Published in final edited form as:
Neuropsychology. 2009 January ; 23(1): 105–116. doi:10.1037/a0013487.

Genetic and Vascular Modifiers of Age-Sensitive Cognitive Skills: Effects of COMT, BDNF, ApoE and Hypertension

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Abstract

Cognitive phenotypes emerge from multiple genetic and environmental influences. Several single nucleotide polymorphisms have been linked to neural and cognitive variation in healthy adults. We examined contribution of three polymorphisms frequently associated with individual differences in cognition (Catechol-O-Methyl-Transferase Val158Met, Brain-Derived-Neurotrophic-Factor Val66Met, and Apolipoprotein E ε4) and a vascular risk factor (hypertension) as well as their interactions in a sample of 189 volunteers (age 18–82). Genotypes were determined from buccal culture samples, and cognitive performance was assessed in four age-sensitive domains – fluid intelligence, executive function (inhibition), associative memory, and processing speed. We found that younger age and COMT Met/Met genotype, associated with low COMT activity and higher prefrontal dopamine content, were independently linked to better performance in most of the tested domains. Homozygotes for Val allele of BDNF polymorphism exhibited better associative memory and faster speed of processing than the Met allele carriers, with greater effect for women and persons with hypertension. Carriers of ApoE ε4 allele evidenced steeper age-related increase in costs of Stroop color interference, but showed no negative effects on memory. The findings indicate that age-related cognitive differences in multiple domains are differentially affected by distinct genetic factors and their interactions with vascular health status.

Keywords

aging; genetics; cognition; COMT; BDNF; APOE; vascular risk; memory; fluid intelligence; single nucleotide polymorphisms; genetic association; speed of processing

Cognitive performance declines with age (Horn & Cattell, 1966). Age-related differences are most prominent in speed of processing (Salthouse, 1996), executive functions (Fisk & Sharp, 2004; Treitz et al., 2007), and episodic memory (Verhaeghen et al., 1993). Nevertheless, observed age-related declines are not uniform and cannot be ascribed entirely to a normal aging process. Within specific cognitive domains (e.g., episodic memory) some aspects (e.g., associative memory) may be more vulnerable to aging than others (Naveh-Benjamin, 2000). Many factors related to aging, such as elevated vascular risk, exacerbate age-related differences

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(Raz & Rodrigue, 2006). Other modifiers of cognitive aging such as genetic predisposition may be unrelated to calendar age or act in synergy with age-related influences. The role of genetic variability in cognition and its late-life development received relatively meager attention in the past. However, recent studies show that many age-sensitive cognitive processes exhibit substantial heritability (Ando et al., 2001; Dixon et al., 2007; Finkel et al., 2005; Kremen et al., 2007; Lessov-Schlaggar et al., 2007), and that heritability may increase with age (McClearn et al., 1997). Recent advances in genomic technology extend the study of genetic modifiers beyond heritability and shift the focus onto a search for variants in specific genes (single nucleotide polymorphisms, SNPs) that may affect age-sensitive cognitive processes. To date, multiple candidate genes have been studied, but some, such as COMT Val158Met, BDNF Val66Met, and ApoEε4 have been examined and linked to performance in age-sensitive cognitive domains more frequently than others (Payton, 2006).

One of most commonly studied candidate genes putatively related to age-sensitive cognitive processes is *COMT*. It is located on chromosome 22 and controls Catechol-O-methyl transferase (COMT), an enzyme that catabolizes dopamine. An exchange of amino acids Valine and Methionine at one location (exon 4, codon 158), produces a common variant of COMT, COMT Val158Met, which is associated with a 3-4-fold variability in enzyme's activity in dopaminergic synapses. The Met allele of that polymorphism reduces COMT activity and consequently increases dopamine availability (Chen et al., 2004; Tenhunen et al., 1994; Tunbridge et al., 2004). That effect is especially prominent in the neocortex, which unlike the striatum, virtually lacks dopamine transporters and depends on COMT for regulation of dopamine availability in the synaptic cleft (Slifstein et al., 2008; Tunbridge et al., 2004). COMT activity is especially important in the prefrontal cortex, which is rich in dopaminergic pathways. Because the prefrontal circuits are widely believed to support executive functions and strategic aspects of memory (Buckner, 2004; Floresco & Magyar, 2006), COMT Val158Met polymorphism has attracted ample attention of cognitive neuroscientists.

Although the effects of dopamine on cognition are nonlinear and complex (Bäckman et al., 2006), research on healthy young adults shows that COMT Val (high-activity) allele carriers perform worse than Met homozygotes on multiple executive tasks (Barnett et al., 2007; Caldú et al., 2007; Diaz-Asper et al., 2008; Egan et al., 2001; Goldberg et al., 2003; Rosa et al., 2004; Tan et al., 2007), and that effect may be enhanced by interaction with other genes (Caldú et al., 2007; Tan et al., 2007; Xu et al., 2007). In addition to its negative effects on executive functions, the Val allele has been associated with increased variability in processing speed and sustained attention (MacDonald et al., 2007; Stefanis et al., 2005). Thus, the effects of COMT may be focused on a single enzyme, but show diffuse effects across multiple cognitive processes.

Because the COMT gene plays an important role in the activity of the prefrontal cortex, a brain region that is differentially vulnerable to aging (Bäckman et al., 2006; Raz & Rodrigue, 2006), it is highly plausible that its influential variant would play a role in shaping age trajectories in executive functions and episodic memory. However, to date, only a handful of studies examined the influence of COMT on cognitive aging. The results of those investigations are inconsistent. In a longitudinal study of Swedish adults (35 to 80 years of age), the Met allele was linked to lesser longitudinal declines on executive tasks (De Frias et al., 2005). In another longitudinal study, homozygocity for Val was associated with both reduced scores as well as steeper decline on a composite index of general cognitive abilities between ages 64 and 68, but not with intelligence measured in childhood (Starr et al., 2007). Those findings suggest that the benefits of higher dopamine availability conferred by the Met allele may become apparent only when that ability and dopamine levels decline. In a recent study of extreme age groups of Met and Val homozygotes, a significant COMT × Age interaction was indeed observed, with Met homozygocity being associated with improved executive performance of

older but not younger adults (Nagel et al., 2008). Not all studies are, however, in accord with the Met advantage hypothesis. For instance, in a sample of older adults (on average about 70 years of age) Val allele of the COMT Val158Met polymorphism was associated with *better* memory performance among men, though not among women (O'Hara et al., 2006).

Notably, the interactions between COMT Val158Met and vascular risk factors (e.g., hypertension) are not usually examined despite well established negative effects of the latter on multiple age-sensitive functions (Elias et al., 1997; Waldstein et al. 1996), the role of dopamine in regulation of blood pressure (Jose et al., 2003), and the reported link between Val/Val COMT genotype and elevated systolic blood pressure (Hagen et al., 2007).

The second SNP that may be highly relevant to cognitive aging is that of the *BDNF* gene that resides on chromosome 11. The gene controls expression of brain-derived neurotrophic factor (BDNF), a neurotrophin that is widely found in neurons and glia (Murer et al., 2001). BDNF plays a crucial role in multiple processes associated with neuronal proliferation, differentiation and survival (Binder & Scharfman, 2004; Murer et al., 2001). BDNF is released in sensory cortices in response to stimulation, implicated in synaptic plasticity, associated with long-term potentiation, and abundant in neocortical, neostriatal, cerebellar, and hippocampal but not pallidal and brainstem neurons (Murer et al., 2001). Thus, it is a good candidate for influencing declarative memory and learning and, indeed, BDNF expression has been associated with learning in rats and other animal models (Finkbeiner, 2000; Lynch et al., 2006). A substitution of methionine for valine at codon 66 of the BDNF gene is recognized as BDNF Val66Met polymorphism, and the Met allele of that polymorphism is associated with reduced BDNF expression (Egan et al., 2003). A recent report showing that the beneficial effects of BDNF on neural plasticity may be reduced with age (Sohrabji & Lewis, 2006) implies that BDNF Met carriers may be especially vulnerable to age-associated cognitive declines, thus suggesting the possibility of another SNP × Age interaction. Moreover, because BDNF is down-regulated by hypertension (Lee et al., 2006) and its expression is reduced by cerebral hypoperfusion (Irikura et al, 1996), hypertensive carriers of the low-activity (Met) allele of the BDNF Val66Met polymorphism may be especially vulnerable to cognitive declines.

Cognitive differences associated with the Val66Met polymorphism in the BDNF gene were investigated in several studies (see Bath and Lee, 2006 for a review). Six studies (three in somewhat overlapping samples) of young and middle-aged adults indicate that Met allele carriers and Met homozygotes have poorer verbal memory than Val homozygotes (Dempster et al., 2005; Egan et al., 2003; Goldberg et al., 2008; Hariri et al., 2003; Ho et al., 2006; Miyajima et al., 2007). However, a study of an age-restricted sample of healthy older adults revealed no BDNF-related difference in memory and a significant effect on fluid reasoning tests that pointed in the opposite direction: Met homozygotes performed better than Val carriers (Harris et al., 2006). No effect of BDNF Val66Met on multiple measures of spatial memory was observed in a large sample of healthy adolescents (Hansell et al., 2007). In one sample, Met homozygotes evidenced better fluid intelligence and verbal reasoning but not verbal fluency (Harris et al., 2006), whereas in another study, Met carriers exhibited lower general intelligence scores (Miyajima et al., 2007). A significant association between Met allele of BDNF Val66Met polymorphism and reduced processing speed was also reported (Miyajima et al., 2007). Thus, it is possible that BDNF effects depend on age, vascular risk, and type of task. To the best of our knowledge the combined effects of BDNF Met allele and hypertension have not been investigated in the context of cognitive aging.

Lastly, the most commonly studied gene in the domain of cognitive aging is *ApoEε*, a gene that resides on chromosome 19 and controls multiple aspects of lipid transport and maintenance through its influence on Apolipoprotein E. A combination of two SNPs of that gene – switches of Arginine for Cysteine in positions 112 and 158 – produces three isoforms: ε2, ε3, and ε4.

The ε4 variant of the ApoE gene is associated with a high affinity for very low density lipoprotein, whereas ε3 is preferentially associated with high-density lipoprotein (Mahley & Huang, 1999). ApoEε4 genotype is associated with a substantially increased risk for cardiovascular disease (Mahley & Huang, 1999) and Alzheimer's dementia (Corder et al., 1993). Moreover, possession of even a single copy of ε4 has been linked to declines in episodic memory in healthy adults (Baxter et al., 2003; Berteau-Pavy et al., 2007; Caselli et al., 2004; Deary et al., 2004; Packard et al., 2007; Tupler et al., 2007; Wilson et al., 2002). Although the literature on cognitive effects of ApoEε4 is significantly more voluminous than the relatively small body of research on BDNF and COMT polymorphisms, it is not without its share of inconsistency.

Although its role as a risk factor for dementia is established, the negative effects of ApoE ε4 on cognition are not uniformly observed in healthy adults. In a meta-analysis of 38 studies, only very small effects (max d = −.09) of ApoEe4 homozygocity on selected cognitive tasks were found, and even those were not observed in all cognitive domains (Small, Rosnick, Fratiglione, & Bäckman., 2004). The effect of ApoE e4 on episodic memory in that meta-analysis was very small indeed: d = −.03, and the magnitude of effects covered a wide range from d = −.5 to d = .4 (Small et al., 2004, Figure 1). According to some studies, negative effects of ApoEε4 may be sex-specific (Sundermann et al., 2007; Zhao et al., 2005), linked to specific task properties (Bunce et al., 2004), expressed only in interaction with vascular risk (DeFrias et al., 2007) or altered androgen levels (Berteau-Pavy et al., 2007), revealed only through epistastic interaction with other genes (Payton et al., 2006), found only in persons older than 70 (Nilsson et al., 2006), or not found at all (Espeseth et al., 2006; Fiocco et al., 2008; Pomara et al., 2005; Rosen et al., 2002; Small et al., 2000). Moreover, a recent report links ApoE ε4 to *better* episodic memory in younger adults (Mondadori et al, 2007). Research on other cognitive skills suggests that ApoEε4 carriers may exhibit accelerated decline in processing speed and executive functions (Greenwood et al., 2005; Lessov-Schlaggar et al., 2007; Rosen et al., 2002; Rosen et al., 2005; Wetter et al., 2005). However, some studies showed no evidence for the effects of ε4 allele on speed of processing, executive functions (inhibition of pre-potent response, fluency, cognitive flexibility), and fluid intelligence of older adults (Alexander et al., 2007; Berteau-Pavy et al., 2007; Caselli et al., 2004; Deary et al., 2004; Packard et al., 2007; Small et al., 2000). Although ApoE ε4 is a significant risk factor for vascular disease (Mahley & Huang, 1999) and its effects on cognitive aging may be enhanced by presence of vascular risk (De Frias et al., 2007), the conjoint influence of the ε4 variant and the phenotypic indices of vascular risk have not been assessed in most studies.

In sum, there is no clear consensus on the effect of selected SNPs on cognition, either in general, or in the specific context of aging. Although gene-gene interactions (epistasis) have been examined in some studies (Espeseth et al. 2006; Greenwood et al., 2005; Harris et al., 2005; Payton et al., 2006), the majority of the reviewed studies have been limited to a single cognitively relevant SNP, and have not accounted for vascular risks factors. Furthermore, almost none of the studies in the extant literature on polymorphisms (especially on ApoE ε4) have examined their effects in a wide age range. A cross-sectional study of a narrow-age cohort, whether old or young, does not inform about the effect of an SNP on aging; it describes its influence on performance within a specific age group (e.g., older adults), and it is clear that studying the old is not the same as studying aging. Thus, the aims of this study were to examine three genetic variants (COMT Val158Met, BDNF Val66Met and ApoEε4) and their interactions with respect to their unique and shared contribution to age-sensitive cognition in an adult lifespan sample and additionally to assess the effects of the three polymorphisms in the context of a major vascular risk factor – arterial hypertension. Selection of the cognitive variables was guided by consideration of sensitivity to aging, and thus we chose measures of fluid intelligence, inhibition of pre-potent response, associative memory, and speed of processing. We hypothesized that COMT Met carriers would show an advantage on inhibition

and fluid reasoning, whereas BDNF Met and ApoEε4 would be associated with poorer episodic memory, and slowing of processing speed would be associated with possession of COMT Val and BDNF Met. We also hypothesized that a well-known precipitous decline in processing speed with age would be explained in part by genetic differences, such as the presence of an ApoEε4 allele. In addition, because the effects of ApoE, BDNF and COMT genotypes may change with age and with increase in vascular risk, we hypothesized Age × Genotype and Hypertension × Genotype interactions, i.e., an increase of the genetic effects on the examined cognitive functions with age and with elevated vascular risk.

Methods

Participants

All participants were screened via health questionnaire for history of cardiovascular, neurological and psychiatric conditions, head trauma, alcohol and drug abuse, thyroid problems, and diabetes. Participants were also screened for dementia and depression with the MMSE (Folstein et al., 1975) and the Geriatric Depression Questionnaire (Radloff, 1977) with cut-offs of 26 and 15, respectively. All participants were strongly right-handed (75% and above on the Edinburgh Handedness Questionnaire; Oldfield, 1971). All participants provided written informed consent in accord with university and hospital review board guidelines.

The sample consisted of 189 Caucasian participants (34% men) with the mean age 54.40 years (SD = 15.01, range 18–82 years), the average education level at almost full college (mean 15.92 years, SD = 2.40 years), and the mean MMSE of 28.85 (SD = 1.03) points. Most of the participants were healthy adult volunteers recruited by advertising in the Metro Detroit area and screened via interview and health questionnaire for history of neurological, psychiatric, endocrine, and cardiovascular diseases. However, 49 participants (26% of the sample) were classified as hypertensive. They had a diagnosis of hypertension and/or were taking antihypertensive medication prescribed by their physician, or evidenced arterial blood pressure that exceeded criteria for hypertension (140 mm Hg systolic and 90 mm Hg diastolic) averaged across three separate occasions. Notably, only 7% of the participants smoked (21–27% expected in the general population) and 81% reported exercising regularly (31% expected in the general population, American Heart Association, 2004). Thus, the participants of this study were significantly healthier and better educated than the general population.

The descriptive statistics for men and women as well as the comparison tests are presented in Table 1. The comparison between the sexes shows that although men and women did not differ significantly in age, men had higher arterial blood pressure and a higher proportion of men than women met criteria for hypertension or had a formal diagnosis. Although men had a marginal advantage in education (less than an extra year of formal schooling), women had slightly higher MMSE scores (.39 point). Thus, it was essential to include sex in all analyses.

Genomic analysis

DNA isolations and genotyping assays were conducted in the Wayne State University Applied Genomics Technology Center. For genotyping quality control, 10% direct repeats and DNA sequencing for verification were performed. Both control DNA and no-template controls were used. All 5'-nuclease assays were run on an Applied Biosystems 7900.

DNA Isolation—DNA was isolated from buccal cultures obtained in mouthwash samples. We used a Gentra Autopure LS under the standard buccal cell protocol.

Genotyping: BDNF, APOE, and COMT Polymorphisms Analysis—Polymorphisms for BDNF (rs6265) and COMT (rs4680) were interrogated using Taqman SNP Genotyping

assays. ApoE (rs429358 and rs7412) polymorphisms were preampli fied with forward 5'-CAATGCTACCGAGTTTTCTTCC-3' and reverse primers 5'-TTCAGATTCTTCACAGATGCGTA-3' in a 25 μl reaction containing 2.5 mmol/l $MgCl_2$, 0.5 μmol/l of the primers, 1.25 U AmpliTaq Gold polymerase, and 200 μmol/l dATP, dCTP, dGTP, and dTTP. The mixture was denatured at 95^0C for 10 minutes and amplification achieved by 15 cycles of 94^0C for 30 seconds, 58^0C for 30 seconds, and 72^0C for 1 minute, followed by a final extension at 72^0C for 10 minutes. One μl of this reaction was subsequently used for rs429358 and rs7412 5'-nuclease assays under standard conditions. The primers and probes for the rs7412 assay were 5'-TCCGCGATGCCGATGAC-3', 5'-CCCCGGCCTGGTACAC-3', VIC-CAGGCGCTTCTGC-NFQ and FAM-CAGGCACTTCGC-NFQ. The primers and probes for the rs429358 assay were 5'-GCGGGCACGGCTGT-3', 5'-GCTTGCGCAGGTGGGA-3', VIC-CATGGAGGACGTGTGC-NFQ and FAM-ATGGAGGACGTGCGC-NFQ.

DNA Sequencing—DNA sequencing reactions was carried out using the 0.5X protocol for ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems). The sequencing extension products were purified utilizing Sephadex. The purified products were analyzed on an ABI PRISM 3700 DNA Analyzer using a 50 cm capillary array.

The data were available on an additional three participants who were identified as ApoE ε2 / ε4 carriers. However, because ApoE alleles ε2 and ε4 may exercise opposite effects on memory (e.g., Wilson et al., 2002), these participants were not included in the analyses. The allelic distribution of all three polymorphisms fit the Hardy-Weinberg equilibrium (all $\chi^2 < 1$). For COMT Val158Met polymorphisms, the distribution included 25% homozygotes for Met, 53% heterozygotes and 22% homozygotes for Val. For BDNF Val66Met polymorphism, 60% of participants were Val homozygotes, 36% were Val/Met heterozygotes, whereas the Met/Met genotype was very rare: 4%. Most of the participants were homozygous for ApoEε3 allele (76%), whereas 22% were carriers of Apoε4 and less then 2% were homozygous for the latter allele, i.e. at least one ApoE ε4 allele was found in 24% of the sample.

Cognitive measures

Fluid Intelligence—We administered a test of fluid reasoning known for its sensitivity to aging, the Cattell Culture Fair Intelligence Test (CFIT, Form 3B; Cattell & Cattell, 1973). CFIT is commonly used as a marker of fluid intelligence in studies of lifespan development aging and consists of nonverbal reasoning problems covering a wide range of difficulty (Rabbitt & Lowe 2000; Raz et al., 1998; Schretlen et al. 2000). Each subtest consists of 10–14 items tapping different nonverbal abstract reasoning domains, including detection of similarities in designs, completing matrices according to specific rules, and solving nonverbal syllogisms. In all problems, the participant has to derive the rule required to solve the problem. At the standard administration, 2.5–4 minutes are allowed for completion of each subtest. The index of performance is the number of total correct items across the subtests. In addition to the standard administration that has time limits imposed on each subtest, we allowed the participants to continue until they finished the test or decided to stop. Thus, two scores were available for CFIT, timed and untimed.

Executive function: Inhibition—A paper version of the color Stroop task (Salthouse & Meinz, 1995; Stroop, 1935) was used as a measure of a pre-potent response inhibition. The participants completed a series of pages containing two columns of 10 stimuli each. The order of conditions (stimuli sets) was as follows: neutral (color naming of X's, compatible (reading aloud words printed in corresponding color, e,g, RED printed in red ink), incompatible (stimuli printed in ink that does not correspond to the name of the color, e.g., RED printed in blue ink), incompatible, compatible, and neutral. The performance index, interference costs score, was

computed as the difference between average reading times in the incompatible and neutral conditions divided over the reading time in the latter and multiplied by 100%. The estimated split-half reliability of reading times on this test is .72 (Salthouse & Meinz, 1995).

Episodic (Associative) Memory—Memory for Names subtest (#1) of the Woodcock-Johnson Psychoeducational Battery – Revised (Woodcock & Johnson, 1989) served as a measure of associative memory. In that task, participants view line drawings of novel stimuli ("space creatures") and are told each "creature's" name, a nonsense word, i.e. also a novel stimulus. After the learning phase, participants are presented with several space creatures and are asked to point to the creature named by the examiner. After a 30 minute delay, the space creatures are displayed again, several to a page, and the participant is again required to point to the creature named by the experimenter. Total number of correct matches at the immediate and the delayed recall phases serve as performance indices.

Processing Speed—Two measures of processing speed were administered. Letter Comparison and Pattern Comparison (Salthouse & Meinz, 1995) tests require participants to make rapid "same-different" judgments on letter strings or line patterns containing three to nine line segments. Participants were given 30 sec per page (for two pages) to complete the items as quickly and as accurately as possible. The total number correct for both pages combined minus the number of incorrect items is the index of performance. Estimated reliability for letter comparison is .77 and .87 for pattern comparison (Salthouse & Meinz, 1995).

Statistical Analyses

The data were analyzed within a General Linear Model framework, with cognitive measures grouped in theoretically determined domains (fluid intelligence, inhibition, speed of processing, and episodic memory serving as dependent variables in four separate models. If more than one index was available for a given domain, such as timed and untimed CFIT score, immediate and delayed recall or verbal and nonverbal speed tests, individual tests were treated as repeated measures. Age, centered at the sample mean, was a continuous predictor. Sex, hypertension status, and polymorphism assignments (Val+ vs. Val- of COMTVal158Met, Met + vs. Met- for BDNFVal66Met, and ApoE ε4+ vs. ApoE ε4-) entered each model simultaneously as categorical predictors. Thus, contribution of each independent variable was adjusted for contribution of the other factors in the model. Second-order interactions among all predictors were also included in the models, but if they were found nonsignificant ($p > .15$), they were deleted and reduced models were evaluated. In the case of repeated measures, all interaction's p values were adjusted by Hyunh-Feld correction factor. We did not test for higher-order interactions because in a sample of this size some categories created by crossing of more than two factors would contain too few cases. The proportion of variance explained by each significant factor was estimated by η^2, a ratio of sum-of-squares of the effect divided by total sum-of-squares.

Results

The correlations among cognitive scores are presented in Table 2 below. As evident from the table, all dependent variables examined in this study were significantly correlated. However, with an exception of the fluid intelligence index, the correlations among them were small.

Fluid Intelligence

One case had missing data and was deleted from the analyses. The interactions between age and the categorical between-subjects variables were not significant and were removed from the model. In the reduced model, a main effect of Age was observed: $F(1,181) = 56.89$, $p <$.

001, η^2 = .229. However, the age differences were diminished by relaxation of time limits: Age × Timing interaction: F(1,181) = 19.17, p < .001, η^2 = .046. The difference between correlations with age for timed (r = −0.56, p < .001) and untimed (r = −0.39, p < .001) versions was significant: Steiger Z* = 5.86, p < .001. A main effect of COMT was observed: F(1,181) = 3.89, p < .05, η^2 = .016. The carriers of COMT Val158 allele had lower reasoning scores than Met homozygotes regardless of time limits: adjusted means ± standard deviations 27.21 ± 4.12 vs. 25.87 ± 4.83 with time limit, Tukey Honestly-Significant Difference, HSD p < .05 and 30.56 ± 4.87 vs. 29.20 ± 5.66, Tukey HSD p < .07 without it. A significant effect of Sex (F (1,181) = 5.65, p < .02, η^2 = .022) was also observed; men attained higher scores than women did: adjusted means ± standard deviations 27.41 ± 4.21 vs. 25.66 ± 5.00, Tukey HSD test p < .005 for testing with time limits and 30.54 ± 4.81 vs. 29.28 ± 4.59, Tukey HSD test p < .08 for testing without time limits.

Inhibition

One outlier, a participant who had a negative Stroop interference costs score (interference reading being faster than neutral color naming, 2.5 standard deviations less than the mean score) was removed from the analyses. The analyses revealed a main effect of age: F (1,180) = 20.50, p < .001, η^2 = .10. That effect was modified by a significant Age × ApoE genotype interaction: F(1,180) = 3.92, p < .05, η^2 = .02. The interaction reflected the difference in the magnitude of age-related differences in interference costs between carriers of ApoE ε4 allele and the rest of the sample. The slope of log-transformed cost index on age was significantly steeper in ApoEε4 carriers (.014 ± .005 units/year ± standard error) than in persons who had no ApoE ε4 allele (.007 ± .002 units/year) without any overlap of 95% confidence limits of the slopes. The correlations between age and Stroop interference costs were r = −.30, p < .01 for ApoEε4- participants and r = −.43, p < .001 for ApoE ε4 carriers. The ApoEε4 related difference in Stroop costs is illustrated in Figure 1. Inspection of the scatterplot in Figure 1 reveals scarcity of APoEε4+ genotype among the younger participants. Restriction of age to 30 years and older increased the ApoE × Age interaction effect to F(1,162) = 6.98, p < .01. The main effect of sex was also significant: F(1,180) = 5.72, p < .02, η^2 = .030. Men evidenced significantly lower interference costs than women did; adjusted means comparison: 4.42 ± .37 vs. 4.54 ± .46 log-cost units, Tukey HSD p < .02.

Speed of Processing

The analyses of log-transformed speed of processing scores yielded a main effect of Age: F (1,179) = 80.44 p < .001, η^2 = .276. Advanced age was associated with reduced speed of comparison: r = −.48 and r = −.51, both p < .001. A significant BDNF × Hypertension interaction (F(1,179) = 9.12, p < .01, η^2 = .031) and a triple interaction of Task × BDNF × Hypertension was significant as well: F(1,179) = 3.85, p = .05, η^2 = .006 were observed. The triple interaction indicated that hypertensive carriers of the BDNF Met allele were slower than the rest of the sample, with Tukey HSD p < .09 for comparison with normotensive BDNF Met-, p < .03 for comparison with hypertensive Met-, and p < .001 for comparison with normotensive Met+ carriers. The effect was significant only for the Letter Comparison task. A significant BDNF × Sex interaction (F(1,179) = 5.62, p < .05, η^2 = .020) showed that women who were Met66 carriers performed slower than the rest of the sample on Letter Comparison test: Tukey HSD p<.05 for comparison to BDNF Met- women; p < .02 in comparison to BDNF Met+ men, and p <.005 in comparison to BDNF Met- men. The Hypertension × Sex interaction was significant as well: F(1,179) = 11.79, p < .001, η^2 = .039. Post-hoc comparisons of adjusted means revealed that hypertensive women performed significantly slower than the rest of the sample, but only on the Letter Comparison task: 2.82 ± 0.049 log-items, with Tukey HSD p < .09 for comparison to normotensive men, p < .03 in comparison to hypertensive men, and p < .001 in comparison to normotensive women. On Pattern Comparison task, hypertensive women tended to be slower than normotensive women (Tukey HSD p=.057) and normotensive

men (Tukey HSD p =.064). All three interactions are illustrated in bar graphs of the adjusted means ± standard errors (SE) in Figure 2–Figure 4 below. A significant Test × COMT genotype interaction ($F(1,179) = 5.67$, $p < .05$, $\eta^2 = .009$) was also observed. Performance of COMT Met homozygotes on Letter Comparison test was slightly better than that of the Val carriers (3.00 ± .25 log units vs. 2.91 ± .29 log units, Tukey HSD $p < .08$; no differences were noted on Pattern Comparison test: 3.47 ± .25 and 3.49 ± .15 log units.

Episodic (Associative) Memory

Because none of the interaction effects reached significance at $p < .05$ level, a reduced model with main effects only was evaluated. The main effects of Age [$F(1,182) = 58.72$, $p < .001$, $\eta^2 = .230$], Sex [$F(1,182) = 4.48$, $p < .05$, $\eta^2 = .017$], COMT [$F(1,182) = 7.09$, $p < .01$, $\eta^2 = .027$], BDNF [$F(1,182) = 4.02$, $p < .05$, $\eta^2 = .015$], and Delay [$F(1,182) = 2646.76$, $p < .001$, $\eta^2 = .93$] were observed. A nonsignificant trend for ApoE effect was noted: $F(1,182) = 3.15$, $p < .08$. The direction of the trend was in favor of ApoEε4 carriers compared to the individuals who lacked that allele: 54.64 ± 10.27 vs. 52.19 ± 12.31 correct for immediate and 23.70 ± 8.62 vs. 20.90 ± 10.29 for delayed recognition.

Association recognition was negatively correlated with age: $r = -.46$ and -.47, for immediate and delayed recall, respectively; both $p < .001$. Women performed better then men on immediate and delayed recognition: 54.77 ± 13.15 vs. 52.06 ± 10.63, Tukey HSD $p < .08$, for immediate and 23.77 ± 10.71 vs. 20.83 ± 8.96, Tukey HSD, $p < .03$, for delayed recognition. COMT Met homozygotes outperformed COMT Val carriers: 55.38 ± 10.60 vs. 51.45 ± 14.42, Tukey HSD $p < .02$, for immediate and 24.16 ± 8.87 vs. 20.44 ± 10.14, Tukey HSD, $p < .007$ for delayed recognition. BDNF Met allele carriers performed worse than Val/Val homozygotes: 52.12 ± 11.01 vs. 54.71 ± 1.22, Tukey HSD $p < .07$, for immediate and 23.58 ± 1.02 vs. 21.02 ± 1.07, Tukey HSD $p < .04$ for delayed recognition. The nonsignificant trend for ApoE was that ε4 carriers performed somewhat better than persons with no ε4 allele. Removal of young participants (age < 30 years), of whom all but one were ApoEε4- genotype, did not alter the effect. The effects of COMT and BDNF polymorphisms on associative memory are illustrated in figure 5 and figure 6 below.

Discussion

The main finding in this study is that in addition to typical influence of age and negative effects of a vascular risk, specific genetic factors play a significant role in cognitive performance of healthy adults. The effects of genetic variants on cognition differ in their specificity vis-à-vis cognitive domains. Presence of the Val allele of the COMT Val158Met SNP was associated with reduced performance in virtually all cognitive domains assessed in this study. It is unclear whether such broad influence indicates a lack of specificity of the COMT effect on executive functions or reflects the presence of executive, strategic components in all of the examined tasks. Moreover, although COMT is especially important in regulation of dopamine in prefrontal circuits, the COMT gene is widely expressed in almost all parts of the central nervous system, including the cerebellum and the striatum (Hong, Leong, Tao, & Ping, 1998). Thus widespread increase in dopamine availability may account for generalized cognitive benefits reaped by Met homozygotes.

Of note is the lack of COMT genotype effect on the only executive function assessed in this study, inhibition of pre-potent response measured by the color Stroop task. In this context we are reminded that direct pharmacological manipulation of dopamine availability has yielded a contradictory body of findings with regards to cognitive performance in general and Stroop task in particular. In some samples, increase in presynaptic dopamine availability produced robust negative effects on episodic memory but not on Stroop and other specific executive tasks (Montoya et al., 2007). In other pharmacological studies, both *increases* (Roesch-Ely et

al., 2005) and *decreases* (Scholes et al., 2007) in dopaminergic activity improved performance on Stroop. In at least one study, interaction of COMT Val158Met with other polymorphisms relevant to dopaminergic activity (e.g., DRD2) was necessary to produce a significant effect on inhibitory control as measured by Stroop interference scores (Reuter et al., 2005).

The effects of two other SNPs, BDNF Val66Met and ApoEε4, were more subtle and differential. We found that speed of processing, a quintessential age-sensitive function (Salthouse, 1996), was affected by BDNF genotype. Carriers of BDNF Met allele were slower in perceptual-motor processing and less proficient in associative memory tasks than their Val-homozygotic counterparts. Moreover, the effect of BDNF on processing speed was exacerbated by hypertension. This finding is consistent with recent reports of reduced BDNF expression in hypertensive rodents (Lee et al., 2006) and suggests that vascular factors need to be taken into account in studies of BDNF effects on cognition. Slowing associated with the presence of BDNF Met and hypertension was more prominent in women. The latter suggests a possibility of a genotype × hormonal status interaction, which could not be assessed in this sample but certainly merits further investigation.

As predicted, the presence of a BDNF Met allele had a negative effect on memory and supports the role of BDNF in that age-sensitive function. The effect, however, was relatively small and independent of age. Thus, while our results support the role of BDNF in memory performance in general, they do not indicate that age-related memory differences are influenced by the BDNF genotype. It is important to note that the negative effects of BDNF Met and COMT Val alleles, and the advantage of women were all stronger for delayed, more difficult, recognition task than for a relatively easier immediate recognition. Thus, it is possible that BDNF Val66Met is more reflective of the processes that require carrying of associative information across even a modest time lag. In the future studies, it may be advisable to examine the impact of task difficulty on the effect magnitude and to ascertain that BDNF indeed is preferentially important for associative memory.

No negative effect of ApoE ε4 allele on memory was noted and a nonsignificant trend in the opposite direction was observed. However, an age-related increase in processing costs incurred by interfering with a pre-potent response was steeper in ApoEε4 carriers. Thus, the results of this study support the reports of adverse effects of ApoEε4 on Stroop performance (Wetter et al., 2005) and not the studies that reported negative results (Packard et al., 2007; Small et al., 2000). However, recent studies support the role of ε4 allele in accelerating age-related slowing (Blair et al., 2005), especially in conjunction with deterioration of cerebral myelin (Bartzokis et al., 2007).

In this sample, we observed no significant effect of a major vascular risk index, arterial hypertension, on any task except perceptual motor speed. It is possible that negative effects of hypertension may be more prominent on executive functions that pertain to cognitive flexibility and carry a heavier load on working memory (e.g. Wisconsin Card Sorting Test, Raz et al., 2003). It is also possible that other vascular risk factors such as indices of glycemic control and inflammatory response might prove more influential than hypertension on age-cognitive functions examined in this study.

We have observed several effects associated with participants' sex. In accord with previously reported findings (Herlitz et al., 1997), women outperformed men on an associative memory task. Men evidenced better performance on a nonverbal reasoning (fluid intelligence) task, showed greater ability to inhibit a pre-potent response, and were faster on perceptual-motor tasks. The latter finding is consistent with the literature only if men in this sample had higher then average levels of total testosterone (Hogevorst et al. 2004), which they might have had,

given the generally selective nature of the sample. Unfortunately, we have no data to test that hypothesis.

Regarding the question of epistastic influence on cognition and age-related differences therein by multiple SNPs, the study yielded negative results. Although statistical power considerations are important and even more so for interaction effects, the analyses conducted on this sample produced no trends that could have been revealed as significant effects in a larger sample. Our findings are in accord with other studies that found, as we did, no significant epistastic effects of COMT, ApoE, and a number of vascular-disease related genes on memory (Harris et al., 2005). We have not replicated a recently reported COMT × BDNF × Age interaction, i.e. modification of COMT effect on executive performance in older adults (Nagel et al., 2008). It is plausible that the discrepancy stemmed from our use of continuous age rather than extreme-group design and accounting for the variance associated with common vascular risk factor as well as a genetic modifier of vascular risk (ApoEε). However, after making all the changes in our analyses to make them similar to those used by Nagel and colleagues, we still found no significant interactions among the SNPs and age on a measure of executive functions used in our study (all $F < 1$). We therefore are left with a possibility that the reported interactive effects are specific to the cognitive processes assessed by Nagel and her colleagues. Further inquiry into multiple executive functions and multiple combinations of candidate SNPs is needed to clarify this issue.

It is important to underscore, that although the observed effects of polymorphisms on cognition are robust, each accounted for no more than 3% of the total variance, in accord with the literature (Heinz & Smolka, 2006). However, small effects of multiple factors may exercise a palpable and clinically meaningful influence on behavior. For example, in this study, the combined (additive) effects of the SNPs and their interactions with other factors ranged from 1.6% of the variance in fluid intelligence to 2% in interference costs, 4.2% in memory, and 6.6% in speed of processing. Therefore, while engendering a cautious attitude, the observed effects of three SNPs cannot be dismissed as too small and therefore irrelevant.

The results of this study should be interpreted in the context of its limitations. First, this is a relatively small sample of convenience deliberately biased towards disease-free and educated adults. It is therefore susceptible to selection biases and survivor effects with respect to the polymorphisms that are associated with lower physical and cognitive fitness. ApoE ε4 carriers recruited for this study and screened for multiple age-related diseases could have been a selected healthier-than-average group than persons without ApoE ε4. Because we recruited only participants who had no history of medical and neurological conditions except for hypertension (diagnosed and treated) it is possible that only the best-functioning ε4 carriers entered the study. In addition, we had only 1.5% of ApoEε4 homozygotes in our sample compared to, for example 25% in some samples that showed a significant negative effect on memory (e.g., Casselli et al., 2004). Notably, in Small et al (2004) meta-analysis of ApoE e4 effects on episodic memory, older average sample age was associated with lesser negative effect of the allele thus suggesting that samples of older adults might have included a disproportionate number of healthy survivors. However, the observed negative effect of ApoEe4 allele on Stroop interference costs weakens the survivor-effect argument.

Second, it is a cross-sectional study, in which age-related change can only be inferred, not measured. It is possible that a longitudinal follow-up, in which true change and variability of change can be assessed, would reveal more subtle effects of the examined polymorphisms on cognition (e.g., Bretsky et al., 2003). Finally, it is commonplace that with more than 30,000 genes and millions of SNPs, it would be highly unlikely that a specific SNP would play a major role in normal cognitive variability. The sample employed in this study, although more than adequate for examining cognitive effects of aging, might not be sufficiently large for

discovering some genetic effects. Moreover, genes and vascular risk factors may exert their effects on cognition in more complicated synergistic patterns than presumed by models with main effects and interactions. Examination of higher-order interactions is necessary but it demands a substantially greater number of subjects than included in this sample.

In sum, the results of this study show that the examined polymorphisms, COMT Val158Met, BDNF Val66Met, and ApoE ε4 exert independent effects on age-sensitive cognitive processes. Some of the negative effects are exacerbated by hypertension, a vascular risk factor; others may be sex-dependent. Investigation of interactions among those and other polymorphisms, hormones (e.g., sex steroids), and vascular risk factors (e.g., indices of glycemic control and inflammatory response) may provide additional insights into epigenetics of cognitive aging. However, in face of complexity of the observed effects it is clear that multiple replications in various populations and with a variety of cognitive measures are necessary for further clarification of the role of specific polymorphisms in cognition. Recruitment of large samples and administration of multiple measures in laboratory setting pose significant logistical and financial difficulties. Thus, accumulation and distillation of knowledge in this area of research will require accrual of multiple findings that would lend power to meta-analyses of a rapidly growing but contradictory literature (Munafò & Flint, 2004).

Acknowledgement

This study was supported in part by a grant from the National Institutes of Health (R37-AG-11230).

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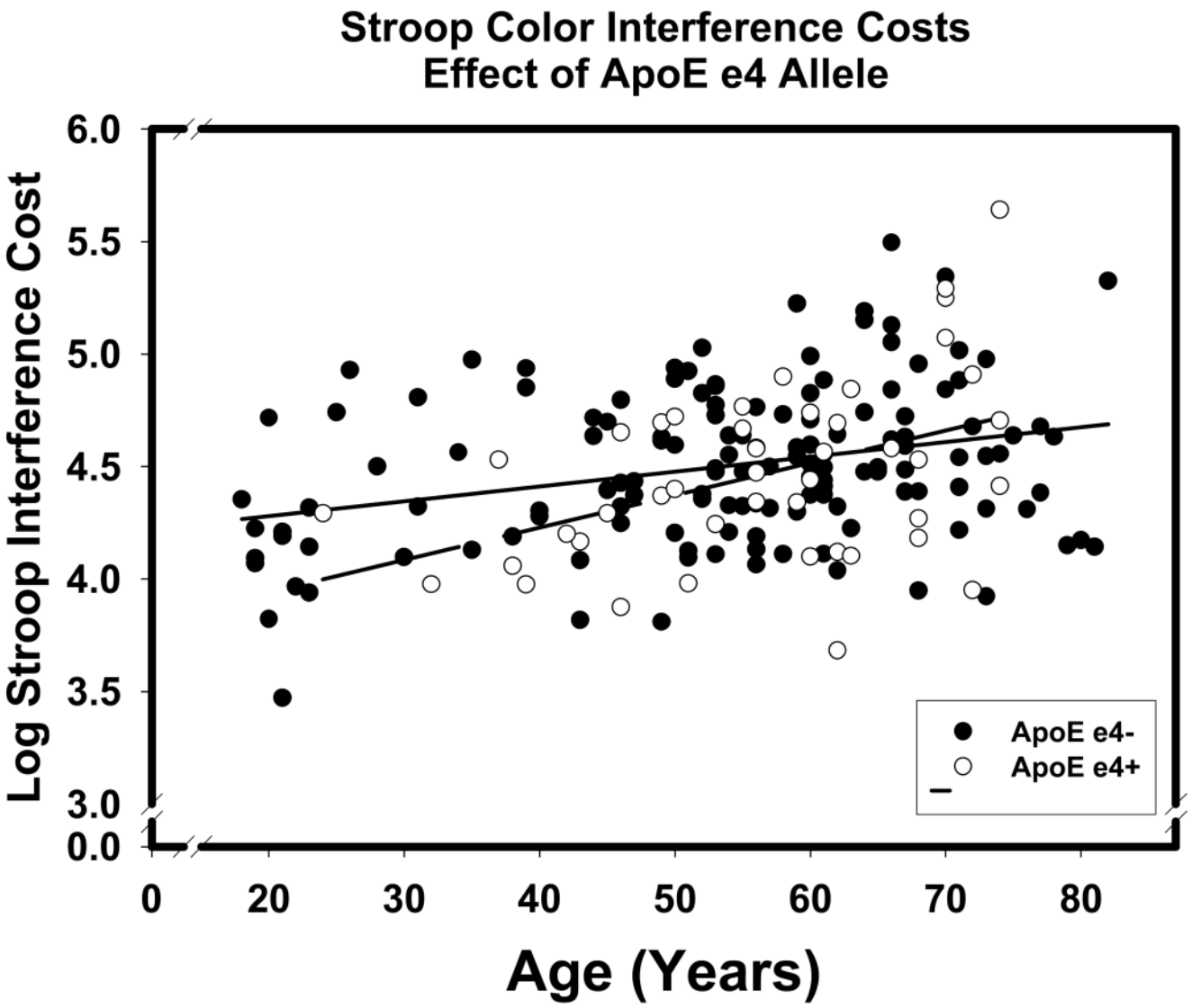

Figure 1.
Modification of age-related increase in interference costs by ApoE: steeper slope for ApoE ε4 carriers.

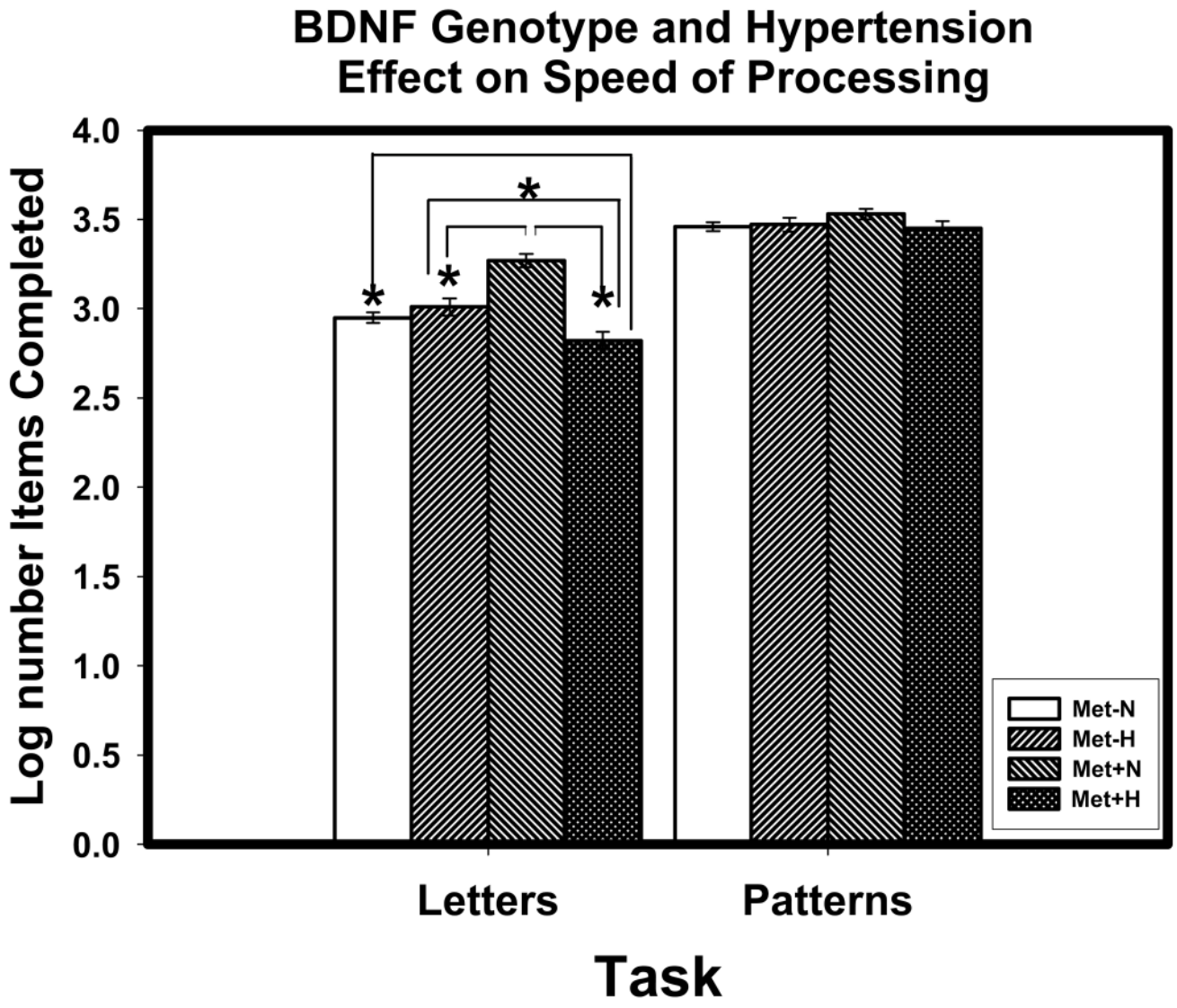

Figure 2.

An illustration of BDNF genotype × Hypertension interaction for processing speed. A bar chart of scores on two tests of speed of processing: Letter Comparison (Letters, blank bars) and Pattern comparison (Patterns, cross-hatched bars). Standard errors of the means are also shown. The bar labels correspond to the presence of at least one BDNF Met allele (Met+ and Met−) and Hypertensive (H) vs. Normotensive (N) status.

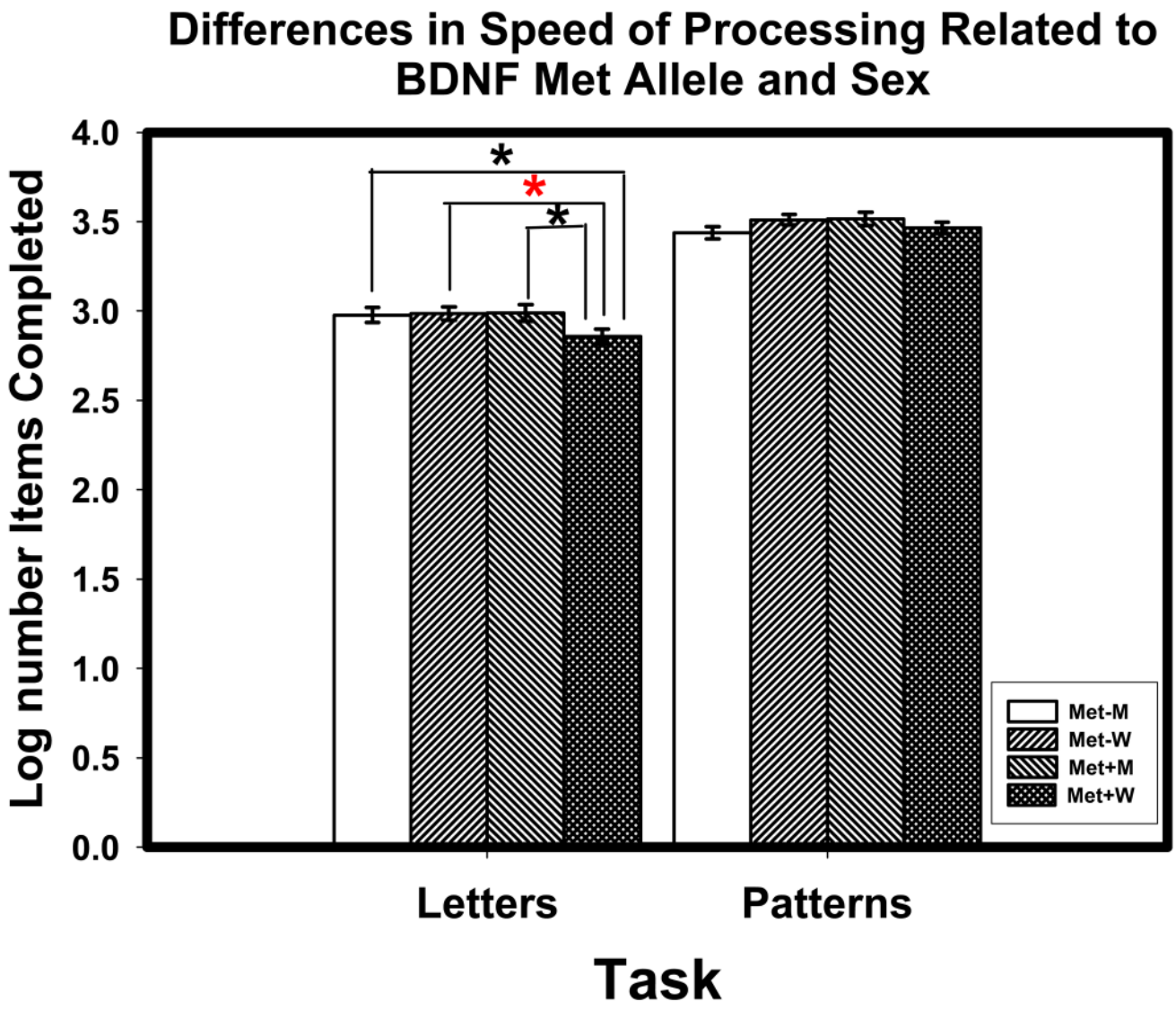

Figure 3.

An illustration of BDNF genotype × Sex interaction on tests of speed of processing: Letter Comparison (Letters, blank bars) and Pattern comparison (Patterns, cross-hatched bars) along with standard errors of the means. The bar labels correspond to the presence of at least one BDNF Met allele (Met+ and Met−) and Sex (Men vs. Women).

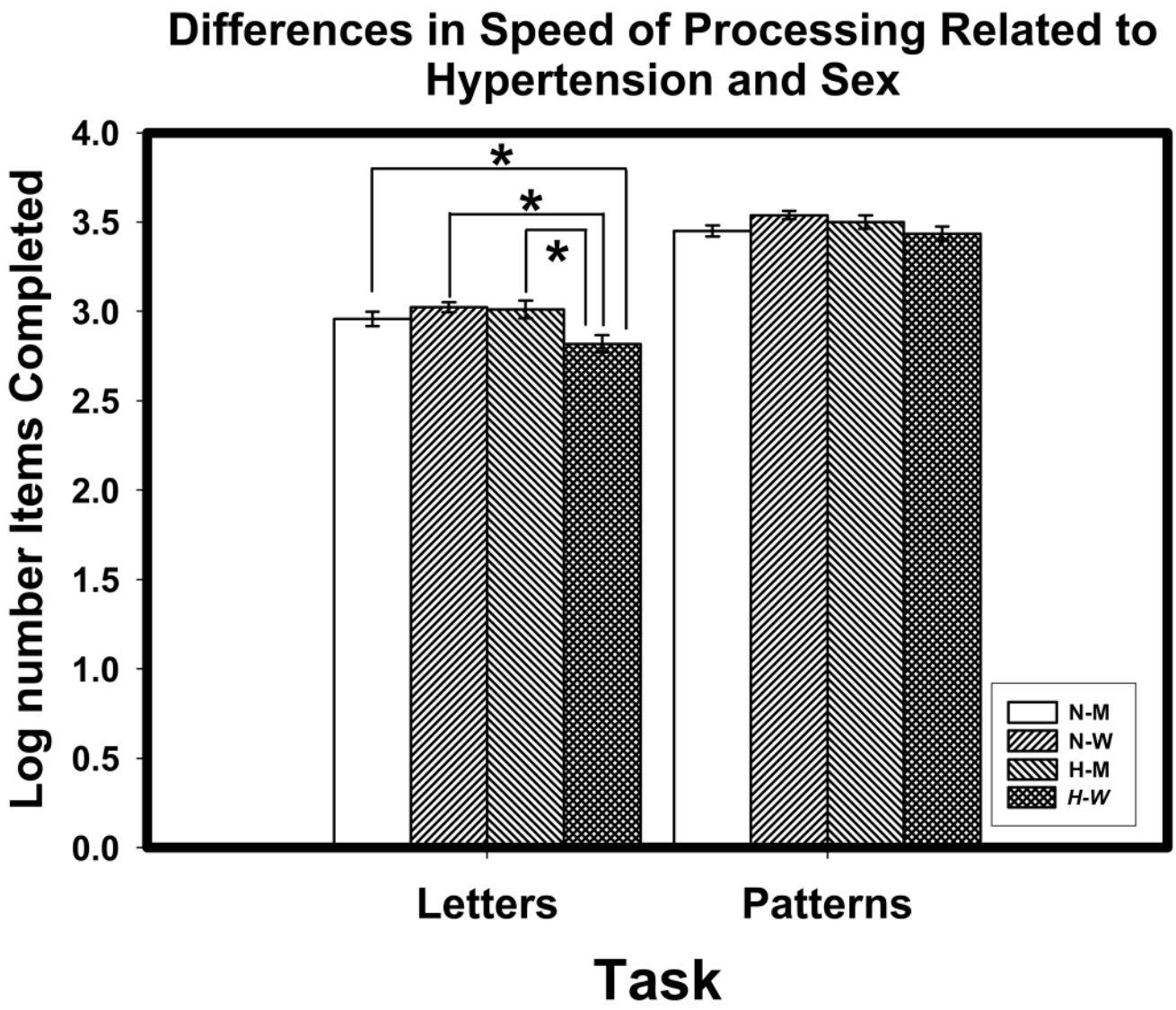

Figure 4.

An illustration of Sex × Hypertension interaction for two tests of speed of processing: Letter Comparison (Letters, blank bars) and Pattern comparison (Patterns, cross-hatched bars). Standard errors of the means are also shown. The bar labels correspond to Sex (Men vs. Women) and Hypertensive (H) vs. Normotensive (N) status.

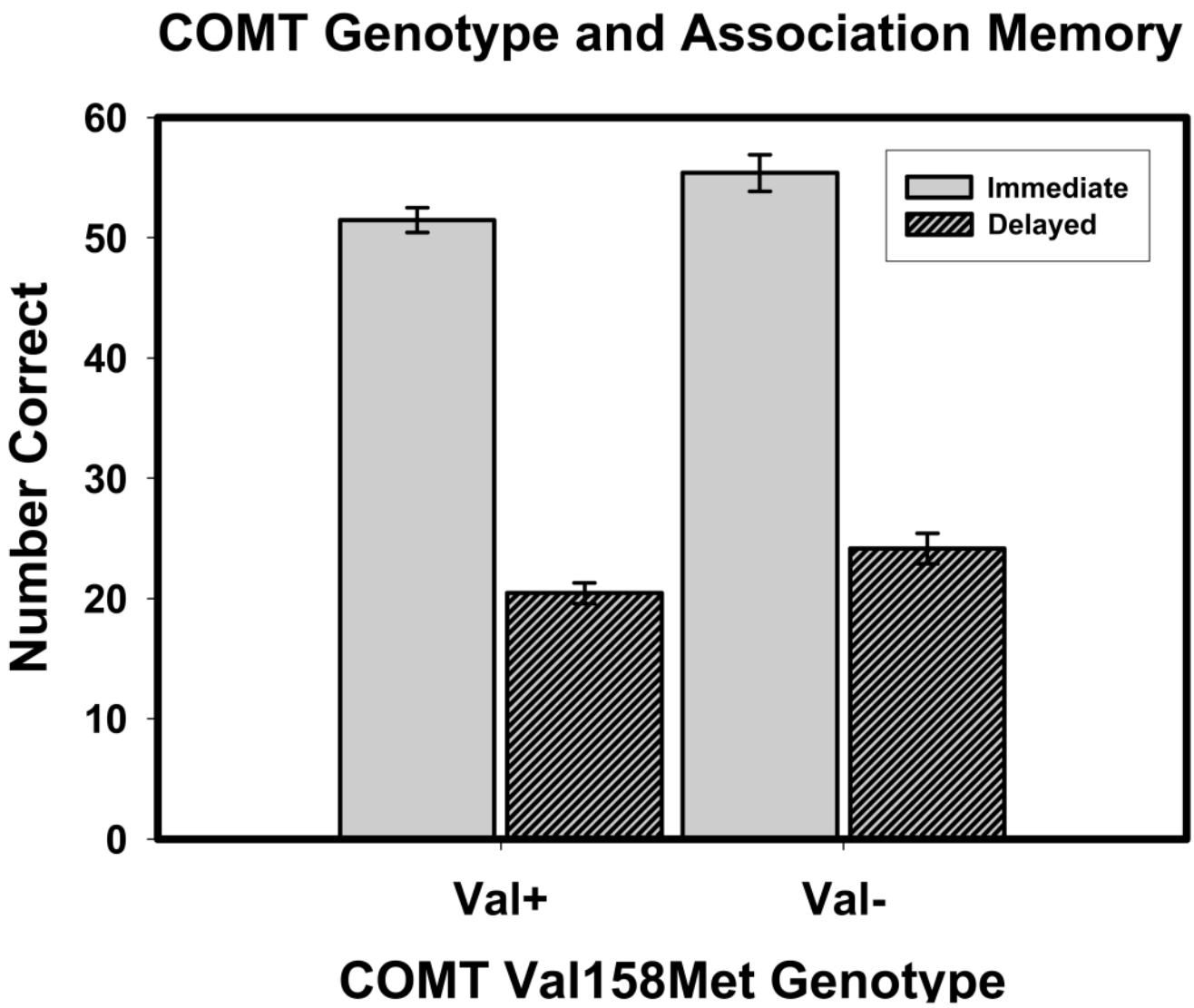

Figure 5.
The effect of COMT Met158 allele on associative memory at immediate and delayed recall. Bars represent mean scores with standard errors around them.

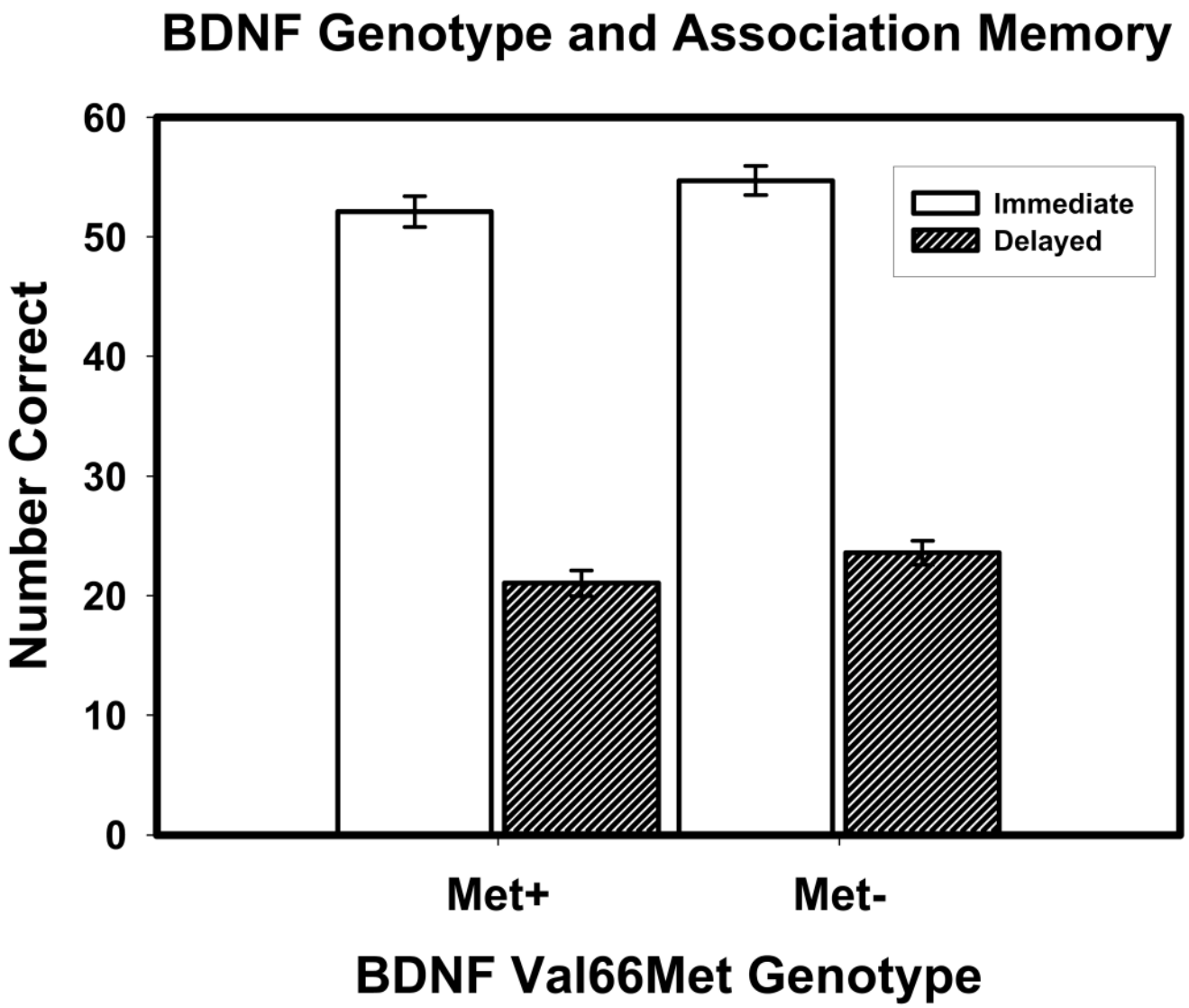

Figure 6.
The effect of BDNF Met allele on associative memory, immediate and delayed.

Table 1

Description of the sample; men and women compared.

Variable	Men	Women	t or $\chi^{2\#}$	p
Age	56.05±15.79	53.56±14.59	1.08	0.28
Education	16.44±2.53	15.66±2.30	2.14	0.034
Systolic blood pressure (mm Hg)	126.94±13.16	122.12±13.97	2.29	0.023
Diastolic blood pressure (mm Hg)	79.02±8.42	74.87±7.39	3.48	0.001
Proportion of hypertensives	36%	21%	$5.05^{\#}$	0.025
MMSE	28.59±1.14	28.98±0.95	2.50	0.013

Note. MMSE = Mini-Mental State Examination.

$^{\#}$a single degree-of-freedom χ^2 test.

Table 2

Correlations among the cognitive, health and demographic variables.

	Age	Educ	MMSE	Cattell, time	Cattell, no time	Names	Names, del	Letters	Patterns	Stroop
Education	−0.02									
MMSE	−0.27***	0.09								
Cattell Culture Fair Test, with time limits	−0.56***	0.15*	0.25**							
Cattell Culture Fair Test, without time limits	−0.38***	0.19*	0.27***	0.89***						
Name-Picture Recognition, immediate	−0.46***	0.09	0.37***	0.52***	0.50***					
Name-Picture recognition, delayed	−0.47***	0.11	0.34***	0.45***	0.46***	0.85***				
Letter Comparison	−0.51***	0.18*	0.31***	0.47***	0.37***	0.38***	0.38***			
Pattern Comparison	−0.52***	0.18*	0.32***	0.43***	0.34***	0.29***	0.29***	0.62***		
Log Stroop Costs	0.32***	−0.02	−0.18*	−0.37***	−0.29***	−0.27***	−0.24**	−0.21**	−0.21**	
Hypertension	0.25***	0.09	−0.08	−0.16*	−0.11	−0.16*	−0.14	−0.21**	−0.20**	0.04

*p < .05

**p<.01

***p <.001