7-21-2011

The Effects of Diabetes, Hypertension, and Hypercholesterolemia on the Severity of Traumatic Brain Injury

Rachel R. Andaloro
Indiana University of Pennsylvania

THE EFFECTS OF DIABETES, HYPERTENSION, AND HYPERCHOLESTEROLEMIA ON THE SEVERITY OF TRAUMATIC BRAIN INJURY

A Dissertation

Submitted to the School of Graduate Studies and Research

In Partial Fulfillment of the

Requirements for the Degree

Doctor of Psychology

Rachel R. Andaloro

Indiana University of Pennsylvania

August 2011

Indiana University of Pennsylvania
The School of Graduate Studies and Research
Department of Psychology

We hereby approve the dissertation of

Rachel Rose Andaloro

Candidate for the degree of Doctor of Psychology

April 31st, 2011 Signature on file
David J. LaPorte, Ph.D.
Professor of Psychology, Advisor

April 31st, 2011 Signature on file
Michael D. Franzen
Associate Professor, Psychiatry,
Drexel University College of Medicine

April 31st, 2011 Signature on file
Dasen Luo, Ph.D.
Professor of Psychology

ACCEPTED

Timothy P. Mack, Ph.D.
Dean
School of Graduate Studies and Research

Title: The Effects of Diabetes, Hypertension, and Hypercholesterolemia on the Severity of Traumatic Brain Injury

Author: Rachel Andaloro

Dissertation Chair: Dr. David J. LaPorte

Dissertation Committee Members: Dr. Michael Franzen
Dr. Dasen Luo

The current study investigated the effects of hyperglycemia, hypertension, and hypercholesterolemia on the severity of sequelae related to traumatic brain injury. Existing data of 209 participants was utilized from an urban hospital, which included neuropsychological evaluations following traumatic brain injury. Specific areas examined included measures of executive functioning, both immediate and delayed memory, and learning. Each participant was placed into a group based on the number of documented diagnoses (hyperglycemia, hypercholesterolemia, and hypertension). The control group consisted of patients that did not carry a record of these health risks. Each of these groups was further stratified according to age. An interaction between the variables of health risk factors and neuropsychological assessment results was predicted specified by decreasing standard scores with the increase in number of health risk factors. Furthermore, age was hypothesized to be a main effect, with the prediction of a decline in scores as age increases. However, results of a factorial MANOVA indicate that age had no effect on performance and scores actually increased (improved) in the older age group. Of the four measures used to assess neuropsychological performance, the increase in performance from the younger to older group was significant for the executive functioning measure. There was also a trend found in all measures except for learning, demonstrated by a decrease in performance as the number of health risks in a participant increased (executive functioning [α=.01, p=.010, 1-β= .805]; immediate [α=.05, p=.013, 1-β= .794]; delayed memory [α=.01, p=.002, 1-β=

.914]). A discriminant function analysis and Tukey's HSD post hoc test were implemented to explore significant findings. Finally, the implications of these results as well as limitations to the current study are discussed.

TABLE OF CONTENTS

Chapter		Page
I	REVIEW OF RELATED LITERATURE	1
	Overview	1
	Hypertension	2
	Prevalence Trends	3
	Vascular Pathophysiology	3
	Diabetes Mellitus	8
	Prevalence	9
	Pre-Diabetes	9
	Type II Diabetes	9
	Type I Diabetes	11
	Vascular Pathophysiology	12
	Treatment	15
	Hypercholesterolemia	16
	Vascular Patholophysiology of Hypercholesterolemia	18
	Traumatic Brain Injury	20
	Mechanisms of Brain Injury	20
	Contusion	22
	Intracranial Hematoma	23
	Vasospasm	24
	TBI induced Systemic Hypertension	25
	Implications	26
	Current Study	27
II	METHODS & PROCEDURES	29
	Participants	29
	Assessment of Cognitive Functioning	32
III	RESULTS	34
	Statistical Analysis	34
IV	DISCUSSION	43
	Implications	43
	Age Conundrum	45
	Confounding Factors	48
	Limitations	49
REFERENCES		52
APPENDIX 1: Dependent Measures		58

Executive Functioning Measures ……..……..58
Trails B……...58
COWAT…….59
Learning and Immediate and Delayed Recall….....60
Hopkins Verbal Learning Test……...60
Brief Visual Memory Test-Revised……...60
Logical Memory I and II……....61

LIST OF TABLES

Table Page

1. Descriptive Statistics of the Current Study…….…….30
2. Dependent measure operational definitions.…… 33
3. Structure Matrix……....……41
4. Functions at Group Centroids……. …..…….. 42
5. Descriptive Statistics for Modified Age Brackets ……....43

LIST OF FIGURES

Figure Page

1. Mean Performance for Young and Old Groups for Each Dependent Measure…….. 35
2. Mean of COWAT and Trails B for Young and Old Groups……...….... 36
3. Estimated marginal means……...…….37
4. Estimated marginal means……...……38
5. Mean performances of each dependent measure..... 39
6. COWAT and Trails B means……. ……..… 40
7. Cannonical Discriminant Functions……...…….…….. 42
8. Mean scores for each dependent measure ……..… 44
9. Mean scores for modified age brackets……..……...…….……. 44
10. Total mean age of participants as risk factors increase..…….45

CHAPTER 1: REVIEW OF RELATED LITERATURE

In the United States, over three million people sustain a traumatic brain injury (TBI) each year (McCrea, 2008). This number fails to take into account the thousands that do not seek treatment, however. For younger people, head injury is the leading cause of mortality and physical and mental impairment each year. The injuries sustained from TBI can result in profound cognitive, psychological, social, and emotional deficits, creating extensive upheaval in both the individual's and his family's way of life. The sequelae related to head injury, however, are largely idiosyncratic, and represent a complex interaction involving the individual's own biological response to the injury based on his or her history of head injury, drug use, general health, etc.

Therefore, a crucial influence on the consequences of brain injury is the premorbid health of the brain (Jennett & Teasdale, 1981). According to Jennet et al (1981), the odds of a successful recovery increase for someone with no history of cerebral dysfunction than for someone with a similar brain injury who has a significant history of a cerebral lesion or dysfunction. The prognosis, even after a comparatively benign brain insult in a person with pre-existing cerebrovascular disease or brain injury is likely to be poorer in comparison to a healthier individual with no history of these maladies. Of these risk factors, hypertension, diabetes, and hypercholesterolemia are arguably the most important and influential in determining the overall health and resiliency of the cerebro-vascular system and will be the main focus of this study.

Hypertension

One ailment which this study aims to provide support for the exacerbation of the effects of head injury is hypertension. This disease affects more than 65 million adults in the United States (Fields, Burt, Cutler, Hughes, Roccella, & Sorlie, 2004). The American Heart Association defines hypertension as the presence of a consistently elevated blood pressure exceeding 140/90mm Hg. The numerator is a measurement of the systolic pressure, or the pressure created from the beating of the heart. The denominator shows the pressure inside the blood vessels when the heart is at rest, or diastolic pressure. Many factors can cause an elevation in either or both of these numbers, and when a specific cause has been identified, this is deemed *secondary* hypertension. This type of hypertension may result from excess sodium in the diet, a tumor in the adrenal gland, alcohol abuse, stress, arteriosclerosis, cocaine use, diabetes, kidney disease, medications, obesity, or multiple other causes. More often, however, the etiology of hypertension is unable to be identified, and is thus labeled *essential* hypertension.

Symptoms of high blood pressure, whether secondary or essential, can include confusion, chest pain, ringing of the ears, irregular heartbeat, fatigue, blurred vision, and nose bleed. The disease poses a serious risk for myocardial infarction, ischemic events, and both renal and heart failure. Although maintaining a healthy control over blood pressure can reduce the deleterious effects of the disease, hypertension can often be asymptomatic, and those inflicted with the disease may not seek medical attention until the dynamics of the illness have already deteriorated and weakened the vascular system (American Heart Association, 2009).

Hypertension Prevalence Trends

Certain populations are at a greater risk of developing hypertension, including those in lower socioeconomic standing, which incorporates level of education, occupation, and income with an inverse relationship existing between socioeconomic status and the prevalence of hypertension (Szromba, 2000). The disease is 50% more common among African Americans than among Caucasians and it seems to physiologically affect this population differently and more severely than it does other racial groups. Comparatively, it can be more difficult to control in African Americans and may cause more acute complications such as cardiovascular disease, left ventricular hypertrophy, atherosclerosis, and renal disease (Weir & Hanes, 1996). In fact, the probability of progression to end stage renal disease is four times greater for African-Americans than Caucasians. An optimistic finding of recent research, however, has actually shown stagnancy in the trends of hypertension in the U.S. and an increase in the control of blood pressure, especially in Mexican American males, the elderly, and obese adults (Ong, Cheung, Man, Lau, & Lam, 2007). Despite this tendency, in consideration of the consistent increase in the prevalence of obesity, the number of hypertensives in the U.S. is unlikely to decline substantially if more preventative, healthier life-style changes are not implemented.

Vascular Pathophysiology of Hypertension

The physical mechanisms of hypertension can cause deleterious effects on the vasculature of a person inflicted with the disease. The presence of hypertension eventually causes progressive degeneration of the micro-vascular system, increased generation of smooth muscle cells, alterations in the lumina of vessels often causing a narrowing of the canals, endothelial hyalinosis (a degeneration of the endothelial cells which line the interior of blood

vessels), which then leads to endothelial dysfunction in cerebral vessels, and finally, fibrosis (Obisesan, Obisesan, Martins, Alamgir, Bond, Maxwell, & Gillum, 2008). Laurent, Katsahian, and Fassot et al. (2003) established the relationship between aortic stiffness and fatal stroke in hypertensive patients. This stiffening of arteries, caused by hypertension, indirectly increases pulse pressure, which is detrimental to the health of the vascular system and is predictive of cerebrovascular events. Laurent and colleagues (2001) also demonstrate a correlation between arterial stiffness and atherosclerosis, which is a consequence of continued stress on the arterial walls and results in a thickening of the vessel.

Amyloid angiopathy is an additional vascular consequence of chronic hypertension. This condition results from the formation of amyloid fibrils which completely replace smooth muscle cells in the vessel walls, producing a brittle vasculature vulnerable to the formation of micro-aneurysms and hemorrhage. Necrosis, inflammation, increased oxidative stress, and release of neurotoxic substances, as well as impairments of brain metabolism, homeostasis, nutrient delivery, and cerebral blood flow can also occur (Manolino, Olson, & Longstreth, 2003). Kalaria (2000) demonstrated a strong interaction between the severity of cerebral amyloid angiopathy and hypertension for the development of cerebral infarction. The vasculature in people with this complication may also be increasingly sensitive to changes in blood pressure and, an important component to the current study, be less able to repair or regenerate after injury (Kalaria, 2000).

Manolino et al. (2003) emphasizes the pathologic differences in the hypertensive brain, including impaired cerebral autoregulation, cerebral microbleeds which can lead to small hemorrhages, cerebral atrophy, as well as amyloid angiopathy related to Alzheimer-like pathology. They suggest that these deficiencies may eventuate in temporary loss of brainstem or spinal reflexes following brain injury and cortical deafferentation, which is the result of an

interruption of the sensory fibers. Disturbances in the blood-brain-barrier may also develop, which may allow poisons or harmful enzymes to move through the damaged vessel walls, causing cerebral edema which then creates additional lesions in the white matter. Normally, in those with healthy blood pressure, the blood-brain barrier remains intact, allowing for a consistent flow of blood along an inclusive range of perfusion pressure. This is the normal function of cerebral autoregulation and it prohibits the leakage of fluid during periods of high pressure. In a hypertensive person, the constant increase in perfusion pressure creates a shift in the threshold of cerebral autoregulation which enables the system to prevent hyperfusion. This prevention, however, actually increases the risk of hypoperfusion when blood pressure is low. Antihypertensive treatment is able to correct these abnormalities in vascular regulation by re-adjusting the autoregulation plateau back to normal ranges (Manolino et al., 2003).

Hypertension can also have damaging effects on the white matter of the brain, causing injury to the axons, or white matter intensities (Xiaohua, Wen, Anstey, & Sachdev, 2009). This phenomenon is associated with lacunar infarctions, and often both are asymptomatic and incidentally found during magnetic resonance imaging in many patients over 60. This "accidental" discovery of white matter lesions and infarctions deep within the brain suggests a lack of awareness of the true prevalence of vessel damage in the brains of adults. Xiaohua et al. (2009) suggests that this white matter damage may, in fact, help explain age-related changes observed in the behavior of older adults.

These age-related alterations in the health and function of the brain may be the result of many factors; however, hypertension likely has a large role in the process. Those with chronic high blood pressure not only produce poorer performance on cognitive measures than do normotensive adults, but the extent of cognitive decline is directly proportional to the duration of

the disease (Swan, Carmelli, & Larue, 1998). The longer a person suffers from the disease, the more likely it is that cognitive changes will occur, causing a reduction in performance. Thus, those developing the disease at a young age are at greater risk. This decline has found to be disassociated from the age, sex, ethnicity, education, income, history of stroke, body mass index, glycosylated hemoglobin, or physical activity (Obisesan, Obisesan, Martins, Alamgir, Bond, Maxwell, & Gillum, 2008). Luckily, these changes can be lessened by efforts to control blood pressure.

The cognitive deficits caused by hypertension are typically subtle; however, Manolino et al. (2003) show that they exist across several measureable domains, including attention, abstract reasoning, cognitive flexibility, learning and memory, psychomotor skills, and visuospatial abilities. Diffuse white matter disease may also affect the frontal lobes and has also been linked with reduced cerebral metabolism in this area (DeCarli et al. 1995). These lesions may further decrease the threshold for the appearance of cognitive impairment, causing a snow-ball-effect from what would be a minor insult in a normotensive person, such as head injury, to a serious, life-altering outcome (Manolino et al, 2003). Thus, lesioned white matter is highly vulnerable to further damage, even in what would appear to be a minor affliction. Schmidt, Fazekas, Offenbacher, Lytwyn, Blematl, Niederkorn, et al. (1991) found hypertensives with white matter intensities to show poorer performance on measures of verbal and visuospatial learning, memory, vigilance, visual attention, and reaction time, similar to the results of Manolino et al. (2003).

Even in those patients where an active medicinal antihypertensive regimen is instituted to treat the disease, the presence of ischemic lesions does not attenuate, and they continue to advance resulting from years of damage to the arteries (Simon, Levenson, Bouthier, Safar, & Avolio, 1985). These lesions are a direct result of the increased intraluminal pressure, forcing the

diameter of the artery to increase, the pulse wave velocity to quicken, and the capability of the artery to adapt to changes in pressure to become less efficient (Armentano, Megnien, Simon, Bellenfant, Barra, Levenson, 1995). These consequences, again, result from a combination of hypertension over time. Thus, the older the person, the greater the vascular changes, and the more brittle the vessels become (Simon et al., 1985).

The longer a person has the disorder, the more probable it is that hypertension will lead to lipohyalinosis, which is a disease in the small vessels of the brain (Pantoni, Garcia, 1995). The vessel walls thicken and the lumen of these vessels, which importantly provide nutrients to deep white matter, narrows. Postmortem studies demonstrate the connection between white matter lesions and atherosclerosis, which causes degenerative changes in the arterioles (Pantoni & Garcia, 1995). Normotensive and hypertensive subjects were compared in terms of the presence of white matter lesions. The ARIC study (1996), whose subjects ranged from 55 to 72 years of age, showed that almost 25% of them had these lesions. Half of this percentage had hypertension (Liao, Cooper, Cai, Toole, Bryan, Hutchinson, et al., 1996). A similar study found the brains of one third of their participants 65 and older to be lesioned, with 44% having been diagnosed with high blood pressure (Longstreth , Manolio, Arnold, Burke, Bryan, Jungreis, et al., 1996). Sierra (2003) postulates that the presence of cerebral white matter lesions could be regarded as early evidence of *brain damage* in hypertensive patients.

Diabetes Mellitus

Cerebral vascular damage and impairment can also result from Diabetes. The American Diabetes Association characterizes this disorder by an elevated level of glucose in the blood, specifically, a fasting blood glucose level of 126mg/dl or higher. The origin of the disease results from a malfunction in either the production or response to insulin, or both, creating an insufficiency of the hormone or resistance to it. Insulin is a crucial hormone in the control and maintenance of blood sugar and converts glucose into energy by moving it from the blood into tissues of the body, such as muscle, fat, and liver cells. In a diabetic person, there may be a decreased generation of insulin by the pancreas or, alternatively, the muscle, fat, or liver cells essentially ignore the insulin and fail to respond to it correctly. After a prolonged period of high levels of blood glucose and the reduction of energy being transferred to tissues in the body, damage can occur to the eyes, kidney, heart, and vasculature system (American Diabetes Association, 2009).

Diabetes Prevalence

Diabetes Mellitus is a potentially serious disease which involves a staggering 23.6 million adults and children, or 8.0% of the population. Among this group, 17.9 million are actually diagnosed with the disorder, leaving a rough 5.7 million people who are unaware of their illness. Of the 12 million men and 11.5 million women inflicted with the disease, one third and one quarter, respectively, do not realize it. Even more bothersome are the 57 million people who are considered pre-diabetic, who have elevated blood-glucose levels not yet considered in the diabetic range, but closely approaching it. Similar to hypertension, African Americans are disproportionately affected by diabetes when compared to other races. Among the non-Hispanic

African American population, 14.7% of those 20 years and older have diabetes. This percentage drops to 9.8 in the non-Hispanic Caucasian population (American Diabetes Association). Although the disease can be prevented and controlled by a healthier, low sugar diet, in addition to the use of insulin, the damaging effects on the vascular system have already taken their toll, estimated to begin as early as the pre-diabetic phase (Donnelly, Emslie-Smith, Gardner & Morris, 2000).

Pre-diabetes

Prior to the diagnosis of diabetes, those with elevated blood sugar are likely to have symptoms associated with pre-diabetes (Dupree & Meyer, 1980). This stage is defined by a fasting blood glucose level between 100 and 125 mg/dl. If caught early, precautions can be taken to delay the progression of the disease. This includes changes in diet, constituted by a reduction of fat and caloric intake by 30%, reduction in saturated fat by 10%, and an increase in fiber intake by more than 15 grams. Ideally, a 5% weight loss reduction is beneficial as a result of dietary changes and an increase in exercise by at least 150 minutes per week (Tuomilehto, Lindstrom, Eriksson, Valle, Hamalainen, Ilanne-Parikka, et al., 2001). If these steps are not taken to retard the disease, a person may go on to develop type II diabetes.

Type II Diabetes

Type II diabetes, or non-insulin dependent diabetes, is typically diagnosed later in life and may result from poor diet, lack of exercise, and obesity, however the true etiology is unknown. People diagnosed with this type of the disease may or may not be able to produce insulin, however, the predominant characteristic is the inability to process and respond to the

insulin properly. An impairment in the ability to tolerate glucose also exists. The progression from insulin resistance into diabetes II is dependent on the increased performance of the cells responsible for producing insulin, the β-cells. If these cells are able to offset resistance by generating higher levels of the hormone, then the onset of the disease may be delayed for the duration of this β-cell compensation (LeRoith, 2004).

Risk factors for type II diabetes include obesity, central distribution of body fat, including intraabdominal fat, and a family history of the disease (LeRoith, 2004). Studies in the United States have shown that not only being obese, but the length of time a person remains obese increases the risk for developing diabetes. Pima Indians who have been classified as obese for more than 10 years double their risk of diabetes compared to those who have been obese for fewer than 5 years (Everhart, Pettitt, Slaine, 1992).

The rate of diagnosis of this type of diabetes has accelerated since the 1980's to levels that some view as an epidemic. It is not clear whether the increase is a result of improved methods for the detection of diabetes, an increase in longevity, the rise in obesity, or a combination of all three. Regardless, it is predicted that in the year 2025 the worldwide population of diabetics will inflate to a staggering 300 million people, foreshadowing grave repercussions for the world economy and, in combination with obesity, may prove to be a daunting burden on future generations (LeRoith, 2004). In addition to the rise in adult diabetes, children and adolescents are increasingly diagnosed with what used to be a disorder which developed later in life. Previously, a diagnosis of diabetes at a young age was indicative of type I, or juvenile onset diabetes; however, with the rise in childhood obesity and the propensity towards a sedentary, inactive, fast-food lifestyle, it appears to no longer be an adult disease.

Type I Diabetes

Type I diabetes is characterized by a serious impairment in the ability of the body to produce insulin. This results in a life-threatening deficiency of the glucose-transporting hormone. This type of diabetes is further broken down into type 1A and type 1B, with the categorization determined by the origin of the insulin deficiency. Type 1A diabetes results from an immune related impairment, whereas the etiology of the disease for those with type 1B is unknown. A strong genetic component has been shown to be a factor in the predisposition to type 1A diabetes, yet 85% of those with this disorder lack a familial history of the disease (LeRoith, 2004).

The progression of type 1A diabetes is a process that occurs over an extended period of time, but begins with the presence of genetic traits which predispose a person to the disorder. Mere existence of the genetic marker which represents the highest risk factor for type 1A diabetes, however, does not prove to be the ultimate deciding factor of whether a person will go on to progress into full fledged type I diabetes. Of those with the genotype, only 1 in 16 develops the type 1A form of diabetes (Bingley, Bonifacio, Williams, 1997). Some studies have shown that breast milk may offer a protective factor against the progression of diabetes and that increased consumption of cow's milk may actually increase the risk, but results are still inconclusive (LeRoith, 2004).

Environmental factors have also been implicated in the activation of diabetes I. Viruses, vaccines, and diets have all been reviewed as triggers in genetically susceptible people. Polypeptides associated with the virus may aggravate the immune system, inflaming and activating a predisposed autoimmune disorder. Autoantibodies are created in response to the virus which react with the insulin and may be correlated with the breakdown of pancreatic β-

cells (LeRoith, 2004). This reduction in β-cells depresses first phase insulin release. As insulin release declines, the probability of the development of type 1A diabetes increases considerably. When approximately 80% of the β-cells have been eradicated, a hyperglycemic state ensues and insulin therapy is subsequently required (LeRoith, 2004).

Vascular Pathophysiology of Diabetes

As in any other illness, Donnelly, Emslie-Smith, Gardner and Morris (2000) affirm that the duration of diabetes mellitus is crucial in determining the extent of complications related to the disease. These authors also suggest other factors which may contribute to the severity of the resulting sequelae, including the combinatory influences of hypertension, cigarette smoking, and hypercholesterolemia. At least half of people who have been diagnosed with diabetes also suffer from high blood pressure. Diabetes causes capillary occlusion, atherosclerosis, diffuse vascular disease, and irreversible ischemic brain damage. Small lacunar infarcts are common, and the risk of atherothrombotic stroke is two to three times higher in those with diabetes. A study involving cats with middle cerebral artery occlusion showed the probability that an extensive hemorrhage would occur was 25 times greater than in those cats without occlusions. If a stroke does occur, the death rate is higher and a poorer neurological outcome is more probable, including a more severe extent of disability in those with diabetes. The less this illness is controlled the greater the microvascular complications will be (de Courten-Myers, Kleinholz, Holm, Schmitt, Wagner, & Myers, 1992).

Hyperglycemia also exacerbates the deteriorative process of intracellular acidosis. This process occurs following an ischemic event and results from local hypoxia which is induced by an increase in glucose being metabolized anaerobically. This causes the generation of

deteriorative lactic acid, resulting from the conversion of glucose into lactate. Research has shown that animals with induced acute hyperglycemia have an increased acidic cerebral pH mean when compared to controls, as well as greater cortical lactate concentration. Acidosis can be destructive, damaging vascular, glial, and neuronal tissue. This intensifies the extent of injury and worsens the magnitude of stroke damage (Kagansky, Levy, & Knobler, 2001).

High levels of blood glucose can also increase the accumulation of extracellular glutamate. A rise in blood sugar has an excitatory effect on amino acids, especially glutamate. This neurotransmitter can lead to neuronal death as a result of its activation of postsynaptic glutamate receptors. This process then causes an extreme influx of calcium in the ion channels eventuating in mitochondrial injury, and finally, cellular death. Glutamate levels have been found to be excessive in hyperglycemic rats as a consequence of ischemia when compared to normoglycemic animals. During acute ischemia, insulin has shown to attenuate the extent of brain damage and is considered neuroprotective. It has decreased tissue damage and ameliorated neurobehavioral prognosis (Wass, Scheithauer, Bronk, Wilson, Lanier, 1996). Regardless of insulin's effect on glucose levels, it may also lessen neuronal necrosis in large cerebral areas, and is increasingly effective when directly injected into the brain's ventricles (Zhu, Auer, Voll, & Auer, 1994).

Impairment and abnormalities in cerebral blood flow have also been shown in those with diabetes. This process develops over a period of months to years, and may begin with a lessening in cerebrovascular reactivity and deterioration of a diffuse array of blood vessels both in and outside of the brain. This process can lead to damage and dysfunction of the endothelial layer of the vessels causing vasoconstriction and improper or complete lack of vasodilation when nitric oxide is released. Fatty acids within the blood can also decrease the amount of nitric oxide

synthase released, a key component to vascular tone, which disrupts the endothelium-dependent vasodilation and increases the chances that the person will develop hypertension. Inflammatory white blood cells can move into the walls of the blood vessels and smooth muscle cells may increasingly migrate and proliferate in certain areas, commencing the creation of atherosclerotic lesions. This inflammation may actually be an important factor in the progression of vascular disease and in combination with endothelial dysfunction, can predict the development of diabetes (LeRoith, Taylor, Olefsky, 2004). Endothelial dysfunction is the first complication in the development of macrovascular disease.

Diabetes can also produce edema, diffuse neuropathy, disrupt the blood-brain barrier similarly to the effects of hypertension, and increase the probability of hemorrhagic transformation of an infarct. The formation of atherosclerotic plaques is also accelerated in those with the disease. The pathogenesis of diabetes not only promotes adhesion of platelets in the blood, but this adhesion is unstable. The production of specific enzymes weakens the plaque's fibrotic cap, creating an unsteady feeble aggregate prone to rupture (Donnelly & Jonas, 2002).

People with hyperglycemia are also at an elevated risk for developing hypertension because of exaggerated blood pressure sensitivity. This sensitivity results from numerous mechanisms, including a 10% higher concentration of sodium in those with diabetes due to the effects of the disease on the kidney. Elevated blood pressure, however, is a consistent finding in those with diabetes, independent of age, obesity, or renal disease. Of those that do have impaired renal function, 90% show signs of hypertension, which accelerates the deteriorative process (LeRoith et al. 2004). When both diseases are present, Dupree and Meyer (1980) have found a correlation between blood pressure and type 2 diabetes and vascular complications. According to Estacio, Jeffers, Gifford, and Schrier (2000), when blood pressure was seriously controlled

compared to a less stringent control the results showed a decline in diabetes-related deaths, cerebral vascular accidents, and microvascular complications.

Treatment

As previously described, certain dietary restrictions and exercise regimens can be initiated to improve the symptoms related to diabetes or delay onset of the disease. Certain pharmacological agents, such as metformin, have been used to reduce fasting glucose levels and improve insulin resistance in those with diabetes. Despite significant medical advances in the treatment of diabetes, including the availability of numerous medications to lower blood glucose, and the relatively recent realization of the importance of controlling diabetes, the achievement of steady, healthy blood glucose levels for an acceptable amount of time is not a common occurrence (Turner, Cull, Frighi, Holman 1999). Even those who are intensely and aggressively treated continue to develop complications related to the disease.

Hypercholesterolemia

Elevated levels of cholesterol are an additional factor which contributes to vascular damage. High levels of cholesterol and triglycerides found in the blood stream characterize this lipid disorder from which 34 million American adults suffer (Arnett, Jacobs, Luepker, Blackburn, Armstrong & Claas, 2005). Cholesterol is a wax-like, fatty substance both generated in the body and also acquired from animal products, such as eggs, meats, and dairy products (Gaziano, M. & Gaziano, T., 2012). The American Heart Association describes the existence of two types of cholesterol: high-density lipoproteins (HDL) which is considered "good" cholesterol, and low-density lipoproteins, which is harmful when elevated. The ratio between these two types of cholesterol is an important predictor of heart disease. Triglycerides are also a type of lipid found in the blood and are inversely related to the levels of HDL cholesterol. An elevation in cholesterol implies elevated LDL cholesterol, average or decreased levels of HDL cholesterol, and a possible increase in the levels of triglycerides. A healthy amount of cholesterol is critical to the construction of cell membranes, production of hormones, and creates important components in the process of the digestion of fat. The normal amount of cholesterol that should be found in the blood varies between 140 and 200 mg per deciliter. Elevated blood cholesterol levels are considered excessive when they reach higher than 240 mg/dL (American Heart Association, 2009).

The disease is associated with a diet rich in fat, hypothyroidism, diabetes, Cushing syndrome, renal failure, certain medications, a sedentary lifestyle, and alcohol abuse. Although high levels of cholesterol are typically asymptomatic, certain physical changes may occur, including the appearance of cholesterol-rich skin deposits, called xanthomas. These can occur on the eyelids (xanthelasmas), or develop on the elbows, knees, buttocks, tendons, and around the

cornea of the eye (Zuliani & Fellin, 2003). Despite the association with environmental influences, genetic transmission is one of the main factors contributing to hypercholesterolemia for many people who suffer from the disease.

Familial hypercholesterolemia is the most common inherited form of the disease. Approximately 1 in 500 people suffer from this type of high cholesterol and the prevalence rates are higher for South Africans, French Canadians, Finns, and Lebanese. Hypercholesterolemia is autosomal dominant and therefore the transmission of the abnormal gene from only one parent is necessary. Those that only inherit one gene are deemed heterozygous. If both parents transmit the gene, the individual is considered homozygous, and the condition becomes more serious with cholesterol levels having the potential of skyrocketing to greater than 600mg/dL (Zuliani & Fellin, 2003).

The culprit which determines the inheritance of hypercholesterolemia is the low density lipoprotein receptor (LDLR) gene. This gene orchestrates the generation of the LDL protein receptor which is a critical protein in maintaining healthy cholesterol because it binds to cholesterol carriers, or LDL particles, thus removing them from the blood stream. Mutations on this gene, specifically, a defect on chromosome 19, inhibits this removal of low density lipoprotein (LDL) from the blood. Other mutations may reduce the number of receptors generated within individual cells (Zuliani & Fellin, 2003). The surplus of cholesterol begins to travel throughout the blood vessels and ultimately aggregates in abnormal areas, creating cholesterol deposits on the tendons, skin, and in arteries, the latter eventually leading to complications such as atherosclerosis. These fatty deposits in the artery can serve as a trap for blood cells which can become caught on the plaque, subsequently forming clots which have the

potential to detach and cause complete occlusion of an artery leading to heart attack or stroke (Gaziano et al., 2007).

Although genes play a large part in acquiring the disease, environmental risk factors also act to accelerate or decelerate the process. Elements such as diet, exercise, and smoking all affect levels of cholesterol as well as age, gender, and co-occurring diabetes and obesity. If a proper regimen of a healthier diet, increase in exercise, and addition of medication is implemented, cholesterol levels can be reduced, especially for heterozygous hypercholesterolemics. A reduction in the intake of fat and cholesterol can be achieved by consuming less meats, especially organ meats, switching to low-fat dairy products, and decreasing the amount of coconut and palm oil consumed. Those who are homozygous may remain unresponsive to these changes and a liver transplant may eventually be necessary. Medications such as fenofibrate, gefibrozil, nicotinic acid (niacin), and statin drugs have been effective in reducing cholesterol levels in combination with aforementioned behavioral changes (Gaziano et al., 2007).

Vascular Pathophysiology of Hypercholesterolemia

Hypercholesterolemia is a risk factor for arthrosclerosis and causes similar effects on the vasculature as does hypertension and diabetes. When rabbits were fed cholesterol-rich diet, an increase of lesions was found in the arteries, however, the severity of the lesions fluctuated depending on where the analyzed blood vessel was located in the body (Verbeuren, Jordaens, Zonnekeyn, Van Hove, Coene, & Herman, 1986). Endothelial dysfunction also occurs, but begins very early on in hypercholesterolemic conditions when atherosclerosis has not yet developed. Research conducted by Creager, Cooke, Mendelsohn, Gallagher, Coleman, Loscalzo, et al. (1990) strongly suggests that broad abnormalities of vascular function occur in

hypercholesterolemic individuals even in the absence of atherosclerosis. Vascular injury may be proliferated by abnormalities in the endothelium or vascular smooth muscle as a result of platelet-vascular wall contact, macrophages, mitogens, or other processes implicated in the development of atherosclerosis (Creager et al., 1990).

High cholesterol can inhibit the effect of nitric oxide and the vasodilation of blood vessels, including a relaxing factor derived from the endothelial layer, which negatively affects the smooth muscle walls of resistance vessels (Creager et al., 1990). This endothelium-mediated ability to relax has shown impairment as quickly as in early stages of hypercholesterolemia due to disruption of the nitric oxide molecule. Nitric oxide is crucial in maintaining normal vascular tone and its release actually reduces the progress of atherosclerosis. This molecule inhibits the accumulation and adherence of platelets and leukocytes to the endothelium, which is the protective agent against atherosclerosis (LeRoith et al., 2004). When atherosclerosis is present in a hypercholesterolemic person, blood vessels are also more susceptible to vasospasm (Cipriano et al., 1979). This occurs as a result of an increase in vasoconstrictor responsiveness to serotonin in combination with the impairment in nitric oxide and the subsequent reduction in the ability for the vessel to relax (Verbeuren, Jordaens, Zonnekeyn, Van Hove, Coene, & Herman, 1986). The complex dynamics of vasospasm will be explained in a following section.

Hypercholesterolemia represents the most common risk factor in the development of atherosclerosis in western society (Faggiotto et al., 1984). It is the most common vascular disorder and is also the most frequent underlying cause of death in those over 50 years of age. Atherosclerosis has been found to begin very early in life due to discoveries of the disorder in infants in children who had passed away accidentally (Toole, 1990). It distorts laminar flow due to the narrowing of the artery as a result of accumulated cholesterol deposits and causes damage

to the arteries. This reduces the amount of blood and oxygen being supplied to various organs. This accumulation eventually becomes hardened by fibrous tissue and calcification, leading to arteriosclerosis. If the vessel becomes entirely occluded, this could lead to heart attack or stroke (Kagansky, Levy, & Knobler, 2001). High cholesterol may not only lead to a fatal outcome by causing internal ischemic events, but it may also weaken the vasculature to a point where the system becomes vulnerable to injury and damage sustained by external forces, specifically, head injury.

Traumatic Brain Injury

Out of the three million people in the U.S. that sustain a Traumatic brain injury (TBI) every year, 52,000 are fatally injured and approximately 80,000 are permanently disabled (Sosin, Sniezek, & Waxweiler, 1995). If the insult is not fatal, severe trauma may result from the dynamics and mechanisms of the injury. The human body has a remarkable ability to absorb impact from an injury in order to preserve and maintain the health of vital organs. These viscoelastic tissues are able to move and stretch in order to reduce the physiological damage. Tissue resistance, however, is confined to certain limits and can only protect against injury to a certain extent, after which the insult delivered causes deformation as a consequence of exceeding the recoverable limits (Committee on Trauma Research, 1985).

Mechanisms of Brain Injury

There are two mechanisms which result in brain injury and deformation: brain insult as a consequence of acceleration/deceleration force, and the effect of contact, either an object striking the head or a collision between the brain and the skull (Silver, McAllister, & Yudofsky, 2005). A

brain injury resulting from acceleration/deceleration can cause devastation on brain tissues, producing shear, tensile, and compressive injuries which may tear veins which bridge various areas of the brain and cause extensive damage to axons, in addition to resulting subdural hematomas. Tensile strain is the outcome of a stretching force exerted on tissue. If this strain is strong enough, the tissue, or artery, will lengthen and eventually tear. If there is an increase in vascular pressure, the blood vessels will dilate, exacerbating the tensile force, ultimately causing it to burst if the pressure is great enough (Committee on Trauma Research, 1985). Shear strain results from opposing forces which move tissues in opposite directions, causing shear injury. Brain damage results when the strain force surpasses the limited resistance of the tissue. Contusion injury is the byproduct of shear and tensile forces, causing deformations of intracranial vessels which raise intraluminal pressures, injure blood vessels, and increase the probability for hemorrhage. Lastly, compressive injuries result from crushing forces and compression on the brain (Silver et al., 2005).

Damage to the brain can be classified as either focal or diffuse. Focal injuries include surface contusions and lacerations and injury to the scalp, intracranial hematoma, and increased intracranial pressure which results in vascular changes. These types of injury are likely to be delivered from a fall. Diffuse brain injury, or multifocal injury, is defined by extensive axonal injury, illnesses such as meningitis, hypoxic-ischemic damage, and finally, vascular injury. Diffuse injury is more likely to occur in acceleration/deceleration head trauma after car accidents or as a result of a fall from a great height (Silver et al., 2005).

Contusion

If a head injury is sustained, the most likely resulting pathology is a contusion. This type of injury is most common in the temporal and frontal poles as a result of protruding ridges of bony skull in these locations (Silver et al., 2005). Various contusions can result from certain injuries. If a fracture contusion is sustained, the contusion will appear at the site of the injury. Coup contusions are the product of contact at the site when a fracture does not occur. Lastly, countercoup contusions are the result of brain injury in the tissue diametrically opposite the area of insult. If these contusions are severe enough, injury may also occur in the white matter causing hemorrhage, necrosis of tissue, and swelling. Petechia hemorrhages are probable in the white matter after a contusion, showing up as small spots of blood in the tissue. Following a contusion, the pia-arachnoid layer remains intact. If a laceration occurs, however, it may tear, causing hemorrhaging into the subdural space (Sosin et al., 1995).

Typically, magnetic resonance imaging following a TBI reveals multiple areas which are lesioned in the brain, including evidence of hemorrhaging in some of these areas. If damage is sustained to the blood brain barrier, it is likely that electrolytes, water, and protein can impede into the tissue of the brain, expanding into the neighboring white matter, eventually leading to vasogenic edema. This occurrence is complicated by damage to the surrounding vessels, collection of fluids, and impaired and insubstantial cerebral perfusion. Furthermore, following head injury there is a substantial increase in extracellular excitatory amino acids, especially glutamate and aspartate. These molecules are harmful in excess, however, and will eventually lead to cell death (Silver et al., 2005).

Intracranial Hematoma

Hematomas are an additional result of brain injury, and can cause potentially serious complications. Despite the apparent mildness of a head injury, the possibility of an intracranial hematoma developing is still possible and may greatly aggravate and intensify the injury. Presence of an intracranial hematoma is the leading cause of sudden decline and eventual death immediately following a seemingly lucid moment where the patient appears to be fine (Sosin et al., 1995). These patients frequently "talk and die" after injury. This increase in fatality of head injury after an intracranial hematoma is mainly due to the late recognition and subsequent delayed treatment of the bleeding. When an injury is sustained, bleeding usually immediately follows. Some do not seek medical attention for sometimes 3 to 4 hours after the injury. By the time the person is admitted to the hospital, a hematoma reportedly has occurred in approximately 30%-60% of patients who resultantly are in a coma upon admission (Silver et al., 2005).

Subdural hematomas occur following vascular rupture in the subdural space between the connection of the cortex and sagittal sinus. This type of hemorrhage increases the chances for morbidity and mortality. Other damage to intracerebral vasculature may also occur after head injury, including a dissection or complete occlusion of the carotid or vertebral arteries, small perforations in an artery through which blood leaks between the vessel walls and surrounding tissue (pseudoaneurysm), or a blood clot which remains in the vein (venous thrombosis) (Silver et al., 2005).

Hematomas are a frequent occurrence in the subarachnoid area when a serious brain injury is sustained. Damage to the posterior fossa, and its surrounding blood vessels is the main cause of subarachnoid hemorrhages (SAH). SAH can lead to vasospasm and may cause acute hydrocephalus if enough blood is leaked into the posterior fossa. If vasospasm occurs in a patient

with SAH, this could greatly complicate the resulting pathology of the injury and negatively influence prognosis (Silver et al., 2005).

Vasospasm

The dynamics of vasospasm related to head injury are complex, but the phenomenon is induced by the presence of blood outside of the blood vessel, or on the adventitial surface. Thus, the presence of a SAH is likely to cause this to occur. Cerebral vasospasm causes luminal narrowing of the blood vessel and contraction of the vessel wall. Vasospasm can be so severe that the artery essentially closes, and blood is unable to flow through the occluded space. Arteries particularly vulnerable to this occurrence exist in the base of the brain and in the Circle of Willis. These arteries have a thicker smooth muscle layer which makes up the vascular wall, and are able to contract more vigorously and forcefully than smaller capillaries and veins (Silver et al., 2005).

Vasospasm begins with the breakdown of red blood cells which creates a blood clot, eventually generating oxyhemoglobin which accumulates in the clot. This process leads to the genesis of "reactive oxygen species" which are free radicals such as superoxide. These free radicals are toxic and lead to damage in the endothelial and smooth muscle cells, nerve fibers, and other cells surrounding the blood vessel wall. When this occurs, the artery's ability to relax and contract is impaired, resulting in the subsequent vigorous contraction response and eventual shutting down of the artery. The severity of the bleeding or amount of oxyhemoglobin produced is not known to be correlated with a more severe vasospasm, however (Silver et al., 2005).

At a molecular level, vasospasm related to head trauma is similar to that of diabetes and hypercholesterolemia. Vasodilators such as nitric oxide and prostacyclin are implicated in the

relaxation ability of the arteries, and the levels of these enzymes are reduced in these three conditions. Similarly, a vasoconstrictor called thromboxane, shows over-activity during vasospasm. Vasospasm is maintained by actual structural changes in the vessel. Not only are the endothelial layer and nerve fibers damaged by vasospasm, but the vessel walls become inflamed as white blood cells infiltrate the vascular tissue. This leads to a thickening in the smooth muscle layer of the vessel and eventually leads to fibrosis, or a stiffening of the vascular wall (Silver et al., 2005). In addition to the resulting pathology from SAH, traumatic brain injury can also induce hemorrhaging in other areas of the brain.

TBI Induced Systemic Hypertension

Lastly, a final pathological result of head injury includes TBI induced hypertension (Shiozaki, 2005). When TBI occurs, the brain not only suffers the initial insult, but also sustains secondary injury as the result of insufficient blood flow, or cerebral ischemia. An increase in intracranial pressure is common following a severe brain injury and causes impairment in intracranial perfusion. While the initial insult cannot be erased, the main focus of medical professionals rests on minimizing secondary injury by maintaining a healthy level of cerebral perfusion and avoiding cerebral ischemia which, if successful, improves prognosis. This task, however, is not a simple process. Despite the discovery of the dangers of intracranial hypertension a distant 60 years ago, there is still little that a clinician can do to achieve therapeutic success once the process has begun (Silver et al., 2005).

Immediately following any type of injury, the sympathetic nervous system elicits a fight or flight response, much of it irreversibly released all at once. This occurs by the expulsion of catecholamines into the blood, creating a hyperadrenergic state as a result of this acute and

abnormal physiologic response. Release of catecholamine is directly proportional to the severity of the brain injury rather than the amount of ischemic damage or rise in intracranial pressure (Van Loon, Shivalkar, Plets, Goffin, Tjandra-Maga, & Flameng, 1993). In the uninjured, or non-hypertensive brain, blood flow and supply are appropriately regulated in order to maintain consistency across large changes in blood pressure. After the release of catecholamine which causes the capacity of this autoregulatory system to exceed its limits, cerebral blood flow and systolic blood pressure are pushed directly into the capillary beds. This increase in cerebral blood flow incites a deterioration of the blood brain barrier, resulting in the aforementioned vasogenic edema. TBI induced intracranial arterial hypertension eventually results in a swelling of the tissue, increasing intracranial pressure, all which negatively influence prognosis (Shiozaki, 2005).

Implications

As demonstrated through available research, hypertension, hyperglycemia, and hypercholesterolemia pose large risk factors for vascular disease and result in systemic damage in the human body. This deterioration becomes especially salient in vital organs such as the heart and the brain and can result in a fatal outcome if proper measures are not taken to ameliorate the effects of the diseases. Despite treatment, however, each disease appears to make its mark prior to behavioral or medicinal changes and, to some degree, during the healing process. The damage which ensues creates a more vulnerable vascular system, leading to an intensification of injury following an internal or external insult, such as stroke or head injury.

Although the connection between the general premorbid health of the brain and severity of head injury has already been established (Jennett & Teasdale, 1981), the specific effects of

hypertension, high cholesterol, and diabetes on traumatic brain injury are still unknown. Furthermore, because these diseases do not usually present singly, and one person is likely to have more than one of these disorders, there are numerous unanswered questions regarding the cumulative nature of these risk factors. The present study aims to establish evidence that a relationship exists between the physiological presence of these factors and the extent or severity of the injury.

Current Study

To achieve this goal, this study attempts to measure the severity of the resulting pathology from the combination of the aforementioned health disorders of hypertension, hyperglycemia, and hypercholesterolemia by reviewing archival neuropsychological data from those with and without these preexisting risk factors who also sustained a head injury. Due to the tendency for these disorders to damage and weaken the vascular system, the purpose of this study is based on the theoretical assumption that an insult to an already weakened system will produce an additive effect of resulting pathology (Jennett & Teasdale, 1981). This research will not only build on existing literature related to diabetes, hypertension, hypercholesterolemia, and head injury, but also bridges a gap between the realm of TBI and medical health research, contributing to an area in which there is a virtual void of previous exploration.

Data will be reviewed from an existing archival database comprised of previous neuropsychological assessments of people with head injuries. These assessments were conducted at an urban hospital following consultation after traumatic brain injury from the past 3 years. Those with anywhere from one to all three health risk factors will be used for the study, in addition to those not affected by these risk factors. All participants will have an overall similarity

in severity of head injury measured by a score of 15 on an initial Glasgow Coma Scale (GCS) administration which occurs at the scene of the accident or upon admission into the hospital. This scale is a rough measure of severity of brain injury and assesses each patient for a range of functions such as degree of eye opening response, verbal response, and motor responses. The scores on this measure range from 3 to 15, where the range of 3 to 8 usually designates a person in a coma.

The first prediction includes the main effect of the variable of health complication on the results of neuropsychological testing; specifically, the presence of a health issue will result in lowered scores in these individuals compared to controls, signifying greater impairment. Each additional health disorder is also hypothesized to exacerbate the resulting sequelae. In other words, the more risk factors a person exhibits, the more severe the complications will be from the injury, evidenced by a decrease in neuropsychological testing results (measured by a z score). Secondly, an interaction effect is also predicted for the variables of age and severity, a finding already demonstrated in previous research. This implies that the length of duration for each disorder increases the extent of vascular pathology, so the older a person is, the worse the outcome.

CHAPTER II: METHODS AND PROCEDURES

Participants

This study reviewed data from 209 inpatients who were evaluated from fall, 2007 through the spring of 2010 at Allegheny General Hospital for sequelae related to head injury. The ages of the participants ranged from 30 to 80 years (M=58.15, SD=14.17). The only information recorded for this investigation pertained to age, gender, and presence or absence of a relevant health condition (hypertension, hypercholesterolemia, and diabetes mellitus). The participants were chosen based on the type of health issues documented in their medical records and also the severity of their injury, measured by their Glasgow Coma Scale scores described below (no less than 15). Each was assigned to a group depending on the number of health risk factors documented in their records, either placed in the zero (age M= 53.70, SD=13.50), one (age M= 56.28, SD=14.89), two (age M= 60.81, SD=14.12), or three risk factor group (age M= 61.97, SD=12.63). The zero factor group served as the control, consisting of participants who did not have documented health risk factors, but were concussed to a similar degree as the clinical groups. Each participant chosen was therefore matched by severity of head trauma. Each group was further separated depending on their age, either placed in the group of those 30-55 or 56-80. The number of participants in each group is depicted in Table 1, and although gender was not analyzed in the study, it is included for informational purposes.

Descriptive statistics of the current study

Variables	Value Label	N
Health Risk Factors	0 factors	51
	1 factor	60
	2 factors	57
	3 factors	41
Age	Young	103
	Old	106
Gender	Male	121
	Female	88

	Young-0	Old-0	Young-1	Old-1	Young-2	Old-2	Young-3	Old-3
Mean Age	42.28	64.69	43.7	68.86	48.92	72.27	50.50	73.43
SD	6.57	8.20	7.9	7.8	7.89	7.84	5.48	5.64

	riskfactors	age	Mean	Std. Deviation	N
Executive Function	0 factors	young	-.8109	1.35221	25
		old	-.5587	1.36909	26
		Total	-.6824	1.35317	51
	1factor	young	-.9398	1.18529	30
		old	-.5359	1.38245	30
		Total	-.7379	1.29283	60
	2 factors	young	-1.2145	1.26723	28
		old	-.7832	1.13761	29
		Total	-.9951	1.21189	57
	3factors	young	-1.8651	1.39874	20
		old	-1.1900	1.51455	21
		Total	-1.5193	1.48088	41
	Total	young	-1.1629	1.32726	103
		old	-.7387	1.34804	106
		Total	-.9478	1.35144	209

	Risk Factors	Age	Mean	Std. Deviation	N
Immed Memory	0 factors	young	-1.1783	1.02240	25
		old	-.9525	.64627	26
		Total	-1.0632	.85064	51
	1factor	young	-1.1599	1.05073	30
		old	-1.0147	.88030	30
		Total	-1.0873	.96380	60
	2 factors	young	-1.5305	.75647	28
		old	-1.2568	.73153	29
		Total	-1.3912	.75002	57
	3factors	young	-1.6480	.92341	20
		old	-1.4446	.74449	21
		Total	-1.5438	.83232	41
	Total	young	-1.3599	.95617	103
		old	-1.1508	.77275	106
		Total	-1.2539	.87221	209
Delayed Memory	0 factors	young	-1.2455	1.21352	25
		old	-1.0723	.89146	26
		Total	-1.1572	1.05445	51
	1factor	young	-1.2268	1.19933	30
		old	-1.1196	.99379	30
		Total	-1.1732	1.09333	60
	2 factors	young	-1.7327	.64695	28
		old	-1.4513	.92555	29
		Total	-1.5895	.80639	57
	3factors	young	-1.7523	.97843	20
		old	-1.8274	.83680	21
		Total	-1.7908	.89794	41
	Total	young	-1.4709	1.05303	103
		old	-1.3390	.95203	106
		Total	-1.4040	1.00284	209

	Risk Factors	Age	Mean	Std. Deviation	N
Learning	0 factors	young	.1240	1.40543	25
		old	.0885	1.05160	26
		Total	.1059	1.22530	51
	1factor	young	.1400	1.17432	30
		old	.3540	1.15730	30
		Total	.2470	1.16095	60
	2 factors	young	.0821	1.07292	28
		old	-.1276	1.08493	29
		Total	-.0246	1.07459	57
	3factors	young	-.5450	.84882	20
		old	-.1524	1.33702	21
		Total	-.3439	1.12939	41
	Total	young	-.0126	1.16843	103
		old	.0568	1.15379	106
		Total	.0226	1.15875	209

Table 1. Descriptive statistics for risk factor group, age group, gender and dependent variables, and for each combination of factors.

Assessment of Cognitive Functioning

A total of 10 different neuropsychological tests were reviewed in order to determine an overall impression of cognitive functioning in four specific domains (See Table 2). These assessments include measures of executive functioning, learning, and immediate and delayed recall. Each outcome was recorded in the specific type of measurement employed for each test (i.e. time in seconds, number correct, etc.). Following data completion, each individual test result was converted into a Z-score in order to serve as a universal metric of comparison between each group. This entailed utilizing the mean and standard deviation available according to age and often gender found in the normative data for each type of assessment. The dependent measures were grouped as reported in Table 2 (See Appendix 1 for full descriptions of each measure):

Dependent measure operational definitions

Executive functioning	**Operational Definition**
Trails B	*Time required to complete task (z-score reversed to reflect direction of impairment)*
Controlled Oral Word Association Test (COWAT)	*Total number of words produced in 1 minute*

Immediate Recall	
Hopkins Verbal Learning Test (HVLT)	*Trials 1, 2 & 3*
Brief Visuospatial Memory Test-Revised (BVMT-R)	*Total recall of trials 1, 2, & 3*
Logical Memory I	*Total items recalled*

Delayed Recall	
Logical Memory II	*Total items recalled*
Brief Visuospatial Memory Test- Revised Delay	*Total points*
Hopkins Verbal Learning Test (HVLT)	*Total number recalled*

Learning	
Hopkins Verbal Learning Test (HVLT)	*Highest 2^{nd} or 3^{rd} trial – 1^{st} trial recall*
Brief Visuospatial Memory Test- Revised	*Highest 2^{nd} or 3^{rd} trial – 1^{st} trial recall*

*Table 2***:** Description of the individual composition and operational definitions for each dependent measure used in this study.

CHAPTER III: RESULTS

Statistical Analysis

The current study measured the effect of two independent variables, each with multiple levels. The predominant focus of the study centered on the effect of the first independent variable: health complications. This variable included the levels of zero, one, two, or three risk factors. A secondary focus of the study also evaluated the independent variable of age, as it has been demonstrated to be a meaningful predictor in past measurements of TBI outcome. Participant data were separated into age brackets, divided into those 30-55 and those 56-80 years of age. This results in a 4 x 2 x 4 factorial research design with four dependent variables. A power analysis was conducted in order to determine an appropriate sample size without sacrificing power and potential effect size, resulting in approximately 25 participants per cell for a total of 200 data sets (α=.05, 1-β=.849, r^2= .25).

Assumptions of univariate normality for each dependent variable were checked using Levene's test, and yielded no significance, indicating equality of variances F(3, 205)=.833, p=.47 (executive function); F(3, 205)=1.492, p=.218 (immediate memory); F(3, 205)= 2.385, p=.07 (delayed memory); F(3, 205)= .043, p=.99 (learning). Due to inequality of group sizes and the need to account for covariances, Box's test was also initially used to compare variance-covariance matrices between groups. This also yielded appropriate non-significant results F(51; 98,224.621)=1.88, p=.07). Because the assumptions of MANOVA were met, this factorial analysis continued with the comparison of the independent variables and their levels according to their effect on the dependent measures.

This analysis yielded both significant and non-significant results. Contrary to expectations and previous findings, the effect of age on the dependent measures was not significant F(1,4)=1.66, p=.161. In addition to the finding of non-significant results for the effect of age, these results were perplexingly characterized by a *better outcome* in mean performance as

age increased (See Figure 1). Although the overall effect of age was not significant, there was a significant difference between the older and younger groups regarding measures of executive functioning F(1,7)=2.49 p=.018, *r*=0.10. This was characterized by a significantly higher scores in the older group compared to the younger group on executive measures. The interactive effect of both age and risk factors on the dependent measures was not significant, F(1,12)=.47, p=.934. Lastly, in this preliminary analysis, the risk factors variable had a statistically significant effect on the dependent measures F(1,12)=1.78, p=.048.

Mean Performance for Young and Old Groups for Each Dependent Measure

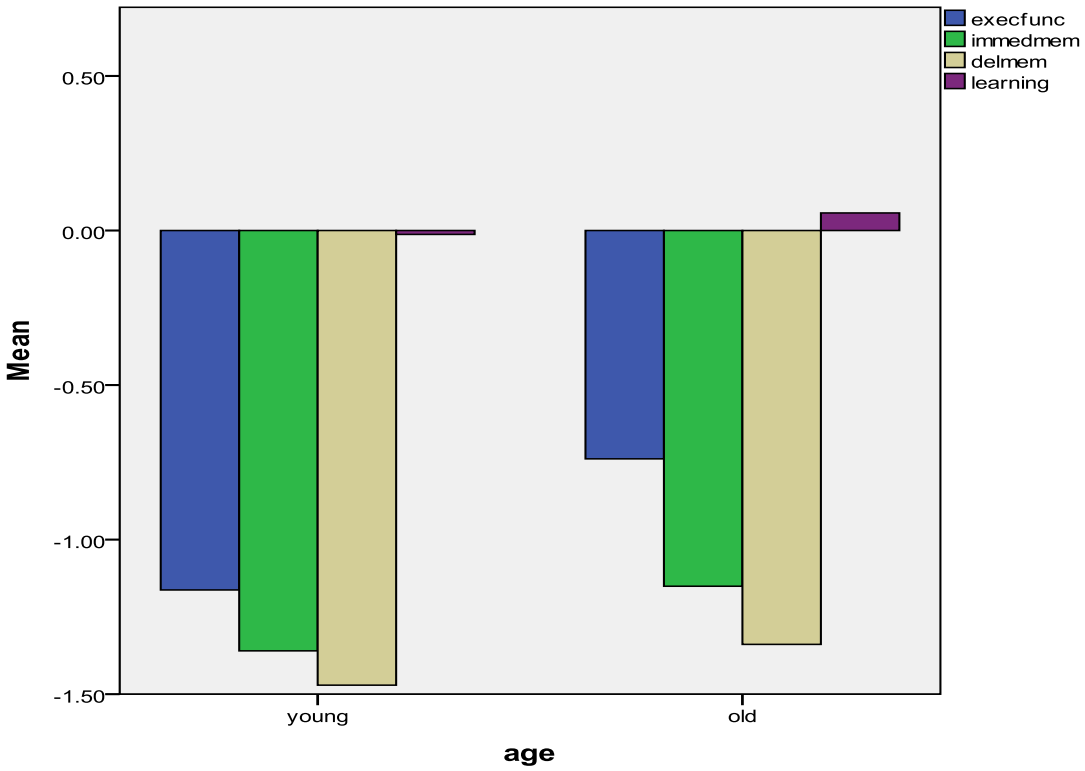


Figure 1: Depicts higher mean scores in the older group compared to the younger group. The difference in executive functioning scores from the younger to older group was significant. (α=.05, p=.018). Total mean Z scores for each measure were as follows: executive functioning (young M= -1.16, SD=1.33, old M= -.74, SD=1.35), immediate memory (young, M= -1.36, SD= .96, old M= -1.15, SD=.77), delayed memory (young, M= -1.47, SD=1.05, old M= -1.33, SD=.95), and learning (young, M= -.01, SD= 1.17, old M= .06, SD=1.15).

The significant effect of executive functioning by age shown in Figure 1 was further examined by determining the extent that each executive measure was contributing to the significance. These two measures (COWAT and Trails B) both showed an individual increase from young to older participants, however, only the COWAT demonstrated a significant increase $F(1)=6.846$, $p=.01$, $r^2=.15$.

Means of COWAT and Trails B for young and old groups

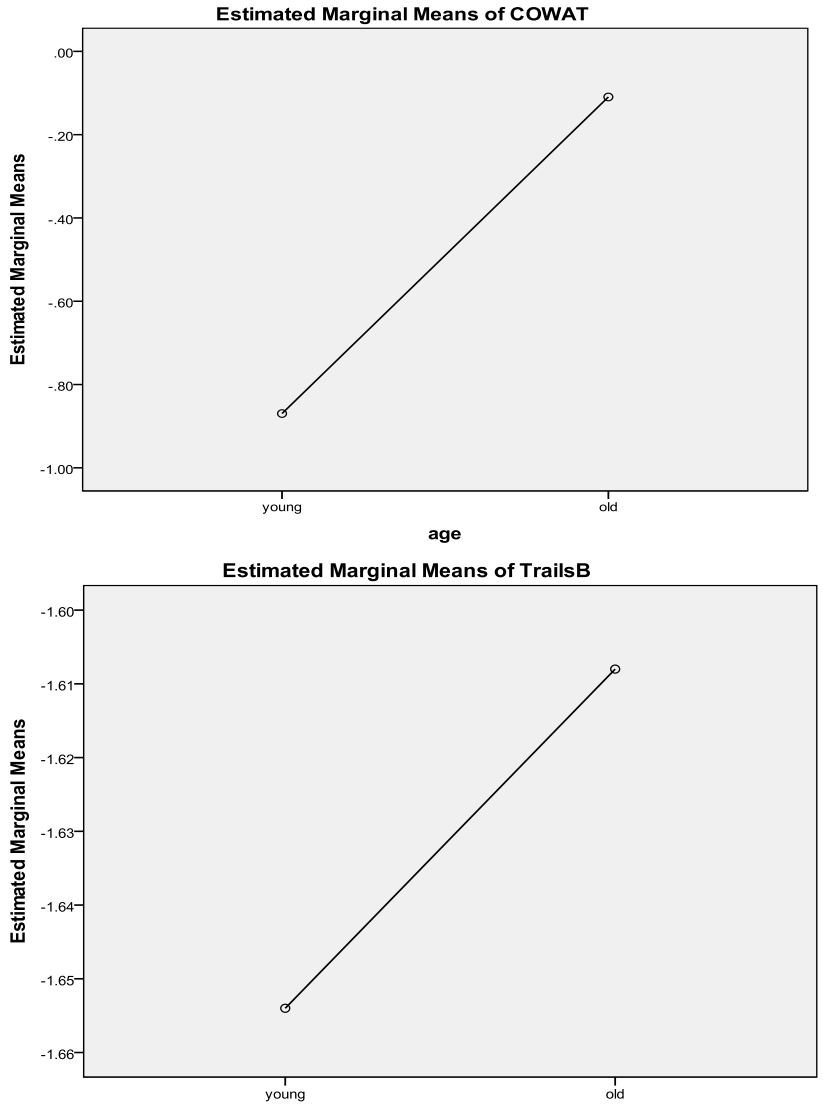


Figure 2. Both means of the COWAT and Trails B increase in the older group compared to the younger group.

Estimated marginal means

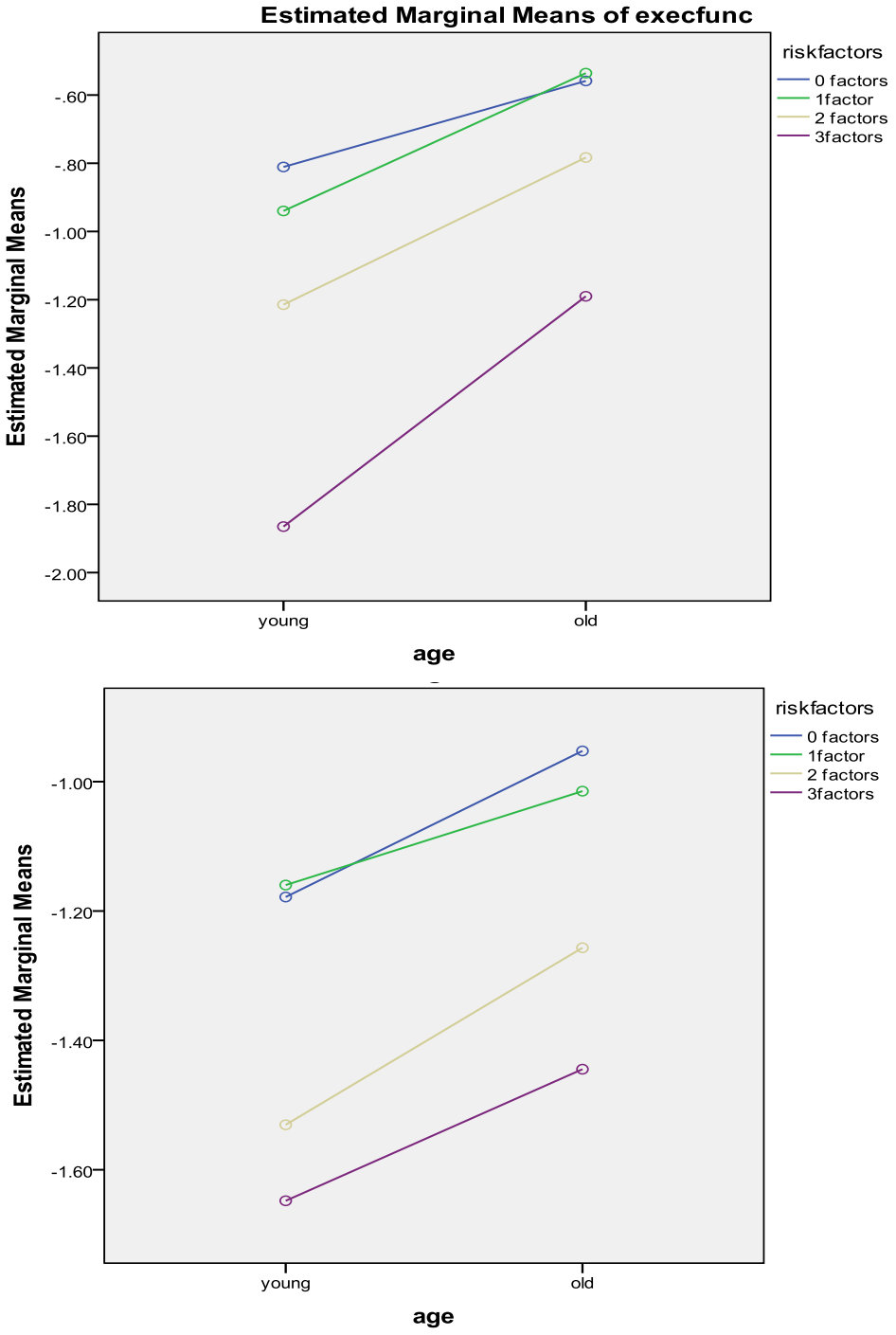


Figure 3. Estimated marginal means of executive functioning (top) and immediate memory (bottom) according to age and risk factors.

Estimated marginal means

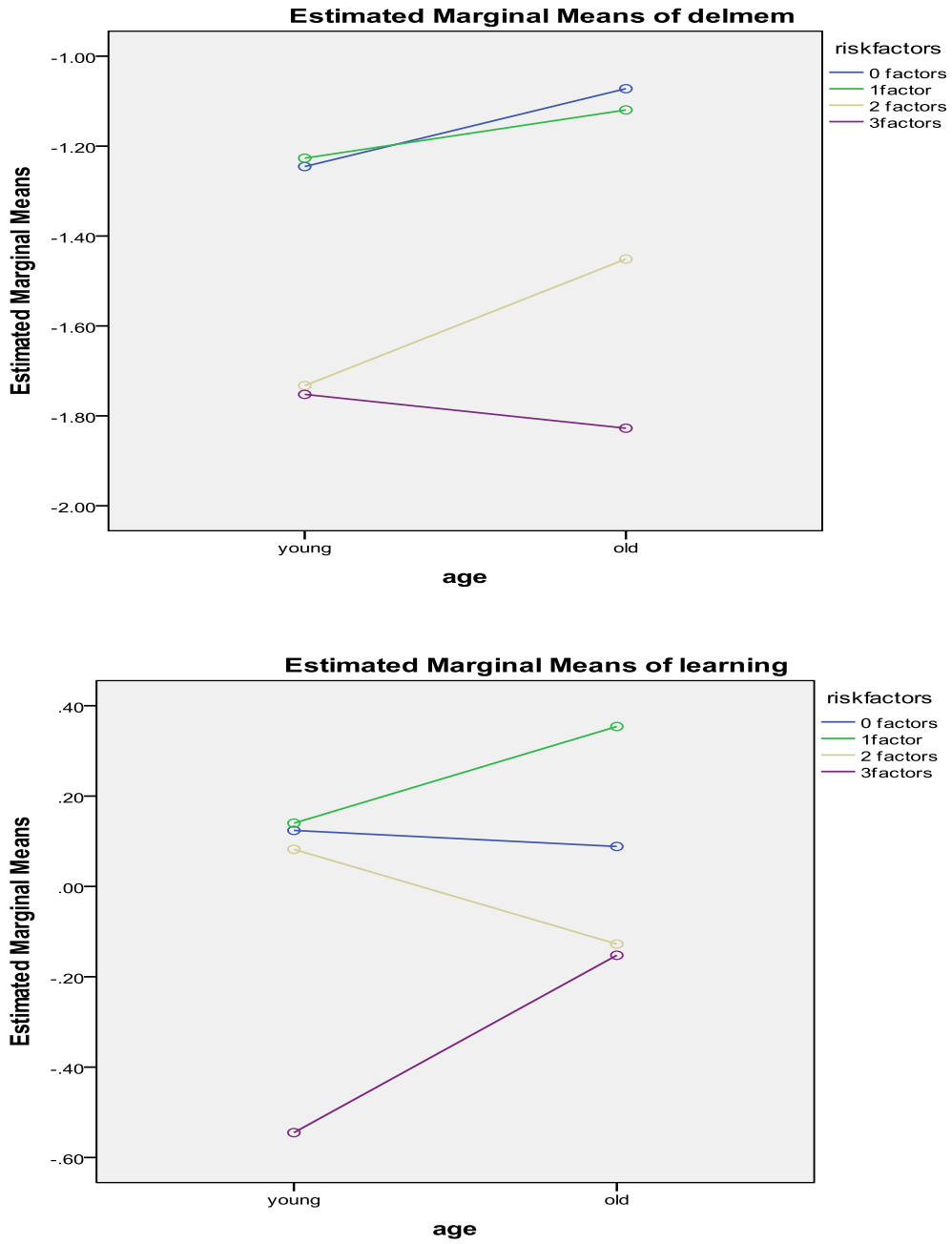
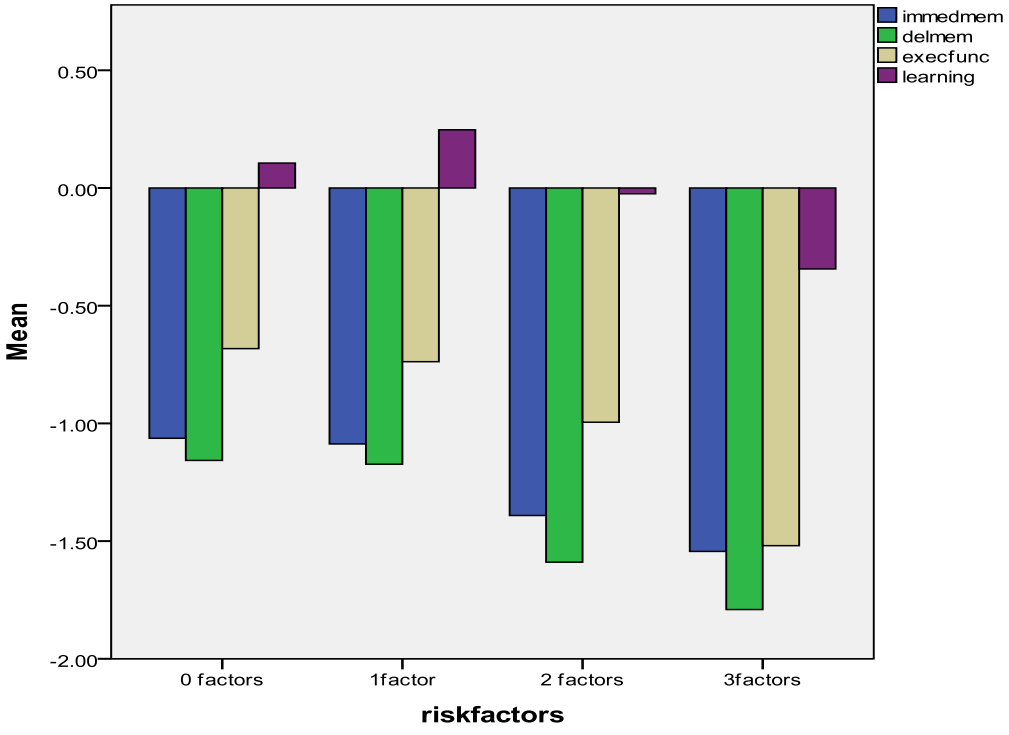


Figure 4. Estimated marginal means of delayed memory (top) and learning (bottom) according to age and risk factors.

In order to further explore the nature of the significant findings, follow-up exploratory analyses were completed. Because Levene's test (described previously) yielded non-significant results, this increases confidence that the multivariate statistics are robust, but also importantly attests to the reliability of the univariate tests to follow. With this reassurance, separate univariate analyses of variance were conducted for each of the dependent variables. Tests of individual between-subjects effects revealed the significance of the risk factors variable on each dependent measure *except* learning. Therefore, the levels (numbers) of risk factors significantly influenced the outcome of executive functioning F(3)=3.75, p=.012, *d*=.80 and both immediate F(3)=3.66 , p=.013, *d*=.79 and delayed memory measures F(3)=5.05 , p=.002, *d*=.99. The means for each variable are displayed in ***Figure 3*** with a visible decline in performance (z-score) as risk factors increased for all variables except for learning.

Mean performances of each dependent measure



t

Figure 5. Depicts mean performances (z-scores) for each dependent measure according to each risk factor group (0-3) showing a decline in mean scores from 0 to 3 factors. Each reduction in scores for each dependent measure was significant except for learning.

The significant variables of immediate memory, delayed memory, and executive functioning were then further separated into individual tests in order to determine each measure's impact on the risk factors by dependent measures. Each individual category measure showed consistence in decline from zero to three risk factors except for the executive measure Trails B depicted in Figure 6.

COWAT and Trails B means

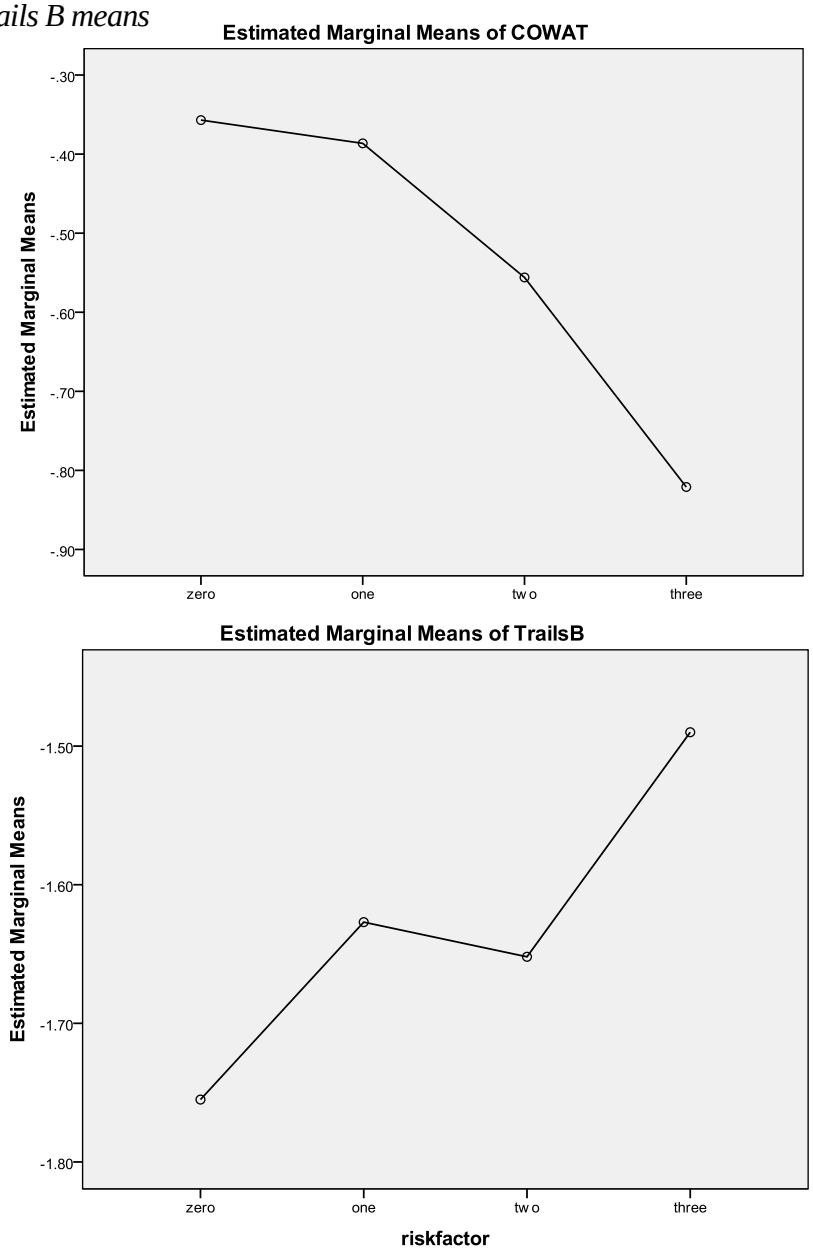


Figure 6. Means of the COWAT and Trails B measures as risk factors increase.

In order to determine how the dependent variables interact and discriminate the groups in relation to the significant results, a discriminant function analyses was performed. The first variate was the focus of the following analyses, as Wilks' Lambda revealed that the group differences shown by the MANOVA are explained by this one underlying dimension $\chi^2(12, N = 209) = 21.14$, $p = .048$. For this analysis, the dependent measures (four types of neuropsychological assessments) were used as the groups, and the risk factor levels (0-3) were used as the predictors. The first variate represented functions 1 through 3 (most variation), the second, 2 through 3 (greatest part of unexplained variation), and the third, function 3 (the next greatest level of variation). The relative contribution of each dependent variable to group separation was relatively equal for the first variate, with the learning variable contributing the least, as is evident in Table 3 which depicts the structure matrix. For the second variate, immediate memory contributed the least and group separation here is determined by the differences between the four dependent variables because of the range of negative and positive scores. The third variate shows similar differences, with immediate memory yet again contributing the least to overall differences. The mean variate scores for each group depicted in Table 4 and Figure 7 show that variate 1 significantly discriminates the three risk factor group from the zero, one, and two risk factor groups. Variates 2 and 3 do not show such significant discriminations.

Structure Matrix

	Function		
	1	2	3
Delayed memory	.867*	-.437	.207
Executive function	.742*	.402	-.482
Immediate memory	.738*	-.379	.080
Learning	.564	.407	.676*

*. Largest absolute correlation between each variable and any discriminant function

Table 3. Depicts the canonical variate correlation coefficients which show the nature of the variates (i.e. relative contribution of each dependent variable to group separation). Those with high canonical variate correlations contribute most to group separation, and those with the lowest, contribute the least for each discriminant function.

Functions at Group Centroids

riskfactors	Function 1	2	3
0 factors	.268	-.079	-.069
1factor	.258	.004	.072
2 factors	-.142	.141	-.027
3factors	-.514	-.103	.018

(Unstandardized canonical discriminant functions evaluated at group means)

Table 4. Mean variate scores for each group. Variate 1 discriminates the 3 factor group from the 0 and 1 factor group the most, and discriminates the 3 factor group from the 2 factor group to a lesser extent.

Canonical discriminant functions

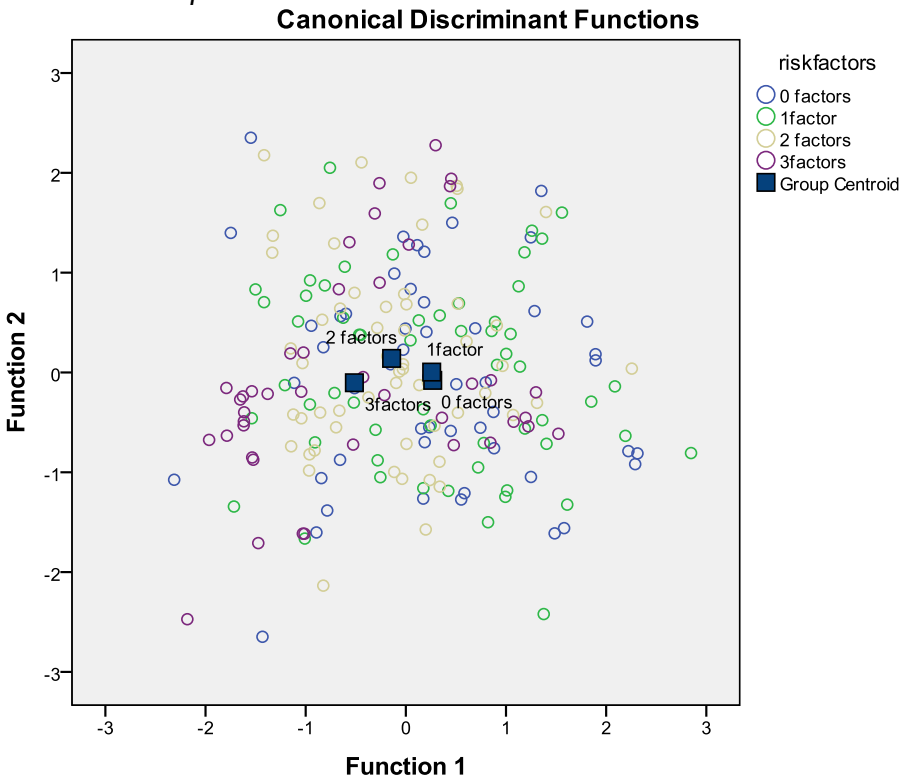


Figure 7. Combined groups plot of variate scores for each person identified according to the group to which they belonged. The group centroids (mean variate scores) are also indicated, depicting variate, or function 1 to be differentiating among groups, specifically between the 3 risk factor group and the 0 and 1 factor groups which was deemed significant by Wilks' Lambda (α=.05, p=.048).

Following the discriminant function, Tukey's Honest Significant Difference (HSD) test was conducted to evaluate the significance between pairs of means. This test was chosen because

of its relatively greater power in detecting a difference. Although the Levine test did not indicate a problem with unequal variances, the Games-Howell test was also employed as a comparison and computed identical results. In analysis of the executive functioning measures, those with 3 risk factors produced results significantly lower than those in the 0 risk factor group (LSD=.837, p=.003) and in the 1 risk factor group (LSD=.781, p=.004) but did not significantly differ from the 2 risk factor group. The immediate memory category was characterized by identical discrepancies, and there was a significant reduction in scores from the 3 risk factors group to those with 1 or no risk factors (LSD=.33 , p=.045 and LSD=.48 p=.040, respectively). Delayed memory measures, again, showed identical results, revealing significant differences from the 3 factor group to the 1 and 0 factor groups (LSD=, p=.011 and LSD=, p=.012, respectively). As stated previously, learning measures did not distinguish significantly between groups.

Due to the unexpected finding that scores increased as *age* increased, this variable was examined further. To determine if this finding remained constant if the oldest participants were compared to the youngest participants, age was stratified into those 30-50 and 70-80. This resulted in the following descriptive statistics depicted in Table 5.

Descriptive statistics for modified age brackets

	N	Minimum	Maximum	Mean Age	Std. Deviation
Zero factors-young	22	30.00	50.00	40.3182	5.98718
Zero factors- old	7	70.00	80.00	76.5714	3.95209
One factor- young	20	30.00	50.00	39.8500	6.44225
One factor- old	15	70.00	80.00	75.8000	3.34237
Two factors- young	12	30.00	50.00	41.5833	6.94731
Two factors- old	18	70.00	80.00	78.2222	2.86060
Three factors- young	7	35.00	50.00	45.1429	6.30948
Three factors- old	15	70.00	80.00	75.7333	3.73146

Table 5. Descriptive statistics for zero through three risk factors and young and old groups.

Wilks' Lambda was not significant for the risk factors or age variables, however, Hotelling's trace showed significance for risk factors (F(12)=1.794, p=.048, d=.88). In the test of between subjects effects, three dependent measures were significant, including executive function (F(3)=4.04, p=.009, d=.83), learning (F(3)=3.51, p=.018, d=.769) and delayed memory (F(3), p=.018, d=.769). Immediate memory was not significant.

Mean scores for each dependent measure

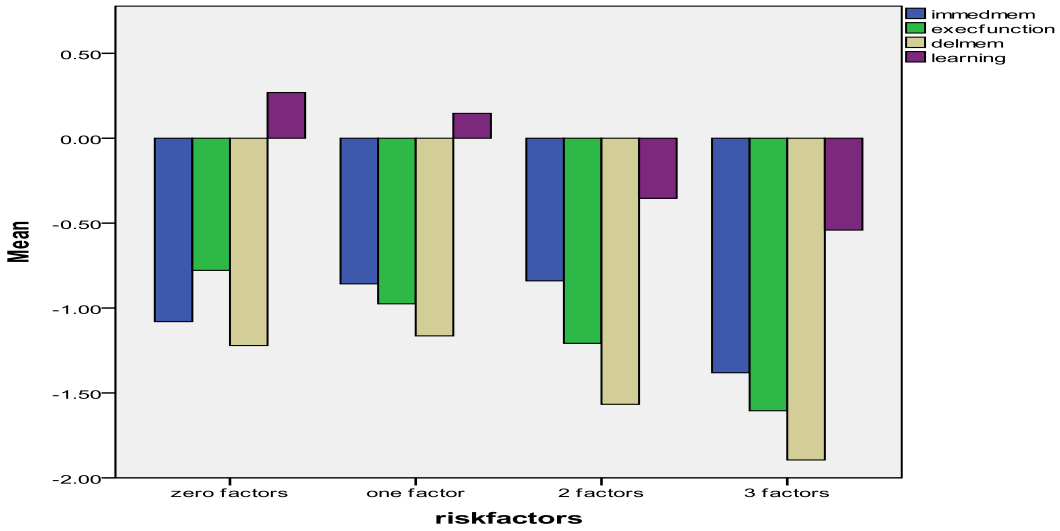


Figure 8. Mean neuropsychological testing scores for each dependent grouped measure in each risk factor group

Mean scores for modified age brackets

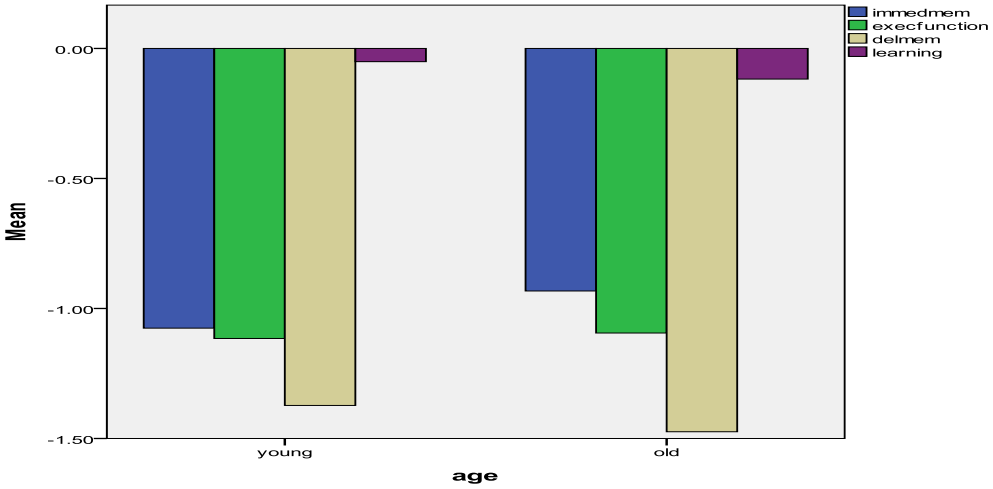


Figure 9. Mean neuropsychological testing scores for each modified age bracket (30-50, 70-80).

In the post hoc evaluation, again using Tukey's HSD, there were multiple significant differences between risk factor groups. In the executive functioning measures, the 3 factor group significantly differed from the 0 factor group (HSD=.827, p=.019). For delayed memory, the 1 risk factor group differed significantly from the 3 factor group (HSD=.731, p=.04) and for the learning measures, the 3 factor group significantly differed from the 0 factor group (HSD=.81, p=.049). As stated previously, no significant differences in risk factor levels for immediate memory.

Although not significant, the comparison of dependent measures versus age (Figure 9) is altered somewhat with this newly stratified evaluation, however, still not to the extent expected. Instead of a consistent increase in scores as age increased, as was the case previously, this analysis shows a maintained non-significant increase in immediate memory and executive function as age increases, yet a decrease in learning and delayed memory scores from the younger to older participants.

Total mean age of participants as risk factors increase

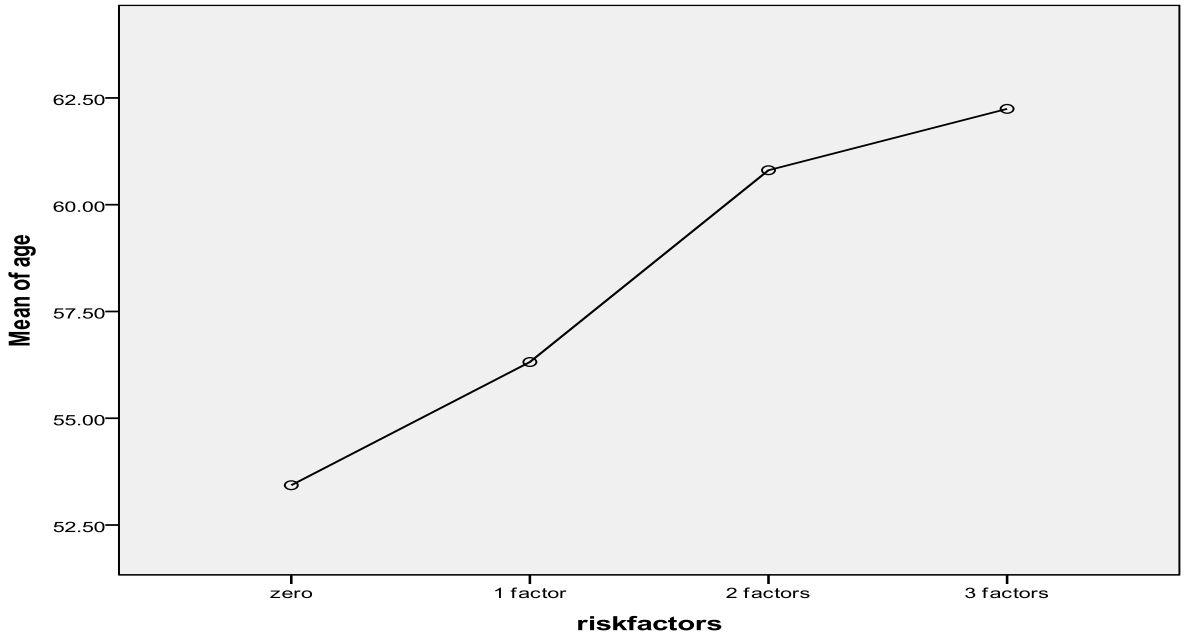


Figure 10. Shows the increase in the mean age of participants as the number of risk factors goes up.

CHAPTER IV: DISCUSSION

This study investigated the possible relationship between the outcome severity of head injury and the extent of premorbid vascular risk factors. These risks included hypertension, hypercholesterolemia, and diabetes mellitus. A secondary interest, and admittedly, expectation of this study based on supporting research was to observe a decrease in dependent measure scores as age increased. Therefore, participants were separated into two age groups, those 30-54 and 55-80. Four specific outcomes were predicted to result from the analyses: (a) Those diagnosed with 1-3 risk factors will show increasingly greater cognitive impairment as risk factors increase, evidenced by lower scores on the dependent measures compared to other groups with lesser risk factors, (b) Those with no history of these risk factors (zero factor group) will fair the best in terms of dependent measures, and (c) Age will play a large role in influencing the dependent measures of those with one risk factor or greater, with a reduction in mean scores in the older group of participants. Hypotheses (a) and (b) were supported and results showed that for most dependent measures, scores declined as risk factors increased.

Implications

Although there were many limitations to the design of this study which suggest caution in interpreting the results, this may lend support to the logical notion that a weakened vascular system is more vulnerable to damage after an insult, in addition to a possibly lengthened recovery time. This could have important repercussions for both those who suffer from and those who treat people with vascular pathology. An otherwise benign head injury could potentially result in a more detrimental outcome, especially in someone with all three risk factors. This suggests the importance for health care providers to communicate to the patient and his or her

family the expectation that these patients may be slower to recover and may be left with more resulting sequelae. Although this study in no way evaluated length and speed of recovery, it can be inferred that those with more sequelae measured by neuropsychological assessment may take longer to recover, if a full recovery is at all possible. In this regard, results of this study may help practitioners more appropriately inform and educate their patients regarding their treatment and help estimate the progression of their recuperation according to diagnosed risk factors, in addition to other available outcome measures (Shukla, Devi, & Aqrawal, 2011).

This information would not only be important following a head injury, but would also be imperative for those receiving an initial diagnosis of vascular pathology. It may give those individuals more incentive to seek medical treatment because of their increased susceptibility to brain injury following head trauma, in addition to other related problems. These findings also may act as a warning, cautioning those with vascular risks that engaging in activities with the potential for head injury may result in worse than previously anticipated results. This could have meaningful implications for those who are involved in sports, especially high-contact sports such as football, hockey, and soccer, and may lead to recommendations to those with vascular pathology to seek treatment or leave the sport. With the increasing awareness in the sports industry of the detrimental effects of head injury (Mitka, 2010), results of this study may provide further impetus to families, advocates, and those involved in the treatment of players to better inform the athletes about the increased risks involved if vascular pathology is present.

Age Conundrum

The single aberrant and initially baffling result was the failure to support hypothesis (c). It has been a somewhat robust finding in extant literature that as age increases, neuropsychological performance decreases as a reflection of "normal" cognitive decline related to age. However, after a more complete review of research on cognition and aging, it is evident that there is a considerable debate regarding the age at which cognitive decline begins. Many believe that decline begins around the age of 60; however, in both longitudinal and cross-sectional studies, there is evidence that some elements of age-related cognitive decline are initiated in healthy adults starting in the 20's and 30's (Salthouse, 2009). At this young age, average performance on measures of reasoning, spatial visualization, episodic memory, and processing speed begin to decline (Salthouse, 2009).

In an attempt to determine the contribution of global, specific, and test-related processes to the measurement of cognitive decline, Tucker-Drob (2011) concluded that cognitive aging is characterized by both global and domain-specific decline. His work also supported the idea that general cognitive change apparent later in life may actually emerge in early adulthood (age 18-49). He postulates that the causes of large mean declines may be biological in nature and the causes of individual differences may relate to protective factors or lifestyle choices. Regardless of when this down-hill process begins, there appears to be an agreement that evidence of decline accelerates around the age of 60 (Salthouse, 2009), making the results of the current study related to age and an increase in scores somewhat perplexing.

Following the initial comparison of the younger and older participants in this study, the unexpected results necessitated an additional analysis. After the age brackets were moved to further separate the "youngest" and "oldest" participants by selecting those 30-50 and 70-80, the

results only changed for half of the measures. Scores for immediate memory and executive functioning maintained their increase from younger to older participants, while learning and delayed memory scores decreased. Although the increase and decrease were both non-significant, the question remained: Why are the older participants performing better than those in the younger group?

This was a difficult question to answer because it contradicts the aforementioned literature supporting a decrease in cognition as one ages. The only explanation that may account for this finding is the possibility that at this hospital, younger patients may have presented to the emergency department with more serious injuries. Because younger individuals tend to be more active and potentially more reckless, the likelihood of involvement in a motor vehicle accident, 4-wheeler accident, or a fall from a roof, etc., is higher. Thus, the patients who made up the younger group in this study may have initially suffered from a more serious head injury, as those with lesser head injuries never made it to the hospital. In contrast, the same injury in an older individual may have resulted in a hospital admission as a precautionary measure. In this regard, those that comprised the older group (56-80) may be more concerned for their health and more likely to present to the ED with more benign injuries, such as falls. Although a fall can certainly produce severe cognitive impairment, in general, it may have had some influence on the current age-related results.

The elderly also tend to utilize the emergency department at a higher rate than younger persons are more likely to be admitted (McCusker, J., Karp, I., Cardin, S., et al., 2003). Whether or not an individual receives Medicaid is also a factor which influences emergency department visits in rural areas (Fan, L., Shah, M.N., Veazie, P.J., et al., 2011). Fan et al. (2011) found that those who reported excellent, very good, good, or fair physical health and also received

Medicaid were more likely to visit the ED than those not on Medicaid. Those on Medicaid reporting poor physical health were less likely to utilize the ED. This leads to the inference that the Medicaid insured elderly in *better health* are reporting to the ED for issues related to circulation, respiratory illness, and injury. Although the insurance providers were not labeled in the medical record, it is possible that a number of older patients with Medicaid may have presented to the hospital from surrounding rural areas in better physical, and suggestively cognitive health.

This characteristic of the current study may have also attenuated the effect of risk factors on the dependent measures. An examination of the trend for each risk factor group will lead one to observe that the mean age of participants increased as the number of risk factors increased (see Table 1, Table 5, and Figure 10). Because younger participants, overall, produced lower scores than the older group, and older participants increasingly represented the 1, 2, and 3 risk factor groups, it makes the findings that much more robust.

Confounding Factors

Unfortunately, there are numerous confounds which muddy the water, rendering a single explanation for the current results unlikely. These confounds include the link between an unhealthy lifestyle and an increase in vascular risk factors. Steyn and Damasceno (2006) describe the relationship between an unhealthy lifestyle and obesity, poorer health, lower income, and chronic diseases, such as hypertension and diabetes. Gunstad, Lhotsky, Wendell et al (2010) have shown that obesity *alone* can cause a decrease in some measures of cognitive functioning, including global screening measures, memory, and verbal fluency tasks. Obesity, however, was also associated in this study with better performance on measures of attention and

visuospatial ability. Although participants with vascular risk factors such as hypertension, diabetes, and high cholesterol purposely were not part of Gunstad et al.'s (2010) study, the physiological mechanisms by which this decrease is occurring are not known and were suggested as further research. It is possible, however, that the problems originate in the vascular system.

Recent research has also shed light on brain volume and obesity, again independent of vascular risks. Visceral fat in the abdomen, especially, is correlated with a reduction in temporal lobe, hippocampal, and total brain volume, which are presumably correlated with cognitive functioning (Debette, Beiser, Hoffmann, et al., 2010). Elevated adiposity has also been associated with an increased risk of dementia (Kivipelto, Ngandu, Fratiglioni, et al., 2005). Because weight and height were not documented or maintained in what remained of each medical record reviewed for the current study, it is impossible to determine the effect that obesity had above and beyond the three vascular risk factors.

Each singular component of the metabolic syndrome, which includes the diagnoses of diabetes II, hypercholesterolemia (a form of dyslipidemia), and hypertension is also linked to dementia and an increased risk for cerebral infarct (Luchsinger, 2010). Other research suggests that those with vascular risk factors measured in the current study may have already evinced a decline in cognitive functioning *before* their head injury due to white matter intensities and other vascular damage (Petrova, Prokopenko, Pronina, et al., 2010). Thus, it is possible that the significance detected by the dependent measures had less to do with the head injury than previously assumed and the vascular pathologies, independent of head injury, may have contributed increasingly to the demonstrated decline.

Furthermore, although a score of 15 on the Glasgow Coma Scale (GCS) was used to ensure that each participant was concussed to a similar degree, this measure was likely not as

precise or rigorous as would be ideal in order to determine true equality of a brain injury. This would also support the possibility that those in the younger group were concussed more severely than the older group. The majority of patients with a head injury who present to Allegheny General Hospital (where the current data were collected), earn a score of 15 on the GCS. Despite diagnosis of a mild brain injury, there is still substantial variation in severity and duration of resultant sequelae. For example, a woman who suffered a relatively mild blow to the head with no loss of consciousness or resulting problems would earn a score of 15, versus a woman who earned a 15 but who sustained a head injury from a MVA, lost conciousness, but could still open her eyes, knew where she was, and was able to obey commands.

Reliability on this initial brain injury measure is also less than desirable, especially with inexperienced physicians or raters (Namiki, Yamakazi, Funabiki et al., 2011; Heim, Schoettker, Gilliard, et al, 2009). Kevric, Jelinek, Knott, et al. (2010) found an inter-rater reliability of k=.59 for the GCS, especially when it was administered by physician-nurse pairs. Considering the unique age results found in this study, it is possible that the older group had more benign brain injuries than the younger group, for reasons stated below, and the difference was not discerned by a less precise measure such as the GCS.

Limitations

In addition to the previously mentioned confounds, and the fact that these results are only correlational, interpretability is restricted due to the limitations of the design of this study. Primarily, the largest limitation was the lack of resources to include comparison groups comprised of those with just the vascular risk factors, excluding head trauma. This would have allowed for the separation of the effects of vascular exacerbation of head injury versus the effects

of vascular risk factors alone. Furthermore, the literature on vascular risks and cognition reveals that a combination of diabetes and hypertension intensifies the vascular pathology. This decline is then discernable in neuropsychological measures, especially as the duration of the illnesses increases (Petrova, Prokopenko, Pronina, et al., 2010). The lack of participants with singular diagnoses of *just* hypertension, or *just* diabetes limited this study's ability to determine the specific effects of each risk factor.

An additional limitation of this study regards the actual data that were collected. In the midst of the review of each medical record, it became clear that the records did not provide as much information as was hoped for. Health complications, including diagnoses of relevant vascular issues, were not always listed, and the amount and depth of information provided in the medical records varied greatly. Often times it was necessary to infer the diagnosis of hypertension, diabetes, or hypercholesterolemia based on the medications listed in the record. Other times, medications were not listed at all, and it is possible that participants were incorrectly placed in the 0, 1, or 2 risk factor groups. It is also possible that some participants who were diagnosed and prescribed medication for the relevant risk factors could have had an amelioration of the deteriorating effects of the diseases, while others, who were not medicated, experienced continued pathology. In addition, other pieces of valuable information, such as weight, height, or previous medical history, etc., were not contained in the remaining records.

Other information that was included in the charts also proved to be problematic. For example, many of the participants also had confounding health issues and the exclusion of them from the current study would have drastically reduced the number of participants. These confounds included cocaine withdrawal, questionable onset of dementia, previous head injuries, sleep apnea, alcohol, nicotine, and other drug abuse, etc. It is likely that even a greater number

had additional confounds that were simply not documented in the remaining records. Overall, it was impossible to garner a true picture of each participant's physical and cognitive heath based on the available medical records. Lastly, following a thorough review of the neuropsychological assessment calculations in the charts, a few mathematical errors were identified in the existent computations of z and t scores. These errors were subsequently corrected, but it is probable that other errors remained, undetected.

Collectively, the limitations and additional confounds of this study suggest interpretation with caution, at the least. Whether the significant results were a product of exacerbation by head injury or premorbidly existed, the restrictions in this study prevent a resolution to this question. Despite this failure, however, the significant differences, in many instances, between the neurocognitive effects of suffering from one, two or three versus none of these vascular risk factors certainly lends evidence to the contribution of the state of vascular health to cognitive functioning. It is clear that an increase in vascular pathology, no matter what age, is a detriment to cognitive function. This is especially pertinent regarding the recent increasing trend in obesity, metabolic syndrome, and related vascular pathology in the United States (Ogden, Carroll, Curtin et al, 2006). If this trend continues, there will be a hefty burden on the healthcare system and the economy as a whole, as the prevalence of stroke, dementia, and cognitive decline will consequently increase. This is not only problematic for the aging population, but the inevitable catastrophe that will occur as a result of the increase in pediatric obesity and resultant pathology. Additional research related to earlier detection, treatment, and especially methods of prevention of these vascular disorders is a necessary component to abating the destined, and seemingly irreversible and overwhelming complications that lie ahead.

References

American Diabetes Association. (1995). How to tell if you have prediabetes. Available from http://www.diabetes.org.

American Heart Association. (2011) About cholesterol: What your cholesterol levels mean. Available from http://www.americanheart.org.

Armentano, R., Megnien, J., Simon, A., Bellenfant, F., Barra, J., & Levenson, J. (1995). Effects of hypertension on viscoelasticity of carotid and femoral arteries in humans. *Hypertension, 26,* 48-54.

Arnett, D., Jacobs, D.R., Luepker, R.V., Blackburn, H., Armstrong, C., & Claas, S. (2005). Twenty-year trends in serum cholesterol, hypercholesterolemia, and cholesterol medication use: The Minnesota heart survey, 1980-1982 to 2000-2002. *Circulation, 112,* 3884-3891.

Bazarian, J.J., Wong, T., Harris, M., Leahey, N., Mookerjee, S., & Dombovy, M. (1999). Epidemiology and predictors of post-concussive syndrome after minor head injury in an emergency population. *Brain Injury, 13,* 173-189.

Benedict, R.H. (1997). *Brief visuospatial memory test-revised*. Odessa, FL: Psychological Assessment Resources.

Benedict, R.H., Scretlen, D., Groninger, L., Dobraski, M., & Shpritz, B. (1996). Revision of the brief visuospatial memory test: Studies of normal performance, reliability, and validity. *Psychological Assessment, 8,* 145-153.

Benton, A.L., Sivan, A.B., Hamsher, K.deS., Varney, N.R., & Spreen, O. (1994). *Contributions to neuropsychological assessment. A clinical manual* (2nd Ed.). New York, NY. Oxford University Press.

Bingley, P.J., Bonifacio, E., & Williams, A.K. (1997). Prediction of IDDM in the general population: Strategies based on combinations of autoantibody markers. *Diabetes, 46,* 1701-1710.

Cipriano, P.R., Guthaner, D.F., Orlick, A.E., Ricci, D.R., Wexler, L., & Silverman, J.F. (1979). The effects of ergonovine maleate on coronary arterial size. *Circulation, 59,* 82-89.

Committee on Trauma Research (1985). *Injury in America a continuing public health problem*. Washington, D.C.: National Academy Press.

Creager, M., Cooke, J., Mendelsohn, M., Gallagher, S., Coleman, S., Loscalzo, J., & Dzau, V., (1990). Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *Journal of Clinical Investigation, 86,* 228-234.

Debette, S., Beiser, A., Hoffmann, U., DeCarli, C., O'Donnell, C.J., Massaro, J. M., Au, R., Himali, J. J., Wolf, P.A., Fox, C.S., & Seshadri, S. (2010). Visceral fat is associated with lower brain volume in healthy middle-aged adults. *Annals of Neurology, 68,* 136-144.

DeCarli, C., Murphy, D., & Tran, M. (1995). The effect of white matter hyperintensity volume on brain structure, cognitive performance and cerebral metabolism in 51 healthy adults. *Neurology, 45,* 2077-2084.

de Courten-Myers, G.M., Kleinholz, M., Holm, P., Schmitt, G., Wagner, K.R., & Myers, R.E. (1992). Hemorrhagic infarct conversion in experimental stroke. *Annals of Emergency Medicine, 21,* 120-125.

Diaz-Asper, C., Schretlen, D.J., & Pearlson, G.D. (2004). How well does IQ predict neuropsychological test performance in normal adults. *Journal of the International Neuropsychological Society, 10,* 82-90.

Dikmen, S., Machamer, J., Temkin, N., & McLean, A. (1990). Neuropsychological recovery in patients with moderate to severe head injury: Two-year follow-up. *Journal of Clinical and Experimental Neuropsychology, 12,* 507-519.

Donnelly, R., Emslie-Smith, A., Gardner, I., & Morris, A. (2000). Vascular complications of diabetes. *British Medical Journal Online, April 15th*.1-7.

Donnelly, R., Jonas, J. (2002). Vascular complications of diabetes: current issues in pathogenesis and treatment. Oxford, UK: Blackwell.

Dupree, E.A. & Meyer, M.B. (1980). Role of risk factors in complications of diabetes mellitus. *American Journal of Epidemiology, 112,* 100-112.

Ernst, J. (1987). Neuropsychological problem-solving skills in the elderly. *Psychology and Aging, 2,* 363-365.

Estacio, R., Jeffers, B., Gifford, N., & Schrier, R., (2000). Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care, 23*(2), 54-64.

Everhart, J.E., Pettitt, D.J, & Slaine, K.R. (1992). Duration of obesity is a risk factor for non-insulin-dependent diabetes mellitus. *Diabetes, 41,* 235.

Faggiotto, A., Ross, R., & Harker, L. (1984). Studies of hypercholesterolemia in the nonhuman primate: Changes that lead to fatty streak formation. *Arteriosclerosis, 4,* 323-340.

Fama, R., Sullivan, E.V., Shear, P.K., Cahn-Weiner, D.A., Yesavage, J.A., Tinklenberg, J.R., & Pfefferbaum, A. (1998). Fluency performance patterns in Alzheimer's disease and Parkinson's disease. *The Clinical Neuropsychologist, 12,* 487-499.

Fan, L., Shah, M.N., Veazie, P.J., & Friedman, B. (2011). Factors associated with emergency department use among the rural elderly. *Journal of Rural Health, 27*(1), 39-49.

Fields, L.E., Burt, V.L., Cutler, J.A., Hughes, J., Roccella, E.J., & Sorlie, P. (2004). The burden of adult hypertension in the United States 1999 to 2000: A rising tide. *Hypertension, 44*, 398–404.

Gariepy J, Massonneau M, Levenson J, Heudes D, & Simon A. (1993).Evidence for in vivo carotid and femoral wall thickening in human hypertension. *Hypertension.*, *22*, 111-118.

Gaziano, M. & Gaziano, T.(2012). Global burden of cardiovascular disease. In P. Libby, R.O. Bonow, D.L. Mann, D.P. Zipes (Eds.) *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed.* Philadelphia, PA: Elsevier.

Guilmette, T.J. & Rasile, D. (1995). Sensitivity, specificity, and diagnostic accuracy in three verbal memory measures in the assessment of mild brain injury. *Neuropsychology, 9*, 338-334.

Gunstad, J.J, Lhotsky, A., Wendell, C.R., Ferucci, L., & Zonderman, A.B. (2010). Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology, 34*(4), 222-9.

Haaland, K.Y., Price, L. & Larue, A. (2003). What does the WMS-III tesll us about memory changes with normal aging? *Journal of the International Neuropsychological Society, 9*, 86-96.

Hayashi, K, Handa H, Nagasawa A, Okumura A, & Moritake K. (1980). Stiffness and elastic behaviour of human intracranial and extracranial arteries. *J Biomech.*, *13*, 175-184.

Heim, C., Schoettker, P., Gilliard, N., & Spahn, D. (2009). Knowlede of Glasgow Coma Scale by air-rescue physicians. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 17*(39).

Ivison, D. (1986). Anna Thompson and the American Liner New York: Some normative data. *Journal of Clinical and Experimental neuropsychology, 8,* 317-320.

Jennett, B. & Teasdale, G. (1981). Management of head injuries. Philadelphia: F.A. Davis.

Kagansky, N., Levy, S., & Knobler, H. (2001). The role of hyperglycemia in acute stroke. *Archives of Neurology, 58*, 1209-1212.

Kalaria, R.N. (2000). The role of cerebral ischemia in Alzheimer's disease. *Neurobiology of Aging, 21,* 321-330.

Kevric, J., Jelinek, G.A., Knott, J., & Weiland, T.J. (2010). Validation of the Full Outline of Unresponsiveness (FOUR) Scale for consciousness state in the emergency department: Comparison against the Glasgow Coma Scale. *Emergency Medicine.* Advance Online Publication. doi:10.1136/emj.2009.085845v

Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kareholt, I., & Winblad, B., et al. (2005). Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of Neurology, 62*(10), 1556–60.

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., Ducimeteire, P., & Benetos, A. (2001). Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension, 37,* 1236-1241.

Laurent, S., Katsahian, S., Fassot, C., Tropeano, A., Gautier, I., Laloux., B., & Boutouyrie, P. (2003). Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke, 34,* 1203-1206.

Leininger, B.E., Gramling, S.E., Farrell, A.D., Kreutzer, J.S., & Peck, E.A. (1990). Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. *Journal of Neurology, Neurosurgery and Psychiatry, 53,* 293-296.

LeRoith, D., Taylor, S., & Olefsky, J. (2004). Diabetes mellitus a fundamental and clinical text. Philadelphia, PA: Lippincott Williams & Wilkins.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). Neuropsychological assessment 4th edition. New York, NY: Oxford University Press.

Liao, D., Cooper, L., Cai, J., Toole, J.F., Bryan, N., Hutchinson, R.G., & Tyroler, H.A. (1996). Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control: The ARIC study, *Stroke, 27,* 2262-2270.

Longstreth W.T., Manolio, T.A., Arnold, A., Burke, G.L., Bryan, N., Jungreis, A., Enright, P.L., et al. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: The cardiovascular health study. *Stroke, 27,* 1274-1282.

Luchsinger, J.A. (2010). Diabetes, related conditions, and dementia. *Journal of the Neurological Sciences, 299,* 35-38.

Manolino T.A., Olson, J., & Longstreth, W.T. (2003). Hypertension and cognitive function: Pathophysiologic effects of hypertension on the brain. *Current Hypertension Report, 5,* 255-261.

McCusker, J., Karp, I., Cardin, S., Durand, P., & Morin, J. (2003). Determinants of emergency department visits by older adults: a systematic review. *Academy of Emergency Medicine, 10*(12),1362-1370.

McCrea, M. (2008). Mild traumatic brain injury and postconcussion syndrome, the new evidence base for diagnosis and treatment. New York, NY: Oxford.

Mitka, M. (2010). Reports of concussions from youth sports rise along with the awareness of the problem. *Journal of the American Medical Association,* 304(16), 1775-6.

Namiki, J., Yamazaki, M., Funabiki, T., & Hori, S. (2011). Inaccuracy and misjudged factors of Gasgow Coma Scale scores when assessed by inexperienced physicians. *Clinical Neurology and Neurosurgery.* Advance Online Publication. doi:10.1016/j.clineuro. 2011.01.001

Obisesan, T.O., Obisesan, O.A., Martins, S., Bond, V., Maxwell, C., & Gillum, R.F. (2008). High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: The third national health and nutrition examination survey. *Journal of the American Geriatrics Society, 56,* 501-509.

Ogden, C.L., Carroll, M.D., Curtin, L.R., McDowell, M.A., Tabak, C.J., & Flegal, K.M. (2006). Prevalence of Overweight and Obesity and the United States, 1999-2004. *Journal of the American Medical Association, 295*(13), 1549-55.

Ong, K.L, Cheung, B., Man, Y.B., Lau, C.P., & Lam, K.S. (2007). Prevalence, awareness, treatment, and control of hypertension among United States adults. *Hypertension, 49,* 69-75.

Pantoni, L., & Garcia, J.H. (1995). The significance of cerebral white matter abnormalities 100 years after Binswanger´s report. *Stroke*, *26*, 1293-1301.

Petrova, M., Prokopenko, S., Pronina, E., & Mozheyko, E.(2010). Diabetes type 2, hypertension and cognitive dysfunction in middle age women. *Journal of the Neurological Sciences, 299,* 39-41.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging,* 30, 507–514.

Schmidt, R., Fazekas, F., Offenbacher, H., Lytwyn, H., Blematl, B., Niederkorn, K., Horner, S., Payer, F., & Friedl, W. (1991). Magnetic resonance imaging white matter lesions and cognitive impairment in hypertensive individuals. *Archives of Neurology, 48,* 417-420.

Seppelt, I. (2004). Intracranial hypertension after traumatic brain injury. Indian *Journal of Critical Care Medicine, 8*(2), 120-126.

Shiozaki, T. (2005). Hypertension and head injury. *Current Hypertension Reports, 7*(6), 450-453.

Shukla, D., Devi, B.I, & Aqrawal, A. (2011). Outcome measures for traumatic brain injury. *Clinical Neurology and Neurosurgery,* Elsevier B.V. In Press.

Sierra, C. (2003). Cerebral white matter lesions in essential hypertension. *Third Congress of Nephrology on Internet. http://www.uninet.edu/cin2003/conf/csierra/csierra.html*

Silver, J.M, McAllister, T.W., & Yudofsky, S.C. (2005). Textbook of traumatic brain injury. Washington, D.C.: American Psychiatric Publishing, Inc.,

Sinnett, E.R. & Holen, M.C., (1999). Assessment of memory functioning among an aging sample. *Psychological Reports*, *84*, 339-350.

Simon A, Levenson JA, Bouthier JD, Safar ME, & Avolio AP. (1985). Evidence of early degenerative changes in large arteries in human essential hypertension. Hypertension., 7, 675-680.

Sosin, D.M., Sniezek, J.E., & Waxweiler, R.J. (1995). Trends in death associated with traumatic brain injury, 1979 through 1992. *Journal of the American Medical Association*, 273, 1778-1780

Steyn K. & Damasceno A. (2006). Lifestyle and related risk factors for chronic diseases. In D.T. Jamison, R.G. Feachem, M.W. Makgoba, E.R. Bos, F.K. Baingana, K.J. Hofman, K.O. Rogo, (Eds). *Disease and Mortality in Sub-Saharan Africa. 2nd edition*. Washington (DC): World Bank.

Swan, G.E., Carmelli, D., & Larue, A. (1998). Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. *Stroke*, *29*, 2334-2340.

Szromba, C. (2000). An evolving picture: Hypertension in African-Americans. Nephrology Nursing Journal, 10 Sep, 2009. http://findarticles.com/p/ articles/mi_m0ICF/is_ 1_27/ ai_n18611211/

Tucker-Drob, E.M. (2011). Global and domain-specific changes in cognition throughout adulthood. *Developmental Psychology*, Advance online publication. doi: 10.1037/a0021361

Tuomilehto, J., Lindstrom, J., Eriksson, J.G., Valle, T.T., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., & Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine, 344*, 1343–1350.

Turner, R.C., Cull, C.A., Frighi, V., & Holman, R.R. (1999). Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49): UK Prospective Diabetes Study (UKPDS) Group. *JAMA*, *281*, 2005–2012.

Vanderploeg, R.D., Schinka, J.A., Jones, T., Small, B.J., Graves, A.B., & Mortimer, J.A. (2000). Elderly norms for the Hopkins Verbal Learning Test- Revised. *The Clinical Neuropsychologist, 14,* 318-334.

Van Loon, J., Shivalkar, B., Plets, C., Goffin, J., Tjandra-Maga, B., & Flameng, W. (1993). Catecholamine response to a gradual increase of intracranial pressure. *Journal of Neurosurgery, 79*(5), 705-711.

Wass, C., Scheithauer, B., Bronk, J., Wilson, R., & Lanier, W.L. (1996). Insulin treatment of corticosteroid-associated hyperglycemia and its effect on outcome after forebrain ischemia in rats. *Anesthesiology, 84,* 644-651.

Wechsler, D. (1997). *Wechsler Memory Scale. Third edition manual.* San Antonio, TX: The Psychological Corporation

Weir, M. & Hanes, D. (1996). Hypertension in African-Americans: A paradigm of metabolic disarray. *Seminars in Nephrology, 16*(2), 102-109.

Xiaohua, C. & Wen, W., Anstey, K., & Sachdev, P. (2009). Prevalence, incidence, and risk factors of lacunar infarcts in a community sample. *Neurology, 73,* 266-272.

Ylikoski, R., Ylikoski, A., Erkinjuntti, T., Sulkava, R., Keskivaara, P., Raininko, R., & Tilvis, R., (1998). Differences in neuropsychological functioining associated with age, education, neurological status, and magnetic resonance imaging findings in neurological healthy elderly individuals. *Applied Neuropsycholoy, 5,* 1-14.

Zhu, C.Z., Auer, R.N., Voll, C.L., & Auer, R.N., (1994). Intraventricular administration of insulin and IGF-1 in transient forebrain ischemia. *Journal of Cerebral Blood Flow Metabolics, 14,* 237-242.

Zuliani, G. & Renato, F. (2003). Autosomal recessive hypercholesterolemia: Genetics and clinical aspects. In: Crepaldi, G., Tiengo, A., Acogaro, A. eds. *The metabolic syndrome: Diabetes, obesity, hyperlipidemia and hypertension.* Amsterdam, The Netherlands: Elsevier B.V.

Appendix

Executive Functioning

Trail Making Test B

The Trail Making Test (TMT) measures scanning and sequencing abilities, cognitive flexibility, attention, and visuomotor tracking. This test is comprised of two parts, Part A and Part B, of which only the latter will be utilized in the current study. Part A involves a connect-the-dot type task, where the subject must connect numbered circles as quickly as possible. The second part, part B, which will be evaluated in this study, involves connecting both numbers and letters by alternating between the two sequences until all circles are correctly connected. If the test taker makes a mistake, he or she is corrected and is encouraged to continue to the end. The total time from start to finish is recorded.

The TMT is highly sensitive to brain injury. Those suffering from damage related to traumatic brain injury complete the task slower than non-concussed control subjects. As brain damage increases, so does the time required to complete the task (Leininger, Gramling, Farrell, Kreutzer, & Peck, 1990). Those with only mild injuries, however, may perform adequately on this test (Lezak et al., 2004). Age and education greatly influence test outcome, especially on Part B, where a gap exists between the performance of those with less than a tenth grade education and those with eleven or more years of schooling (Lezak et al., 2004). Ernst (1987) suggests that older women may yield poorer results on Part B than do men, showing slower performance on this measure.

Controlled Oral Word Association Test (phonetic)

The Controlled Oral Word Association Test (COWAT) task measures phonetic verbal fluency abilities which are mainly subserved by the left frontal lobe. This fluency task involves three trials of one minute each where the participant lists as many words as he or she can that begin with a certain letter, but are not proper nouns, numbers, or the same words with different endings. The trials progress from the letter "F," to "A," and finally "S." Any rule violations or perseverations are noted during each trial and finally, the total correct words produced are counted for final scoring. This score is then corrected for education, age, and gender.

Education, age, and sex have all been demonstrated to have an influence on fluency abilities. Women tend to perform better than men after age 55 (Benton, Sivan, Hamsher, Varney, Spreen, 1994), but scores do not drop for the most part until about age 75, however this drop does not represent a statistically significant decline (Spreen & Strauss, 1998). Although the task is a sensitive measure of impairment in the frontal lobes, patients with diffuse brain injury can also show brain dysfunction on this task as well as with mild TBI.

Learning and Immediate and Delayed Recall

Hopkins Verbal Learning Test (HVLT)

This task involves a list of 12 words made up of three categories with four words in each category that are semantically similar. The list is read three times, each word every 1.5 seconds, and the participant is to recall as many words as he or she can after each of thel three trials. These trials are followed by a warned recall after a 20-25 minute delay, where as many words as possible are recalled from the original list. Individual scores are derived from the total words recalled after each of the three separate trials, the total words recalled in sum, the number of

words recalled after a delay, and the amount learned from trial 1 to trial 3. An additional recognition score is obtained after a list of 24 words are read, 12 from the original list and 12 new words consisting of 6 words that are semantically similar to the categories included in the original list, and 6 unrelated words. This score is composed by subtracting the false positives (semantically related and unrelated words) from the true positives (correct words), yielding a discrimination index score for the recognition items.

The HVLT has been demonstrated to discriminate between males who go on to develop postconcussive syndrome following a head injury, with a score of 25 or higher in total recall showing a good probability that the syndrome would not develop (Bazarian, Wong, Harris, Leahey, Mookerjee, Dombovy, 1999). Age accounts for a large amount of variance (19%) on the total initial recall, however drops to 3% for retention after a delay (Brandt & Benedict, 2001). Education and IQ have been shown to affect recall, accounting for 5% of the residual variance, however these factors do not appear to influence recognition scores (Diaz-Asper, Schretlen, & Pearlson, 2004). Gender has been shown to account for a small portion of remaining variance (1.7%) for adults, but not for adolescents (Brandt & Benedict, 2001). In adult aged participants, women slightly outperformed men by an average of 3 words in the amount of total recall (Vanderploeg, Schinka, Jones, Small, Graves, & Mortimer, 2000).

Brief Visuospatial Memory Test- Revised (BVMT-R)

This memory task is employed to measure visual learning and memory and involves three learning trials and a delayed recall trial presented 25 minutes after initial administration. A display containing six figures is shown to the patient for ten seconds and she is asked to reproduce as many figures as she can on a blank sheet of paper. Scoring is not only based on the

correct depiction of the figure, but also on the correct placement of the figure on the page. One point is given for the accuracy of the design, and one for correct location.

Benedict (1997) describes that 11% of the variance in the BVMT-R scores is associated with age. Gender and education, however does not have a significant effect on performance. This test is sensitive to impairments in memory, including effects related to head injury, dementia, and HIV (Benedict, Scretlen, Groninger, Dobraski, & Shpritz, 1996). A drawback to this form of assessment, however, is the requirement of a motor response, disabling the use of the test on those with motor impairments. This limits its application in victims of accidents or falls who may not be physically able to move their arms due to pain or physical confinement.

Logical Memory I and II

The ability to attend to and recall parts of a story is an important assessment reflecting the realistic requirements of a person's memory. Logical Memory (LM) I is a subtest of the Wechsler Memory Scale (WMS), and the first story has remained virtually the same since the original version of the WMS. A short paragraph is read to the patient and she is to recall as much of the story, as close to the same words, as she can following its presentation. Immediately after as much of the story is recalled as possible, a second story is read and the process is repeated. After a warned 30 minute delay, the patient is asked to recall as much of each separate story as possible. The total recall of the possible 25 items is scored.

Significant age-related decline has been demonstrated with story recall. This decline begins around age 55 and steadily decreases until around 85 where recall is almost half of what it is for someone in their 20's (Wechsler, 1997). Delayed recall also appears to decline after age 45; however, this decline may be due to decreased immediate recall abilities rather than a

reduction in memory after a delay (Haaland, Price, & Larue, 2003). Sex differences are negligible, with women performing somewhat better on the first story, and men outperforming women on the second story (Ivison, 1986). This difference is most likely a result of the varied content of the two stories, the first depicting a woman who was robbed, and the second a male truck driver who breaks his truck's axle. Education, however, does have a substantial influence on LM performance, with years of education positively correlated with testing results (Ylikoski, Ylikoski, Erkinjuntti, Sulkava, Keskivaara, Raininko, et al., 1998). Socioeconomic status also reflects this influence on performance, as it correlates highly with education (Sinnett & Holen, 1999). Logical Memory has effectively differentiated between mild TBI patients and controls shortly following injury (Guilmette & Rasile, 1995) and also two years after the injury, even when positive improvements were shown (Dikmen, Machamer, Temkin, McLean, 1990).