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4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4712
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Name of Candidate: Heather L. Rogers
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Thesis and Abstract Approved:

David Krantz, Ph.D.
Committee Chairperson

8/30/06
Date

Willem Kop, Ph.D.
Committee Member

8-30-06
Date

Wendy Law, Ph.D.
Committee Member

11 Aug 06
Date

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Heather L. Rogers, M.A.
Department of Medical and Clinical Psychology
Uniformed Services University of the Health Sciences

Abstract

Title of thesis: Cognitive profile and emotional status of middle-aged Chinese hypertensive patients without detectable white matter brain lesions or lacunar infarctions on MRI

Heather L. Rogers, Master of Science 2006

Thesis directed by: David S. Krantz, Ph.D.

Professor

Department of Medical and Clinical Psychology

Introduction: Essential hypertension (EH) is associated with cognitive deficits, and higher blood pressure levels have been related to lower levels of cognitive function. Executive functions, speed of processing, memory and attention are especially impacted. Hypertension may affect cognitive function because of pathological physiological changes in the brain (e.g., white matter lesions and/or lacunar infarctions) or behavioral/emotional alterations associated with hypertension (e.g., stress, anxiety, and depression). Objectives: (1) Rule out white matter lesions and lacunar infarctions as necessary causes of cognitive deficits in EH; (2) Examine the role of anxiety and depression as a potential mechanism for the relationship between EH and cognitive function; and (3) Determine socio-demographic and medical moderators of this relationship in individuals without structural brain changes. Methods: Ninety five Chinese with EH and 95 age- and education- matched normotensive controls were recruited into the study. All participants had a medical history interview and physical exam, completed Zung's Anxiety and Depression Surveys, and completed the Mini-Mental State Examination (MMSE) and a computerized neuropsychological battery. All

participants had an MRI scan of the brain. For the present study, individuals with white matter lesions or lacunar infarctions were excluded from analysis. The remaining sample consisted of 46 hypertensives and 66 controls. Results: Multivariate analyses, controlling for medical/risk factor differences between hypertensive and normotensive groups, revealed no relationship between EH and cognitive function nor EH and emotional status. Two-factor ANOVAs revealed significant EH x Gender interactions for digit discrimination response time ($p<0.01$) and the MMSE ($p<0.05$). Conclusions: The present findings suggest that gender moderates the influence of hypertension on cognitive function in the absence of structural brain changes. The adverse neuropsychological sequela associated with hypertension are seen only in female participants. The digit discrimination test, involving cognitive domains of attention, vigilance, and psychomotor speed, and the Mini-Mental State Examination, a test general cognitive ability were significantly affected. Self-reported anxiety was not associated with objective cognitive performance measured by neuropsychological tests and did not account for the relationship between hypertension and cognitive function in females. Future research, especially with female hypertensive patients, is needed to determine the mechanisms associated with cognitive deficits in hypertension.

Cognitive Function and Emotional Status of Middle-aged Chinese Hypertensive Patients without Detectable White Matter Brain Lesions or Lacunar Infarctions

by

Heather L. Rogers, M.A.

Master's Thesis submitted to the faculty of the
Department of Medical and Clinical Psychology
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Introduction

Epidemiological studies have shown that essential hypertension (EH) is associated with cognitive deficits. Some research indicates that this reduced cognitive function may be related to functional cerebral changes, such as perfusion deficits, or structural changes caused by chronic high blood pressure, including white matter lesions and lacunar infarctions. Other evidence suggests that behavioral or emotional changes associated with hypertension, such as stress, anxiety, and/or depression may explain the changes in cognitive function observed in hypertensive individuals. Medical variables associated with hypertension may also account for the relationship with cognitive function. The present cross-sectional study examines two potential mechanisms underlying the relationship between essential hypertension and cognitive deficits in a group of Chinese middle-aged hypertensive individuals and normotensive controls. To provide background for this study, the definition of hypertension, as well as its epidemiology, pathophysiology, and consequences will be reviewed. The relationship between blood pressure and cognitive function will then be examined. Finally, the specific cognitive deficits related to hypertension and potential mechanisms to explain these relationships will be explored.

Hypertension

Definition and Epidemiology. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003b) designated four categories of blood pressure. The previous JNC VI classification ("The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure") was updated by (1) re-

labeling what was previously considered optimal blood pressure in 1997 as normal, (2) combining the previously recognized categories of normal and high normal into a new "pre-hypertension" classification, and (3) combining the previous stage 2 and 3 hypertension into stage 2 hypertension (Table 1).

Table 1. Comparison of JNC VI and JNC VII blood pressure classifications

Blood Pressure Level	**Old Category Designated by JNC VI (1997)**	**New Category Designated by JNC VII (2003)**
SBP < 120 mm Hg DBP < 80 mm Hg	Optimal	Normal
SBP = 120 –129 mm Hg DBP = 80 – 84 mm Hg	Normal	Pre-hypertension
SBP = 130 – 139 mm Hg DBP = 85 – 89 mm Hg	High Normal	
SBP = 140 – 159 mm Hg DBP = 90 – 99 mm Hg	Stage 1 Hypertension	Stage 1 Hypertension
SBP = 160 – 179 mm Hg DBP = 100 – 109 mm Hg	Stage 2 Hypertension	Stage 2 Hypertension
SBP > 180 mm Hg DPB > 110 mm Hg	Stage 3 Hypertension	

Cases of essential hypertension (EH) have no identifiable pathological cause (Beevers, Lip, & O'Brien, 2001). EH, also referred to as primary hypertension, is 90% to 95% of all cases of hypertension. Secondary hypertension is hypertension caused by another disorder. The definition of hypertension can vary, although most experts agree that sustained diastolic pressure (DBP) greater than 90 millimeters of mercury (mm Hg) constitutes a cause for diagnosis; the cut-off for diagnosis using systolic blood pressure (SBP) falls between 140 mm Hg (Chobanian et al., 2003a) and 160 mm Hg (Beevers, Lip, & O'Brien, 2001). From a clinical perspective, hypertension is present if blood pressure levels are accurately measured and found to be elevated to these levels at three separate doctor's visits.

Hypertension is a chronic, age-related condition associated with multiple changes in the vascular system (Marin & Rodriguez-Martinez, 1999). Hypertension accounts for about 30 million outpatient visits annually in the US and is the second most common principle diagnosis given by family physicians. The annual direct medical cost of caring for hypertension exceeds $10 billion (Dosh, 2001). Hypertension is also a major risk factor for stroke and vascular dementia (Meyer, Rauch, Rauch, & Haque, 2000; Meyer, Rauch, Rauch, Haque, & Crawford, 2000; Neaton, Wentworth, Cutler, Stamler, & Kuller, 1993).

Hypertension affects almost 65 million Americans, or 28.7% of the adult US population, according to National Health and Nutrition Examination Survey (NHANES) data (Hajjar & Kotchen, 2003). NHANES survey data from 1999-2000, compared with previous phases (1988-1991), indicated an increase of hypertension of 3.7%. Hypertension increases with age. Of those 60 years or older, 65.4% had hypertension. The prevalence of hypertension is also higher in women. Over 30% of women in the NHANES study had hypertension. Furthermore, different ethnicities have varying hypertension prevalence rates. Thirty three and a half percent of non-Hispanic blacks had hypertension, the highest prevalence of any ethnicity (Hajjar & Kotchen, 2003).

Hypertension is also a particularly prominent problem in China. The prevalence and absolute numbers of hypertension in China has increased dramatically during the past several decades (Wang et al., 2004). Results of the InterASIA study indicate that 27.2% of adults age 35 to 74 in China have hypertension (Gu et al., 2002). This prevalence exceeds that of many developing countries and is similar to that of many industrialized

nations such as the U.S. Moreover, the trend of increase in prevalence was found to be much greater in younger age groups compared with older age groups (Gu et al., 2002).

The consequences of hypertension may also be differentially affected by ethnicity. For example, high blood pressure has been found to be a larger contributor to the incidence of stroke in Asian populations compared to Western populations (Zhang, Liu, & Li, 1996). The Cooperative Research Group on the Study of Trends of Cardiovascular Diseases in China and Preventative Strategies for the 21st Century (2001) reports that the overall relative risk of stroke associated with hypertension is 5.43 and that hypertension may account for about half of all deaths from stroke in China (Khor, 2001). Thus, it is important to examine neuropsychological correlates of hypertension in Chinese individuals.

Pathophysiology and consequences of hypertension. Blood pressure is the pressure required to move blood through the circulatory bed. It is primarily determined by the pumping action of the heart, or cardiac output (CO), and the tone of the arteries, known as peripheral resistance (PR) or systemic vascular resistance. Both CO and PR are, in turn, affected by a number of factors that have complex interactions, including diet, stress, genetics, and obesity (Vikrant, 2001). Although an increase in CO may be involved in the initiation of essential hypertension, individuals with established hypertension have elevated PR and normal CO (Cowley, 1992). Elevated PR promotes damage to the heart, kidneys and brain.

1. Heart. In order to adequately pump blood through the body in the face of increased resistance, the heart must pump harder. Because the heart muscle is constantly exercised, ventricular hypertrophy may develop. Eventually, the heart is unable to

maintain this continuous output and the hypertrophied muscle demands more oxygen than can be supplied. Hypertension also causes other changes in the heart (e.g., increases in shear stress, in lipid deposition, in adhesion molecules, etc.) that contribute to atherosclerosis and lead to coronary artery disease (Wong, Black, & Gardin, 1999). Hypertension is a major risk factor for coronary heart disease and coronary heart disease is the leading cause of death in hypertensive patients (Watkins, 2004).

2. Kidneys. Because the blood vessels become less elastic (more stiff) in EH, lipids are more readily deposited in the vascular wall (atheromas), which, in turn, may lead to thrombus formation and possible emboli. Hypertension-induced arteriosclerosis may cause atrophy of the renal vasculature, resulting in a malignant form of hypertension. Without adequate blood supply, renal failure is also a frequent cause of death in patients with hypertension (Guyton & Hall, 2000).

3. Brain. Hypertension can lead to swelling in the brain and hemorrhage. As previously discussed, hypertension plays a significant role in the development of arteriosclerosis and atherosclerosis. The plaques that develop in the stiff blood vessels can impede blood flow to the brain and result in ischemic disease. Hypertension-mediated atherothrombotic lesions also cause stroke and cerebrovascular disease. Hypertension is a major risk factor for stroke, vascular dementia, and possibly Alzheimer's Disease (Meyer, Rauch, Rauch, & Haque, 2000; Meyer, Rauch, Rauch, Haque, & Crawford, 2000; Neaton, Wentworth, Cutler, Stamler, & Kuller, 1993), and can cause cognitive dysfunction by acting on the cerebral vasculature and directly on the brain itself.

Blood pressure and cognitive function

Although some researchers argue that the association between blood pressure and cognitive dysfunction is not yet fully established, epidemiological studies consistently support this hypothesis (Papademetriou, 2005). Even among stroke-free and dementia-free individuals, hypertension or higher blood pressure levels have been related to lowered levels of cognitive function in various cross-sectional and longitudinal investigations (Elias, 1998; M. F. Elias, R. B. D'Agostino, P. K. Elias, & P. A. Wolf, 1995; Elias, Wolf, D'Agostino, Cobb, & White, 1993; P. K. Elias, R. B. D'Agostino, M. F. Elias, & P. A. Wolf, 1995; Farmer et al., 1990; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Waldstein, Brown, Maier, & Katzel, 2005; Waldstein, Ryan, Manuck, Parkinson, & Bromet, 1991). Very low blood pressure has also been found to be related to cognitive impairment. Recent reports (e.g., Glynn et al., 1999) suggest an inverted U-shaped relationship between blood pressure level and cognitive function such that very low and very high levels of blood pressure are associated with worsened cognitive function. This relationship may depend on age (Guo, Viitanen, Fratiglioni, & Winblad, 1996; Pearce, 1996). Confirmation of this relationship across ethnicities is also warranted given that the decline in cognitive function associated with extremes of systolic blood pressure in older Caucasians appears to be muted in elderly African Americans (Bohannon, Fillenbaum, Pieper, Hanlon, & Blazer, 2002). In addition, the Honolulu-Asia Aging Study also found that midlife systolic blood pressure predicted reduced cognitive function in later life among individuals of Asian ethnicity living in Hawaii (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995).

The relationship between cognition and blood pressure is complex and may be influenced by individual differences that include (1) sociodemographic factors (e.g., age, ethnicity, educational level, and socioeconomic status), (2) medical factors, especially cardiovascular risk factors that may potentiate the adverse effects of high blood pressure (e.g., diabetes mellitus, hypercholesterolemia, and hyperinsulinemia), (3) the duration of extreme blood pressure, and/or (4) side effects of anti-hypertensive medications (Glynn et al., 1999). Despite these complexities, recent literature reviews have concluded that hypertensives exhibit mild but epidemiologically important cognitive deficits (Waldstein, 1995; Waldstein, Brown, Maier, & Katzel, 2005).

Hypertension and specific cognitive deficits. Although results vary across studies as a result of sampling variability and specific measures used, hypertensive patients compared to normotensive individuals have been shown to have impaired performance in cognitive domains of memory (e.g., nonverbal, episodic, working, recall), executive function, abstract reasoning, mental flexibility, constructional ability, attention, perception, reading, speed of cognition, psychomotor or perceptuo-motor speed, and manual dexterity (Boone, Miller, & Lesser, 1993; M. F. Elias, R. B. D'Agostino, P. K. Elias, & P. A. Wolf, 1995; P. K. Elias, R. B. D'Agostino, M. F. Elias, & P. A. Wolf, 1995; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Ostrosky-Solis, Mendoza, & Ardila, 2001; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Strandgaard & Paulson, 1995; Waldstein, Brown, Maier, & Katzel, 2005; Waldstein, Ryan, Manuck, Parkinson, & Bromet, 1991; Waldstein et al., 2003). The negative effects of hypertension on cognitive function appear to be especially pronounced on tasks that tap executive functions, speed of processing, memory, and attention (Elias, Wolf, D'Agostino, Cobb, &

White, 1993; Raz, Rodrigue, & Acker, 2003; Robbins, Elias, Croog, & Colton, 1994). These effects are observed even when hypertensive participants are compared to controls with borderline high blood pressure (Harrington, Saxby, McKeith, Wesnes, & Ford, 2000). Interestingly, neuropsychological sequelae of hypertension appear to be more pronounced in younger hypertensive individuals (e.g., those ages 23 to 40). There is also some evidence to suggest that this relationship is independent of certain demographic, psychosocial, and behavioral-related factors such as alcohol use (Waldstein et al., 1996). In a later study, Waldstein also found that the adverse consequences of hypertension in older adults was more pronounced for female than male hypertensive patients, findings which suggest that specific gender subgroups are more differentially vulnerable to certain cognitive deficits associated with hypertension (Waldstein & Katzel, 2004)

Mechanisms to explain the relationship between hypertension and cognitive function

As noted previously, cognitive deficits in hypertension have been attributed to a variety of biological and behavioral mechanisms. A model of these potential mechanisms in provided in Figure 1. This model will be explicated in this section.

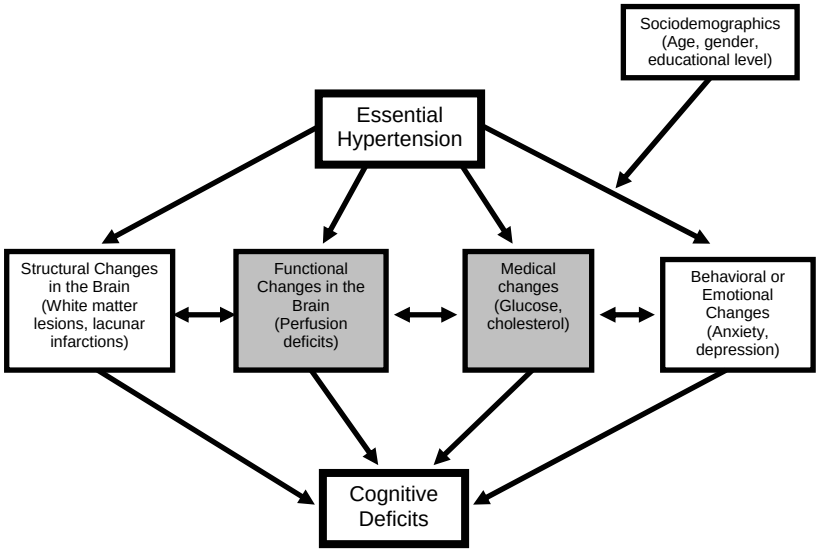


Figure 1: Model of describing the relationship between EH and Cognitive Function

The relationship between cognitive function and hypertension may be explained by physiological changes associated with the disease process, anti-hypertension medication use, and/or behavioral and emotional alterations associated with hypertension. This section will review each mechanism in detail, specifying the functional and structural brain changes that result from hypertension, the impact of various types of anti-hypertensive drugs on cognitive performance, and the role of psychological factors such as stress, anxiety, and depression in the association between hypertension and cognitive function.

1. Physiological. Chronic hypertension leads to vascular remodeling with narrowing of the lumen and wall thickening (Strandgaard & Paulson, 1994). This, in turn, may affect cerebral blood flow and disturb cerebral metabolism and structure. The Rotterdam Study (Breteler et al., 1994; Hofman et al., 1997), among other investigations, provides evidence to support the hypothesis that alterations in cerebral white matter may explain the relationship between high blood pressure levels and cognitive deficits.

a. *Functional changes in the brain*. Under normal conditions, human cerebral blood flow is approximately 50 ml/100 g/min. This blood flow is kept constant, despite changes in perfusion pressure, through a mechanism known as the autoregulation of cerebral perfusion. If perfusion pressure is increased, vasoconstriction occurs and if pressure decreases, vasodilation follows. This auto-regulatory mechanism prevents the risk of cerebral hyper- and hypo- perfusion respectively. The remodeling of the cerebral vasculature that occurs as a result of hypertension prevents cerebral hyperperfusion at high blood pressure, but increases the risk of hypoperfusion at a perfusion pressure higher than normal (Semplicini, Maresca, Sartori, Calo, & Pessina, 2001).

Despite a normal mean cerebral perfusion, hypertension is associated with regional alteration of cerebral perfusion, particularly in the frontal and temporal lobes (Semplicini, Maresca, Sartori, Calo, & Pessina, 2001). Hypoperfusion and hypoxia-ischemia may result in structural changes, such as a loss of myelin in the white matter (Skoog, 1998) or the destabilization of neurons and synapses (Qiu, Winblad, & Fratiglioni, 2005) in these area, thus affecting cognitive function.

b. *Structural changes in the brain: Lacunar infarctions and white matter lesions*. Microvascular alterations in hypertension may also lead to lacunar infarction caused by consequent focal ischemia, perivascular oedema, disruption of the blood-brain barrier, cerebal diaschisis, and cortical deafferentation. In asymptomatic hypertensive patients, small lacunae have been found to be associated with a small, but significant, reduction in cortical perfusion (Semplicini et al., 2000). Neuropsychological researchers have hypothesized that these infarcts are associated with cognitive impairments (den Heijer et al., 2005; Ostrosky-Solis, Mendoza, & Ardila, 2001), however evidence is controversial. Cerebral lacunar infarctions have been shown to be associated with cognitive impairment (Koga et al., 2002; Kuller et al., 1998; Longstreth et al., 1998), yet contradictory findings have also been reported (Chodosh et al., 1988; Matsubayashi, Shimada, Kawamoto, & Ozawa, 1992; Snowdon et al., 1997).

Chronic elevation in blood pressure adversely affects the brain in other ways. In otherwise asympotmatic older adults, it increases the likelihood of structural brain abnormalities (DeCarli et al., 1999; Salerno et al., 1992; Schmidt et al., 1995; Strassburger et al., 1997), especially white matter hyperintensities (Sierra et al., 2004). Leukoaraiosis, or white matter lesions, can be detected as white matter hyperintensities

by T2-weighted Magnetic Resonance Imaging (MRI) images or by white matter hypodensities on computed tomography. White matter lesions are relatively non-specific radiographic lesions which are associated with normal aging (Raz, Rodrigue, & Acker, 2003) and may be produced by a variety of pathophysiological processes. In the elderly, white matter lesions are predominately found in patients with vascular risk factors and cerebrovascular diseases and in people with various degrees of mental deterioration (Pantoni et al., 1999). Hypertension, particularly high systolic blood pressure, is a main risk factor for white matter lesions (Dufouil et al., 2001; Pantoni & Garcia, 1997; Roman, 1987; Skoog et al., 1996). However, some authors have reported contradictory findings of either no relationship or an inverse relationship between white matter lesions and blood pressure levels (Guo, Viitanen, Fratiglioni, & Winblad, 1996; Pohjasvaara et al., 1998; Raiha, Tarvonen, Kurki, Rajala, & Sourander, 1993). Other vascular risk factors associated with white matter lesions include history of stroke and heart disease (Breteler et al., 1994; Raiha, Tarvonen, Kurki, Rajala, & Sourander, 1993), atrial fibrillation (Raiha, Tarvonen, Kurki, Rajala, & Sourander, 1993) and diabetes mellitus (Kinkel, Jacobs, Polachini, Bates, & Heffner, 1985).

The fact that white matter lesions can be found in hypertensive individuals in particular suggests that long-standing hypertension may cause lipohyalinosis and thickening of the vessel walls with narrowing of the lumen of the small perforating arteries. This could, in turn, lead to ischemia in the terminal distribution territories of these vessels, i.e., the deep white matter ((Rigaud, Seux, Staessen, Birkenhager, & Forette, 2000). Some researchers purport that hypertension may cause demyelination of

the white matter and consequent cognitive decline (van Swieten et al., 1991). In these examples, functional changes in the brain may lead to structural changes.

Several studies with neurologically healthy individuals have shown that white matter hyperintensities are associated with a decline in cognitive function, independent of the size of the lesion and the age of the patient (Garde, Lykke Mortensen, Rostrup, & Paulson, 2005). White matter hyperintensities, especially around the periventricular area, are related to deficits in speed of cognitive processing and attention (de Groot et al., 2000; Fukui, Sugita, Sato, Takeuchi, & Tsukagoshi, 1994; Ylikoski et al., 1993). Furthermore, executive functions mediated by the frontal lobe are also particularly vulnerable to alteration in the presence of white matter hyperintensities (Cohen et al., 2002; DeCarli et al., 1995), possibly as a result of a disruption in the frontal-subcortical circuits which compromise frontal lobe functions (O'Sullivan et al., 2001; Pugh & Lipsitz, 2002; Tekin & Cummings, 2002). Although lesions tend to be more prevalent in the frontal lobe in hypertensive individuals (possibly resulting from perfusion changes that differentially affect the frontal and temporal lobes), lesions may be found in any area of the brain. Their exact location may influence which cognitive functions may be affected. Therefore, it is not surprising that some studies have reported the absence of an association between white matter lesions and specific cognitive functions (Fein et al., 1990; Hendrie, Farlow, Austrom, Edwards, & Williams, 1989; Hunt et al., 1989; Tupler, Coffey, Logue, Djang, & Fagan, 1992; Wahlund, Almkvist, Basun, & Julin, 1996).

Other structural brain changes. Other structural brain changes have been associated with hypertension. For example, increased neurofibrillary tangles and brain atrophy, specifically in the structures affected by Alzheimer's Disease pathology such as

the hippocampus and amygdale, have been found in the brains of hypertensive individuals upon autopsy (Petrovitch et al., 2000). Animal studies with a strain of spontaneous hypertensive rats, who shown a range of impairment in cognitive ability, have demonstrated a reduction in the expression of cortical nicotinic acetylcholine receptors (Hernandez, Hoifodt, & Terry, 2003). These changes in nicotinic receptors were found to be associated with impaired performance on both spatial and non-spatial learning and memory-related tasks (Gattu, Terry, Pauly, & Buccafusco, 1997).

Measurement of white matter lesions. T2-weighted MR images of the brain are used to determine the presence of white matter lesions and lacunar infarctions. Several scales have been developed that quantify white matter hyperintensities (WMH), often for use in specific studies of particular patient or subject cohorts. Some scales may focus on a specific type of lesion (for example those in the periventricular areas of the white matter immediately surrounding the ventricle), while other are interested in diffuse WMH. Independent evaluations of inter- and intra-rater reliability in one study found high intra-observer agreement (with kappas ranging from 0.90 to 0.95) and good inter-observer agreement (kappas ranging from 0.72 to 0.84) (Mantyla et al., 1997). The observer reliability of seven different rating scales employed in seven distinct studies was examined (Wardlaw, Ferguson, & Graham, 2004). Weighted kappas ranging from 0.20 to 0.88 were reported and inter-observer reliability was consistently directly proportion to the amount of WMH. The varying levels of reliability may also account for the disparate findings regarding the association between white matter lesions and specific cognitive changes reported in the literature.

2. Medications and cognitive function. Various classes of drugs can be used to treat hypertension. Diuretics, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, Ca^{2++} channel blockers, and sartanes are some common examples. Early studies of the impact of anti-hypertensive medication on cognitive function focused specifically on impairments of cognitive performance resulting from their use. More recently, however, studies have begun to investigate the positive effect of these drugs on cognitive function in hypertensive individuals. Amenta and colleagues (2002) (Amenta, Mignini, Rabbia, Tomassoni, & Veglio, 2002) conducted an analysis of published clinical data from studies including the Framingham study, the Systolic Hypertension in Europe trial, and the Rotterdam Study. Diuretics neither improved nor worsened cognitive function. Although there were no initial changes in cognitive function after beta-blocker administration, propranolol was found to be associated with cognitive worsening and beta-1 selective compounds were associated with slight cognitive improvement. ACE inhibitors positively influenced cognitive function (e.g., Starr, Whalley, & Deary, 1996). ACE inhibitors are hypothesized to positively influence cognitive function because of their affinity to inhibit brain ACE activity and to remove the angiotensin-II-induced inhibition upon brain cholinergic-mediated function (Barnes et al., 1990). Angiotensin-I metabolism may then be activated by alternate pathways, which would increase the synthesis of angiotensin-IV, a byproduct that has vasodilating and cognitive-enhancing properties.

Amenta and colleagues (2002) found that, in general, treatment of hypertension with Ca^{2++} antagonists was accompanied by an improvement in cognitive function and a lower incidence of vascular dementia. Although nifedipine was reported to impair

cognitive function, other dihydropyridines and verapamil significantly improved performance on cognitive tests. Previous research suggests that dihydropyridine-type Ca^{2++} antagonists are the class of drugs with the most documented protective effect on hypertensive brain damage (Amenta, Di Tullio, & Tomassoni, 2003). Interestingly, the Ca^{2++} channel blockers positively impact cognitive function in non-hypertensive individuals as well (Rigaud, Seux, Staessen, Birkenhager, & Forette, 2000). Losartan, a selective non-peptide angiotensin-II receptor antagonist, is one is one particular sartane that has been found to improve even minimal deficits in memory, attention, and concentration, as well as depression and anxiety in elderly hypertensive patients (Tedesco et al., 1999). Barnes and colleagues (1990) (Barnes et al., 1990) found that losartan has an anxiolytic-like effect without reducing alertness while enhancing cognitive performance in mice.

3. Behavioral and emotional alterations. Several decades ago, research psychologists proposed that behavioral or emotional changes, such as stress, anxiety, or depression, associated with hypertension may influence cognitive performance (e.g., Elias, Robbins, Schultz, Streeten, & Elias, 1987). There is considerable literature dating back to the 1970's documenting the importance of psychological factors in the development of hypertension. Julius, Pickering, and other behavioral cardiovascular health researchers have proposed a general model in which environmental stressors interact with psychological factors to cause hypertension. The psychological factors determine how the stressful stimulus is interpreted. Psychological factors that can influence this evaluation of the environment include personality variables (i.e., trait anxiety) and previous experience. Perceived stress leads to activation of the sympathetic

nervous system (SNS) and other biological consequences such as stimulation of the hypothalamo-pituitary axis. Increased blood pressure is one result of SNS activation.

Experimental studies measuring regional sympathetic activity in individuals with essential hypertension using eletrophysiologic (sympathetic nerve recording) and neurochemical (measure of norepinephrine spillover) techniques have confirmed activation of sympathetic outflow to the heart, kidneys, and skeletal muscle in individuals under age 45 (Esler, Rumantir, Kaye, & Lambert, 2001). Increase in SNS activity is a mechanism proposed for both initiating and sustaining blood pressure elevation. Sympathetic hyperactivity and parasympathetic underactivity are central mechanisms that have been found to explain the development of early and borderline hypertension, as well as maintain sustained essential hypertension (Esler et al., 1991; Esler, Zweifler, Randall, Julius, & DeQuattro, 1977; Guzzetti et al., 1988; Jennings, 1998; Julius, 1991, 1998; Julius, Pascual, & London, 1971; Mancia, Grassi, Parati, & Zanchetti, 1997; Mark, 1996). Microneurography studies have revealed high sympathetic nerve fiber activity to be organ system specific, to parallel the magnitude of hypertension, and to be more characteristic of essential hypertension than of secondary hypertension (Grassi, Colombo, Seravalle, Spaziani, & Mancia, 1998).

Besides physiological measures of SNS activation, self-report questionnaires that measure perceived stress, anxiety, and/or depression can also be used to document the relationship between distress and cognitive function. Professional diagnoses of anxiety or depression could be another proxy measure of SNS activation. Recently, a meta-analytical review of prospective studies on psychosocial factors and hypertension (Rutledge & Hogan, 2002) found that the sample-weighted effect sizes for anxiety (r =

0.09, 95% CI, 0.06–0.12) and depression (r = 0.09, 95% CI, 0.07–0.11) differed significantly from zero ($p < 0.001$). However, four prospective studies failed to show an association between hypertension and anxiety (Jonas, Franks, & Ingram, 1997). There are various self-report measures of stress with diverse reliability and validity standards, and these variations in methodology may account for the inconsistencies across studies.

Early studies confirmed cognitive deficits in individuals with hypertension, even after controlling for anxiety and depression (Elias, Robbins, Schultz, & Pierce, 1990; Pentz, Elias, Wood, Schultz, & Dineen, 1979; Schultz, Dineen, Elias, Pentz, & Wood, 1979; Waldstein, Manuck, Ryan, & Muldoon, 1991). However, anxiety and depression, often at pathological levels, have been shown to be related to cognitive decline (DeLuca et al., 2005; Sinoff & Werner, 2003). If the level of anxiety or depression is based on self-report, researchers have not found such associations with cognitive deficits (e.g., (Collie, Shafiq-Antonacci, Maruff, Tyler, & Currie, 1999; Waldstein, Ryan, Jennings, Muldoon, & Manuck, 1997). These studies were based on data collected from Causacian American individuals. A re-examination of the impact of self-reported anxiety and depression on the association between hypertension and cognitive function in individuals of a different ethnicity, i.e., Chinese participants, may provide evidence that these findings extend across ethnic groups.

Summary and overview

Essential hypertension (EH) has been shown to be associated with cognitive deficits in numerous epidemiological studies. The mechanism to explain this relationship is not well-established. Reduced cognitive function may be a consequence of functional or structural changes in the brain caused by chronic high blood pressure, including white

matter lesions and lacunar infarctions. Behavioral or emotional changes, such as stress, anxiety, and/or depression, may also account the changes in cognitive function observed in hypertensive individuals.

The present cross-sectional study examines two potential mechanisms underlying the relationship between essential hypertension and cognitive deficits in a group of Chinese middle-aged hypertensive individuals and normotensive controls. Those with MRI-detected white matter hyperintensities or lacunar infarctions were excluded from analysis in order to rule out these particular structural changes as a possible mechanism explaining the relationship between EH and cognitive function. The relationship between EH and cognitive performance was determined for this sample. The role of emotional alterations as a mechanism for cognitive dysfunction in hypertensive individuals without structural brain change was examined. To date, there are no neuropsychological studies in the literature examining the cognitive function of healthy, middle-aged hypertensives without these brain abnormalities as documented by MRI. Furthermore, the importance of structural brain changes identified via MRI brain scans and emotional alterations in explaining the relationship between EH and cognitive deficits has not been clearly delineated. Lastly, although evidence suggests that hypertension may not affect cognitive function in the same manner across ethnicities, no research has been published on the potential cognitive deficits that may exist in a middle-aged Chinese sample with hypertension.

Hypotheses

(1) Middle-aged individuals with hypertension without white matter lesions or lacuna infarctions detectable on an MRI scan will perform significantly worse

than controls on neuropsychological tests measuring memory, attention, and speed of processing.

(2) (a) Individuals with hypertension will have significantly higher self-reported anxiety and depression scores compared to controls, however, (b) the association between hypertension and cognitive function will be independent of these self-report ratings. It is expected that, based on prior research, self-reported anxiety and depression ratings in the hypertensive group will not be significantly associated with objective neuropsychological battery performance.

(3) The association between hypertensive status and (a) emotional status and (b) cognitive function will be moderated by socio-demographic variables (age, educational level, gender), and/or medical variables (serum glucose levels, total cholesterol levels, triglyceride levels, and HDL and LDL levels).

Methods

Sample

The present study is a sub-analysis of a database from a study conducted at Beijing Anzhen Hospital by Principal Investigator and Deputy Director of the Beijing Institute of Heart, Lung & Blood Vessel Diseases Dong Zhao, M.D., Ph.D. The original study database was provided without identifiers and consisted of information from 95 hypertensive patients and 95 age- and education-matched controls. These data were collected from participants in a surveillance study of more than 60,000 subjects established in 1980. In 1996, all participants over age 35 were assessed for hypertension. In 2002, these individuals were randomly mailed information about participation in the

original study and a screening questionnaire used to determine eligibility for the original study. To be included in the sample, individuals had to be between the ages of 50 and 65. Those with a history of stroke, angina, myocardial infarction, peripheral vessel diseases, diabetes mellitus, cancer, and/or depression were excluded from the study. In addition, those with self-reported cognitive problems and those unable to have an MRI scan of the brain were excluded from participation.

Of the 190 individuals who met inclusion criteria for the original study database, for this sub-analysis those participants with any identifiable periventricular or deep-seated lesion(s)/white matter hyperintensities were excluded (n = 73). In addition, those participants with lacuna infarctions were also excluded (n = 12). Seven participants had both identifiable lesions and lacuna infarction, thus the resulting sample consisted of 112 participants – 46 hypertensives and 66 normotensive controls. Approximately one third of the controls were excluded as a result of the presences of MRI-identifiable white matter lesions and/or lacunar infarctions. As previously discussed, white matter lesions are relatively non-specific radiographic lesions which are associated with normal aging (Raz, Rodrigue, & Acker, 2003), as well as various pathophysiological processes. It is possible that the control individuals who were excluded on this basis had other vascular risk factors and/or susceptible to structural brain abnormalities because of their age. Individuals with a self-reported history of transient ischemic attacks (TIA) were not excluded from the present sample because the attacks were transient and did not result in lacunar infarctions or white matter lesions.

All participants in the study provided informed consent and the study was approved by the Scientific and Ethics Committee of the Beijing Institute of Heart, Lung

& Blood Vessel Diseases before data collection began. Permission was given by Principal Investigator and Deputy Director Dong Zhao to use the dataset (see Appendix 1). Moreover, The Institutional Review Board of Uniformed Services University of the Health Sciences approved collaboration with the Beijing Institute of Heart, Lung & Blood Vessel Diseases and the use of this database for analysis (see Appendix 2).

Instruments

1. Interview. An interview was conducted to obtain socio-demographic information (e.g., age, gender, ethnicity, years of education completed), behavioral data (e.g., smoking history, drinking history, frequency of physical activity and activeness during leisure time), medical history [history of hypertension, hypertension stage, history of hypertensive medication, highest past blood pressure and most recent blood pressure, history of transient ischemic attacks (TIA), history of coronary heart disease (CHD), history of peripheral artery disease (PAD), history of diabetes), and family medical history (e.g., history of hypertension, CAD, and stroke in either or both parents).

2. Medical examination. A medical examination was conducted on all participants. Height and weight was used to calculate Body Mass Index (BMI). Two blood pressure readings and one blood sample were taken. Blood was tested for levels of serum glucose, total cholesterol, triglycerides, high density lipoproteins (HDL), and low density lipoproteins (LDL).

3. Self-report questionnaires. Zung's Self-Report Anxiety Survey (SAS) (Zung, 1971) and Zung's Self-Report Depression Survey (SDS) (Zung, 1965) were used to determine participant-rated levels of anxiety and depression.

4. Neuroimaging scan. All participants received a Magnetic Resonance Imaging scan of their brain using a Siemens Sonata 1.5T MRI. A neurologist identified the presence of periventricular and/or deep-seated lesions and the grade of leukoaraiosis on a scale from 0 to 3 (Salerno et al., 1992). Lacunar infarction was identified if the lesion was between 3mm and 10 mm on the MRI scan.

5. Neuropsychological testing. Seven neuropsychological tests were administered via a computer software program developed by the Institute of Psychology at the Chinese Academy of Sciences. It was first employed in the present study and measures reaction time, arithmetic ability, visual-spatial perception, working memory, and visual and verbal recognition memory. The program randomly generated the specific questions to be answered from a database of numbers, Chinese characters, and figures. All tests were scored by the computer based on the participant's response entered by pressing a key (or not responding) as required. The following seven tests were completed and scored as indicated below.

a. *Digit discrimination test***.** This test is used to assess sustained attention and vigilance and motor speed. Ten single digit numbers (0-9) are shown on the computer screen one by one. After each number, the subject must press the corresponding computer key as quickly as possible. The dependent variable is the response time averaged across the 10 trials.

b. *Mental arithmetic test*. This test is used to assess arithmetic ability. The time to take the test measures information processing speed. Ten addition or subtraction equations are shown on the computer screen one by one. The participant must respond to each equation by key pressing the single digit number answer (0-9). Once the participant

provides an answer to the equation, a new equation appears. This test gets progressively harder. The first 3 equations involve the addition or subtraction of 2 single digit numbers (0-9). The next 4 equations require subtraction of 2 double-digit numbers (10-99) and the following 3 equations involve addition and/or subtraction of 3 double-digit numbers (10-99). There are 3 dependent variables: the total number of correct answers out of 10, the total time to complete the task, and the efficiency at the task (calculated by dividing the number correct by the total time).

c. *Chinese character rotation test*. This test is used to assess visual-spatial perception and spatial orientation. The time to complete the test measures speed of information processing. The test requires discriminating a Chinese character from its mirror image even when it is rotated. Ten Chinese characters (from a database of approximately 100 Chinese characters) are shown to the participant one by one. Five are correct characters and five are mirror image characters. Some are rotated and others are not. The participant must identify if the character is a correctly drawn character or a mirror image, despite rotation, by pressing one of two fixed bars. There are 2 dependent variables: the number correct out of 10 and the total score on the task, which ranges from 0-20 and takes into account the difficulty of the character and its rotation.

d. *Digit working memory test*. This test is used to assess working memory (maintenance and manipulation). In this task, addition or subtraction equations composed of 2 single digit numbers (0-9) are shown one by one on the screen. After the equation disappears for a while, the participant is asked to key press the answer, which is also always a single digit (0-9). If successful, the participant has a working memory of 1 digit. Next, another equation is displayed. It disappears and is replaced by a second equation.

The participant must remember both answers and key press each answer sequentially when the computer asks for the answer. Successful completion gives the participant a working memory score of 2 digits. This process continues. Three equations are presented and the participant must remember and key press the 3 answers, etc., etc. All numbers are randomly generated. When the participant makes an error, the task ends immediately. The dependent variable, then, is the extent of working memory as defined by the number of answers to equations that can be remembered and key pressed.

The following three recognition tests are designed to measure recognition memory and response inhibition. The three computerized tasks are structured similarly, but different symbols groupings (e.g., words, numbers, figures) are substituted for each test. Ten to 20 symbols are displayed one by one. Then the participant is presented with 20 to 40 more symbols also presented one by one. He/she must decide whether the symbol is has been seen before or has not been presented. He/she responds by pressing the space bar or not responding at all, respectively. There are 4 dependent variables for these tests: the number of symbols correctly identified as having been seen before (number correct), the number of symbols that were not correctly identified as having been seen before (number of errors), the number of symbols incorrectly identified as having been seen before (number of false identifications), and the total score for the task calculated by subtracting the number correct from the number of false identifications.

e. *Dual word recognition test*. This test is used to assess verbal recognition memory. In this task, the symbol is a word made up of two Chinese characters. The 20 words are presented one by one. Then 40 words are displayed one by one and the participant must decide if he/she has seen it before, in which case he/she hits the space

bar, or if he/she has not seen it before, in which case he/she does nothing. The 4 dependent variables include the number correct out of 20 possible words previously displayed, the number of errors out of 20 possible words previously displayed, the number of false identifications out of 20 possible words not shown previously, and the total score, which was calculated by subtracting the number correct from the number of false identifications.

f. *Tri-digit recognition test*. This test is used to assess visual recognition memory. In this task, the symbol is a 3-digit number. The 10 3 digit numbers are presented one by one. Then 20 3-digit numbers are displayed one by one and the participant must decide if he/she has seen it before, in which case he/she hits the space bar, or if he/she has not seen it before, in which case he/she does nothing. The 4 dependent variables include the number correct out of 10 possible numbers previously displayed, the number of errors out of 10 possible numbers previously displayed, the number of false identifications out of 10 possible numbers not shown previously, and the total score, which was calculated by subtracting the number correct from the number of false identifications and doubling this answer.

g. *Meaningless figure recognition test*. This test is used to assess visual recognition memory. In this task, the symbol is a meaningless figure. The 10 figures from a database of 20 figures are randomly chosen to be presented one by one. Then, the 20 figures are displayed one by one and the participant must decide if he/she has seen it before, in which case he/she hits the space bar, or if he/she has not seen it before, in which case he/she does nothing. The 4 dependent variables include the number correct out of 10 possible figures previously displayed, the number of errors out of 10 possible

figures previously displayed, the number of false identifications out of 10 possible figures not shown previously, and the total score, which was calculated by subtracting the number correct from the number of false identifications and doubling this answer.

In summary, the cognitive abilities measured by each of the seven tasks are:

(1) Digit discrimination response time = sustained attention and vigilance and motor speed

(2) Mental arithmetic = arithmetic ability, speed of information processing

(3) Chinese character rotation = visual-spatial perception, spatial orientation, speed of information processing

(4) Digit working memory = working memory (maintenance and manipulation)

(5) Dual word recognition = verbal recognition memory

(6) Tri-digit recognition = visual recognition memory

(7) Meaningless figure recognition = visual recognition memory

Total score was calculated by hand. The total score from tests 1 to 4 were scaled from 0-30 and tests 5 to 7 were scaled from 0 – 20, according to the participant's age using tables provided by the program. The scaled scores for tests 5 to 7 were averaged and then added to the scaled scores from the 4 other tests. The range of the total score variable is 0 to 140.

As previously discussed, the computerized neuropsychological battery was created by the Chinese Academy of Sciences and employed for the first time in the present study. There is no validation data available, thus Table 2 presents the inter-test correlations and task-total score correlations. Correlations with the Mini-Mental State Examination (MMSE) is also shown.

Table 2. Neuropsychological task-total correlations, inter-task correlations, and correlations with the MMSE

	MMSE	Battery total score	Digit discrimination response time	Mental arithmetic total score	Mental arithmetic total time	Mental arithmetic efficiency	Chinese character rotation total score	Chinese character rotation total time	Chinese character rotation efficiency	Digit working memory	Dual word recognition total score	Tri-digit recognition total score	Meaning-less figure recognition total score
MMSE	-	0.35**	-0.37**	0.10	-0.30**	0.26**	0.20*	-0.09	0.29**	0.17	0.84	0.22*	0.21*
Battery total score		-	-0.63**	0.17	-0.62**	0.61**	0.31**	-0.45**	0.65**	0.72**	0.43**	0.39**	0.46**
Digit discrimination response time			-	-0.08	0.53**	-0.47	-0.10	0.24*	-0.31**	-0.32**	-0.17	-0.14	-0.27**
Mental arithmetic total score				-	-0.02	0.44**	0.03	0.19*	-0.13	0.31**	0.06	0.01	0.10
Mental arithmetic total time					-	-0.84**	-0.07	0.39**	-0.40**	-0.33**	-0.18	-0.10	-0.26**
Mental arithmetic efficiency						-	0.06	-0.27**	0.30**	0.40**	0.19*	0.02	0.24*
Chinese character rotation total score							-	0.05	0.49**	0.20*	-0.04	0.21*	0.05
Chinese character total time								-	-0.73**	-0.12	-0.20*	-0.14	-0.17
Chinese character rotation efficiency									-	0.25**	0.21*	0.23*	0.24*
Digit working memory										-	0.28**	0.28**	0.21*
Dual word recognition											-	0.35**	0.24*
Tri-digit recognition												-	0.19*
Meaning-less figure recognition total score													-

* $p < 0.05$, ** $p < 0.01$

h. *Mini-Mental State Examination*: In addition, a Chinese version of the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was also given to all participants to measure general cognitive ability. The MMSE is often used to indicate possible presence of dementia if the person scores 23 out of 30 or lower. The Chinese version of the MMSE has been used and validated in other Chinese samples (Zhao, personal communication). There are two differences between the English and Chinese versions. With respect to attention and calculation, the Chinese version uses 100 minus 7 minus 7 minus 7, etc. and does not allow the person to spell the word "world" backwards if he/she does not know how to subtract. For the repetition item, a Chinese sentence was used.

Data Analyses

Characteristics of the sample**.** Descriptive statistics were performed on the sample. Independent sample t-tests (for continuous variables) and chi square analyses (for categorical variables) were conducted to determine if the hypertensives and controls differed significantly on socio-demographic, behavioral, medical, medical history, and emotional variables. These univariate analyses determined the factors that were adjusted for in further multivariable analyses.

Cognitive function. A multivariate analysis of covariance (MANCOVA) was conducted with essential hypertension status (EH) as the independent variable (IV) and neuropsychology test scores as the dependent variables (DVs), adjusting for factors that were significant in the univariante analyses. Anxiety and depression were added as

additional factors to determine if the relationship remained, independent of their contribution. Correlations between clinical SBP, DBP, and neuropsychological test scores were conducted. Also, within the hypertensive groups, correlational analyses between self-reported anxiety and depression scores and neuropsychological test scores were conducted.

Emotional status. A MANCOVA was conducted with EH as the IV and self-reported anxiety and depression as the DVs, adjusting for factors that were found to be significant in the univariate analyses.

Testing for moderators. To determine the role of sociodemographic and medical variables as possible moderators of the relationship between hypertension and either emotional status or cognitive function, potential moderator variables were dichotomized and individual two-factor analyses of the variance (ANOVAs) with EH were conducted on emotional status and cognitive function dependent variables. According to Baron & Kenny (1986), a significant interaction term signals a moderator of the relationship between EH and the specific cognitive ability tested in the ANOVA.

Results

Characteristics of the sample. Table 3 shows the socio-demographic, behavioral, and medical characteristics of the sample. MMSE scores were 24 or higher, confirming that no participant showed evidence of dementia. The cutoff point for determining psychological problems using Zung's SAS and SDS is 53. Only three participants were above the cutoff on the SAS and two of them were also above the cutoff on the SDS.

Therefore, scores on these questionnaires in this sample tended to reflect sub-clinical levels of anxiety and depression.

Table 3: Characteristics of the sample

	Sample (N = 112)	**Range**
SOCIO-DEMOGRAPHICS		
Sex – male	35.7% (n = 40)	
Martial status – married	95.5% (n = 107)	
Ethnicity – Han	97.3% (n = 109)	
Age	56.56 yrs (4.86)	50 – 65 yrs
Total years of education	13.13 yrs (3.92)	6 – 24 yrs
BEHAVIORAL FACTORS		
Total years smoking	6.06 yrs (11.56)	0 – 36 yrs
Smoking status – smoker	13.4% (n = 15)	
Total years drinking	2.27 yrs (7.67)	0 – 40 yrs
Drinking status – drinker	12.5% (n = 14)	
Physical activity > 20 minutes 2–5 days/week	84.0% (n = 94)	
BMI	25.32 (3.40)	15.1 – 38.3
Self-reported anxiety	33.70 (6.43)	25 – 57
Self-reported depression	34.63 (7.56)	25 – 63
MMSE	28.37 (1.30)	24 – 30
MEDICAL FACTORS		
Average SBP during medical exam	130.29 mm Hg (19.14)	90 – 180 mm Hg
Average DBP during medical exam	82.17 mm Hg (11.69)	60 – 110 mm Hg
Serum glucose level [+]	79.98 mg/dL (9.56)	63 – 130 mg/dL
Total cholesterol level	190.04 mg/dL (39.58)	111 – 360 mg/dL
Triglycerides level	127.87 mg/dL (69.10)	36 – 395 mg/dL
HDL level	49.88 mg/dL (12.91))	28 – 85 mg/dL
LDL level	118.14 mg/dL (32.06)	57 – 252 mg/dL
MEDICAL HISTORY		
History of TIA – positive	3.6% (n = 4)	
History of CHD – positive	5.4% (n = 6)	
History of PAD	0.0% (n = 0)	
Hisotry of diabetes	0.0% (n = 0)	
FAMILY HISTORY		
Family hx of hypertension – positive	58.1% (n=61)	
Family hx of stroke – positive	33.4% (n = 35)	
Family hx of CHD – positive	34.6% (n = 36)	

Characteristics of the hypertensive group. The characteristics of the hypertensive group are shown in Table 4.

Table 4: Characteristics of the Hypertensive group

	Hypertensive group (n = 46)	**Range**
Years of hypertension	11.33 yrs (10.17)	1 – 35 yrs
Average stage [a]	2.35 (0.71)	1 – 3
Stage 1 [a]	13.0% (n = 6)	
Stage 2 [a]	39.1% (n= 18)	
Stage 3 [a]	47.8% (n = 22)	
Most recent SBP [b]	134.55 mm Hg (13.29)	120 – 170 mm Hg
Most recent DBP [b]	87.73 mm Hg (10.03)	70 – 110 mm Hg
Highest past SBP [b]	167.34 mm Hg (19.26)	130 – 220 mm Hg
Highest past DBP [b]	102.20 mm Hg (12.75)	70 – 140 mm Hg
Taking anti-hypertensive medication in past 2 weeks [c]	65.2% (n = 30)	

[a] Stage measured according to JNC VI criteria.
[b] All blood pressure measures obtained via patient self-report.
[c] Specific type of medication not recorded.

Comparison of hypertensives vs. controls on socio-demographic, behavioral, and medical variables

Table 5 compares socio-demographic, behavioral, and medical differences between the normotensive (n = 66) and hypertensive (n = 46) groups. Hypertensive patients had significantly higher BMIs and lower HDL levels compared to normotensive individuals ($t = 4.71$, $df = 110$, $p < 0.001$ and $t = 3.17$, $df = 110$, $p < 0.01$ respectively). Hypertension was also significantly associated with parental history of hypertension and CHD ($X^2 = 9.86$, $df = 1$, $p < 0.01$ and $X^2 = 6.55$, $df = 1$, $p < 0.05$). Marginally significant differences between groups on serum glucose levels ($t = 1.71$, $df = 110$, $p = 0.092$) and self-identified smoking status ($X^2 = 3.18$, $df = 1$, $p = 0.075$) were found such that hypertensive patients tended to have higher serum glucose levels and be less likely to report smoking.

Table 5: Univariate analyses comparing normotensives and hypertensives

	Controls n = 66	**Hypertensives n = 46**	**T or X^2 value**	**p value**
SOCIO-DEMOGRAPHICS				
Sex – male	33.3%	39.1%	0.397[#]	0.529
Martial status – married	93.9%	97.8%	0.960[#]	0.327
Ethnicity – Han	97.0%	97.8%	0.076[#]	0.782
Age	56.86 yrs (4.95)	56.13 yrs (4.74)	0.785	0.434
Total years of education	13.14 yrs (3.98)	13.11 yrs (3.88)	0.037	0.971
BEHAVIORAL FACTORS				
Total years smoking	5.89 yrs (11.71)	6.30 yrs (11.45)	0.184[a]	0.854
Smoking status – smoker	18.2%	6.5%	3.177[#]	0.075
Total years drinking	2.39 yrs (7.79)	2.09 yrs (7.57)	0.205	0.838
Drinking status – drinker	13.6%	10.9%	0.190[#]	0.663
Physical activity > 20 minutes 2–5 days/week	84.8%	82.6%	0.101[#]	0.751
BMI	24.16 (2.65)	26.98 (3.68)	4.708[a]	<0.001***
Self-reported anxiety	33.02 (5.64)	34.67 (7.38)	1.348[a]	0.180
Self-reported depression	34.22 (7.13)	35.23 (8.19)	0.693[a]	0.490
MEDICAL FACTORS				
Serum glucose level [+]	78.61 (7.50)	81.96 (11.73)	1.709[a]	0.092
Total cholesterol level	192.98 (42.85)	185.83 (34.37)	0.941	0.349
Triglycerides level	120.98 (71.51)	137.76 (64.98)	1.267[a]	0.208
HDL level	52.98 (13.68)	45.43 (10.32)	3.166	0.002**
LDL level	119.00 (36.22)	116.91 (25.23)	0.338	0.736
MEDICAL HISTORY				
History of TIA – positive	4.5%	2.2%	0.443[#]	0.506
History of CHD – positive	3.0%	8.7%	1.716[#]	0.190
FAMILY HISTORY				
Family hx of hypertension +	45.0%	75.6%	9.862[#]	0.002**
Family hx of stroke +	27.0%	40.0%	2.030[#]	0.154
Family hx of CHD +	24.6%	48.8%	6.551[#]	0.010*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[+] Unequal variance was assumed due to significant Levene's test.
[#] X^2 value reported.
[a] Hypertensive > controls.

Comparison of hypertensives vs. controls on cognitive function

In order to test Hypothesis 1, hypertensive patients and normotensive individuals were compared on neuropsychological variables, statistically controlling for the factors found to be statistically significant or marginally statistically significant between groups. The MANCOVA for the neuropsychological variables (adjusting for BMI, HDL levels,

parental history of hypertension and CHD, serum glucose levels, and smoking status) was not significant ($F_{(13,81)} = 1.52$, $p = 0.127$). Univariate analyses showed significant differences found on digit discrimination response time ($F_{(1,93)} = 4.47$, $p < 0.05$) and the MMSE ($F_{(1,93)} = 8.20$, $p < 0.01$) and a trend toward differences on total time for Chinese character recognition ($F_{(1,93)} = 3.22$, $p = 0.076$) and the total score composite variable ($F_{(1,93)} = 3.39$, $p = 0.069$). Hypertensive patients performed worse than controls on all of these tasks.

Correlations of clinical visit average SBP and DBP with neuropsychological task scores without adjusting for risk factor differences between groups showed that both SBP and DBP were negatively correlated with total score on the battery ($r = -0.20$, $p<0.05$ and $r = -0.26$, $p<0.01$ respectively), positively correlated with total time on Chinese character rotation ($r = 0.20$, $p<0.05$ and $r = 0.21$, $p<0.05$ respectively) and negatively correlated with extent of digit working memory ($r = -0.29$, $p<0.01$ and $r = -0.32$, $p<0.01$ respectively) and dual word recognition score ($r = -0.20$, $p<0.05$ and $r = -0.25$, $p<0.01$ respectively). In addition, DBP was negatively correlated with efficiency on the Chinese character rotation task ($r = -0.20$, $p<0.05$) and SBP was positive correlated with digit discrimination response time ($r = 0.20$, $p<0.05$).

Comparison of hypertensive patients vs. controls on emotional status

In order to test Hypothesis 2A, hypertensive patients and controls were compared on self-reported emotional variables, statistically controlling for the factors found to be significant or marginally significant between groups. The MANCOVA for self-reported anxiety and depression scores (controlling for controlling for BMI, HDL levels, parental history of hypertension and CHD, serum glucose levels, and smoking status) was not

significant ($F_{(2,92)} = 2.29$, $p = 0.107$). Univariate analyses showed a trend toward differences in anxiety ($F_{(1,93)} = 3.36$, $p = 0.070$) such that the hypertensive patients reported higher anxiety than the controls.

Relationship between hypertension and cognitive function independent of anxiety and depression

In order to test Hypothesis 2B, self-reported anxiety and depression were added as additional covariates to the initial control factors in the MANCOVA comparing hypertensives and controls on cognitive function. The MANCOVA for neuropsychological variables was not significant ($F_{(13,79)} = 1.29$, $p = 0.235$). Univariate analyses showed significant differences on the MMSE ($F_{(1,91)} = 7.14$, $p < 0.01$) and a trend toward differences on digit discrimination response time ($F_{(1,91)} = 3.71$, $p = 0.057$), total time for Chinese character recognition ($F_{(1,91)} = 3.18$, $p = 0.078$) and the total score composite variable ($F_{(1,91)} = 2.91$, $p = 0.091$). Hypertensive patients performed worse than controls on all these tasks.

Correlational analyses between self-reported emotional status and neuropsychological test performance within the hypertensive group (n = 46) were conducted (Table 6). Zung Anxiety scores did not significantly correlate with any neuropsychological test score. Zung Depression scores were significantly positively correlated with the extent of digit working memory ($r = 0.30$, $p < 0.05$) such that the higher the level of report depression, the higher the extent of digit working memory. All other neuropsychological tests were not significantly correlated with depression.

Table 6: Correlational analyses of self-reported anxiety and depression scores and neuropsychological test scores within the hypertensive group

Neuropsychological test	**SAS: Anxiety *r***	**SDS: Depression *r***
Digit discrimination response time	-0.04	-0.02
Mental arithmetic score	0.15	0.12
Mental arithmetic total time	-0.06	-0.01
Efficiency of mental arithmetic	0.08	0.02
Chinese character rotation score	-0.18	-0.10
Chinese character rotation total time	-0.06	0.09
Chinese character rotation efficiency	-0.01	-0.15
Digit working memory	0.21	0.30*
Dual word recognition score	-0.01	-0.19
Tri-digit recognition score	0.11	-0.08
Meaningless figure recognition score	0.10	-0.01
Total score	0.19	0.06
MMSE	0.01	0.02

* $p < 0.05$

Moderators of the association between hypertension and emotional status

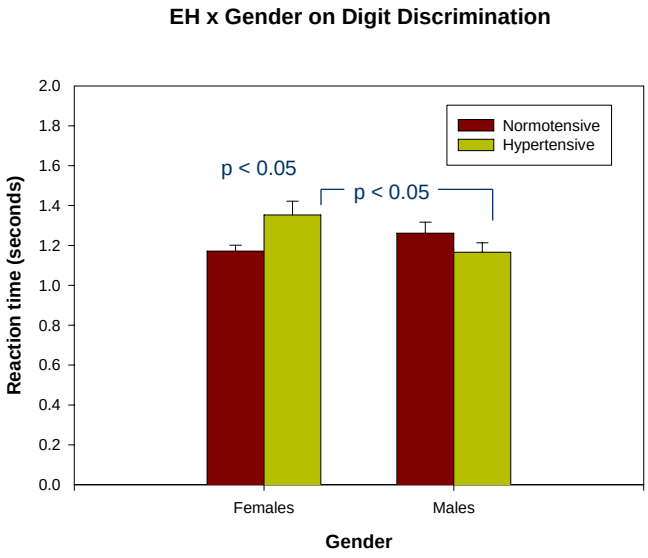
(1) Anxiety: With age dichotomized using a mean/median split at age 56, there was no main effect for age; however there was a trend towards a main effect of EH ($F_{(1,108)} = 3.60$, $p = 0.061$) on Zung Anxiety scores, and a significant age by EH interaction ($F_{(1,108)} = 8.48$, $p < 0.01$). Analyses of the simple effects showed that of those with EH, older individuals had significantly higher levels of anxiety than younger individuals ($t = 2.39$, $df = 28.47$, $p < 0.05$). Within the older age group, those with EH had significantly more anxiety than those without ($t = 2.76$, $df = 22.96$, $p < 0.05$).

There was a lack of main effects, but a trend towards an EH by dyslipidemia (one abnormality among total cholesterol, triglyceride levels, and HDL levels) interaction ($F_{(1,108)} = 2.92$, $p = 0.09$). Analyses of simple effects showed that among those without an abnormality, there was a trend for those with EH to have higher levels of anxiety than those without ($t = 1.77$, $df = 25.01$, $p = 0.088$).

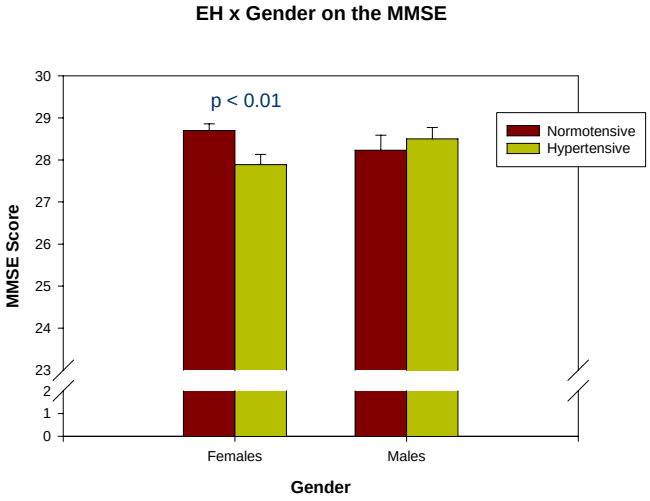
(2) Depression: There were no main effects for triglyceride levels or EH on Zung Depression scores, but a trend towards an EH by triglyceride level interaction ($F_{(1,108)}$ = 3.06, p = 0.083). Analyses of simple effects showed no significant differences within levels of either independent variable.

Moderators of the association between hypertension and cognitive function

(1) Digit discrimination response time: There were no main effects for EH or gender on digit discrimination response time, but the gender by EH interaction was significant ($F_{(1,108)}$ = 6.99, p < 0.01) (Figure 2). Simple effect analyses showed that within females, those with EH had significantly longer reactions times than those without (t = 2.41, df = 37.07, p < 0.05). Of those with EH, the females had significantly longer reaction times than the males (t = 2.23, df = 43.15, p < 0.05).



(2) MMSE: There were no main effects for EH or gender on MMSE performance, but the gender by EH interaction was significant ($F_{(1,108)}$ = 4.57, p < 0.05) (Figure 3). Analyses of simple effects showed that within females, those with EH scored



significantly lower than those without EH ($t = 2.93$, $df = 70$, $p < 0.01$).

(3) Extent of working memory: There was a main effect for EH ($F_{(1,108)} = 8.20$, $p < 0.01$), but not triglyceride levels on the extent of working memory. There was also a triglyceride by EH interaction ($F_{(1,108)} = 5.62$, $p < 0.05$). Analyses of simple effects showed that of those with high triglyceride levels (> 150), those with EH had significantly lower digit working memory than those without ($t = 3.28$, $df = 28$, $p < 0.01$).

Interestingly, the effects of hypertension on cognitive function were found in females in this sample, but not the males. Therefore, gender differences in the sample were examined. .

Gender differences in the sample

Based on the findings that gender moderated the relationship between EH and two cognitive deficits and, in particular, the findings that female hypertensive patients had worse cognitive functioning than normotensive female individuals and in some cases hypertensive male patients, the sample was split by gender. The gender groups (72 female and 40 male) were compared on all socio-demographic, behavioral, and medical psychological variables (Table 7).

The females had significantly higher total cholesterol levels ($t = 2.26$, $df= 110$, $p < 0.05$) and HDL levels ($t = 3.12$, $df = 110$, $p < 0.01$). Significantly more females than males reported engaging in physical activity for at least 20 minutes from 2-5 days a week ($X^2 = 6.94$, $df = 1$, $p < 0.01$). Significantly more males than females were self-identified current smokers ($X^2 = 10.68$, $df = 1$, $p < 0.001$) and drinkers ($X^2 = 12.80$, $df = 1$, $p < 0.001$). Consistent with these findings, males also reported smoking and drinking

Table 7: Univariate analyses comparing females and males

	Females n = 72	**Males n = 40**	**T or X^2 value**	**p value**
SOCIO-DEMOGRAPHICS				
Martial status – married	93.1%	100.0%	2.908[#]	0.088
Ethnicity – Han	97.2%	97.5%	0.008[#]	0.930
Age	55.90 (4.74)	57.75 (4.90)	1.953[a]	0.053
Total years of education	12.81 (3.70)	13.70 (4.29)	1.159[a]	0.249
BEHAVIORAL FACTORS				
Total years smoking [+]	1.29 (6.85)	14.65 (13.80)	5.80[a]	0.0001***
Smoking status – smoker	5.6%	27.5%	10.676[#]	0.001***
Total years drinking [+]	0.34 (2.41)	5.70 (11.68)	2.87[a]	0.006**
Drinking status – drinker	4.2%	27.5%	12.800[#]	0.0001***
Physical activity > 20 minutes 2–5 days/week	68.1%	42.5%	6.939[#]	0.008**
BMI	25.23 (3.66)	25.48 (2.90)	0.368[a]	0.713
Self-reported anxiety	34.06 (6.45)	33.05 (6.43)	0.792	0.430
Self-reported depression	35.03 (7.76)	33.91 (7.22)	0.751	0.454
MEDICAL FACTORS				
Serum glucose level	79.42 (8.27)	81.00 (11.59)	0.838[a]	0.404
Total cholesterol level	196.24 (41.01)	178.90 (34.63)	2.262	0.026*
Triglycerides level	128.08 (67.92)	127.50 (72.05)	0.043	0.966
HDL level	52.61 (12.67)	44.98 (11.99)	3.115	0.002**
LDL level	119.83 (33.84)	115.10 (28.73)	0.747	0.456
MEDICAL HISTORY				
History of TIA – positive	5.6%	0%	2.305[#]	0.129
History of CHD – positive	5.6%	5.0%	0.016[#]	0.900
FAMILY HISTORY				
Family hx of hypertension +	52.9%	67.6%	2.106[#]	0.147
Family hx of stroke +	29.0%	38.5%	1.021[#]	0.312
Family hx of CHD +	39.1%	25.7%	1.847[#]	0.174
HYPERTENSION				
Hypertensive status	38.9%	45.0%	0.397[#]	0.529
Years of hypertension	10.36 (8.92)	12.83 (11.98)	0.803[a]	0.426
Average stage	2.39 (0.74)	2.28 (0.67)	0.535	0.595
Most recent SBP	134.63 (12.40)	134.41 (14.99)	0.052	0.959
Most recent DBP	86.30 (10.06)	90.00 (9.84)	1.199[a]	0.237
Highest past SBP	171.59 (17.25)	160.59 (20.83)	1.901	0.064
Highest past DBP	101.00 (13.62)	104.12 (11.35)	0.786[a]	0.436
Taking anti-hypertensive medication in past 2 weeks	71.4%	55.6%	1.217	0.270

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[+] Unequal variance was assumed due to significant Levene's test.
[#] X^2 value reported.
[a] Males > females.

significantly more years than females ($t = 5.80$, $df = 110$, $p < 0.001$ and $t = 2.87$, $df = 109$, $p < 0.01$).

There was a trend towards (1) females being younger than males ($t = 1.95$, $df = 110$, $p = 0.053$) and (2) more males than expected being married ($X^2 = 2.91$, $df = 1$, $p = 0.088$). There was also a trend toward the female hypertensive patients having higher reported highest past systolic blood pressure value compared to hypertensive male patients ($t = 1.90$, $df = 42$, $p = 0.064$).

Discussion

Cognitive function in hypertension without structural brain changes: Effects of gender

Results of this study demonstrate that, even in the absence of MRI-detected white matter lesions and lacunar infarctions, middle-aged *female* hypertensive patients show deficits in cognitive function compared to female normotensive controls. There was no relationship between hypertension and cognitive function in males. The relationship between hypertension and cognitive function in individuals without structural abnormalities as defined by MRI has not previously been examined in the literature. These results partially support Hypothesis 1. It was hypothesized that cognitive deficits would still exist even without MRI-detected white matter lesions and lacunar infarctions. This was found to be true in the sub-sample of females only and suggests that an alternative mechanism, possibly perfusion changes in the brain that have not yet caused identifiable structural changes, may be responsible for the decline in cognitive function observed in middle-aged Chinese females. Previous studies have found the older female hypertensives perform worse than male hypertensives on various neuropsychological

tests (e.g., Waldstein, 2004) and the present study of Chinese middle-aged hypertensives confirmed this finding.

Specific cognitive functions: The results of the present study have also shown that the tasks most sensitive to the effects of hypertension in females without MRI-detected white matter lesions and lacunar infarction are the digit discrimination task, which requires attention and vigilance and psychomotor speed, and the MMSE, a test of general cognitive ability. These results also partially support Hypothesis 1. It was hypothesized that, even though the sample was free of white matter lesions and lacunar infarction, hypertensive patients would perform worse than normotensive controls on tasks measuring memory, attention, and speed of processing. There was a trend towards female hypertensive patients requiring more time to process visual-spatial information from the Chinese character rotation task, yet no differences in their visual-spatial abilities were apparent given that there were no significant differences in the number of correctly identified rotated characters vs. mirror images on this task. It was surprising that sub-clinical lowering on the MMSE, a screening test for dementia that is used to measure general cognitive ability by assessing orientation, learning and memory, recall, attention, calculation, and language (Folstein, Folstein, & McHugh, 1975), was a robust finding of the present study.

Other studies of hypertensive individuals that have not considered potential structural brain changes have found similar results. For example, Waldstein (2004) reported that the cognitive sequelae associated with hypertension was more pronounced for female vs. male hypertensive individuals on tests measuring delayed visual memory, visual attention and working memory, visual-constructional ability, motor speed and

manual dexterity for the non-dominant hand. In the present study, female hypertensive patients showed poorer performance on a task involving in motor speed and visual attention, confirming some of the specific cognitive function affected in Waldstein (2004). The findings of the present study also found a trend towards poorer visual-spatial processing time, which extend the findings of Waldstein (2004), who did not study this cognitive function. The results of the present study did not find significant differences in visual-constructional ability, visual memory, or working memory, in contrast to Waldstein (2004). These differences may be due to possible white matter lesions or lacunar infarctions, which were not controlled for in Waldstein (2004), or to the use of different neuropsychological tests. Manual dexterity for the non-dominant hand was not measured in the present study of Chinese hypertensives because, in Chinese culture, individuals are forced to be right handed, thus handedness and dominant vs. non-dominant handedness are difficult constructs to validate in this population. The effects of hypertension on the MMSE were also not examined in the Waldstein (2004) investigation.

Explanations for gender differences: Gender was shown to moderate the relationship between hypertension and two cognitive tasks: digit discrimination and the MMSE. The fact that significant differences in cognitive function between hypertensive patients and normotensive controls without MRI-detected white matter lesions or lacunar infarctions were only evident in the females was an unexpected but potentially interesting. Female and male hypertensive patients had similar characteristics: the groups had been diagnosed with hypertension for approximately the same amount of time, were at similar average stages of EH, etc. It is possible that differences in the association

between hypertension and cognitive function may have been different in males and females because of differences in risk factors between the two groups (e.g., HDL levels, reported physical activity, smoking and drinking habits). However, these differences were in the opposite expected direction: fewer females than males currently smoked and drank and for significantly less years, females reported significantly more physical activity than males, etc. Females did tend to report having a higher past systolic blood pressure than males by more than 10 mmHg on average. Despite the self-report and recall biases that may affect these data, the trend suggests that cognitive differences between hypertensive patients and normotensive controls in female group may not be the result of gender differences. Instead, these differences in cognitive function may have resulted from the physiological changes caused by reaching a certain high blood pressure threshold, independent of gender.

It is also possible that physiological variables that were not measured in the present study such as estrogen levels may have interacted with hypertension and/or its consequences on the vascular to cause females to be more vulnerable to the neuropsychological consequences associated with hypertension. Moreover, given the lack of validity and reliability data on this computerized battery, it is possible that the neuropsychological tests themselves may have been gender-biased. Yet, male and female controls performed similarly on these tasks.

Cultural variables may have also influenced the findings of the present study. For instance, males and females had similar average years of education, but it is possible that the quality of education differed for males and females attending gender-segregated grade school in China 40-60 years ago. Educational levels are known to influence

neuropsychological test performance (Brito-Marques & Cabral-Filho, 2005; Leckliter & Matarazzo, 1989) and may have been a confounder in the present study. Cultural variables have also been shown to influence neuropsychological test performance (Anger et al., 1997; Ardila, 1995), and the generalizablity of the present study is limited to Chinese adults age 50-65 with hypertension.

Relationship of self-reported anxiety and depression to hypertension

Hypothesis 2A predicted a significant difference in anxiety and depression scores between hypertensive patients and normotensive controls. This hypothesis was not supported by the results of the present study. The multivariate F was not significant, although univariate analyses showed a trend for hypertensive patients to have more self-reported anxiety. This univariate finding is in line with the Rutledge and Hogan (2002) meta-analysis suggesting that hypertension is significantly associated with anxiety. However, the present study did not find an association of hypertension with depression.

Distress as a mediator of the relationship between hypertension and cognitive function

The role of anxiety and depression as a potential mechanism for cognitive dysfunction in hypertension without structural brain change was not supported by the findings of the present study. Hypothesis 2B stated that cognitive change would exist independent of self-reported emotional status. When the self-report anxiety and depression scores were added as additional covariates, the overall F was not significant, thus no significant differences between hypertensive groups in cognitive function. These findings are in contrast to earlier studies confirming the presence of specific cognitive dysfunction in hypertensive patients after controlling for anxiety and depression (Elias, Robbins, Schultz, & Pierce, 1990; Pentz, Elias, Wood, Schultz, & Dineen, 1979; Schultz,

Dineen, Elias, Pentz, & Wood, 1979; Waldstein, Manuck, Ryan, & Muldoon, 1991). Thus, the present study does not support the role of self-reported anxiety and depression as a mechanism underlying the relationship between hypertension and cognitive dysfunction in individuals without structural brain change.

Moreover, as expected, this study did not find a significant relationship between self-reported anxiety and depression scores and objective performance on neuropsychological tests. These results could mean that the null hypothesis is true and that there truly is no relationship between anxiety or depression and neuropsychological scores, or the lack of significant results could also be due to Type II error. It is unlikely that these findings are the result of Type II error because of the large number of analyses would actually lead to an increase in Type I error and a reciprocal decrease in Type II error. In fact, it is likely that the significant negative correlation between depression and working memory is the result of Type I Error. The results of the present study coincide with previous research (such as Waldstein, 1995) documenting that self-reported emotional ratings do not correspond to objective neuropsychological test performance.

Limitations

This study is a cross-sectional study of hypertension and its association with self-reported anxiety and cognitive function. Self-reported anxiety is associated with hypertension, but may or may not cause hypertension. Those individuals who have hypertension may become more anxious as a function of being diagnosed with this disorder.

Statistical Type I Error is another limitation of the present study, i.e. some of the significant findings may have occurred by chance due to the multiple analyses conducted

in the present study. If a Bonferroni correction had been used, many results would not have been significant. Finding gender differences was not specified in the a priori hypotheses and represents another limitation of the present study. It is possible that the significant findings in the female sample reported in this study are the result of chance alone, and do not reflect actual differences in female hypertensive patients vs. controls.

The present results may not be generalizable beyond Chinese living in China with hypertension.

In addition, self-report questionnaires were used to measure anxiety and depression, and those with extreme depression were excluded from the study during screening. Self-report measures are inherently biased -- memory of past events may be flawed, and social desirability may affect these responses. Moreover, the self-report measure of anxiety and depression used in this study measured sub-clinical levels of distress and may not have been sensitive to true emotional alteration in this population.

The computerized neuropsychological battery used in the present study was not validated, which is a major limitation of the present study. However, the significant inter-test correlations and task-total score correlations, as well as significant correlations of various tests with the MMSE (Table 2), lend support to the validity of the battery.

Use of anti-hypertensive medications. Use of anti-hypertensive medications may have been a confounder in this study. Research has shown that the type of anti-hypertensive medication may positively or negatively affect cognitive function. In this study, 62% of hypertensive patients reported taking anti-hypertensive medication in the past two weeks, but the type of medication was not specified. However, when analyses were conducted to compare the cognitive functioning of those hypertensive patients

taking medication vs. those hypertensive patients not on medications in the past two weeks vs. normotensive controls, those with hypertension had or tended to have worse cognitive function compared to controls, but hypertensive patients taking medications and those not taking medications had similar cognitive performances. In this study, medication does not appear to have influenced the results.

Use of a translated neuropsychological test. As previously indicated, it was surprising that sub-clinical relative lowering on the MMSE, a screening test for dementia (Folstein, Folstein, & McHugh, 1975), was found in the present study. It is possible that this test, although validated in Chinese samples, does not measure the same constructs as in English when translated into another language. Back translation (translating an instrument from English into another language, then having a different person translate the instrument from the other language into English) is often used to assure culturally appropriate translation of the constructs that a particular instrument seeks to measure (Pedhauzer & Schmelkin, 1991). However, this test was not back-translated. It was adapted to Chinese by eliminating the alternate subtraction task of spelling the word "world" backwards (which is a very difficult skill due to the way words are constructed in Chinese language) and by asking the participant to repeat a Chinese proverb instead of an English sentence.

It is also possible that other items on the test are not culturally appropriate. For example, in the orientation section, one point is earned for providing the year and another for the correct month and another of the correct date. Because the Chinese use a calendar that is different from the Judeo-Christian calendar and follow years according to name's

of animals, it is possible that correctly answering this question would require cognitive abilities that are not used by an American English-speaker to answer this same question.

Implications

Further research. This study provides several avenues for further research. Because of the unexpected findings that (1) gender moderated the relationship between EH and cognitive function in individuals without white matter lesions and lacunar infarctions and (2) that MMSE sub-clinical changes were found between female hypertensives and controls, the present study should be replicated in other countries in order to determine if the results are generalizable beyond those Chinese with hypertension living in China. Research with female hypertensive patients is needed. Most studies in the literature have recruited more men than women and larger numbers of women study participants are necessary in order to examine the alternative mechanisms that may explain the cognitive deficits associated with hypertension in this subsample. In order to elucidate potential mechanisms, employment of functional neuroimaging techniques (e.g., SPECT, PET, fMRI) may be warranted. In addition, prospective studies are needed in order to determine the pattern of cognitive decline, which may be distinct for males and females. Moderating factors, such as a clinical diagnosis of hypertension, have been the focus of recent research in this field. More attention must be paid to socio-demographic and medical factors that may change the relationship between hypertension and cognitive function.

Previous research (e.g., Waldstein, 1995) has demonstrated that self-reported emotional ratings are not associated with objective neuropsychological measures of cognitive performance. The present study supported these findings. Future investigation

of the stress hypothesis as a possible contributor to cognitive dysfunction in EH could benefit from obtaining more objective markers of stress. For example, physiological variables (e.g. heart rate variability, levels of neuro-hormones, etc.) that measure stress, anxiety and depression and/or third person ratings/checklists of emotions may be more valid in studies of neuropsychological functioning than self-report data.

Future neuropsychological studies of cognitive function in hypertension can be improved. Specific cognitive deficits have been reportedly associated with hypertension, and results are not consistent across studies. Therefore, comprehensive culturally-appropriate neuropsychological batteries should be used to define a cognitive profile associated with hypertension. Neuropsychological tests tend to load heavily on one or more factors. Employing factor analysis procedures may decrease the number of analyses that need to be conducted and consequently Type I Error, leading to increased confidence in the findings that result from neuropsychological studies. Finally, neuropsychological studies conducted in other countries must carefully chose tests and questions that accurately measure the particular cognitive ability of interest. Validity studies comparing versions of the same neuropsychological tests (such as the MMSE) across cultures that examine the influence of cultural variables on test understanding and performance are warranted.

Clinical implications. This study suggests that among individuals age 50-65, females are potentially vulnerable to subtle cognitive impairments associated with hypertension, even in the absence of MRI-determined structural cerebral abnormalities. These findings highlight the need for increased attention to blood pressure control in older adults for preservation of cognitive function. The deficits uncovered in the present

study are unlikely to be noticeable to the patient and may remain ignored until a stroke occurs or dementia is diagnosed. Medical personnel have the opportunity to intervene early and treat these sub-clinical cognitive deficits before major cognitive dysfunction results. Over half of the present sample was currently taking anti-hypertensive medication prior to participation in the study. Thus, it appears that medication does not improve cognitive functioning to the level of a normotensive's ability. Cognitive rehabilitation psychologists and other specialists may need to develop techniques and strategies that might assist older adults with hypertension in improving or, at the very least, preserving their current levels of cognitive functioning and preventing further cognitive decline.

Furthermore, the findings of age as a moderator of the association between sub-clinical anxiety and hypertension suggests that older patients may benefit from clinician assessment of anxiety. Anxiety symptoms can influence quality of life and physical health. Alternatively, anxiety and depression may occur as early warnings of subtle cognitive changes (e.g., Berger, et al., 1999). Clinicians may need to educate patients and family members about the symptoms of anxiety, how to manage these symptoms, and when to seek professional help.

Summary

The present findings suggest that gender moderates the influence of hypertension on cognitive function independent of MRI-detected structural cerebral abnormalities. Specifically, females are potentially vulnerable to the adverse neuropsychological sequela associated with hypertension. Tasks measuring attention, vigilance, psychomotor speed, and general cognitive ability are most affected in female Chinese hypertensive patients age 50-65. Although hypertensive individuals tended to have higher levels of self-

reported anxiety, anxiety was not associated with objective cognitive performance on neuropsychological tests and did not account for the relationship between hypertension and cognitive function. Future research, especially with female hypertensive patients, is needed, and alternate mechanisms that may explain the relationship between hypertension and cognitive function need to be explored.

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Appendix 1

From: "deezhao" <deezhao@anzhen.org>
To: <hrogers@usuhs.mil>
Date: 8/26/2005 3:07:24 AM
Subject: Letter to IRB

Dear IRB members in Uniformed Services University of the Health Sciences

I am writing you to certify that Heather Rogers, graduate student at Uniformed Services University of the Health Sciences, has my permission to use the data our Dept. of Epidmeiology collected on 95 hypertensive patients and 95 age- and education-matched controls. The dataset does not contain any personal identifiers and these identifiers will never be provided to Heather Rogers. The dataset consists of demographic, behavioral, and medical variables in addition to a self-reported rating of anxiety and depression levels and the results of a computerized neuropsychological battery of cognitive function. This project was approved by Scientific and Ethics Committee of our institute before it started to collect data.

Sincerely yours

Dong Zhao MD,PHD
Deputy Director
Beijing Institute of Heart, Lung & Blood Vessel Diseases
Beijing Anzhen Hospital
Tel: 8610 64456524
Fax: 8610 64419738

Appendix 2

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4712
www.usuhs.mil

November 18, 2005

MEMORANDUM FOR MS. HEATHER ROGERS, , MEDICAL AND CLINICAL PSYCHOLOGY

SUBJECT: IRB Exemption of Study (DoD Assurance No. P60001 and FWA # 00001628)

1. Your research protocol T072HN entitled, "Cognitive Profile and Emotional Status of Neuronically Healthy Middle-Aged Chinese Hypertensive Patients," was reviewed and approved for execution on November 16, 2005 as an EXEMPT human use study under the provisions of 32 CFR 219.101(b)(4).

2. An exempt study signifies that you will not be required to submit renewal applications for full Board review **as long as that portion of your project involving human subjects remains unchanged.** If during the course of your project, you intend to make changes which may significantly affect the human subjects involved, you should contact the IRB office for guidance prior to implementing these changes.

3. Any unanticipated problems related to your use of human subjects in this project must be promptly reported to this full Board through this office. This is required so that the IRB can institute or update protective measure for human subjects as necessary.

4. The purpose of this study is to determine the cognitive profile and self-rated emotional status of a group of Chinese hypertensives without identifiable lacuna infractions or white matter hyperintensities detected by magnetic resonance imaging (MRI) brain scans. As part of a summer experience abroad to learn about research and research methods in China the IRB understantds that the PI learned about a database from a study conducted at Beijing Anzhen Hospital and was offered access to this database. Data from this database will be provided to the PI without identifiers and consists of information from 90 hypertensives and 90 controls. Written permission to use the de-identified data was provided by Dr. Dong Zhao, Deputy Director, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Beijing Anzhen Hospital.

5. Exemption is granted with the understanding that no further changes or additions will be made to the procedures followed or investigators involved without the knowledge and approval of the IRB.

6. You are required to keep all research-related documents in a permanent file in an area designated for that purpose that is accessible to your chain of command and inspectors of official audit agencies. Your study and its documentation are subject to inspection at any time. You must maintain your records to facilitate such inspections. **You are to notify the USU IRB Office upon completion of the study.**

7. If you have questions regarding specific issues on your protocol, or questions of a more general nature concerning human subjects protection, please contact me at 301-295-3303/9534 or rlevine@usuhs.mil

Richard R. Levine, Ph.D.
Assistant Vice-President for Research
and Executive Secretary, IRB

cc: Director, Research Administration
Chair, MPS
File

Learning to Care for Those in Harm's Way