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ORIGINAL RESEARCH

Untreated Hypertension Decreases Heritability of Cognition in Late Middle Age

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Abstract Hypertension is a risk factor for cognitive decline, but the mechanisms underlying the effects of hypertension on cognition, particularly in midlife, are unclear. We examined whether hypertension modifies genetic influences on individual differences in cognition. Nine cognitive domains and general cognitive ability were assessed in a sample of 1,237 male twins aged 51–60 who were divided into three blood pressure groups: non-hypertensive; medicated hypertensive; and unmedicated hypertensive. Heritability was significantly lower among unmedicated hypertensives compared to medicated hypertensives and non-hypertensives for visual-spatial ability ($p = 0.013$) and episodic memory ($p = 0.004$). There were no heritability differences between non-hypertensives and medicated hypertensives. In addition, there were no significant differences in mean level cognition across the three blood pressure groups. These results suggest that in middle-aged men, untreated hypertension suppresses normal genetic influences on individual differences in certain domains of cognition prior to the emergence of hypertension-related effects on cognitive performance. These results further suggest that antihypertensive medication may protect against or reverse this effect.

Keywords Hypertension · Cognition · Twins · Heritability · Aging

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Introduction

Hypertension is a risk factor for Alzheimer's disease, dementia and age-related cognitive deficits (Stampfer 2006). Both cross-sectional and longitudinal studies have linked hypertension to poorer cognition in later life (Birns and Kalra 2008). In addition, there is increasing evidence

that hypertension may already begin to impact cognition at midlife. For example, the Whitehall II study reported an inverse relationship between blood pressure and cognition in a sample of individuals aged 46–68 years old after adjusting for age, smoking, cardiovascular disease and antihypertensive medication use. Furthermore, after controlling for other health factors, blood pressure has been shown to still account for a significant portion of the variance in cognition at midlife (44–65 years old) (Knecht et al. 2009). However, the effects of blood pressure and hypertension on cognition appear to be relatively domain specific. In a meta-analysis by van den Berg et al. (2009), domains of memory were most commonly influenced by hypertension. Smaller effects of hypertension were found on measures of processing speed, executive function, verbal fluency, and abstract reasoning, with virtually no study finding effects of hypertension on verbal ability (van den Berg et al. 2009).

One well-known complication in the investigation of cognition-hypertension associations is the fact that some individuals will be treated for hypertension and some will not. Many studies focusing on the relationship between hypertension and cognition adjust for antihypertensive medication use; however, antihypertensive medication use itself has been shown to reduce or even reverse some cognitive deficits (Haag et al. 2009; Muldoon et al. 2002; Murray et al. 2002). For example, in a sample aged 65 years and older, individuals who were taking antihypertensive medication had a 38% reduced odds of cognitive impairment compared to individuals without medication (Murray et al. 2002). In a four-year prospective study, individuals on antihypertensive medication had an 8% reduction in dementia risk per year of medication use compared to individuals who reported never using antihypertensive medication (Haag et al. 2009). The present study aims to investigate the distinct influences of antihypertensive medication use on cognition in addition to the influences of untreated hypertension on cognition.

While prior research suggests that hypertension and antihypertensive medication use cause changes in levels of cognitive function, the mechanisms by which this happens are unclear. Furthermore, it is important to note that, even in the absence group mean differences in cognition due to hypertension, there could still be hypertension-related differences in the mechanisms underlying cognitive function. For example, it is widely accepted that older adults may retain cognitive performance levels by compensating for less efficient processing (Nielson et al. 2002). Two people might have the same score on a task, but one might need to exert far more effort than the other to achieve that same level of performance. This scenario is supported by neuroimaging findings in which older adults may perform equally well as young adults, but the former activate significantly more brain regions as compared with the latter (Nielson et al. 2006). In other words, they arrived at the same endpoint but via different routes.

One way to estimate the underlying mechanisms that contribute to cognitive function is to utilize twin analyses, which can estimate the proportion of variance in a trait that is attributable to genetic factors (heritability) and environmental factors. That is, we can address the question of whether individual differences in a trait are due primarily to genes or to the environment. Twin studies have demonstrated that cognitive function is a complex process influenced by both genetic and environmental factors. Heritability of midlife general cognitive ability generally ranges between 0.60 and 0.80, with non-shared environmental factors accounting for the remaining 20–40% of variance (McGue et al. 1993; Plomin et al. 2001). However, developmental behavior genetic studies indicate that genetic influences on individual differences in cognition over the life course are dynamic. For example, prior research has shown that the heritability of general cognitive ability increases from childhood to adolescence to young adulthood, with this increase leveling off from young adulthood to midlife (Haworth et al. 2009; Lyons et al. 2009), but the importance of genetic factors may then begin to decline during old age (Finkel et al. 1995). While the mechanisms underlying these changes in heritability are likely to be complex, one plausible explanation is that genes may be turned "on" or "off" as the brain undergoes major transitions associated with normal developmental processes (Wallace et al. 2006). Thus, physiological factors may influence normal genetic influences in humans.

Indeed, a growing body of research using animal models has begun to identify factors that may alter genetic influences in the brain. Aging itself is associated with differing gene expression in the mouse and rat brain, including both the downregulation and the upregulation of genes related to a variety of processes, such as energy metabolism, synaptic plasticity, inflammation, and oxidative stress (Blalock et al. 2003). Furthermore, physiological changes due to calorie restriction, increased exercise and a diet high in healthy fats may promote gene expression profiles in rodents that benefit brain function (Cotman and Berchtold 2002; Kitajka et al. 2002; Weindruch et al. 2002).

In light of research supporting that physiological processes, such as calorie restriction, alter the genes influencing brain function, it is possible that hypertension may cause disruptions in genetic factors underlying individual differences in cognition. However, to our knowledge, no published study has used genetically-informative human samples (e.g., twins) to quantify how a physiological process such as hypertension may modify the importance of genetic and environmental influences on individual differences in cognition. In summary, the present study utilizes a

large sample of middle-aged male twins to examine two questions: (1) whether hypertension or antihypertensive medication use contribute to group mean differences in cognitive performance at midlife; and (2) whether hypertension or antihypertensive medication treatment moderates the heritability of cognition.

Materials and methods

Sample

Data were obtained from Wave 1 of the Vietnam Era Twin Study of Aging (VETSA), a longitudinal study of cognition and aging beginning in midlife (Kremen et al. 2005). All participants in VETSA were from the Vietnam Era Twin Registry, a nationally representative sample of male–male twin pairs who served in the US military sometime between 1965 and 1975. Detailed descriptions of the Registry and ascertainment methods have been previously reported (Eisen et al. 1987; Henderson et al. 1990). VETSA twins resembled those of the larger Registry sample and were representative of the general population of similarly-aged adult males in terms of demographic and health characteristics based on U.S. census and Center for Disease Control data (Center for Disease Control 2007). During Wave 1, twins had the option to travel to Boston University or to the University of California, San Diego, for a day-long session that included physical assessments and an extensive neurocognitive battery. The study was approved by local Institutional Review Boards in both Boston and San Diego. The VETSA Wave 1 sample included 1,237 individuals (697 monozygotic twins (MZ), 540 dizygotic (DZ) twins). The average age was 55.4 years (range 51–60). Wave 2 data collection is ongoing through 2013.

Measures

Blood pressure

Blood pressure was calculated by the mean of four measurements taken throughout the day-long testing session. Blood pressure was assessed at specified times in the morning and afternoon. During each measurement occasion, participants rested for 5 min prior to the first blood pressure reading, waited 1 min, and then had a second reading. Systolic and diastolic pressures were then each averaged across the four measurements. Antihypertensive medication use was assessed using self-report, which has been shown to have adequate reliability (Glintborg et al. 2007). Blood pressure measurements and antihypertensive medication use were combined to create three blood pressure groups: (a) unmedicated hypertensives (UnMed), i.e., individuals with mean systolic readings greater than or equal to 140 mm Hg and/or mean diastolic readings greater than or equal to 90 mm Hg who were not taking any antihypertensive medication ($n = 265$); (b) medicated hypertensives (Med), i.e., individuals who reported any antihypertensive medication use, regardless of their current blood pressure readings ($n = 424$); and (c) non-hypertensives (Non), i.e., unmedicated individuals with mean systolic readings below 140 mm Hg and mean diastolic readings below 90 mm Hg ($n = 548$). The non-hypertensive group contains both normotensives (i.e., below 120/80) and pre-hypertensives. There were too few normotensives ($n = 141$) to include as a separate group in genetic analyses. However, mean cognitive scores were not different between normotensives and pre-hypertensives, and genetic analysis that included only pre-hypertensives did not change the results (available from author). Two DZ twins who reported taking antihypertensive medication but had blood pressure values >5 SD above the group mean were excluded from the analyses, for a total sample $N = 1{,}235$.

Cognition

Cognition was measured with extensive battery of standard neuropsychological tests that are both reliable and well-validated. Performance on individual tests was standardized (z-scored) and then combined to create nine cognitive domains. (1) Verbal ability was indexed by the WASI Vocabulary test (Wechsler 1997a). (2) Visual Spatial Ability was measured by the Hidden Figures Test (Thurstone 1944) and the Card Rotation task (Ekstrom et al. 1976). (3) Episodic Memory included tests of Logical Memory and Visual Reproduction, using both immediate and delayed recall conditions (Wechsler 1997b). (4) Short Term Memory was indexed by Digit Span Forward and Spatial Span Forward. (5) Working Memory was indexed by Digit Span Backward, Spatial Span Backward and Letter-Number Sequencing (Wechsler 1997b). (6) Processing Speed was measured by Trail Making conditions 2 and 3 (Delis 2001) and Stroop Color-Word, word reading condition (Golden 1978; Stroop 1935). (7) Verbal Fluency was indexed by two tests of Category Fluency, boys' names and animals (Delis 2001). (8) Executive Function was measured by Trail Making condition 4 and Verbal Fluency Category Switching (Delis 2001). (9) Abstract Reasoning was indexed by Matrix Reasoning (Wechsler 1997a). For all cognitive domains, higher scores indicated better performance. Furthermore, several tests (e.g. delayed conditions, Trails 4) were adjusted for the more elementary condition of the test (e.g. immediate conditions, Trails 2 and 3). For more details on the individual tests used to create these domains, please see the online supplement.

In addition to the nine cognitive domains, we also measured general cognitive ability in VETSA Wave 1 using the Armed Forces Qualification Test (AFQT; Bayroff and Anderson 1963), a 100-item multiple-choice test that is highly correlated with Wechsler IQ (WAIS) and other general cognitive ability measures (Uhlaner and Bolanovich 1952; McGrevy et al. 1974). The mean AFQT percentile score during the VETSA study was 64, which translates into a score of 105 on the WAIS. Cross-domain correlations, as well as correlations between each domain and AFQT, are reported in the online supplement.

Covariates

Several demographic and health characteristics were considered as covariates in these analyses to adjust for potential differences between hypertension groups in, including age, body mass index (BMI), diabetes, cardiovascular disease, education and general cognitive ability in early adulthood. BMI was calculated from measured weight and height. Both diabetes and cardiovascular disease were indexed by the absence or presence based on participant self-report of having been diagnosed by a doctor. Education, for both the twins and their parents, was measured in years. General cognitive ability in early adulthood was measured by the AFQT administered just prior to military induction (average age = 20). AFQT test–retest reliability between scores at induction and at VETSA Wave 1 was 0.74 (Lyons et al. 2009).

Statistical analysis

Linear mixed modeling in SPSS 17 was used to test for mean differences in each cognitive domain across the three blood pressure groups. This procedure adjusted for the clustering of twins within pairs. Behavioral genetic analyses were conducting using the statistical program, Mx (Neale et al. 2004). Under standard assumptions, the traditional twin design can be used to estimate the proportion of variance in a trait that is attributable to additive genetic (A), shared environmental (C) and nonshared environmental (E) factors (please see Neale and Cardon 1992; Jinks and Fulker 1970 for details on assumptions of twin models). In the twin design, MZ twins are assumed to share 100% of their segregating genes while DZ twins share, on average, 50%, so that MZ twins correlate 1.0 for additive genetic effects (A) while DZ twins correlate 0.5. Both MZ and DZ twins share 100% of their shared environmental influences (C), which are defined as non-genetic influences that make twins similar to one another. Conversely, nonshared environmental factors (E) refer to non-genetic influences that make twins different from one another. E also includes measurement error. By definition, E does not correlate between either MZ or DZ twins.

We used a multiple group approach to examine whether the genetic and environmental influences on individual differences in cognition differed among blood pressure groups (Neale and Cardon 1992). In the multiple group approach, each twin in a pair was assigned to a blood pressure group, irrespective of co-twin status. Data groups were then created that included both twin pairs concordant for blood pressure group, as well as discordant twin pairs. Two models were fit to the data. First, we allowed the genetic and environmental influences to differ across the blood pressure groups. Next, we tested submodels that equated the genetic and environmental parameters across the blood pressure groups. Goodness-of-fit for each submodel was assessed using the difference in two times the log likelihood (−2LL) between the full and constrained models. This difference in −2LL has a chi-square distribution with degrees of freedom equal to the difference in the number of parameters estimated in the two models. Submodels that had a worse fit (i.e., those that significantly increased the chi-square value) indicate that parameters could not be equated across the blood pressure groups; i.e., the magnitudes of genetic and environmental influence on individual differences in cognition significantly differed according to blood pressure status. Conversely, submodels that did not significantly worsen the model fit indicated that parameters were not statistically different across blood pressure groups. Separate genetic analyses were applied to each cognitive variable. All models were fit to raw data. Chi-square tests of group differences in genetic and environmental influences on individual differences in cognition were based on unstandardized parameter estimates.

Results

Descriptive statistics and preliminary analysis

Table 1 presents means, standard deviations, and ranges of blood pressure values for each of the three blood pressure groups. For both systolic and diastolic blood pressure, mean levels were highest in the unmedicated hypertensive group and lowest in the non-hypertensive group, with levels for the medicated hypertensives in-between the other two groups. Standard deviations of both systolic and diastolic blood pressure were higher in medicated hypertensives than either the non-hypertensive or unmedicated hypertensive groups. Likewise, in the medicated hypertensive group, systolic blood pressure ranged from 100 to 178 mm Hg and diastolic blood pressure ranged from 58 to 118, indicating that the medicated hypertensive group included a subgroup whose blood pressure was normalized

Table 1 Blood pressure and demographics for each blood pressure group

	Non-hypertensive (Non) $n = 548$	Medicated hypertensive (Med) $n = 422$	Unmedicated hypertensive (UnMed) $n = 265$	Effect size[c]
Systolic blood pressure[a,†] [mean (Sd), range]	125 (8), 98–139	136 (14), 100–178	149 (11), 123–211	1.00–2.64
Diastolic blood pressure[a,†] [mean (Sd), range]	79 (6), 58–90	84 (9), 58–118	93 (7), 68–128	0.67–2.21
Age[†] [mean (Sd)]	55.2 (2.5)	55.8 (2.5)	55.4 (2.5)	0.08–0.24
BMI[†] [mean (Sd)]	28.1 (4.5)	31.2 (5.9)	29.3 (4.5)	0.27–0.60
Diabetes diagnosis[‡] [*N* (%)]	24 (4.4)	72 (17.0)	8 (3.0)	0.22
Cardiovascular disease[‡] [*N* (%)]	53 (9.7)	141 (33.3)	20 (7.5)	0.31
Education years [Mean (Sd)]	13.8 (2.2)	13.9 (2.1)	13.8 (2.0)	–
Parent education year [Mean (Sd)]	11.1 (2.7)	10.9 (2.5)	11.1 (2.3)	–
AFQT (age 20)[b] [Mean (Sd)]	61.9 (22.5)	60.6 (22.6)	61.1 (22.3)	–

Cohen's d for comparison of continuous variables is reported in ranges to encompass all comparisons. Cramer's Φ reported for all categorical variables, based on chi-square test

† Significant group differences in ANOVA; ‡ significant group differences in chi-square test

[a] In mm Hg

[b] AFQT (general cognitive ability) reported as mean percentile scores

[c] Effect sizes are reported only for significant comparisons

by medication and a subgroup whose blood pressure was not entirely normalized.

There were significant differences across blood pressure group for average age, BMI, and prevalence of diabetes and cardiovascular disease diagnosis. Individuals on antihypertensive medication had higher BMI and were more likely to have diabetes or other cardiovascular disease diagnoses than both non-hypertensives and unmedicated hypertensives. Likewise, medicated hypertensives were significantly older than non-hypertensives, while the difference in age between medicated hypertensives and unmedicated hypertensives approached significance ($p = 0.07$). Non-hypertensives and unmedicated hypertensive did not significantly differ in age. Given the evidence for group differences in these variables, all cognitive outcome variables were adjusted for BMI, diabetes, cardiovascular disease, and age in subsequent analyses.

In contrast, there was no evidence for group differences in years of education, years of parent education (averaged across mother and father) or general cognitive ability at age 20. However, because prior research has suggested that education/cognitive ability could influence antihypertensive medication use and hypertension (Vargas et al. 2000; Lowry et al. 2005), we used logistic regression analyses to examine whether either AFQT score at age 20 or education significantly predicted midlife clinical hypertension diagnosis and midlife antihypertensive medication use. Results revealed that general cognitive ability at age 20 did not significantly predict either clinical hypertension diagnosis ($\beta = -0.08$, $p = 0.35$) or antihypertensive medication use ($\beta = -0.03$, $p = 0.68$). Similarly, education did not predict either clinical hypertension diagnosis ($\beta = -0.003$, $p = 0.92$) or midlife antihypertensive medication use ($\beta = 0.10$, $p = 0.72$). Based on these results, we did not adjust our cognitive domain scores for prior AFQT or education in our primary analyses.

Group differences in mean levels of cognition

Table 2 presents the means and standard deviations for each of the nine cognitive domains and for general cognitive ability (AFQT) at midlife, adjusted for age, BMI, and history of diabetes and cardiovascular disease, separately by blood pressure group. Due to small amounts of missing data on the individual cognitive tasks, sample sizes for the analyses ranged from $N = 1{,}227$ to $N = 1{,}235$. No differences across group were found for any of the cognitive variables (see Table 2). Calculation of effect sizes using Cohen's d statistic (Cohen) for each pair of group comparisons revealed that the average effect size across all between-group comparisons was $d = 0.05$, with a range of $d = 0.01$ to $d = 0.13$. Additionally, we compared variances of each cognitive measure across all three groups (results not shown in table). Out of 30 individual contrasts, there were no variance differences across blood pressure groups for any of the cognitive variables (F-ratio tests range from 1.00 to 1.13, all p-values > 0.05), except for differences between the medicated and unmedicated hypertensive groups for abstract reasoning ($F = 1.27$, $p = 0.02$) and between the non-hypertensive and medicated groups for verbal ability ($F = 1.20$, $p = 0.05$). Phenotypic correlations between both systolic and diastolic blood pressure with measures of cognition ranged from r = −0.05 to r = +0.05, and were not statistically significant (all $p > 0.05$, results not shown in table).

Table 2 Means (sd) for cognitive domains and general cognitive ability measured at midlife, by blood pressure group

	Non	Med	UnMed	*F*-test	*p*-value
Visual-Spatial Ability	0.04 (1.02)	−0.03 (0.99)	−0.04 (0.99)	0.10	0.75
N	547	423	265		
Episodic Memory	0.02 (1.02)	0.00 (0.99)	−0.04 (0.98)	0.23	0.63
N	546	421	264		
Abstract Reasoning	0.00 (0.99)	0.01 (1.05)	−0.01 (0.93)	0.15	0.69
N	546	423	262		
Processing Speed	0.05 (0.99)	−0.04 (1.04)	−0.04 (0.96)	0.85	0.35
N	545	421	264		
Short-Term Memory	0.03 (0.99)	0.01 (0.99)	−0.08 (1.01)	0.94	0.33
N	547	424	264		
Working Memory	0.03 (1.00)	−0.03 (1.00)	−0.02 (0.98)	1.17	0.27
N	547	424	263		
Verbal Ability	0.02 (1.02)	−0.01 (1.02)	−0.03 (0.93)	0.31	0.57
N	546	421	263		
Executive Function	0.00 (1.05)	−0.01 (0.99)	0.02 (0.97)	0.31	0.57
N	546	421	264		
Verbal Fluency	0.07 (1.03)	−0.07 (0.98)	−0.03 (0.96)	2.18	0.11
N	542	421	264		
General Cognitive Ability	0.03 (0.98)	−0.01 (1.02)	−0.03 (0.99)	0.32	0.73
N	548	424	264		

Cognitive domain scores and general cognitive ability were adjusted for age, BMI, and diabetes and cardiovascular disease. Scores across the entire sample were standardized to z-scores with mean = 0 and standard deviation = 1. *F*-tests and *p*-values are shown for one-way ANOVA examining group differences in cognition

Non non-hypertensive, *Med* medicated hypertensive, *UnMed* unmedicated hypertensive

Genetic analysis

For comparison with other samples, univariate genetic analyses estimating additive genetic (A), shared environmental (C), and non-shared environmental (E) influences in the full sample were conducted for each domain and for general cognitive ability (AFQT) at midlife, after adjusting for age, BMI, diabetes and cardiovascular disease (Table 3). Moderate to high heritabilities, ranging from $h^2 = 0.30$ to 0.69, were estimated for all domains; non-shared environmental variance estimates ranged from 0.30 to 0.63. Estimates of shared environmental variance (C) were small and non-significant for all domains, ranging from 0.00 to 0.17. In preliminary multiple group analyses (not shown), estimates of C were not statistically significant in any of the three blood pressure groups

Table 3 Estimates of additive genetic (A), shared environmental (C) and nonshared environmental (E) variance for measures of cognition in the full Wave 1 VETSA sample

	A	C	E
Verbal Ability (95% CI)	0.43 (0.23–0.65)	0.17 (0.00–0.35)	0.40 (0.33–0.46)
Visual-Spatial Ability (95% CI)	0.69 (0.48–0.74)	0.01 (0.00–0.20)	0.30 (0.26–0.36)
Episodic Memory (95% CI)	0.49 (0.24–0.59)	0.03 (0.00–0.24)	0.48 (0.41–0.56)
Abstract Reasoning (95% CI)	0.44 (0.21–0.62)	0.12 (0.00–0.31)	0.44 (0.37–0.52)
Processing Speed (95% CI)	0.55 (0.32–0.62)	0.00 (0.00–0.20)	0.45 (0.38–0.52)
Working Memory (95% CI)	0.30 (0.02–0.45)	0.07 (0.00–0.31)	0.63 (0.55–0.72)
Executive Function (95% CI)	0.41 (0.22–0.49)	0.00 (0.00–0.15)	0.59 (0.51–0.68)
Short-Term Memory (95% CI)	0.58 (0.41–0.64)	0.00 (0.00–0.15)	0.42 (0.36–0.49)
Verbal Fluency (95% CI)	0.52 (0.41–0.59)	0.00 (0.00–0.08)	0.48 (0.41–0.56)
General Cognitive Ability	0.64 (0.55–0.77)	0.10 (0.00–0.27)	0.26 (0.22–0.31)

Cognitive variables are adjusted for age, BMI, and diabetes and cardiovascular disease

for any of the cognitive variables. Moreover, an omnibus test comparing the AE model to the full ACE model did not result in a significant reduction in model fit for any of the nine domains or for general cognitive ability (results available from author). Thus, subsequent genetic analyses testing for group differences included estimates of genetic (A) and non-shared environmental (E) influences, only.

When considering differences in genetic and environmental influences for all three groups independently, the unstandardized parameters for additive genetic and nonshared environmental influences could be equated among twins in the *non-hypertensive* and *medicated hypertensive* groups for all nine cognitive domains and for general cognitive ability (please see online supplement for details). In contrast, unstandardized parameters for additive genetic and nonshared environmental influences could not be equated between *unmedicated hypertensives* and *medicated hypertensives* or between *unmedicated hypertensives* and *non-hypertensives* for visual-spatial ability ($\chi^2 = 7.45$, df $= 2$, $p = 0.02$, for the comparison of unmedicated vs. medicated; $\chi^2 = 5.90$, df $= 2$, $p = 0.05$, for comparison of unmedicated and non-hypertensives) or for episodic memory ($\chi^2 = 9.35$, df $= 2$, $p = 0.01$ for the comparison of unmedicated vs. medicated; $\chi^2 = 9.32$, df $= 2$, $p = 0.01$ for comparison of unmedicated and non-hypertensives). In addition, unstandardized parameters for genetic and nonshared environmental influences could not be equated across the *unmedicated hypertensives* and the *medicated hypertensives* for abstract reasoning ($\chi^2 = 6.19$, df $= 2$, $p = 0.05$), although the unstandardized parameters for abstract reasoning could be equated between the *unmedicated hypertensives* and the *non-hypertensives* ($\chi^2 = 3.29$, df $= 2$, $p = 0.19$). Given evidence of significant differences between the unmedicated hypertensives with *both* the medicated hypertensives and the non-hypertensive groups, combined with the lack of differences between the medicated hypertensive and non-hypertensive groups, our final analyses therefore tested for differences between unmedicated hypertensives (UnMed) and the combined non-hypertensives and medicated hypertensives (Non/Med).

Table 4 presents the MZ and DZ twin correlations for each cognitive variable, separately for twins concordant for the Non/Med group, twins concordant for the UnMed group, and twins discordant for blood pressure group status, as well as the number of twin pairs in each group. MZ correlations were higher than DZ correlations in all instances, providing evidence for genetic influences on each cognitive domain for both the UnMed and Non/Med groups. Overall, MZ correlations were lower in twin pairs concordant for unmedicated hypertensive status and in discordant twin pairs as compared to twins concordant for non-hypertensive or medicated hypertensive status. In contrast, there was no clear pattern of DZ correlations across groups. Structural equation models equating the unstandardized genetic and nonshared environmental parameters between the Non/Med and UnMed groups were then compared to models in which the unstandardized parameters were allowed to vary across group in order to

Table 4 Twin correlations for cognition, by zygosity and blood pressure group

N twin pairs:	Twin pairs concordant for Non/Med group		Twin pairs concordant for UnMed group		Discordant twin pairs	
	r_{MZ} (95% CI) $N = 222$	r_{DZ} (95% CI) $N = 167$	r_{MZ} (95% CI) $N = 22$	r_{DZ} (95% CI) $N = 18$	r_{MZ} (95% CI) $N = 102$	r_{DZ} (95% CI) $N = 82$
Visual-Spatial Ability	0.75 (0.69–0.79)	0.37 (0.24–0.49)	0.55 (0.25–0.73)	0.46 (0.02–0.70)	0.63 (0.51–0.72)	0.31 (0.14–0.46)
Episodic Memory	0.61 (0.53–0.68)	0.30 (0.16–0.43)	0.38 (0.02–0.62)	0.23 (−0.15–0.53)	0.33 (0.13–0.48)	0.22 (0.02–0.39)
Abstract Reasoning	0.60 (0.50–0.67)	0.33 (0.20–0.45)	0.51 (0.17–0.71)	0.53 (0.18–0.73)	0.47 (0.30–0.60)	0.30 (0.11–0.46)
Processing Speed	0.60 (0.51–0.67)	0.25 (0.10–0.38)	0.50 (0.14–0.71)	0.29 (−0.10–0.98)	0.47 (0.30–0.59)	0.30 (0.11–0.46)
Short-Term Memory	0.58 (0.49–0.65)	0.31 (0.16–0.44)	0.59 (0.29–0.77)	−0.11 (−0.52–0.36)	0.60 (0.29–0.77)	0.19 (−0.02–0.37)
Working Memory	0.39 (0.28–0.49)	0.22 (0.07–0.36)	0.37 (0.06–0.59)	0.19 (−0.14–0.48)	0.33 (0.15–0.48)	0.25 (−0.04–0.47)
Verbal Ability	0.62 (0.54–0.69)	0.40 (0.27–0.51)	0.72 (0.42–0.84)	0.50 (0.11–0.72)	0.55 (0.40–0.67)	0.33 (0.14–0.50)
Executive Function	0.46 (0.35–0.55)	0.16 (0.01–0.30)	0.31 (−0.16–0.62)	0.14 (−0.24–0.47)	0.36 (0.18–0.50)	0.15 (−0.08–0.35)
Verbal Fluency	0.57 (0.47–0.64)	0.13 (−0.02–0.26)	0.48 (0.12–0.69)	0.28 (−0.23–0.62)	0.51 (0.35–0.63)	0.18 (−0.03–0.36)
General Cognitive Ability	0.76 (0.70–0.81)	0.42 (0.25–0.54)	0.79 (0.57–0.90)	0.68 (0.34–0.86)	0.67 (0.54–0.76)	0.34 (0.22–0.46)

Non/Med combined non-hypertensive and medicated hypertensive, *UnMed* unmedicated hypertensive, *MZ* monozygotic twin pairs, *DZ* dizygotic twin pairs, *95% CI* 95% confidence interval

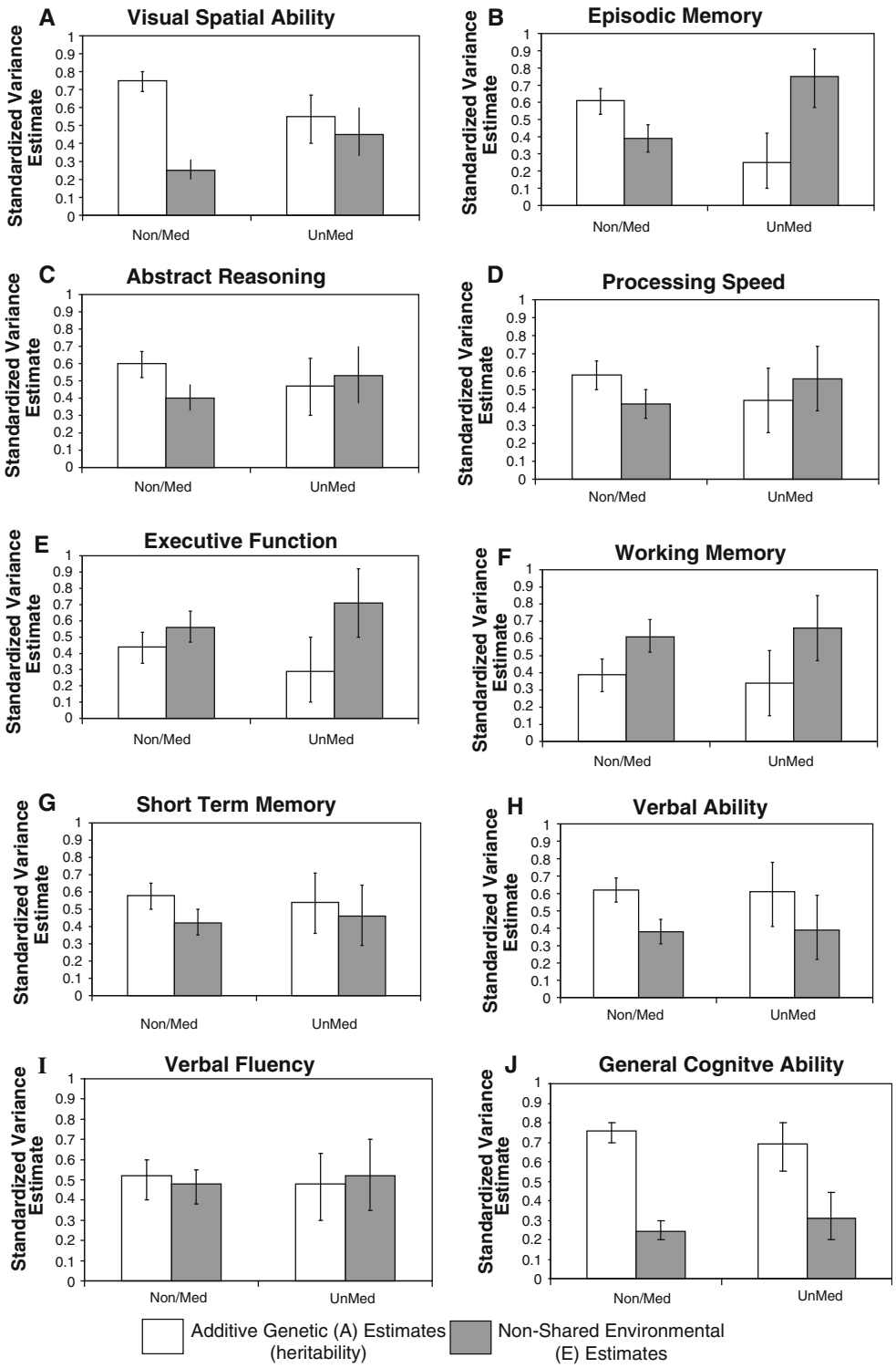

Fig. 1 Standardized genetic (*A*) and nonshared environmental (*E*) estimates for cognitive outcomes, by blood pressure group. *Non/Med* combined non-hypertensives and medicated hypertensive group, *UnMed* unmedicated hypertensives

formally test for group differences in genetic and environmental influences.

Figure 1 shows standardized estimates of genetic (i.e., heritability) and nonshared environmental estimates for the unmedicated hypertensives (UnMed) and the combined non-hypertensive and medicated hypertensives (Non/Med) for each of the nine cognitive domains and for general cognitive ability. Consistent with results from analysis with

all three groups independently, significant group differences in unstandardized parameter estimates between the UnMed and Non/Med groups were found for visual-spatial ability ($\chi^2 = 8.62$, df = 2, $p = 0.01$) and episodic memory ($\chi^2 = 11.23$, df = 2, $p = 0.004$). Figure 1a and b shows that heritability estimates for visual spatial ability and episodic memory were lower among the UnMed group compared to the Non/Med group. For visual spatial ability, heritabilities were $h^2 = 0.55$ (95% CI 0.40–0.67) for the UnMed group compared to $h^2 = 0.75$ [95% CI 0.69–0.80) for the Non/Med group. Heritabilities for episodic memory were $h^2 = 0.25$ (95% CI 0.10–0.42) for the UnMed group and $h^2 = 0.61$ (95% CI 0.53–0.68), for the Non/Med group.

While a similar pattern was observed for abstract reasoning (Fig. 1c), this trend only approached statistical significance ($\chi^2 = 5.40$, df = 2, $p = 0.07$), with $h^2 = 0.47$ (95% CI 0.30–0.63) for UnMed vs. $h^2 = 0.60$ (95% CI 0.52–0.67) for Non/Med. Heritability estimates also followed the same pattern for processing speed ($h^2 = 0.44$, UnMed vs. $h^2 = 0.58$, Non/Med; Fig. 1d) and executive function ($h^2 = 0.29$, UnMed vs. $h^2 = 0.44$, Non/Med; Fig. 1e), but differences were not statistically significant ($\chi^2 = 2.65$, df = 2, $p = 0.27$; $\chi^2 = 1.65$, df = 2, $p = 0.43$, respectively). Finally, heritability estimates were virtually identical across blood pressure groups (i.e., difference in $h^2 \leq 0.05$) for working memory ($h^2 = 0.34$, UnMed vs. $h^2 = 0.39$, Non/Med, Fig. 1f), short-term memory ($h^2 = 0.54$, UnMed vs. $h^2 = 0.58$, Non/Med, Fig. 1g), verbal ability ($h^2 = 0.61$, UnMed vs. $h^2 = 0.62$, Non/Med. Figure 1h), and verbal fluency ($h^2 = 0.48$, UnMed vs. $h^2 = 0.53$, Non/Med, Fig. 1i), with p-values > 0.30 for all χ^2 tests. For general cognitive ability (AFQT), heritability differences between the combined non-hypertensive/medicated hypertensive group and the unmedicated hypertensive group were also not significantly different ($h^2 = 0.69$, UnMed vs. $h^2 = 0.76$, Non/Med, $p = 0.65$, Fig. 1j).

Discussion

The primary goals of this study were to evaluate how hypertension influences both mean differences in cognition and genetic and environmental influences on individual differences in cognition at midlife, and to test whether antihypertensive medication alters the effect of hypertension on cognition. As part of the first wave of data collection in a longitudinal twin study of aging, this study focused on a specific phase of midlife (men in their 50s). Several notable findings resulted from our analysis. First, in this age cohort, no mean differences due to blood pressure group were detected in any of the nine cognitive domains or in our measure of general cognitive ability. Second, heritability was significantly lower in the unmedicated hypertensives as compared to the combined non-hypertensive and medicated hypertensive groups for visual-spatial ability and episodic memory. Finally, genetic and environmental influences on all cognitive measures did not differ between the non-hypertensive and medicated hypertensive groups.

Differences in mean cognitive levels

The present study did not find significant mean levels differences in any of the nine cognitive domains or in general cognitive ability among non-hypertensive, medicated hypertensive, or unmedicated hypertensive individuals. Our findings are in contrast with a handful of studies that have reported significant blood pressure-related differences in cognitive performance in middle age (Knecht et al. 2009; Singh-Manoux and Marmot 2005; Tsivgoulis et al. 2009). Lack of statistical power is unlikely to explain why we did not find significant group differences in mean levels of cognitive function. Post-hoc power calculations based on the current sample sizes revealed that we had 80% power to detect differences with minimum effect sizes between 0.16 and 0.19, which is below the threshold of $d = 0.20$ which is commonly used to designate a small effect (Cohen 1988). All of the mean level differences observed in our study had effect sizes <0.14. One important difference between the present study and prior research is that our sample was younger (mean = 55.4 years) and had a narrower age range (51–60) than previous studies. While the average age of participants in the Singh-Manoux and Marmot (2005) study was similar to ours (M = 55.5), their study included individuals aged 46–68 years old, which is a much broader age range compared with the present study. Knecht et al. (2009) also included a larger age range for midlife (44–65 years). Thus, hypertension-related cognitive performance differences may emerge as the individuals in our sample become older. In midlife, hypertensive individuals may be able to compensate and maintain performance equivalent to that of normotensives, but as they age they may reach a point where they can no longer compensate and cognitive deficits would begin to emerge. Thus, our more homogeneous sample may have captured the point in middle age just prior to the time when mean cognitive performance differences that are associated with hypertension begin to surface. Follow-up assessments that are currently underway will be able to address this issue.

Prior research in other samples has also shown the education may be associated with incident hypertension and antihypertensive medication use and adherence (Vargas et al. 2000; Lowry et al. 2005). In our sample, however, we

found that there were no significant mean differences in years of education or prior general cognitive ability across blood pressure groups. Furthermore, neither prior cognitive ability at age 20 nor education predicted either clinical diagnosis of hypertension at midlife or antihypertensive medication use at midlife. We note that while other studies have reported associations between education and hypertension in other samples, there is evidence that this relationship may attenuate with age. Specifically, Vargas et al. (2000) found that the relative risk of incident hypertension in people with less than 12 years of education was significantly higher than that of individuals with more than 12 years of education for individuals aged 25–44 years, but there were no significant differences in relative risk of incident hypertension due to education level in individuals aged 45–64 years. This may explain why the present study, which was based on a sample of men aged 51–60, did not find associations between education and general cognitive ability with hypertension or medication use.

Differences in heritability across blood pressure groups

Even though group mean performance levels did not differ across blood pressure groups, our results indicate that the mechanisms underlying cognitive function, i.e., genetic and environmental influences on the individual difference in cognition, differed between unmedicated hypertensives and both non-hypertensives and medicated hypertensives. To the best of our knowledge, this is the first study to explicitly examine the moderating effects of hypertension and its treatment on the latent genetic and environmental influences on individual differences in cognition using twin methodology. Our findings reveal that genetic factors have a significantly weaker impact on cognitive function in the untreated hypertensive group, but only for visual-spatial ability and episodic memory. Interestingly, this pattern of results for different cognitive functions parallel findings of mean-level differences found in prior research in age-related disorders. For example, visual-spatial ability and episodic memory, as well as reasoning, are considered some of the most age-sensitive cognitive abilities (Verhaeghan 2011). Moreover, visual-spatial ability and episodic memory are some of the first cognitive processes impacted by neurodegenerative disorders such as Alzheimer's disease and dementia (Johnson et al. 2009; Lindeboom and Weinstein 2004), and hypertension has been shown to be a risk factor for these disorders (Stampfer 2006). In addition, according to a recent meta-analysis, domains of memory were most commonly influenced by hypertension (median effect size = 0.4), with smaller effects of hypertension on measures of processing speed (median effect size = 0.2) (van den Berg et al. 2009), which directly relates to results of the current study. Median effect sizes from this meta-analysis for the effects of hypertension on executive function, verbal fluency, and abstract reasoning were 0.1, and virtually no study found effects of hypertension on verbal ability. Our findings partially correspond to this meta-analysis in that the heritabilities of episodic memory and visual-spatial ability were most affected by hypertension status, with a smaller, albeit non-significant effect ($p = 0.07$) for abstract reasoning, and no effect on verbal ability. Our findings that hypertension modifies the genetic influences of these domains *prior to observed differences in levels of cognitive performance* suggests that hypertension already begins to impact these cognitive process at midlife and that these differences in genetic influences may be a precursor to later-life cognitive deficits.

The hypothesis that alterations in genetic influences may precede observed differences in performance has been supported by research in animals. Using a sample of young, middle-aged and old-aged rats, Blalock et al. (2003) demonstrated that, while declines in cognitive performance (as measured by two memory tasks) were only evident in old-aged rats, differences in gene expression profiles associated with aging and cognitive decline could be detected in middle-aged rats, even though these middle-age rats performed no worse on cognitive tasks than their younger counterparts (Blalock et al. 2003). While our study did not explicitly measure gene expression, the findings from Blalock et al. (2003) support our results that differences in the genetic influences on cognition can emerge prior to observed cognitive performance differences. There is also biological plausibility to the hypothesis that hypertension may disrupt genetic influences underlying cognition. Several biological pathways are influenced by hypertension; for example, hypertension is associated with changes in brain structure and vasculature, such as increases in white matter lesions and dysregulated cerebral blood flow (Firbank et al. 2007; Liao et al. 1996). Both increased white matter lesions and dysregulated cerebral blood flow are associated with cognitive deficits (de Groot et al. 2000; Kitagawa et al. 2009).

The present study also adds to our growing understanding that genetic influences on cognitive development are dynamic, and that environmental, physiological, and lifestyle factors all have the capacity to modify genetic influence on cognition and cognitive-related factors. A number of behavioral genetic studies have demonstrated that the heritability of cognition can vary based on different environmental exposures. For example, several studies have demonstrated that the heritability of cognitive function is reduced, indicating that genetic factors have substantially lower impact on cognitive abilities, in children and adolescents from lower socioeconomic backgrounds compared to those from higher socioeconomic strata (Rowe et al. 1999; Turkheimer et al. 2003; Harden et al.

2007; Friend et al. 2009). It has been hypothesized that the lower heritability of cognitive ability in children from poorer socioeconomic environments reflects the fact that these environments are not "good enough" to reveal underlying differences due to genetic factors (Scarr 1992). As such, we could view unmedicated hypertension as a poor "internal environment" that suppresses underlying genetic potential. Therefore, our findings further confirm hypotheses posed by both Bronfenbrenner and Ceci (1994) and Scarr (1992), proposing that the heritability of a trait would be higher in more favorable environmental conditions (Bronfenbrenner and Ceci 1994; Scarr 1992).

Likewise, our results are also consistent with a growing number of molecular genetic studies using measured genotypes that have found evidence for gene X environment interaction in studies of brain structure, cognitive decline, dementia, and Alzheimer's disease. For example, the effect of the APOE genotype has been shown to be modified by hormonal factors, such as testosterone levels (Panizzon et al. 2010; Yaffe et al. 2000), diabetes and other cardiovascular conditions (Haan et al. 1999), lifestyle factors, such as use of alcohol and tobacco (Dufouil et al. 2000), and psychosocial factors, including depression, stress, and life events (Reynolds et al. 2007). In a prospective study of a large cohort of Japanese-American men in the Honolulu-Asian Aging Study, men with *both* the APOE e4 genotype *and untreated* high systolic blood pressure showed the highest rates of cognitive impairment (OR = 10.8–13.0), while men with the e4 variant but without elevated blood pressure did not show elevated risk (Peila et al. 2001). This interaction between the APOE genotype and blood pressure was replicated in a separate longitudinal study of Swedish men (Qiu et al. 2003). Thus, along with our current findings that untreated hypertension decreases the heritability of cognition, evidence from both prior behavior genetic and molecular genetic studies support the hypothesis that environmental, physiological and lifestyles factors all can influence genetic factors underlying cognitive function.

Effects of antihypertensive medication

In the present study, we found that heritability estimates were not significantly lower in medicated hypertensives as compared to non-hypertensives, indicating that medication may normalize, prevent, or delay the disrupted genetic influences found among untreated hypertensives. Antihypertensive medication use has been shown to decrease the risk for white matter lesion formation (Liao et al. 1996; Semplicini et al. 2000), normalize cerebral blood flow (Zhang et al. 2006), and reduce cognitive deficits (Haag et al. 2009; Muldoon et al. 2002; Murray et al. 2002). Our findings further suggest that the effect of antihypertensive medication may operate via alterations in the influence of genes that determine cognitive function. This is consistent with results from molecular genetic studies that have found that the interaction between APOE and blood pressure on cognitive decline and dementia does not appear among men treated for hypertension (Peila et al. 2001; Qiu et al. 2003). In terms of the theories of Bronfenbrenner and Ceci (1994) and of Scarr (1992), medication use may "normalize" an individual's internal environment, returning it to a more favorable state, thus providing an optimal environment for the expression of genetic potential.

Limitations

While reviewing our findings, some limitations must be considered. First, we acknowledge that we did not apply any correction for multiple comparisons given our *a prior* hypotheses that the effects of hypertension would be domain-specific. However, if we applied the Benjamini–Hochberg–Yekutieli procedure, the *p*-values for tests of the heritability differences in episodic memory and visual-spatial ability would remain statistically significant. Next, it is possible that violations of standard underlying assumptions of twin modeling may have influenced these results. For example, we assumed that the latent genetic and environmental influences were orthogonal in each of the blood pressure groups. Likewise, because there were no phenotypic relationships between blood pressure or medication status with mean levels of cognition in this sample, we did not use a bivariate model to control for potential gene → environment correlation. While the purpose of our study was to examine specifically whether the heritability of cognition varied as a function of hypertension and medication use, there are other factors related to other forms of gene × environment interaction that have might influenced results. For example, as discussed above, heritability of cognitive measures is often higher among adolescents and adults from more educated families (Rowe et al. 1999; Kremen et al. 2005; Turkheimer et al. 2003; Grant et al. 2010). We note, however, that there were no differences in prior general cognitive ability (i.e., AFQT at age 20), twins' own education levels, *or* parental education levels across the three blood pressure groups. Thus, the pattern of lower heritabilities found in the unmedicated hypertensive group cannot be explained by group differences in educational or socioeconomic factors. Finally, we were unable to examine how violations of the equal environments assumption would have biased these results. Twins who were treated more similarly in childhood and/or who have greater contact as adults may be more similar in medication use, which could have increased heritabilities in *either* the medicated *or* the unmedicated hypertension groups. However, it is not clear why there would be lower

heritability only among the unmedicated hypertensive group, nor could this explain why the differences in heritability were found only in a subset of the cognitive domains. Nevertheless, we are currently collecting data on twin contact in our second wave of VETSA, so will be able to examine these questions more directly in the future.

Second, our results may not generalize to all individuals. Because there were too few women enlisted in the military at the time the VET Registry was created, the present study was comprised of all male participants, so our results may not generalize women. Similarly, VETSA participants are mostly non-Hispanic Caucasians, so our results may not generalize to other ethnicities. While a strength of this study is that our sample consists of participants within a fairly narrow age range, we do note that there were modest age differences across our three blood pressure groups. However, as our cognitive variables were adjusted for age, it is unlikely that age range could have biased our results. Nevertheless, the question of whether untreated hypertension can suppress genetic influence in either younger or older samples has yet to be explored.

Third, our classification of individuals into the three blood pressure groups may be imperfect. For example, the medicated hypertensive group included some individuals whose blood pressure levels were still in the hypertensive range, indicating that their blood pressure was not optimally controlled by the medication. To determine whether the heterogeneity of this group may have biased our results, we conducted follow-up analyses (available from author) that removed individuals who were on medication yet still had hypertension ($N = 184$, 43% of the medicated hypertensive group). Even with this reduced sample size, we were still able to detect the same patterns of differences in heritability that were found using the full sample, so the inclusion of medicated individuals who are still hypertensive did not substantively affect our findings. Additionally, our classification of hypertension was based on a single day of blood pressure readings (although we did obtain multiple readings throughout the day) and/or use of antihypertensive medication and not on observed long-term presence of elevated blood pressure. This could have increased the error in our classification of unmedicated hypertensives and non-hypertensives, which is likely to have attenuated the differences between these groups. It is also possible that there may be other variables that we have not considered (e.g., certain personality characteristics) that could be related to whether middle-aged men see their doctors and/or to compliance with medication use. However, we did examine most of the relevant cognitive, demographic and health-related characteristics that have been related to hypertension and/or medication use in prior studies (e.g., Knecht et al. 2009), and have controlled for any significant differences (i.e., differences in age, BMI, diabetes, and other cardiovascular disease) in our analyses. Finally, our analyses used a categorical measure of hypertension rather than a continuous blood pressure measure. While systolic or diastolic blood pressure levels also did not correlate with cognitive scores in the present sample, continuous blood pressure measures may have had more power to detect moderation effects on the underlying genetic and environmental architecture of cognition. However, the use of continuous measures of blood pressure in our genetic analyses would not have allowed us to readily examine *interactions between* hypertension and medication use. Our multiple group approach, which allowed us to neatly differentiate between hypertensive individuals being treated with medication from untreated hypertensives, therefore offered the most direct test of our research questions. Because ethical considerations prohibit random assignment to medicated vs. unmedicated groups for hypertension, it is exceedingly difficult to tease apart treatment and disease severity effects. However, our novel use of the twin design enabled us to discern a difference in the importance of genetic factors underlying cognition in medicated and unmedicated hypertensive groups, even in the absence of performance differences.

Conclusions

The present study is the first to demonstrate hypertension-related differences in the heritability of cognition. This suggests that hypertension has the capacity to alter normal genetic function on cognition, prior to observed differences in cognitive performance, and that use of antihypertensive medication may protect against or reverse these effects. Thus, studies seeking to identify specific genes associated with cognitive decline, dementia, and Alzheimer's disease should consider the effects of hypertension and hypertension treatment in their analysis. Moreover, future studies of cognition-related gene expression can begin to identify the specific genes that are affected by untreated hypertension, and can explore how antihypertensive medication may reverse these effects. These strategies could lead to enhanced, or more targeted treatment of hypertension-related cognitive decline.

Our results demonstrating that health-related characteristics can influence the importance of genetic factors on cognition in middle age add to an existing body of research using twin models indicating that the importance of genetic factors on individual differences in cognition can vary among individuals in different ecological contexts. In addition, our results complement extant animal studies of aging suggesting that differences in the underlying genetic architecture of cognition can appear prior to the emergence of differences in cognitive performance. Finally, our study

shows that the differences in heritability occur first among cognitive domains most strongly related to hypertension, which also show some of the first age-related declines. As such, our study makes an important and unique contribution to current research on the interplay between hypertension and genetic factors on cognitive aging.

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Conflicts of interest None.

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