Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2016;41:27–34
DOI: 10.1159/000439585
Accepted: August 21, 2015
Published online: October 22, 2015

1420–8008/15/0412–0027$39.50/0
www.karger.com/dem

Original Research Article

The *COMT p.Val158Met* Polymorphism and Cognitive Performance in Adult Development, Healthy Aging and Mild Cognitive Impairment

Christina Degen[a] Johannes Zschocke[e] Pablo Toro[f] Christine Sattler[b]
Hans-Werner Wahl[b] Peter Schönknecht[d] Johannes Schröder[a, c]

[a]Section of Geriatric Psychiatry, [b]Institute of Psychology, and [c]Institute of Gerontology, University of Heidelberg, Heidelberg, and [d]Department of Psychiatry, University of Leipzig, Leipzig, Germany; [e]Division of Human Genetics, Innsbruck Medical University, Innsbruck, Austria; [f]Department of Psychiatry, Faculty of Medicine, Catholic University of Chile, Santiago, Chile

Key Words
Catechol-O-methyltransferase · Cognitive capacity · Cognitive flexibility · Aging · Mild cognitive impairment · Dopamine

Abstract
Background: The impact of genetic polymorphisms on cognition is assumed to increase with age as losses of brain resources have to be compensated for. We investigate the relation of catechol-O-methyltransferase *(COMT) p.Val158Met* polymorphism and cognitive capacity in the course of adult development, healthy aging and the development of mild cognitive impairment (MCI) in two birth cohorts of subjects born between 1930 and 1932 or between 1950 and 1952. ***Methods:*** Thorough neuropsychological assessment was conducted in a total of 587 participants across three examination waves between 1993 and 2008. The *COMT* genotype was determined as a restriction fragment length polymorphism after PCR amplification and digestion with *Nla*III. ***Results:*** Significant effects of the *COMT p.Val158Met* polymorphism were identified for attention and cognitive flexibility in the younger but not the older cohort. ***Conclusion:*** These results confirm the importance of the *COMT p.Val158Met* genotype on tasks assessing attention and cognitive flexibility in midlife but not in healthy aging and the development of MCI. Our findings suggest that the influence of *COMT* changes as a function of age, decreasing from midlife to aging.

Christina Degen, MSc
Section of Geriatric Psychiatry
University of Heidelberg
Vossstrasse 4, DE–69115 Heidelberg (Germany)
E-Mail Christina.degen@med.uni-heidelberg.de

Dement Geriatr Cogn Disord 2015;41:27–34
DOI: 10.1159/000439585

Introduction

Cognitive functioning is commonly linked to dopaminergic activity, and studies have associated age-related losses of dopaminergic activity with age-related cognitive decline [1]. Catechol-O-methyltransferase *(COMT)* is involved in the modulation of dopamine in the prefrontal cortex (PFC), where its resultant enzyme operates postsynaptically by inactivating neurotransmission [2, 3]. *COMT* contains a functional polymorphism, which enables the substitution of valine *(Val)* with methionine *(Met)*. The *Met* allele results in the production of an enzyme that is unstable at body temperature with approximately ¼ of the activity of the *Val* polypeptide [4]. Thus, the *Met* allele is associated with lower enzyme activity, elevated dopamine levels and superior cognitive performance, while the *Val* allele is associated with higher enzyme activity, reduced dopamine levels and inferior cognitive performance [5, 6]. While feasible, the association of *COMT* and cognitive capacity has been the focus of debate. Some studies identified an association, such that individuals with a homozygous *Met/Met* genotype exhibit increased efficiency and superior performance on tests of executive functions and working memory in comparison to individuals with a homozygous *Val/Val* genotype [4, 7, 8]. By contrast, other studies, including a meta-analysis [9], describe this association to be rather limited or even absent [for a review, see 5; 8, 10].

The respective discrepancies may partially arise from differential effects of the *COMT* polymorphism on cognitive capacity during midlife development and old age. It has been put forward that the impact of genetic polymorphisms on cognitive capacity increases when resources decline – as is the case in aging [11]. As such, a decline in anatomical and neurochemical brain resources may lead to subsequent decline in compensatory skills, thereby amplifying genetic effects on cognitive capacity. In line with this are results reported by Nagel et al. [12] who found a negative effect of the *Val* allele on the number of perseverative errors in the Wisconsin Card Sorting Test in older (between 60 and 70 years of age), but not younger (between 20 and 30 years of age), participants. However, longitudinal studies yield contradictory results. De Frias et al. [13] found *Val/Val* carriers' performance on tasks of executive functioning to decline over a 5-year interval in contrast to *Met* carriers and identified a *COMT* × age interaction for middle-aged adults (50–60 years). Fiocco et al. [14] found the opposite, such that individuals (aged 70–79) with a homozygous *Val/Val* genotype displayed significantly less decline in the performance on the Digit Symbol Substitution Test than carriers of the *Met/Met* genotype across an 8-year interval, indicating an approximation of genotypes in cognitive test performance in aging. Other longitudinal studies have found no genetic impact on cognitive decline (n = 53, mean age 75.5, SD = 5.3 [15]; n = 473, age 64–68 [16]).

No overall conclusion can be drawn based on the respective studies, as they differ regarding their overall design, neuropsychological instruments, age of subjects, and length of follow-up interval. Previous research has focused on cognitive domains most commonly linked to PFC activity, e.g. executive functioning and working memory [4, 17], while from a neuropsychological standpoint, the inclusion of other cognitive domains relying on PFC activation (e.g. episodic memory retrieval [18]) is important to investigate the domain specificity of the respective effects. Here, we sought to examine the role of the *COMT p.Val158Met* genotype in different aspects of cognitive capacity in the course of adult development, healthy aging and the development of mild cognitive impairment (MCI) in the Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE), which involves two large birth cohorts of subjects born between 1930 and 1932 (C30) or between 1950 and 1952 (C50) [19, 20]. We hypothesized that there are specific effects of *COMT p.Val158Met* polymorphism on tests of executive functioning, which are more pronounced in older than in younger subjects.

Dement Geriatr Cogn Disord 2015;41:27–34
DOI: 10.1159/000439585

Methods

Participants

Participants were recruited via local registries. For the purpose of the present study, exclusion criteria were psychiatric diagnoses affecting cognitive functioning apart from MCI, as defined by the Aging-Associated Cognitive Decline criteria [21]. Participants with mild cognitive disorder due to a medical condition, manifest Alzheimer's disease, other forms of dementia, or mood disorders were excluded. Examinations of both birth cohorts were conducted in parallel.

Measures

The first examination (T1) took place in 1993/1994, the second examination (T2) in 1998/1999, and the third examination (T3) was conducted between 2006 and 2008. Each time, careful screening of physical and mental health using extensive physical examination and the German version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders [22] was performed by trained physicians. DNA was extracted at T3 from whole blood using the Nucelon® Genomic DNA Extraction Kit BACC1. The *COMT* genotype was determined as a restriction fragment length polymorphism after PCR amplification and digestion with *Nla*III, as described by Lachman et al. [23]. The same kit was used for both cohorts.

To assess cognitive capacity, the subtests Word List (WL) and Digit Symbol Test (DST) of the Nuremberg Age Inventory [24], the subtests Mosaic Test (MT) and Finding Similarities (FS) of the Wechsler Intelligence Test Battery [25], the subtests Word Fluency (WF) and Visual Thinking (VT) of the Performance Evaluation System [26] as well as the Attentiveness Endurance Test 'd2' (D2)[27] were administered. Due to time restrictions, certain subtests were not administered to the younger birth cohort at T2.

Statistical Analyses

Statistical analyses were performed using the SPSS 14.0 statistical package. After data description, analyses of variance (ANOVAs) and χ^2 tests were conducted to test for significant differences between (a) cohorts, healthy participants and participants with MCI, and (b) carriers of different *COMT p.Val158Met* genotypes. Afterwards, repeated-measures ANOVAs were performed with test scores at all three examination waves being treated as repeated measures. A separate analysis was conducted for healthy individuals using cohort (C30/C50) and *COMT* genotypes as independent variables and controlling for the level of education. Afterwards, C30 was analyzed separately to allow for the inclusion of cognitive status (MCI) in the model. In case assumption of sphericity was violated, Greenhouse-Geisser corrected values were used. The Bonferroni correction was applied to correct for multiple testing.

Results

Demographics and Baseline Characteristics

A total of 587 participants were included in the analysis: 188 healthy individuals from C30, 93 individuals diagnosed with MCI from C30, and 306 healthy individuals from C50, respectively. Distribution of genotypes was consistent with the Hardy-Weinberg equilibrium (*Val/Val* = 21.98%, *Val/Met* = 52.30%; *Met/Met* = 25.72%; $\chi^2 = 1.32$; $p = 0.251$). Demographic and baseline characteristics across genotypes can be inferred from table 1, while demographic characteristics across cohorts can be inferred from table 2.

Cognition

Results of the repeated-measures ANOVAs are presented in table 3. For the healthy participants from C30 and C50, no significant main effect of the *COMT* genotype on cognitive performance was identified. Cohort effects were evident for subtests DST (mean difference = –6.897; SE = 0.847; $p < 0.001$), MT (mean difference = –2.467; SE = 0.716; $p = 0.001$), VT (mean difference = –2.103; SE = 0.532; $p < 0.001$), WL (mean difference = –1.783; SE = 0.236; $p < 0.001$), D2 (mean difference = –14.888; SE = 7.023; $p = 0.035$) and FS (mean difference = –0.814; SE = 0.323; $p = 0.012$), with C50 performing better than C30. A significant inter-

Table 1. Demographic characteristics and baseline cognitive performance across the *COMT* genotype

	Val/Val (n = 129)	Val/Met (n = 307)	Met/Met (n = 151)	ANOVA/χ^2	Duncan
Demographics					
Age baseline	52.98 (9.30)	52.78 (9.43)	53.72 (9.28)	F = 0.521, p = 0.594	
Education	13.71 (2.74)	13.94 (2.77)	13.95 (2.74)	F = 0.382, p = 0.683	
APOE genotype (% ε4 allele)	19.38	25.41	18.54	χ^2 = 3.39, d.f. = 2 p = 0.183	
Sex (% females)	48.83	48.86	47.68	χ^2 = 0.062, d.f. = 2 p = 0.970	
Cohort (% C30)	47.29	46.58	50.99	χ^2 = 0.813, d.f. = 2 p = 0.666	
Cognitive status (% MCI)	15.50	15.64	16.55	χ^2 = 0.079, d.f. = 2 p = 0.961	
Cognitive performance baseline					
DST	48.29 (10.95)	51.10 (10.31)	50.61 (10.02)	F = 3.40, p = 0.034	Val/Val < Val/Met, Met/Met
MT	29.77 (8.07)	30.68 (8.44)	30.73 (8.13)	F = 0.632, p = 0.532	
WL	12.70 (3.16)	12.76 (3.40)	12.81 (3.35)	F = 0.038, p = 0.963	
D2	147.51 (42.52)	156.21 (33.12)	159.19 (38.85)	F = 3.77, p = 0.023	Val/Val < Val/Met, Met/Met
FS	26.02 (4.33)	26.70 (4.17)	26.43 (4.18)	F = 1.204, p = 0.301	
WF	31.26 (7.98)	33.11 (9.00)	32.40 (9.28)	F = 2.008, p = 0.135	
VT	23.33 (6.69)	24.27 (6.19)	24.38 (5.96)	F = 1.242, p = 0.290	

Figures in parentheses are SD.

Table 2. Demographic characteristics and baseline cognitive performance across cohorts and cognitive status groups

	Healthy		MCI C30 (n = 93)	ANOVA/χ^2	Duncan
	C30 (n = 188)	C50 (n = 306)			
Demographics					
Mean age baseline ± SD, years	62.78±0.897	44.15±0.904	62.76±0.877	F = 31525.63, p < 0.001	Healthy C50 < Healthy C30, MCI
Mean education ± SD, years	13.77±3.027	14.47±2.525	12.25±2.170	F = 25.48, p < 0.001	Healthy C50 > Healthy C30 > MCI
APOE genotype (% ε4 allele)	22.34	22.55	21.51	χ^2 = 0.03, d.f. = 2, p = 0.983	
Sex (% females)	53.19	46.08	47.31	χ^2 = 2.427, d.f. = 2, p = 0.297	

action of *COMT* and cohort arose for DST, suggesting that an effect of the *COMT* genotype on executive functioning was apparent in C50 but not in C30 (fig. 1). A triple interaction of the *COMT* genotype, time and cohort was found for MT as illustrated in figure 2.

The second repeated-measures analysis examined the influence of the *COMT* genotype and diagnosis of MCI on cognitive performance over 14 years in C30. No significant effects of the *COMT* genotype appeared. Significant main effects of diagnosis (MCI/cognitively healthy) emerged for DST (mean difference = 8.018; SE = 2.252; p < 0.001), MT (mean difference = 3.693; SE = 0.934; p < 0.001), VT (mean difference = 2.689; SE = 0.770; p = 0.001), WF (mean difference = 4.902; SE = 1.091; p < 0.001), WL (mean difference = 1.427; SE = 0.325; p < 0.001),

Table 3. Results of the repeated-measures analyses

Test	Healthy subjects C30 and C50	C30 (healthy and MCI)
DST	COMT: $F_{2, 451} = 1.149$, p = 0.318 Cohort: $F_{1, 451} = 66.263$, p < 0.001 COMT × cohort: $F_{2, 451} = 3.326$, p = 0.037 Time: $F_{2, 902} = 0.258$, p = 0.772 COMT × time: $F_{4, 902} = 0.152$, p = 0.962 Time × cohort: $F_{2, 902} = 9.765$, p < 0.001 Time × COMT × cohort: $F_{4, 902} = 0.522$, p = 0.719	COMT: $F_{2, 249} = 0.972$, p = 0.380 Diagnosis: $F_{1, 249} = 4.992$, p < 0.001 COMT × diagnosis: $F_{2, 249} = 1.8$, p = 0.167 Time: $F_{2, 498} = 0.653$, p = 0.521 COMT × time: $F_{4, 498} = 0.701$, p = 0.591 Time × diagnosis: $F_{2, 498} = 0.951$, p = 0.387 Time × COMT × diagnosis: $F_{4, 498} = 1.453$, p = 0.215
MT	COMT: $F_{2, 454} = 0.288$, p = 0.750 Cohort: $F_{1, 454} = 11.885$, p = 0.001 COMT × cohort: $F_{2, 454} = 0.871$, p = 0.419 Time: $F_{1, 454} = 0.053$, p = 0.817 COMT × time: $F_{2, 454} = 1.162$, p = 0.314 Time × cohort: $F_{1, 454} = 8.350$, p = 0.004 Time × COMT × cohort: $F_{2, 454} = 4.909$, p = 0.008	COMT: $F_{2, 250} = 0.622$, p = 0.538 Diagnosis: $F_{1, 250} = 14.156$, p < 0.001 COMT × diagnosis: $F_{2, 250} = 1.113$, p = 0.330 Time: $F_{2, 500} = 3.561$, p = 0.029 COMT × time: $F_{4, 500} = 2.127$, p = 0.076 Time × diagnosis: $F_{2, 500} = 0.267$, p = 0.766 Time × COMT × diagnosis: $F_{4, 500} = 0.572$, p = 0.683
VT	COMT: $F_{2, 453} = 1.820$, p = 0.163 Cohort: $F_{1, 453} = 15.644$, p < 0.001 COMT × cohort: $F_{2, 453} = 0.143$, p = 0.867 Time: $F_{1, 453} = 2.170$, p = 0.141 COMT × time: $F_{2, 453} = 0.265$, p = 0.767 Time × cohort: $F_{1, 453} = 20.291$, p < 0.001 Time × COMT × cohort: $F_{2, 453} = 0.536$, p = 0.585	COMT: $F_{2, 249} = 1.572$, p = 0.210 Diagnosis: $F_{1, 249} = 15.193$, p < 0.001 COMT × diagnosis: $F_{2, 249} = 0.277$, p = 0.758 Time: $F_{2, 498} = 3.692$, p = 0.026 COMT × time: $F_{4, 498} = 1.976$, p = 0.097 Time × diagnosis: $F_{2, 498} = 2.942$, p = 0.054 Time × COMT × diagnosis: $F_{4, 498} = 0.681$, p = 0.605
WF	COMT: $F_{2, 453} = 1.247$, p = 0.288 Cohort: $F_{1, 453} = 0.003$, p = 0.960 COMT × cohort: $F_{2, 453} = 0.367$, p = 0.693 Time: $F_{1, 453} = 3.352$, p = 0.068 COMT × time: $F_{2, 453} = 1.199$, p = 0.302 Time × cohort: $F_{1, 453} = 9.596$, p = 0.002 Time × COMT × cohort: $F_{2, 453} = 2.766$, p = 0.064	COMT: $F_{2, 248} = 0.334$, p = 0.717 Diagnosis: $F_{1, 248} = 24.633$, p < 0.001 COMT × diagnosis: $F_{2, 248} = 0.264$,p = 0.768 Time: $F_{2, 496} = 0.410$, p = 0.664 COMT × time: $F_{4, 496} = 0.971$, p = 0.423 Time × diagnosis: $F_{2, 496} = 7.027$, p = 0.001 Time × COMT × diagnosis: $F_{4, 496} = 1.188$, p = 0.315
WL	COMT: $F_{2, 451} = 0.622$, p = 0.537 Cohort: $F_{1, 451} = 57.018$, p < 0.001 COMT × cohort: $F_{2, 451} = 1.614$, p = 0.200 Time: $F_{2, 902} = 0.225$, p = 0.798 COMT × time: $F_{4, 902} = 0.602$, p = 0.661 Time × cohort: $F_{2, 902} = 0.546$, p = 0.580 Time × COMT × cohort: $F_{4, 902} = 0.616$, p = 0.651	COMT: $F_{2, 250} = 0.689$, p = 0.503 Diagnosis: $F_{1, 250} = 26.705$, p < 0.001 COMT × diagnosis: $F_{2, 250} = 0.095$, p = 0.909 Time: $F_{2, 500} = 9.960$, p < 0.001 COMT × time: $F_{4, 500} = 0.099$, p = 0.983 Time × diagnosis: $F_{2, 500} = 3.969$, p = 0.019 Time × COMT × diagnosis: $F_{4, 500} = 1.865$, p = 0.115
D2	COMT: $F_{2, 442} = 1.237$, p = 0.291 Cohort: $F_{1, 442} = 4.494$, p = 0.035 COMT × cohort: $F_{2, 442} = 1.269$, p = 0.282 Time: $F_{2, 884} = 12.590$, p < 0.001 COMT × time: $F_{4, 884} = 0.152$, p = 0.962 Time × cohort: $F_{2, 884} = 31.965$, p < 0.001 Time × COMT × cohort: $F_{4, 884} = 0.823$, p = 0.511	COMT: $F_{2, 241} = 0.355$, p = 0.702 Diagnosis: $F_{1, 241} = 32.309$, p < 0.001 COMT × diagnosis: $F_{2, 241} = 0.802$, p = 0.450 Time: $F_{2, 482} = 9.122$, p < 0.001 COMT × time: $F_{4, 482} = 0.992$, p = 0.412 Time × diagnosis: $F_{2, 482} = 1.143$, p = 0.320 Time × COMT × diagnosis: $F_{4, 482} = 0.556$, p = 0.694
FS	COMT: $F_{2, 454} = 0.013$, p = 0.987 Cohort: $F_{1, 454} = 6.353$, p = 0.012 COMT × cohort: $F_{2, 454} = 0.09$, p = 0.914 Time: $F_{1, 454} = 0.140$, p = 0.709 COMT × time: $F_{2, 454} = 1.561$, p = 0.211 Time × cohort: $F_{1, 454} = 1.899$, p = 0.169 Time × COMT × cohort: $F_{2, 454} = 0.339$, p = 0.713	COMT: $F_{2, 251} = 1.147$, p = 0.319 Diagnosis: $F_{1, 251} = 31.246$, p < 0.001 COMT × diagnosis: $F_{2, 251} = 0.298$, p = 0.743 Time: $F_{2, 502} = 4.832$, p = 0.008 COMT × time: $F_{4, 502} = 2.352$, p = 0.053 Time × diagnosis: $F_{2, 502} = 3.814$, p = 0.023 Time × COMT × diagnosis: $F_{4, 502} = 1.784$, p = 0.131

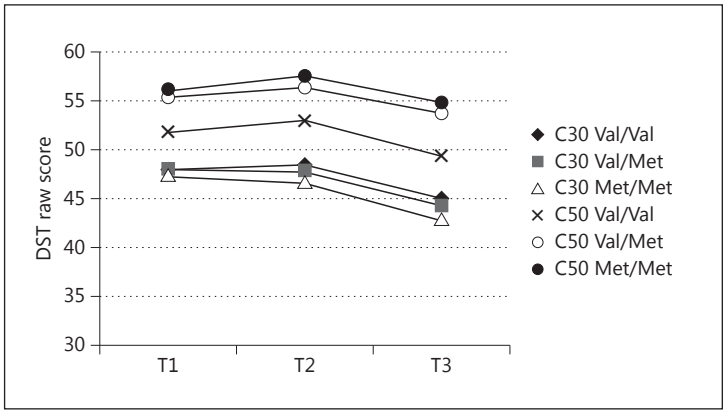

Fig. 1. Interaction of *COMT* and cohort for DST.

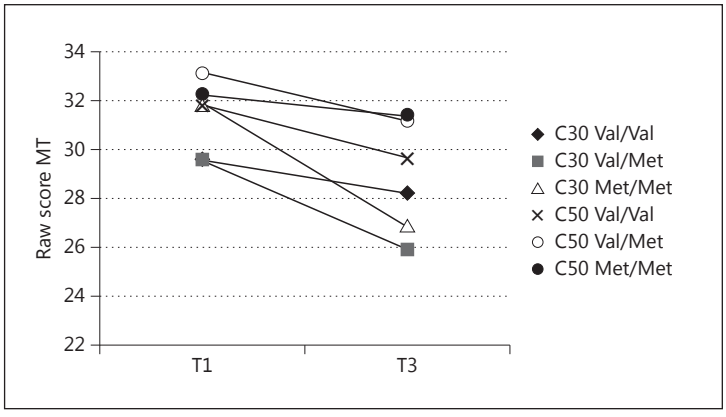

Fig. 2. Interaction of *COMT,* cohort and time for MT.

D2 (mean difference = 57.102; SE = 10.046; $p < 0.001$), and FS (mean difference = 2.920; SE = 0.515; $p < 0.001$), with healthy individuals outperforming those diagnosed with MCI. No interaction of the *COMT* genotype and diagnosis was found. No significant interaction effects of the *COMT* genotype and time appeared, while interaction effects by trend emerged for MT, VT, and FS. Significant interaction effects of time and diagnosis of MCI were found for WF, WL, and FS. No triple interaction was observed.

Discussion

In this study, we investigated the effect of the *COMT p.Val158Met* polymorphism on cognitive performance in a sample of 587 participants of two distinct age cohorts, born between 1930 and 1932 (C30) or between 1950 and 1952 (C50). Our results suggest that the *COMT* genotype exerts a different influence on cognitive functioning for the C50 than for the C30 cohort. For C50, we find significant differences in baseline test performance between *COMT* genotypes on the subtests D2 and DST, such that homozygous *Val* carriers perform more slowly than heterozygotes and homozygous *Met* carriers. We identified an interaction suggesting that this effect is only applicable to C50, but not to C30, contrary to our second hypothesis. The minimal effects of the *COMT p.Val158Met* polymorphism are more pronounced in tests of executive functioning than other cognitive domains. However, no interaction with time was identified, indicating that the *COMT* genotype does not influence cognitive trajectories over time. An individual analysis for the C30 cohort suggests that cognitive perfor-

Dement Geriatr Cogn Disord 2015;41:27–34
DOI: 10.1159/000439585

mance trajectories in older subjects are largely independent on the *COMT* genotype. No effect was found for subjects diagnosed with MCI. These results confirm the importance of the *COMT p.Val158Met* genotype on tasks assessing attention and cognitive flexibility in midlife but not in healthy aging and the development of MCI.

De Frias et al. [13] found that the performance of *Val/Val* carriers on tasks of executive functioning declined over a 5-year interval compared to that of *Met* carriers. An interaction of *COMT* and age was identified for middle-aged participants (aged 50–60), supporting the idea that discrepancies due to genetic effects are greater in midlife than in aging. Fiocco et al. [14] identified a difference in cognitive decline across an 8-year interval, such that individuals with a homozygous *Val/Val* genotype displayed significantly less decline in the Digit Symbol Substitution Test performance compared to *Met* homozygotes, indicating an approximation of different genotypes in test performance in the course of healthy aging. Generally, the respective studies are in line with our findings, even though we did not identify an interaction effect of time (age) and the *COMT* genotype. However, a few studies point to a potential amplification of genetic effects in old age [12]. While it is plausible that losses of brain resources such as decline of striatal and extrastriatal dopamine or atrophy affecting the PFC may amplify the effects of genetic polymorphisms such as *COMT p.Val158Met* on cognition [11], our results show that the *COMT* genotype on its own is not a determining factor. Further studies have demonstrated inefficient cortical processing as reflected by low performance and greater activity in *Val* homozygotes compared to *Met* homozygotes in tasks demanding working memory capacity in participants in their mid-thirties [4, 28] and attentional control [29]. Remarkably, neurological differences were sometimes identified in the absence of effects on behavioral measures such as test performance [28], suggesting a compensatory mechanism. Since we did not find an effect of the *COMT* genotype on cognitive trajectories, we must consider that certain factors related to the birth cohort are determinative rather than age per se.

A potential limitation to studies examining specific cognitive domains is their reliance on neuropsychological test batteries that are largely classified by their content. Assessment instruments can only partially reflect differential cognitive domains or phenotypes (for a review, see Harris and Deary [30]). Moreover, an interplay of different candidate genes affecting dopamine regulation seems likely. There exists relatively robust evidence for risk of increased cognitive decline from *APOE ε4* allele as well as *BDNF* [30, 12]. However, in this study, we were able to consider a follow-up interval of 14 years, allowing for conclusions on the influence of the *COMT* genotype on the process of healthy aging and the development of MCI, while previous research was limited to a few years only. Moreover, directly contrasting two different birth cohorts allowed us to delineate cohort effects from aging effects. Our findings can shed light on the often somewhat contradictory findings reported in the literature. Another strength of this study is the use of extensive neuropsychological testing. Given the role of the *COMT* genotype in dopaminergic pathways, it is likely that areas relying on the PFC are affected differently than other areas. Results of our study suggest that the *COMT p.Val158Met* polymorphism has a larger genetic contribution to tests of attention, cognitive flexibility and information processing speed at ages 43–56 than at ages 63–76. The effects of *COMT* were therefore specific to tests assessing executive functioning rather than tests of memory, verbal fluency or visuospatial thinking.

Acknowledgements

The Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE) is supported by the 'Research Program of the State of Baden-Württemberg', the 'Federal Ministry for Family, Senior Citizen, Women, and Youth, Germany' and the 'Dietmar-Hopp-Stiftung'.

References

1 Backman L, Nyberg L, Lindenberger U, Li S, Farde L: The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci Biobehav Rev 2006;30:791–807.
2 Mattay VS, Goldberg TE: Imaging genetic influences in human brain function. Curr Opin Neurobiol 2004;14:239–247.
3 Egan M, Goldman D, Weinberger D: The human genome: mutations. Am J Psychiatry 2002;159:12.
4 Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR: Effect of COMT Val108/158Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 2001; 98:6917–6922.
5 Savitz J, Solms M, Ramesar R: The molecular genetics of cognition: dopamine, COMT and BDNF. Genes Brain Behav 2006;5:311–328.
6 Sheldrick AJ, Krug A, Markov V, Leube D, Michel TM, Zerres K, Eggermann T, Kircher T: Effect of COMT val158met genotype on cognition and personality. Eur Psychiatry 2008;23:385–389.
7 Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D: A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 2002;159:652–654.
8 Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM, Gilliam TC: Catechol-O-methyltransferase (COMT) genotypes and working memory: associations with differing cognitive operations. Biol Psychiatry 2005;58:901–907.
9 Barnett JH, Scoriels L, Munafo MR: Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. Biol Psychiatry 2008;64:137–144.
10 Ho B, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC: Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. Mol Psychiatry 2005;10:287–298.
11 Lindenberger U, Nagel IE, Chicherio C, Li S, Heekeren HR, Bäckman L: Age-related decline in brain resources modulates genetic effects on cognitive functioning. Front Neurosci 2008;2:234–244.
12 Nagel IE, Chicherio C, Li S, von Oertzen T, Sander T, Villringer A, Heekeren HR, Bäckman L, Lindenberger U: Human aging magnifies genetic effects on executive functioning and working memory. Front Hum Neurosci 2008;2:1–8.
13 De Frias CM, Annerbrink K, Westberg L, Eriksson K, Adolfsson R, Nilsson LG: Catechol O-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. J Cogn Neursci 2005; 17:1018–1025.
14 Fiocco AJ, Lindquist K, Ferrel R, Li R, Simonsick EM, Nalls M, Harris TB, Yaffe K: COMT genotype and cognitive function: an 8-year longitudinal study in white and black elders. Neurology 2010;74:1296–1302.
15 Erickson KI, Kim JS, Suever BL, Voss MW, Francis BM, Kramer AF: Genetic contributions to age-related decline in executive function: a 10-year longitudinal study of COMT and BDNF polymorphisms. Front Hum Neurosci 2008; 2:11.
16 Starr JM, Fox H, Harris SE, Deary IJ, Whalley LJ: COMT genotype and cognitive ability: a longitudinal aging study. Neurosci Lett 2007;421:57–61.
17 Aguilera M, Barrantes-Vidal N, Arias B, Moya J, Villa H, Ibanez MI, Ruiperez MA, Ortet G, Fananas L: Putative role of the COMT gene polymorphism (Val158Met) on verbal working memory functioning in a healthy population. Am J Med Genet B Neuropsychiatr Genet 2008;147B:898–902.
18 Schröder J, Buchsbaum MS, Shihabuddin L, Tang C, Wei T-C, Spiegel-Cohen J, Hazlett EA, Abel L, Luu-Hsia C, Ciaroavolo TM, Marin D, Davis KL: Patterns of cortical activity and memory performance in Alzheimer's disease. Biol Psychiatry 2001;49:426–436.
19 Schröder J, Kratz B, Pantel J, Minnemann E, Lehr U, Sauer H: Prevalence of mild cognitive impairment in an elderly community sample. J Neural Transm Suppl 1998;54:51–59.
20 Schönknecht P, Pantel J, Kruse A, Schröder J: Prevalence and natural course of aging-associated cognitive decline in a population-based sample of young-old subjects. Am J Psychiatry 2005;162:2071–2077.
21 Levy R: Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. Int Psychogeriatr 1994;6:63–68.
22 Wittchen H, Zaudig M, Schramm E, Spengler P, Mombour W, Klug J, Horn R: Strukturiertes klinisches Interview für DSM-III-R. Weinheim, Beltz-Test, 1991.
23 Lachman HM, Papolos DF, Saito T, et al: Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 1996; 6:243–250.
24 Oswald W, Fleischmann V: Nürnberger Alters-Inventar. Erlangen, Universität Erlangen-Nürnberg, 1991.
25 Tewes U (ed): HAWIE-R: Hamburg-Wechsler-Intelligenztest für Erwachsene. Revision 1991. Handbuch und Testanweisung. Bern, Hans Huber, 1991.
26 Sturm W, Willmes K, Horn W: Leistungsprüfsystem für 50–90jährige. Göttingen, Hogrefe, 1993.
27 Brickenkamp R: Test d2: Aufmerksamkeits-Belastungstest. Göttingen, Hogrefe, 1978.
28 Dennis NA, Need AC, LaBar KS, Waters-Metenier S, Cirulli ET, Kragel J, Goldstein DB, Cabeza R: COMT val108/158met genotype affects neural but not cognitive processing in healthy individuals. Cereb Cortex 2010;20:672–683.
29 Blasi G, Mattay VS, Bertolino A, Elvevag B, Callicott JH, Das S, Kolachana BS, Egan MF, Goldberg TE, Weinberger DR: Effect of catechol-O-methyltransferase val158met genotype on attentional control. J Neurosci 2005;25:5038–5045.
30 Harris SE, Deary IJ: The genetics of cognitive ability and cognitive ageing in healthy older people. Trends Cogn Sci 2011;15:388–394.