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Effects of Stress, Sex Differences, and Cognitive Reserve on Cognitive Decline in Healthy Elderly Subjects

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Effects of Stress, Sex Differences, and Cognitive Reserve on Cognitive Decline in Healthy Elderly Subjects

by

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the requirements for the degree
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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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Above all, I praise God Who guided me through this journey and Who has been faithful to the promise found in James 1:5--"If any of you lacks wisdom, you should ask God, who gives generously to all without finding fault, and it will be given to you."

CONTENT

FIGURES

Figures Page

TABLES

Tables Page

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AMNART	American version of the National Adult Reading Test
AVP	Arginine vasopressin
BRC	Brain reserve capacity
CNS	Central nervous system
CRH	Corticotrophin releasing hormone
EAA	Excitatory amino acids
fMRI	Functional magnetic resonance imaging
HPA	Hypothalamus-pituitary-adrenal
LCU	Life Change Units
RAVLT	Rey Auditory Verbal Learning Test II
RCFT	Rey Osterrieth Complex Figure Test
SRRS	Social Readjustment Rating Scale
VOSP	Visual Object and Space Perception Battery
WAHA	Walnuts and Healthy Aging
WAIS	Wechsler Adult Intelligence Scale

ABSTRACT OF THE DISSERTATION

Effects of Stress, Sex Differences, and Cognitive Reserve
on Cognitive Decline in Healthy Elderly Subjects

by

Courtney Ray

Doctor of Philosophy, Graduate Program in Psychology
Loma Linda University, September 2016
Dr. Adam E. Arechiga, Chairperson

Extensive research has been conducted linking stress to increased allostatic load and degradation of various organs over time. In the brain, the hippocampus appears to be particularly vulnerable. This deterioration is manifest clinically by impaired performance on tasks of declarative memory.

The Social Readjustment Ratings Scale (SRRS) is an inventory of high intensity psychosocial stressors. This instrument has previously been used to help calculate risk of disease. Using measurements of stressful life events, it may be possible to similarly predict risk of cognitive impairment. To test this, the current study explored the cumulative effect of discreet psychosocial stressors that have occurred within the past year and their effect on changes in cognitive functioning as measured by individuals' performance on hippocampus-dependent tasks.

In addition to psychosocial stress, the study examined the effects of variables thought to positively impact cognition and potentially stave off decline. As the elderly population grows, there is an increased interest in slowing cognitive decline and promoting healthy aging. Studies have indicated that an increase in activities that promote cognitive reserve can be beneficial in attenuating cognitive decline in the face of

various injuries. Various studies have also demonstrated that sex is correlated with between group differences in cognitive functioning. This study explored the potential effects of both cognitive reserve and sex differences on changes in performance on declarative memory tasks.

CHAPTER ONE

INTRODUCTION

Background

The effects of stress on cognitive function are well known to people—either through their examination of empirical evidence or from observations borne out of their own life experiences. Many of us are familiar with the detrimental effects of stressful situations on our ability to think clearly and function well. However, research has long concluded that stress is not entirely bad. In fact, some stress is necessary for optimal functioning. But stress in excess can hamper performance. The oft cited descriptor of this phenomenon, first noted by Yerkes and Dodson (1908), is the inverted-U; that is, optimal performance occurs at a point where there is "just enough" stress (Anderson, 1990; Anderson, 1994; Broadhurst, 1959; Duffy 1962; Lupien, Maheu, Tu, Fiocco & Schramek, 2007). Performance begins to decline as stress levels deviate from that level: either as it begins to get to be too much or too little.

Neuroscience researchers have observed changes in the anatomical structures of the brain in response to stressors that seem consistent with this phenomenon. The stress response includes a cascade of neurotransmitters on receptors that facilitate changes in neurons. Although there are a number of chemical reactions that take place, the chemicals most central to this cascade are the glucocorticoids. Glucocorticoids have been shown to affect neurons in various areas of the brain (most notably the hippocampus, CA1 and CA3) so that neurons actually adapt to stressful situations. This is a beneficial action as long as the stress response is not prolonged. Exposure to chronic stress, however, which results in the prolonged actions of glucocorticoids, has been shown to have a deleterious

effect on neurons, including cell death, which impacts cognitive functioning. As research in this area has proliferated, several models of stress have been tested. The particular model of stress examined by this study concerns the effects of repeated acute stressors on memory in a healthy elderly population. That is, do several discreet stressors that take place over time have a cumulative effect so as to impair cognitive functioning in similar ways as compared to chronic stressors?

As the elderly population begins to grow in number, the health and research community has had an increasing interest in those factors that can impact healthy aging. In a population of otherwise healthy adults, could psychosocial stressors impact them cognitively to the extent that it decreases their actual cognitive performance as compared to their estimated premorbid level of functioning? Additionally, if this is found to be the case, what measures can be taken to help facilitate healthy cognitive functioning over time? Are there protective factors that can be identified? This research explored that point.

It has long been observed that individuals with the same type of brain injury who are otherwise matched by age and sex will express varied levels of impairment. Determining why the type of injury does not correlate directly to predictable decreases in functioning has been a subject of study for many years. Several theories have been postulated, one of which is the theory of cognitive reserve. The concept of cognitive reserve maintains that the amount of brain volume is not the key to functioning. Instead, some individuals have the ability to recruit and use their brain networks in a more efficient way than others. It is believed that various domains of life enrichment such as physical activity and leisure engagement contribute to cognitive reserve and can facilitate

a neuroprotective effect in the face of brain insult. The current study attempted to determine whether higher levels of cognitive reserve could attenuate the deleterious effects of stress on brain functioning.

Additionally, research on cognitive performance has demonstrated that there are group differences in performance between men and women that can be detected when comparing mean scores for different tasks. These differences are observable across the life span. This research explored the ability for sex and cognitive reserve to moderate any observed differentials in cognitive functioning that would be affected by stressful life events in healthy elderly individuals.

Stress

Stress is often defined as real or implied threats to the body's homeostasis—the delicate balance of physiological functioning that allows the body to maintain vital functioning and survival (McEwen, 2004). Stressors are the events that precipitate a physiological response in the body. When perceived negatively, stress is referred to as 'distress'; but stress can also stem from a positive source and may be referred to as eustress. Distressing events can include life changes such as the death of a loved one, experiencing a natural disaster, or facing a financial burden. Examples of eustressful events are getting a raise, the healthy birth of a planned child, or a graduation. Some events can be perceived as both distressing and eustressful, such as moving, receiving a promotion, or getting married.

In addition to the differentiation between eustress and distress, there are other important distinctions that can be made between various types of stress. All stress is not

equal and may have differing impacts on the body. Stress can be controllable or outside of one's locus of control; predictable or very random. When faced with a task, the task itself may contribute a certain amount of stress or the stress may be exogenous. Another well-studied dimension of stress involves its duration: that is, whether the stressful event is acute or chronic. Stressors may vary in intensity as well: as will be discussed further, research has demonstrated that whether experienced levels of stress are of high intensity or low intensity makes a profound difference in facilitating either ideal performance or suboptimal completion of a task (Anderson, 1990; Anderson, 1994; Broadhurst, 1959; Duffy 1962; Lupien, et al., 2007).

Cognitive Functioning

Just as "stress" has many facets, the term "cognition" comprises many concepts, each dealing with a slightly different way in which the brain processes and manipulates information. Some aspects include perception, attention, language and executive tasks, and memory (Keeler & Robbins, 2011). The overwhelming majority of studies that have explored the effect of stress on cognition have examined the impact of stress on memory in particular.

Memory

Memory is the cognitive process by which information gets encoded, stored, and retrieved. The first stage of memory—encoding--entails the reception, processing, and synthesis of sensory information (Byrne, Becker & Burgess, 2007; Jensen & Lisman, 2005, Sara, 2000). The storage stage involves the formation of a record of the encoded

information that the brain can access again in the future. Information can be stored as a short-term memory or a long-term memory. Without rehearsal, the rate of decay for short-term memory is approximately 18 to 30 seconds (Revlin, 2012). Short-term memory is very closely related to working memory (discussed later) although--despite its name--working memory is actually a cognitive function grouped with executive tasks. Memories that must be held for longer periods of time are stored in long-term memory. In a model of memory known as the Atkinson–Shiffrin model, (Atkinson & Shiffrin, 1968) it is postulated that short-term memories are moved to long-term memory with continual rehearsal and use. In this way, long-term storage is related in a way to the concept of learning where data is stored for later recall when needed. As opposed to short term memory, long term memories can (theoretically) be retained forever. The third process of memory is retrieval. In this phase, data that has been stored is recalled and brought back to consciousness. "Memory problems" can be caused by a disruption during any one of these phases.

The concept of "memory" can be further deconstructed into implicit or procedural versus explicit or declarative (McDougall, 1923; Sandi, 2003). Procedural memory is the encoding, storage and recall of habits, actions, and movements. Procedural memories may be enacted upon without conscious effort or awareness. Declarative memory is a type of long term memory which comprises data that can be consciously recalled such as facts, lists, and events. The striatum, basal ganglia, and cerebellum each participate in memory formation and retrieval--particularly in procedural memory (Foerde & Poldrack, 2009; Molinari, et al., 1997). However, one of the most critical brain regions involved in

the formation and retrieval of memories is the limbic system. Two limbic structures deserving of special note are the amygdala and hippocampus.

The amygdala significantly impacts episodic-autobiographical memory. Research by Markowitsch & Staniloiu (2011) demonstrated that the chief role of the amygdala is to flag emotionally charged events for their significance. In this way, the information from that event can be retrieved for later use when needed. This is particularly helpful in situations where survival is at stake. This is why the amygdala is often associated with high valence emotions such as fear. This also highlights why the amygdala is involved in important cognitive processes such as selective attention and social processing (Kheirbek & Hen, 2011; Todorov & Engell, 2008).

One of the most important brain regions involved in declarative memory—the hippocampus--has been widely researched in its role in memory processes. Research has shown that the dorsal hippocampus plays a key part in the generation of new neurons (neurogenesis). Studies have shown that neurogenesis and the formation of new neural circuits in the hippocampus can be generated through task rehearsal resulting in learning (Eichenbaum, 2007; Kheirbek & Hen, 2011). The simultaneous firing of cell networks help in the creation of stronger memory formation. Conversely, when the hippocampus is damaged, it results in observable impairment of cognitive functioning—memory in particular. This damage may be resultant from physical trauma, exogenous drugs, or even prolonged effects of endogenous hormones. The hippocampus appears to be particularly vulnerable to some of the hormones activated in the stress response, namely the glucocorticoids. Research detailing the effects of glucocorticoids will be expanded in a later section.

Executive Functioning

As mentioned previously, another type of memory—working memory—is actually part of executive functioning. Tasks of working memory include holding information for the short term and manipulating it (like remembering a phone number). As with other executive tasks, working memory largely depends on the pre-frontal cortex (West, 1996)

In addition to working memory, other executive functions include attending, solving problems, planning, using cognitive flexibility and inhibition. While other brain regions also play a significant part in executive functioning, the frontal lobes are involved in virtually all executive functioning processes (Alvarez & Emory, 2006). The orbitofrontal cortex is integral to inhibition, maintaining set, and behavior monitoring. The anterior cingulate cortex is crucial to information integration and emotional drive (Lezak, Howieson & Loring, 2004). But it is the dorsolateral prefrontal cortex that is key to working memory, semantic fluency, organization, planning, set switching and the ability to maintain sets, response inhibition, reasoning, and problem solving (Clark, et al, 2008; Lezak, et al. 2004).

Stress and Memory

The multitude of ways in which stress can be defined, coupled with the various aspects of memory to be studied results in a plethora of study designs that can be derived from the various combinations. The potential combinations can be visually conceptualized by pairing different aspects of memory with different types of stress as illustrated in Figure 1. This illustration is not meant to display an exhaustive list, but is

instead meant to display a sample of the varied possibilities of combinations for research. The current study examined how performance on goal-directed declarative memory recall tasks are impacted by stress that is induced from discreet, remote, high intensity psychosocial stressors that are unrelated to the tasks.

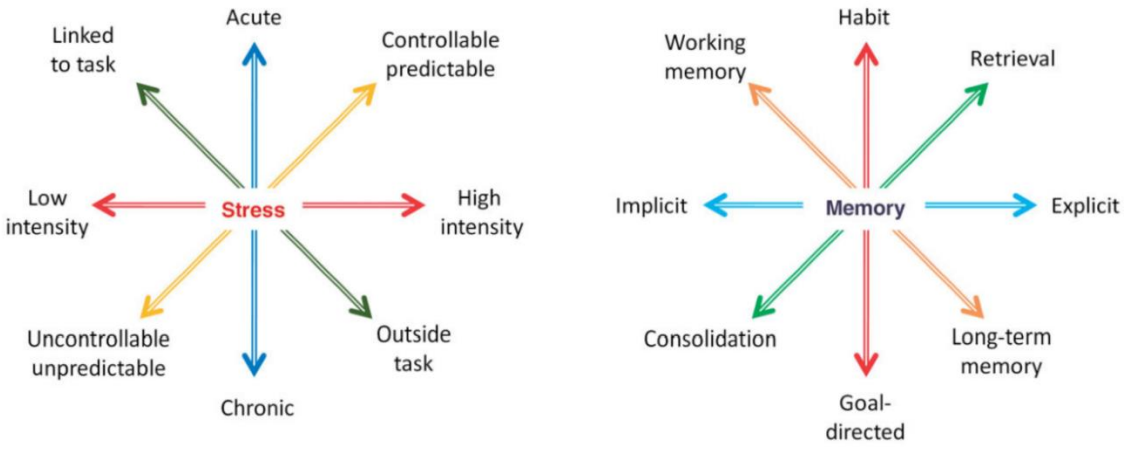

Figure 1. Constellations of stress and memory. Reprinted from "Stress and cognition" by C. Sandi, 2013, *Wiley Interdisciplinary Reviews: Cognitive Science*, *4*(3), 247, Copyright 2013, John Wiley & Sons, Ltd.

Allostasis and Allostatic Load

All types of stress trigger the body to respond and attempt to adapt to new situations and challenges. In fact, a certain level of stress is necessary for optimal cognitive performance. Various research findings have indicated that, in general, the effects of the types of stress on the aspects of memory indicated in Figure 2 are usually beneficial. In other words, medium intensity acute stressors that are generated by an implicit memory task generally lead to enhanced memory consolidation (De Kloet, Oitzl, & Joëls, 1999; Joëls, Pu, Wiegert, Oitzl & Krugers, 2006; Sandi, 1988; Sandi & Pinelo-

Nava, 2007). In contrast, the types of stress highlighted in Figure 3 generally inhibit the types of memory illustrated in that figure. That is, high intensity chronic stressors that occur prior to retrieval in an explicit memory task will typically inhibit optimal performance of retrieval (Joëls, et al., 2006; Sandi, et al, 2007; Sandi & Pinelo-Nava, 2007). Furthermore, studies have demonstrated that graphing correlations of stress and performance in learning and memory task follows an inverted-U-shape (Anderson, 1976; Salehi, Cordero & Sandi, 2010). In other words, at the extremes of stress exposure—when either the individual's abilities exceed the challenge of the task or when the demands of the task are beyond the individual's abilities—performance suffers (Figure 4). However, there exists a balance point at which one's abilities match the demands wherein performance is at its peak. Therefore, having some stress is beneficial in that it allows the individual to adapt to changing circumstances.

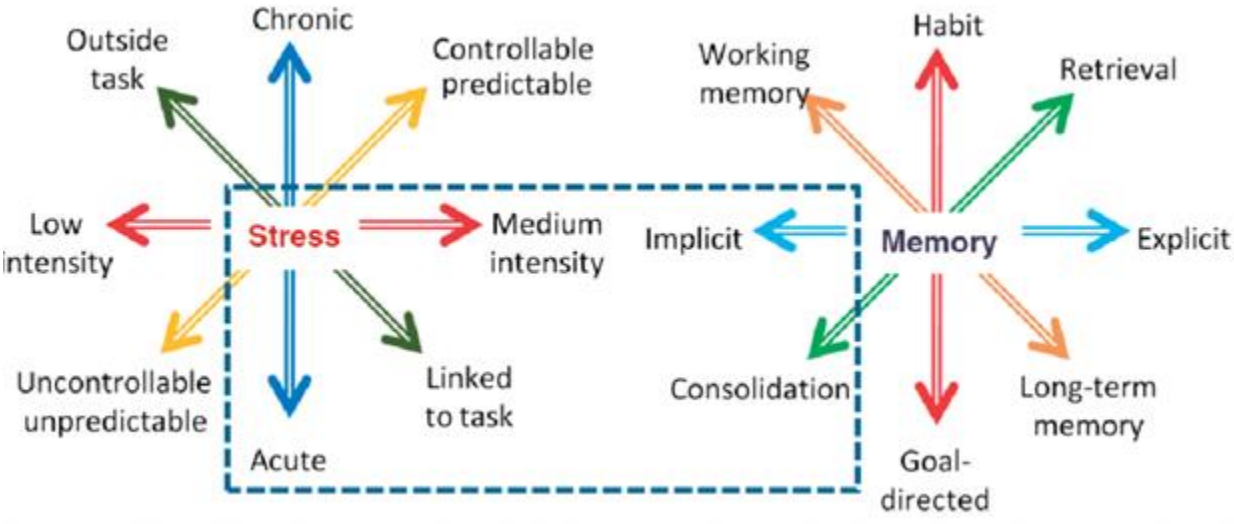

Figure 2. Stress and memory combination one. Reprinted from "Stress and cognition" by C. Sandi, 2013, *Wiley Interdisciplinary Reviews: Cognitive Science*, *4*(3), 248, Copyright 2013, John Wiley & Sons, Ltd.

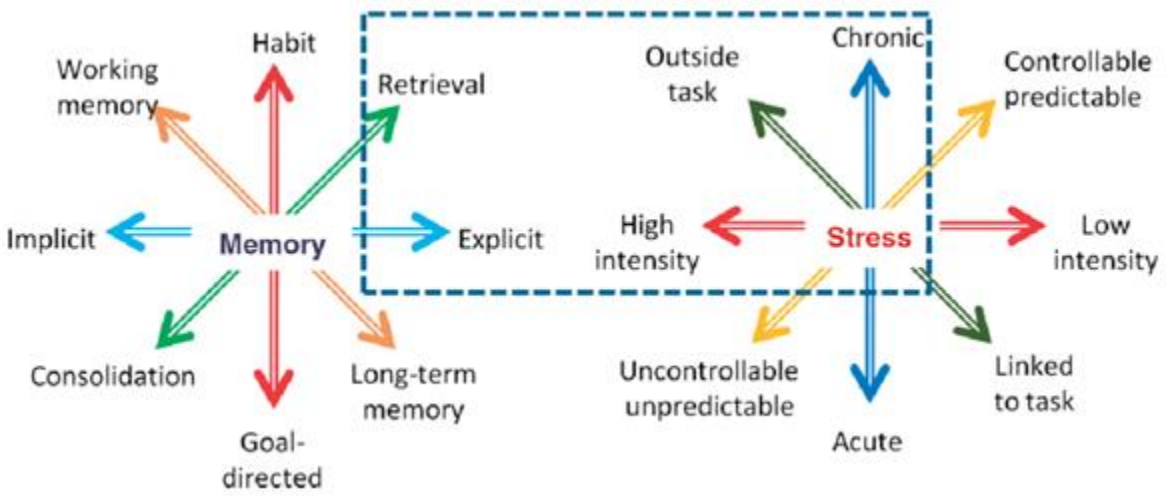

Figure 3. Stress and memory combination two. Reprinted from "Stress and cognition" by C. Sandi, 2013, *Wiley Interdisciplinary Reviews: Cognitive Science*, *4*(3), 248, Copyright 2013, John Wiley & Sons, Ltd.

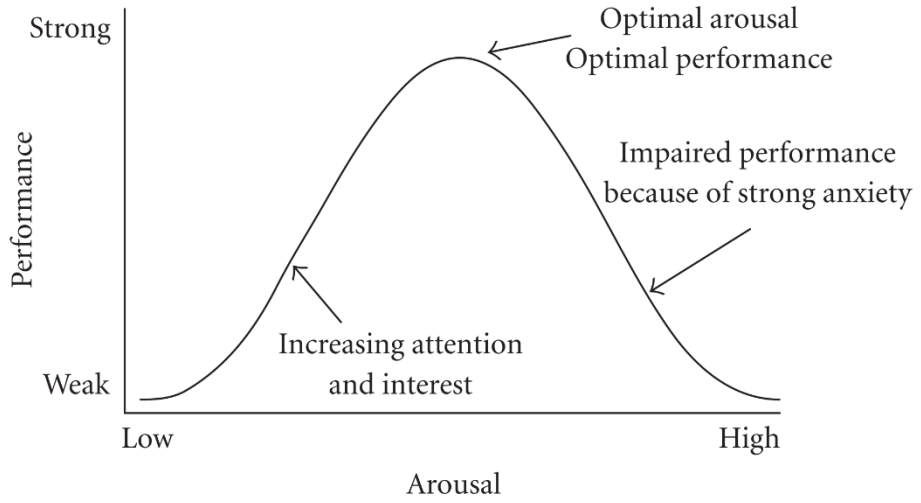

Figure 4. Yerkes-Dodson Inverted-U. Reprinted from "The Temporal Dynamics Model of Emotional Memory Processing: A Synthesis on the Neurobiological Basis of Stress-Induced Amnesia, Flashbulb and Traumatic Memories, and the Yerkes-Dodson Law. ," by D. M Diamond, A. M. Campbell, C. R. Park, J. Halonen & P.R. Zoladz, 2007, *Neural Plasticity, 2007, 3.* Copyright 2007 by David M. Diamond et al. Reprinted with permission.

The autonomic nervous system, immune system, and endocrine system are all engaged in this attempt at adapting to challenges. Endogenous chemicals involved in these processes include catecholamines and glucocorticoids.

When presented with a stressor, receptors in several tissues and organs, including the brain, are activated. One of the integral mechanisms in the stress response is the function of the hypothalamus-pituitary-adrenal (HPA) axis (Figure 5). Neurons in the hypothalamus release corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP). This causes the pituitary gland to release adrenocorticotropic hormone (ACTH), which subsequently initiates the adrenal cortex to produce glucocorticoids. During the stress response, catecholamines (adrenaline and noradrenaline) are also being released by the adrenal medulla. The responsiveness of the HPA axis to stress is in part determined by the ability of glucocorticoids to regulate the secretion of ACTH and CRH by binding to corticosteroid receptors. The adrenal gland will provide feedback to the hypothalamus, hippocampus and the frontal cortex system. Ideally, once the stressful stimuli have been removed or addressed, the various brain regions will be signaled that the "threat" has been neutralized and the HPA axis will terminate the stress response. The neurotransmitters would be removed from the synaptic cleft via reuptake or metabolism so as not to continue their effects and the body will return to homeostasis (Bellavance & Rivest, 2014; Del Rey, Chrousos, & Besedovsky, 2008; Engelmann, Landgraf & Wotjak, 2004).

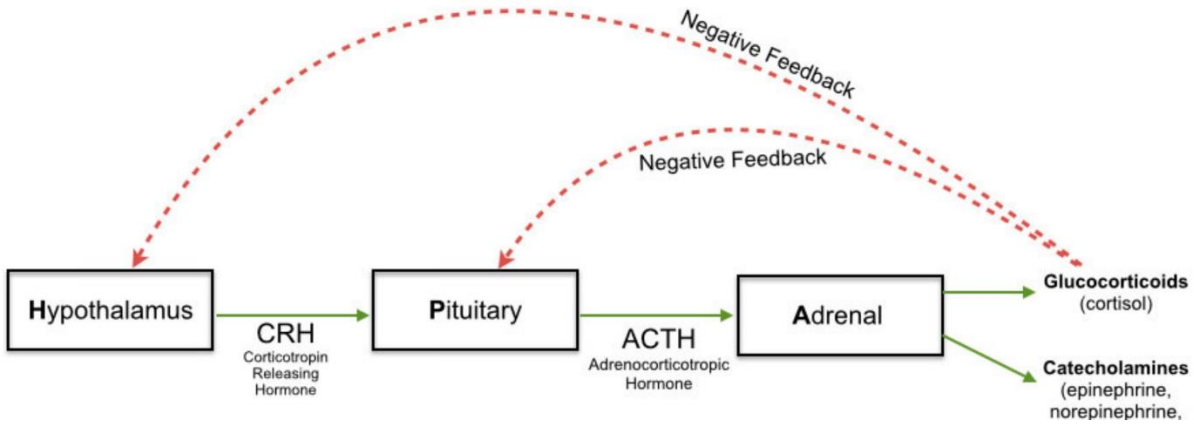

Figure 5. HPA Axis dysfunction. Reprinted from *The Adrenal Fatigue Solution*, by F. Hansen, retrieved from http://adrenalfatiguesolution.com/hpa-axis/ Copyright 2014-2016 by Perfect Health.

The activation of the stress response can be beneficial in attempts to meet immediate changes in physiological and psychological demands as long as the state of taxation is short in duration. Yet, it is possible that damage to affected tissues can occur if exposure is prolonged or the chemical cascade continues past the point of necessity. This may result in deleterious effects such as tissue damage and receptor desensitization. This overactivity caused by dysregulation of the stress response mediators is known as allostasis. The resultant accumulated damage on the body systems and organs is known as the "allostatic load". The amount of allostatic load observed between subjects exposed to the same event is not necessarily the same. The overall impact on an organism is attributable to a number of factors including genetics, developmental factors, and the ability to habituate to stimuli at a variable rate. All of these factors in concert affect functioning over time and account for the differences in the aging process between individuals (McEwen, 1998; McEwen, 2002; McEwen & Seeman, 1999; Seeman, Singer, Rowe, Horwitz & McEwen, 1997).

Catecholamines

When the stress response is initiated, the first chemicals to be secreted are catecholamines. In turn, they trigger post-synaptic second messenger receptors within various organs of the body. This activation occurs almost immediately upon exposure to the stress inducing stimuli (Gunnar & Vazquez, 2006). Two of the most well studied catecholamines are epinephrine and norepinephrine. The release of catecholamines is connected to an individual's emotional state and physical activity. These hormones assist in the preservation of optimal functioning of the HPA and are associated with the maintenance of metabolism and body temperature, cardiac function, and fluid and electrolyte balance. As they relate to central nervous system (CNS) functioning, the catecholamines contribute to arousal, vigilance, attention, and the ability to create memories that are tied to strong emotions such as fear and anger. This adaptive response can help the individual recall important information necessary for survival (Cannon, 1915).

The colloquially termed "fight-or-flight response" to stress is activated as adrenaline and norepinephrine is released by the adrenal medulla. Exposure to acute stress results in constricted blood vessels and subsequently increased heart rate, blood pressure and respiration, a release of glucose from energy stores, greater blood flow to skeletal muscles, heightened awareness, focused attention, and increased arousal and alertness (Purves, et al, 2008). These physiological and psychological changes are necessary to attend to a perceived threat including the facilitation of memory for the arousing event. Acute stress also has a beneficial effect in the immune system by boosting its functioning. But the stress can also take a toll on the various systems of the

body if it is prolonged (chronic stress). Among other things, the effects of sustained periods of arousal may manifest as high blood pressure, increased blood clotting, and an increased risk of stroke and heart attack in the cardiovascular system; suppression of functioning in the immune system; respiratory distress in the respiratory system; muscle tension and chronic pain in the skeletal-muscular system; and neurogenesis inhibition, increased anxiety and restlessness, impaired cognitive performance in the CNS.

Glucocorticoids

Glucocorticoids in Allostasis

Corticosteroids are a type of steroid hormone which are created in the adrenal cortex. Corticosteroids affect several physiological processes, including, but not limited to: the stress response, the immune response, metabolism rates, and regulation of blood electrolyte levels (Nussey & Whitehead, 2001).

Glucocorticoids are a class of corticosteroids which, among other things, control the metabolism of carbohydrates, fats, and protein (Pelt, 2011). One of the most well studied glucocorticoids is cortisol. As mentioned before, glucocorticoids play an active role in the stress response. At various points in the process, glucocorticoids can both work in concert and inhibit the action of catecholamines. In the adrenal medulla, the release of adrenaline is promoted by the regulation of enzymes by glucocorticoids. Feedback by glucocorticoids can also limit adrenaline's release (McEwen & Sapolsky, 1995; Gunnar & Vazquez, 2006).

As compared to the catecholamines, glucocorticoids are slower to be released and their effects are longer acting. As opposed to the immediate actions of adrenaline and

norepinephrine, the effects of glucocorticoids might not take place for several hours and have the ability to impact functioning for days at a time. Because of their potential to effect body systems over a longer duration, most literature that examines hormonal contributions to allostatic load focus on the role of glucocorticoids.

Like catecholamines, glucocorticoids help regulate several vital functions including cardiovascular functioning, fluid regulation, the body's response to hemorrhage, immunity, inflammation, metabolism, brain functioning, and even reproduction. Glucocorticoid receptors can be found in throughout all body systems. Glucocorticoids inhibit glucose-uptake potentiated by catecholamines that increase cardiovascular activity and enhance blood flow. In the digestive system, glucocorticoids work as an antagonist to CRH. The effect is an increase in appetite. And, because CRH is also involved in the release of ACTH from the pituitary, glucocorticoids effect this function as well (Margioris & Tsatsanis, 2011).

Glucocorticoid Effects on Brain Anatomy and Physiology

Key to this study is the fact that glucocorticoids have been shown to have notable effects on brain structures, their physiology and, consequently, cognitive functioning. A high density of glucocorticoid receptors can be found in those brain areas responsible for memory, cognition and executive functioning; in humans that would be the hippocampus and frontal lobe in particular (De Kloet, et al., 1999; Lupien & McEwen, 1997). During the stress response, glucocorticoids work synergistically with excitatory amino acids (EAA), such as glutamate, to morphologically affect brain structures. The plasticity of the brain is an asset in dealing with stressors. While the ability of the brain to adapt is vital to

meet changing demands, the impact of glucocorticoids and EAA's has be shown to result in the atrophy of dendrites (Krugers, Koolhaas, Bohus& Korf, 1993; Lowy, Gault & Yamamoto, 1993). The areas that appear to be the most severely impacted are the CA3 and CA1 regions of the hippocampus (Magarin & McEwen, 1995; Watanabe, Gould & McEwen, 1992). This brain structure is crucial to declarative, episodic, spatial, and contextual memory consolidation and retrieval. The hippocampus is also involved in the modulation of responses by the autonomic, endocrine, and immune systems. After the exposure to an acute stressor has subsided, the body recovers quickly and the observed neuronal atrophy can be reversed. This temporary dendritic remodeling resulting from stress exposure is an example of the brain's resilience, and may serve a neuroprotective function warding off permanent damage (Conrad, Magariños, LeDoux, & McEwen, 1999; McEwen, 1999). However, in cases of highly intense and chronic stress, glucocorticoid induced CA3 and CA1 neuron loss appears to be permanent.

Several researchers have demonstrated this effect of chronic glucocorticoid exposure in rats. In one study, subjects were exposed to glucocorticoid amounts comparable to that which is released during the stress response. Researchers administered the glucocorticoids over several months. Results showed that neurons in the hippocampus were permanently lost (Mizoguchi, Kunishita, Chui & Tabira, 1992). The observed pattern of hippocampal damage was similar to the pattern that is observed in aging subjects, but these effects were observable at an accelerated rate. Additionally, it was shown that there was a positive correlation between the age of the subject and its vulnerability to such damage—older subjects had greater amounts of damage (Kerr, Campbell, Applegate, Brodish & Landfield, 1991). The precise mechanism by which

glucocorticoids and excitatory amino acids convert reversible atrophy to permanent neuron loss is still unknown.

A primate study by Sapolsky, Uno, Rebert & Finch (1990) set out to observe any anatomical damage to the hippocampus following prolonged glucocorticoid exposure. Scientists inserted cortisol pellets into the primate brains. All cortisol-treated hippocampi showed irregular cells. The neurons of the treated hippocampi showed severe damage including shrinkage of neuron somas and atrophy of dendrites. It was interesting to note that the most significant amounts of degeneration occurred in the CA2 and CA3 regions despite the fact that these were not the hippocampal regions most proximal to the glucocorticoid pellets. This suggests that the neurons in these regions are the most susceptible to the deleterious effects of glucocorticoids. Research has also demonstrated that glucocorticoids can hamper neuronal electrophysiology and hippocampal long-term potentiation which is a key action for memory formation (Diamond, Bennett, Fleshner & Rose, 1992; Joels & DeKloet, 1989; Kerr, Campbell, Hao & Landfield, 1989; Bodnoff, Humphreys, Lehman, Diamond, Rose & Meaney, 1995). During cognitive tests of attention, results from electrophysiological observations have shown that acute administration of glucocorticoids to humans diminishes the average evoked potential response to relevant stimuli. Notably, it does not have the same effect in the presence of irrelevant stimuli (Kopell, Wittner, Lunde, Warrick & Edwards, 1970).

Glucocorticoids and Cognition

In that glucocorticoids have a morphological and physiological impact on brain structures, one might postulate that these changes would have a demonstrable effect on

observed performance on cognitive tasks. Indeed, research has shown that stress and increased glucocorticoid levels influence cognitive performance both positively and negatively (Lupien & Lepage, 2001; Lupien, et al., 2007; Sandi & Pinelo-Nava, 2007; Wolf, 2003). As previously discussed, some stress can be beneficial. Research has shown that performance on memory tasks can be facilitated by stress and these results are mediated by glucocorticoids (Beylin & Shors, 2003; Payne, Jackson, Hoscheidt, Ryan, Jacobs & Nadel, 2007; Sandi & Pinelo-Nava, 2007; Shors, 2001; Shors, 2004; Shors 2006; Smeets, Otgaar, Candel & Wolf, 2008). Even the administration of exogenous corticosterone has been demonstrated to help facilitate memory function (Buchanan & Lovallo, 2001; Putman, van Honk, Kessels, Mulder & Koppeschaar, 2004). Studies involving both animals and humans have demonstrated that stress effects on the performance of hippocampus- and prefrontal cortex-dependent memory tasks follow the inverted U-shape described previously. That is, moderate stress levels enhance memory formation while high levels hinder cognitive performance on memory tasks (Cordero & Sandi, 1998; Del Arco, Segovia, Garrido, de Blas & Mora, 2007; Sandi and Pinelo-Nava, 2007 ; Sandi, Loscertales & Guaza, 1997; Selden, Cole, Everitt & Robbins, 1990). It has been concluded that glucocorticoids play an integral part in facilitating these stress effects (Abrari, Rashidy-Pour, Semnanian & Fathollahi, 2009, Joëls, 2006; Sandi and Rose, 1997) since it has been shown that the correlation of glucocorticoid exposure and memory task performance similarly follows the inverted U pattern.

As mentioned previously, prolonged exposure to elevated levels of glucocorticoids results in an increased loss of hippocampal neurons. This neuronal destruction is accompanied by severe cognitive impairments. Studies in rodents have

shown that measurements of glucocorticoid levels can predict the magnitude of hippocampal neuron loss and deficits in cognitive functioning (Landfield, Baskin, & Pitler, 1981). Research by Issa, Rowe, Gauthier and Meaney (1990) showed that only elderly rats that display impairments in their ability to complete spatial memory tasks have elevated glucocorticoid levels. Those aged rats with normal spatial memory also had normal corticoid levels. Additionally, the performance of elderly unimpaired rats shows no significant difference in measures of HPA activity as compared with young rats (Levin et al., 1992; Sarrieau et al., 1992). These finding provide strong evidence that increased HPA activity contributes to differences in the amount of age-related hippocampal pathology and impaired memory functioning observed between subjects.

In humans, morphological changes to brain regions induced by stress have a wide range of emotional and cognitive consequences. Stress-associated damage to areas such as the hippocampus have been correlated with increases in clinical sequelae such as depression and post-traumatic stress disorder, and with steeper declines in mental capacity during aging (McEwen, 2000). Results of the aforementioned Kopell study of neuronal electrophysiology (1970) demonstrate that glucocorticoids impair selective attention and impede individuals' ability to discriminate relevant from irrelevant information. Additionally, the neural atrophy that arises as a consequence of glucocorticoid exposure during prolonged periods of stress results in decreased memory functioning. Studies in human subjects have shown impaired explicit memory and working memory formation in the presence of exogenously administered corticosteroids and external psychological stressors (Kirschbaum, Wolf, May, Wippich & Hellhammer, 1996; Lupien, Fiocco, Wan, Maheu, Lord, Schramek & Tu, 2005; Lupien, Gillin &

Hauger, 1999; Newcomer, Craft, Hershey, Askins & Bardgett, 1994; Newcomer, Selke, Melson, Hershey, Craft, Richards & Alderson, 1999; Oei, Everaerd, Elzinga, Van Well & Bermond, 2006 ; Payne, et al., 2007; Sauro, Jorgensen, & Teal Pedlow, 2003; Wolf, 2006). There are numerous studies that demonstrate that memory recall is particularly impaired as result of prolonged exposure (Beckner, Tucker, Delville & Mohr, 2006; de Quervain et al., 2003; Dominique, Roozendaal, Nitsch, McGaugh & Hock, 2000; Het, Ramlow & Wolf, 2005; Roozendaal, 2002; Sandi & Pinelo-Nava, 2007; Smeets, et al., 2008).

In a study by, Lupien, Lecours, Lussier, Schwartz, Nair & Meaney (1994), an increase in glucocorticoids positively correlated to the frequency of declarative errors made by research participants (i.e. mistakes on both immediate and delayed recall of information from a paragraph read to them). Interestingly, however, glucocorticoids appeared to have a neutral effect on tasks that were more procedural and less declarative like serial addition or line orientations tasks.

Other human studies have shown differences in glucocorticoid levels and the level of cognitive impairment. Results from cognitive testing in individuals who have elevated glucocorticoid levels due to disease have bolstered the association between glucocorticoids and impairment. This linkage is observable in patients with Cushing's syndrome (Starkman & Schteingart, 1981), Alzheimer's disease, and in individuals given on high-doses of glucocorticoids as part of their treatment regimens (Jenike & Albert, 1984; Varney, 1984). Again, the strongest deficits are those dealing with declarative tasks. These findings provide more evidence pointing to damage to the hippocampus specifically. For example, in one study of patient's with Cushing's syndrome, deficits

were noted on verbal paired association tasks and a visual episodic memory task, but not for copying visual design (Nasrallah, Coffman, & Olson, 1989).

Admittedly, the ability to make conclusive associations would be limited given the fact that subjects with neurodegenerative diseases already have a compromised cognitive profile due to their illness. However, other studies with healthy individuals demonstrate corroborating results. A longitudinal study (Lupien, Lecours, Lussier, Schwartz, Nair & Meaney, 1994) using healthy elderly human subjects measured glucocorticoids levels over four years. They were split in three groups: those whose basal glucocorticoid level rose over the four years to at least mildly clinical levels; those whose glucocorticoid levels had risen, but still remained within a normal range (that one would expect in a non-agitated state); and those whose glucocorticoid levels had either remained stable or decreased. Neuropsychological assessments of declarative tasks (using hippocampal-dependent memory) showed a significant impairment in performance within the group with increased glucocorticoid levels. The group with stable or decreased glucocorticoid levels demonstrated no significant differences in their performance. Those in the second group produced intermediate results in their performances. The findings of these studies support the conclusions that exposure to stressors impair cognitive efficiency and negatively affect tasks that necessitate conscious and intentional information processing (Lupien, et al., 1999; Luethi, Meier & Sandi, 2009; Oei, et al., 2006; Robinson, Sünram-Lea, Leach & Owen-Lynch, 2008; Schoofs, Preuß & Wolf, 2008).

Psychosocial Contributions to Allostatic Load

The cumulative effect of experiences, habits and life style, and major stressful life events are large contributors to allostatic load. As previously mentioned, every body system is affected by stress. The chemical mediators of allostasis contribute to the rate of aging experienced by various organs including the heart and brain. For this reason, there has been great scientific interest in developing specific instruments to measure the impact of contributors to allostatic load. These measures can be used in the prediction of later vulnerability to disease. This does not just include furthering our understanding of biochemical pathways. It also includes exploring the contributors of stress on the macro level and finding ways to either prevent or ameliorate the subsequent damage through various means.

Even before the vast advancement of knowledge regarding the biochemical mechanisms involved in the stress response, various studies concluded that facing stressful events and challenging life circumstances was linked to the onset of illness. (Fischer, Dlin, Winters, Hagner & Weiss, 1962; Graham & Stevenson, 1963; Greene Jr, Young & Swisher, 1956; Hawkins, Davies & Holmes, 1957; Kjager, 1959; Greene & Miller, 1958; Smith 1962; Rahe & Holmes,1965; Weiss, Dlin, Rollin, Fischer & Bepler, 1957). Resultant from these studies was a cataloguing of life events that were thought to belong to a "stress cluster" that significantly contribute towards the level of stress necessary to trigger illness and disease. In 1963, Rahe and Holmes sought to derive some quantitative estimation of the weighted impact each of these events--termed Life Change Units (LCU)--contributed to disease acquisition. Their study resulted in the creation of the Holmes Rahe Social Readjustment Rating Scale (SRRS) to measure the effect of

stressful events on physiological health. In their research, over 5,000 human subjects underwent a structured interview to measure their experiences with various stressful life events within the previous two years. Holmes and Rahe selected 43 life events for the SRRS. A sample consisting of 394 adults reviewed and evaluated the life events using psychophysical scaling (this technique was developed and described by Stevens and Galanter [Stevens, 1957, 1966; Stevens & Galanter, 1957]). Reviewers examined and rated the amount of psychosocial stress and social readjustment associated with each of the items on a scale ranging from 1 to 100. Holmes and Rahe asked reviewers to use the event of "marriage" as a midpoint—it was to be considered a 50 on the scale. Mean scores were used to derive weights for each life change event.

Since their original study, this instrument has been validated in numerous epidemiological studies: elevated LCU scores been positively correlated with increased inflammatory biomarkers, increased levels of CRH, increased levels of cortisol, and suppressed immunofunctioning (Calvo & Morrison, 2016; Ganzel, Morris, & Wethington, 2010; Manzanares, Monseny, Ortega, Montalvo, Franch, Gutiérrez-Zotes... & Labad, 2014; Tsigos & Chrousos, 2002) As the SRRS is administered today, subjects endorse various LCU's on the measure and the higher the cumulative score, the greater the risk for illness.

This framework for assessing illness risk is logical in the light of what is known regarding the biochemical mechanisms contributing to allostatic load. The greater the exposure to stress, the greater the activation of the HPA axis and subsequent effects on tissues and organs. It stands to reason that the same would hold true when attempting to measure the effects on the structures of the brain and, consequently, cognitive

functioning. These facts notwithstanding, it is evident that there are individual differences in the rate of aging—even among those exposed to similar LCU's. It behooves the scientific community to discover those factors that minimize allostatic load, and contribute to physiological and psychological resilience. If these factors are identified, they can be used to promote healthy aging.

Neuroprotective Factors

Heretofore, this paper has discussed the destructive impact of an elevated and prolonged stress response and its contribution to allostatic load. A point has been made to emphasize the cognitive effects of the subsequent neuronal damage. However, it is important to note that research on an array of brain injury models has long observed that there is not a direct correlation between the amount of total structural brain damage and the impairment on cognition. In other words, between demographically matched individuals with similar volumes of brain lesions, there can still be significant differences in their performance on cognitive tasks. Therefore, it should come as no surprise that when dealing with allostasis and its impact on functioning, the same amount of exposure to stressors does not necessarily produce the same observable effect between individuals. There are some factors among individual differences that are believed to attenuate the effects of stress on functioning.

Sex Differences

Anatomical sex appears to be a neuroprotective factor. A study by Mineur, Belzung and Crusio (2007) assessed the differences in learning and hippocampal

neurogenesis between groups of mice exposed to chronic stress. Learning was evaluated by observing the performance of animals in cognitive tasks that were both hippocampus dependent and independent. They also conducted histological analyses wherein they examined tissue samples and calculated the rate of survival of newly generated brain cells. Overall results showed that the rate of survival for new neurons and glial cells in the hippocampus was greatly decreased in animals exposed to chronic stress as compared to those animals that were not exposed to chronic stress. As it related to cognitive functioning, the data gleaned from behavioral testing demonstrated impairment in performance in hippocampus-dependent tasks for animals exposed to chronic stress as compared to those not exposed. Tasks that were hippocampus independent did not demonstrate a significant difference in performance between groups. Notably, the results showed strong correlations with sex. Female mice seemed to be less adversely affected by the exposure to chronic stress. That is, upon histological analysis, females were shown to have a higher volume of cells as compared to male mice. Furthermore, the results of behavioral testing revealed that females had less errors on tasks of working memory. A number of animal studies have corroborated the findings that estrogens increase the rates of neurogenesis in the female rat brain (Tanapat, Hastings, Reeves & Gould, 1999). Other studies demonstrate that when exposed to stress, female rats are resistant to dendrite atrophy that is observed in the hippocampus of male rats (Galea, McEwen, Tanapat, Deak, Spencer & Dhabhar, 1997).

While studies have demonstrated the association of estrogens on neurogenesis and neuroprotection, it is still unclear if these effects would be observed in the absence of other developmental changes that take place in female hippocampi during sexual

differentiation (Gould, Westlind-Danielsson, Frankfurt, & McEwen, 1990; Juraska, 1991; Roof, 1993; Williams & Meck, 1991). For instance, one question for further research would be to determine whether or not the administration of exogenous estrogen would have the same neuroprotection on male subjects or if these effects require the interaction of estrogen on structures within the female brain that have been specifically affected during sexual development.

The applicability of these findings to human populations is still questionable: particularly with regards to individuals of advanced age. In general, it has been shown that men have a greater HPA activation and produce a greater amount of cortisol in response to psychosocial stressors than women do (Uhart, Chong, Oswald, Lin, & Wand, 2006). However, findings from additional research indicate that HPA activity in women tends to increase following menopause (Van Cauter, Leproult, & Kupfer, 1996). It has also been shown that, among women, the increase in cortisol levels during exposure to laboratory induced stress is age-dependent. Furthermore, the correlation for age and increased cortisol secretion is observed to be stronger for women than it is for men (Seeman, Singer, Wilkinson, & McEwen, 2001). And, findings from human studies with postmenopausal women demonstrate that performance on hippocampal dependent cognitive tasks is negatively correlated with elevated cortisol levels (Seeman, et al., 1997). It seems as though estrogen replacement therapy might be able to offset some of the increased vulnerability that appears to occur post menopause. Studies of perimenopausal subjects have demonstrated a reduction in HPA reactivity and sympathetic nervous system reactivity in the presence of estrogen replacement therapy (Komesaroff, Esler & Sudhir, 1999; McEwen, 1998; Seeman, et al., 2001). Other

research measuring the amount of excitotoxic damage observed in the brain have demonstrated that estrogens ameliorate this effect and glucocorticoids increase it (Goodman, Bruce, Cheng & Mattson, 1996). Taken together, these studies indicate that estrogens may help regulate the HPA axis, reduce allostatic load, and possess neuroprotective qualities and attenuate damaging effects increased levels of glucocorticoids have on nerve cells.

Cognitive Reserve

While the neuroprotective effects of estrogens are a source of hope for women, it is of little comfort for men who are seeking to stem cognitive decline related to the accumulation of allostatic load that comes with aging. However, the concept of cognitive reserve and the potential humans have to increase their reserve capacity represents an area that may be of benefit to those interested in facilitating healthy aging.

With regards to the concept of reserve, there exist various theories among researchers. Some neuroscientists subscribe to the construct of brain reserve capacity (BRC) (Katzman 1993; Mortimer et al., 1981; Satz 1993; Stern, 2002). The model these researchers espouse hinges on the premise that there is a certain amount of damage that the brain can withstand. Damage beyond this threshold will assuredly manifest as cognitive impairments. However, individual differences in the volume of brain matter plays a key role in what that threshold is for each person. In other words, greater amounts of brain matter can mitigate against greater amounts of brain damage so that a person who has a larger amount of brain matter, or greater amount of BRC, can sustain more damage before reaching the threshold toward functional deficit.

A counter-theory to the concept of BRC is the concept of cognitive reserve. Unlike the BRC model, the cognitive reserve model does not presume a fixed threshold of damage that the brain can sustain beyond which functional impairment will inevitably occur. Instead, the factor that defines the ability to attenuate functional impairment is the brain's ability to maximize the efficiency of using its structures and networks—regardless of the actual volume of tissue or density of neurons. When faced with challenges, cognitive reserve in unimpaired individuals is cultivated by the brain learning to employ the use of networks and paradigms less susceptible to disruption. And when insulted, the brain compensates for the damage by using brain structures or networks not ordinarily utilized in the absence of damage. Those who have more cognitive reserve display the ability to use their brain networks with the most efficiency and, when responding to stressors, they can recruit alternate brain networks. The cognitive reserve theory emphasizes how efficiently the brain uses what remains after damage. The cognitive reserve model recognizes individual differences and that the same type of brain injury may not necessarily manifest itself with the same clinical results across individuals. Additionally, individual responses to injury may differ even if the amount of brain matter is the same between people.

Cognitive reserve may be defined as "the ability to optimize or maximize performance through differential recruitment of brain networks, which perhaps reflect the use of alternate cognitive strategies". Because the brain must recruit various networks as a part of normal adaptation to stressors, this definition acknowledges the fact that cognitive reserve is employed by both those with and without brain damage.

Researchers that subscribe to the cognitive reserve theory do so in part due to evidence in neuroimaging studies that demonstrate how brain networks are activated during increasingly more challenging tasks (Grasby et al., 1994; Gur et al., 1988; Rypma, Prabhakaran, Desmond, Glover & Gabrieli, 1999; Stern, 2002). Using brain imaging of human subjects, researchers have observed that, when presented with an increasingly difficult task, individuals will recruit brain networks that were utilized in easier versions of the same task. For example, a study on young and old human subjects by Grady et al. (1996) compared regional cerebral blood flow and subjects' performance on tasks of visual perception and memory. It was found that older subjects often recruited the use of brain areas that younger subjects typically did not. Their findings indicated that older brains compensated by deviating in the utilization of the networks typically required for completion of some cognitive tasks. This is demonstrative of the brain's ability to adjust and use other areas if the networks that would commonly be used are either unavailable or if the task becomes too challenging. According to this perspective, when brain areas sustain insult, it is merely another challenge, similar to a difficult task. So when brain tissues are compromised, an individual whose brain networks have previously been used to utilizing various pathways to meet task demands in an efficient way will already possess the ability to do so to meet this new "task demand". The efficiency with which one can do this is a function of cognitive reserve capacity. Those who possess more proficiency in a particular task are those who, studies demonstrate, activate fewer networks in the completion of that task as compared to someone who is not as proficient in that task. And, if someone who has mastery in a task utilizes their networks to maximum capabilities, they are able to complete the task at a higher level than someone

with less skill. Colloquially, this is commonly observable in performance of any task that requires practice and refinement (e.g. participating in a sport, playing an instrument, solving equations, etc.). Those who are experts at a task are those whose brains have mastered the ability to activate their brain networks in the most efficient manner. Additionally, those who have gained mastery in an area have likely derived multiple networking paths to achieve the desired outcome. Therefore, a redundancy is created in their networking such that, if one pathway is unavailable, the brain is still able to compensate. This understanding of cognitive reserve indicates that cognitive reserve can be built by exposure to various life experiences and training; this leads us to the ways in which cognitive reserve is measured.

Without resorting to positron emission tomography scans and functional magnetic resonance imaging (fMRI**)**, cognitive reserve is often measured by proxy. Because the mastery of certain skills has the effect of increasing the efficiency with which brain networks are activated, logically, activities that stimulate the brain to "practice" deriving various solutions to challenges are also those activities that can help increase cognitive reserve. Studies have shown correlations between increased time in pursuing educational, occupational, and mentally stimulating activities and decreases in brain activity during challenging tasks. Therefore, the most often used proxies for cognitive reserve include educational/occupational attainment, engagement in cognitively challenging pastimes (e.g.: reading, writing, playing an instrument, creating artwork), participation in physical activity (e.g.: playing sports, exercising regularly), and social engagement (e.g.: participating social clubs, volunteering for charity) (Scarmeas & Stern, 2003; Scarmeas, 2007, Sole-Padulles, et al., 2004; Valenzuela & Sachdev, 2005). Because cognitive

reserve is thought to be protective in the face of all sorts of neuronal damage, the current study hypothesized that cognitive reserve would also be able to attenuate the functional effects of the accumulated allostatic load acquired through psychosocial stressors experienced by healthy human elders.

Summary

Through the action of several catalysts, especially glucocorticoids, the HPA axis has been shown to impact functioning. Although glucocorticoid receptors are found in several brain regions, the hippocampus seems to be especially vulnerable. Therefore, this project hypothesized that cumulative stress from life events would impact performance on hippocampal dependent tasks such that there would be a negative correlation between stress scores and performance on these tasks. It was hypothesized that non-hippocampal dependent tasks such as tasks of working memory, set shifting, and visual perception would not demonstrate this correlation. To test these hypotheses, subjects were given tasks of verbal memory (the Rey Auditory Verbal Learning Test II) and visual memory (Rey Osterrieth Complex Figure Test) to assess declarative memory. Tests of visuospatial perception (Visual Object and Space Perception Battery), working memory (WAIS Digit Span), maintaining and switching set (Trail Making Test) and semantic fluency (FAS), were given as measures of performance on tasks that are not hippocampal dependent.

CHAPTER TWO

SPECIFIC AIMS AND HYPOTHESES

The current study assessed the ability of cognitive reserve and sex differences to moderate cognitive decline subsequent to exposure to discreet, remote psychosocial stressors experienced by elderly adults. Hierarchical linear modeling was conducted to assess the direct and indirect effects.

Aim 1

The first aim was to examine the cumulative effect of psychosocial stressors on cognitive functioning in elderly adults. Numerous studies have been conducted demonstrating the contributions of stressors to allostatic load. Mediated by the hypothalamus-pituitary-adrenal (HPA) axis, unregulated elevated stress has been shown to facilitate damage to numerous organs including the brain. The hippocampus is especially vulnerable to damage from the prolonged stress response. This is evidenced by impaired cognitive performance on declarative, hippocampal-dependent tasks. Prolonged chronic stress has been shown to result in decrease cognitive functioning. Additionally, studies have shown decreased performance on tasks immediately following the administration of stressful stimuli. However, this study examined the cumulative effects of discreet stressors that are not task related that have transpired in the life of the subjects within the previous year. Previous research has shown that tabulating the weighted contributions of various life stressors can be a useful tool in the assessment of disease risk subsequent to increased allostatic load. This study attempted to see if this same assessment correlated to decreased cognitive functioning.

Specific Hypothesis 1

Elderly adults exposed to higher levels of stressful events as measured by the Social Readjustment Rating Scale would show a larger difference between their actual performance on hippocampus dependent cognitive tasks and their estimated premorbid performance as predicted by a measure of premorbid verbal intelligence.

Specific Hypothesis 2

No such correlation was predicted to be observed with regards to performance on tasks that are not hippocampus dependent.

Aim 2

The second aim was to examine the ability of cognitive reserve to moderate cognitive decline in elderly subjects exposed to psychosocial stress. Studies on human subjects have demonstrated that, in the presence of brain insult, individuals who score higher on measures of cognitive reserve perform better on cognitive tests. Because stress-induced cognitive decline is mediated by allostatic damage, it was hypothesized that, just as cognitive reserve acts as a neuroprotective factor in the face of other damage, it would attenuate stress-induced functional impairment as well.

Specific Hypothesis 3

The difference between estimated expected cognitive performance (as measured by a test of premorbid functioning) and actual cognitive performance on hippocampal

tasks was predicted to be less in individuals who score higher on measures of cognitive reserve.

Specific Hypothesis 4

No such correlation was predicted to be observed with regards to performance on tasks that are not hippocampus dependent.

Aim 3

The third aim was to examine the ability of sex differences to moderate cognitive decline in elderly subjects exposed to psychosocial stress. Studies in both animal and human models have demonstrated that male subjects show a greater HPA activity, higher cortisol production, and a steeper decline in cognitive performance when exposed to stress than do females. However, this appears to be largely mediated by the presence of estrogens. It is inconclusive as to whether or not the effects of sex differences in the absence of estrogens or exogenous estrogens administered to males will produce the same effects. Studies on postmenopausal women have indicated that stress-induced cortisol production increases with age as does HPA activity. Although estrogen replacement may help, in general, aging appears to amplify the effects of stress to greater degree in women than it does in men. Therefore, it was expected that the degree to which stressors negatively impact the cognitive functioning of elderly women would be greater than the effect on elderly men.

Specific Hypothesis 5

It was expected that among all subjects, there would be an observable difference between the estimated expected performance (as measured by a test of premorbid functioning) and their actual performance on hippocampus dependent cognitive tasks. However, this difference was predicted to be greater among elderly women as compared to elderly men.

Specific Hypothesis 6

No such correlation was predicted to be observed with regards to performance on tasks that are not hippocampus dependent.

CHAPTER THREE

MATERIALS AND METHODS

Subjects

The current study used data collected through the Walnuts and Healthy Aging (WAHA) Study. Three hundred sixty-five healthy, elderly participants (aged 65-75 years old; mean=69.6 years old; 245 female) from the Southern California area were recruited via radio, newspaper and internet advertisements as well as posted fliers. None of the subjects were residents of assisted living or nursing homes—all lived independently within the community.

Volunteers had to be free of any chronic diseases. Prior to enrollment in the study, participants were pre-screened via questionnaire, clinic records, and the results of recent (within 6 months) blood test showing glucose control, renal and liver functioning. They were asked if they had any diagnosed mental health concerns. Those that endorsed any psychiatric illnesses, including depression, were excluded. Other exclusion criteria included: illiteracy or inability to understand protocols or undergo the neuropsychological testing; morbid obesity defined by body mass index greater than or equal to 40; uncontrolled diabetes defined by HbA1c levels greater than 8%; uncontrolled hypertension defined by treated blood pressure greater than or equal to 150/100 mmHg; a prior cerebrovascular accident; death of a loved one within the previous year, advanced cognitive deterioration or dementia; neurodegenerative diseases such as Parkinson's; any chronic illness expected to shorten survival such as heart failure, chronic liver disease, blood disease, cancer or kidney failure; customary use of fish oil or flax seed supplements; or macular degeneration.

Instruments

Participants were given a packet containing several questionnaires that were completed prior to neuropsychological testing. Participants underwent a series of neuropsychological tests administered by trained clinical psychology doctoral students from the Department of Psychology in the School of Behavioral Health at Loma Linda University.

Holmes-Rahe Social Readjustment Scale

The Holmes-Rahe Social Readjustment Rating Scale (SRRS) was developed in 1967 by Thomas Holmes and Richard Rahe (Holmes & Rahe, 1967). The measure lists life events believed to be major contributors of psychosocial stress (Appendix A). These included distressful events (e.g.: being fired, foreclosure) as well as eustressful events (e.g.: marriage, addition of a new family member, a vacation). In the creation of this measure, the clinical histories of 5,000 patients were evaluated. Their research and subsequent validation studies have demonstrated the links between stress and illness. Reliability testing by Gerst et al. (1978) concluded that it had a high reliability for both healthy adults ($r = 0.96 – 0.89$) and patients ($r = 0.91$ to 0.70). Validity testing found a positive correlation between LCU's and illness (+0.12), which was sufficient to support the hypothesis of a link between life events and illness.

A modified version of the SRRS was created by researchers from the National Institute of Mental Health (Mellinger, Balter, Manheimer, Cisin & Parry, 1978) reducing the number of events from 43 to 32, eliminating those 11 items that are least severe. In their research, itemizing the most severe life events and crises would be able to capture

those experiences that would be most highly correlated to physiological adaptation and wear on health. Since the current project is focused on capturing stressors that are hypothesized to be the best predictors of cognitive change, the modified scale was used.

Subjects in this study were asked to endorse those life events that occurred with the previous year. The weighted LCU scores were summed to calculate a total stress score.

American Version of the National Adult Reading Test

The American version of the National Adult Reading Test (AMNART) was developed for American English speaking adults in the United States. The version administered in this study consists of 45 irregularly spelled English words that subjects are asked to pronounce aloud, reading the list from top to bottom. The AMNART is used as an estimate of premorbid ability for elderly subjects (Gorber, Sliwinsk & Korey, 1991; Gladsjo, Heaton, Palmer, Taylor & Jeste, 1999; Smith, Bohac, Ivnik, & Malec, 1997).

Questionnaire of Variables Related to Cognitive Reserve

The Questionnaire of Variables Related to Cognitive Reserve is an instrument developed by David Bartes-Faz and Cristina Sole-Padulles to measure proxies associated with cognitive reserve. In their analyses, cognitive reserve scores were positively correlated with fMRI patterns r = .83-.93. This instrument was originally developed in Spanish. For the purposes of the WAHA study, it was translated into English by an advanced clinical psychology graduate student who was fluent in both Spanish and English.

Participants were asked to share information about various life experiences, each of which was coded on a Likert scale (Appendix B). The variables measured the participants' exposures in the following domains: education–culture, professional activities, intellectual leisure activities, physical activity and social activities. The scores were tabulated within each domain and each of the domains was added together to create a composite cognitive reserve score with greater scores indicating greater amounts of cognitive reserve (Solé-Padullés, et al., 2009).

Rey Auditory Verbal Learning Test II

In the Rey Auditory Verbal Learning Test II **(**RAVLT; Schmidt, 1996), the test administrator reads a list of 15 words out loud at the rate of one word per second. The participant is asked repeat all the words that he or she remembers. The words can be repeated in any order. This process is repeated four more times. The summation of the total amount of words recalled across these 5 trials is what will be used as the immediate recall score in this analysis. Next, the administrator reads a second (distractor) list of 15 words. This time the participant is instructed to repeat as many of the words from the second list as he or she can remember, but none of the words from the first list. Again, these words can be stated in any order. The second list is only read once and the participant is only asked to recall words from the second list once. Immediately following the participant's attempt to recall words from the second list, he or she is asked to repeat many words as possible from the first list that was repeated 5 times. In the last test condition, the participant is handed a paper with words from the first list that the test administrator read aloud mixed in with several "distractor" words. The participant is

given the written list and a pencil and instructed to review the paper and check off those words that occurred in the first list that the administrator repeated several times. The RAVLT is used to evaluate verbal learning and memory, inhibition, retention, encoding, retrieval, and organization. In this analysis we are using score from the short delayed recall as the delayed score.

Rey Osterrieth Complex Figure Test

In the Rey Osterrieth Complex Figure Test (RCFT; Rey & Osterrieth, 1993), participants are tasked with reproducing a complicated line drawing (Appendix C). In the initial testing condition, the participant is given a pencil and paper and the test stimulus is placed in front of them. They are asked to copy the stimulus as carefully as possible. They have no maximum time limit in the copy portion although the amount of time it takes for the participant to complete their reproduction is noted by the test administrator. After the participant indicates that he or she has completed the copy, the test administrator removes the stimulus and the participant's reproduction from the subject's view. After a three-minute delay, the participant is given another blank paper and asked to reproduce the figure from memory (Immediate Recall). Following the completion of that drawing, the administrator, once again, removes the participant's drawing from view. After a 20 to 30-minute delay, the participant is again given a blank paper and again asked to reproduce the figure from memory (Delayed Recall). Participants are not told that they will be asked to recall and reproduce the drawing from memory before either of the recall conditions.

All of the participant's copies are scored for accurate reproduction and placement of stimulus design elements. The RCFT measures visuospatial perception, attention, and executive domains.

Wechsler Adult Intelligence Scale Digit Span

Digit Span is a subtest of the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Weschler, 1997). In the Digits Forward test condition, the test administrator reads a sequence of numbers. The participant is asked to repeat the numbers in the same order. For the Digits Backward test condition, the test administrator reads a sequence of number aloud. The participant is asked to recall the numbers in reverse order.

This test measures the executive functions of working memory, mental manipulation, cognitive flexibility, rote memory and learning, and attention and is primarily a frontal lobe task. As it is not a hippocampal dependent task, so comparison of participants' performance on this task served to explore the differences in effects seen in hippocampus-dependent tasks and those that are not dependent on the hippocampus.

Visual Object and Space Perception

The subtests contained within the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991) assess object and space perception. In the incomplete letters task, participants are presented with fragments of alphabetic characters that they must identify. In the numbers location task the participant is shown pictures of numbers placed randomly within a square. Underneath that picture is a picture with a dot placed where one of the numbers is located on the top picture. The participant is asked to

look at the dot and tell the administrator which number in the top picture is represented in the dot in the lower picture.

Unlike the memory tasks, the VOSP tests do not involve declarative memory. Comparison of participants' performance on this task served to explore the differences in effects seen in hippocampus-dependent tasks and those that are not dependent on the hippocampus.

Trail Making Test

The Trail Making Test comprises two parts, Trails A and Trails B (Corrigan & Hinkeldey, 1987; Lezak, et al., 2004). Each part consists of 25 circles on a sheet of paper. For Trails A, the circles are numbered 1 – 25. The subjects are tasked with drawing lines connecting the numbers in ascending order as quickly as possible without lifting their pencil or making a mistake. Trails B (Appendix D) has 13 numbered circles (1 – 13) and 12 lettered circles (A – L). As in Trails A, subjects are tasked with drawing lines connecting the circles in ascending order. However, this time, they must alternate between numbers and letters (i.e., 1-A-2-B-3-C, etc.). Errors are promptly pointed out by the test administrator and the subject starts from the last correctly connected circle.

Trails B is a test of executive functioning and is primarily a frontal lobe task. As it is not hippocampus dependent, so comparison of participants' performance on this task served to explore the differences in effects seen in hippocampus-dependent tasks and those that are not dependent on the hippocampus.

FAS Test of Verbal Fluency

The FAS Test was originally developed as a subtest of the Neurosensory Center Comprehensive Examination for Aphasia (Spreen & Benton, 1977). During this test, participants are asked to list aloud as many words that begin with the letter F as they can in one minute. Participants are asked to refrain from listing proper nouns and alternate tenses of the same word (for example: "faster" and "fastest"). The second trial provides the participant with the same instructions, this time with the letter A; and the last trial uses the letter S as the phonemic cue (Borkowski, Benton, & Spreen, 1967, Spreen & Benton, 1977; Spreen & Risser, 2003, and Strauss, Sherman, & Spreen, 2006).

The FAS test assesses verbal fluency which entails exercising executive control over several cognitive process such as set shifting, selective attention, internal response generation, inhibition and self-monitoring. As it is not hippocampal dependent, comparison of participants' performance on this task served to explore the differences in effects seen in hippocampus-dependent tasks and those that are not dependent on the hippocampus.

Statistical Analysis

Of the 365 participants, 22 were excluded crosswise from the analyses due to incomplete data entry or missing data. All analyses were run using IBM SPSS version 23.

The weighted values for each of the life stressors endorsed on the modified SRRS were summed to derive a cumulative stress score for each participant. Scores for each of the neuropsychological measures were converted to Z-scores. To determine how the various tasks were related to various domains of cognition, a principal-components

analysis was computed. As a result, the analysis extracted four with eigenvalues greater than 1.0 (Table 1).

The first factor explained 20.08% of the variance of the result. This factor consisted of the RCFT tasks. The second factor explained 17.49% of the variance and consisted of the Digit Span Scores, FAS, and Trails B tasks. The third factor explained 15.84% of the variance. This factor included the RAVLT tasks. The fourth factor explained 10.14% of the total variance and consisted of the VOSP tasks. These four factors together explained 63.54% of the variance. Thus, the factor analysis indicated that the tasks formed clusters by cognitive domain: visual memory, executive functioning, verbal memory, and visuospatial perception.

Initially, RCFT Copy was to be used in this analysis. However, in the principal-components analysis, it loaded on factor 1 (the visual memory factor) as opposed to factor 4 (the visuospatial perception factor). Although clinically, the RCFT Copy task is used as a measure of visuospatial perception, because it did not load onto this fact, it was decided that it would not be used in this analysis. However, it is still important to note that the task was completed as part of the routine administration of the RCFT test because it is necessary for proper encoding.

Table 1. Tasks Included in the Principal-Components Analysis with Rotated Factor Loadings and Percentage of Explained Variance.

	Component			
	1	2	3	4
Digit Span		.499		
RCFT Delay	.935			
RCFT Immediate	.941			
VOSP Letters				.760
VOSP Numbers				.571
Trails B		.810		
FAS		.453		
RAVLT Immediate			.921	
RAVLT Delay			.926	

Note: only highest loadings have been retained in table.

The AMNART scores were converted to get the z-scores of premorbid functioning. Following an analysis method used by Lewin, Wolgers and Herliz (2001), the z scores of the tasks within each factor were added together and divided by the number of tasks within that factor to get the domain score. The domain performance score was subtracted from the estimated premorbid functioning score to get an estimated decline score. Regression analyses were run on each factor performance score with stress, sex, and cognitive reserve as independent variables. Further analyses were done using the estimated decline score as the dependent variable. In addition, each assessment measure was analyzed individually. Regression models were analyzed for the z-scores of each individual task to determine the effect of stress, sex, and cognition. Lastly, the z-scores for each individual task were subtracted from the estimated premorbid functioning z-score to get an estimated decline score for each task individually. So for each of the four

domains, four scores were analyzed: the overall factor performance score; the estimated decline score for the factor; the actual performance score for each individual task; and the estimated decline score for that task.

It is important to this research to not only look at the performance scores, but also to examine the decline scores. Individuals may score similarly on a task, but having one person whose premorbid level of intelligence was in the superior range scoring as well as someone whose premorbid intelligence was in the average range would suggest that there is a factor influencing that difference. If only performance scores were used, this effect would be masked.

Because several regression analyses were run, post hoc Bonferroni corrections were used to determine significance. To correct for family wise error for the analyses of estimated decline scores for individual tests, it was determined that a p value of .005 was required to indicate significance. Similarly, a p value of .005 was indicative of significance for analyses of individual test performance scores. For domain scores and estimate decline of domain scores, a p value of .0125 was needed to indicate significance.

To prevent having to run even more regressions on the data set, when cognitive reserve was identified as having had a significant effect on the variables, a correlation was run to determine which of the constituents of cognitive reserve was most highly correlated with that particular factor and/or task. The result of that correlation analysis is included in the summary of results.

The a priori hypothesized model took into consideration the following: as the amount of stressors affects the change in cognitive functioning, the degree of this effect depends on sex and amount of cognitive reserve. Therefore, it was hypothesized that the

indirect effect of stress on change in cognitive functioning is moderated by sex and cognitive reserve. Where X is the reported level of stress, W is sex, Z is cognitive reserve, and Y is the change in cognitive functioning, the relevant regression equations is

$$Y = b0 + b1X + b2W + + b3Z + b4XW + b5XZ + b6WZ + b7XWZ + e$$

CHAPTER FOUR

RESULTS

In this study it was hypothesized that the amount of stress (as measured by the SRRS), sex, and cognitive reserve (as measured by the Questionnaire of Cognitive Reserve) would affect cognition in elderly adults. The following results are reported by individual domains.

The first hypothesis posited that increases in stress scores would correlate with greater differences between estimated premorbid functioning (as measured by the AMNART) and actual performances in various cognitive tests focused on different domains. Because prior research demonstrated that the hippocampus is particularly vulnerable to glucocorticoids, it was hypothesized that the greatest differences in the estimated pre-morbid functioning and actual performance would be demonstrated in those tasks that are hippocampus dependent. Namely, the immediate and delayed recall tasks on the RAVLT, and the immediate and delayed recall tasks on the RCFT would evidence this difference. Non-hippocampus dependent tasks such as tests of perception, executive functioning (the subtests of the VOSP, the WAIS Digit Span subtests, Trails B, and FAS) were hypothesized not to demonstrate these differences.

The second hypothesis posited that sex would be a significant predictor of performance. It was thought that women would demonstrate a greater difference between their estimated pre-morbid functioning scores and their actual performance in hippocampus dependent tasks as compared to men.

Lastly, it was hypothesized that cognitive reserve would also be a significant predictor of performance. It was hypothesized that increases in cognitive reserve would be inversely related to the quantitative difference between the estimated pre-morbid functioning and actual performance in hippocampal dependent tasks.

Descriptives of Variables

Descriptives of Independent Variables

There were no significant differences between men and women in their ages (Table 2), AMNART scores (Table 3), stress scores (Table 4), or cognitive reserve scores (Table 5). A full range of scores was noted for both cognitive reserve and stress (Table 6).

Table 2. Mean ages by sex.

Sex	Mean	SD
female	69.31	3.86
male	70.42	4.15

Table 3. Mean AMNART Z scores by sex.

Sex	Mean	SD
female	1.12	.71
male	1.10	.55

Table 4. Mean stress scores by sex.

Sex	Mean	SD
female	69.65	72.29
male	69.98	68.45

Table 5. Mean cognitive reserve scores by sex

Sex	Mean	SD
female	15.87	3.41
male	15.23	3.58

Table 6. Descriptives of Independent Variables.

Variable	Minimum	Maximum	Mean	SD
Stress	0	422	71.84	70.91
Cognitive Reserve	5	23	15.65	3.48

Descriptives of Dependent Variables

Boxplots were created and variables were inspected for outliers (observations >1.5 times the interquartile range) which were subsequently trimmed. Most variables demonstrated slight skew and kurtosis but not greater than |2| (Table 7). However, the scores for the VOSP letter task and VOSP number task did exhibit an extreme negative skew due to the low ceiling for these tests. That is, the vast majority of subjects achieved the maximum scores. Despite this, error variances of all variables were checked for homoscedasticity and normal distribution and did not violate the assumptions for regression.

Table 7. Descriptive Statistics for Individual Test Z Scores.

Test	Minimum	Maximum	Mean	SD	Skew	Kurtosis
RAVLT Immediate	-2.68	4.79	1.60	1.35	-.21	-.32
RAVLT Delay	-2.92	3.33	1.20	1.39	-.50	-.20
RCFT Immediate	-2.32	2.04	-.42	.90	.10	-.52
RCFT Delay	-2.60	2.33	-.41	.97	.07	-.48
WAIS Digit Span	-2.00	3.00	.32	.91	.42	-.06
FAS	-2.55	2.54	-.12	1.02	.18	-.35
Trails B	-1.07	1.65	.55	.62	-.62	-.20
VOSP Letters	-1.18	.64	.22	.56	-.96	-.10
VOSP Numbers	-1.41	.86	.43	.53	-1.31	1.18

Verbal Memory Domain

Verbal Memory Factor

Looking at overall verbal memory factor performance, the model of best fit ($F(2, 323) = 34.89$, $p = .001$, $R^2 = .15$, $R^2_{Adjusted} = .14$) demonstrated that sex ($\beta = -.34$, $t(342) = -6.60$, $p < .001$; Table 12) and cognitive reserve ($\beta = .14$, $t(342) = -7.49$, $p < .005$; Table 12) had a significant effect on the performance scores, while stress did not significant predictors. Of the cognitive reserve variables, intellectual leisure was shown to be the most highly correlated of the factors ($\beta = .16$, $t(342) = -3.40$, $p < .005$). These results did not support the hypothesis. When looking at the verbal memory factor scores, on average females performed better (M= 1.78; SD=1.09) than did males (M= .84; SD=1.23; Table 8).

Table 8. Means and Standard Deviations of Verbal Memory Z-Scores as Predicted by Sex

	M	SD
Women	1.78	1.09
Men	.84	1.23

Note. p <.001

When looking at the estimated decline in the verbal memory factor, the model of best fit ($F(1, 324) = 38.90$, $p = .001$, $R^2 = .11$, $R^2_{Adjusted} = .10$) demonstrated that sex alone had a significant effect on the estimated decline scores ($\beta = .33$, $t(342) = 6.24$, $p < .001$; Table 12). These results did not support the hypothesis. When looking at the verbal memory factor scores, on average females had less estimated decline (M= -.65; SD=1.21) than did males (M=.27; SD=1.17; Table 9).

Table 9. Means and Standard Deviations of Estimated Decline in Verbal Memory Z-Scores as Predicted by Sex

	M	SD
Women	-.65	1.21
Men	.27	1.17

Note. p <.001

Verbal Memory Tasks

Sex was demonstrated to have a significant effect on RAVLT Immediate Recall performance scores ($\beta = -.39$, $t(342) = 7.16$, $p < .001$) and Delayed Recall performance scores ($\beta = -.32$, $t(342) = -6.23$, $p < .001$; Table 12). Cognitive reserve also significantly predicted RAVLT Immediate Performance scores ($\beta = .14$, $t(342) = 2.86$, $p < .005$) with intellectual leisure activities being most highly correlated with this task. Females had better Z-scores on both the RAVLT Immediate Recall task (M=1.98; SD=1.21) and the RAVLT Delayed Recall task (M=1.55; SD=1.15) than did males did on the Immediate Recall task (M=.95; SD=1.20) and the Delayed Recall task (M=.64; SD=1.44; Table 10).

Table 10. Means and Standard Deviations of RAVLT Z-Scores as Predicted by Sex.

	M	SD
RAVLVT Immediate		
Women	1.98	1.21
Men	.95	1.20
RAVLVT Delayed		
Women	1.55	1.15
Men	.64	1.44

Note. $p < .001$

Examining the results of the full model, the stress score was not a significant predictor of the estimated decline scores for either of the RAVLT tasks (Table 12). When looking at the estimated decline scores for the RAVLT Immediate Recall task, model trimming revealed that the model of best fit was acquired by removing both the stress variable and the cognitive reserve variable ($F(1, 339) = 50.08$, $p < .001$, $R^2 = .13$, $R^2_{Adjusted} = .13$). In other words, a sex alone was demonstrated to have a significant effect on the decline scores in the RAVLT Immediate Recall task ($\beta = .36$, $t(342) = 7.06$, $p < .001$; Table 12). However, the results were not congruent with the hypothesis. Similar results were seen between males (M=.48; SD=1.40) and females (M=-.41; SD=1.21) in the estimated decline scores on the RAVLT Delayed Recall subtest (Table 11). The model of best fit for the RAVLT Delayed Recall estimated decline scores ($F(2, 336) = 18.24$, $p < .001$, $R^2 = .10$, $R^2_{Adjusted} = .09$) included only sex ($\beta = .31$, $t(342) = 6.04$, $p < .001$) as a significant predictor.

Table 11. Means and Standard Deviations of Estimated Decline in RAVLT Z-Scores as Predicted by Sex.

	M	SD
RAVLT Immediate		
Women	-.83	1.25
Men	.20	1.19
RAVLT Delayed		
Women	-.41	1.21
Men	.48	1.40

Note. p <.001

The model of best fit for the RAVLT Immediate Recall performance scores ($F(2, 337) = 31.65$, $p < .001$, $R^2 = .14$, $R^2_{Adjusted} = .14$) included both sex ($\beta = -.39$, $t(342) = -7.16$, $p < .001$) and cognitive reserve ($\beta = .14$, $t(342) = 2.86$, $p = .005$) with leisure activities being the most highly correlated. The model of best fit for the RAVLT Delayed Recall Z-scores ($F(2, 336) = 23.56$, $p < .001$, $R^2 = .12$, $R^2_{Adjusted} = .11$) only sex as a significant predictor ($\beta = -.32$, $t(342) = -6.19$, $p < .001$).

Table 12. Summary of Significant Results of Predictors for Verbal Memory

	β	t	p	$R^2_{Adjusted}$
Verbal Memory Factor Performance				.14
Sex	-.34	-6.60	< .001	
Cognitive reserve	.146	2.83	.005	
RAVLT Immediate Performance				.14
Sex	-.39	7.16	< .001	
Cognitive reserve	.14	2.86	< .005	
RAVLT Delayed Performance				
Sex	-.32	-6.23	< .001	
Verbal Memory Factor Estimated Decline				.13
Sex	.33	-6.24	< .001	
RAVLT Immediate Estimated Decline				.12
Sex	.36	7.06	<.001	
RAVLT Delayed Estimated Decline				.09
Sex	.31	6.04	< .001	

Visual Memory Domain

Visual Memory Factor

Looking at overall visual memory performance, none of the independent variables had a significant effect on the performance scores or estimated decline scores.

Visual Memory Tasks

Examining the results of the full model, the stress score, sex, and cognitive reserve failed to be significant predictors of the estimated decline scores or performance scores for the RCFT Delayed recall scores. Analyses indicated that the sex variable

trended toward significance for Delayed performance and estimated decline. Males trended to perform better and have less decline than females. However, this significance for these analyses failed to reach the .005 threshold. For the delayed scores, males performed better than females, but p = .01; and males exhibited less estimated decline than females at on the delated task, but only at the p =.007 level.

Executive Functioning Domain

Executive Functioning Factor

When looking at overall executive functioning factor performance, the model of best fit ($F(2, 296) = 9.63$, $p < .001$, $R^2 = .06$, $R^2_{Adjusted} = .06$) demonstrated that the cognitive reserve variable ($\beta = .25$, $t(342) = 4.34$, $p < .001$; Table 13) had significant effects on scores. Looking at the overall executive functioning factor, none of the independent variables were significant predictors of the estimated decline score.

Executive Functioning Tasks

In comparing the on the absolute scores for FAS, neither stress nor sex were significant predictors. The model of best fit for the FAS performance scores ($F(1, 337) = 16.31$, $p < .001$, $R^2 = .05$, $R^2_{Adjusted} = .04$; Table 13) demonstrated that cognitive reserve ($\beta = .21$, $t(342) = 4.03$, $p < .001$) had the most significant influence.

In comparing the absolute scores on the WAIS-III Digit Span tasks, neither stress nor sex were significant predictors Digit Span performance scores. The model of best fit for the Digit Span performance scores ($F(1, 331) = 14.50$, $p < .001$, $R^2 = .04$, $R^2_{Adjusted} = .04$) demonstrated that cognitive reserve ($\beta = .21$, $t(342) = 3.81$, $p < .001$) had the most

significant influence (Table 13). Correlation analyses showed that the variable of intellectual leisure activities demonstrated the highest correlation.

With regards to Trails B, neither the stress score nor sex was a significant predictor of the actual performance scores (Table 13). The model of best fit for the Trails B performance scores ($F(3, 299) = 3.59$, $p < .001$, $R^2 = .03$, $R^2_{Adjusted} = .03$) demonstrated that the cognitive reserve variable ($\beta = .18$, $t(342) = 3.21$, $p = .001$) had the most significant influence (Table 13) with intellectual leisure activities demonstrating the highest correlation. The model of best fit for the FAS performance scores ($F(2, 326) = 8.29$, $p < .001$, $R^2 = .05$, $R^2_{Adjusted} = .04$) demonstrated that the cognitive reserve variable ($\beta = .21$, $t(342) = 4.03$, $p < .001$) had the most significant influence (Table 13) with intellectual leisure activities demonstrating the highest correlation.

Examining the results of the full model, none of the independent variables were shown to be significant predictors of the estimated decline scores for Digit Span, Trails B nor FAS (Table 13). These results were congruent with the hypothesis.

Table 13. Summary of Significant Results of Predictors for Executive Tasks.

	β	t	p	$R^2_{Adjusted}$
Executive Functioning Factor Performance				.06
Cognitive reserve	.25	4.34	< .001	
Digit Span Performance				.04
Cognitive reserve	.21	3.81	< .001	
Trails B Performance				.03
Cognitive reserve	.18	3.21	.001	
FAS Performance				.04
Cognitive reserve	.21	4.03	< .001	
Executive Functioning Factor Estimated Decline				
No significant predictors				
Digit Span Estimated Decline				
No significant predictors				
Trails B Estimated Decline				
No significant predictors				
FAS Estimated Decline				
No significant predictors				

Visuospatial Perception Domain

Visuospatial Perception Factor

Looking at the overall perception factor, none of the independent variables were significant predictors of the actual performance score. The model of best fit for the perception factor estimated decline score ($F(2, 330) = 9.83$, $p < .001$, $R^2 = .06$, $R^2_{Adjusted} = .05$; Table 14) demonstrated that the cognitive reserve variable was a significant predictor

($\beta = .24$, $t(332) = 4.40$, $p < .001$) (Table 14) with intellectual leisure activities demonstrating the highest correlation.

Visuospatial Perception Tasks

Examining the results of the full model, none of the independent variables were shown to be significant predictors of the actual performance scores for VOSP Letters or VOSP Numbers. These results were congruent with the hypothesis.

With regards to the VOSP Letters and Numbers subtests, neither the stress score nor sex was a significant predictor of the estimated difference scores (Table 14). Subsequent model trimming revealed that the model was actually improved by removing both the Stress variable and the sex variable. The model of best fit for the VOSP letters estimated decline scores ($F(1, 335) = 14.21$, $p < .001$, $R^2 = .08$, $R^2_{Adjusted} = .08$) demonstrated that the cognitive reserve variable ($\beta = .28$, $t(336) = 5.31$, $p < .001$) had the most significant influence (Table 14) with intellectual leisure activities demonstratinf the highest correlation. The model of best fit for the VOSP numbers estimated decline scores ($F(3, 335) = 21.48$, $p < .001$, $R^2 = .06$, $R^2_{Adjusted} = .06$) demonstrated that cognitive reserve variable ($\beta = .25$, $t(335) = 4.63$, $p < .001$), had the most significant influence (Table 14) with intellectual leisure activities demonstrating the highest correlation.

Table 14. Summary of Significant Results of Predictors for Visuospatial Perception Tasks.

	β	t	p	$R^2_{Adjusted}$
Visuospatial Perception Factor Performance				
No significant predictors				
VOSP Letters Performance				
No significant predictors				
VOSP Numbers Performance				
No significant predictors				
Visuospatial Perception Factor Estimated Decline				.05
Cognitive reserve	.24	4.40	< .001	
VOSP Letters Estimated Decline				.08
Cognitive reserve	.28	5.31	< .001	
VOSP Numbers Estimated Decline				.06
Cognitive reserve	.25	4.63	< .001	

Summary

The results of this analysis found that stress did not have a significant effect on any of the cognitive performance or decline scores. Sex was a significant predictor of performance and decline in verbal memory. None of the independent variables (sex, stress, nor cognitive reserve) were predictive of performance or decline for visual tasks. However, there was a trend towards significance predicted by sex where men tended to perform slightly better than women and showed less decline in the visual domain. Cognitive reserve significantly predicted differences in scores within the verbal, executive functioning, and perception domains. None of the interaction effects (sex*cognitive reserve, sex*stress, nor cognitive reserve*stress) had any significant effects on any of the domains or on the individual tasks.

CHAPTER FIVE

DISCUSSION

Stress Variable

One of the most glaring results is the fact that the analysis demonstrated that stress as measured by the SRRS did not have any significant effects on performance or the estimated change in performance on any of the tasks. Does this mean that cumulative stressors don't have an effect on the change in cognition? There are other conclusions that may be more congruent with the results of previous research on stress and cognition.

There have been some criticisms of the SRRS regarding the fact that it captures only large life events. While these events may be significant, one notable critique is that although cataloguing and tabulating major life events may be one way to assess stress, it omits information about events that transpire in day-to-day life (Kanner, Coyne, Schaefer & Lazarus, 1980). Several researchers have proposed that it is necessary to account for these everyday events in order to capture the accumulated effects of stress on individuals (Coyne et al., 1979; Coyne, 1979; Delongis et al., 1982; Lazarus, 1980; Lazarus, 1984; Lazarus et al., 1985; Lazarus and Cohen, 1977; Lazarus et al., 1980; Luborsky et al., 1973; Stahl et al., 1975). It has been suggested that these "microstressors" have a cumulative effect that is often easily taken for granted (McLean, 1976). Furthermore, because some of these minor stressors (e.g., arguments, job strain) might occur with greater frequency, they may have a cumulative effect that is greater overall than life events that may occur significantly less often (Brantley, Waggoner, Jones, and Rappaport, 1987). In analyses of a scale developed by Kanner et al. that catalogued these minor stresses, they concluded that their scale accounted for more variance in the

prediction of psychological symptoms than did a measurement the only included major life stressors. However, using both scales in combination, they were able to account for more variance than either of the scales did alone. Therefore, to comprehensively assess the effect of stress, it may be necessary to investigate both major and minor stresses (Brantley, et al, 1987; DeLongis et al., 1982; Kanner et al., 1981). One of the limitations for some of the measures that have been designed to itemize and tabulate the cumulative effect of daily stressors is that they are intended to be administered on a monthly or even weekly basis so as to capture the subjects' daily experiences (Brown, 1981; Brantly et al, 1987; Cleary, 1980; Kanner et al., 1981). Participation in such frequent assessment could be difficult to maintain for some research subjects.

Another factor for consideration is the possible existence of additional moderating variables in the stress-disorder mechanism. Although the initial hypothesis of this research did take into account cognitive reserve as a possible moderator, there are other potential sources that may have an effect. In their research, Kanner, et al. (1980) argue that a full stress assessment also ought to take into consideration positive events that may ameliorate stress effects. They concluded that it was helpful to not only account for everyday negative events, what they called "hassles", but to also have subjects endorse various coping experiences, what they term "uplifts". These attenuating experiences are not to be confused with eustressful events. As opposed to an experience that may be "happy", but that itself may be a source of stress (such as a wedding), these "uplifts" are themselves behaviors that are seen as restorative and non-stress inducing (such as getting sleep). They argued that uplifts may include distractions from stressful events, things that prolong a coping activity, and facilitators of relaxation that help "restore" taxed mental

resources when an individual is dealing with stress. Other moderators that have been suggested include idiosyncratic variables such as personality and environmental factors like social support (Cleary, 1980; Dohrenwend and Dohrenwend, 1978; Lazarus, 1984; Pearlin, 1982; Perkins, 1982; Rabkin and Struening, 1976). It should be noted here, that a measure of social support had been administered to subjects in the present study. The scores from this measure were included in post hoc analyses and no significant effects were found. However, because the moderation effect of social support was not included in the a priori hypothesis, it was not mentioned in the aforementioned results.

Other suggestions for future studies include adjustment of LCU scores. Although the SRRS was developed with a large sample and subsequent weights were assigned to various life events, perhaps the normative "weight" for those stressors require adjustment for age. For example, although a 20-year-old, 30-year-old, and 75-year-old may each have experienced "changing residences" in the past year, does the experience of each of those individuals carry the same valence? In the SRRS, it is recorded as the same LCU for all of them, but it is not a stretch to say that moving from your college dorm room does not trigger the same amount of stress as downsizing from your family home in which you have spent the past 50 years of your life. Along that same vein, some researchers have noted stratifications with regards to the stresses that most significantly impact groups in various demographics. In their 1980 study, Kanner, et al compared the most frequent hassles endorsed by three groups: a college-aged group, a middle-aged group, and a group of older health professionals. They noted different patterns of experiences that were most frequent for each group. For example, financial issues were prominent within the middle aged group, academic concerns were most prevalent for the

college aged group, and work/life balance issues were most frequent amongst the health professional group. Likewise, coping and restorative experiences were found in different frequency between groups, entertainment, music, and friends were sources of uplift for the college aged group while family togetherness was frequently endorsed as an "uplift" within the older groups. Although an elderly sample was not specifically included in the Kanner, et al study, it would be consistent with theory that older adults would likely demonstrate certain frequencies of stress and coping events that are unique to their demographic. Indeed, in analyzing item endorsement in this study, the most frequently endorsed item was taking part in a major holiday, followed by having a foreclosure on a loan or home, and marital reconciliation coming in third. Although participation in holidays is fairly universal, the other top items would likely not be the items most frequently endorsed by groups of adults in young adulthood. A 1998 study by Hobson, et al. assessed relationships between subjects' ages and life event ratings. They analyzed responses between the following four groups: 18-31 year olds, 32-50 year olds, 51-64 year olds, and those over 65 years old. Analysis revealed statistically significant mean differences as a function of age 80% of the life events. Considerations for cohort differences have led to the creation of versions of the SRRS that have been modified specifically for preschoolers, elementary school students, junior high school students, senior high school students, and college aged adults. (Bieliausras and Webb, 1974; Coddington, 1972; Rabkin and Struening, 1976). Yet, there does not appear to have been a modified version created specifically for the elderly population.

Sex Differences

Of those analyzed, **t**he variable that seemed to be the strongest predictor of differences in scores was sex. However, these differences were not always in the direction predicted by the a priori hypotheses. The hypothesis that females would perform worse in various hippocampal dependent tasks was largely connected to the belief that sex would mediate the effects of stress resultant from increased HPA axis activity seen in postmenopausal women. However, this analysis found no direct or indirect effects of stress to moderate! Instead, there was evidence of direct effects of sex; these results followed a pattern seen in other studies of sex differences in performance across cognitive domains.

In 1974, researchers Maccoby and Jacklin concluded that sex differences had a significant effect on various cognitive domains including verbal abilities. A meta-analysis of 165 studies analyzed data on sex differences in verbal ability (Hyde & Linn, 1988). This analysis found that on average, women performed better on tasks of verbal memory; analyses demonstrated a mean effect size of +0.11. Studies completed since then have corroborated this significant sex difference in performance on verbal memory tasks (Berenbaum, Baxter, Seidenberg, & Hermann, 1997; Bolla, Wilson & Bleecker, 1986; Geffen, Moar, O'Hanlon, Clark, & Geffen, 1990; Herlitz, Airaksinen & Nordström, 1999; Herlitz, Nilsson & Bäckman, 1997; Herlitz & Rehnman, 2008; Hill et al., 1995; Hultsch, Masson, & Small, 1991; Kramer, Delis, & Daniel, 1988; Kramer, Delis, Kaplan, O'Donnell, & Prifitera, 1997; Larrabee & Crook, 1993; Lewin, et al, 2001; Rabbitt, Donlan, Watson, Mclnnes, & Bent, 1995; Ruff, Light, & Quayhagen, 1988; Schaie & Willis, 1993; West, Crook, & Barren, 1992; Wiederholt et al., 1993; Zelinski, Gilewski,

& Schaie, 1993). The present study revealed results that were congruent with this large body of work, by demonstrating that women's performance scores were, on average, higher than men's scores on tests of verbal memory. However, the present study revealed additional information in that this analysis showed that the women's scores of estimated decline in this domain were lesser than men. In other words, women not only performed better, but the estimated decline scores suggest that their superior abilities in this domain were better preserved as compared to men.

Many of the aforementioned studies used subject samples whose mean age was younger than this mean age for this study. And yet the trends remained comparable. The findings of the present study are in line with cross sectional and longitudinal studies (Bleecker, Bolla-Wilson, Agnew & Meyers, 1988; Finkel, Reynolds, McArdle, Gatz, & Pedersen, 2003; Schaie, 2005) that suggest that sex differences are preserved over time and postmenopausal women may indeed retain the same advantage over men in areas of verbal ability as do their younger counterparts. Contrary to the hypothesis of the current study and other works that have concluded that elderly women are particularly vulnerable to memory decline (Zelinski & Stewart, 1998). However, these results should be interpreted with caution since it is not clear which women did or did not have hormone replacement therapy.

These findings do not necessarily preclude any expected post-menopausal effects on the hippocampus: a 1997 study by Berenbaum, Baxter, Seidenberg & Hermann assessed 57 subjects who underwent left anterior temporal lobectomies. On a test of verbal memory, they found that while both sexes declined in performance post-operatively, both pre and post-operative scores demonstrated that the women performed

better than the men despite the extent of hippocampal damage. They hypothesized that this was due in large part to the women's employment of better encoding strategies—such as semantic clustering--which remained unaffected by hippocampal damage. Their conclusions suggested that while verbal memory itself may be a hippocampal facilitated task, the observed sex differences on performance in tasks of verbal memory may not be due to the hippocampus itself. As it relates to the present study, it is possible that even if further research reveals that stress does effect the cognition through hippocampal damage, femaleness may still be enough of a protective factor to attenuate some potential effects on verbal memory performance.

On the other hand, no sex differences were observed with regards to tasks of visual memory. Although the results did trend toward significance. When the post-hoc Bonferroni correction was applied however, the threshold of significance was not met. Although there was not a significant difference, this analysis demonstrated that men performed better on average and that they also evidenced lower scores of estimated decline. One explanation is, as with verbal memory, the results of this analysis are simply further evidence of slight sex differences that are apparent at all ages. In addition to proposing sex differences in verbal memory, the previously alluded to 1974 study by Maccoby and Jacklin also concluded that there were differences in visual ability between sexes: this time, they concluded that men had the advantage in performance. Subsequent studies have also demonstrated males' slight superior performance on tasks of visual episodic memory as compared to females (Lewin, et al., 2001; Lowe, Mayfield, Reynolds, 2002).

Cognitive Reserve

Cognitive reserve was shown to be a positive predictor for improved performance in verbal memory tasks and executive functioning tasks. These results are consistent with prior research on cognitive reserve and cognition in the elderly (Douglas, 1964; Evans et al., 1993; Geerlings, Schmand, Jonker, Lindeboom, & Boulter, 1999; Richards & Sacker, 2003; Rutter, 1985; Schumacher & Martin, 2009, Stern et al., 1994; White et al., 1994; Wilson et al., 2005).

It was notable, however, that cognitive reserve was correlated to higher estimated decline scores in the domain of perception. Although this seems paradoxical, these result are in line with other studies regarding cognitive reserve that associate higher levels of cognitive reserve with measurements of somewhat faster cognitive decline in some domains (Alley, Suthers & Crimmins, 2007; Andel, Vigen, Mack, Clark & Gatz, 2006). The studies that discovered this negative correlation found these significant results on tasks of memory. None of the cited studies that found cognitive reserve was negatively associated with performance made mention of exploring the association between cognitive reserve and visuospatial perception. In this point, the current study appears to be somewhat unique in its finding.

Those studies that have found this negative association between cognitive reserve and declarative memory or working memory have explained this primarily by citing the fact that a paradoxical relationship has sometimes been found in Alzheimer's disease patients. Some studies that have found this paradoxical relationship in healthy populations, the researchers have conjectured that the results were possibly confounded by participants who were in the prodromal stages of the disease (Andel et al., 2006; Van

Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008). However, this does not seem to be a likely explanation for why a negative association between cognitive reserve and visuospatial perception was found by the current study. If it were true that these results were due to prodromal symptomatology of cognitive impairment or dementia, it would stand to reason that these effects would be notable in other domains of cognition as well. As it stands, in the results of the current study, the domains of verbal memory and executive functioning were improved with cognitive reserve.

The findings of this study with regards to cognitive reserve may be resultant from the fact that the scores for the visual spatial task also had a low ceiling. That is, a large portion of the sample got the maximum score for the task. Cognitive reserve correlated positively with better performance and less decline on other tasks. The low ceiling in this task may have made individuals who are high functioning appear to do worse because on the perception tasks their performance was simply "average". Those who had a high (above average) premorbid score may have appeared to "fall" more as compared to those who performed average (or below average). Conversely, those who performed in a below average range on other tests performed well on the perception tasks and may have appeared to actually "improve" because the task was so easy. Therefore, they wound up appearing to do better as compared to other subjects. Clearly, this represents an area for further study using a measure of visuospatial perception that has a potential (and likelihood) for a greater range of scores.

CHAPTER SIX

FUTURE DIRECTIONS

The vast amount of literature linking stress and cognition suggests that it is highly probable that there does exist an association between cumulative life stressors and decline in cognitive domains. Continuing to explore this path in research would prove fruitful. There are some alterations in future research design that could be made in service of this direction. For reasons put forth in the discussion, alternative instruments besides the SRRS may be more sensitive in capturing the cumulative amount of relevant stressors. As also noted, several of the instruments that might be able to more comprehensively serve this purpose are designed to be given on a very frequent basis (monthly and even weekly). In the current study individuals were asked to fill out the questionnaire on site. Asking subjects to return on such a frequent basis may present a barrier to participation and may result in attrition. However, there are several technological options that may be used to provide a convenient way for participants to catalogue their frequent microstressors. Having participants log in electronically by computer or by phone may allow then to continually update this information over the course of a longitudinal study. Electronic responses could be programmed to be tabulated automatically; and, direct entry by participants would have the added benefit of reducing potential errors by data entry personnel.

It is important that regardless of method, the instrument used should be one that takes into account, not only hassles, but also "uplifts" that may attenuate the impact of negative stresses. Such a methodology should keep in mind the importance of factoring in the way in which each individual responds to change. The development and use of an

instrument that is not only able to itemize a stressor, but also able to quantify and control for the individual's reaction to said stressor would help to provide more accuracy in calculating the effect of stress. In doing so, researchers may begin to synthesize a more complete picture in the actual role of stress in subjects' lives.

Any future study should also be designed so as to have a pre- and post-measurement of intelligence. One limitation of the current study is that participants were given the AMNART as an instrument to derive pre-morbid intelligence. While the usage of a pre-morbid intelligence instrument is a common practice and has high validity, it still only provides an estimate. The AMNART establishes premorbid intelligence through a verbal test. When used to create the difference scores, this premorbid level was now being used as the estimated measure of intelligence across all domains. Yet, it is likely that individuals might have varying degrees of strengths and weaknesses in difference domains. If in future studies, participants were given various cognitive tests to establish their baseline performances, any subsequent measurements at the end of the study would be a direct comparison in performance. Of course, this would necessitate that the time frame for the study be long enough as to mitigate against any practice effects.

Another limitation to using the AMNART was that one of the determinants of the premorbid intelligence score is the subject's level of education. So it was concerning that the cognitive reserve variable of education would show high correlations with the estimated decline scores. Therefore, it was necessary to control for education. Interestingly enough, though, in the correlation analysis, it was discovered that intellectual leisure was the most highly correlated component of cognitive reserve when cognitive reserve was considered to be a significant predictor. Nevertheless, future

studies should either avoid using an estimate of premorbid intelligence and directly test pre- and post-performance (which would be the preferred method) and/or select a test of premorbid intelligence that avoids this confound.

Seeing the strong effects of sex on several of the domains, it would be helpful to have a way to tease apart the effects of estrogens. In the current research, although the age of subjects places all of the female participants in the post-menopausal category, women in our sample were not queried about their use of HRT. Because of previous research that has shown linkages to estrogen and cognition, this could be an important element to control for. A study with post-menopausal women using subjects that are on HRT, not using HRT, and those with a phytoestrogen rich diet, may help clarify the role of estrogen in elderly cognition.

Specifically as it relates to the population of interest, it would also be beneficial to derive an instrument that is especially tailored to the elderly population. As noted, various scales for different age groups have been developed previously—with good reason. Having an instrument available which contains items that were specifically designed to be germane to the life stage of the participants would be an important consideration of any future research. The creation of a measurement that is focused on the particular stresses of an aging population can prove useful in determining the effects of stress in both the physiological and psychological research.

Another interesting avenue to pursue would be the further examination of the positive effects of cognitive reserve. Engaging in intellectual leisure activities has been shown to have positive effects on cognition. Is there any difference depending on when these pursuits were first taken up? In other words, would someone who completed began

these pursuits at a later age derive the same benefit as someone who engaged in the same activities, but began at an earlier time in life? Also, with regards to intellectual leisure, designing a study that helps explore which potential activities have the greatest influence can help distinguish if some activities are better at increasing cognition than others.

Additionally, given the novel results regarding the associations between cognitive reserve and visuospatial perception that were found, this line of research represents an area of potential future study. A future direction might involve not only determining if these findings are replicable with regards to visuospatial perception, but also seeing if this result is present in other areas of perception as well. Additionally, it would be important that any measure in future studies have a larger potential range for scores so the effects could be analyzed more clearly.

The WAHA study provides a unique opportunity to determine if these results are replicable and generalizable to various populations. There is a simultaneous collection of data that occurred using a cohort in Barcelona. Taking this data and comparing it to the information gathered in the Spanish cohort may demonstrate whether or not these findings are unique to this population or not.

CHAPTER SEVEN

CONCLUSIONS

Although this study was not able to reveal significant effect of stress on cognitive change in elderly adults, information about sex effects and cognitive reserve were shown. This does not prove that these effects are non-existent, but rather, provide an opportunity for future research in this area.

With regards to the effects of sex on cognition, this study is consistent with the body of research that demonstrates small but significant sex differences in domains. This study has also added to the research by demonstrating that for those areas where sex predicts poorer performance, it also predicts greater decline in the same domain.

Of the independent variables, cognitive reserve is the one that is the most controllable by the individual. Increased participation in intellectual leisure activities was shown to be predictive of higher cognitive performance in verbal memory and executive functioning. In applying these findings clinically, participation in various intellectual pursuits should be encouraged to not only improve performance in various area, but also to stave off decline.

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APPENDIX A

SOCIAL READJUSTMENT RATINGS SCALE

Social Readjustment Rating Scale

INSTRUCTIONS: Mark down each of these life events that has happened to you during the previous year.

Life Event	Mean Value
1. Death of spouse	100
2. Divorce	73
3. Marital Separation from mate	65
4. Detention in jail or other institution	63
5. Death of a close family member	63
6. Major personal injury or illness	53
7. Marriage	50
8. Being fired at work	47
9. Marital reconciliation with mate	45
10. Retirement from work	45
11. Major change in the health or behavior of a family member	44
12. Pregnancy	40
13. Sexual Difficulties	39
14. Gaining a new family member (i.e.. birth, adoption, older adult moving in, etc)	39
15. Major business readjustment	39
16. Major change in financial state (i.e.. a lot worse or better off than usual)	38
17. Death of a close friend	37
18. Changing to a different line of work	36
19. Major change in the number of arguments w/spouse (i.e.. either a lot more or a lot less than usual regarding child rearing, personal habits, etc.)	35
20. Taking on a mortgage (for home, business, etc..)	31
21. Foreclosure on a mortgage or loan	30
22. Major change in responsibilities at work (i.e. promotion, demotion, etc.)	29
23. Son or daughter leaving home (marriage, attending college, joined mil.)	29
24. In-law troubles	29
25. Outstanding personal achievement	28
26. Spouse beginning or ceasing work outside the home	26
27. Beginning or ceasing formal schooling	26
28. Major change in living condition (new home, remodeling, deterioration of neighborhood or home etc.)	25
29. Revision of personal habits (dress manners, associations, quitting smoking)	24
30. Troubles with the boss	23
31. Major changes in working hours or conditions	20
32. Changes in residence	20

APPENDIX B

QUESTIONNAIRE OF VARIABLES RELATED TO COGNITIVE RESERVE

Questionnaire of Variables Related to Cognitive Reserve

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EDUCATION/CULTURE

-Total years of formal education:
0. No education / 1. Elementary (until 11 years) / 2. Junior high/High school (11-18) / 3. College or higher (>18)

- Have you ever been told that you had a lot of or a little difficulty learning how to read or write?
0. A lot of difficulty / 1. Normal / 2. Little difficulty

- Are you currently going to school or university? State the type of degree/concentration.
0. No / 1. Yes

- Do your parents have an education? Was there a scholarly environment in your home growing up (literary, artistic, musical hobbies)?
0. No / 1. At least one has a high school education / 2. At least one has higher education

- Have you learned another language other than [English]?
0. None / 1. Some knowledge / 2. Fluent in another language / 3. Fluent in 2 or more foreign languages

PROFESSIONAL ACTIVITIES

- When you were working, what was your profession(s)? List them.
0. No certification / 1. Certified / 2. No Certification, secretary or technician (requires a license, no superior education) / 3. Professional (requires superior education) / 4. Manager

INTELLECTUAL LEISURE ACTIVITIES

- During childhood did you read often? If yes, estimate the number of hours weekly.
0. Not often or sporadically / 1. Often (>3h/wk)

- Do you read now? If yes, estimate the number of hours weekly:
0. Not often or sporadically / 1. Often (>3h/wk)

- Did you learn how to play a musical instrument? If yes, which one(s)?

- Did you learn music in a conservatory or academy or did you teach yourself how to play or with friends?
0. No / 1. Learned how to play an instrument and still know how to play

- Do you wish to share any other activity that you consider 'cognitive' or intellectual that you developed throughout your life? (eg. writing, painting, etc..)

PHYSICAL ACTIVITY

- During your childhood or teens did you play any sports? If yes, estimate how many hours weekly.
1. Yes / 0. No

- Do you currently participate in any sports (including walking often)? If yes, estimate how many hours weekly.
1. Yes / 0. No

SOCIAL ACTIVITES

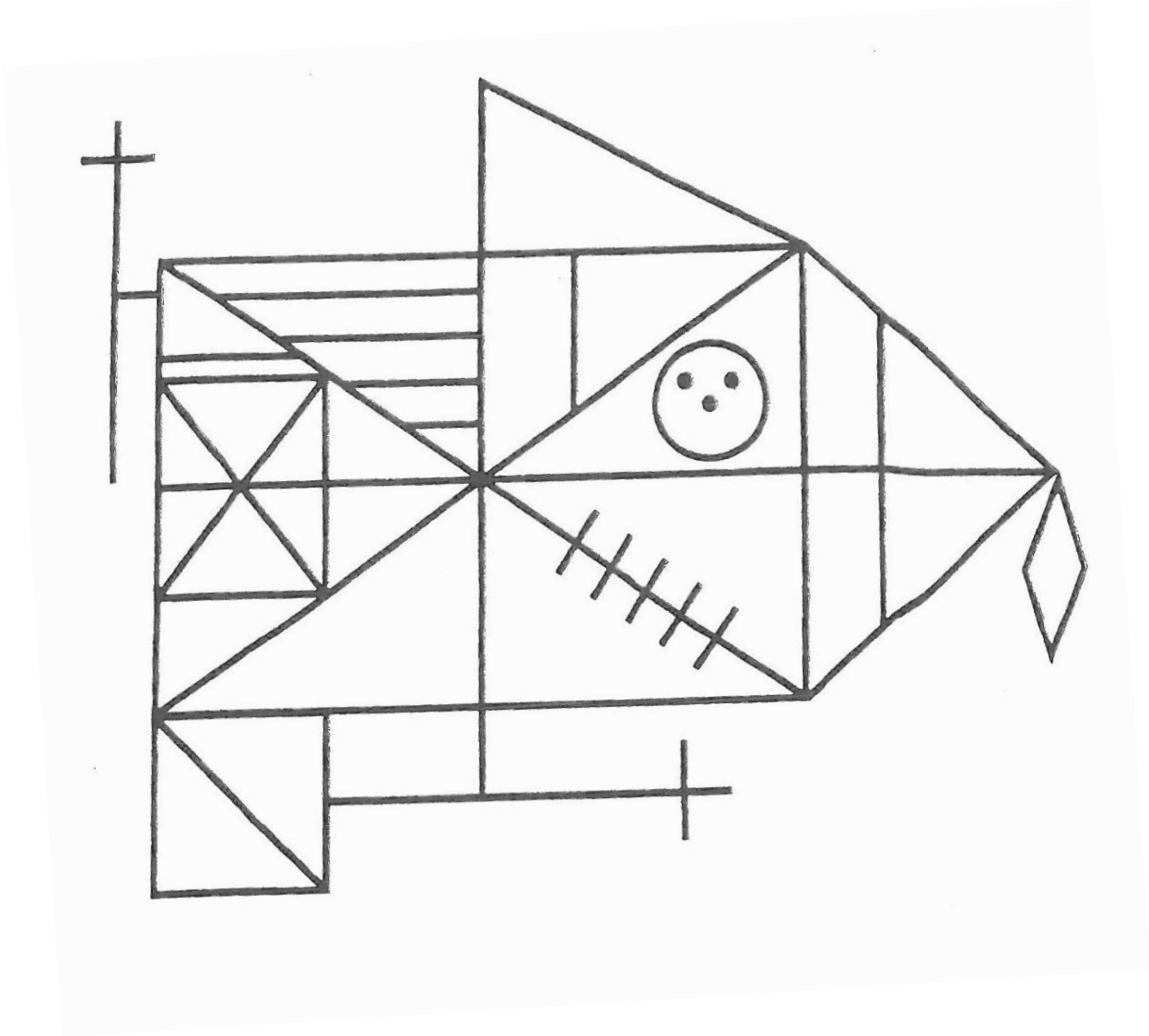
- Throughout your life, would you say that you have had a lot of friends?
0. Few / 1. Normal / 2. Lots

- How would you define your degree of involvement in social activities (includes going out with friends, participating in societies, volunteer work, etc.) that you have had throughout your life?
0. Low / 1. Normal / 2. High

- Currently, what is your degree of involvement in social activities?
0. Low / 1. Normal / 2. High

APPENDIX C

REY OSTERRIETH COMPLEX FIGURE TEST

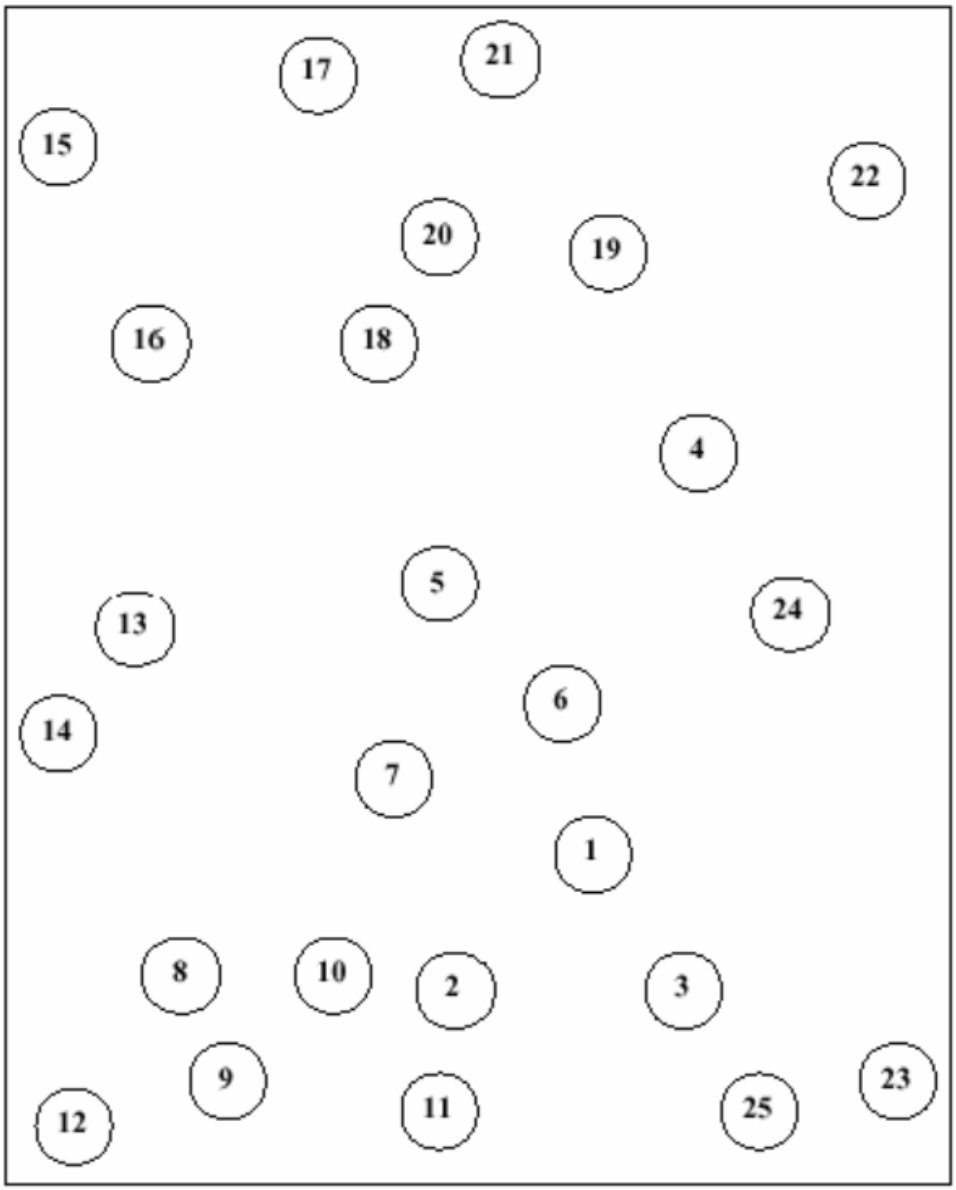


APPENDIX D

TRAIL MAKING TEST

Trail Making Test Part A

Patient's Name: _____ Date: _____



Trail Making Test Part B

Patient's Name: _____ Date: _____