Neural Correlates of Visuospatial Working Memory in Healthy Young Adults at Risk for Hypertension

Andreana P. Haley · John Gunstad · Ronald A. Cohen ·
Beth A. Jerskey · Richard C. Mulligan ·
Lawrence H. Sweet

Abstract Family history of hypertension (FH+) has been associated with subtle deficits in cognitive function. In search of an early marker that may identify individuals predisposed to developing cognitive difficulties, we employed fMRI to test for FH+ related differences in hemodynamic response to a working memory challenge in healthy young adults with intact working memory. Fourteen healthy adults (ages 18 to 40 years) participated in an fMRI study of working memory. Seven of the participants were FH+. Groups were matched for working memory performance. Relative to FH− controls, FH+ participants exhibited lower 2-Back-related activation in the right inferior parietal lobule and the right inferior temporal gyrus as well as significantly more deactivation in the posterior cingulate cortex. These results indicate that FH+ is associated with subtle changes in visuospatial attention even in healthy young adults.

A. P. Haley (✉)
Department of Psychology, The University of Texas at Austin,
1 University Station, A8000,
Austin, TX 78712, USA
e-mail: haley@psy.utexas.edu

J. Gunstad
Department of Psychology, Kent State University,
Kent, OH, USA

R. A. Cohen · B. A. Jerskey · R. C. Mulligan · L. H. Sweet
Department of Psychiatry and Human Behavior,
Warren Alpert Medical School of Brown University,
Providence, RI, USA

Introduction

Hypertension (HTN), defined as systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg (American Heart Association 2004), is a common human disease associated with significant morbidity and mortality worldwide (Dickson and Sigmund 2006). HTN is the most common risk factor for multiple serious medical conditions such as coronary heart disease (Clarke et al. 2002; Lawes et al. 2002; Lewington et al. 2002) and stroke (Sacco et al. 1999; Gorelick 2003; Dennis et al. 1989). HTN is also a known risk factor for poor neurocognitive outcome, including cerebral white matter disease (Hassan et al. 2003; O'Brien et al. 2003; Pantoni and Garcia 1997) and generalized cerebral atrophy (van Dijk et al. 2004; Farkas and Luiten 2001). Many HTN patients also develop serious cognitive problems later in life (Farkas and Luiten 2001; Lindsay et al. 1997; Prince et al. 1994). While cognitive sequelae have historically received less attention than the cardiac and cerebrovascular effects of HTN, there is accumulating evidence that cognitive functioning is an important determinant of health status, quality of life, and functional ability (Ades et al. 1992; Cohen et al. 1999). These findings provide a compelling reason for identifying early markers of risk for cognitive impairment among individuals with current HTN as well as those at risk for HTN in order to improve prevention of dementia, and ensure early treatment.

Positive family history of HTN (FH+), defined as HTN before age 60 in a first-degree relative, is a powerful risk factor for future development of the disease. The risk increases progressively as a function of the number of affected parents and younger parental

age of onset (Hunt and Williams 1994). FH+ has now become an accepted surrogate marker of genetic risk for HTN (Kailasam et al. 2000; Lacy et al. 1998; O'Connor et al. 2002; Schneider et al. 2003; Song et al. 2000). FH+ is associated with pre-clinical pathological changes in a number of important physiological domains (Brinton et al. 1996; Grunfeld et al. 1990; Kailasam et al. 2000; Lacy et al. 1998; Li et al. 2005; O'Connor et al. 2002; Schneider et al. 2003; Song et al. 2000; Zhang et al. 2004) as well as diminished performance on neuropsychological tests (Thyrum et al. 1995; Waldstein et al. 1994; Ditto et al. 2006). Affected cognitive domains include visuospatial/constructional ability, verbal learning, attention, and short-term memory. These cognitive findings have been found to be independent of psychological state and health (e.g., anxiety, depression) as well as other commonly found confounds such as age, gender, ethnicity, education, and current blood pressure (Thyrum et al. 1995; Waldstein et al. 1994). Therefore, FH+ appears to identify a sub-group of individuals at especially high risk for cognitive impairment.

In this study, we employed functional magnetic resonance imaging (fMRI) to determine how the pattern of brain activity during a working memory task may vary as a function of family history of HTN in healthy young adults with intact working memory performance. We chose a working memory task because it taxes attention and short-term memory, both known to vary as a function of family history of HTN (Thyrum et al. 1995; Waldstein et al. 1994). Based on previous studies indicating that FH+ individuals exhibit vascular alterations (e.g., mild endothelial dysfunction) at a very early age (Li et al. 2005), we hypothesized that positive family history of HTN would be associated with lower BOLD response to a cognitive challenge due to mild cerebral hypoperfusion. Our hypothesis extended previous literature documenting that poor peripheral perfusion is related to diminished cerebrovascular health and impaired cognitive function in patients with cardiovascular disease (Gunstad et al. 2005; Haley et al. 2007a, 2007b; Hoth et al. 2007; Jefferson et al. 2007a, 2007b; Paul et al. 2005). We hypothesized that sub-clinical abnormalities in the vasculature of FH+ individuals will result in lower, yet sufficient, levels of oxygenated hemoglobin being delivered to active brain areas and lower BOLD response to a cognitive challenge at normal levels of behavioral performance. Our confidence in the sensitivity of fMRI was based on a growing body of clinical research literature indicating that fMRI can detect altered brain function among individuals at risk before clinical symptoms or behavioral deficits are present (Bookheimer et al. 2000; Chang et al. 2001; Sweet et al. 2006).

Materials and methods

Participants

Fourteen right-handed participants (9 women and 5 men) between the ages of 18 and 40 were recruited through flyers posted in the Providence, RI area.

Family history of hypertension (FH+) Participants with positive family history of HTN were especially solicited during recruitment. Upon enrollment in the study, participants' family history of HTN was confirmed using the Ohio Blood Pressure History Survey, a brief instrument used to document family history of HTN in past studies (France et al. 2000). The overall accuracy of the measure as compared to medical records has been documented at 94.2% (Page and France 2001). The participants' parents completed the survey. Parental medical records were not solicited. The sensitivity and specificity of the Ohio Blood Pressure History Survey have been noted at 95.4% and 92.4%, respectively (Page and France 2001). Consistent with previous studies, positive family history of HTN (FH+) was defined as HTN before age 60 in a first-degree relative (parent) (Kailasam et al. 2000; Lacy et al. 1998; Schneider et al. 2003; Song et al. 2000). Included in the FH− group were participants with two normotensive parents. The final sample included seven FH− and seven FH+ normotensive young adults. Both groups were mixed in terms of sex, and balanced in terms of age, education, and weight. Details about the demographics of the two groups are available in Table 1.

Participants were excluded from participation if they had a history of neurological disease (i.e., large vessel stroke, seizure disorder, Parkinson's disease, clinically significant traumatic brain injury, multiple sclerosis, or brain infection/meningitis), major psychiatric illness (e.g. schizophrenia, bipolar disorder), substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse), diagnosed current hypertension, or MRI contraindications.

Table 1 Demographic information

	FH+ Group	FH− Group	t	p value
Number of patients	7	7		
Sex (female/male)	4/3	5/2		
Age	27.14 (3.53)	29.00 (6.32)	−0.678	0.510
Education	18.14 (3.67)	18.29 (1.80)	−0.092	0.928
Weight	147.57 (34.49)	147.43 (32.71)	0.008	0.994

Working memory paradigms

Working memory was assessed using visuospatial and verbal n-Back tasks (Awh et al. 1996; Braver et al. 1997; Smith and Jonides 1997). During the visuospatial n-Back task, a series of black dots was visually presented for 500 ms each with a 2500 ms inter-stimulus interval (Fig. 1). The location of the black dot changed with each presentation. Participants were asked to determine if the location of each dot was the same as, or different from, a previously presented stimulus. During the verbal n-Back, consonants were presented at the same rate in the center of the screen. For each stimulus participants were asked to determine if the consonant was the same as, or different from, a previously presented consonant. Responses were collected using a two-button response box. A right index finger response indicated affirmative and a right middle finger response indicated negative. In both the visuospatial and verbal paradigms a 0-Back control condition was alternated with the 2-Back condition in a block design. An imaging run consisted of four blocks of the 0-Back and four blocks of the 2-Back lasting approximately 6 min.

Visuospatial processing was the focus of the current investigation. The visuospatial 2-Back has been used in previous studies involving both patient populations and healthy participants (Awh et al. 1996; Smith et al. 2006; Chang et al. 2004; Kwon et al. 2001). Visuospatial perception, short-term memory buffering, attention, and executive coordination are all required for successful task performance.

0-Back control condition This task consisted of four blocks of nine visual stimuli in random order, 33% of which were targets. Participants responded "yes" when a dot appeared in the center of the screen, and "no" if a dot appeared in any other location.

2-Back working memory condition The experimental condition consisted of four blocks, each containing 15 visual

stimuli in random order, 33% of which were targets. A stimulus was considered a target if it was in the same location as the stimulus presented two stimuli earlier.
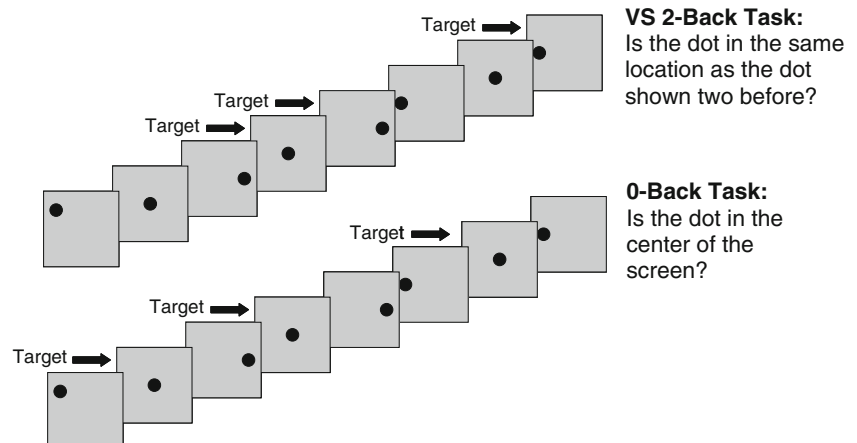
Procedures

The local Institutional Review Board approved the study and all volunteers provided written informed consent before enrollment. Participants completed a medical history interview with one of the team members (LS or JG). Cardiovascular risk factors such as hypertension, hypercholesterolemia, tobacco use, and diabetes were coded as either present or absent according to participants' self-report. Handedness was recorded according to participants' stated hand preference and confirmed by observing a writing sample. Family history of HTN was assessed as described above.

Each imaging session included at least four blocks of visuospatial 0-Back/2-Back practice, at least four blocks of verbal 0-Back/2-Back practice, one imaging run of the visuospatial 2-Back task, one imaging run of the verbal 2-Back task, and T_1-weighted imaging for anatomical reference. If necessary, more practice blocks were administered. All participants practiced the task until they performed above chance levels. The 2-Back task was presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA), back-projected onto a screen positioned at the participant's feet, and viewed through a double-mirror attached to the head coil. Participants' responses were collected using an MR-compatible piano-key response box.

MRI data acquisition

MRI data for each participant were acquired in a single session on a 1.5T Siemens Symphony scanner equipped with a standard head coil. Functional imaging was

Fig. 1 0-Back and 2-Back visuospatial working memory task example stimuli

VS 2-Back Task: Is the dot in the same location as the dot shown two before?

0-Back Task: Is the dot in the center of the screen?

performed using a whole brain echo-planer imaging (EPI) sequence (TR=3860 ms, TE=38 ms, FOV=192 mm², 64× 64 matrix, 48 axial slices, 3 mm slice thickness). Structural imaging sequences included a high-resolution (256×256 matrix, FOV=256 mm², 1 mm slice thickness) magnetization prepared rapid gradient echo (MP-RAGE) anatomical scan of the entire brain in the saggital plane.

fMRI data preprocessing

All EPI images were processed using Analysis of Functional NeuroImages (AFNI) software (Cox 1996). Each time series was spatially registered to the sixth volume of the session to reduce the effects of head movement. This AFNI 3-dimensional registration program also yields information on displacement and rotation for each volume that was used later to further correct motion. Data preprocessing also included temporal smoothing, spatial filtering, and transformation to standard stereotaxic space (Talairach and Tournoux 1988). Task-related brain activation was determined using voxel-wise multiple regression analyses with the following parameters: a 0-Back/2-Back reference waveform convolved with a gamma function, and covariates accounting for instruction screens, head movement, and linear trends.

An empirically defined set of ROIs (group mask) was created as follows: First, results from individual multiple regression analyses were transformed into z scores, corrected for multiple comparisons using the false discovery rate (FDR) correction supplied by AFNI, and thresholded at $p<0.05$. Voxels with task-related activation exceeding this threshold were included the mask if they were active in either group of participants. Finally, active voxels were defined as a cluster if they were contiguous and formed a volume of at least 300 μL. Four cortical regions of interest (ROIs) resulted (Table 2, Fig. 2). This empirically defined mask was applied to individual data to determine mean task-related activation intensity (corrected $p<0.05$) within each ROI.

Statistical analyses

All variable distributions were examined using the Shapiro-Wilk test of normality recommended for small samples. The

two groups were compared on working memory performance and mean 2-Back related activation intensity within each empirically defined ROI using independent samples t-tests. Data were analyzed using SPSS 11.0 computer software (SPSS Inc., Chicago, IL). A two-tailed alpha level of 0.05 was used as the criterion for statistical significance.

Results

All variable distributions fulfilled the assumption of normality (Mean Shapiro-Wilk=0.94, mean $p=.52$). No variable transformations were performed.

All participants exhibited intact working memory performance (mean accuracy>60%), which was not surprising considering that they were over-trained to perform the tasks. Mean accuracy (SD) on the verbal 2-Back task was 82% (11%) correct responses, and mean reaction time (SD) was 1071.93 (240.00) ms. The performance of the two groups was equivalent in both accuracy ($t(10)=0.163$, $p=.874$), and reaction time ($t(10)=0.73$, $p=.484$). All participants moved less than 1.5 mm per imaging run.

Figure 2 represents the areas of significant 2-Back related activity for at least 90% of our participants. The identified areas of activity also served as our ROI mask. The areas are consistent with regions of 2-Back related activity in the published literature (Braver et al. 1997; Smith et al. 1997; Sweet et al. 2008). Relative to FH− controls, FH+ participants exhibited lower BOLD response to the 2-Back task in the right inferior parietal lobule ($t(12)=2.42$, $p=.033$) and the right inferior temporal gyrus ($t(12)=2.33$, $p=.038$) (Fig. 3). Relative to FH− controls, FH+ participants also exhibited substantially more deactivation in the posterior cingulate cortex, bilaterally ($t(12)=4.14$, $p=.001$).

Discussion

This study examined the relationship between family history of HTN and brain response to a working memory challenge in healthy young adults with intact working memory performance. We found that family history of HTN, a marker of increased genetic risk for developing the disease, was associated with lower task-related activation in

Table 2 Differences in the BOLD response to a visuospatial working memory task according to family history of HTN

ROI	|X|	Y	Z	Region	t	p value
1	55	−44	−11	Right inferior temporal gyrus	2.33	0.038
2	2	−55	15	Bilateral posterior cingulate	4.14	0.001
3	26	−68	37	Right precuneus	0.49	0.630
4	48	−49	41	Right inferior parietal lobule	2.42	0.033

Fig. 2 Regions of interest on template anatomy. *1* Right inferior temporal gyrus (*green*); *2* bilateral posterior cingulate gyrus (*red*); *3* right precuneus (*yellow*); *4* right inferior parietal lobule (*blue*)
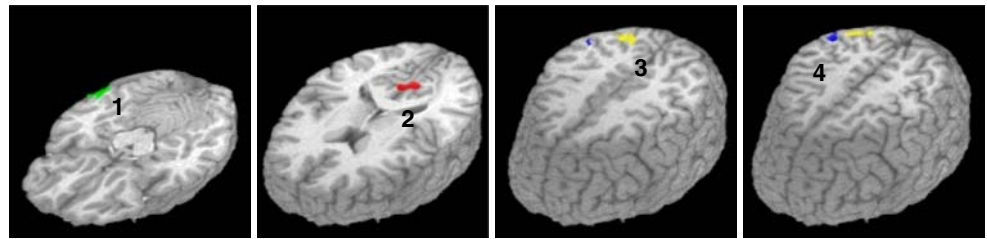
the right inferior parietal lobule and right inferior temporal gyrus as well as substantially greater deactivation of the posterior cingulate during a visuospatial working memory task.

Our results fit well with a growing body of clinical research literature indicating that fMRI is able to detect altered brain function among individuals at risk, before clinical symptoms or behavioral deficits are present (Bookheimer et al. 2000; Chang et al. 2001; Sweet et al. 2006). Unlike those prior studies, however, the alterations we detected consisted of lower, rather than higher, BOLD response to a cognitive challenge in the population at risk. We believe that these differences are significant, and indicative of a different underlying mechanism. Our study sample was exclusively comprised of individuals at increased risk for vascular cognitive impairment, while other studies have included populations at risk for cognitive deficits related to multiple sclerosis (Sweet et al. 2006), HIV (Chang et al. 2001), and genetic risk for Alzheimer's disease (Bookheimer et al. 2000). Therefore, the mechanisms underlying the observed changes are likely to be different, e.g., hypoperfusion in our case vs. inflammatory or other non-vascular processes in the other cases. Our current findings of lower BOLD response to a cognitive challenge in participants at risk for HTN with intact behavioral performance can be explained by the nature of the BOLD contrast itself. Under normal circumstances, oxygenated hemoglobin is delivered to areas of increased neuronal activity in excess of neuronal oxygen consumption, resulting in a change in the ratio of oxygenated vs. deoxygenated hemoglobin in the activated brain area and detectable BOLD signal. We propose that, in the present case, mild cerebral hypoperfusion related to sub-clinical

pathological vascular changes, results in lower, yet sufficient, amounts of oxygen being delivered to activated neurons, thus producing a lower BOLD response to the cognitive challenge in the at-risk population while maintaining intact cognitive performance. This proposition is supported by a growing literature documenting that reduced peripheral perfusion is related to poor cerebrovascular health and diminished cognitive function in patients with cardiovascular disease (Gunstad et al. 2005; Haley et al. 2007a; Hoth et al. 2007; Jefferson et al. 2007a, 2007b; Paul et al. 2005). Following the same logic, one might hypothesize that as the vascular problems get worse, and some of the healthy FH+ participants go on to develop clinical cardiovascular disease, cerebral hypoperfusion will exacerbate, eventually leading to a decline in cognitive performance. This hypothesis is supported by results from our lab documenting that in patients with cardiovascular disease, higher levels of large vessel atherosclerosis are related to both lower BOLD response to cognitive challenges and lower levels of behavioral performance (Haley et al. 2007b).

The task-related deactivations in the posterior cingulate observed in the FH+ participants in our study are also very interesting, and in our opinion, consistent with our reasoning that lower BOLD response to a cognitive challenge in our population provides evidence of subclinical cognitive impairment. Task-related deactivations in several brain regions including the posterior cingulate have been increasingly reported in imaging studies (Binder et al. 1999; Mazoyer et al. 2001; Shulman et al. 1997). These deactivations, indicating higher neural activity during the baseline/low-demand conditions as opposed to the experimental/high-demand conditions, appear to be associated
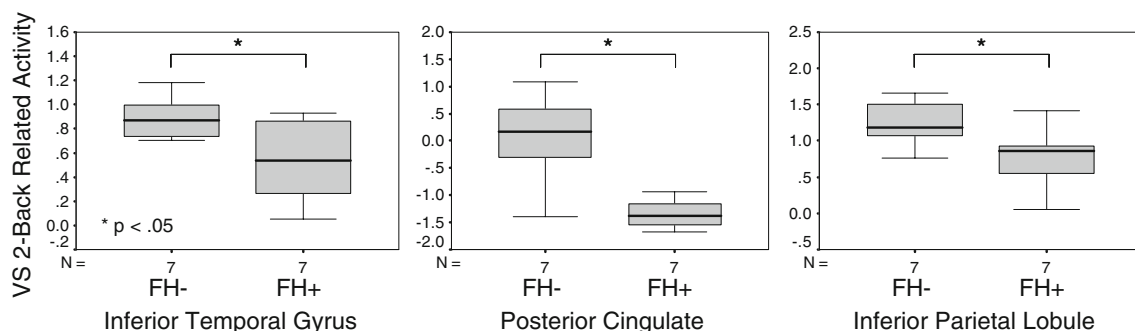
Fig. 3 Boxplots of averaged task-related signal intensity within the ROIs demonstrating significantly lower BOLD response to a VS WM task in healthy young adults with family history of HTN (FH+)

with internally generated thoughts involving episodic memory, planning, problem solving, processing emotions and self-monitoring (Greicius and Menon 2004; McKiernan et al. 2006). Task-related deactivations have been shown to increase in magnitude (i.e., deactivate further) with increasing task difficulty thus giving rise to the hypothesis that selective withdrawal of attention from self-referential, stimulus-independent thought in favor of more challenging cognitive tasks may be a compensatory mechanism employed by participants who are struggling to complete the task at hand (McKiernan et al. 2003; Sweet et al. 2008). Withdrawal of resources from this so-called "default-mode" brain network responsible for stream of consciousness type mental images and thoughts (Greicius et al. 2003) has also been associated with nicotine induced enhancement of visual spatial attention (Hahn et al. 2007). Therefore, while in some contexts withdrawal of resources from self-referential thought may indicate more efficient concentration and better performance, in cases such as ours, where participants are maintaining normal cognitive performance in suboptimal conditions (e.g., reduced cerebral perfusion), this increased withdrawal of resources from irrelevant brain areas seems to indicate a passive compensatory mechanism that allows patients at risk to maintain normal cognitive functioning.

Thus, our results indicate that family history of HTN may be associated with sub-clinical dysfunction of visuospatial attention, storage and rehearsal requiring increased effort for successful visuospatial working memory performance necessitating higher levels of concentration in order to maintain normal levels of behavioral performance. These results fit well with the idea of a continuum of vascular related brain dysfunction from the brain-at-risk to vascular-related cognitive impairments, where disturbances in neural systems supporting attention are among the earliest signs (Haley et al. 2007a; Jefferson et al. 2007a; Moser et al. 1999; Paul et al. 2005).

The improved sensitivity of fMRI (over behavioral performance) to detect sub-clinical cognitive difficulties may be attributed to our ability to more directly observe brain function, which minimizes response biases and other measurement error associated with human behavior. Another reason is that fMRI allows the simultaneous observation of the complex and interrelated neural processes that underlie human behavior. Since observed behavior is the product of complex interactions among neural networks, direct observation of activity among these networks allows us to determine not only which brain regions are involved, but how they interrelate to yield a behavioral product. While demonstration of decreased behavioral performance and brain response during cognitive challenges has been a typical goal in fMRI clinical research, there is now sufficient empirical support to predict altered brain function among asymptomatic at-risk individuals. Greater brain activity in expected task-related brain regions, significant recruitment of unexpected brain regions, and suspension of unrelated brain activity have each been described among normally performing at-risk samples (Bookheimer et al. 2000; Chang et al. 2001; Penner et al. 2003; Staffen et al. 2002; Sweet et al. 2004, 2006). Therefore, we hypothesized that an fMRI examination would allow us to detect differences in the patterns of brain activity in response to a cognitive challenge among healthy individuals at varying degrees of risk for HTN and vascular cognitive impairment.

In conclusion, the present study presents promising preliminary data indicating that genetic history of HTN may be related to subtle alterations in brain function even in healthy young adults. The study had a few important limitations including a relatively small sample size and the use of self-report to document both family history of HTN, and current medical status. However, considering the relatively young age of the participants (average age 28), and the high rates of agreement between responses to the Ohio Blood Pressure History Survey and medical records reported in the literature (~94%, Page and France 2001), it is unlikely that undetected current HTN in the participants, or reporting error on behalf of the parents contributed significantly to our results. Soliciting medical records for both participants and parents in future studies will nonetheless improve the design and help alleviate any concerns about the use of self-report. A larger sample size on the other hand will allow us to extend the present results by examining any potential gender effects. Future studies may also benefit from comprehensive evaluations of peripheral cardiovascular functioning as well as examination of particular gene polymorphisms. The pathways by which family history of HTN may affect brain function are also of considerable interest as they may lead to new ways to treat and prevent the development of vascular cognitive impairment. Finally, the sensitivity of this measurement for predicting cognitive function over time should be investigated further.

References

Ades, P. A., Huang, D., & Weaver, S. O. (1992). Cardiac rehabilitation participation predicts lower rehospitalization costs. *American Heart Journal, 123*, 916–921.

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. *Psychological Science, 7*, 25–31.

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S., Rao, S. M., & Cox, R. W. (1999). Conceptual processing during the conscious

resting state. A functional MRI study. *Journal of Cognitive Neuroscience*, *11*, 80–95.

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., et al. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine*, *343*, 450–456.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage*, *5*, 49–62.

Brinton, T. J., Kailasam, M. T., Wu, R. A., Cervenka, J. H., Chio, S. S., Parmer, R. J., et al. (1996). Arterial compliance by cuff sphygmomanometer. Application to hypertension and early changes in subjects at genetic risk. *Hypertension*, *28*, 599–603.

Cardiovascular disease statistics: American Heart Association (2004). American Heart Association [On-line]. Available: http://www.americanheart.org

Chang, K., Adleman, N. E., Dienes, K., Simeonova, D. I., Menon, V., & Reiss, A. (2004). Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. *Archives of General Psychiatry*, *61*, 781–792.

Chang, L., Speck, O., Miller, E. N., Braun, J., Jovicich, J., Koch, C., et al. (2001). Neural correlates of attention and working memory deficits in HIV patients. *Neurology*, *57*, 1001–1007.

Clarke, R., Lewington, S., Youngman, L., Sherliker, P., Peto, R., & Collins, R. (2002). Underestimation of the importance of blood pressure and cholesterol for coronary heart disease mortality in old age. *European Heart Journal*, *23*, 286–293.

Cohen, R. A., Moser, D. J., Clark, M. M., Aloia, M. S., Cargill, B. R., Stefanik, S., et al. (1999). Neurocognitive functioning and improvement in quality of life following participation in cardiac rehabilitation. *American Journal of Cardiology*, *83*, 1374–1378.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers in Biomedical Research*, *29*, 162–173.

Dennis, M. S., Bamford, J. M., Sandercock, P. A., & Warlow, C. P. (1989). A comparison of risk factors and prognosis for transient ischemic attacks and minor ischemic strokes. The Oxfordshire Community Stroke Project. *Stroke*, *20*, 1494–1499.

Dickson, M. E., & Sigmund, C. D. (2006). Genetic basis of hypertension: revisiting angiotensinogen. *Hypertension*, *48*, 14–20.

Ditto, B., Seguin, J. R., & Tremblay, R. E. (2006). Neuropsychological characteristics of adolescent boys differing in risk for high blood pressure. *Annals of Behavioral Medicine*, *31*, 231–237.

Farkas, E., & Luiten, P. G. (2001). Cerebral microvascular pathology in aging and Alzheimer's disease. *Progress in Neurobiology*, *64*, 575–611.

France, C., Suhr, J. A., Fox, L., Gunstad, J., & Spitznagel, B. (2000). Neuropsychological performance in men and women at risk for hypertension. *Archives of Clinical Neuropsychology*, *15*, 704–705.

Gorelick, P. B. (2003). Prevention of stroke recurrence. *International Psychogeriatrics*, *15*(Suppl 1), 167–171.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 253–258.

Greicius, M. D., & Menon, V. (2004). Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *Journal of Cognitive Neuroscience*, *16*, 1484–1492.

Grunfeld, B., Perelstein, E., Simsolo, R., Gimenez, M., & Romero, J. C. (1990). Renal functional reserve and microalbuminuria in off-spring of hypertensive parents. *Hypertension*, *15*, 257–261.

Gunstad, J., Cohen, R. A., Tate, D. F., Paul, R. H., Poppas, A., Hoth, K., et al. (2005). Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Pressure*, *14*(6), 353–358.

Hahn, B., Ross, T. J., Yang, Y. H., Kim, I., Huestis, M. A., & Stein, E. A. (2007). Nicotine enhances visuospatial attention by deactivating areas of the resting brain default network. *Journal of Neuroscience*, *27*, 3477–3489.

Haley, A. P., Forman, D. E., Poppas, A., Hoth, K. F., Gunstad, J., Jefferson, A. L., et al. (2007a). Carotid artery intima-media thickness and cognition in cardiovascular disease. *International Journal of Cardiology*, *121*, 148–154.

Haley, A. P., Sweet, L. H., Gunstad, J., Forman, D. E., Poppas, A., Paul, R. H., et al. (2007b). Verbal working memory and atherosclerosis in patients with cardiovascular disease: an fMRI study. *Journal of Neuroimaging*, *17*(3), 227–233.

Hassan, A., Hunt, B. J., O'Sullivan, M., Parmar, K., Bamford, J. M., Briley, D., et al. (2003). Markers of endothelial dysfunction in lacunar infarction and ischaemic leukoaraiosis. *Brain*, *126*, 424–432.

Hoth, K. F., Tate, D. F., Poppas, A., Forman, D. E., Gunstad, J., Moser, D. J., et al. (2007). Endothelial Function and White Matter Hyperintensities in Older Adults With Cardiovascular Disease. *Stroke*, *38*(2), 308–312.

Hunt, S. C., & Williams, R. R. (1994). Genetic factors in human hypertension. In J. Swales (Ed.), *Textbook of Hypertension* (pp. 519–538). Oxford: Blackwell.

Jefferson, A. L., Poppas, A., Paul, R. H., & Cohen, R. A. (2007a). Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients. *Neurobiology of Aging*, *28*, 477–483.

Jefferson, A. L., Tate, D. F., Poppas, A., Brickman, A. M., Paul, R. H., Gunstad, J., et al. (2007b). Lower cardiac output is associated with greater white matter hyperintensities in older adults with cardiovascular disease. *Journal of the American Geriatrics Society*, *55*(7), 1044–1048.

Kailasam, M. T., Parmer, R. J., Tyrell, E. A., Henry, R. R., & O'Connor, D. T. (2000). Circulating amylin in human essential hypertension: heritability and early increase in individuals at genetic risk. *Journal de l'hypertension*, *18*, 1611–1620.

Kwon, H., Menon, V., Eliez, S., Warsofsky, I. S., White, C. D., Dyer-Friedman, J., et al. (2001). Functional neuroanatomy of visuo-spatial working memory in fragile X syndrome: relation to behavioral and molecular measures. *American Journal of Psychiatry*, *158*, 1040–1051.

Lacy, F., O'Connor, D. T., & Schmid-Schonbein, G. W. (1998). Plasma hydrogen peroxide production in hypertensives and normotensive subjects at genetic risk of hypertension. *Journal de l'hypertension*, *16*, 291–303.

Lawes, C. M., Bennett, D. A., Lewington, S., & Rodgers, A. (2002). Blood pressure and coronary heart disease: a review of the evidence. *Seminars in Vascular Medicine.*, *2*, 355–368.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, *360*, 1903–1913.

Li, L. J., Geng, S. R., & Yu, C. M. (2005). Endothelial dysfunction in normotensive Chinese with a family history of essential hypertension. *Clinical and Experimental Hypertension*, *27*, 1–8.

Lindsay, J., Hebert, R., & Rockwood, K. (1997). The Canadian Study of Health and Aging: risk factors for vascular dementia. *Stroke*, *28*, 526–530.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., et al. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Research Bulletin*, *54*, 287–298.

McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N., & Binder, J. R. (2006). Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage*, *29*, 1185–1191.

McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J., & Binder, J. R. (2003). A parametric manipulation of factors affecting task-

induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience, 15,* 394–408.

Moser, D. J., Cohen, R. A., Clark, M. M., Aloia, M. S., Tate, B. A., Stefanik, S., et al. (1999). Neuropsychological functioning among cardiac rehabilitation patients. *Journal of Cardiopulmonary Rehabilitation, 19,* 91–97.

O'Brien, J. T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., et al. (2003). Vascular cognitive impairment. *Lancet Neurology, 2,* 89–98.

O'Connor, D. T., Kailasam, M. T., Kennedy, B. P., Ziegler, M. G., Yanaihara, N., & Parmer, R. J. (2002). Early decline in the catecholamine release-inhibitory peptide catestatin in humans at genetic risk of hypertension. *Journal de l'hypertension, 20,* 1335–1345.

Page, G., & France, C. R. (2001). Identifying hypertension using the Ohio Blood Pressure History Survey. *Military Medicine, 166,* 233–236.

Pantoni, L., & Garcia, J. H. (1997). Pathogenesis of leukoaraiosis: a review. *Stroke, 28,* 652–659.

Paul, R. H., Gunstad, J., Poppas, A., Tate, D. F., Foreman, D., Brickman, A. M., et al. (2005). Neuroimaging and cardiac correlates of cognitive function among patients with cardiac disease. *Cerebrovascular Diseases, 20,* 129–133.

Penner, I. K., Rausch, M., Kappos, L., Opwis, K., & Radu, E. W. (2003). Analysis of impairment related functional architecture in MS patients during performance of different attention tasks. *Journal de neurologie, 250,* 461–472.

Prince, M., Cullen, M., & Mann, A. (1994). Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. *Neurology, 44,* 97–104.

Sacco, R. L., Wolf, P. A., & Gorelick, P. B. (1999). Risk factors and their management for stroke prevention: outlook for 1999 and beyond. *Neurology, 53,* S15–S24.

Schneider, G. M., Jacobs, D. W., Gevirtz, R. N., & O'Connor, D. T. (2003). Cardiovascular haemodynamic response to repeated mental stress in normotensive subjects at genetic risk of hypertension: evidence of enhanced reactivity, blunted adaptation, and delayed recovery. *Journal of Human Hypertension, 17,* 829–840.

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., et al. (1997). Common blood flow changes across visual tasks.2. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience, 9,* 648–663.

Smith, A. M., Fried, P. A., Hogan, M. J., & Cameron, I. (2006). Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. *Neurotoxicology and Teratology, 28,* 286–295.

Smith, E. E., & Jonides, J. (1997). Working memory: a view from neuroimaging. *Cognitive Psychology, 33,* 5–42.

Song, C. K., Martinez, J. A., Kailasam, M. T., Dao, T. T., Wong, C. M., Parmer, R. J., et al. (2000). Renal kallikrein excretion: role of ethnicity, gender, environment, and genetic risk of hypertension. *Journal of Human Hypertension, 14,* 461–468.

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., et al. (2002). Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. *Brain, 125,* 1275–1282.

Sweet, L. H., Paskavitz, J. F., Haley, A. P., Gunstad, J., Mulligan, R., Nyalakanti, P. K., et al. (2008). Imaging phonological similarity effects on verbal working memory. *Neuropsychologia, 46,* 1114–1123.

Sweet, L. H., Rao, S. M., Primeau, M., Durgerian, S., & Cohen, R. A. (2006). Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. *Human Brain Mapping, 27,* 28–36.

Sweet, L. H., Rao, S. M., Primeau, M., Mayer, A. R., & Cohen, R. A. (2004). Functional magnetic resonance imaging of working memory among multiple sclerosis patients. *Journal of Neuroimaging, 14,* 150–157.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain 3-D proportional system: an approach to cerebral imaging.* New York: Thieme Medical.

Thyrum, E. T., Blumenthal, J. A., Madden, D. J., & Siegel, W. (1995). Family history of hypertension influences neurobehavioral function in hypertensive patients. *Psychosomatic Medicine, 57,* 496–500.

van Dijk, E. J., Breteler, M. M., Schmidt, R., Berger, K., Nilsson, L. G., Oudkerk, M., et al. (2004). The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension, 44,* 625–630.

Waldstein, S. R., Ryan, C. M., Polefrone, J. M., & Manuck, S. B. (1994). Neuropsychological performance of young men who vary in familial risk for hypertension. *Psychosomatic Medicine, 56,* 449–456.

Zhang, L., Rao, F., Wessel, J., Kennedy, B. P., Rana, B. K., Taupenot, L., et al. (2004). Functional allelic heterogeneity and pleiotropy of a repeat polymorphism in tyrosine hydroxylase: prediction of catecholamines and response to stress in twins. *Physiological Genomics, 19,* 277–291.