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Effects of age, genes, and pulse pressure on executive functions in healthy adults

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Abstract

Executive functions (EF) evidence significant age-related declines, but the mechanisms underpinning those changes are unclear. In this study, we focus on two potential sources of variation: a physiological indicator of vascular health, and genetic variants related to vascular functions. In a sample of healthy adults ($n = 158$, ages 18–81), we examine the effects of age, pulse pressure, and two polymorphisms (*comt* val158met and *ace* insertion/deletion) on working memory and cognitive flexibility. Results indicate that in addition to often-replicated age differences, the alleles of two polymorphisms that promote vasoconstriction (*comt* val and *ace* D) and reduced availability of dopamine in neocortical synapses (*comt* val), negatively impact virtually all aspects of EF tasks that involve working memory. In some cases, suppression of cognitive performance is limited to men or necessitates a combination of both risk-associated alleles. After accounting for genetic and age-related variation, pulse pressure had no additional effect on EF. These findings suggest that in healthy adults, the effects of genetic risk factors significantly modulate the course of cognitive aging.

Keywords

aging; working memory; ACE; COMT; vascular risk; polymorphism

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1. Introduction

Many cognitive skills decline with age, but the magnitude of the age differences varies across functional domains (Horn, 1986). Executive functions (EF) that comprise goal setting, planning, and coordinating multiple tasks while storing information, shifting between stimulus and response sets, and deployment of attentional resources are among the most age-sensitive cognitive skills (Hultsch et al., 1992; West, 1996). Although the mechanisms that underpin such sensitivity are unclear, predilection of EF for age-related declines is likely to reflect heightened vulnerability of their neural substrates to diverse physiological, neurochemical, and genetic factors.

One of the important contributors to age-related vulnerability of EF is vascular risk. Vascular health declines with age (Fleg, 1986) and clinical, epidemiological, and experimental findings indicate that increasing vascular risk and overt cardiovascular disease have a significant negative impact on EF (Apter et al., 1951; Elias et al., 2003; Elias et al., 2004; Waldstein et al., 2008). Although EF is not a homogenous construct (Miyake et al., 2000), many of the executive component processes depend on structural integrity of the tertiary association cortices (especially the prefrontal cortex, PFC) and the associated white matter (Demakis, 2003; Gunning-Dixon and Raz, 2003; Raz et al., 1998). Age-related increase in vascular risk and vascular disease seem to exert an especially significant influence on prefrontal structures (e.g., DeCarli et al., 1995; Kuczynski et al., 2009; Raz et al., 2003, Raz et al., 2007a; Raz et al., 2007b; see Román et al., 2002 for a review). Moreover, even in healthy adults, high-normal values of vascular health indicators may be associated with reduced EF (e.g., Dahle et al., 2009).

Essential hypertension, one of the most common vascular risk factors, occurs in otherwise healthy adults and its prevalence increases with age (Franklin et al., 1997). Among multiple mechanisms proposed for the development of hypertension, an important role belongs to alterations in renin-angiotensin system (RAS) and specifically in activity of a vasoactive peptide angiotensin II (Safar, 2005). Availability of angiotensin II, a vasoconstrictor, is controlled by the angiotensin converting enzyme (ACE), which in addition to enabling its synthesis from angiotensin I, inhibits a vasodilator bradykinin (Vauquelin et al., 2002; von Bohlen und Halbach and Albrecht, 2006). Through its vasoconstrictive effects, ACE plays an important role in regulation of blood pressure, and ACE inhibitors are effective in the treatment of hypertension (Wong et al., 2004). Although it is abundant in the peripheral nervous, renal, and pulmonary systems, angiotensin II has a significant presence in the brain, where its receptors reside in the blood brain barrier and endothelial cells of cerebral vasculature (Saavedra, 2005).

Recent studies show that ACE may influence age-sensitive cognitive processes (Vauquelin et al., 2002; von Bohlen und Halbach and Albrecht, 2006) and promote cognitive impairment (He et al., 2006). Alternately, administration of ACE inhibitors reverses cognitive deficits in hypertensive rats (Srinivasan et al., 2005), reduces incidence of cognitive impairment in older adults (Yasar et al., 2008), slows progression to dementia in persons at risk (Rozzini et al., 2006), and ameliorates cognitive declines in patients with a diagnosis of Alzheimer's disease (AD; He et al., 2006). In mice, chronically elevated angiotensin II reduces cerebral blood flow and impairs learning (Inaba et al. 2009). However, in some samples, variation of ACE activity had no effect on cognitive functions (Harrap et al., 2003; Visscher et al., 2003), suggesting that the effect of ACE may materialize only in conjunction with other physiological, neurochemical, or genetic factors.

One such established neurochemical modifier of EF is dopamine (DA), and specifically, activity at its D₁ receptors located in the prefrontal synapses (see Arnsten and Li, 2005;

Floresco and Magyar, 2006; Goldman-Rakic, 1996 for reviews). As aging is associated with a significant decline in dopaminergic functions (Bäckman et al., 2006), the DA system is a highly plausible candidate for explanation of age-related deficits in EF. Because the availability of DA in the PFC depends predominantly on the enzymatic activity of catechol-O-methyl-transferase (COMT; Slifstein et al., 2008; Tunbridge et al., 2004), factors that affect COMT levels may be crucial for maintaining normal EF through the life span.

Although the effects of angiotensin II and DA on cognitive performance can be studied by pharmacological manipulations, an alternative approach is to observe the effects of naturally occurring variations therein. Common mutations in the genes that affect enzymatic control of angiotensin II and DA availability in fact randomly assign individuals to high or low levels of the target compounds. As a substantial share of observed differences in EF stems from genetic factors (Anokhin et al., 2003; Friedman et al., 2008; but see Kremen et al., 2007), examination of specific polymorphisms is a plausible way to clarify the specifics of the genetic influence on EF.

Indeed, recent studies revealed several specific associations between behavioral phenotypes of EF and genetic polymorphisms. Although the extant literature is still relatively scarce, probably no polymorphism has received more attention in the study of EF genetics than *comt* val158met, a single nucleotide variant in a gene that controls the activity of COMT. In comparison to the double dose of the wild val allele, a double dose of the mutant met allele of that polymorphism is associated with an almost fourfold reduction in COMT activity.

Since publication of the seminal paper by Egan and colleagues (2001), the investigations of genetic associations between selected EF and *comt* val158met genotypes have thus far delivered mixed results. In multiple studies of healthy adults, carriers of the met allele outperformed the val carriers on many executive tasks, including measures of working memory (WM) capacity and resistance to perseveration (Barnett et al., 2008; Caldú et al., 2007; Diaz-Asper et al., 2008; Goldberg et al., 2003; Rosa et al., 2004; Tan et al., 2007). In a longitudinal study, met carriers showed less decline in EF performance in comparison to val homozygotes across the adult age range (de Frias et al., 2005), and in at least one sample, met homozygosity was associated with improved WM and reduced perseveration in older participants (Nagel et al., 2008). However, no effect of the *comt* val158met genotype has been observed on other EF, such as inhibition of prepotent response (color Stroop; Raz et al., 2009), or task switching (Erickson et al., 2008). Furthermore, in accord with the inverted-U model of DA effect on cognition that holds optimization rather than maximization of cortical DA as a predictor of better EF performance (Bäckman et al., 2006; Williams and Castner, 2006), a study of two independent samples of children and young adults found a positive heterosis effect of *comt* val158met on WM (Gosso et al., 2008). To complicate things even further, in several samples, *comt* val158met showed significant epistasis with other genes (Caldú et al., 2007; Gosso et al., 2008; Nagel et al., 2008; Tan et al., 2007; Xu et al., 2007). Thus, the effect of *comt* val158met may depend on complex interactions with age, type of task, and the action of other genes. Therefore, the extant literature on associations between *comt* val158met and various EF could benefit from further clarification.

One of the genetic variants that may modify the effects of DA on EF is an insertion/deletion (I/D) polymorphism in the *ace* gene that affects vasoconstriction through control of ACE availability. Insertion (I) or deletion (D) of an Alu repetitive element in the intron of *ace* produces three genotypes: *ace* II, *ace* ID, and *ace* DD, and presence of *ace* D allele accounts for almost 50% of the phenotypic variation in ACE plasma concentration (Rigat et al., 1990). The dose of *ace* I allele is associated with proportionate reduction in ACE activity, and as a consequence, limitation of vasoconstriction. Carriers of *ace* D (high activity) allele

evidence increased vascular risk and higher prevalence of vascular disease (Bautista et al., 2008; Bonnet et al., 2008; Castellano et al., 1995; Hassan et al., 2002; Hosoi et al., 1996; Julve et al., 2001; Lao et al., 2005; Morris et al., 1994; Niemiec et al., 2007; Saidi et al., 2007). In contrast, *ace* I (low activity) allele is associated with reduced vascular risk, e.g., better arterial compliance (Benetos et al., 1996; Mattace-Raso et al., 2004; Taniwaki et al., 1999).

The investigations of the effects of *ace* I/D polymorphism on cognition are still limited and their results are contradictory. Older carriers of the I allele show less memory decline (Bartrés-Faz et al., 2000; Richard et al., 2000) than D homozygotes, and D homozygosity is excessively frequent among persons with age-related cognitive impairment (Amouyel et al., 1996). However, in some population-based studies, the *ace* I allele increased risk for dementia (Sleegers et al., 2005; Wang et al., 2006), a finding born out of a recent meta-analysis (Lehmann et al., 2005). As with *comt* val158met, the discrepancy in findings may reflect variability in vascular risk within specific samples and inclusion of persons with overt vascular disease as well as possible epistasis. In addition, reliance on relatively crude cognitive indices (e.g., Mini-Mental State Examination, MMSE, Folstein et al., 1975) and restriction of the age range to older adults could attenuate the observed effects. Thus, the effects of *ace* on normal cognitive aging may be overlooked because of failure to take into account synergistic effects of the genotype and vascular risk.

Because vascular risk plays a significant role in cognitive and neural declines associated with aging, it is important to evaluate the potential synergistic effects of vascular health indicators and genetic factors on the aspects of performance that are vulnerable to both. Unfortunately, the number of studies investigating interaction between vascular risk factors and the genetic variant is too small even to allow quantitative comparisons (Wisdom et al., in press). Studies that examined such interactions found that the effect of genetic polymorphisms on cognition is exacerbated by heightened vascular risks (de Frias et al., 2004; Deshmukh et al., 2009; Peila et al., 2001; Raz et al., 2009; see Zeng et al., 2004 for a review).

Measures of arterial blood pressure - systolic, diastolic, mean arterial, and pulse pressure - provide assessment of vascular health and vascular risk (Franklin et al., 1997). However, those indices are too numerous and mutually dependent to be taken into account simultaneously, and in a limited scale study it is prudent to limit their number. Pulse pressure (PP), a surrogate of arterial compliance (Mattace-Raso et al., 2006), appears an optimal candidate, as it is a convenient summary index of systolic and diastolic pressure, two distinct but highly correlated measures. Population-based studies of vascular risk in older adults reveal steep age-related increase in PP, which rises at a greater rate than systolic blood pressure and does not follow an inverted-U curve characteristic of diastolic blood pressure (Franklin et al., 1997). In contrast to PP, another composite vascular measure, mean arterial pressure (MAP) evidences a shallow increase with age reaching its asymptote at the sixth decade (Franklin et al., 1997). Daytime PP is a significantly better predictor of cardiovascular morbidity and mortality than are MAP or systolic blood pressure (Blacher et al., 2000; Boutouyrie et al., 1999; Chae et al., 1999; Glynn et al. 2000; Khatrar et al., 2001; Mitchell et al., 2007). Moreover, in young adults, elevated PP is an independent predictor of structural changes such as intima-media thickness in the common carotid artery (Oren et al., 2006), a major vascular risk factor (Bots et al., 1997). Finally, PP is a significant predictor of age-related cognitive differences in healthy adults (Waldstein et al., 2008).

The aim of this study was to examine the joint effects of two polymorphisms, *comt* val158met and *ace* I/D, and a vascular risk indicator (PP), on age-sensitive measures of EF: working memory and cognitive flexibility. We hypothesized that a combined influence of

older age, increased arterial stiffness (PP), and genetic factors (high-activity *ace* D and *comt* val alleles) that affect PFC function and structure of the PFC would have a negative impact on EF performance. We predicted that persons who carry both genotypes deemed detrimental to cognition would show incrementally lower performance, and we expected that the effects of genes would be amplified by high-normal PP.

2. Method

2.1. Participants

The participants were recruited through advertisements in the local media as part of an ongoing longitudinal study of healthy aging, and were screened via a telephone interview and health questionnaire. The reasons for exclusion were history of cardiovascular, neurological and psychiatric conditions, head trauma with a loss of consciousness for more than 5 minutes, history of alcohol and drug abuse, thyroid problems, hypertension, and diabetes. The items used to screen for cardiovascular disease included any sort of “heart troubles” and cardiovascular complaints as well as taking specific medications prescribed for treatment of cardiovascular symptoms. The participants had corrected visual acuity of 50/20 or better (Optic 2000, Stereo Optic) and hearing of 40 dB or better for frequencies of 500–4000 Hz (Maico, MA27). To screen for dementia and depression we used the MMSE (Folstein et al., 1975) and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Only persons who scored 26 or above on MMSE and 15 or below on CES-D were invited to participate. All participants provided written informed consent in accord with university and hospital review board guidelines. Because of geographic and ethnic differences in the distribution of *comt* and *ace* alleles, we used only the data from North American Caucasian participants.

A full set of data were available for 158 participants (113 women and 45 men), age range 18–81 (mean $\pm$ SD, 52.20 ± 15.50). Education as assessed by years of formal schooling corresponded to a typical duration required for obtaining a college degree (16.02 ± 2.27). The participants were normotensive (systolic blood pressure range 91–140 mm Hg, mean 119.14 ± 10.63 mm Hg; diastolic blood pressure range 57–89 mm Hg, 73.46 ± 6.77 mm Hg), and those for whom fasting glucose data were available ($n = 113$) were normoglycemic (fasting blood glucose range 65–113, 86.23 ± 9.55 mg/dl). None of the participants were taking anti-hypertensive, antidepressant, antipsychotic, or anxiolytic medications. The MMSE scores ranged from 26 to 30 (28.87 ± 1.05) out of a possible 30. With an MMSE score ≥ 26 , the likelihood ratio for dementia ranges from 0.06 to 0.10 (Siu, 1991), and the only person who scored at MMSE = 26 was a 53-year old, an age with extremely low incidence of dementia. Men and women did not differ on any demographic or clinical parameters (see Table 1) except for a small but significant advantage of men in formal schooling (about 10 months on average). The findings on additional SNPs and cognitive measures on part of this sample have been reported elsewhere (65% of participants in Raz et al., 2008; 91% of Raz et al., 2009).

2.2. Measures of blood pressure

We measured blood pressure on three separate days by a mercury sphygmomanometer (BMS 12-S25) with a standard blood pressure cuff (Omron Professional) on the left arm, with participants seated in a comfortable chair with feet flat on the floor. The systolic and diastolic measures were averaged for each individual across sessions. Only participants with a mean systolic pressure not exceeding 140 mm Hg and a mean diastolic pressure at or below 90 mm Hg entered the study. Given a relatively small sample size and a relatively high correlation between systolic and diastolic blood pressure (see Table 2 below), we used a derived index of vascular health: pulse pressure (PP = systolic - diastolic pressure).

2.3. Genomic analysis

DNA was isolated from buccal cultures obtained in mouthwash samples. We used a Gentra Autopure LS under the standard buccal cell protocol. For genotyping quality control, we performed 10% direct repeats and DNA sequencing for verification, using both control DNA and no-template controls and beta-globin as an amplification control. All 5'-nuclease assays were adapted from a quantitative PCR method (Lo et al., 2000) and implemented on an Applied Biosystems 7900. We amplified DNA through either ACE-1721F (insertion) or ACE-1428F (deletion) and ACE-1826R, and interrogated it with the TaqMan probe 1745T. Polymorphism for COMT (rs4680) was interrogated using Taqman SNP Genotyping assay under the 0.5X protocol for ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems). The sequencing extension products were purified utilizing Sephadex, and the purified products were analyzed on an ABI PRISM 3700 DNA Analyzer using a 50 cm capillary array.

The insertion/deletion heterozygotes constituted approximately half the sample (56%, 88 individuals), and 22% of the participants fell into each homozygotic group (D/D = 35, I/I = 35). The distribution of *ace* I/D alleles conformed to Hardy-Weinberg equilibrium: $\chi^2 = 2.05$, $p = 0.15$. For *comt* val158met polymorphisms, the distribution included 37 (23%) homozygotes for met, 84 (53%) heterozygotes, and 37 (23%) homozygotes for val. The distribution of *comt* val158met alleles did not deviate from Hardy-Weinberg equilibrium: $\chi^2 = 0.63$, $p = 0.43$. For both polymorphisms, the genotype frequencies were equal between the sexes ($\chi^2(2) = 1.33$ and 0.75 for *comt* val158met and *ace* I/D, both *ns*), and were unrelated to age: both $F < 1$.

2.4. Cognitive measures

2.4.1. Wisconsin Card Sorting Test (WCST)—We administered a computerized version of the WCST (WCST: Computer Version 4 – Research Edition, Psychological Assessment Resources, Inc., Lutz, FL) on a 17-inch high-resolution color monitor. Participants were to match a card that appeared in the lower center of the computer screen with one of the four key cards displayed at the top of the screen according to the color, shape, or number of geometric designs on the target card. To respond they used four designated keys on the keyboard. Categories appeared in two repeated sets of blocks ordered as color, shape, and number, with category switch occurring after 10 successive correct trials. The participants, who were informed whether each response was correct or incorrect, continued until achieving six categories or completing 128 trials.

The indices of performance were the total number of errors (incorrect matches) and number of perseverative errors, as well as the number of non-perseverative errors. A perseverative error was a perseverative response that was also incorrect. A perseverative response was a response that was incorrect according to the current rule, but would have been correct using the rule for the previous sorting principle. An example of a perseverative response that was also a perseverative error was matching solely on number when the correct response was color. If among the incorrect responses that were matched solely on number, the participant matched according to number and color (an ambiguous correct response), but then continued to incorrectly match on number, then the correct response was counted as a perseverative response that happens to be correct.

2.4.2. Working memory: n-back task—Participants performed two computerized versions of the *n*-back task modeled after Dobbs and Rule (1989). In the verbal version, digits of variable length appeared in sequence. After the presentation, participants named the digit shown 1-, 2-, or 3-back in blocked trials of the same *n*-back. Participants were aware of the condition being tested and were familiarized with each condition before the test trials. In

the nonverbal version, the stimuli were abstract drawings. The test-retest reliability for the verbal version of the task is .68, .88, and .91, for 1-, 2-, and 3-back conditions respectively (Salthouse et al., 1996).

2.4.3. Working memory: Size Judgment Span task—We used a modified Size Judgment Span task (Cherry and Park, 1993) as a measure of nonverbal working memory. In this task, the examiner read a list of objects and animals, and the participants' task was to re-order the items from smallest to largest. The first block contained three trials with two items in each trial. For each successive block, the number of items per trial was increased by one. Testing stopped when the participant missed two of the three trials. The sum of the number of correct trials was the index of performance. The estimated test-retest reliability of this task is .79 (Cherry and Park, 1993).

2.5. Statistical analyses

The data were analyzed within a General Linear Model (GLM) framework, with separate models fitted to each of the following indices of EF: errors on WCST (perseverative and non-perseverative), *n*-back working memory speed of processing (RT), *n*-back accuracy (number of errors), and Size Judgment Span (number of correct trials). Altogether, we fitted four general linear models. Multiple within-subject indices (error type on WCST) or experimental conditions (1-, 2-, and 3-back load or verbal vs. nonverbal task) were repeated measures. In every model, age and PP (centered at their sample means) served as continuous independent variables. Sex, as well as *comt* val158met and *ace* I/D genotypes were also categorical predictors, with two levels for sex, and three levels for each genotype. We also tested if the quadratic age component and its interactions with other predictors made significant contributions in each model.

Altogether, each full GLM contained five independent variables and their interactions. Limiting the tested effects to the linear term of PP and adding a quadratic term for age plus second-order interactions among age terms and other independent variables produced 18 independent variables, i.e. less than 10 subjects per variable. We decided therefore to forego testing higher-order interactions and additional nonlinear contributions.

Because of a considerable skew in their distributions, WM speed and accuracy indices as well as the error counts on WCST were transformed using the natural log function. In each analysis, a full model that included all second-order interactions was tested first. All interactions that did not reach statistical significance ($p > 0.10$) were removed from the model and the data were fitted to a reduced model. The GLM analyses were followed by univariate analyses of simple effects, and testing the differences among the levels of the categorical variables with Fisher's Least Significant Difference (LSD) test, or slopes of regressions on the continuous variables by comparing the 95% confidence intervals around them.

3. Results

With age, sex, both genotypes and interactions among them taken into account, the vascular health indicator (PP) was unrelated to the genotypes ($F < 1$). However, PP increased with age: $F(1, 150) = 41.76$, $p < 0.00001$. Moreover, in accord with the reported normative data (Franklin et al., 1997), it exhibited a significant quadratic trend ($F(1, 150) = 4.73$, $p = 0.031$), which indicated that the increase in PP accelerated with age: $b_{\text{lin}} = 0.27253 \pm 0.04041$, $p < 0.00001$, $b_{\text{quad}} = 0.00466 \pm 0.00204$, $p = 0.024$, $R^2 = 0.27$. Correlations between age and vascular indicators were 0.45 for pulse and systolic, (both $p < 0.0001$), and 0.18 ($p = 0.021$) for diastolic pressure (see Table 2).

3.1. Wisconsin Card Sorting Test

The analyses of errors on WCST (Table 3) revealed main effects of age and *ace* I/D genotype. The main effect of age was modified by a significant Age $\times$ Error Type interaction. The analysis of simple effects revealed that although errors increased with age, the magnitude of age-related increase in perseverative errors ($F(1, 147) = 20.08$) was smaller than in non-perseverative errors ($F(1, 147) = 32.80$), both $p < 0.00001$. For non-perseverative errors the slope of regression on age was $b = 0.02370 \pm 0.00331$, $r = 0.50$, $p < 0.0001$, whereas for perseverative errors the slope was $b = 0.01636 \pm 0.00302$, $r = 0.40$. The 95% confidence limits around the slopes did not overlap and the difference between correlated r 's was significant: Steiger's $Z^* = 2.39$, $p = 0.0017$.

The main effect of *ace* I/D genotype is illustrated in Figure 1. Post-hoc comparisons with Fisher's LSD test indicated that *ace* D homozygotes made more errors than the rest of the sample, with no differences between *ace* I homozygotes and heterozygotes: $p = 0.082$ for DD vs. II, and $p = 0.003$ for DD vs. ID, and $p = 0.352$ for ID vs. II.

A significant *comt* $\times$ Sex interaction reflected an effect of *comt* genotype on WCST performance among men but not among women (see Figure 2). Post-hoc comparison showed that male *met* homozygotes committed fewer errors than all other participants (Fisher's LSD $p = 0.005$ to 0.029 , median $p = 0.001$).

3.2. Working memory: n-back task

3.2.1. Speed of working memory processing—The results of analyses of that task (Table 4) revealed significant main effects of age, sex, stimulus type (task), and working memory load. Slower response times were associated with older age, male sex, and greater *n*-back load.

Response time increased with age: $b = 0.00627 \pm 0.000720$ log-ms/year, $r = 0.56$, $p < 0.00001$. The main effect of task indicated that the nonverbal stimuli elicited significantly longer response times ($3,596.59 \pm 49.37$ ms) than did the verbal ones ($1,903.43 \pm 35.62$ ms). The main effect of load was due to the progressive load-dependent slowing from 1-back to 3-back tasks across verbal and nonverbal stimuli: $2,104.78 \pm 32.81$ ms for 1-back, $2,473.62 \pm 38.23$ ms for 2-back, and $3,671.63 \pm 65.84$ ms for 3-back tasks.

Decomposition of a significant Task $\times$ Load $\times$ Age interaction revealed that although age-related slowing was noted across all task and load combinations, the slopes of age-related increase in the response time varied according to the stimulus type and WM loads. For nonverbal stimuli, the slopes were equally steep at 1-back ($b = 0.00923 \pm 0.00086$, $r = 0.65$, $p < 0.00001$) and 2-back ($b = 0.00876 \pm 0.00086$, $r = 0.63$, $p < 0.00001$) loads, with lesser decline rate evident at 3-back ($b = 0.00432 \pm 0.00115$, $r = 0.29$, $p = 0.0003$). For verbal stimuli, the slopes became progressively shallower from 1-back ($b = 0.00603 \pm 0.00083$, $r = 0.50$, $p < 0.00001$), to 2-back ($b = 0.00530 \pm 0.00107$, $r = 0.37$, $p < 0.00001$), to 3-back ($b = 0.00483 \pm 0.00186$, $r = 0.20$, $p = 0.010$).

A significant main effect of sex indicated that women responded faster than men did. However, as indicated by a significant Sex $\times$ Load interaction, the advantage was evident only at the easier WM loads: 1-back ($F(1, 142) = 20.43$, $p = 0.00001$) and 2-back ($F(1, 142) = 19.28$, $p = 0.00002$) task, but not at 3-back ($F < 1$). Significant Age $\times$ Sex and Age² $\times$ Sex interactions reflected the difference in the shape of age-RT relationship between men and women. For men, linear slowing was observed: $b_{lin} = 0.00487 \pm 0.00139$, $p = 0.001$, $b_{quad} = -0.00001 \pm 0.00007$, $p = 0.886$. For women, the age-related increase in the rate of slowing was noted: $b_{lin} = 0.00850 \pm 0.00102$, $p < 0.000001$, $b_{quad} = 0.00016 \pm 0.00005$, $p = 0.003$,

$R^2 = 0.40$. After removal of two outliers (age 80 and 73), the effect increased to $b_{\text{lin}} = 0.00996 \pm 0.00105$, $p < 0.00001$, $b_{\text{quad}} = 0.00023 \pm 0.00005$, $p = 0.00003$, $R^2 = 0.46$.

Although neither of the two examined genetic variants alone influenced speed of working memory processing, the combination of the two affected the response time, as indicated by a significant $ace \times comt \times \text{Load}$ interaction. Decomposition of that interaction showed that the effect of the two-genotype combination was significant only for the highest load (3-back): $F(4, 142) = 3.48$, $p = 0.010$, $F(4, 142) = 1.97$, $p = 0.110$ for 1-back, and $F < 1$ for 2-back condition. The post-hoc comparisons of 3-back response times for nonverbal stimuli among genotype combinations revealed that homozygotes for both *ace* D and *comt* val alleles were consistently slower than the rest of the sample: Fisher's LSD p 's ranging from 0.0002 for val/val-II to 0.078 for the met/met-DD combination, median $p = 0.025$ (Figure 3).

The analyses were conducted under the assumption that responses on the n -back task were valid. However, on any given trial, each participant had a 0.11 probability to answer correctly by chance, thereby making 13.5 errors out of 20 trials equivalent to chance level of performance. Thus, response times for participants whose accuracy was at that level (14 errors or more) could be questionable indicators of their speed of processing. A substantial part of the sample (29 participants) showed chance-level accuracy on the nonverbal 3-back task. On average, participants who performed above chance level were slightly (1.6 years) younger than the whole sample but they covered the same age range of 18 through 81 years. We therefore analyzed response times in 3-back condition without those participants. All main effects and interactions remained unchanged.

3.2.2. Accuracy of working memory processing—With almost no errors on the 1-back task and very few errors on the 2-back tasks, we could use only 3-back errors (log-transformed to reduce the skew) for accuracy analyses. One observation (a 65-year old woman, MMSE = 30) exercised undue influence on the model with a Studentized residual of -4.18 . That data point was removed from the analyses of n -back accuracy that are summarized in Table 5.

The main effect of age reflected greater number of errors committed by older participants: $b = 0.01322 \pm 0.00254$, $r = 0.39$, $p < 0.0001$. For both nonverbal and verbal stimuli, errors increased with age. The main effect of task stemmed from a substantial difference in the number of verbal (4.75 ± 0.27) vs. nonverbal (8.39 ± 0.37) errors.

Although the main effect of *comt* val158met genotype fell short of significance, decomposition of a significant *comt* $\times$ Sex interaction indicated that men with met/met genotype committed fewer errors than the rest of the sample: Fisher's LSD p 's ranging from 0.002 to 0.044 for all paired comparisons. The effect is illustrated in Figure 4 below.

Task $\times$ Age² interaction reflected a significantly steeper increase in errors with age for nonverbal than for verbal stimuli: $b = 0.01724 \pm 0.00281$, $r = 0.44$, $p < 0.00001$ vs. $b = 0.00843 \pm 0.00369$, $r = 0.18$, $p = 0.024$. Moreover, as indicated by a significant Task $\times$ *ace* $\times$ Age interaction, the rate of age-related declines in accuracy varied among *ace* genotypes. For verbal errors, age-related increase was small and significant only among the *ace* I/D heterozygotes: $b = 0.01282 \pm 0.00493$, $r = 0.27$, $p = 0.011$. For nonverbal errors, age-related increases were significant for all *ace* genotypes, but the slope was steeper for *ace* II homozygotes ($b = 0.03248 \pm 0.00649$, $r = 0.66$, $p = 0.00002$) than for the other genotypes ($b = 0.01372 \pm 0.00377$, $r = 0.37$, $p = 0.00046$ for ID, and $b = 0.01380 \pm 0.00514$, $r = 0.42$, $p = 0.011$ for DD).

3.3. Working Memory: Size Judgment Span task

There were no significant interactions in the full model. One outlier, an observation with a Studentized residual of -3.89 (a 54 y.o. woman with MMSE = 29) was removed from the analysis. In the reduced model, the main effects of age (linear) and *comt* val158met genotype were significant (Table 6). The effects of age reflected better performance by younger participants: $b = -0.05156 \pm 0.00860$, $r = -0.43$, $p < 0.0001$. Although there was a trend for age-related acceleration of declines in SJ Span, the quadratic component of age did not reach significance.

A significant main effect was observed for *comt* genotype. Post-hoc comparisons revealed that met homozygosity on the *comt* val158met polymorphism was beneficial to performance: met homozygotes performed better than val homozygotes ($p = 0.003$), and heterozygotes ($p = 0.035$), who did not differ from val homozygotes ($p = 0.153$), Fisher's LSD test. This effect is illustrated in Figure 5.

4. Discussion

The results of this study demonstrate that in healthy adults, age-sensitive cognitive functions are affected by common genetic variants. The genetic variant associated with increased vasoconstriction (*ace* D allele) has a negative impact, whereas the polymorphism associated with increased DA availability (*comt* met allele) conveys an advantage in EF performance. The advantage of *comt* 158met homozygotes was apparent on all EF tasks, although on some tasks the positive effect was observed only among men. On some EF measures, e.g., speed of WM processing, an epistatic effect of two polymorphisms was evident. The disadvantage conveyed by homozygosity for *ace* D allele that is associated with increased vasoconstriction was observed only in combination with a double dose of another allele linked to reduced cognitive performance – *comt* val, and only in the most difficult task condition.

The finding of *comt* 158met advantage across disparate measures is consistent with the previous studies (e.g., de Frias et al., 2004), including the one conducted on an overlapping sample (Raz et al., 2009), in which we observed the benefits of *comt* 158met homozygosity on nonverbal reasoning and episodic memory (Raz et al., 2009). The common feature of those indices of cognition is their dependence on working memory (Fristoe et al., 1997; Hartman et al., 2001; Jarrold and Towse, 2006; Kane and Engel, 2002). Thus, it is highly plausible that any task, inasmuch as it relies on WM, would be affected by the genes linked to DA regulation that has been proposed as a key factor in EF (Bäckman et al., 2006; Savitz et al., 2006).

However, the locus of the DA effect on cognition is unclear. According to the most common interpretation, *comt* val158met influences cognition through its effect on DA availability in the synapses of the prefrontal cortex that are populated with D₁ receptors (e.g., Egan et al., 2001). The key role of PFC D₁ receptors in WM has been outlined in several theoretical models (Nieoullon, 2002; Williams and Castner, 2006). However, DA, via the same receptors, affects vasodilation and regulation of blood pressure (Jose et al., 2003; Zeng et al., 2004), and the low-activity val allele of *comt* val158met is linked to increased prevalence of hypertension (Hagen et al., 2007). Therefore, in addition to synaptic effects of *comt* val158met polymorphism, its vascular effects merit further consideration, especially in the context of aging. A gene $\times$ gene interaction (*ace* DD $\times$ *comt* val/val) observed in this sample may represent such synergy of vasomotor effects. Low availability of dopamine in *comt* val homozygotes may result in an insufficient vasodilatory response, whereas concomitant high angiotensin II activity brought by *ace* DD genotype adds excessive vasoconstriction. A combination of these two alleles may create hypoperfusion even at ostensibly normal levels

of arterial pressure and result in sluggish processing, especially on a difficult WM task. Other factors, such as sex steroids, may modify the effects of *comt* val158met on cognition and sex differences therein. The observed sex differences in COMT 158met could reflect the attenuation of COMT variations in women, who have 20 to 30% lower COMT activity compared to men (Fähndrich et al., 1980; Floderous et al., 1981). There is evidence that estrogen inhibits COMT gene transcription (Xie et al., 1999; Weinshilboum, 2006), whereas testosterone levels are associated with vasoconstriction and elevated vascular risk (Kienitz, and Quinkler, 2008).

The hypothesized negative effect of PP on EF performance did not materialize in this sample. Although simple correlations showed the association between elevated pulse pressure and WM (slowing of processing and shorter span), the effects disappeared once the influence of age, sex and genetic variants were taken into account. In past studies on partially overlapping samples, we found that hypertension and vascular risk alleles acted synergistically to suppress cognitive performance (Deshmukh et al., 2009; Raz et al., 2009) and without accounting for genetic variants, pulse pressure had a negative impact on some EF measures (Dahle et al., 2009). The findings in this sample indicate that although high-normal blood pressure may be a risk factor for vascular disease in healthy adults (Vasan et al., 2001; Knecht et al. 2008), the impact of such relatively mild elevations is uncertain. It may be offset by genetic effects and may depend on which part of the life-span is measured (Kennelly et al., 2009). For example, *comt* val158met heterozygosity and intermediate levels of DA availability that it brings may be beneficial for EF performance in children and adolescents (Gosso et al., 2008) but not in adults (this sample) who can take advantage of higher DA levels. Notably, the genetic effects were adjusted for age that was present in all models, and we found no gene $\times$ age interactions. Thus, the neurochemical and vasomotor mechanisms that are controlled by the polymorphisms examined in this study operate in young as well as in older adults. The observed impact of genes associated with vascular function in young normotensive adults suggests that the negative effects of the genes on cognition may be present at a relatively early age without overt cardiovascular risk increase. Early developmental factors predict adult vascular disease (Barker and Fall, 1993) and could have interacted with the polymorphisms examined in this sample. However, lack of relevant developmental data precludes testing of this hypothesis.

Interpretation of the presented results depends on several limitations of the study design. First, in a cross-sectional quasi-experimental study, we could not assess the true age-related change in cognitive performance. As this study represents a first wave of an ongoing longitudinal investigation, we hope that follow-up will permit a more detailed analysis of the effects of age and individual variability therein. Second, the vascular health/vascular risk indices based on measurements of the arterial blood pressure (e.g., PP in this study) are only convenient surrogates of the important vascular characteristics. For example, although PP is a valid surrogate of arterial stiffness, its sensitivity in a healthier-than average sample of a wide age range could have been limited. A more precise evaluation of carotid-femoral pulse wave velocity (PWV) could have shown a more clear exacerbation of age-related cognitive declines by increased arterial stiffness (Elias et al., 2009). However, no genetic effects were assessed in the latter study and it is unclear, therefore, if PWV effects would not be offset by genetic influence as well.

Third, multiple genes, some of which are linked to variations in cognitive performance (Corella and Ordovas, 2004; Lao et al., 2005; McDonald, 2002) affect vascular health. At least in one study, the combined effect of the *ApoE* ϵ 4 allele and *ace* deletion-homozygosity was associated with the lowest cognitive scores at baseline and the largest declines at follow-up (Richard et al., 2000). Our sample was too small for investigation of simultaneous effects of additional genes and interactions among them. The same limitation also affected

the number of vascular risk indicators that we could investigate. In this sample, only two polymorphisms and one vascular health indicator were assessed. Even for the evaluated polymorphisms, the consequences of genetic variation are broader than would be predicted from their specific action on the enzymes. For example, whereas *ace* I/D mutation affects availability of angiotensin II, negative effects of that vasoconstrictor on blood pressure, cerebral blood flow, and learning, are mediated by angiotensin II type 1 receptors and alleviated by AT1-receptor blockers (Benicky et al., in press; Inaba et al., 2009). Taking these variables into account may clarify the effects of angiotensin II on cognitive performance. In addition to its vasoconstrictive effects, ACE also promotes inflammation that may have an additional negative impact on cognitive performance (Alley et al., 2008; Benicky et al., in press). Thus, it is imperative to replicate these findings in a study that takes into account other genetic variants, especially those that regulate response to chronic inflammation and variation in the genes controlling AT1 receptors.

Finally, the key limitation of many genetic association studies is statistical power. In this sample, we had enough power to observe medium and large effects that are on par with the values reported in the literature (Barnett et al., 2008; Heinz and Smolka, 2006). The influence of genetic variants (*ace* I/D and *comt* val158met) amounted to medium-size effects (partial $\eta^2 \sim 0.05$) across tasks, and the *ace* $\times$ *comt* interaction produced a relatively large effect of partial $\eta^2 = 0.10$ on *n*-back speed of processing. Those effect sizes fall within a roughly delineated category of medium effects (Cohen, 1988). Several interactions hovered on the border of the conventional $p < 0.05$ limit and with a larger sample, they could have reached statistical significance. That consideration is important in planning future studies.

In sum, in healthy adults, a significant proportion of variance in performance on age-sensitive cognitive tasks depends on genetic factors linked to vascular health. The effects are complex and at times synergistic and their magnitude may vary between the sexes; they are more apparent on tasks of greater difficulty. Future investigations should pay greater attention to the synergistic interactions among clinical and genetic factors, as the combination thereof may place healthy individuals at increased risk of cognitive decline.

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Figure 1.

The effect of *ace* Insertion-Deletion genotype on the number of Wisconsin Card Sorting Test (WCST) total errors. The *ace* genotypes are: II – insertion homozygotes; I/D – insertion-deletion heterozygotes; DD – deletion homozygotes. Significance levels for comparisons (two-tailed): $*p < .05$; $**p < .01$. The scores are least-square adjusted means from the model; the bars represent standard errors of those means.

***comt* val158met Genotype and WCST Performance Sex Differences**

Figure 2.

Sex difference in the effect of *comt* val158met genotype on the Wisconsin Card Sorting Test (WCST) errors. The effect of genotype is significant among men but not among women. Significance level for comparisons: * $p < .05$. The scores are least-square adjusted means from the model; the bars represent standard errors of those means.

Figure 3.

The epistatic effect of *ace* I/D and *comt* val158met genotypes on speed of working memory processing. Response times are averaged across verbal and nonverbal *n*-back tasks (3-back conditions). The *ace* genotypes are: II – insertion homozygotes; I/D – insertion-deletion heterozygotes; DD – deletion homozygotes; the *comt* val158met genotypes are: VV – val homozygotes, VM – val/met heterozygotes, MM – met homozygotes. The scores are least-square adjusted means from the model; the bars represent standard errors of those means.

Working Memory Accuracy and *comt* val158met Genotype Sex Differences

Figure 4.

Sex differences in the effect of *comt* val158met genotype on working memory accuracy (*n*-back tasks, 3-back condition). Significance level for comparisons: * $p < .05$, two-tailed. The scores are least-square adjusted means from the model; the bars represent standard errors of those means.

Figure 5.

The effect of the *comt* val158met genotype on working memory (Size Judgment Span). Significance levels for comparisons (two-tailed): * $p < .05$; ** $p < .01$. The scores are least-square adjusted means from the model; the bars represent standard errors of those means.

Table 1

Description of the sample: men and women compared.

Variable	Men	Women	<i>t</i>	<i>p</i>
Age	54.40 ± 17.42	51.33 ± 14.66	1.13	0.26
Education	16.58 ± 2.15	15.80 ± 2.29	1.97	0.05
Systolic blood pressure (mm Hg)	121.16 ± 9.02	118.33 ± 11.14	1.51	0.13
Diastolic blood pressure (mm Hg)	75.79 ± 6.64	73.92 ± 6.77	1.57	0.12
Pulse Pressure (mm Hg)	45.37 ± 7.63	44.41 ± 7.81	0.71	0.48
MMSE	28.71 ± 1.12	28.93 ± 1.01	-1.23	0.21

Abbreviations. MMSE: Mini-Mental State Examination; *t*: t-test statistic; *p*: probability value.

Data are presented as means ± standard deviations.

Table 2

Zero-order correlations among age, vascular and cognitive variables.

Variable	Age	PP	Sys	Dias	P Err	NP Err	Total Err	RT 1n	RT 2n	RT 3n	RT 1v	RT 2v	RT 3v	Err 3v	Err 3n
PP	0.45														
Systolic	0.45	0.77													
Diastolic	0.18	0.07	0.69												
P Err	0.40	0.14	0.11	-0.00											
NP Err	0.50	0.21	0.17	0.03	0.82										
Total Err	0.47	0.19	0.15	0.02	0.95	0.96									
RT 1n	0.65	0.28	0.23	0.04	0.39	0.43	0.43								
RT 2n	0.63	0.33	0.29	0.08	0.33	0.43	0.40	0.74							
RT 3n	0.29	0.19	0.21	0.12	0.18	0.16	0.17	0.34	0.27						
RT 1v	0.50	0.24	0.19	0.03	0.30	0.41	0.37	0.64	0.54	0.19					
RT 2v	0.37	0.17	0.17	0.07	0.27	0.34	0.31	0.54	0.53	0.27	0.69				
RT 3v	0.20	0.05	0.10	0.11	0.08	0.09	0.09	0.31	0.23	0.33	0.29	0.47			
Err 3v	0.17	0.11	0.13	0.08	0.13	0.13	0.13	0.06	0.14	0.09	0.06	0.04	0.07		
Err 3n	0.41	0.18	0.15	0.02	0.36	0.34	0.37	0.23	0.28	0.09	0.16	0.18	0.22	0.45	
SJ Span	-0.42	-0.26	-0.22	-0.06	-0.26	-0.26	-0.27	-0.38	-0.45	-0.14	-0.22	-0.28	-0.18	-0.46	-0.44

Note. N = 158, critical *r*-values are: $r = .16$ for $p = .05$, $r = .21$ for $p = .01$, $r = .26$ for $p = .001$, and $r = .30$ for $p = .0001$.

Abbreviations: PP – pulse pressure; Sys – systolic blood pressure; Dias – diastolic blood pressure; P Err and NP Err – perseverative and nonperseverative errors on Wisconsin Card Sorting Test; RT – response time and Err – number of errors on the *n*-back tasks, with indices 1–3 indicating number of back steps, v – verbal stimuli, n – nonverbal stimuli; SJ – size judgment.

Table 3

Summary of results for Wisconsin Card Sorting Test (WCST) errors.

Effect	df	F-ratio	Partial η^2	p-value
Between Subjects Error df = 147				
Age	1	29.56	0.172	0.00000
Age ²	1	0.06	0.001	0.804
Sex	1	0.24	0.002	0.624
Pulse Pressure	1	0.12	0.001	0.726
<i>comt</i>	2	2.17	0.030	0.117
<i>ace</i>	2	3.51	0.047	0.032
<i>comt</i> × Sex	2	3.28	0.044	0.040
Within Subjects Error df = 147				
Error Type	1	0.21	0.001	0.648
Error Type × Age	1	7.12	0.046	0.009

Note. Non-significant interactions ($p > 0.10$) were removed from the models.

Table 4

Speed of processing in working memory (n-back tasks): Summary of results.

Effect	df	F-Ratio	Partial η^2	p-Value
Between Subjects Error df = 143				
Age	1	59.76	0.295	0.00000
Age ²	1	3.56	0.050	0.061
Sex	1	9.79	0.064	0.002
comt	2	1.73	0.024	0.181
ace	2	1.30	0.018	0.276
Pulse Pressure	1	0.25	0.002	0.618
ace $\times$ comt	4	1.20	0.008	0.314
Sex $\times$ Age	1	5.79	0.039	0.017
Sex $\times$ Age ²	1	6.89	0.046	0.010
Within Subjects Error df = 143				
Task	1	795.63	0.847	0.00000
Task $\times$ Age	1	3.46	0.023	0.065
Within Subjects Error df = 286				
Load	2	236.36	0.623	0.00000
Load $\times$ Age	2	5.27	0.035	0.010
Load $\times$ Sex	2	3.99	0.042	0.028
Load $\times$ ace	4	2.25	0.030	0.079
Load $\times$ ace $\times$ comt	8	3.86	0.097	0.0008
Within Subjects Error df = 286				
Task $\times$ Load	2	16.17	0.101	0.00000
Task $\times$ Load $\times$ Age	2	4.11	0.028	0.026
Task $\times$ Load $\times$ ace $\times$ comt	8	1.90	0.050	0.078

Note. Non-significant interactions ($p > 0.12$) were removed from the models.

Table 5

Accuracy of working memory processing (3-back task): Summary of results.

Effect	df	F-ratio	Partial η^2	p-value
Between Subjects Error df = 142				
Age	1	11.03	0.072	0.001
Age ²	1	0.04	0.001	0.834
Sex	1	0.12	0.001	0.734
Pulse Pressure	1	0.28	0.002	0.590
comt	2	3.85	0.051	0.024
ace	2	1.74	0.024	0.180
ace $\times$ comt	4	0.57	0.016	0.684
Sex $\times$ comt	2	4.69	0.062	0.011
Within Subjects Error df = 142				
Task	1	55.24	0.280	0.00000
Task $\times$ Age²	2	3.88	0.027	0.050
Task $\times$ ace $\times$ comt	4	2.19	0.058	0.074

Note. Non-significant interactions ($p > 0.15$) were removed from the models. One outlier was removed from the analyses (see text).

Table 6

Summary of the analyses of working memory span (Size Judgment task) scores

Effect	df	F-ratio	Partial η^2	p-value
Between Subjects Error df = 148				
Age	1	26.82	0.153	0.00000
Age ²	1	3.42	0.027	0.066
Sex	1	0.27	0.000	0.867
Pulse Pressure	1	0.94	0.006	0.334
<i>comt</i>	2	4.79	0.061	0.010
<i>ace</i>	2	0.57	0.008	0.565

Note. Non-significant interactions ($p > 0.15$) are not shown.