control.

We investigated age and fatigue condition effects during WM encoding (presentation of a target for memorization) 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, Fox, & Paus, 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). We examined 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.

2. Materials and methods

2.1. 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, flyers 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, Osborn, & Maclean, 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 minimize variance between repeated measures and age groups (in relation to brain activation, minimizing functional localization 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, McIntosh, Winocur, & Grady, 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.

2.2. Procedure

Young and middle-aged participants were compared in a to-the-tester blind, randomized 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.
to the first test session. During the training session, participants completed a battery of neuropsychological tests (Section 2.3) and practiced the WM task in the dummy MRI scanner (for about 11 min) to become familiarized with the scanning environment and minimize 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 (Section 2.4). 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 randomized. Subjective rating scales (Section 2.5) 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.

2.3. Neuropsychological testing

A battery of standardized 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, Van Boxtel, Van Breukelen, & Jolles, 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, Howieson, & Loring, 2004). General cognitive functions were tested using the Letter digit substitution test (LDST) (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006a) and the Letter verbal fluency test (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006b). Finally, the Dutch version of the National Adult Reading test (Nelson, 1991) was administered as a measure of mental ability (crystallized intelligence) in adults based on vocabulary.

2.4. Fatigue manipulation

During the fatigue condition, participants performed the following tasks: 2 and 3 N-back task (3 × 10 min), Stroop task with additional simultaneous auditory presentation of incongruent color words (2 × 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.

2.5. Subjective rating scales

The fatigue subscale of the Dutch visual analog scale (VAS) version of the Profile of Mood States (POMS) was administered (Wald & 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, p. S7). The NASA Task Load Index (NASA TLX: Hart & 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.

2.6. 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) organized 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 memorize 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 center of the screen (for a jittered interval of 3–6 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 center of the screen). In addition to jittering, partial trials were also included to reduce the problem of multicollinearity (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, Maccotta, Ollinger, Petersen, & Buckner, 2000; Ollinger, Corbetta, & Shulman, 2001; Ollinger, Shulman, & Corbetta, 2001; 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) (Goghi & 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.

2.7. 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 × 64, voxel size = 4 mm × 4 mm × 3.5 mm). A T1 weighted anatomical scan was also acquired for anatomical reference and coregistration of the two test sessions (image matrix = 256 × 256, number of slices = 150, voxel size = 1 mm × 1 mm × 1 mm).

2.8. 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 scans), spatial normalization (Montreal Neurological Institute (MNI) space, echo-planar imaging (EPI) template), and smoothing (with a Gaussian kernel with a full-width at half maximum (FWHM) of
8 mm). Data were analyzed 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 memorization 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. These activation contrasts were then entered into two second-level Full Factorial models (one for encoding phase activation and one for maintenance phase activation). At the second-level, two analyses were carried out. The first analysis combined activation across low and high load activation contrasts (low + high load) to examine the effect of age group and fatigue condition on WM load-independent activation. The second analysis contrasted low and high activation contrasts (high > low) to examine the effect of age group and fatigue on WM load-dependent activation. Age group and fatigue condition effects were investigated within the frontal-parietal network by small volume correcting (reducing the risk of false positives) using a mask constructed in the SPM8 WFUpickatlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003; Maldjian, Laurienti, & Burdette, 2004; 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 (load-independent or WM load-dependent) task-related activation (across both fatigue conditions and age groups) 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.

2.9. Analysis of neuropsychological tests, subjective rating scales and working memory task behavioral 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 analyzed 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).

3. 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.

3.1. 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 = .050), 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 = .010) 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).

3.2. Subjective rating scales

Ratings on the fatigue and effort subscales are presented in Fig. 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.

**Fig. 1.** Mean ratings (±SE) 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).
3.3. Working memory task behavioral results

Mean percentage accuracy and RT are presented in Fig. 2A and B 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.

3.4. Working memory task fMRI results

Task-related load-dependent and load-independent activation during encoding and maintenance phases across the control and fatigue conditions in all participants 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, Liddle, Woodward, & Ngan, 2004; Veltman, Rombouts, & Dolan, 2003; Woodward et al., 2006). Load-dependent encoding phase activation was found in the DMPFC, right DLPFC and bilateral parietal cortices. Load-dependent maintenance phase activation was found in the DMPFC, bilateral DLPFC and bilateral inferior parietal cortices. Load-independent encoding phase activation was found in the DMPFC, bilateral DLPFC and bilateral inferior parietal cortices. Load-independent maintenance phase activation was found in the right DLPFC extending into the VLPFC and DMPFC, and in the bilateral superior parietal cortices.

**Age group main effects:** A main effect of age group was found on load-independent encoding phase activation in the left DLPFC (MRI coordinates: $x = -39, y = 36, z = 36; t$-value = 4.41; $p = .049$) and the left superior parietal cortex (MRI 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 (Fig. 3). There was no effect of age group on activation in the maintenance phase.

**Fatigue condition main effects:** There was no main effect of fatigue condition on activation in either the encoding or maintenance phase.

**Age group × fatigue condition interaction effects:** 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 (MRI coordinates: $x = -9, y = 3, z = 72; t$-value = 5.12; $p = .004$) (Fig. 4). We investigated this interaction with follow-up t-tests comparing WM load-dependent activation within the DMPFC in the various age groups and task conditions. We focused on the comparison of activation within the activated DMPFC area with a region of interest (ROI) analysis using the MarsBar toolbox for SPM (Brett, Anton, Valabreque, & Poline, 2002). The DMPFC ROI was created around the reported peak activation coordinates (10 mm sphere masked with a gray matter mask). These follow-up comparisons revealed significantly greater DMPFC activation in middle-aged than young adults in the control condition ($t$-value = 2.93, $p = .002$), but a lack of difference between the age groups in the fatigue condition. Furthermore, young adults showed an increase in load-dependent DMPFC activation in the fatigue compared to the control condition ($t$-value = 2.61, $p = .005$).
whereas middle-aged adults showed a significant decrease in load-dependent activation in this area (t-value = 2.03, p = .023).

3.5. Post hoc analyses

In order to assist with the interpretation of our results, we examined the strength of the relationship between brain activation (in the DMPFC, left DLPCF and left superior parietal cortex) and behavioral 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 behavioral measures was investigated using regression analyses in SPM within regions of interest (ROIs) created around peak activation coordinates (10 mm sphere masked with a gray matter mask) in each of the activation areas. Correlations were examined at a more lenient p(FWE) < .1 in order to gain a more complete impression of the relationship between activation and performance in our relatively small sample, however we did Bonferroni correct for the number of ROIs in each comparison (two ROIs in load-independent activation correlations and one in load-dependent correlations) and the number of task conditions (control and fatigue condition, and the change from the control to fatigue condition) which increased the strictness of the examination. ROI analyses were conducted using the MarsBaR toolbox for SPM (Brett et al., 2002).

### Table 2

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Clusters significant at p < .05 following small-volume correction for the fronto-parietal network. Italics are used to indicate additional activation peaks within a cluster. Abbreviations: L = left; R = right; BA = Brodmann area; PFC = prefrontal cortex; MNI = Montreal Neurological Institute space.

**Neuropsychological task performance:** In the fatigue condition, load-independent activation showed a significant positive relationship with scores on the LDST in both the left DLPCF (t-value = 2.59, p = .015) and the left superior parietal cortex (t-value = 2.59, p = .015). In the fatigue condition, load-dependent activation in the DMPFC showed a significant negative relationship with scores on the LDST (t-value = 2.56, p = .008).

**Subjective fatigue and effort ratings:** 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 significant negative relationship with change in effort ratings (t-value = 2.23, p = .024). No correlations were found with subjective fatigue ratings.

Hence, increased DMPFC activation was associated with lower effort ratings and poorer LDST performance. Whereas, increased activation in the left DLPCF and superior parietal cortex was associated with better LDST 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 the association within both the young and middle-aged groups between age and neuropsychological task performance, fMRI task performance and brain activation. Within-group differences in
Participants consisted of eight individuals within each age group (projected N = 24). The 140 fMRI scans were acquired at a 3T MRI scanner (Philips Achieva, Best, The Netherlands). First, we examined middle-aged adults and young adults in separate experiments to confirm our hypotheses, and later we conducted a mixed factorial design, where each participant was scanned in the WM load-dependent condition, and in the WM load-dependent condition in which the task was performed with a fatigue induction (fatigue condition). This allowed us to compare performance and activation levels between groups and conditions.

**Fig. 3.** Main effect of age: greater activation in middle-aged than in young participants in the left dorsolateral prefrontal cortex and left superior parietal cortex (projected on a three-dimensional rendering; left to right, top to bottom: anterior, posterior, right, and left hemisphere views) of a single brain in MNI space [SPM8 default rendered brain].

![Image](https://via.placeholder.com/150)

**Fig. 4.** Interaction effect: encoding phase activation (contrast estimates for load-related activation in each age group and fatigue condition with error bars showing 90% confidence intervals) in the dorsomedial prefrontal cortex.

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 from fronto-parietal network areas and examined at p(FWE) < .05). There was no significant relationship 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.

**4. 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 and a decrease in activation in middle-aged adults. Results are discussed below in the context of theories of cognitive aging and fatigue.

Performance accuracy on the Digits 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 behavioral level. However, performance on the WLT did show age group differences reflecting the typical pattern of aging 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; Nagel et al., 2009; Schneider-Garcés et al., 2010). 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, as was the case in this study) (Cabeza, Anderson, Houle, Mangels, & Nyberg, 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. Specifically, an age-related increase in activation in relation to compensation may be expected to show a positive association with performance. In the present study, correlations between activation in the left DLPFC and superior parietal cortex and WM task behavioral performance did not survive Bonferroni correction, however significant correlations with scores on the neuropsychological measure of general speed of processing (LDST performance) were evident. Specifically, greater activation in the left DLPFC and superior parietal cortex was associated with faster speed of processing as indicated by higher scores on the LDST. Hence, it can be tentatively suggested that the age-related increase in activation in these areas may have 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 compared to young adults regardless of WM load level or fatigue condition. Hence, the level of DLPFC and superior parietal cortex over-activation in middle age did not depend on the level of task demand in terms of WM load or fatigue. This finding is somewhat consistent with studies...
in older adults demonstrating a plateauing of load-dependent activation after about 4 or 5 items (Cappell et al., 2010; Nagel et al., 2009; Schneider-Garcés et al., 2010) 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, a finding that has been consistently reported in studies examining age-related differences in WM activation between young and old adults (Turner & Spreng, 2012). Furthermore, DMPFC activation in young and middle-aged adults was differentially affected by fatigue induced by the sustained performance of demanding tasks. The fatigue condition increased activation in young adults, but reduced already elevated activation in middle-aged adults, perhaps reflecting the exhaustion of neural resources with higher WM load and fatigue in middle age. Therefore, neural recruitment in the DMPFC, but not the DLPFC or superior parietal cortex, appeared to reach a ‘crunch’ point (Reuter-Lorenz & Cappell, 2008) in the context of fatigue in middle-aged adults.

Unlike activation in the DLPFC and superior parietal cortex, greater activation in the DMPFC was associated with poorer behavioral performance (on the LDST). Furthermore, 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 associated with the use of a less effortful approach to the task. Several possible explanations can be suggested in relation to these findings. Firstly, DMPFC (supplementary motor) activation has been associated with increasing demand for error monitoring and cognitive control in working memory (Braver & Barch, 2006). Hence, Turner and Spreng (2012) suggested that greater activation in older adults reflected greater monitoring demands in this age group. Therefore, increased DMPFC activation may reflect error monitoring demands in relation to a greater reliance on evaluative processes engaged by participants, perhaps to ensure that their minimal effort expenditure generally met the minimal requirements of the WM task. Secondly, increased DMPFC activation may reflect the role of this area in energizing task-related areas that lack resources due to fatigue (Vallesi, 2012). However, it is difficult to reconcile DMPFC mobilization for energizing purposes with our findings of an associated reduced level of subjective effort (one may expect greater subjective effort in association with greater energizing needs). Thirdly, increased DMPFC activation may be indicative of an affective or motivational signal for the mobilization of affective systems in response to negative affect or boredom (Liu, Collins, & Tucker, 2000). This explanation is consistent with subjective effort ratings; lower effort ratings in relation to greater DMPFC activation may reflect decreased motivation on the task, boredom or even negative affect such as frustration. However, subjective ratings also indicated that participants were quite highly interested and engaged in the test session regardless of age group or fatigue condition, arguing against low motivation or boredom.

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 aging effects in the encoding phase, but not in the maintenance phase, several previous studies have also reported differences in the effects of aging 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, Gmeindl, & Reuter-Lorenz, 2010; Holtzer et al., 2005; Rypma & D’Esposito, 2000; Zarahn et al., 2007).

Interestingly, despite equivalent education level and employment type in the two age groups, middle-aged adults were characterized by near—significantly higher letter fluency scores and significantly higher Dutch adult reading test scores. This finding is indicative of higher verbal intelligence in the middle-aged group, as although crystallized intelligence measured by the reading test can be expected to increase with age, letter fluency has been shown to decline with age (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 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 aging was investigated in a homogeneous population of working adults, rather than using the typical comparison between young university students and retired older adults, often utilized in aging studies. This comparison minimized many of the drawbacks of using a cross-sectional design to investigate age-related changes in brain activation (as, for example, significant differences in WM task performance between the two age groups were not evident). However, it should be noted that while cross-sectional analyses have shown over-recruitment of frontal areas with increasing age, longitudinal analyses have shown under-recruitment of frontal areas with age (attributing cross-sectional findings to the effects of a small group of high performing older adults, who when followed longitudinally, also demonstrated reduced recruitment with age) (Nyberg, Loveden, Riklund, Lindenberger, & Backman, 2012). As such, although our high performing middle-aged adults show relative over-recruitment compared to the younger group, they may show reductions in brain activation with age when followed longitudinally.

The 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-age is of relevance to an increasingly greater proportion of the working population and is particularly relevant within 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 localization, increasing the reliability of our findings and therefore the ability to detect differences despite a less extreme age-group comparison), it does limit the generalizability 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 workload.

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 over-activation of the fronto-parietal network during a WM maintenance task is already present in middle age. However, the age-related difference in the recruitment of these areas was not modulated by WM load or fatigue. As such, there was no evidence for the earlier exhaustion of neural resources in these areas in middle-aged adults as a result of increased task demand associated with greater WM load or fatigue. On the other hand, age and fatigue-induced activation differences in the DMPFC did provide support for the CRUNCH hypothesis. The load-dependent over-recruitment of this area by middle-aged adults in the control condition was reduced when task demands were further increased in the fatigue condition. Therefore, the fatigue condition may have exhausted activation in the DMPFC in middle-aged adults, whereas it increased activation in young adults, indicating differential age-dependent effects of fatigue on brain activation.

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### References


