Published in final edited form as:

Biol Psychol. 2009 February ; 80(2): 240–245. doi:10.1016/j.biopsycho.2008.10.003.

Synergistic Effects of the *MTHFR* C677T Polymorphism and Hypertension on Spatial Navigation

Awantika Deshmukh^{a,b}, Karen M. Rodrigue^a, Kristen M. Kennedy^a, Susan Land^c, Bradley S. Jacobs^d, and Naftali Raz^{a,b,*}

^a Institute of Gerontology, Wayne State University, Detroit, MI

^b Department of Psychology, Wayne State University, Detroit, MI

^c Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI

^d Division of Neurology, Department of Internal Medicine, Wright State University, Dayton, OH

Abstract

Navigation skills deteriorate with age, but the mechanisms of the decline are poorly understood. Part of the decrement may be due to age-related vascular risk factors. The T allele in a C677T variant in methylenetetrahydrofolate reductase (*MTHFR*) gene is associated with elevated plasma homocysteine, which is detrimental to vascular integrity and has been linked to cognitive decline. We inquired if a combination of physiological (hypertension) and genetic (*MTHFR* 677T) vascular risks has a synergistic negative impact on cognitive performance in otherwise healthy adults. We tested 160 participants (18–80 years old) on a virtual water maze. Advanced age, female sex, and hypertension were associated with poorer performance. However, hypertensive carriers of the T allele performed significantly worse than the rest of the participants at all ages. These findings indicate that hypertension combined with a genetic vascular risk factor may significantly increase risk for cognitive impairment.

Keywords

aging; cognition; hypertension; vascular risk; single nucleotide polymorphism; homocysteine; genetic association; virtual water maze

The ability to navigate in one's environment, an important component of everyday cognition, declines with age. Studies in rodents (Barnes, 1979; Ingram, 1988) and humans (Moffat, Zonderman, & Resnick, 2001; Moffat, Kennedy, Rodrigue, & Raz, 2007; Moffat, & Resnick 2002; Moffat, Elkins, & Resnick, 2006) reveal age-related deficits in navigation and way-finding ability in a wide variety of real and virtual environments. As a rule, when compared to their younger counterparts, older adults take longer time and travel a greater distance to reach the targeted destination (Moffat et al., 2001; Moffat, & Resnick 2002; Driscoll et al., 2003; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005).

Spatial navigation is a complex skill. Tasks that assess navigational ability have multiple perceptual, mnemonic, and executive components and rely on a broad network of cortical and subcortical circuits and structures. However, executive dysfunction may play a critical role in age-related impairment, which is related to reduced prefrontal volumes in older adults

*Corresponding author: Institute of Gerontology, Wayne State University, Detroit, MI 48202, e-mail E-mail: nrnz@wayne.edu, fax 1-508-256-5689, telephone 1-313-577-2297.

compared to their younger peers (Moffat et al., 2007) as well as in persons with dementia compared to healthy elderly (deIpoli et al., 2007). Hypertension, a vascular risk factor that is especially detrimental to executive functions (Apter et al., 1951; Raz, Rodrigue, & Acker, 2003) also contributes to less than optimal navigational performance (Moffat et al., 2007).

Physiological indicators of vascular health, such as blood pressure, are negatively affected by age and are influenced by many aspects of an individual's life history (Pinto, 2007 for a review). The increasing burden of vascular risk and vascular disease accelerate aging of the brain and have a significant negative impact on brain structures associated with navigational skills, such as prefrontal gray and white matter (Raz et al., 2003, 2005) and hippocampus (Wiseman et al., 2004; Raz et al., 2005). Age-related increase in physiological vascular risk factors and the prevalence of overt vascular disease play an important role in modifying cognitive performance of middle-aged and older adults (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Elias et al., 1997; Waldstein et al., 1996, 2008). Environmentally modifiable blood markers of vascular risk, such as plasma homocysteine (Hcy) levels, have been linked to pathological changes in the brain (Censori, Partziguian, Manara, & Poloni, 2007; Seshadri et al., 2008) as well as declines in age-sensitive cognitive abilities such as processing speed (Prins et al., 2002; Aleman, Muller, de Haan, & van der Schouw, 2005), attention (Dufouil, Alperovitch, Ducros, & Tzourio, 2003), and episodic memory (Prins et al., 2002). Thus, to understand age related declines in navigational skills, one needs to take into account the influence of vascular risk factors.

Although the effects of environment and life-style on vascular risk factors are substantial, a significant proportion of variance in vascular risk is under genetic control. For example, circulating plasma levels of Hcy are affected by a gene that controls activity of methylenetetrahydrofolate reductase (MTHFR). That enzyme catalyzes the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is needed to convert Hcy to methionine. The MTHFR gene has a common mis-sense polymorphism, in which a cytosine is changed to a thymine at nucleotide 677 and as a result the amino acid sequence is changed from valine to alanine. The T allele of that polymorphism produces a thermolabile variant of MTHFR enzyme resulting in reduced MTHFR activity and subsequent higher blood concentrations of Hcy. Thus, plasma Hcy concentration is positively related to the T allele dose in MTHFR C677T genotype (Frosst, et al., 1995, Andreassi et al., 2003; Ilhan, Kucuk, Kaman, Ilhan, & Ozbay, 2008). In fact, MTHFR C677T provides a "Mendelian randomization" (Lawlor, Harbord, Sterne, Timpson, & Davey Smith, 2007) of Hcy levels, which may assist in evaluating the effect of that vascular risk factor on cognition independent of physiological, nutritional and lifestyle variables. Moreover, it enables examination of the interaction between environmental and genetic risks, and it is possible that in healthy adults, the effects of such interactions on cognitive performance may prove more important than the influence of genetic variants alone (de Frias et al., 2007; Raz, Dahle, Rodrigue, Kennedy, Land, & Jacobs, 2008; Raz, Rodrigue, Kennedy, & Land, in press).

Although MTHFR has been identified as a viable candidate gene for explaining a significant part of age-related differences in cognition (see Mattay, Goldberg, Sambataro, & Weinberger, 2008 for a review), thus far only a handful of investigations have assessed its effects in nondemented adults. The results of those investigations are inconclusive. A large population-based study of Caucasian women reported a decline in executive functions and processing speed for T homozygotes (Elkins et al., 2007). On the other hand, several negative results have been reported (Almeida et al., 2005; Bathum et al., 2007; Visscher et al., 2003; Ravaglia et al., 2004; Gussekloo et al., 1999). Moreover, in one sample, the opposite effect was observed, with MTHFR 677T homozygotes performing better on multiple cognitive tests than C carriers (Durga et al., 2006).

The observed discrepancy in findings is likely to reflect differences in two aspects of design: sample selection criteria and measures of cognitive attainment. All studies that reported lack of cognitive differences attributable to MTHFR C677T genotype (Gussekloo et al., 1999; Visscher et al., 2003; Ravaglia et al., 2004; Almeida et al., 2005; Bathum et al., 2007) were limited to old and very old adults, with the mean age of the sample ranging from seventies to nineties. The sample in which T homozygotes showed cognitive advantage (Durga et al., 2006) was biased by exclusion of persons with Hcy levels above 13 $\mu\text{mol/L}$, thus possibly selecting only those with TT genotype who might have compensated for its detrimental effects. Most studies (except for Almeida et al., 2005) employed cognitive measures that were either crude screening indices (e.g., Mini-Mental State Examination, MMSE) or tests of global cognitive performance with predominantly verbal items (Visscher et al., 2003). Such global indices of cognition may be insensitive to the hypothesized effects as the MTHFR C677T polymorphism may affect only aspects of cognition with a significant executive component known to be sensitive to other vascular risk factors such as hypertension (Raz, Rodrigue, & Acker 2003; Korf, White, Scheltens, & Launer, 2004; Wiseman et al., 2004). If this is the case, employing tasks that rely heavily on executive control would maximize the observed genotype-related differences. Notably, none of the studies evaluated the interaction between MTHFR genotype and common vascular risk factors such as hypertension and none examined the effects of MTHFR C677T in a context of life-span age range.

The objective of this study was to evaluate the effects of vascular risk, genetic and physiological, on age differences in navigational performance, while paying attention to the problematic areas outlined above. We examined the effect of MTHFR C677T polymorphism on a cognitive task with known sensitivity to aging and to vascular risk in a sample of healthy adults spanning a wide age range. We hypothesized that presence of the MTHFR T allele, which is associated with life-time exposure to elevated Hcy blood levels, would compromise navigation performance, that the effect would be stronger in older persons due to longer exposure to the adverse influence of Hcy, and that the detrimental impact of the T allele would be exacerbated by the presence of another vascular risk – hypertension.

2. Methods

2.1 Participants

The sample was part of a larger ongoing study of neural correlates of cognitive aging. Participants were residents of a major Midwestern metropolitan area in the United States and all lived independently. Individuals who reported a history of cardiovascular (except treated essential hypertension), neurological, or psychiatric illness, diabetes, head trauma with a loss of consciousness for more than 5 min, thyroid problems, treatment for drug and alcohol problems, or a habit of taking three or more alcoholic drinks per day were excluded from the study, as were participants who use anti-seizure medication, anxiolytics, or antidepressants. Only persons who scored below 16 on the geriatric depression questionnaire CES-D (Radloff, 1977) and above 25 on the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975) were admitted. All participants were strongly right-handed as indicated by the Edinburgh Handedness Questionnaire (75% and above; Oldfield, 1971); left-handers were excluded from this study. Participants were classified as hypertensive if they had a diagnosis of hypertension, were taking antihypertensive medications, or if their blood pressure averaged over three to four testing sessions exceeded 140 mm Hg (systolic) or 90 mm Hg (diastolic).

One-hundred and sixty Caucasian participants who had a full set of navigation task data and met the health screening criteria were included in the study. Approximately 29% of our participants were part of a previous study conducted in our laboratory (Moffat et al., 2007) and 99% of the participants took part in another study on genetics and cognition (Raz, Rodrigue, Kennedy, & Land, in press). The sample (age range from 18–80 years, 106 women and 54

men) contained 42 persons classified as hypertensive according to the above listed criteria. Only 7% of the participants smoked tobacco (21–27% expected in the general population) and 81% reported exercising regularly (31% expected in the general population, American Heart Association, 2004).

The men and women did not differ in age ($t = -0.75$, n.s.) or education ($t = -1.58$, n.s.); women had higher MMSE ($t = 2.25$, $p < 0.05$); men had higher systolic ($t = -2.48$, $p = 0.01$), and diastolic blood pressure ($t = -3.01$, $p < 0.01$). For demographic information see Table 1.

2.2 Procedure

2.21 Blood pressure measures—Blood pressure was measured on three or four separate days at the start of each cognitive test session by a mercury sphygmomanometer (BMS 12–S25) with a standard blood pressure cuff (Omron Professional) on the left arm with participants seated, and their forearm positioned on the table. Trained laboratory technicians conducted the measurements. The systolic and diastolic means across the measurement occasions were computed for each individual.

2.22 Spatial Navigation Task (Virtual Morris Water Maze)—All participants completed a Virtual Morris Water Maze (vMWM) task developed and validated by Moffat and Resnick (2002). The initial step was to familiarize participants with the environment to ensure they were comfortable with the computer-administered task and could execute sufficient control over the joystick. The practice water maze environment was a circular pool surrounded by several cues that served as navigation guides. Hidden beneath the surface of the pool was a platform, and the participants were instructed to locate the platform as quickly as possible via the use of external objects and cues. When participants passed over the platform, the platform became visible, and an audio signal signified that the platform was correctly located. Participants were informed that the platform remained in the same location on each trial and that they should try to remember its location. On the six experimental learning trials, participants were virtually “placed” at random into one of the three quadrants of the pool not containing the platform and faced in a different direction on each trial. The primary dependent measure was the distance traveled between the starting point and the platform on each trial.

2.221 Control Tests: Pretest training and assessment of joystick visuomotor control: Prior to performing the actual water maze task, the participants were familiarized with the virtual environment (VE) via the use of a joystick for their “movement.” The experimenter read the instructions, and allowed a period of free exploration of the VE (not the virtual pool). The first virtual environment consisted of two rectangular rooms adjoined by a corridor which the participants explored freely to become comfortable with the joystick and movement within the environment. The second environment contained an arena with platforms and the participants were guided to each platform. After participants were comfortable with the joystick and had satisfactorily demonstrated their ability to guide themselves to targets designated by the experimenter, the participants underwent a joystick control speed test. During the speed test, participants were required to navigate a long winding corridor as quickly and accurately as possible until they reached an image of a trophy at the goal point. Participants were required to demonstrate their competency with the joystick by completing the corridor in less than 120 seconds.

2.222 Visible platform performance: As a further experimental control for age-related differences in perceptual-motor speed, on the first trial the participants performed the navigation task with a visible platform. Subjects were instructed to move onto the platform from the starting location as quickly as possible. The magnitude of any age differences observed on this task should be considerably smaller than those observed in the vMWM trials.

2.23 MTHFR C677T Genotyping—DNA was isolated from buccal samples obtained in mouthwash. Isolation was performed using a Gentra Autopure LS with the standard buccal cell protocol. For genotyping quality control, 37% direct repeats and DNA sequencing for verification were performed. Both control DNA and no-template controls were used. The MTHFR C677T polymorphism (rs1801133) was interrogated with the 5'-nuclease assay using a TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA). The assays were run using an Applied Biosystems 7900. Genotyping revealed that 64 participants were heterozygous (CT), 22 were homozygous for the T allele (TT) and 74 were homozygous for the C allele (CC). The distribution of the alleles conformed to the Hardy-Weinberg equilibrium: $\chi^2 = 1.78, p < 0.18$. Because cross-section of the T homozygote group with sex and hypertension groupings created cells that were too small for valid analyses, the CT group was identified as T carriers and contrasted to C homozygotes. Thus, the two compared genetic variants were MTHFR T+ and MTHFR T- (i.e., carriers of the 677T allele and C homozygotes).

Success rate of genotyping at the first run was 96.25%. However, after direct repeat quality control runs with at least four successful identifications required for a call, only one sample showed an allele dropout (99.38%). After direct repeat analyses were performed seven times, the sample was genotyped with an estimated error of 0.33%. Thus the final genotyping success rate for this study was 100%. There was no association between MTHFR C677T genotype and age ($F(2, 157) = 2.54, p = .08$), sex ($\chi^2(2) = .59, ns$), or hypertension status ($\chi^2(2) = 1.25, ns$).

2.3 Data Analysis

Data were examined for inhomogeneity of variance and outliers. The distribution of distance traveled on each of the six trials was highly skewed and a natural log transformation was applied. The transformed distance traveled served as a dependent variable in a general linear model, with repeated measures across trials. Age (centered at its sample mean) was a continuous predictor, and MTHFR allele presence (T+ vs. T-), hypertension diagnosis, and sex were binary between-group variables. To conserve degrees of freedom, in addition to the main effects only second order interactions among the independent variables were tested. Interaction terms with significance levels of $p > .15$ were removed from the analyses and the reduced model was tested. The linear regressions for individual trials revealed four outliers for trial 1. However, the removal of the outliers did not change the results therefore these values were retained in the sample.

3.0 Results

In the general linear model, all interactions with age as well as sex $\times$ MTHFR T allele interactions were not significant (all $F < 1.50, p \geq .24$) and therefore were removed from the model. The reduced model revealed a significant main effect of age ($F(1, 153) = 18.42, p < .001, \eta^2 = .10$) indicating that older age was associated with longer distances traveled in search of the platform ($\beta = .38$). A significant main effect of hypertension favoring normotensives was also observed ($F(1, 153) = 5.69, p = .02, \eta^2 = .03$). No main effects of sex or MTHFR T allele were found in the model (both $F < 2.11, n.s.$). A significant within-group main effect of trial reflected improvement in performance across trials: $F(5, 765) = 8.53, p < .001, \eta^2 = .05$; displayed in Figure 1. A spike on trial four was due to the random “placement” of the participant at the start of the experiment. In trial four the participant is “farthest” away from the platform and consequently had to travel the longest distance to reach the platform. The linear component of trial effect was significant ($F(1, 153) = 28.85, p < .001$), as was the fifth order polynomial component ($F(1, 153) = 8.93, p = .003$).

The main effects were qualified by two significant interactions: MTHFR T allele $\times$ hypertension ($F(1, 153) = 5.45, p = .02, \eta^2 = .03$; see Figure 2) and sex $\times$ hypertension ($F(1, 153) = 4.32, p = .04, \eta^2 = .02$ see Figure 3). Specifically, hypertensive T carriers traveled longer

distances to reach the platform than hypertensive C homozygotes, Bonferroni difference test = $-.37$, $p < .001$. In the normotensive group, a non-significant trend (Bonferroni difference = $.17$, $p = .08$) was observed as MTHFR 677T carriers tended to take a shorter route to find the platform than did C homozygotes. The significant hypertension $\times$ sex interaction showed that within the normotensive group, men found the platform after a shorter travel ($M = 3.42$) than women ($M = 3.67$). In the hypertensive group, no significant sex differences were observed ($F < 1$). Although we had a sufficient number of subjects to test only the hypotheses regarding the effect of MTHFR 677T allele, for illustration purpose only, we present the results for all three allelic groups in Figure 4.

3.0 Discussion

The main finding in this study is that the impact of a genetic vascular risk factor on cognitive performance is apparent only in conjunction with physiological risk. Carriers of the high-risk T allele of MTHFR C677T polymorphism who escaped hypertension showed no deficits in spatial navigation despite presumably higher Hcy levels. The negative effect of hypertension on navigational skills replicates previous findings (Moffat et al., 2007). In addition, this study has replicated prior reports of poorer navigational performance in older adults (Moffat et al., 2001; Moffat and Resnick, 2002; Driscoll et al., 2005; Moffat et al., 2007) and sex differences in navigational ability (Driscoll et al., 2005; Lövdén et al., 2007). The influence of genetic and physiological vascular risk factors was independent of age, whereas sex differences were affected by hypertension: unlike normotensive men, their hypertensive peers did not perform better than women. Improvement across trials was observed regardless of age, sex, or vascular risk.

It is important to note that no main effect of MTHFR C677T genotype was observed. That finding replicates previous reports (Almeida et al., 2005; Bathum et al., 2007; Visscher et al., 2003; Ravaglia et al., 2004; Gussekloo et al., 1999) and in conjunction with the observed interaction effect between the “risky” genotype and hypertension, it underscores the importance of focusing on a more nuanced view of vascular risks and cognitive aging than espoused in the reviewed studies. The results of this study argue that elevated blood levels of homocysteine in MTHFR 677T carriers may be a risk factor only in synergy with other influences that are detrimental to the cerebrovascular system and as a consequence, to cognitive performance. On the other hand, MTHFR 677C homozygotes may be able to “afford” higher levels of vascular risk than the T allele carriers without incurring negative cognitive effects. Studies in different populations show that maintaining normal levels of homocysteine was significantly more difficult for T homozygotes than for carriers of other MTHFR C677T genotypes (Huh, Chi, Shim, Jang, & Park, 2006; Durga et al., 2006). The implication of the observed synergistic effect for possible cognitive rehabilitation strategies is that persons with MTHFR 677T allele and existing hypertension may need more aggressive intervention to produce the gains predicted for C homozygotes.

Past studies have also shown that not only older adults evidence impairment in way-finding tasks but they also avoid unfamiliar routes (Burns, 1999; Sixsmith & Sixsmith, 1993). Such strategy can be maladaptive in a rapidly changing world and may exert especially strong negative influence on driving (Burns, 1999; Ott et al., 2008); it imposes significant limitations on autonomy of older adults, thereby limiting their quality of life. Thus, designing rehabilitation strategies that may help to alleviate age-related way-finding deficits should become a high priority. The results of this study suggest, however, that such interventions may need to consider individual genetic predisposition to experiencing greater declines if they happen to suffer from such a common age-related condition as hypertension. All those deficits are observed in addition to the previously reported age-related declines. On a positive note, we

may mention that persons with the same vascular risk genotype show no additional deficits in navigation if they manage to avoid developing hypertension.

The results of this study should be interpreted in the context of its limitations. First, we evaluated well educated, healthy Caucasian volunteers who were free of cardiovascular and metabolic conditions that frequently accompany typical aging. Second, the cross-sectional design allows only an estimate of age-related changes in navigation performance and a longitudinal study is necessary to assess the influence of the examined vascular risk factors on such change. Third, in a typical sample of convenience, selection biases may be at play as vascular risks carried by the participants might be offset by unmeasured factors thus attenuating the effect of measured variables. It must be noted that although the impact of individual genetic variants and their interaction with vascular factors is relatively small (less than 3% of the total variance) it is comparable to the effects of vascular factors and, in this highly selected sample, to the effect of calendar age (under 10%). Finally, as all genetic association studies, this one is at risk of producing false positive results and needs to be replicated on several independent samples.

In summary, we conclude that although genetic elevation of vascular risk alone is not sufficient to compromise execution of a complex cognitive skill, it exerts a significant detrimental effect in the presence of a physiological risk factor – hypertension. Because many physiological risks can be greatly reduced by behavioral and pharmacological interventions, it may be beneficial to provide carriers of the genetic risk factors with early diagnosis and intervention.

Acknowledgments

This study was supported in part by NIH grant R37-AG11230.

References

- Aleman A, Muller M, de Haan EH, van der Schouw YT. Vascular risk factors and cognitive function in a sample of independently living men. *Neurobiology of Aging* 2005;4:485–490. [PubMed: 15653177]
- Almeida OP, Flicker L, Lautenschlager NT, Leedman P, Vasikaran S, van Bockxmeer FM. Contribution of the MTHFR gene to the causal pathway for depression, anxiety and cognitive impairment in later life. *Neurobiology of Aging* 2005;26:251–257. [PubMed: 15582752]
- American Heart Association . Heart Disease and Stroke Statistics 2005 Update. Dallas, TX: American Heart Association;
- Andreassi MG, Botto N, Cocci F, Battaglia D, Antonioli E, Masetti S, et al. Methylenetetrahydrofolate reductase gene C677T polymorphism, homocysteine, vitamin B12, and DNA damage in coronary artery disease. *Human Genetics* 2003;112:171–177. [PubMed: 12522558]
- Apter NS, Halstead WC, Heimbürger RF. Impaired cerebral functions in essential hypertension. *American Journal of Psychiatry* 1951;107:808–813. [PubMed: 14829603]
- Barnes CA. Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. *Journal of Comparative Physiology & Psychology* 1979;93:74–104.
- Bathum L, von Bornemann Hjelmberg J, Christiansen L, McGue M, Jeune B, Christensen K. Methylenetetrahydrofolate reductase 677C-->T and methionine synthase 2756A-->G mutations: no impact on survival, cognitive functioning, or cognitive decline in nonagenarians. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences* 2007;62:196–201.
- Burns PC. Navigation and mobility of older drivers. *The Journals of Gerontology Series B, Psychological Sciences and Social Sciences* 1999;54:S49–55.
- Censori, Partiguian; Manara, &. Poloni. Plasma homocysteine and severe white matter disease. *Neurological Science* 2007;28:259–263.
- de Frias CM, Bunce D, Wahlin A, Adolfsson R, Slegers K, Cruts M, et al. Cholesterol and triglycerides moderate the effect of apolipoprotein E on memory functioning in older adults. *Journal of Gerontology B Psychological Science Social Science* 2007;62:P112–P118.

- deIpolyi AR, Rankin KP, Mucke L, Miller BL, Gorno-Tempini ML. Spatial cognition and the human navigation network in AD and MCI. *Neurology* 2007;69:986–997. [PubMed: 17785667]
- Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, et al. The aging hippocampus: cognitive, biochemical and structural findings. *Cerebral Cortex* 2003;13:1344–1351. [PubMed: 14615299]
- Driscoll I, Hamilton DA, Yeo RA, Brooks WM, Sutherland RJ. Virtual Navigation in humans: the impact of age, sex and hormones on place learning. *Hormones and Behavior* 2005;47:326–35. [PubMed: 15708762]
- Dufouil C, Alperovitch A, Ducros V, Tzourio C. Homocysteine, white matter hyperintensities and cognition in healthy elderly people. *Annals of Neurology* 2003;53:214–221. [PubMed: 12557288]
- Durga J, van Boxtel MP, Schouten EG, Bots ML, Kok FJ, Verhoef P. Folate and the methylenetetrahydrofolate reductase 677C-->T mutation correlate with cognitive performance. *Neurobiology of Aging* 2006;27:334–343. [PubMed: 16399216]
- Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, et al. NIDDM and blood pressure as risk factors for poor cognitive performance: The Framingham Study. *Diabetes Care* 1997;20:1388–1395. [PubMed: 9283785]
- Elkins JS, Johnston SC, Ziv E, Kado D, Cauley JA, Yaffe K. Methylenetetrahydrofolate reductase C677T polymorphism and cognitive function in older women. *American Journal of Epidemiology* 2007;166:672–678. [PubMed: 17638709]
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research* 1975;12:189–198.
- Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RW, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nature Genetics* 1995;10:111–113. [PubMed: 7647779]
- Gussekloo J, Heijmans BT, Slagboom PE, Lagaay AM, Knook DL, Westendorp RG. Thermolabile methylenetetrahydrofolate reductase gene and the risk of cognitive impairment in those over 85. *Journal of Neurology and Neurosurgery and Psychiatry* 1999;67:535–538.
- Huh HJ, Chi HS, Shim EH, Jang S, Park CJ. Gene-nutrition interactions in coronary artery disease: correlation between the MTHFR C677T polymorphism and folate and homocysteine status in a Korean population. *Thrombosis Research* 2006;117:501–506. [PubMed: 15935452]
- Ilhan N, Kucukusu M, Kaman D, Ilhan N, Ozbay Y. The 677 C/T MTHFR polymorphism is associated with essential hypertension, coronary artery disease, and higher homocysteine levels. *Arch Med Research* 2008;39:125–130. [PubMed: 18068006]
- Ingram DK. Complex maze learning in rodents as a model of age related memory impairment. *Neurobiology of Aging* 1988;9:475–485. [PubMed: 3062459]
- Korf ES, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension* 2004;44(1):29–34. [PubMed: 15159381]
- Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *Journal of the American Medical Association* 1995;274:1846–1851. [PubMed: 7500533]
- Lawlor DA, Harbord RM, Sterne J, Timpson N, Davey Smith G. Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Statistics in Medicine* 2007;27:1133–1163. [PubMed: 17886233]
- Lövdén M, Herlitz A, Schellenbach M, Grossman-Hutter B, Kruger A, Lindenberger U. Quantitative and qualitative sex differences in spatial navigation. *Scandinavian Journal of Psychology* 2007;48:353–358.
- Mattay VS, Goldberg TE, Sambataro F, Weinberger DR. Neurobiology of cognitive aging: Insights from imaging genetics. *Biological Psychology* 2008;79:9–22. [PubMed: 18511173]
- Moffat SD, Resnick SM. Effects of age on virtual environment place navigation and allocentric cognitive mapping. *Behavioral Neuroscience* 2002;116:851–859. [PubMed: 12369805]
- Moffat SD, Elkins W, Resnick SM. Age differences in the neural systems supporting human allocentric spatial navigation. *Neurobiology of Aging* 2006;27:965–972. [PubMed: 15982787]
- Moffat SD, Zonderman AB, Resnick SM. Age differences in spatial memory in a virtual environment navigation task. *Neurobiology of Aging* 2001;22:787–796. [PubMed: 11705638]

- Moffat SD, Kennedy KM, Rodrigue KM, Raz N. Extrahippocampal contributions to age differences in human spatial navigation. *Cerebral Cortex* 2007;17:1274–1282. [PubMed: 16857855]
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113. [PubMed: 5146491]
- Ott BR, Heindel WC, Papandonatos GD, Festa EK, Davis JD, Daiello LA, Morris JC. A longitudinal study of drivers with Alzheimer disease. *Neurology* 2008;7:1171–1178. [PubMed: 18216302]
- Pinto E. Blood pressure and ageing. *Postgraduate Medical Journal* 2007;83:109–114. [PubMed: 17308214]
- Prins ND, Den Heijer A, Hofman A, Koudstaal PJ, Jolles J, Clarke R, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. *Neurology* 2002;59:1375–1380. [PubMed: 12427887]
- Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement* 1977;1:385–401.
- Ravaglia G, Forti P, Maioli F, Scali RC, Arnone G, Talerico T, et al. Common polymorphisms in methylenetetrahydrofolate reductase (MTHFR): relationships with plasma homocysteine concentrations and cognitive status in elderly northern Italian subjects. *Archives of Gerontology and Geriatrics* 2004;(Supplement):339–348. [PubMed: 15207432]
- Raz N, Rodrigue KM, Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behavioral Neuroscience* 2003;117:1169–1180. [PubMed: 14674838]
- Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex* 2005;15(11):1676–89. [PubMed: 15703252]
- Raz N, Dahle C, Rodrigue KM, Kennedy KM, Land S, Jacobs BS. Brain-Derived Neurotrophic Factor Val66Met polymorphism, blood glucose, and memory in healthy adults: The synergy of genetic and vascular risks. *Frontiers in Human Neuroscience*, 2, article 2008;12:1–6.
- Raz N, Rodrigue KM, Kennedy KM, Land S. Genetic and Vascular Modifiers of Age-Sensitive Cognitive Skills: Effects of COMT, BDNF, ApoE and hypertension. *Neuropsychology*. in press
- Seshadri S, Wolf PA, Beiser AS, Selhub J, Au R, Jacques PF, et al. Association of plasma total homocysteine levels with subclinical brain injury: cerebral volumes, white matter hyperintensity, and silent brain infarcts at volumetric magnetic resonance imaging in the Framingham Offspring Study. *Archives of Neurology* 2008;65:642–649. [PubMed: 18474741]
- Sixsmith J, Sixsmith A. Older people, driving and new technology. *Applied Ergonomics* 1993;24(1):40–43. [PubMed: 15676896]
- Visscher PM, Tynan M, Whiteman MC, Pattie A, White I, Hayward C, et al. Lack of association between polymorphisms in angiotensin-converting-enzyme and methylenetetrahydrofolate reductase genes and normal cognitive ageing in humans. *Neuroscience Letters* 2003;347:175–178. [PubMed: 12875914]
- Waldstein SR, Jennings JR, Ryan CM, Muldoon MF, Shapiro AP, Polefrone JM, et al. Hypertension and neuropsychological performance in men: Interactive effects of age. *Health Psychology* 1996;15:102–109. [PubMed: 8681917]
- Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension* 2008;51:99–104. [PubMed: 18025297]
- Wiseman RM, Saxby BK, Burton EJ, Barber R, Ford GA, O'Brien JT. Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. *Neurology* 2004;63:1892–1897. [PubMed: 15557507]

Figure 1.

Total distance traveled in search of the submerged platform at six successive trials. See text for a comment on peak at trial 4. The bars are standard errors of the means.

Effects of Hypertension and MTHFR C677T Genotype on Navigation Performance

Figure 2.

Effects of hypertension and MTHFR 677T allele on Virtual Water Maze performance (distance traveled in search of the platform; log transformed). T+ and T- label the groups of participants who carry at least one T allele of MTHFR C677T polymorphisms versus CC homozygotes. See text for definition of the hypertensive group. The vertical bars are group means adjusted for age and sex. The error bars are standard errors of the means. The stars indicates significant differences (* $p < .05$; *** $p < .001$).

Figure 3.

Sex differences in navigational performance in normotensive and hypertensive participants (see text for definition of the hypertensive group). The vertical bars represent group means adjusted for age and the effect of MTHFR C677T genotype. The error bars are standard errors of the means. The star indicates a significant difference ($p < .05$).

Figure 4.

Effects of hypertension and MTHFR C677T Genotype on Virtual Water Maze performance (mean distance traveled in search of the platform; log transformed). See text for definition of the hypertensive group. The error bars are standard errors of the means.

Table 1

Descriptive statistics of the study sample

Diagnostic Groups	Sex (N)	MTHFR C677T Genotype (N)	Mean Age (yrs. $\pm$ SEM)	Education (yrs. $\pm$ SEM)	Systolic	Diastolic
Normotensive (118)	F (83)	C/C (40)	52.95 ($\pm$ 2.08)	15.55 ($\pm$ 0.36)	118.34 ($\pm$ 1.67)	74.11 ($\pm$ 1.03)
		C/T (32)	50.69 ($\pm$ 2.16)	16.00 ($\pm$ 0.37)	117.17 ($\pm$ 1.63)	73.53 ($\pm$ 1.03)
		T/T (11)	38.55 ($\pm$ 4.46)	15.64 ($\pm$ 0.54)	111.61 ($\pm$ 4.98)	70.06 ($\pm$ 3.04)
	M (35)	C/C (12)	52.58 ($\pm$ 4.94)	15.58 ($\pm$ 0.66)	126.10 ($\pm$ 1.86)	77.53 ($\pm$ 1.95)
		C/T (16)	51.69 ($\pm$ 4.51)	16.88 ($\pm$ 0.48)	116.58 ($\pm$ 2.20)	74.89 ($\pm$ 1.66)
		T/T (7)	46.43 ($\pm$ 8.44)	16.14 ($\pm$ 0.91)	122.43 ($\pm$ 3.99)	76.55 ($\pm$ 2.04)
Hypertensive (42)	F (23)	C/C (10)	55.40 ($\pm$ 4.23)	15.80 ($\pm$ 0.76)	130.53 ($\pm$ 5.33)	81.37 ($\pm$ 3.30)
		C/T (11)	61.18 ($\pm$ 2.93)	16.00 ($\pm$ 0.93)	136.99 ($\pm$ 3.28)	80.53 ($\pm$ 1.79)
		T/T (2)	71.00 ($\pm$ 0.00)	14.5 ($\pm$ 0.50)	146.67 ($\pm$ 6.67)	78.33 ($\pm$ 0.33)
	M 19)	C/C (12)	57.92 ($\pm$ 2.53)	17.42 ($\pm$ 0.91)	135.06 ($\pm$ 4.14)	83.33 ($\pm$ 3.13)
		C/T (5)	62.80 ($\pm$ 4.27)	15.40 ($\pm$ 1.66)	137.33 ($\pm$ 7.26)	81.87 ($\pm$ 2.32)
		T/T (2)	65.00 ($\pm$ 5.00)	14.00 ($\pm$ 1.00)	147.25 ($\pm$ 8.75)	95.00 ($\pm$ 1.00)