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COMT gene polymorphisms, cognitive performance, and physical fitness in older adults

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ABSTRACT

Objective: It is well known that genetic predispositions might influence cognitive performance, particularly in older adults. One gene related to executive functioning is the COMT gene with met/met carriers outperforming val/val carriers in cognitive tasks. Further, it has been shown that fitness is positively related to cognitive functioning in older adults. As both, the COMT genotype and physical exercise have been shown to influence dopamine availability and as changes in dopamine metabolism seem to play a key role in cognitive aging, the aim of this study was to analyze the association of the COMT gene polymorphisms with the relationship between fitness and cognition.
Design: We used a cross-sectional design.
Method: Sixty-eight healthy older adults between 62 and 79 years of age were analyzed in this study. DNA was extracted from capillary blood samples. Participants performed a modified version of the Flanker Task as an indicator of executive control and a battery of motor and physical tests as indicators of fitness.
Results: Hierarchical regression analyses revealed a positive influence of overall fitness and an interactive effect of fitness and COMT polymorphisms on Flanker accuracy performance. Val/val carriers revealed the highest positive correlation between fitness and cognition.
Conclusions: Our data suggest that particularly val/val allele carriers benefit from exercise by improved cognitive functioning whereas met/met carriers already perform closer at their optimum level.

Introduction

Aging is associated with a decline in a multitude of motor, sensory, and cognitive processes and brain functions. During the last decades a large amount of studies has accumulated that investigated the reasons and consequences of these age-related changes (e.g., Park & Reuter-Lorenz, 2009; Seidler et al., 2010). However, little is known about the interplay between different factors such as genetic predisposition and lifestyle, or between different body systems, like the motor and cognitive systems.

In recent years, genetic predispositions have attracted more and more interest in conjunction with differences in cognitive performance as well as with disease-related changes in cognition (Mier & Meyer-Lindberg, 2009). The Catechol-O-methyltransferase (COMT) gene has been identified as a candidate gene associated with executive functions (Goldberg & Weinberger, 2004). The COMT gene is located on chromosome 22 and contains a functional polymorphism that translates into a substitution of methionine (met) for valine (val) at codon 158 (val158met). Met allele carriers show about 40% lower prefrontal enzymatic activity than val allele carriers (Chen et al., 2004). Less enzymatic activity among met allele carriers is assumed to lead to less prefrontal cortical dopamine (DA) degradation and hence greater DA availability. In turn, the resulting

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higher cortical DA signaling (Weinberger et al., 2001) seems to be associated with more efficient cortical processing (Witte & Flöel, 2012). DA plays a pivotal role in executive processing (Goldberg & Weinberger, 2004). Numerous human studies showed advantages of met/met allele carriers in tasks of executive functioning (Akil et al., 2003; Blasi et al., 2005; de Frias et al., 2005). For example, de Frias et al. (2005) revealed that COMT val/val and val/met allele carriers performed worse on executive tasks (i.e., verbal fluency, working memory, tower of Hanoi) and visuo-spatial tasks as compared to met/met allele carriers. Furthermore, val/val allele carriers showed an age-related decline in these tasks across a five-year period whereas performance of carriers of the met/met allele remained stable (de Frias et al., 2005). Other studies revealed a more focused response of met/met allele carriers during working memory tasks (cited by Heinz & Smolka, 2006) and better performances in the Wechsler Adult Intelligence Scale (WAIS-R) of long-term memory, working memory, and attention (Enoch, Waheed, Harris, Albaugh, & Goldman, 2009). Overall, studies suggest that COMT and its polymorphisms account for performance differences between individuals in executive functions that are associated with prefrontal brain areas (Goldberg & Weinberger, 2004).

Aging studies suggest that the effect of the COMT genotype on cognitive functioning is magnified in old age (Erickson et al., 2008; de Frias et al., 2005; Nagel et al., 2008) and that the COMT genotype might be one contributing factor to the increasing heterogeneity in cognitive functioning of older adults (Lindenberger et al., 2009). Nagel et al. (2008) revealed a significant interaction between COMT genotype and age with older val homozygotes showing lowest performances. This effect was even stronger if COMT val homozygotes were also met allele carriers of another gene, namely, BDNF. In a longitudinal study, Erickson et al. (2008), however, found no effect of the COMT polymorphisms on the trajectory of age-related decline in executive control over a period of 10 years (for an overview see Jagust, 2009).

Besides genetic predispositions, also lifestyle factors influence cognitive functioning in older adults. In this context, we and others have shown that the older persons' motor status and physical fitness level are associated with and also influence cognitive performance (Colcombe & Kramer, 2003; Dustman, Emmerson, & Shearer, 1994; Voelcker-Rehage, Godde, & Staudinger, 2010; 2011). A meta-analysis by Colcombe and Kramer (2003) revealed that different regimes of regular fitness training led to increases in cognitive performance by 0.5 *SD* on average. The metabolic mechanisms underlying the relationship between physical activity and cognitive functioning, however, are still unresolved. In animal studies, regular physical exercise led to an increase in levels of brain catecholamines, including DA (Hattori, Naoi, & Nishino, 1994; He et al., 2012, after 10 weeks of exercise; Kim et al., 2001, after 4 weeks of exercise; Meeusen & de Meirleir, 1995; Sutoo & Akiyama, 2003). Also in older adults an increased plasma concentration of DA was found after six months of physical training (Ruscheweyh et al., 2011). This association between physical activity and DA concentration is, however, still controversial; some other studies did not find an increase in DA level during (Kraemer et al., 1999; Nybo, Nielsen, Blomstrand, Moller, & Secher, 2003) or after (Wang et al., 2000) exercise. Also acute facilitating effects of exercise on catecholamine levels (particularly DA) in the central nervous system of rats (Hattori et al., 1994; Meeusen et al., 1997; Pagliari & Peyrin, 1995) and humans during (McMorris, Collard, Corbett, Dicks, & Swain, 2008) and after exercise (Winter et al., 2007) were reported. Given the relationship between cognitive performance and prefrontal DA availability as well as the advancing effect of physical activity on plasma DA level and probably dopaminergic neurotransmission, one may hypothesize that the COMT polymorphisms moderate the effect of fitness on cognitive performance.

Until now, to our knowledge only few studies have investigated the cross-link between lifestyle factors such as physical activity, cognitive performance and the COMT polymorphisms. Stroth et al. (2010) revealed in a sample of healthy adults (17–47 years of age) that COMT val homozygotes improved cognitive performance (Stroop Task, Dots-Mixed task) after 17 weeks of running training to a greater extent as compared to met allele carriers. Similarly, investigating the effect of a 6-month multicomponent training (cognitive, aerobic and activities of daily living) in healthy older adults, Pieramico, Esposito, Sensi, Cilli, and Mantini (2012) revealed the greatest exercise benefits in COMT val/val and val/met allele carriers (and DRD3 ser9gly carriers; for other lifestyle factors and the relation to cognitive performance and COMT cf. Loughead et al. (2009) for smoking and Witte, Jansen, Schirmacher, Young, and Flöel (2010) for dietary interventions). The investigation of the link between physical activity, COMT polymorphisms and cognitive functioning might be of special interest in older adults, because both, a val/val COMT genotype and physical *in*activity are key risk factors for the development of age-related cognitive impairment (Rasmussen et al., 2006).

Based on the current literature, we hypothesized that the relationship between a person's fitness level and his/her performance in an executive control task is moderated by his or her genetic predispositions. Particularly COMT val/val allele carriers might benefit from a high fitness level such that high-fit COMT val/val allele carriers can reach cognitive performances comparable to low-fit met/met allele carriers. Since COMT val/val allele carriers should have a lower prefrontal DA level as compared to met/met allele carriers, we assumed that particularly val/val allele carriers benefit from physical activity by elevated DA availability. Following existing research results, effects were mainly expected for performance accuracy in executive control tasks (e.g., Blasi et al., 2005).

Thus, the aim of this study was to examine the influence of the COMT gene polymorphisms and fitness on cognitive performance in a sample of high- and low-fit older adults. We investigated whether fitness level and genotype have additive (significant effect of both factors), compensatory (significant interaction effect) or discrete (effect of one factor only) associations with executive functioning.

Material and methods

Participants

Data were collected as part of the 'Old Age on the Move Study' conducted at Jacobs University Bremen ($N = 92$). We excluded four participants from data analysis due to incomplete cognitive data, and 15 participants due to incomplete motor data. One participant was excluded due to cognitive impairment (score in Mini Mental Status Examination (MMSE) < 27) and four participants due to missing gene data. Sixty-eight healthy older adults between 62 and 79 years of age ($M = 68.81$ years, $SD = 3.61$, 48 females) were analyzed. Participants were recruited from a member registry of a German health insurance company (DAK). Participants had medical clearance and were screened for health restrictions before inclusion in the study by means of a telephone interview. They were excluded from the study if they had a history of cardiovascular diseases, any neurological disorder (e.g., self-report of neurological diseases such as brain tumor, Parkinson's disease, stroke), any other motor or cognitive restriction (a score of less than 27 in the MMSE (Folstein, Folstein, & McHugh, 1975)). All

subjects participated voluntarily in the study and provided written informed consent to the procedures of the study, which was approved by the ethics committee of the German Psychological Society. The study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants were given a demographics and health questionnaire supplemented by personal interviews to determine the characteristics of the sample (e.g. years of education) and self-reported health status (e.g., BMI, diseases) and subjective health ("In general, how would you say your health is?" – 5 point Likert scale from *poor* to *excellent*). No participant had to be excluded from the study due to his or her health status. Participants had normal or corrected to normal vision (Freiburg Visual Acuity Test (Bach, 2007)) and hearing (simultaneous auditory thresholds at multiple frequencies for both ears; presentation software: Neurobehavioral Systems, Albany, Canada (Yund, 2003)), and no color blindness. IQ-performance score (*T scores*: $M = 50$, $SD = 10$) was calculated from seven tests reflecting five primary intellectual abilities (cf. Li et al., 2004): (a) Perceptual speed, measured by the mean performance of Digit-Symbol Substitution and Identical Picture test, (b) reasoning, measured by the mean performance of tests of Figural Analogies and Letter Series, (c) memory, measured by Paired Associate, (d) verbal fluency, measured by the test of naming names of animals, and (e) verbal knowledge, measured by Vocabulary test. For a detailed sample description separated by genotype see Table 1. When split by genotype, analyses revealed that participants were similar in age, sex, education, IQ, MMSE, and subjective health.

Genotyping of the COMT single nucleotide polymorphisms

DNA was extracted from capillary blood samples using Qiagen Blood DNA purification kit (Qiagen, Germany). Genotyping of the Adenosine/Guanin (A/G) single nucleotide polymorphisms (SNP) in the COMT gene (SNP(refSNP) Cluster Report: rs4680) was conducted as described by Al-Hendy and coworkers (Al-Hendy & Salama, 2006). Briefly, the COMT gene fragment containing the SNP was amplified by polymerase chain reaction (PCR) from the genomic DNA and the allelic state was determined by NlaIII restriction enzyme digestion. In each analysis, negative controls for the PCR and digestion controls with PCR products of known allelic state were included. The G-allele encodes for val at position 158 of the COMT protein (NP_000745.1), the A-allele for met. The frequency for the three COMT genotypes was 12 for val/val, 27 for val/met and 29 for met/met (cf. Table 1). The distribution was not significantly different from Hardy–Weinberg equilibrium ($p = .972$, Pearson's χ^2 test).

Executive control task

Executive control was measured by a modified version of the Flanker Task with three response conditions and one control condition (Li et al., 2004). The stimuli consisted of five colored discs presented on a black background on a 17″ computer screen. Participants were given a response pad and instructed to respond by pressing a green button to green targets and a red button to red target discs using their index and middle finger of the right hand, respectively. The central target disc was always flanked by four additional discs: one above and below and one to the left and right of the central target cue. Participants underwent eight 30-s blocks per condition presented in a randomized order (fixation cross exposure time 300 ms, intermediate blank period 200 ms, stimulus duration 300 ms, reaction period until a response was made or 1000 ms had passed, mean random trial variance 150 ms, inter-block break duration 25 s). In the congruent condition the color (green or red) of the distractors was the same as the color of the target. In the incongruent condition, the flanker stimuli were of the color associated with the opposite response than the central target (i.e., red target and green flanker or vice versa). In the neutral condition the flanker stimuli were also of a different color (blue) than the central target (red or green) but not associated with a particular response. In the control condition white targets with white distractors were presented, thus, representing a pure perceptual speed task without any cognitive processing. All trials within each test block were of the same type (congruent, incongruent, neutral, control). It is known that a block design may attenuate the incongruency effect in the Flanker Task ("Gratton effect" Gratton, Coles, & Donchin, 1992). However, it was chosen due to experimental constraints of the "Old age on the Move Study" and revealed significant age effects in the previous analyses (Li et al., 2004). Performance of the Flanker Task was indexed by speed of the correct trials (reaction time (RT)) and accuracy (percentage of correct answers per condition). Participants performed one practice block prior to testing to ensure that they understood the directions for the task. To assure that participants understood the task, only participants were included in the analyses that performed at least 70% correct trials in the congruent conditions of the Flanker Tasks. Trials with response times below 150 ms and above 900 ms were discarded from the analysis to assure that participants reacted to the targets as fast as possible but without anticipating. In previous research, a statistically significant effect of COMT genotype on executive control could be found only under conditions where a high level of attentional control was required (e.g., Blasi et al., 2005). Thus, for statistical analysis we used the

Table 1
Comparison of Demographic Information (Sex (Female/Male), Age), IQ, and Mini Mental Status Examination (MMSE) Scores, Years of Education (Education), Subjective Health, Flanker Performance Scores (Reaction Time (RT) and Percentage Correct Answers (%)) and Fitness Status for the COMT Polymorphisms (Val/Val, Val/Met, Met/Met).

	Descriptives			F-statistic			
	Val/Val	Val/Met	Met/Met	F	df	p	η^2
N	12	27	29				
Sex (F/M)	9/3	17/10	22/7			.538[a]	
Age (years)	69.17 (4.35)	68.89 (3.86)	68.59 (3.15)	0.12	2	.889	.01
IQ (*T-scores*)	50.44 (3.05)	49.74 (3.86)	50.00 (3.82)	0.15	2	.861	.01
MMSE	28.91 (0.94)	28.52 (0.85)	28.68 (1.02)	0.63	2	.535	.02
Education (years)	12.88 (2.86)	11.85 (2.44)	11.88 (2.13)	0.88	2	.419	.03
Subj. Health	3.58 (0.52)	3.42 (0.81)	3.52 (0.79)	0.21	2	.809	.01
Flanker RT (ms)	568.44 (49.83)	568.98 (64.39)	612.76 (61.55)	4.33	2	.017*	.12
Flanker (%)	79.17 (17.79)	89.35 (11.51)	89.33 (8.90)	3.64	2	.032*	.10
Fitness (*z-scores*)	−0.89 (2.36)	0.55 (1.80)	0.02 (2.90)	1.48	2	.236	.04

Note. Standard deviations are presented in parentheses. F = female; M = male; subj. Health = subjective Health; RT = reaction time; MMSE = Mini Mental Status Examination; ANOVAs were performed to test for differences between COMT polymorphisms (val/val, val/met, met/met).
*$p < .05$.
[a] To test for sex differences a Kruskal-Wallis-Test was performed.

performance in the most complex Flanker Task condition, that is, the incongruent condition of the Flanker Task.

Fitness assessment

According to Godde and Voelcker-Rehage (2010) who investigated whether the fitness status of older adults influenced brain activation patterns in simple and complex walking tasks and to Voelcker-Rehage et al. (2010) who revealed that motor and physical fitness are both related to cognitive performance in older adults, fitness was assessed using a heterogenous battery of 10 tests. Tests of *motor fitness* comprised tests to assess *flexibility* (shoulder flexibility), *movement speed* (hand tapping, feet tapping, and agility test), *balance* (backwards beam walk and one-leg-stand with eyes open and closed), and fine coordination (Purdue Pegboard test) (Voelcker-Rehage et al., 2010). In the shoulder flexibility test (Rikli & Jones, 1999) the distance between the fingertips of the right and left hand reaching behind the back was measured for the right and left arm (mean value of the best out of three trials for the right and left arm). In the hand tapping task (Oja & Tuxworth, 1995) participants had to place the non-dominant hand on a table and to tap with the dominant hand across the non-dominant hand (time required for 25 cycles was measured, best out of two trials was selected for analysis). The feet tapping test (Voelcker-Rehage & Wiertz, 2003) required participants to tap with both feet simultaneously in a sitting position across a marker at the floor in front of them (number of taps within 20 s were counted, the best of two trials was selected for analysis). Agility was measured by the Foot up and go test (Rikli & Jones, 2001). Participants had to sit on a chair, stand up, walk around a cone 8 feet in front and sit down on the chair again (best out of three trials was measured). In the one-leg stand (Ekdahl, Jarnlo, & Andersson, 1989) participants were asked to stand on one leg with the other slightly flexed and looking straight ahead. Compensatory movements of arms and the lifted leg but not of the standing leg were accepted. Participants performed three trials standing on the right and left leg each. Duration of standing in seconds (maximum 20 s) was noted for each trial and the mean of the best trial with the right and left leg was used for data analysis. The one-leg-stand with eyes closed was performed accordingly. The beam walk test (Kiphard & Schilling, 1974) required participants to walk backwards on three balance beams with widths of 6 cm, 4.5 cm, and 3 cm. The number of steps on each beam was counted (maximum 8 steps per beam). In the Purdue Pegboard Test (Tiffin & Asher, 1948) participants placed as many pegs as possible into the holes of a pegboard in 30 s. Participants performed this task three times with each hand, and both hand simultaneously. A mean was calculated from the best out of three trials per condition.

Physical fitness was assessed by measuring grip force (as an indicator of muscular strength) and oxygen uptake volume (VO_2peak) by spiroergometry (ZAN300, a measurement system of oxygen consumption and for indirect calorimetric assessment) as an indicator of cardiovascular fitness. During spiroergometry participants completed a submaximal graded exercise test using a ramp-like treadmill protocol (modified Porszasz protocol (2003) on a Lode Valiant motor-driven treadmill with electrocardiography activity monitored by a 10-lead fully digital stress system (Kiss, GE Medical Systems) as reported elsewhere (Voelcker-Rehage et al., 2010)). For data analysis the mean VO2 of the highest complete performance level achieved by the participant was used. Grip force (Igbokwe, 1992) was measured by use of a grip force dynamometer (T.K.K. 5101 Grip-D, Takei Scientific instruments Co., Ltd.; mean value of the best out of two trials for the right and left hand).

As described in a previous study investigating the effect of fitness on movement imagery (Godde & Voelcker-Rehage, 2007), all test scores were z-transformed. For the dimensions movement speed, balance, and physical fitness the z-scores of the respective subtests were averaged. Then an overall fitness index was calculated using a sum score of the five fitness dimensions (flexibility, movement speed, balance, fine coordination, physical fitness).

Statistical analysis

Statistical analysis was conducted with SPSS for Windows version 20.0 (IBM Corp., Armonk, NY). Pearson product–moment correlations were computed using scores for two variables from the Flanker Task (RT and response accuracy), age, sex (coded as 1 = female, 2 = male), COMT gene (coded as 1 = val/val, 2 = val/met, 3 = met/met corresponding to the assumption that met/met allele carriers outperform val/met and val/val allele carriers due to higher cortical DA signaling), and for the overall fitness score (for descriptive variables cf. Table 1). Sex and age were included to identify covariates for inclusion in the subsequent regression analyses.

Further, we performed two four-step hierarchical regression analyses to determine predictors of performance accuracy or performance speed in the Flanker Task, and whether associations between Flanker performances and fitness changed depending on COMT genotype. All multiple regressions were run with centered (mean = 0) independent variables, to reduce multicollinearity among the independent variables (as we included an interaction term; Aiken & West, 1991). In the first step, the dependent variables from the Flanker Task (speed or accuracy) were regressed on age and sex. In the second step, COMT genotype, and in the third step, fitness level was entered. Finally, in the fourth step a COMT by fitness interaction term (based on a product of mean-centered scores) was entered into the regression analysis. The fourth step was conducted to examine whether fitness effects on task performance were dependent upon COMT genotype or vice versa. ΔR^2 displays the change in R^2 resulting from adding an independent variable. It is used to evaluate how much predictive power was added to the model by the addition of another variable. Analyses were conducted separately for the two cognitive outcomes (accuracy, speed). The level of significance was set to $p < 0.05$ ($p < 0.10$ for marginally significant results).

Results

Intercorrelations between variables

Results of the correlational analyses indicated that COMT genotype was positively associated with RT and response accuracy for the incongruent condition of the Flanker Task ($p < .05$, for correlation coefficients cf. Table 2), with COMT met/met allele

Table 2
Intercorrelations between Variables for All Participants.

	Subscale	1	2	3	4	5	6
1	Age	–					
2	Sex	.22	–				
3	COMT	−.06	−.04	–			
4	Fitness	−.35**	.11	.08	–		
5	Flanker acc.	−.25*	.01	.25*	.53**	–	
6	Flanker speed	.00	−.29*	.30*	−.29*	.01	–

Note. Sex coded as 1 = female, 2 = male, COMT gene coded as 1 = val/val, 2 = val/met, 3 = met/met corresponding to the assumption that met/met carriers outperform val/met and val/val carriers due to higher enzymatic activity.
*$p < .05$. **$p < .01$.

carriers showing longest RT and highest performance accuracy. As to be expected, fitness was positively correlated with performance accuracy and negatively related with performance speed (faster RT with higher fitness level; $p < .02$). Age was negatively associated with performance accuracy in the Flanker Task and with fitness ($p < .04$). Additionally, sex was negatively associated with performance speed in the Flanker Task ($p < .02$), with female participants showing slower Flanker performance. Because of correlations with either fitness or Flanker performance, age and sex were treated as covariates in the respective regression analyses of the two dependent variables from the Flanker Task, COMT genotype, and fitness level (see Table 2 for intercorrelations for all participants).

Regression analyses on performance accuracy, fitness, and the COMT polymorphisms

Step one of the regression analysis with age and sex as independent variables was not significant (cf. Table 3). Adding COMT genotype in step two led to a significant model ($F(3, 67) = 3.06$, $p = .034$) and significant change in R^2 ($\Delta R^2 = .06$, $p = .047$). Here age (lower performance of older participants) and COMT genotype were significant predictors of Flanker performance (cf. Table 3 for R^2 and beta estimates for single predictors). Carriers of the met/met allele performed more accurate as compared to val/met and val/val allele carriers, with val homozygotes showing lowest performance levels. When adding fitness into the analysis, the effect of fitness level was significant (Step three, $F(4, 67) = 7.80$, $p < .001$; significant change in R^2; $\Delta R^2 = .21$, $p < .001$), with high-fit participants showing better performances, whereas the effect of COMT genotype and age disappeared (cf. Table 3). Finally, step four was also significant ($F(5, 67) = 11.05$, $p < .001$; see Table 3) and revealed again a significant change in R^2 ($\Delta R^2 = .14$, $p < .001$) by adding the interaction term of fitness and genotype. The effect of fitness and of the COMT × fitness interaction were significant, indicating that the effect of fitness is moderated by the COMT genotype. The moderation effect of the COMT gene on the relation between fitness and cognitive performance is illustrated in Fig. 1. Particularly, for val/val allele carriers higher fitness was associated with greater accuracy in Flanker performance ($r = .90$, $p < .01$). A less pronounced but still significant correlation was observed for the val/met ($r = .40$, $p = .04$) and met/met allele carriers ($r = .45$, $p = .01$).

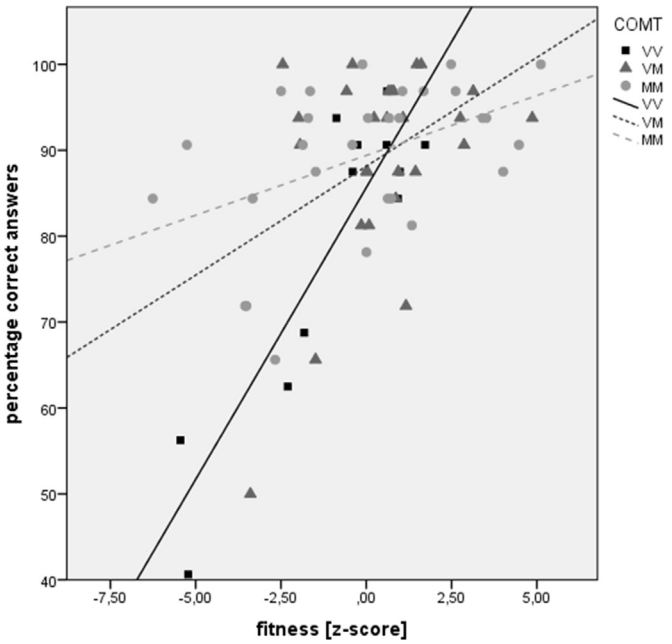

Fig. 1. The Association between Performance Accuracy (Percentage of Correct Answers in Incongruent Condition of Flanker Task) and Fitness (*z*-score) Split by COMT Gene Polymorphisms. ■ = Val/Val. ▲ = Val/Met. ● = Met/Met.

Regression analyses on performance speed, fitness, and the COMT polymorphisms

Step one of the regression analysis on performance speed indicated a significant overall effect ($F(2, 67) = 3.23$, $p = .046$), with a significant effect of sex (lower performance of female participants), but not age (cf. Table 4 for R^2 and beta estimates for single predictors). Step two was also significant ($F(3, 67) = 4.59$, $p = .006$, with a significant change in R^2; $\Delta R^2 = .09$, $p = .012$) revealing significant effects for sex and COMT genotype indicating slower performance speed with the occurrence of met allele. The Step three regression analysis was also significant ($F(4, 67) = 5.269$, $p = .001$) as well as R^2 change ($\Delta R^2 = .07$, $p = .016$). Here sex and COMT as well as fitness revealed significant effects (cf. Table 4). As expected, participants with higher fitness levels performed faster on the Flanker Task. Step four of the analysis was also significant ($F(5$,

Table 3
Summary of Hierarchical Regression Analysis for Variables Predicting Performance Accuracy During Flanker Task: Age, Sex, COMT Gene Polymorphisms (COMT), Fitness, and COMT × Fitness (F) Interaction.

	Step							
	1		2		3		4	
	B	ß	*B*	ß	*B*	ß	*B*	ß
Step 1								
Age	−0.92	−.27*	−0.88	−.26*	−0.22	−.06	0.22	.07
Sex	2.00	.07	2.20	.08	−0.23	−.02	−2.76	−.10
Step 2								
COMT			3.95	.24*	3.39	.20	1.97	.12
Step 3								
Fitness					2.51	.50***	3.24	.64***
Step 4								
COMT × F							−2.64	.41***
Total R^2	.07		.13*		.33***		.47***	
Total ΔR^2			.06*		.21***		.14***	

Note. COMT = COMT gene polymorphism. F = Fitness.
*p < .05. ***p < .001.

Table 4
Summary of Hierarchical Regression Analysis for Variables Predicting Performance Speed during Flanker Task. Age, Sex, COMT Gene Polymorphisms (COMT), Fitness, and COMT × Fitness (F) Interaction.

	Step							
	1		2		3		4	
	B	*ß*	*B*	*ß*	*B*	*ß*	*B*	*ß*
Step 1								
Age	1.21	.07	1.45	.08	−0.57	−.03	−0.70	−.04
Sex	−42.94	−.31*	−41.63	−.30*	−33.47	−.24*	−32.78	−.24
Step 2								
COMT			25.44	.30*	27.16	.32**	27.59	.32**
Step 3								
Fitness					−7.78	−.30*	−8.00	−.31*
Step 4								
COMT × F							0.79	.02
Total R^2	.09*		.18**		.25**		.25**	
Total ΔR^2			.09*		.07*		.00	

Note. COMT = COMT gene polymorphism. F = Fitness.
*$p < .05$. **$p < .01$.

67) = 4.16, $p = .003$, $R^2 = .251$), but the change in R^2 was not. Thus there was no significant effect of the COMT × fitness interaction on performance speed and there rather seems to be an additive effect of fitness level and COMT genotype.

Discussion

The aim of the study was to analyze the interaction between COMT polymorphisms and fitness level on executive functioning in older adults. We hypothesized that the relationship between a person's fitness level and his/her performance in an executive control task is moderated by his or her genetic predispositions. Overall results confirmed our expectations. They differed, however, depending on the indicator of cognitive performance (i.e., performance speed or accuracy).

The differential effects of accuracy and speed

Performance accuracy seems to be positively associated with fitness and even more so for carriers of the val/val COMT genotype (interaction effect, cf. Table 3). The significant effects of fitness and fitness by genotype interaction indicate that a high fitness level might compensate for a lower performance accuracy associated with the val/val genotype (cf. Table 3). That is, val/val allele carriers, who usually show lower performance in executive tasks, might benefit most from DA enhancing strategies like physical exercise and profit in particular from high fitness levels (cf. Fig. 1). Improved dopaminergic neurotransmission might be a potential mechanism by which physical exercise exerts beneficial effects on cognitive functioning in val/val allele carriers (Witte & Flöel, 2012).

For *performance speed* results were less pronounced (see Table 4). Here we found an additive effect of fitness and genotype. Similar to Blasi et al. (2005) we found a stronger effect of COMT polymorphisms for performance accuracy than for RT. Blasi et al. (2005) investigated the effect of the COMT polymorphisms on performance in an attention control task with three levels of attentional control. An effect of the COMT polymorphisms was only found on accuracy and only at the highest level of attentional control. They did not find a significant effect of the COMT polymorphisms on reaction time. Descriptively, similar to our data (cf. Table 1), met/met allele carriers performed even slower than val/met allele carriers in their study. Blasi et al. (2005) argued that the lack of a genotype effect on RT might appear to be counterintuitive, but is consistent with animal studies suggesting that the effect of dopamine signaling in the medial prefrontal cortex during attention is more evident for discriminative performance than for speed (Chudasama & Robbins, 2004). Also human studies suggest that response latency is not specifically influenced by dopaminergic signaling (Bertolino et al., 2004; Goldberg et al., 2003). That might be a reason why the majority of studies that investigated the relationship between COMT polymorphisms and executive functioning (e.g., Blasi et al., 2005; Egan et al., 2001; Lipsky et al., 2005) reported effects for performance measures such as accuracy, number of words or time to task completion as outcome variables for cognitive performance.

Dopamine signaling, fitness, and cortical functioning

Tunbridge, Harrison, and Weinberger (2006) described an inverted U-shaped relationship between prefrontal cortex function and cortical dopamine. Li, Lindenberger, and Bäckman (2010) proposed such a U-shape relationship for DA signaling and cognitive functions in the prefrontal cortex (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). COMT met/met allele carriers are located at the peak of the curve whereas COMT val/val allele carriers are located further left on the curve. Thus, for COMT met/met carriers a high fitness level might be associated with low additional benefit on cognitive functioning since they already perform at their upper range. Moreover, as the curve is very flat at the maximum, differences in DA levels based on fitness will have neither a strong positive nor a negative effect on performance (shift further right). On the contrary, COMT val/val allele carriers' fitness influences the DA level and in turn also cognitive performance. A high fitness level locates val/val allele carriers further right on the curve, where it has a steep slope and thus strong DA level effects on performance. Our results might be related to studies investigating the effect of stimulating drugs (amphetamines), that have been shown to only increase cognitive performance of val allele carriers, but not of met homozygotes (Hamidovic, Dlugos, Palmer, & de Wit, 2010). Furthermore, age-related decline might lead to less efficient processing in prefrontal brain regions. An overall reduction in dopaminergic neuromoduation have repeatedly been shown (Rieckmann et al., 2011; Volkow et al., 1998) and might magnify the genotype-dependent differences in cognitive performance. Normal aging might move an individual further left on the U-shaped function of cortical DA, and COMT val/val allele carriers start this shift further to the left than met/met allele carriers. This might explain why we found also benefits of fitness for met/met allele carriers.

Voelcker-Rehage et al. (2010) showed that high-fit participants needed less resources for visual processing (less occipital activation) and cognitive control (reduced activations in several superior and middle frontal areas such as BA 6, 8, 9 and 46), possibly related to the availability of more resources for executive-control processes. Blasi et al. (2005) revealed that COMT met/met allele carriers had lower brain activity and better performance in an attentional control task than val/met and val/val allele carriers in the cingulate cortex. It seems that a higher DA availability improves the processing efficiency (i.e., lower brain activity) and in turn cognitive performance. These two studies together might explain why we found a compensatory effect of fitness for less preferable genotype on performance accuracy.

Stroth et al. (2010) investigating the effect of 17 weeks of running training on cognitive functions in a sample of 75 healthy younger adults also revealed that COMT val/val allele carriers improved cognitive performance (Stroop Task, Dots-Mixed Task) after the intervention to a greater extent as compared to met allele carriers (val/met and met/met pooled to any met). They concluded that DA might serve as a mediator in the relationship between exercise and cognition in a way that exercise might entail optimization of central DA availability. Pieramico et al. (2012) found that cognitive functioning improved after a multicomponent exercise program in individuals carrying the COMT val/val and val/met polymorphisms. They concluded that this may be due to a higher sensitivity to changes that reduce the enzymatic activity, thereby favoring increased dopamine levels in the posterior cingulate cortex. These results are in line with results of the present study and strongly support the above interpretation of our results.

The effect of genotype on performance *speed* remained stable when we entered fitness into the analysis (no significant interaction, cf. Table 4). Gene and fitness seemed to have separate effects. Carriers of the met allele performed the task slower, high fitness was associated with higher speed. Although sex was correlated with Flanker speed performance, the correlation between fitness and Flanker speed remained when controlled for sex. Interestingly, Stroth et al. (2010) working with young adults and different executive tasks found effects of genotype on performance changes only for reaction speed but not for performance accuracy. Whether this result depends on the selected task (Stroop Task, Dots-Mixed Task) or on the age of the participants is difficult to judge.

Limitations of the study

In the present study, for the first time, we were able to show that the COMT genotype and fitness levels interact in their associations with cognitive functioning in older adults. There are, however, some limitations of our study. First, there might be a kind of selection bias: Older participants willing to participate in this kind of study probably represent a positive selection. This might explain why we had a comparably high amount of COMT met/met allele carriers in our study (cf. e.g., Nagel et al., 2008; Stroth et al., 2010). Participants were, however, similar in age, sex, education, IQ, MMSE, and subjective health. Second, we investigated a relatively small sample size and might thus have overestimated the effects. Future studies should replicate the results in larger populations and different age groups. Third, we investigated only one gene related to executive control. Executive control and the association between fitness and cognition is, however, likely to be underpinned by many genes (e.g., DRD4, DAT1, MAOA, BDNF, APOE, for a review cf. Goldberg & Weinberger, 2004; Hillman, Erickson, & Kramer, 2008; Weinberger et al., 2001), each with a relatively small effect. Associations between single polymorphisms and single cognitive processes are always a simplification, or to refer to Goldberg and Weinberger (2004), "[…] a single gene can affect multiple processes, multiple genes can impact on a single process, and multiple cognitive processes are intercorrelated". A further limitation is the assessment of cross-sectional data that does not allow establishing cause–effect relationships between the interaction of fitness and genotype and cognitive functioning. Thus, we are only at the beginning of understanding the complex interaction between genes, fitness, and cognitive functioning.

Conclusions

COMT gene polymorphisms and fitness interact in their association with executive functioning (performance accuracy) in older adults. Particularly carriers of the val/val genotype seem to benefit from a higher fitness level. A high fitness level might entail optimization of dopaminergic neurotransmission and thus compensate for being a COMT val/val carrier.

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