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COMT Polymorphism and Memory Dedifferentiation in Old Age

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According to a neurocomputational theory of cognitive aging, senescent changes in dopaminergic modulation lead to noisier and less differentiated processing. The authors tested a corollary hypothesis of this theory, according to which genetic predispositions of individual differences in prefrontal dopamine (DA) signaling may affect associations between memory functions, particularly in old age. Latent correlations between factors of verbal episodic memory and spatial working memory were compared between individuals carrying different allelic variants of the Catechol-O-Methyltransferase (COMT) Val158Met polymorphism, which influences DA availability in prefrontal cortex. In younger adults (n = 973), correlations between memory functions did not differ significantly among the 3 COMT genotypes (r = .35); in older adults (n = 1333), however, the correlation was significantly higher in Val homozygotes (r = .70), whose prefrontal DA availability is supposedly the lowest of all groups examined, than in heterozygotes and Met homozygotes (both rs = .29). Latent means of the episodic memory and working memory factors did not differ by COMT status within age groups. However, when restricting the analysis to the low-performing tertile of older adults (n = 443), we found that Val homozygotes showed lower levels of performance in both episodic memory and working memory than heterozygotes and Met homozygotes. In line with the neurocomputational theory, the observed dedifferentiation of memory functions in older Val homozygotes suggests that suboptimal dopaminergic modulation may underlie multiple facets of memory declines during aging. Future longitudinal work needs to test this conjecture more directly.

Keywords: COMT, dopamine, aging, dedifferentiation, memory

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The Catechol-O-Methyltransferase (COMT) gene codes for an enzyme that degrades dopamine (DA) in the prefrontal cortex, resulting in three to four times higher turnover rates in Val than in Met homozygotes (e.g., Lotta et al., 1995). Thus, Val homozygotes have lower levels of synaptic DA in prefrontal cortex than Met carriers. In light of DA's critical involvement in prefrontal functioning (e.g., Kimberg & D'Esposito, 2003; Luciana, Depue, Arbisi, & Leon, 1992; Sawaguchi & Goldman-Rakic, 1991; Vijayraghavan, Wang, Birnbaum, Bruce, Williams, & Arnsten, 2007; Williams & Goldman-Rakic, 1995), studies have investigated the link between individual differences in the COMT gene and cognitive performance. Specifically, the Met allele has been associated with better performance in tasks assessing executive functioning (e.g., Nagel et al., 2008; Sheldrick et al., 2008) and working memory (e.g., Dumontheil et al., 2011; Nagel et al., 2008; Störmer, Passow, Biesenack, & Li, 2012). However, several studies have failed to replicate these associations (e.g., Blanchard, Chamberlain, Roiser, Robbins, & Müller, 2011; Bolton et al., 2010; de Frias et al., 2010; Zilles et al., 2012) and meta-analyses indicate that the COMT genotype has limited effects on cognitive functioning (Barnett, Jones, Robbins, & Müller, 2007; Barnett, Scoriels, & Munafò, 2008). These observations form part of a larger picture suggesting that individual genes exert small and often negligible effects on cognitive performance (Deary et al., 2010; Payton et al., 2009).

On the other hand, arguments have been made that brain processes are more likely to reveal influences of genetic polymorphisms, because they are more proximal to molecular mechanisms than the behaviors associated with them (Rasch, Papassotiropoulos, & de Quervain, 2010). Brain imaging studies have shown that, in the absence of reliable behavioral differences between allelic groups during working memory tasks, Val homozygotes showed less focused neuronal activity in the cortical working memory network (Bertolino et al., 2006) and exhibited greater prefrontal brain activity (Egan et al., 2001), thus suggesting less efficient cognitive processing in carriers of this genotype. In addition to increased frontal activation, COMT Val homozygotes showed increased activation in the parietal lobes during a visuospatial working memory task (Dumontheil et al., 2011), decreased medial temporal lobe activity (Dennis et al., 2010), and increased prefrontal activity during episodic encoding (Dennis et al., 2010; Schott et al., 2006). Taken together, the extant evidence suggests that the Val allele appears to be associated with less efficient and less distinct recruitment of task-relevant brain networks (for review, see Witte & Flöel, 2012).

Aging is associated with declines in the DA systems (for review, see Bäckman, Lindenberger, Li, & Nyberg, 2010) and working memory depends critically on prefrontal DA (for review, see Cools & D'Esposito, 2011). As with the COMT Val genotype, a less focused activation pattern during working memory and episodic memory is often observed in older compared to younger adults (e.g., Bäckman et al., 1997; Dennis & Cabeza, 2011; Grady, McIntosh, & Craik, 2005; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Park et al., 2012; Rajah & D'Esposito, 2005). Thus, we expected that the confluence of being older and being a COMT Val carrier would result in dedifferentiated brain activity during memory-related processing relative to younger adults, or to older adults carrying the Met variant. For example, in COMT Val carriers, aging may lead to an increased reliance of episodic memory processing on typical working memory structures (e.g., the fronto-parietal circuitry; Berryhill & Olson, 2008; Cabeza, Dolcos, Graham, & Nyberg, 2002; Naghavi & Nyberg, 2005) and, conversely, working memory may be more dependent on typical episodic memory structures (e.g., the medial temporal lobe; Axmacher, Elger, & Fell, 2009; Ezzyat & Olson, 2008; Squire, Stark, & Clark, 2004). In line with this assertion, a functional magnetic resonance study reported that normal aging increases the dependence of these two memory functions on common networks, with older adults showing increased recruitment of brain regions within a prefrontal-parietal-occipital network during both working and episodic memory (Sambataro et al., 2012). Moreover, working memory and episodic memory may be more dedifferentiated in older adults whose genetic predisposition for prefrontal DA modulation is suboptimal.

At the behavioral level, dedifferentiation also denotes increases in the correlations or dependence between various cognitive processes or abilities, such as different aspects of intelligence (e.g., Balinsky, 1941; Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; de Frias et al., 2007; Ghisletta & Lindenberger, 2005; Li et al., 2004; Lindenberger & Ghisletta, 2009; Tucker-Drob, 2009; Schaie, Maitland, Willis, & Intrieri, 1998; but see Anstey, Hofer, & Luszcz, 2003; Zelinski & Lewis, 2003) or between sensory and cognitive processes (Baltes & Lindenberger, 1997; Lindenberger & Ghisletta, 2009; Lindenberger & Baltes, 1994). However, it should be noted that longitudinal evidence suggests stronger dedifferentiation among processes in the cognitive domains compared to cross-domain cognitive-sensory dedifferentiation (Lindenberger & Ghisletta, 2009).

Over a decade ago, a neurocomputational theory of cognitive aging suggested that increased processing noise due to suboptimal DA modulation results in increased within-network coactivation of distinct processing pathways in simulated older networks (Li & Sikström, 2002) and higher correlations between the networks' performance tested with different memory tasks (Li, Lindenberger, & Sikström, 2001).

Given the well-described effects of the COMT gene on working and episodic memory (for a review, see Witte & Flöel, 2012), in this study we focus specifically on behavioral dedifferentiation of these two types of memory in old age to investigate whether aging-related memory dedifferentiation is related to individual differences in genetic predispositions for suboptimal prefrontal DA signaling. We investigated these questions in large samples of younger (n = 973) and older (n = 1,333) adults by comparing the latent structure, correlations, and means between a spatial working memory factor and a verbal episodic memory factor across COMT genotypes. Of special interest was the question whether increasing age is associated with increased correlations between working memory and episodic memory in the suboptimal COMT genotype. In line with the resource modulation hypothesis, which states that genetic variability is more likely to result in performance differences when brain resources are more limited, as in old age (Lindenberger, Nagel, Chicherio, Li, Heekeren, & Bäckman, 2008), we expected to find the highest correlation between episodic memory and working memory in older COMT Val homozygotes, that is, in older adults carrying the genetic variant associated with the lowest level of prefrontal DA.

Methods

Participants

We recruited 1,051 younger (20 to 31 years; 54.2% female) and 1,657 older (59 to 71 years; 61.0% female) adults via newspaper announcements and advertisements in public transportations. All subjects reported normal or corrected to normal vision and were right-handed, as indexed by the Edinburgh Handedness Index (Oldfield, 1971). Written informed consent was obtained from all participants, who were paid 10 Euro per hour for their participation. The ethics committees of the Charité University Medicine Berlin approved the study. Older participants that scored below 28 on the Mini-Mental State Examination were excluded from the sample (4.9%), as scores below 28 may indicate mild cognitive impairment in highly educated elderly samples (O'Bryant et al., 2008). Furthermore, participants with a history of medical (e.g., heart attack), neurological (e.g., epilepsy), or psychiatric disease (e.g., depression) were excluded (younger adults: 6.3%; older adults: 10.2%), as well as participants taking drugs that may affect dopaminergic neuromodulation (younger adults: 1%; older adults: 3.8%). Finally, participants that had received less than 8 years of education were excluded (<1% for both age groups). The final sample included 973 younger (53.4% female) and 1,333 older (60.4% female) adults. The COMT genotypes did not differ with respect to the percentage of excluded participants within age groups (all *p*s > .05 for all exclusion criteria). Table 1 presents demographics and self-reported health data across age and COMT genotypes. Notably, the COMT groups did not differ with respect to demographic and self-reported health data in either age group. Althoug parts of the data have been published elsewhere (Li et al., 2010; Nagel et al., 2008), here we present data from a considerably larger sample and address a question that has not been investigate so far, namely the relationship between suboptimal DA modulation and cognitive dedifferentiation.

Genotyping

DNA was extracted from peripheral blood using standard methods. The COMT single nucleotide polymorphism (SNP, rs4680; Val158/108Met) was genotyped using the commercially available TaqMan 5′ nuclease assay (C__25746809_50; TaqMan SNP genotyping Assay; Applied Biosystems, Forster City, CA), following established procedures (Livak, 1999). Genotyping was performed on 384-well microtiter plates in 5-μl reaction volumes. For each reaction we combined 10 ng DNA template, 5× TaqMan genotyping assay and 5× TaqMan Genotyping Master Mix. Thermal cycling was done on a PTC-240 PCR instrument using the following cycling conditions: preamplification phase at 50°C (2 min), initial denaturation at 95°C (10 min), followed by 45 cycles of denaturation at 95°C (15 s), annealing and extension at 60 °C (60 s). The genotype frequencies in the younger adults were 263 (27.0%) for Met/Met, 504 (51.8%) for Met/Val, and 206 (21.2%) for Val/Val. The corresponding distributions for the older sample were 368 (27.6%) for Met/Met, 680 for Met/Val (51.0%), and 285 (21.4%) for Val/Val. In both age groups, the COMT distributions were in Hardy–Weinberg equilibrium (*p*s > 0.1) and in line with the distributions reported in previous studies (e.g., Starr, Fox, Harris, Deary, & Whalley, 2007).

Spatial Working Memory Task

The task used to assess spatial working memory has been described in detail by Nagel and colleagues (2008). Briefly, dots were presented one at a time in a specific location in a 4 × 4 grid. After a sequence of seven dots was presented, a probe appeared in one of the 16 locations. Participants were required to determine whether a dot was presented in this specific location (i.e., location memory condition). If the participant gave a yes response, a digit was presented in this location to probe participants to indicate whether the digit matched the serial position of the dot in the presented series (i.e., sequence memory condition). A total of 48 trials were presented. We used location memory accuracy and sequence memory accuracy to represent spatial working memory in latent space.

Verbal Episodic Memory Task

The task used to assess episodic serial order memory was the same as described by Li and colleagues (2010). Participants were asked to memorize three lists of 12 words each presented via headphones. Although the participants listened to the words, they simultaneously saw numbers on the computer screen, which represented the serial positions of the words. After list presentation, subjects recalled the items in backward order, beginning with the last item presented (i.e., Item 12 to Item 1). Given that the recency portion of backward serial recall relies more on short-term memory (Richardson, 2007), for later analysis only two indicator vari-

Table 1
Demographic Variables and Self-Reported Health Across Age and COMT Genotype Groups

	Younger adults (n = 973)			Older adults (n = 1333)		
Demographics	Met/Met (n = 263)	Met/Val (n = 504)	Val/Val (n = 206)	Met/Met (n = 368)	Met/Val (n = 680)	Val/Val (n = 285)
Age ($M \pm SD$)	26.4 (2.8)	25.9 (2.8)	25.9 (2.7)[a]	65.3 (2.8)	65.1 (2.8)	64.9 (3.0)[a]
% female	53.2%	53.0%	54.9%[b]	58.7%	61.6%	59.6%[b]
Years of education ($M \pm SD$)	12.7 (1.1)	12.6 (1.2)	12.6 (1.1)[a]	10.7 (1.7)	10.8 (1.7)	10.9 (1.7)[a]
State of health ($M \pm SD$)	4.2 (0.6)	4.2 (0.6)	4.2 (0.7)[a]	3.9 (0.7)	4.0 (0.6)	4.0 (0.6)[a]
MMSE ($M \pm SD$)				29.23 (0.8)	29.39 (0.7)	29.42 (0.7)[a]

Note. State of health is based on the mean of four self-ratings on 5-point scales from 1 (*poor*) to 5 (*excellent*). COMT = Catechol-O-Methyltransferase; MMSE = Mini-Mental State Examination.
[a] One-way analyses of variance: *n.s.* [b] χ^2 = *n.s.*

ables were used to form the latent episodic memory factor: backward recall accuracy for the primacy (Items 1–4) and middle (Items 5–8) portions of the lists.

Statistical Analysis

To test whether the COMT gene affects memory dedifferentiation at the level of latent factor correlations, invariance of measurement models between COMT genotypes was evaluated by means of multiple group confirmatory factor analyses using AMOS 7.0 (Arbuckle, 2006; Byrne, 2004). A series of progressively more stringent models was evaluated, constraining different aspects of the measurement models (factor loadings, intercepts, residual variances, and interfactor correlations) to be equal across COMT genotype groups. Because the more constrained models were nested within the reference model, the difference in χ^2 fit statistics ($\Delta\chi^2$) was used to determine whether the models with more constraints yielded relatively better fits given the fewer number of parameters involved. The alpha-level for statistical decisions regarding differences in χ^2 fit statistics was set to 0.05. Gender and chronological age were included as covariates in all analyses. The proportion of missing data was rather minimal. In total, about 1.9% of the trials for the working memory task and less than 1% of the trials for the episodic memory task yielded missing data due to nonresponse of the participants.

Both univariate and multivariate outliers were examined. Specifically, cases exceeding ±3.29 *SD* (Tabachnick & Fidell, 2005) were treated as univariate outliers and multivariate outliers were determined using Mahalanobis distance, with the recommended $p < .001$ threshold for the χ^2 value (Tabachnick & Fidell, 2005). In total, less than 1% of memory accuracy measures were deemed as outliers and were not included in further analyses (i.e., treated as missing by the program). AMOS accommodates analyses based on full information maximum likelihood estimation (FIML), assuming that data values that are missing are missing at random (Arbuckle, 1996). Older adults had more missing data on sequence memory accuracy in the working memory task, $\chi^2 = (1, 2306) = 38.8$, $p < .01$, indicating that they failed to respond in this condition more frequently than younger adults. Frequency of missing cases on the other indicators did not differ across age groups, $\chi^2 = (1, 2306) = ns$. Importantly, within age groups, the COMT groups did not differ with respect to missing values on any of the indicators (all *p*s > .05). For all following analyses, the raw variables were divided by an integer (i.e., 5) to avoid potential numeric estimation problems due to different scaling of indicators (cf. Kline, 2005).

Results

The Effect of COMT Genotype on the Correlation Between Working Memory and Episodic Memory

In the first step, a factor model was specified with two latent variables, each with two indicators. Figure 1 displays a graphical representation of the factor model. The reference model was identified by fixing the variances of the latent variables to 1 and constraining the factor loadings for each factor to be equal in each of the COMT genotype groups. Further analyses were conducted separately for younger and older adults, given that metric invariance could not be established across age groups, as indicated by a significant loss in fit when constraining the factor loadings to be equal across age groups, $\Delta\chi^2 = 37.46$, $\Delta df = 2$, $p < .05$. The lack of metric invariance between age groups is in line with evidence indicating life span age differences in the organization of cognitive abilities (e.g., Baltes et al., 1980; de Frias et al., 2007; Li et al., 2004; Tucker-Drob, 2009).

In the younger adults, the fit of the reference model (Model 1) was very good, indicating configural invariance in the three COMT groups, $\chi^2(21) = 38.74$, $p < .05$, AIC = 158.7, RMSEA = .030, 90% CI_{RMSEA} (.014, 044), CFI = .98 (all fit statistics are summarized in Table 2). The second, more constrained, model (Model 2) tested the hypothesis of identical magnitude of factor loadings across COMT genotypes; that is, metric (or weak) factorial invariance (Meredith, 1964). Model 2 also yielded very good fit, $\chi^2(25) = 39.42$, $p < .05$, AIC = 151.4, RMSEA = .024, 90% CI_{RMSEA} (.007, 038), CFI = .98, and the restriction did not result in significantly worse fit compared to Model 1, $\Delta\chi^2 = 0.68$, $\Delta df = 4$, $p > .05$. Next, in addition to factor loadings, intercepts were constrained to be the same across COMT genotype groups (Model 3) to test for strong invariance. The fit of Model 3 remained very good, $\chi^2(33) = 44.34$, $p > .05$, AIC = 140.3, RMSEA = .019, 90% CI_{RMSEA} (.000, 032), CFI = .99. Subsequently, residual variances across genotype groups were equated (Model 4), establishing strict metric invariance, $\chi^2(41) = 52.37$, $p > .05$, AIC = 132.4, RMSEA = .017, 90% CI_{RMSEA} (.000, 029), CFI = .99. Finally, a model with equal interfactor correlations for the three COMT groups was tested, $\chi^2(43) = 54.02$, $p > .05$, AIC = 130.0, RMSEA = .016, 90% CI_{RMSEA} (.000, 029), CFI = .99 (Model 5). Again the chi-square difference test was not significant, $\Delta\chi^2 = 1.65$, $\Delta df = 2$, $p > .05$, indicating that the interfactor correlations could be equated across the three COMT genotype groups (i.e., *r*s = .35, $p < .05$). Thus, strict metric invariance was achieved and the three interfactor correlations could be equated across the COMT genotype groups in younger adults. Factor loadings and interfactor correlations for the best fitting model in younger adults are displayed in Figure 1A.

The corresponding analysis in the older adults revealed very good fit of the reference model (Model 1), $\chi^2(21) = 28.80$, $p > .05$, AIC = 148.8, RMSEA = .017, 90% CI_{RMSEA} (.000, 031), CFI = .99 (see Table 2 for all summary fit statistics). Constraining factor loadings (Model 2) across COMT genotypes to be equal did not significantly worsen the fit, $\Delta\chi^2 = 5.97$, $\Delta df = 4$, $p > .05$. Further, it was possible to achieve strong metric invariance (Model 3), $\chi^2(33) = 38.59$, $p > .05$, AIC = 134.6, RMSEA = .011, 90% CI_{RMSEA} (.000, 024), CFI = .99, as well as strict metric invariance (Model 4), $\chi^2(41) = 51.50$, $p > .05$, AIC = 131.5, RMSEA = .014, 90% CI_{RMSEA} (.000, 025), CFI = .98. Importantly, however, the critical direct comparison of factor intercorrelations across older COMT genotype groups revealed that this constraint was associated with a significant decrement in model fit, $\Delta\chi^2 = 10.36$, $\Delta df = 2$, $p < .05$, indicating that factor intercorrelations differed significantly among the three COMT groups in older adults. The interfactor correlations in the heterozygotes and in Met homozygotes, however, could be equated without a significant loss in fit as compared to Model 4, $\Delta\chi^2 = 0.02$, $\Delta df = 1$, $p > .1$. Thus, Model 6 with strict metric invariance, but different factor correlations between Val homozygotes and the other two COMT groups, exhibited the best fit. In this model, the correlation between the

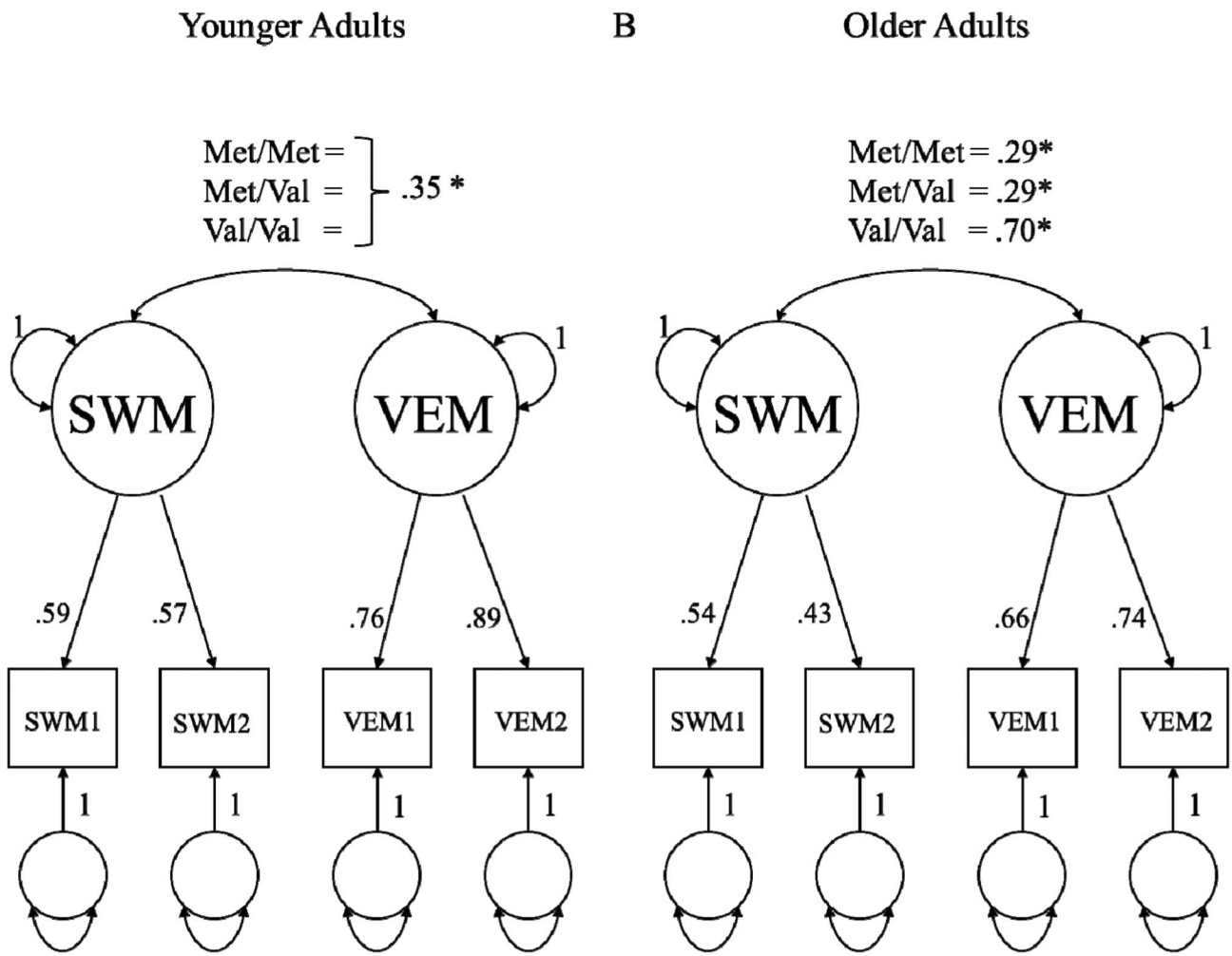

Figure 1. Factor model used in multiple group analyses on the relation between Catechol-O-Methyltransferase (COMT) genotype and dedifferentiation of memory functions. The figure depicts standardized factor loadings and interfactor correlations. A: Young adults (Met/Met: $n = 263$; Met/Val: $n = 504$; Val/Val: $n = 206$): Shown here is the strict metric invariant model with equated interfactor correlations across all COMT genotypes. B: Older adults (Met/Met: $n = 368$; Met/Val: $n = 680$; Val/Val: $n = 285$): Shown here is the strict metric invariant model with equated interfactor correlations across Met homozygotes and heterozygotes. Sex and chronological age are not shown in the figure but were included as covariates on the latent constructs in all analyses. SWM = spatial working memory factor; VEM = verbal episodic memory factor; SWM1 = SWM accuracy for the location memory condition; SWM2 = SWM accuracy for the sequence memory condition; VEM1 = backward recall for the primacy portion (Items 1–4); VEM2 = backward recall for the middle portion (Items 5–8) of the lists. * $p < .001$.

working memory and episodic memory factors was higher in older Val homozygotes ($r = .70$, $p < .001$) compared to older heterozygotes and Met homozygotes ($rs = .29$, $p < .01$). Figure 1B displays the standardized factor loadings and the interfactor correlations of Model 6 for older adults.

In additional analyses, we tested whether the interfactor correlations could also be constrained to be equal across age groups. As before, the highest level of invariance that we could establish was strict metric invariance across genotype groups within each of the two age groups in a model involving all six groups, $\chi^2(80) = 103.87$, $p > .05$, AIC = 263.4, RMSEA = .011, 90% CI_{RMSEA} (.000, 017), CFI = .98. Across age groups, configural invariance was achieved. In the next step, a model with equal interfactor correlations across all six COMT groups was tested. Equating the interfactor correlations across all six groups resulted in significant decrement in model fit, $\Delta\chi^2 = 12.05$, $\Delta df = 5$, $p < .05$, indicating that interfactor correlations differed significantly among the six groups. However, the interfactor correlations across all three younger COMT groups, the older heterozygotes, and the older Met homozygotes could be equated without significant loss in fit, $\Delta\chi^2 = 2.32$, $\Delta df = 4$, $p > .1$, compared to a model that imposed strict metric invariance within age groups and configural invariance across age groups. In line with the main results reported above, the correlation between the working memory and episodic

Table 2
Fit Indices for Models Testing Different Types of Measurement Invariance

Models	χ^2	*df*	χ^2/df	AIC	RMSEA	90% CI for RMSEA	CFI	$\Delta\chi^2$	Δdf	Δp
Younger adults										
Model 1: Configural invariance	38.74	21	1.85	158.7	.030	[.014, .044]	.98	—	—	—
Model 2: Metric invariance	39.42	25	1.58	151.4	.024	[.007, .038]	.98	0.68	4	.954
Model 3: Strong invariance	44.34	33	1.34	140.3	.019	[.000, .032]	.99	4.93	8	.765
Model 4: Strict invariance	52.37	41	1.28	132.4	.017	[.000, .029]	.99	8.02	8	.431
Model 5: Strict invariance and equal interfactor correlation across all COMT groups	54.02	43	1.26	130.0	.016	[.000, .029]	.99	1.65	2	.439
Older adults										
Model 1: Configural invariance	28.80	21	1.37	148.8	.017	[.000, .031]	.99	—	—	—
Model 2: Metric invariance	34.77	25	1.39	146.8	.017	[.000, .030]	.98	5.97	4	.201
Model 3: Strong invariance	38.59	33	1.17	134.6	.011	[.000, .024]	.99	3.82	8	.873
Model 4: Strict invariance	51.50	41	1.26	131.5	.014	[.000, .025]	.98	12.90	8	.115
Model 5: Strict invariance and equal interfactor correlation across all COMT groups	61.85	43	1.44	137.9	.018	[.006, .028]	.97	10.36	2	.006
Model 6: Strict invariance and equal interfactor correlation across Met carriers	51.51	42	1.23	129.5	.013	[.000, .024]	.98	0.02	1	.890

Note. AIC = Akaike's information criterion; RMSEA = root mean square error of approximation; CI = confidence interval; CFI = comparative fit index; COMT = Catechol-O-Methyltransferase.

memory factors was higher in older Val homozygotes ($r = .71$, $p < .001$) compared to the three younger COMT groups, older heterozygotes, and Met homozygotes ($rs = .33$, $p < .001$). However, given that metric invariance did not hold across age groups, the results of these analyses need to be interpreted cautiously.

Differences in Latent Means of Memory Factors Between COMT Groups

In addition to testing differences in latent correlations, we investigated whether the COMT genotypes differed with respect to performance levels (i.e., latent means) in the two memory domains. Again, analyses were conducted separately for the two age groups. Given that strong invariance was established in both age groups (see above), latent mean differences could be compared across COMT groups. The latent means of the episodic memory and working memory factors were freed in the heterozygotes and Val homozygotes, and fixed to 0 in the Met homozygotes. In this way, the latent means are estimated as a relative difference from the reference point established by the Met homozygotes. In younger adults, the latent mean estimation for the best fitting model (Model 5) suggested that neither the heterozygotes nor the Val homozygotes differed reliably on verbal episodic memory (all $ps > .1$) or spatial working memory (all $ps > .1$) from the Met homozygotes. The same was true when freeing the latent means in the groups of older heterozygotes and Val homozygotes for Model 6, the best fitting model for the older age group. Thus, despite higher interfactor correlations in the group of older Val homozygotes, the latent means did not differ overall among COMT genotypes with respect to the two memory factors (all $ps > .1$).

The Low Performing Older Adults From the Lower Tertile of the Distribution

Although older Val homozygotes exhibited a higher link between memory functions, they did not differ in their latent means from the other two COMT genotype groups. However, task condition or genotype effects on mean performance levels may only be apparent at the low performance range (cf. Nagel et al., 2009; Papenberg et al., 2011). We, therefore, tested whether mean differences among older COMT genotypes would be apparent among the lower tertile of the distribution within each of the three allelic groups. Specifically, we expected that Val homozygotes in the lower tertile would perform worse than the other genotype groups on both memory measures.

Individuals in the lower tertile of the distribution (Met/Met: $n = 123$; Met/Val: $n = 226$; Val/Val: $n = 94$) were selected based on an aggregate of the mean factor scores of episodic and working memory, which were computed from the best fitting model (i.e., Model 6 of strict metric invariance and equated factor correlations across Met homozygotes and heterozygotes). Bar graphs in Figure 2 portray factor scores on the two memory measures for the COMT genotype groups in the low-performing older adults. Univariate analyses of covariance, with sex and age as covariates, revealed main effects of COMT genotype with respect to both verbal episodic memory, $F(1, 438) = 3.7$, $p < .05$, partial eta squared = .017, and spatial working memory, $F(1, 438) = 4.6$, $p < .05$, partial eta squared = .020. In line with our expectations, planned contrasts indicated that Val homozygotes performed worse than heterozygotes and Met homozygotes with respect to both episodic memory, $t(438) = 2.52$, $p < .05$, Cohen's $d = .24$, and working memory, $t(438) = 3.02$, $p < .05$, Cohen's $d = .29$.

Discussion

We investigated whether suboptimal prefrontal DA modulation, associated with COMT Val homozygosity, affects the correlation between spatial working memory and verbal episodic memory. Our findings show that the latent correlations between the two memory factors was considerably higher in older Val homozygotes ($r = .70$), compared to older heterozygotes and Met homozygotes ($rs = .29$). This finding was unique to the older adults. For

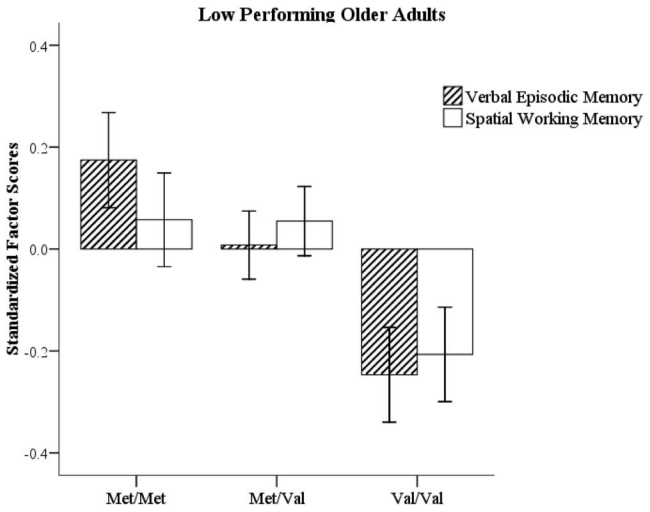

Figure 2. Bar graphs indicate standardized factor scores for verbal episodic and spatial working memory for the lower tertile of the distribution within each of the COMT groups (Met/Met: $n = 123$; Met/Val: $n = 226$; Val/Val: $n = 94$). Error bars represent 1 standard error around the mean.

younger adults, the relation between the two memory factors was invariant across the COMT genotypes ($rs = .35$). The pattern of increased genetic effects on the coupling between working and episodic memory in old age is consistent with the resource modulation model, which assumes that genetic effects are magnified when cognitive resources decline, such as in aging (Lindenberger et al., 2008). In line with the predictions derived from earlier neurocomputational simulations (Li et al., 2001; Li & Sikström, 2002), our findings thus lend empirical support for the theoretical conjecture postulating suboptimal DA modulation as one possible mechanism for the dedifferentiation of cognitive functions in old age.

Working memory and episodic memory have been shown to partly share common underlying neural networks (e.g., Cabeza et al., 2002; Ranganath, Johnson, & D'Esposito, 2003). Our data also suggest that when frontal DA declines in late life (for review, see Bäckman et al., 2010), Val carriers' working memory may become increasingly dependent on other brain regions, such as those involved in episodic memory, and vice versa. This may result in higher correlations between memory functions at the behavioral level. Further, imaging studies have reported less focused brain activation patterns as well as recruitment of additional brain regions in older compared to younger adults (Grady et al., 2005; Rajah & D'Esposito, 2005) and as a function of the COMT Val allele (for review, see Witte & Flöel, 2012) during working memory and episodic memory. Our observation of less efficient and specific brain activations in Val carriers is in line with evidence showing that Val homozygotes are characterized by more noise in the neural signal and less distinctive brain activations during attentional processing (Winterer et al., 2006). Indeed, neurocomputational work has shown that simulated deficient DA modulation in networks with separate processing pathways for verbal and spatial memory leads to increased activation overlap across the two modules as a consequence of increased processing noise (Li & Sikström, 2002). In addition to reduced functional specificity within networks, intercorrelations of different variants of memory tasks were higher in older networks with simulated suboptimal DA modulation (Li & Lindenberger, 1999; Li et al., 2001). Thus, in line with the theory, our empirical evidence suggests that deficient DA modulation in older Val homozygotes may result in less specific neural processing during working memory and episodic memory, subsequently leading to an increased coupling between memory functions at the behavioral level.

In the total sample, COMT genotypes did not differ in latent means in either age group. Given previous reports of small or nonexistent effects of the COMT gene on mean performance of cognitive functions (see Barnett et al., 2007, 2008, for meta-analytic evidence), this result is not surprising. However, among the low-performing tertile of older adults, Val homozygotes performed less well in both memory functions than heterozygotes and Met homozygotes. This is also in line with the neurocompuational modeling results (Li & Lindenberger, 1999; Li et al., 2001), which suggested that suboptimal DA modulation increases between-person heterogenity and lowers performance levels. Genotype effects on memory functions were not large enough to lower mean performance in the total sample of Val homozygotes below the mean of the heterozygotes and the Met homozygotes. However, when restricting the mean comparisons to the lower tertile of the distributions, we found that older Val homozygotes performed less well than the other two older groups on both cognitive abilities. In this sense, greater dedifferentiation of memory functions may serve as an early marker of future cognitive decline in older Val carriers. With advancing aging-related structural (e.g., Raz et al., 2005, 2008) and neuromodulatory (for review, see Bäckman et al., 2010) declines, genotype differences in performance levels may become apparent in the total sample. Indeed, longitudinal imaging studies have found that older adults with more diffuse brain activation patterns declined more in their clinical and neurological status, although these individuals did not differ in baseline memory performance from those with more distinct activation patterns (Bookheimer et al., 2000; O'Brien et al., 2010). Cross-sectional studies with even older samples and longitudinal studies are needed to confirm whether deficient DA modulation and its link to dedifferentiation result in worse performance outcomes with advancing adult age.

In this study, the candidate-gene approach served as a proxy for investigating the effects of individual differences in dopaminergic neuromodulation on adult age differences in the association between working and episodic memory. It would be desirable to complement our findings with molecular imaging studies, which permit a more direct assessment of individual differences in DA signaling. That said, a recent molecular imaging study in Parkinson's disease patients reported that Met exhibit higher DA levels in frontal regions than Val homozygotes (Wu et al., 2012).

In sum, we document novel evidence for an association between deficient frontal DA neuromodulation and aging-related dedifferentiation of memory functions at the behavioral level. Specifically, the correlation between working memory and episodic memory was higher in older COMT Val homozygotes relative to heterozygotes and Met homozygotes; in contrast, the COMT gene did not affect the correlation of memory functions in younger adults, suggesting an age-related magnification of genetic effects (Lindenberger et al., 2008). Future studies should test whether suboptimal DA availability in old age is related to dedifferentiation

among broader domains of cognitive functions. The DA systems have also been strongly implicated in executive functioning (e.g., Nagel et al., 2008; Sheldrick et al., 2008) and recently also in attentional modulation (Störmer et al., 2012). Thus, interindividual differences in DA modulation of these processes and the interactions to episodic (e.g., Buckner, 2004; Chun & Johnson, 2011; Sun et al., 2005) and working memory (e.g., Fisk & Sharp, 2003; Zanto, Rubens, Thangavel, & Gazzaley, 2011) may lead to stronger aging-related increases in correlations among these cognitive processes as well.

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