Human aging magnifies genetic effects on executive functioning and working memory

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INTRODUCTION

Individual differences in complex phenotypes result from gene-gene and gene-context interactions (McClearn, 2006). Between-person variation in brain functions and cognitive abilities is associated with genetic factors (Klein et al., 2007; Meyer-Lindenberg et al., 2007; Savitz et al., 2006), and changes across the lifespan (Baltes et al., 1999; Cabeza et al., 2005; Diamond, 2007; Diamond et al., 2004; Posner et al., 2007). Recently, the Catechol-O-Methyltransferase (COMT) gene, implicated in executive functions, and the Brain-Derived Neurotrophic Factor (BDNF) gene, associated with memory-related functions, have received increasing attention in gene-cognition association studies (Goldberg and Weinberger, 2004; Savitz et al., 2006). Here, we examine whether normal human aging magnifies the effects of these genes on executive functioning and working memory.

COMT enzymatic activity results in degradation of dopamine (DA) and thus has an impact on endogenous DA levels in prefrontal cortex (PFC). A common polymorphism of the COMT gene is associated with most of the human variation in intrinsic DA levels in the PFC. The COMT single nucleotide polymorphism leads to a substitution of valine (Val) with methionine (Met) at the codon 158 on chromosome 22q11 (Val158Met). This substitution affects enzymatic activity, which is three to four times higher in Val than in Met homozygotes. Lower enzymatic activity among Met carriers leads to less frontal DA degradation and hence greater DA availability at the receptors (Meyer-Lindenberg et al., 2007).

Some behavioral studies using tasks that tax executive functioning such as the Wisconsin Card Sorting Test (WCST) and n-back task have found an advantage of Met over Val carriers in young adults. However, effect sizes are generally small (Egan et al., 2001; Malhotra et al., 2002; Meyer-Lindenberg et al., 2006) and not always statistically reliable (Barnett et al., 2007). One reason for the relatively small effects may be that the advantage of Met carriers inexecutively demanding tasks applies to sustained processes such as maintaining a cognitive set, but not to transient processes related to cognitive flexibility (Bilder et al., 2004; Grace et al., 2007).

Animal and human data suggest that the relation between DA levels and cognitive functioning follows an inverted U-shaped function (Goldman-Rakic et al., 2000; Li and Sikström, 2002; Li et al., 2001; Mattay et al., 2003; Vijayraghavan et al., 2007). The DA system undergoes a marked decline with increasing adult age, with a gradual loss of both pre- and post-synaptic markers of DA neurotransmission from early through late adulthood (Antonini and Leenders, 1993; Eriksen-Lindroth et al., 2005; Kaasinen et al., 2000; Suhara et al., 1991). This loss is consistently found in striatal, neocortical (e.g., frontal), and limbic areas (Bäckman et al., 2006). Normal human aging is also associated with decline across a range of cognitive abilities (Baltes and Lindenberger, 1997). Higher-order...
cognitive functions that rely on PFC and medial-temporal lobe (MTL) integrity (e.g., working memory, executive functions) show a particularly robust age-related decline (Bäckman et al., 1999; Raz et al., 2007; West, 1996). Further, molecular imaging studies indicate that age-related DA losses are powerful mediators of age-related impairment in multiple cognitive tasks, including those assessing working memory and executive functions (Bäckman et al., 2000, 2006; Erixon-Lindroth et al., 2005; Volkow et al., 1998). Moreover, BDNF infl uences performances on cognitive tasks, including those assessing working memory and related functions (Bäckman et al., 2000, 2006; Erixon-Lindroth et al., 2005; Volkow et al., 1998). Secretion of BDNF is higher in Val homozygotes than in Met carriers of the COMT gene. Thus, we predict that human aging magnifies the effects of the COMT polymorphism on cognitive performance (Figure 1). Therefore, we also predicted that the relation between COMT status and adult age is modulated by BDNF genotype. We expected that older COMT Val carriers who also carry the Met allele of the BDNF gene would show particularly low levels of executive functioning. To test these predictions, younger and older adults were tested on the WCST and on a spatial working memory (SWM) task. We chose a SWM task because spatial processing is known to be particularly sensitive to aging (Jenkins et al., 2000) as well as to dopamine status (Bäckman et al., 2006).

Figure 1. Inverted U-shaped function linking the efficacy of frontal DA signaling in early versus late adulthood to performance. The shape of the curve implies that the difference in performance between older Met and Val carriers of the COMT gene.

MATERIALS AND METHODS
Participants
We studied 318 healthy volunteers from two age groups: 164 younger adults (age range = 20–31, mean age = 25, SD = 2.2, 65 women and 99 men) and 154 older adults (age range = 60–70, mean age = 65, SD = 2.9, 65 women and 89 men). All subjects were right-hand dominant and had normal or corrected vision. The older sample had no symptoms of dementia (all scores on the Mini-Mental Status Examination were over 27 out of 30) and none of them reported a history of medical, neurological, or psychiatric disease. Subjects were categorized according to their alleleic variants of the COMT and BDNF polymorphisms. They were recruited via newspaper announcements, posters in public transportation, and postcards. Subjects gave informed consent and were paid for their participation. The study was approved by the ethics committees of the Max Planck Institute for Human Development and the Charité University Medicine, Berlin. For detailed sample description, see Tables 1 and 2.

Genotyping
DNA was extracted from peripheral blood using standard methods. The non-synonymous mutation of rs4680 of the COMT Val158Met polymorphism as well as the rs6265 BDNF Val66Met polymorphism were genotyped in a 384-well microtiter plate format using the TaqMan 5′-exonuclease assay as described elsewhere (Egan et al., 2001; Hariri et al., 2003). Both SNPs were selected from the dbSNP (http://www.ncbi.nlm.nih.gov/SNP). The sequences of primers and TaqMan probes for the SNP genotyping were designed and synthesized by Applied Biosystems (Foster City, CA, USA).

The frequencies of the three COMT genotypes were 0.21 for Val/Val, 0.53 for Val/Met and 0.26 for met/met for the younger subjects and 0.23 for Val/Val, 0.50 for Val/Met and 0.27 for Met/Met for the older subjects. The frequencies of the two BDNF genotypes were 0.34 for any Met and 0.66 for Val/Val for the younger subjects and 0.29 for any Met and 0.71 for Val/Val for the older subjects. The allelic distributions of the each gene did not deviate significantly from those expected according to Hardy-Weinberg equilibrium in the younger, COMT: χ²(1) = 0.68, p > 0.10; BDNF: χ²(1) = 0.01, p > 0.10, or the older subjects, COMT: χ²(1) = 0.03, p > 0.10; BDNF: χ²(1) = 1.43, p > 0.10. The observed frequencies did not differ between the two age groups, COMT: χ²(2) = 0.24, p > 0.10; BDNF: χ²(1) = 1.15, p > 0.10. After genotype determination, the groups were...
Aging magnifies genetic effects

Participants underwent two cognitive testing sessions, lasting approximately 2.5 h each. These sessions were held in groups of about six subjects of the same age. The cognitive tasks were administered to investigate executive functioning, episodic memory, verbal ability, processing speed, and robustness. Two tasks (i.e., WCST and SWM) were used in the present study to assess executive functioning.

Wisconsin card sorting test. A computer-administered adapted version of the standard 128-cards WCST was used (Heaton et al., 1993). This task is considered as a standard neuropsychological index of executive functioning. Four key cards are presented at the top of the screen. A response card is shown at the bottom center of the screen and has to be sorted by the participant to one of the cards presented on the top of the screen. The cards can be matched based on three dimensions: color, form, and number. Subjects respond by pressing one of the four corresponding buttons with the index finger of the right hand. A limited time is given to allow participants to correct their answer. Then, feedback about the correctness of the response appears briefly on the screen. Participants must use this feedback to sort the next response card as no explicit information about the current sorting rule or the switch to a new sorting rule is provided. The first sorting principle is color, followed by form and then number. When a person attains 10 correct consecutive sorting orders (referred to as completing a category), the sorting principle changes (in the order noted). This sequence is repeated once. Because no warning is given about these changes, subjects must make the necessary shift of mental set on the basis of the feedback given. The test continues until six categories have been completed.

### Table 1. Between-genotype comparisons of demographic data in the sample of younger adults (age range = 20–30 years).

| Genotype | Younger participants (n = 164) |
|----------|-------------------------------|
|          | COMT Val/Val | Val/Met | Met/Met |
|          | BDNF Any Met | Val/Val | Any Met | Val/Val | Any Met | Val/Val |
| Demographics | | | | | | |
|           | n | 12 | 22 | 34 | 53 | 10 | 33 |
| Age (SD)  | 25.6 (3.5) | 24.2 (3.2) | 25.1 (3.1) | 25.5 (3.2) | 26.0 (3.0) | 25.4 (3.3) |
| Women/Men | 7/5 | 10/12 | 12/22 | 22/31 | 12/22 | 22/31 |
| Years of education (SD) | 12.3 (2.1) | 12.7 (1.2) | 12.9 (1.3) | 12.9 (1.5) | 13.2 (0.4) | 12.7 (1.2) |
| State of health (SD) | 4.2 (0.9) | 4.0 (0.7) | 4.2 (0.6) | 4.3 (0.7) | 4.4 (0.5) | 4.2 (0.7) |
| M.M.S.E. (SD) | – | – | – | – | – | – |

State of health is based on four self-ratings assessed on 5-point scales (1 = poor; 5 = excellent).

*Two-way analyses of variance = n.s.

### Table 2. Between-genotype comparisons of demographic data in the sample of older adults (age range = 60–70 years).

| Genotype | Older participants (n = 154) |
|----------|-------------------------------|
|          | COMT Val/Val | Val/Met | Met/Met |
|          | BDNF Any Met | Val/Val | Any Met | Val/Val | Any Met | Val/Val |
| Demographics | | | | | | |
|           | n | 9 | 26 | 18 | 60 | 17 | 24 |
| Age (SD)  | 65.7 (3.8) | 64.9 (3.3) | 64.3 (2.8) | 64.4 (2.6) | 62.8 (2.3) | 65.6 (2.6) |
| Women/Men | 2/7 | 10/16 | 6/12 | 32/28 | 6/11 | 9/15 |
| Years of education (SD) | 10.8 (1.9) | 11.5 (1.7) | 10.6 (1.7) | 11.1 (1.8) | 11.1 (2.0) | 10.9 (1.5) |
| State of health (SD) | 3.9 (0.6) | 3.8 (0.6) | 4.1 (0.6) | 4.0 (0.6) | 3.6 (0.7) | 3.8 (0.6) |
| M.M.S.E. (SD) | 29.4 (0.7) | 29.4 (0.7) | 29.5 (0.6) | 29.4 (0.7) | 29.5 (0.9) | 29.3 (0.7) |

State of health is based on four self-ratings assessed on 5-point scales (1 = poor; 5 = excellent).

*Two-way analyses of variance = n.s., except for a significant COMT × BDNF interaction for age, F(2,148) = 3.83, p < 0.05, η² = 0.05. The pattern and statistical significance of the results reported in the article remain unchanged when individual differences in age within age groups are added as a covariate.

*χ² = n.s.

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*Two-way analysis of variance = n.s., except for a significant effect of COMT on state of health, F(2,148) = 3.08, p < 0.05, η² = 0.04.
or until the entire set of 128 cards has been sorted. Participants were instructed to perform as fast and accurately as possible. Performance was evaluated by applying the WCST standard scoring rules as described by (Heaton et al., 1993). The percentage of perseverative errors and reaction times for correct responses were used to index performance.

**Spatial working memory.** We modified a computerized SWM task devised by Klingberg and colleagues (1997). In this task, participants were visually presented with a series of dots, displayed consecutively in a specific location in a 4 × 4 grid of circles. They had to decide if a dot was presented on the position of a specific circle (i.e. location memory condition). If subjects responded “yes” to the spatial location, a digit was presented in this position. Subjects then had to decide if the digit matched the serial position of the dot in the presented order (i.e. sequence memory condition). They responded with a right index-button press if the location or the serial position was correct, and with a left index-button press if the location or serial position was wrong. Load level was manipulated by the number of dots in the sequence; either four or seven (i.e., set size 4 and set size 7 conditions, respectively). One third of the items were associated with correct location and temporal order, one third with correct location and incorrect order, and another third with incorrect location (and, by implication, missing order information). The timing of the sequence was set up with a 1000 ms fixation, immediately followed by the stimulus presentation (600 ms per dot) and a marked circle for a maximum duration of 5000 ms. When serial order was assessed, a digit was presented in the same position for a maximum of 5000 ms. The interstimulus interval was 400 ms. The task involved 4 blocks of 24 trials each, each load level (i.e. size 4 or 7) being repeated twice, for a total of 48 trials per condition. The different load levels were presented in counterbalanced order (4-7-7-4), which was kept constant across participants. Reaction time and accuracy were recorded for each trial separately.

**Statistical analysis**

Demographic data were analyzed with analyses of variance and χ² tests, using SPSS for Windows 15.0 (SPSS, Chicago, IL). Behavioral data were analyzed with mixed-effect models with maximum-likelihood estimation (“Proc Mixed” procedure), using SAS 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). In contrast to standard ANOVA, mixed-effect models allow for differences in variances and covariances between groups. Variances and covariances were allowed to differ between age groups because older adults were reliably more variable than younger adults. Allowing for unequal variances and covariances in the presence of variance-covariance heterogeneity permits unbiased tests of statistical significance, whereas standard ANOVA procedures would yield biased results. Here, the bias of standard ANOVA was progressive because the critical triple interaction originated from a subsample that was more variable than average. Thus, all effects reported here were also statistically reliable when standard ANOVA methods were used. The alpha level was set to α = 0.01, and exact p values are reported if 0.01 < p < 0.05. Effect sizes are indicated by the intraclass correlation coefficient (ρ). The ρ values were squared to ease interpretation in terms of the percentage of total variance associated with an effect.

**RESULTS**

**Wisconsin card sorting test (WCST)**

Percent perseverative errors and reaction times for correct responses on the WCST are presented in Figures 2A,B. For both measures, 3-way ANOVAs were conducted to examine the associations among age (young, old), COMT genotype (Val/Val, Val/Met, Met/Met), and BDNF genotype (Val/Val, any Met), using sex as a covariate. Older participants committed more perseverative errors than younger participants, F(1, 256) = 77.76, p < 0.01, $\rho_I = 0.48$, explaining 23.3% of the total variance.
variance in the data. There was no main effect of COMT genotype, $F(2, 255) = 1.36$, n.s., but the interaction between age and COMT was reliable, $F(2, 256) = 3.01$, $p = 0.05$, $\rho = 0.15$ (2.3%), reflecting a Val disadvantage for older adults only (for older Val versus older Met homozygotes, $t = -2.22$, $p = 0.03$; see Figure 2A).

With respect to reaction times for correct responses, older adults responded more slowly than younger adults, $F(1, 215) = 159.06$, $p < 0.01$, $\rho = 0.65$ (42.5%). The effect of COMT genotype, $F(2, 214) = 4.18$, $p = 0.02$, $\rho = 0.19$ (3.8%), and the age x COMT interaction, $F(2, 214) = 4.54$, $p = 0.01$, $\rho = 0.20$ (4.1%), were significant. This interaction was qualified by a significant triple interaction of age, COMT, and BDNF, $F(2, 214) = 3.43$, $p = 0.03$, $\rho = 0.18$ (3.1%). Older homozygotic Val carriers of the COMT gene with at least one BDNF allele were particularly slow (compared to the five other groups of older adults, $t = -2.82$, $p < 0.01$; see Figure 2B).

Spatial working memory (SWM) task
Performance accuracy in the SWM task was examined in a 5-way mixed ANOVA with age (young, old), COMT (Val/Val, Val/Met, Met/Met), and BDNF (Val/Val, any Met) as between-subject factors, load (4 items, 7 items) and test (identity, sequence) as within-subject factors, and sex as a covariate.

No significant main effects or interactions involving either polymorphism were found, $F(2, 239) = 1.41$, n.s., for COMT; $F(1, 240) = 2.11$, n.s., for BDNF; and $p > 0.05$ for all interactions involving COMT or BDNF. For details on age, load, and test effects see Table 3.

The corresponding 5-way mixed ANOVA on reaction times for correct responses revealed a significant 4-way interaction of age, COMT, BDNF, and load, $F(2, 269) = 3.71$, $p = 0.02$, $\rho = 0.16$ (2.7%), (for other effects of the 5-way ANOVA, see Table 4).

To trace the source of the 4-way interaction, separate analyses for each load level were conducted. At set size 4, we found main effects of age, $F(1, 256) = 288.97$, $p < 0.01$, $\rho = 0.73$ (53.0%), test, $F(1, 222) = 106.76$, $p < 0.01$, $\rho = 0.57$ (32.5%), and an interaction between age and test, $F(1, 222) = 3.98$, $p = 0.05$, $\rho = 0.13$ (1.8%). Critically, the interaction between age and COMT was reliable, $F(2, 255) = 3.29$, $p = 0.04$, $\rho = 0.16$ (2.5%), indicating that slower responding among homozygotic Val carriers was restricted to the old (for older Val versus older Met homozygotes, $t = -2.16$, $p = 0.03$; Figure 2C; see also Table 4).

At set size 7, we found significant main effects of age, $F(1, 261) = 131.69$, $p < 0.01$, $\rho = 0.58$ (33.5%) and test, $F(1, 239) = 14.20$, $p < 0.01$, $\rho = 0.24$ (5.6%). None of the two-way interactions were statistically reliable, all $p > 0.10$. Here, the triple interaction among age, COMT, and BDNF was significant, $F(2, 259) = 3.44$, $p = 0.03$, $\rho = 0.16$ (2.6%). Older Val/Val COMT individuals who carry BDNF Met genes showed particularly elevated response times (compared to the five other groups of older adults, $t = -2.55$, $p = 0.01$; Figure 2D).

**DISCUSSION**

We hypothesized that (a) human aging magnifies the influence of the Val/Met COMT polymorphism on executive functioning and working memory, and (b) this effect is modulated by the Val/Met BDNF polymorphism. Data obtained on two tasks were consistent with both predictions. First, for a standard measure of executive functioning, the WCST, the COMT Val allele was associated with a higher number of perseverative errors in older adults. This association was not observed in younger adults. In addition, reaction times for correct responses were also dependent on BDNF status: Older adults carrying two COMT Val alleles and at least one BDNF Met allele took particularly long time to respond, resulting in an age x gene x gene interaction.

Second, for the SWM task, genetic modulation of performance was restricted to reaction times for correct responses. In the low-load condition (set size 4), COMT effects on processing efficiency were not reliable in younger adults but present in older adults. This age x gene interaction pattern closely resembled the pattern found for perseverative errors in the WCST (cf. Figures 2A,C). In the high-load condition (set size 7), we again found a triple interaction of age, COMT, and BDNF. Response times were particularly slow in older adults carrying two COMT Val alleles and at least one BDNF Met allele. This pattern mirrors the WCST latency data for correct responses (cf. Figures 2B,D). The results from both tasks support the notion that effects of the Val/Met COMT polymorphism on executive functioning and working memory increase in old age, and are further accentuated by the corresponding BDNF polymorphism. Note that the genetic effects were stronger for latency than for accuracy, likely reflecting greater sensitivity of the former measure. However, the interactive effects of age, COMT, and BDNF reported here did not generalize to other speeded tasks in our cognitive battery such as simple reaction time. Thus, the present interactive effects are not a byproduct of age-differential genetic effects on response speed per se, but rather reflect demands on executive or working memory functioning.

Most investigations on cognitive effects of the COMT gene have included younger adults (Bilder et al., 2004; Egan et al., 2001; Ho et al., 2005; Mattay et al., 2003; Montague et al., 2004). It may seem surprising that we did not observe reliable COMT effects in younger adults, as such effects have been observed in earlier studies with smaller samples (Egan et al., 2001; Mattay et al., 2003; Montague et al., 2004). However, the evidence on COMT effects on executive functioning and working memory in early adulthood is not unequivocal, as several studies have failed to find such effects (Barnett et al., 2007; Bilder et al., 2004; Ho et al., 2005; Tsai et al., 2003). In contrast, the few cognitive studies with older adults have invariably reported COMT effects in the expected direction (de Frias et al., 2004, 2005; Harris et al., 2005; Mattay et al., 2006; Starr et al., 2007). The direct age-comparative evidence obtained in this study provides novel support for the view that COMT effects are unmasked in old age, presumably because older adults are operating at suboptimal levels of dopaminergic neuromodulation.

Based on animal research, molecular imaging studies in humans, and neurocomputational modeling, we assumed that age-related declines in DA signaling lead to noisier and less efficient processing in...
...presence of sizeable mean-level decline (Deary et al., 2004; de Fries et al., 2007; Raz et al., 2007). Reliable between-person variation in cognitive change appears relatively late in life (e.g., around age 70), widening the gap between high-functioning and impaired older individuals (e.g., de Fries et al., 2007). We found that aging magnifies the functional consequences of common genetic polymorphisms on executive functioning and working memory. We conclude that genetic factors boost individual differences in the aging of human cognition, and contribute to the marked heterogeneity in late-life cognitive functioning. 

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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