Age-related and Genetic Modulation of Frontal Cortex Efficiency

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Abstract

■ The dorsolateral pFC (DLPFC) is a key region for working memory. It has been proposed that the DLPFC is dynamically recruited depending on task demands. By this view, high DLPFC recruitment for low-demanding tasks along with weak DLPFC upregulation at higher task demands reflects low efficiency. Here, the fMRI BOLD signal during working memory maintenance and manipulation was examined in relation to aging and catechol-O-methyltransferase (COMT) Val[158]Met status in a large representative sample (n = 287). The efficiency hypothesis predicts a weaker DLPFC response during manipulation, along with a stronger response during maintenance for older adults and COMT Val carriers compared with younger adults and COMT Met carriers. Consistent with the hypothesis, younger adults and met carriers showed maximal DLPFC BOLD response during manipulation, whereas older adults and val carriers displayed elevated DLPFC responses during the less demanding maintenance condition. The observed inverted relations support a link between dopamine and DLPFC efficiency. ■

INTRODUCTION

Working memory (WM) performance is reduced in older age (Park et al., 2002; Hultsch, Hertzog, Small, McDonald-Miszczak, & Dixon, 1992). The age at which a reduction is apparent as well as the shape of the age–performance function remains unclear, not least because of the scarcity of longitudinal data (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). Moreover, the magnitude of age-related impairment is strongly influenced by type of WM task. In general, age differences are more marked on WM tasks that require supracapacity information maintenance or on tasks that require both maintenance and manipulation of information (e.g., Craik & Jennings, 1992). Common to age-sensitive WM tasks may be that they tax dorsolateral pFC (DLPFC) to a high degree (Rypma & D'Esposito, 2000). There is converging evidence from several independent studies that older adults fail to effectively upregulate DLPFC brain activity when the task demands increase, such when the n increases in n-back tasks (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Nagel, Preuschhof, et al., 2009; Nyberg, Dahlin, Stigsdotter Neely, & Bäckman, 2009; Nagel, Chicherio, et al., 2008; Mattay et al., 2006). At the same time, these studies found that the DLPFC recruitment of older adults at lower levels of WM demands tends to be higher than that for younger adults.

DLPFC functioning and associated task performance has been suggested to relate to dopaminergic neurotransmission in a nonlinear inverted-U fashion (e.g., Arnsten & Goldman-Rakic, 1998). Such a nonlinear relationship may account for the observations of stronger DLPFC responses of older than younger adults when WM demands are low, along with higher responses for young when the demands increase. Indeed, there is substantial evidence that age-related dopamine losses are associated with age-related cognitive deficits, in particular on demanding cognitive tasks (see e.g., Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006), and pharmacological depletion of dopamine has been found to reduce WM performance and load-dependent frontoparietal BOLD activity in younger adults (Fischer et al., 2010).

A similar pattern to that seen in aging studies has been found in studies of the Val[158]Met *catechol-O-methyltransferase* (*COMT*) gene, where COMT Val carriers show stronger DLPFC responses than COMT Met carriers at lower levels of WM demands whereas the opposite is true when demands increase (Mier, Kirsch, & Meyer-Lindenberg, 2010). The COMT gene is important for dopaminergic activity in the pFC (Matsumoto et al., 2003) and has been associated with WM executive processes (e.g., de Frias et al., 2004; Goldberg et al., 2003).

Common to older adults and COMT Val carriers could be lower levels of synaptic dopamine, translating into reduced DLPFC efficiency (Mier et al., 2010; Mattay et al., 2006). However, inconsistent results have been reported, likely because most previous studies were underpowered

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(Mier et al., 2010) and the existence of marked interindividual variability in basal dopamine levels (Cools & D'Esposito, 2011).

Here, we examined a large sample of adults who contributed behavioral, genetic, and imaging data. We first analyzed when age differences in WM become apparent and whether differences are elevated on more demanding WM tasks. Next, fMRI data from WM manipulation and maintenance conditions were contrasted as the BOLD response in the DLPFC is elevated by manipulation demands (Pudas, Persson, Nilsson, & Nyberg, 2009; Chee & Choo, 2004; Rypma & D'Esposito, 2000). We hypothesized a stronger BOLD response modulation during manipulation relative to maintenance for younger compared with older adults, and a comparable difference was predicted for COMT Met versus Val carriers. To specifically examine age and COMT influences on DLPFC efficiency, quantitative comparisons of BOLD signal changes during maintenance and manipulation were made relative to a control condition. The efficiency hypothesis predicts a weaker DLPFC response during manipulation along with a stronger response during maintenance for older adults and COMT Val carriers.

METHODS

Participants

The participants included in this study were drawn from a sample of 376 individuals from the Betula study (Nilsson et al., 1997), who were scanned with structural and fMRI in 2009–2010. Participation in the imaging sample was randomly offered to participants who had completed cognitive testing in the fifth wave of data collection in the Betula study, until a preallotted number of slots were filled, stratified by age and sex. At the time of initial contact, screening and exclusions were made for self-reported stroke, neurosurgery, severe visual impairment, and other standard MR contraindications. For the off-line 2-back task, data were available for 356 participants. For the imaging analyses, a total of 89 participants were excluded. First, all participants who did not perform ($n = 10$), understand ($n = 5$), or reach performance criteria (>4 Hits-False Alarms and >50% responses for each task condition; $n = 47$) on the scanner task were excluded. The remaining participants were screened, and additional exclusions were made for technical/quality issues ($n = 20$) and diseases/brain pathologies ($n = 7$, including history of psychotic disorder, epilepsy, and remarks from a radiologist screening the structural images). To retain the diversity of the sample, exclusions were not made for handedness or for diabetes, hypertension, mild depressive symptoms, and other moderately severe medical conditions, which are common among the elderly.

The final sample of 287 participants (of whom 279 were represented in the off-line analyses) had all successfully completed a ~2-hr cognitive assessment, with Mini Mental State Examination scores (Folstein, Folstein, & McHugh, 1975) of >24, indicating absence of dementia. For the purposes of initial age effect analyses, the sample was divided into four subgroups based on age (25–50, 55–60, 65–70, and 75–80 years) and two subgroups for the two-way ANOVA that focused on DLPFC activation (see Table 1 for subgroup characteristics).

Genotyping data were available for 211 of the 287 participants aged 55–80 years. Because of genotyping exclusion criteria (see below), 14 participants were excluded, leaving 197 participants for the genetic analysis (see Table 2).

fMRI WM Task

The WM task was modeled after a previous publication (Chee & Choo, 2004) and piloted in-house (Pudas et al.,

Table 1. Demographics and Cognitive Performance for Different Age Groups

	Younger (n = 54)	*Older (n = 233)*			*Matched Older Groups*	
	25–50 years (n = 54)	*55–60 years (n = 97)*	*65–70 years (n = 88)*	*75–80 years (n = 48)*	*Performance (n = 58)*	*Education (n = 44)*
Age at MRI	37.9 (8.7)	58.8 (2.3)	68.6 (2.6)	76.9 (2.1)	66.3 (6.4)	66.8 (5.5)
Females/males	28/26	50/47	49/39	27/21	29/29	27/17
Education, years	14.9 (2.7)	14.4 (3.2)	13.1 (4.1)	10.7 (4.2)	12.5 (2.7)	17.9 (2.2)
MMSE	28.57 (1.3)	28.30 (1.4)	28.09 (1.5)	28.13 (1.5)	28.34 (1.4)	28.55 (1.4)
Control, Hits-FA	8.89 (0.3)	8.72 (0.6)	8.65 (0.7)	8.40 (1.0)	8.67 (0.5)	8.75 (0.5)
Maintenance, Hits-FA	8.67 (0.6)	8.37 (0.9)	8.26 (1.0)	8.04 (0.9)	8.50 (0.7)	8.34 (0.8)
Manipulate, Hits-FA	7.96 (0.8)	7.36 (1.3)	7.03 (1.4)	6.46 (1.5)	8.41 (0.5)	7.36 (1.2)

Values are means (*SD*) except for females/males that represent number of participants. MMSE = Mini-Mental State Examination; FA = false alarms. Control, Maintenance, and Manipulation refer to scanner task conditions. MMSE was assessed on average of 9 months before MRI. The matched older groups consist of subsamples of participants from age groups 55–80 years that were matched on performance and education to the young individuals in the 25- to 50-year-old group.

Table 2. Demographics and Cognitive Performance by COMT Genotype

	Val/Val (n = 43)	*Val/Met (n = 97)*	*Met/Met (n = 57)*	*p*
Age at MRI	66.1 (7.6)	66.4 (7.3)	66.1 (7.6)	.9
Females/males	28/29	56/41	28/15	.3
Education, years	13.6 (3.6)	13.4 (4.0)	13.1 (4.6)	.5
MMSE	27.65 (1.9)	28.12 (1.5)	27.96 (1.4)	.3
Control, Hits-FA	8.6 (0.5)	8.6 (0.8)	8.6 (0.8)	.9
Maintenance, Hits-FA	7.84 (1.8)	7.79 (1.8)	7.84 (1.4)	1.0
Manipulate, Hits-FA	6.63 (2.6)	6.05 (2.5)	6.33 (2.5)	.6

Values are means (*SD*) except for females/males that indicate numbers of participants per subgroup. *p* Values are calculated with *t* and chi-square tests between Val/Val and Met/Met. FA = False Alarms; MMSE = Mini-Mental State Examination. Control, Maintenance, and Manipulate refer to scanner task conditions. MMSE was assessed on average of 9 months before MRI.

2009). The task had a blocked design with three different conditions: manipulation, maintenance, and control (Figure 1). In the manipulation condition, two target letters were shown to the participants who were instructed to generate and keep the subsequent letters in the alphabet in memory. A fixation star and a probe letter followed. Now, participants needed to respond to whether the probe letter was the subsequent letter in the alphabet to any of the two target letters. In the maintenance condition, participants were shown four target letters for 2 sec, followed by a fixation star. Thereafter, one probe letter was shown together with a question mark. Participants were instructed to keep the four letters in memory and respond yes or no with a button press to indicate whether the probe letter was one of the four target letters. The control condition was equal to the maintenance condition with the difference that four identical letters were shown so that participants only needed to keep one letter in WM. Participants were instructed to give a response for each item. Target letters were presented in lower case and probe letters in capital to decrease memorization purely based on visual representation.

Each block consisted of three stimulus presentations of the same condition and lasted for 27 sec. A fixation cross was shown after each probe letter to signal a new stimulus presentation. An instruction screen was shown for 4 sec before each new block. There were six blocks each of maintenance, manipulation, and control, presented in a randomized order. The experiment lasted for about 10 min and comprised a total of 290 whole-brain acquisitions.

Before entering the scanner, all participants were required to perform a short practice version of the fMRI task repeatedly until the instructions were understood properly. All participants were also offered to familiarize themselves to the scanner environment in a 0T mock scanner before the fMRI investigation.

Off-line 2-Back Task

This test measures the ability to maintain and update information in WM. A list of 40 words was presented visually to the participants. The words were presented, one at the time, at a rate of one word per 3 sec. The task of the participant was to say "yes," if the current word also occurred two words back in the list. For words that did not occur two words back, the response should be "no." An example with a few words was shown on paper to illustrate the procedure. The participants were also told that they had to remember the last few words to solve this task, and one way to do this would be to repeat the words silently.

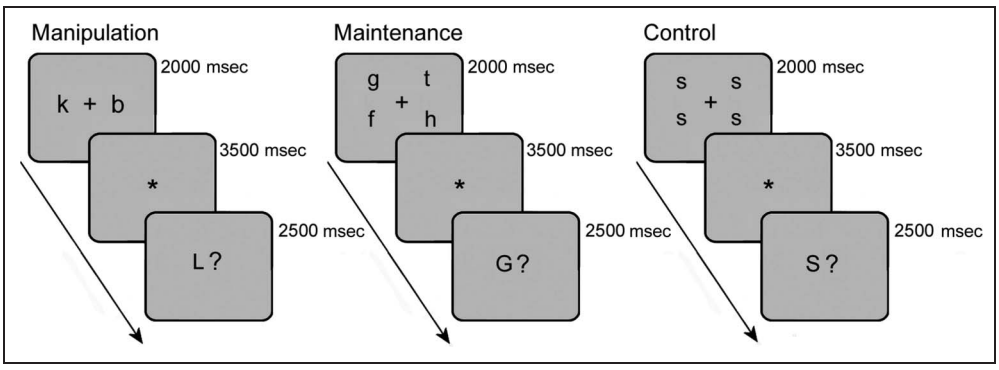

Figure 1. Overview of the WM task. The manipulation condition required the participants to encode and maintain the next positions in the alphabet based on two visual cue letters, whereas the maintenance and control conditions taxed storage of four and one items, respectively.

Image Acquisition

A 3-T GE scanner with a 32-channel head coil was used. A gradient-echo-planar imaging sequence was used with the following scanner parameters: repetition time = 2000 msec, echo time = 30 msec, flip angle = 80°, field of view = 25 cm. Thirty-seven transaxial slices with a thickness of 3.4 mm (0.5 mm gap) were acquired. Ten initial dummy scans were collected to allow for the fMRI signal to reach equilibration. The stimuli were presented on a computer screen seen through a tilted mirror. E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) was used for stimulus presentation and recording of responses from the response pad.

Preprocessing and Data Analysis

SPM8 (Wellcome Department of Cognitive Neurology, London, UK) run under Matlab 7.13 (Mathworks, Inc., Natick, MA) was used for preprocessing and data analysis. An in-house developed software (DataZ) was used for batching and visualization of statistical maps and BOLD signal changes. Before analysis, the data were preprocessed in the following way: slice timing correction, movement correction by unwarping and realignment to the first image of each volume, normalization to a sample-specific template (using DARTEL; Ashburner, 2007) and affine alignment to Montreal Neurological Institute standard space and smoothing with an 8-mm FWHM Gaussian kernel (Nyberg et al., 2010). The final voxel size was 2 × 2 × 2 mm.

The first-order analyses were set up by including the experimental conditions as regressors of interest in the general linear model, convolved with the hemodynamic response function. Six realignment parameters were included as covariates of no interest to account for movement artifacts. For each participant, a contrast file was made by subtracting the manipulation effect with the maintenance effect. Group analyses were based on random effects models of the manipulation–maintenance contrasts from each participant. A one-way ANOVA with the manipulation–maintenance contrast for the four age groups (25–50 years, n = 54; 55–60 years, n = 97; 65–70 years, n = 88; 75–80 years, n = 48) was conducted. For the analyses of genotype groups, a one-way ANOVA with the manipulation–maintenance contrast for the three groups Met/Met (n = 57), Val/Met (n = 97), and Val/Val (n = 43) was conducted. For both the aging and genetic analyses, we used common statistical levels, with a voxel threshold of $p <$ .0005, uncorrected for multiple comparisons, and a cluster size threshold of 10 voxels, corresponding to 80 mm^3. The ANOVAs were followed up by post hoc tests (t tests, linear contrasts) of the directionality of effects. All analyses were done at the whole-brain level.

Genotyping

Genotyping of COMT Val^{158}Met (rs4680) was performed on the same platform as described previously (Kauppi, Nilsson, Adolfsson, Eriksson, & Nyberg, 2011). Primers for PCR amplification were designed using the Sequenom MassARRAY System Designer software and are available on request. Participants with a sample call rate of <0.9 (MIND 0.10) or indications of genotyping errors were excluded. The genotypic distribution of COMT Val^{158}Met did not deviate significantly from Hardy–Weinberg equilibrium in the total sample of n = 2279 from the Betula project that was genotyped on this platform (p = .6, exact test using the PLINK toolbox). Genotype counts were Met/Met: 57, Val/Met: 97, and Val/Val: 43.

RESULTS

Age-related Decline in WM Performance

The behavioral results from the scanner task revealed age-associated WM decline, with a more pronounced effect for manipulation (Figure 2A). An ANOVA confirmed a main

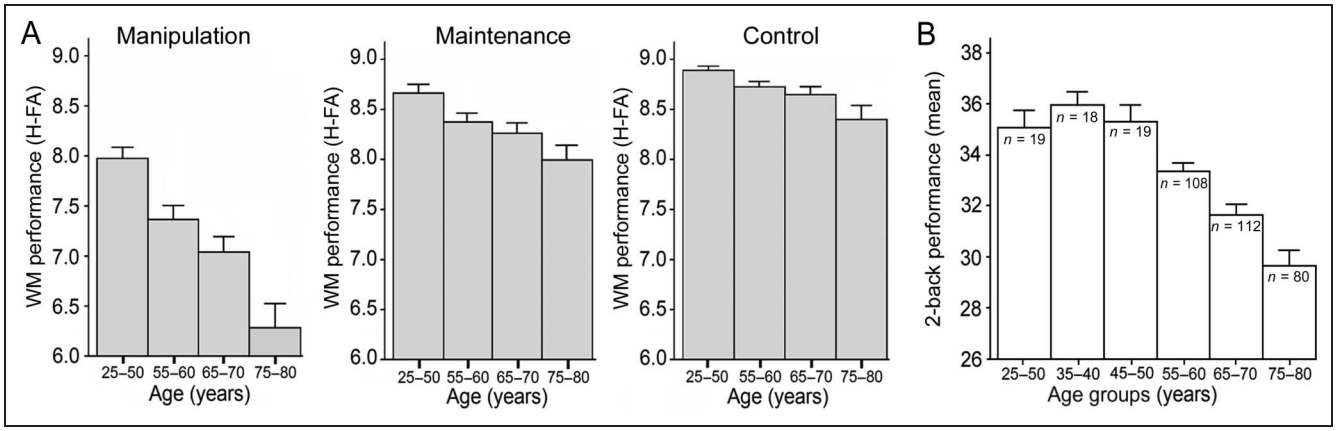

Figure 2. Behavioral results. (A) Mean performance on the WM scanner task. Bars represent 1 *SEM*. H = hits; FA = false alarm (max = 9). (B) Mean performance on the off-line 2-back task (max = 40).

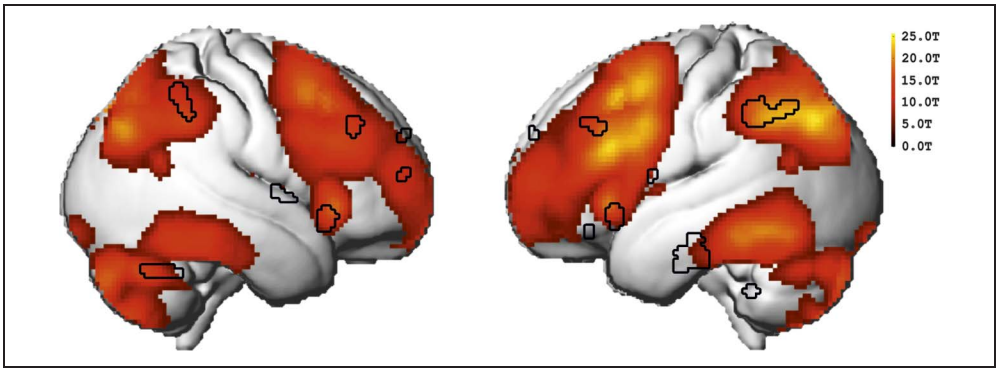

Figure 3. Modulation of the BOLD signal by manipulation demands and age. A large-scale network was identified in the (manipulation > maintenance) contrast (thresholded at $p < .01$ family-wise error-corrected; cluster extent > 10 voxels; color scale in T scores; range = 4.97–24.38). Regions in which a change in the BOLD signal was observed as a function of age group are outlined black contours ($p < .0005$ uncorrected; cluster extent > 10 voxels).

effect of Age Group, $F(3, 283) = 13.13$, $p < .001$, and an Age Group × Condition (maintenance vs. manipulation) interaction, $F(3, 283) = 3.78$, $p < .01$. The age–performance relation was approximately linear across the examined age groups [test of linear effect was significant, $t(285) = -6.25$, $p < .0001$, whereas tests for quadratic and cubic trends were nonsignificant]. A Bonferroni-adjusted post hoc test revealed that the performance of the youngest group was significantly higher than that in all other groups, whereas the only significant difference among the three older groups was 55–60 versus 75–80.

Critically, within the youngest group (25–50 years), there was no significant relation between age and WM performance in the manipulation and maintenance conditions, respectively (both $R^2 < 0.01$, $p > .50$). A similar pattern was observed for the 2-back WM task administered outside the scanner, such that the age effect was significant only after age 50 (Figure 2B). These patterns of results indicated stability in WM performance up until age 50 and approximately linear decline thereafter. We formally tested this nonlinear age–performance relation using an ANOVA contrast for the six age groups (2 2 2 −1 −2 −3) and observed a significant result, $t(350) = 7.73$, $p < .001$.

Modulation of WM Brain Responses by Task Demands and Age

Manipulation was associated with a widespread BOLD signal increase relative to maintenance across all participants ($n = 287$; Figure 3). The identified network included bilateral parietal cortex, cerebellum, and bilateral inferotemporal cortex. Also, as expected (e.g., Pudas et al., 2009), the bilateral DLPFC (peaks at $x, y, z = -26, 30, 34$; 48, 24, 28) was a salient component of an extensive pFC cluster sensitive to manipulation demands.

The manipulation–maintenance response was influenced by age in several of the identified regions (outlined with black contours in Figure 3). Regions in which an age effect was seen included the bilateral parietal cortex ($x, y, z = 40, -48, 50; -26, -62, 42$), bilateral ventral pFC ($x, y, z = 32, 22, -10; -32, 18, -8$), and bilateral dorsal pFC ($x, y, z = 42, 34, 34; -48, 28, 34$). To specifically reveal areas in which age had a decreasing effect on BOLD signal responsivity, a t test with the contrast [3 1 −1 −3] was made across the four groups. As predicted, this test identified the DLPFC ($x, y, z = 46, 36, 28; -48, 26, 32$) as an age-sensitive region. In addition, a declining response was seen in the bilateral parietal cortex ($x, y, z = 40, -48, 48; -32, -50, 38$) and in ventral pFC ($x, y, z = 32, 22, -10; -32, 20, -8$).

Age-related Reduction in DLPFC Efficiency

The efficiency hypothesis predicts a weaker DLPFC response during manipulation along with a stronger response during maintenance for older adults. Thus, after having established an age-related reduction in DLPFC responsivity during manipulation, we next focused on maintenance. An age-related increase in the BOLD signal was seen in a DLPFC peak when maintenance was contrasted with the control condition [ANOVA, linear contrast (−3 −1 1 3), $t(283) = 2.04$, $p < .05$; Figure 4A]. The localization of this left DLPFC peak overlapped with the region in which an age-related reduction was seen in the contrast of manipulation versus maintenance (black contour in Figure 3).

In a post hoc analysis, we conducted a median split of the individuals in the oldest group based on the magnitude of their DLPFC response (peak = −48, 28, 34) and thereafter compared their WM performances. It was found that 75- to 80-year-olds with high DLPFC recruitment during maintenance had significantly higher performance in the WM maintenance condition than those with low DLPFC recruitment, $t(46) = 2.10$, $p < .05$. A similar comparison of WM performance after a median split in the youngest group revealed no significant differences ($p > .40$).

The older adults thus showed a stronger DLPFC response during maintenance relative to the control condition along with a weaker upregulation of the DLPFC

response during manipulation compared with maintenance (Figure 4B). We statistically tested for an inverted relation between age and WM demands in the DLPFC. In this analysis, to increase power, the sample was divided into younger and older subgroups, where "older" included the three subgroups 55–60, 65–70, and 75–80 years. This division was based on the behavioral results, showing age-related decline after age 50, and the finding that the most marked group difference in the manipulation–maintenance contrast was between the youngest group versus the three older groups (Figure 4C). A 2 (younger vs. older) by 2 (manipulation vs. maintenance) ANOVA revealed a significant interaction, $F(1, 285) = 23.57$, $p < .001$, in the left DLPFC peak (Figure 4C). A similar interaction effect was seen in the right DLPFC ($x, y, z = 42, 34, 34$), $F(1, 285) = 18.31$, $p < .001$.

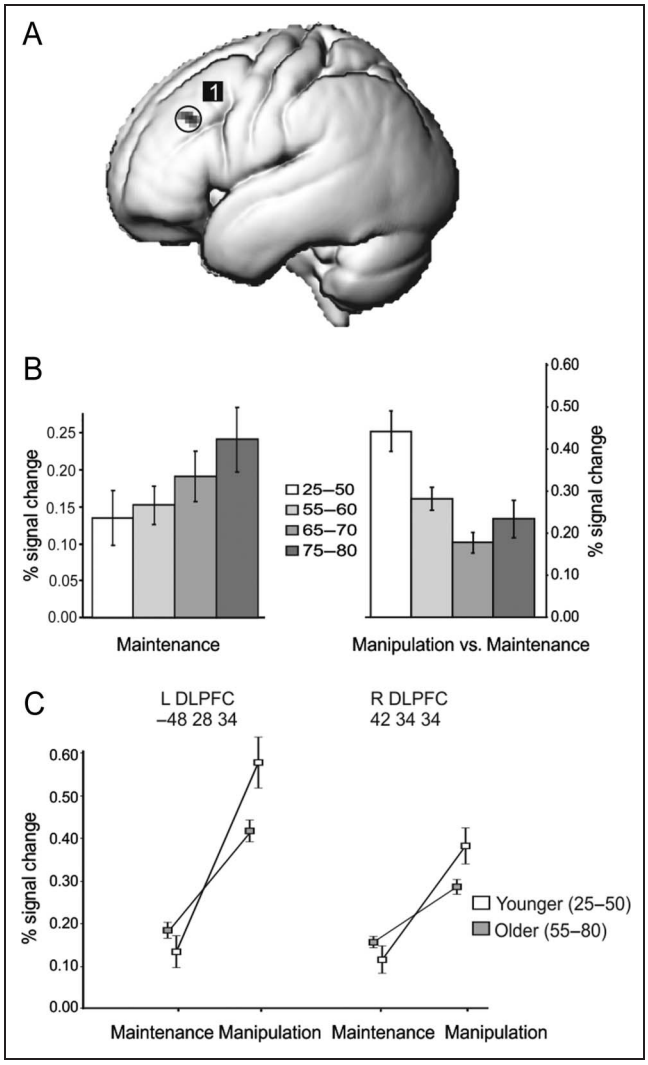

Figure 4. DLPFC efficiency. The left DLPFC (A; $x, y, z = -48, 28, 34$) was more strongly engaged by older than younger adults during maintenance and more strongly engaged by younger than older adults during manipulation (B). An age-related reduction in DLPFC efficiency was confirmed by a significant age group by condition interaction in left and right DLPFC (C). The DLPFC regions analyzed were from the ANOVA as reported in Figure 3.

Controlling for Age Differences in Levels of Performance and Education

We compared younger adults (25–50 years; $n = 54$) with performance-matched older adults (Table 1), as WM responses in pFC have been found to be similar for high-performing older and younger adults (Nagel, Preuschhof, et al., 2009). Still, a significant age by WM condition interaction was found in the left DLPFC, $F(1, 110) = 18.1$, $p < .001$. Thus, an age-related reduction in DLPFC efficiency remained when performance was equal for younger and older adults.

A second control analysis was done to compare younger adults (25–50 years; $n = 54$) with older adults with a comparable level of education (education-matched older, $n = 44$, Table 1), as pFC responses have been found to be differently influenced by level of education in younger and older adults (Springer, McIntosh, Winocur, & Grady, 2005). However, the age-related reduction in DLPFC efficiency remained when education was matched for younger and older adults, as revealed by a significant interaction between Age Group and WM load, $F(1, 96) = 12.2$, $p < .001$.

COMT Influences on WM Brain Responses

We next considered the influence of COMT. Genotype data were available for participants aged 55–80 years. There were no significant COMT group differences in performance (Table 2). An ANOVA of the fMRI data revealed a COMT effect on multiple pFC regions during manipulation versus maintenance (Figure 5A). Plots of the BOLD response in the identified regions showed a "dose-response" effect with the weakest response for Val homozygotes, an intermediate response for Val/Met heterozygotes, and strongest upregulation for Met homozygotes (Figure 5B). A linear contrast within the ANOVAs confirmed a linear trend for all peaks [$ts(194) > 3.80$; $ps < .001$].

The efficiency hypothesis predicts a weaker DLPFC response during manipulation along with a stronger response during maintenance for Val carriers. To test this hypothesis, the BOLD responses in the DLPFC regions identified in the ANOVA (Figure 5A, B) were plotted using data from the contrast of maintenance versus control. It was found that the Val homozygotes displayed the strongest response, Val/Met heterozygotes an intermediate response, and Met homozygotes the weakest response (Figure 5C). An ANOVA revealed a significant COMT group × WM load interaction in the right DLPFC peak that was identified in the initial analysis [Region 4 in Figure 5A, B; $F(2, 194) = 9.25$, $p < .001$; Figure 5D]. A comparable effect was observed in a more ventral

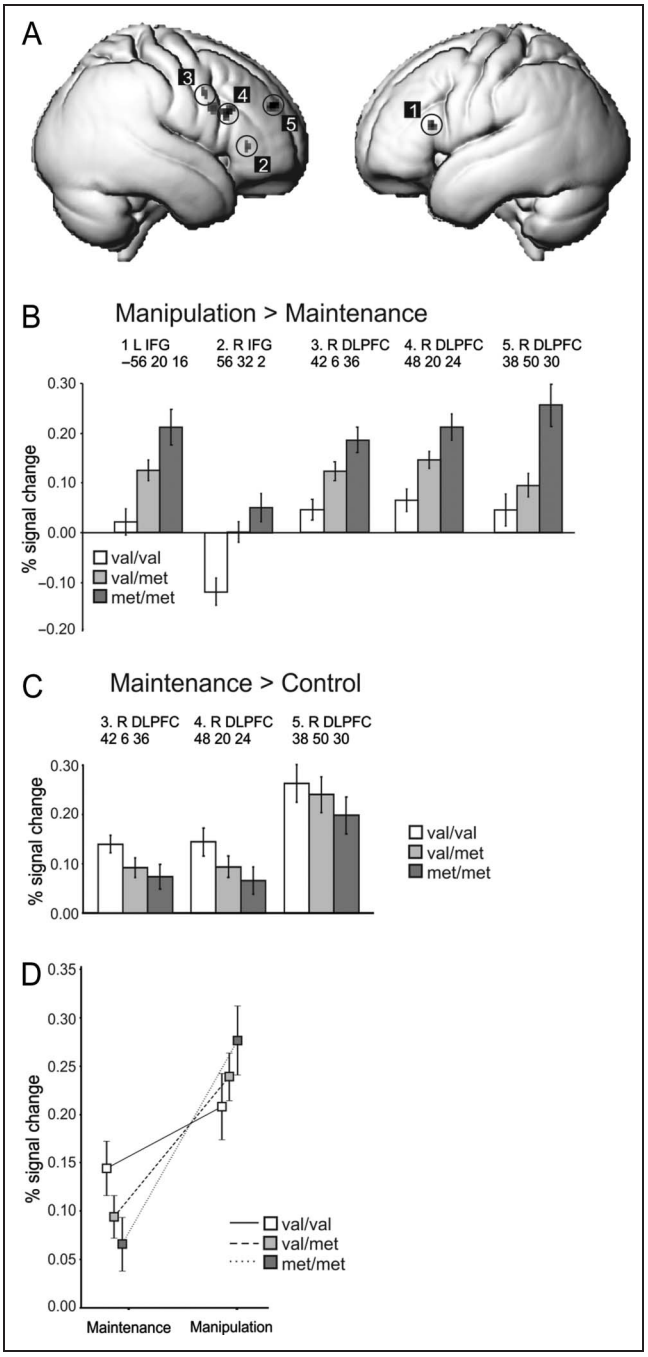

Figure 5. COMT influenced frontal cortex recruitment (A) in a dose-response fashion during (B) manipulation versus maintenance and during (C) maintenance versus control. (D) A COMT influence on DLPFC efficiency was directly supported by a significant group by condition interaction in the right DLPFC (x, y, z = 48, 20, 24).

pFC region in the left hemisphere ($x, y, z = -56, 20, 16$), $F(2, 194) = 8.98$, $p < .001$.

DISCUSSION

The behavioral results from the examined tasks confirm previous reports of age-related WM decline and show that age differences magnify with increasing WM demands. In the behavioral analyses (Figure 2), no evidence for age-related decline was obtained within the youngest group (25–50 years). Thus, although firm conclusions on the nature of age-related changes in WM have to await longitudinal data, our cross-sectional results indicate that significant average WM decline is apparent after age 50 (cf. Nyberg et al., 2012).

The bilateral DLPFC was part of a network of brain regions that responded more strongly during WM manipulation than during maintenance, which is in line with several previous observations (e.g., Pudas et al., 2009). However, it should be stressed that, although the DLPFC, particularly in the left hemisphere, was among pFC regions most sensitive to elevated WM demands (cf. the color scale in T scores in Figure 3), the BOLD response in a large portion of the lateral frontal cortical surface was indeed affected (cf. Figure 3). The present finding that elevated WM demands influenced the response quite broadly and not specifically in the DLPFC was based on an analysis with unusually high statistical power (n = 287). As such, it provides support for the position that regional specializations are statistical rather than absolute (see Duncan, 2001).

WM decline has been linked to age-related changes in the DLPFC (Wang et al., 2011; Rypma & D'Esposito, 2000). Here we found that older adults displayed weaker modulation of DLPFC responses during WM manipulation. Relatedly, COMT was linked to modulation of DLPFC responses in a dose-dependent manner, with the weakest DLPFC response during manipulation for COMT val carriers. By contrast, older adults and COMT val carriers (age range = 55–80 years) displayed elevated DLPFC responses during the less demanding maintenance condition. Collectively, these findings support the efficiency hypothesis of a weaker DLPFC response during manipulation along with a stronger response during maintenance for older adults and COMT val carriers (Mier et al., 2010; Mattay et al., 2006).

The present results converge with findings of previous studies (e.g., de Frias et al., 2009) in suggesting that to achieve the same level of performance as younger adults and COMT Met carriers, older adults and COMT Val carriers need to recruit the DLPFC to a high degree already during WM maintenance. Lowered dopamine for older adults and COMT Val carriers could impair sustained DLPFC processing via D1 receptors during the delay phase (Cohen, Braver, & Brown, 2002), which cascades into stronger DLPFC engagement during maintenance. In the manipulation condition, in which demands were higher, the DLPFC response was strongest for younger adults and COMT met carriers. The requirement to transform the input and store the outcome may have resulted in less sharp representations, necessitating increased dopamine release to facilitate DLPFC stability during the delay (Cohen et al., 2002). By this view, increased dopamine burden during manipulation (cf. Bäckman et al., 2011; Aalto, Brück, Laine, Någren, & Rinne, 2005) shifted the older adults and COMT val carriers beyond the peak

of the hypothesized inverted-U function, resulting in nonoptimal DLPFC engagement. Thus, our findings suggest a link between dopamine and DLPFC efficiency (cf. Wimber et al., 2011).

A complex issue is how neural efficiency relates to behavioral performance (cf. Motes, Biswal, & Rypma, 2011). In the present COMT analyses, there were no significant behavioral differences, and the age effect on DLPFC efficiency remained when comparisons were restricted to subsamples of high-performing (and highly educated) older adults. Hence, lowered DLPFC efficiency does not necessarily imply a performance reduction on a given task but may translate into impairment given higher task demands or still lowered integrity of the dopamine system. Here it is critical to stress that within the oldest group (75–80 years), it was found that higher DLPFC recruitment during maintenance was associated with better behavioral performance (cf. Motes et al., 2011). In other words, although age-related DA changes may have induced lower DLPFC efficiency in these older individuals, as manifested by weaker upregulation of DLPFC responses during manipulation relative to maintenance, they were still able to upregulate DLPFC processing when the maintenance demands increased from a load of 1 (control) to one of 4—and this ability apparently facilitated their performance. A prediction for future studies is that age and COMT jointly affect DA and related DLPFC efficiency, such that older val homozygotes would display the lowest efficiency with only weak DLPFC upregulation during maintenance relative to control and no further upregulation during manipulation. Here, we did not test this prediction as genotype data were not available for the youngest cohort and we only had a limited number of val homozygotes in the oldest cohort, but there is suggestive supportive evidence from independent studies (Nagel, Chicherio, et al., 2008).

In conclusion, future studies should examine the borderline conditions of the concept of neural efficiency. In the present experimental context (where $\gg$ reflects maximal difference; $>$ some difference; and $=$ no difference), individuals may range from "no efficiency" (maintenance = control = manipulation), "weak efficiency" (maintenance > control; manipulation = maintenance), "moderate efficiency" (maintenance $\gg$ control; manipulation > maintenance), and "maximal efficiency" (maintenance > control; manipulation $\gg$ maintenance). By this view, dynamic recruitment of the DLPFC depending on task demands might be conceived of as an indicator of a well-functioning brain.

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