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The Effect of Acute Pain on Executive Function

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THE EFFECT OF ACUTE PAIN ON EXECUTIVE FUNCTION

by

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(Under the Direction of Nicholas Murray)

ABSTRACT

Background: Executive functions are high-level cognitive processes that allow a person to successfully engage in an independent and self-fulfilling life. Previous literature indicates that acute pain can affect executive function, which may be due to a limited amount of shared neural resources of the brain.

Objective: The purpose of this study was to determine if acute pain affects executive function in recreationally active individuals who sustain a musculoskeletal injury.

Methodology: Twenty-four participants who presented with acute pain due to a musculoskeletal injury underwent a neuropsychological battery within 72 hours of injury and within two weeks from the initial testing session. Pain intensity was measured using the Visual Analog Scale (VAS). The neuropsychological battery consisted of the following tests: Digit Span (DS), Rey Auditory Verbal Learning Test (RAVLT), and Trail Making Test B (TMT-B). The DS was broken into two separate scores, the RAVLT 4 scores, and TMT-B one score. Seven paired samples t-tests were conducted using an adjusted alpha level of .007.

Significance: Participants had significantly improved scores when pain free in DS forwards ($T(1,23)=-3.943$; $p<0.001$) and TMT-B ($T(1,21)=4.488$; $p<0.001$). No significant difference was observed for the DS backward ($p=0.023$), RAVLT A1 ($p=.563$), RAVLT sum A1 to A5 ($p=0.953$), RAVLT A6 ($p=1.0$), RAVLT recognition list A ($p=0.009$).

Outcomes: Improved neuropsychological scores were seen in immediate recall (DS forward) and set switching (TMT-B) when participants were pain free. No significance was found between conditions for working memory and auditory verbal learning.

INDEX WORDS: Musculoskeletal, Pain, Cognition, Executive Function, Neuropsychology

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DEDICATION

To Lynn Van Ost and Karen “Doc” Manfre, who have taught me to never shortchange the journey and who have changed my entire life path. You’ve picked me up from the basketball court when I could barely stand, and helped me recover to the person I am today. I strive to be the athletic trainers you are and to have a profound impact on someone else’s life like you have had on mine. I know I can never repay you for what you have done for me.

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CHAPTER 1

INTRODUCTION

Pain serves as one of the most basic mechanisms for survival.[3] Although pain plays a valuable role in the body, such as a protective mechanism or a promoter of rest, it can be very difficult to treat. Pain may decrease the quality of life of those who suffer from it, which is a major public health concern.[3,4] A prominent example is the epidemic of back pain, migraines, and overall chronic pain in the general population.[5,6] In 2006 the American Pain Foundation estimated that in the United States alone approximately 25 million people were suffering from acute pain, and 50 million people were suffering from chronic pain.[7] The American Pain Foundation anticipated that number would double by 2030.[7] More recently the Institute of Medicine (IOM) stated 116 million adults in the United States suffer from chronic pain, which is a greater number than those who suffer from heart disease, cancer, and diabetes combined. [8] As of 2012, the total estimated annual cost in the United States due to pain ranges from $560 billion to $635 billion, straining the nation's already burdened healthcare system and economy.[7] It is also worth noting that in the past 20 years there has been an extreme increase in therapeutic opioid consumption and abuse, with the United States having the highest consumption of narcotics worldwide.[9]

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with the actual or potential tissue damage."[4] Since pain is considered an unpleasant experience, it includes an emotional component as well.[10] Thus, a patient's beliefs can strongly affect their personal interpretation of pain.[11] Previous literature suggests that even an episode of acute pain can trigger a cascade of long term neural remodeling

and psychological distress, which indicates that although pain is typically classified into either acute or chronic, there are many associations between them.[11]

Even though the experience of pain is not fully understood, it has been noted in the literature to affect executive function and cognition.[12,13] Executive function is the capacity to plan purposeful and flexible behavior. [14] It is what allows someone to modify his or her thoughts and behaviors to respond to a similar situation in a different way. If these functions are impaired, an individual may lack self-control, have a hard time focusing, planning, and may feel irritable.[5] Because executive functions are considered to be higher order thinking processes, impairments have the potential to decrease the quality of life of those who suffer from such impairments.[15,16]

Since executive functions and cognitive functions work so closely together, if executive function is impaired, that can in turn affect cognitive function. Cognition differs from executive function because it is primarily involved with information processing of behavior. [5] Furthermore, cognition itself is one of three branches of behavior and can be broken into four subcategories: receptive functions, memory and learning, thinking, and expressive functions. Receptive functions integrate sensory information into meaningful memories. [5] Sensory reception (awareness and encoding) and perception (awareness and discrimination) are key parts to this process.[5] Memory and learning refer to storing and retrieving information. [5] Memory can be broken into long-term memory and short-term memory. Long-term memory can be conscious (explicit) or unconscious (implicit).[5] Explicit memory is typically what people are referring to when they complain of "memory" issues. [5] Thinking refers to mental processes that relate pieces of information consciously or unconsciously.[5] Expressive functions make up observable behavior and are things such as writing, speaking, drawing, movements, etc.[5]

Although each subcategory of cognition functions together and shares the same basic framework, each has its own specific purpose within the brain and can be assessed separately.[5] Neuropsychological tests evaluate cognitive functions by assessing the brain through a behavioral outcome.[5] While it is founded among the same principles as psychological testing, neuropsychological testing specifically focuses on brain function. A basic test battery will typically include tests that target the major dimensions of cognition.[5] Broad testing measures may be used to measure complex functions; where as more specific tests may be used to measure the discrete functions of each cognitive subcategory.[5] For example, the Automated Neuropsychological Assessment Metrics (ANAM) is a common test battery that evaluates cognitive domains such as attention, concentration, memory, processing speed, etc. These domains can be measured by a plethora of other tests and are not limited to the use in clinical neuropsychology. Other fields, such as athletic training, use neuropsychological tests to gauge cognitive impairment post injury. These tests are crucial in understanding the patient's overall cognitive state and will aid in the rehabilitation process.

Previous literature indicates that pain can affect cognition in both the chronic and acute pain populations. [5] Although pain estimates vary across studies and are still misunderstood, Casey and colleagues indicated 20% of the population experiences chronic pain, and other studies indicate many chronic conditions and symptoms consequently overlap.[17,18] Conditions such as fibromyalgia, low back pain, lingering headaches, joint/regional pain syndromes, post surgical syndromes, and general musculoskeletal pain present a public health challenge across a wide spectrum of pain.[17] Furthermore, chronic conditions can be very hard to adjust to since the patient must learn to self-regulate his or her symptoms for the rest of his or her life. The ability to self regulate one's thoughts, feelings, and behaviors relies heavily on executive functions, which

may be impaired due to chronic pain conditions.[18] Studies have suggested this is due to shared neural resources in the prefrontal cortex of the brain, which causes processing complications in the central nervous system (CNS).[18,19] Stuad noted abnormal cerebral blood flow in patients with fibromyalgia, suggesting pain processing abnormalities. However, the cause of these abnormalities is still unknown.[19]

Although the relationship between acute pain and cognition is less understood, it has been documented that when pain is present attentional capacity, processing speed, and psychomotor speed may be reduced [5] Keogh and colleagues [20] found that pain can interfere with higher order cognitive processes (executive functions), which supports previous literature that indicates pain can alter attention.[5,20-22] Seminowicz and Davis [22] examined acute pain-cognition interactions and found that activity in cognitive related brain regions increased when pain was present.[16] These authors theorize that the increase could be due to a faster motor response or a higher arousal response. [22] Furthermore, a study in 2011 by Hutchison used the Automated Neuropsychological Assessment Metrics (ANAM) computerized test battery to compare a healthy control group, a concussed group, and an injured musculoskeletal group. The concussed group and the musculoskeletal group demonstrated cognitive deficits compared to the healthy control group. Findings of this study suggested that acute musculoskeletal injuries have the potential to disrupt cognitive function. [12]

One rationale supported in the literature is that pain may affect cognition as a result of shared amount of neural resources in the brain.[22] It is unclear whether or not there is a certain pain intensity or cognitive load needed to observe these effects, and there is controversial evidence as to whether pain perception is reduced when cognitive distractions are present. [22] Many studies investigate the mystery of chronic pain, but few have examined the cognitive

response to acute pain. Furthermore, there are not many studies that examine the recreationally active population, which is a shame since most results based on the athletic population cannot be generalizable to the public. Knowing the cognitive domains that may be impaired during acute pain could impact clinical practice and further benefit patients suffering from pain and its associated symptoms.

The purpose of this study was to determine if acute pain affects cognition in recreationally active individuals who sustain a musculoskeletal injury. It was hypothesized that a difference in neuropsychological testing scores would be present among participants experiencing acute pain from a musculoskeletal injury compared to their testing scores when they were not in acute pain. Furthermore, it was expected that acute pain would lead to a decreased cognitive ability based on neuropsychological testing measures.

CHAPTER 2

LITERATURE REVIEW

Background

Cognition is involved with information processing of behavior in neuropsychology. [5] It is one of three branches of behavior, which can be broken into four classes: receptive functions, memory and learning, thinking, and expressive functions.[5] Although, each subcategory works together and shares the same basic framework, each has its own specific neuroanatomical structure and discrete function. [5] There have been different names for these subcategories, but generally these four classifications are accepted. [5] In regards to testing, broad neuropsychological assessments may be used to measure complex cognitive functions. While, more specific tests may be used to measure the discrete functions of each cognitive subcategory. [5] Although the theory of cognition is a complex process, previous literature indicates that pain can affect cognition.[5]

Pain serves as one of the most basic mechanisms for survival. [3] Although pain plays a valuable role in the body it can be difficult to treat.[3] Some prominent examples are the epidemics of back pain, migraines, and overall chronic pain in the general population.[5,6] The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with the actual or potential tissue damage". [10] Pain can cause a decrease in the quality of life of those who suffer from it. Pain models date back to the 17th century, and pain is undoubtedly a major public health concern.[4]

Epidemiology

Many people will experience pain at some point in their life. Casey and colleagues [17] indicated 20% of the population experiences chronic pain. [17] Many pain phenomena commonly seen today include psychological symptoms and disabling pain that cause restrictions to daily living. [17] Chronic conditions such as low back pain, lingering headaches, joint/regional pain syndromes, post surgical syndromes, and general musculoskeletal pain present as a public health challenge across a wide spectrum of pain. [23]

Pain has been noted to continue in the absence of a trigger or a specified injury. [23] Research suggests that many personal factors contribute to whether or not someone will develop disabling pain in his or her lifetime. [23] Factors such as symptom experience, age, level of education, social support, anxiety, depression, resilience, specific pain, and lifestyle factors may contribute to developing chronic pain when triggers are present. [23] Emotions, attitudes, and perceptions of pain may originate in childhood and set the foundation for future pain experiences which can be a risk factor for experiencing chronic pain. [23]

Pain can affect cognitive networks over time, which may in turn exacerbate the sensory experience of pain. [6] Pain may affect cognition through the shared amount of neural resources in the brain. [22] It is unclear whether or not there is a certain pain intensity or cognitive load needed to see these effects. There is controversial evidence as to whether pain perception is reduced when cognitive distractions are present. [22]

Four Classes of Cognition

Cognition can be broken down into four classes: receptive functions, memory and learning, thinking, and expressive functions. [5] All four of these classes work together and share

the same basic neuroanatomical framework. [5] The difference lies in their specific roles and unique neuroanatomical structure.[5]

Receptive functions integrate sensory information into meaningful memories.[5] Traditionally, research in receptive functions focuses on the five senses: sight, taste, hearing, smelling, and touch. [5] Sensory reception (awareness and encoding) and perception (awareness and discrimination) are key components to this process.[5] Sensory information enters the brain and is usually perceived with a previously learned meaning.[5] Sensations are hardly experienced in isolation and are usually significantly affected by attention.[5]

Memory and learning refer to storing and retrieving information. Memory is essential to all cognitive functions. Memories are the reasons why humans have emotionally independent and meaningful contact with the world. [5] According to the literature, there are many different perspectives on memory and how many systems are at work. [5] Naturally when people think of memory, they think of short-term memory and long-term memory.

Short-term memory temporarily holds information and is closely linked to attention.[5] Immediate memory has a limited retrieval system and can hold about seven pieces of information at once. [5] Working memory has evolved as a subcategory of short-term memory. Working memory is controlled by the executive system.[5] Working memory differs from short-term memory because it tries to actively remember information while performing other distracting tasks. [5]

Foundationally it is accepted that there are two different classifications of long-term memory: conscious (declarative/explicit) memory and nonconscious (nondeclaritive/implicit) memory. [5] Declarative (explicit) memory requires an intentional recollection process and is typically what people are referring to when they complain of "memory" issues. [5] The

effectiveness of declarative (explicit) memory involves recognition and free recall. Free recall is the more taxing of the two tasks because it requires a complex and active search process within the brain. [5] Recall could be tested by asking a question such as "*What is the capital of Georgia?*" where as recognition could be tested by asking the same question but providing multiple answers to select from. Recognizing the correct answer when options are present is a simpler task than relying on the free recall process. [5]

Nondeclaritive (implicit) memory is expressed without awareness and can be broken down into procedural (skill) memory and priming (perceptual) memory.[5] Procedural (skill) memory involves learning how to do a task involving motor and cognitive skills.[5] Priming (perceptual) memory is when there is a cued recall that causes a response.[5] Overall, each memory system has its own neuroanatomical structure and corresponding neurotransmitters.[5]

Thinking refers to mental processes that relate pieces of information consciously or unconsciously. [5] Complex processes such as concept formation, reasoning, judgment, generalizing, and problem solving are involved with thinking. [5] The type of information being used and the manner in which it is being used determines which category of thinking the information will fall under. [5] For example, "verbal reasoning" involves processing words. This could be done in many different ways- analyzing, synthesizing, comparing, etc.[5] What separates thinking from other cognitive functions is that it does not have a specific neuroanatomical network. [5]

Lastly, expressive functions make up observable behaviors. Expressive functions are classified as writing, speaking, drawing, movements, etc.[5] When expressive pathways are disturbed and information cannot be processed, this may result in the patient not being able to express him or herself (apraxia).[5]

Executive Function

Executive functions are high-level processes that allow a person to successfully engage in an independent and self-fulfilling life.[5] The ability to plan and go on a trip, voluntarily switch tasks, react a different way to a familiar event, and to resist temptation are all examples of executive function.[16] Executive functions are not as fully understood in comparison to other brain functions, but it is believed that the frontal lobes and the prefrontal cortex (PFC) play a main role.[1,16] The PFC is thought to control various brain systems since it sends and receives crucial information from all motor and sensory systems.[16] Patterns seen in the PFC are thought to represent behavioral patterns, goals, and ambitions, which can affect processing in the posterior region of the brain.[16] Furthermore, the ventrolateral prefrontal cortex (VLPFC) is believed to be involved in short-term information such as temporarily memorizing a phone number while the dorsolateral prefrontal cortex (DLPFC) is thought to be involved in manipulating information such as dialing a phone number in reverse order or making future plans. [16] Seminowicz and Davis [24] found that the DLFPC was only partially activated with high cognitive loads, implying that less demanding tasks may not rely heavily on this area.[24] In cases of chronic pain, the DLPFC can undergo anatomical changes further affecting cognitive abilities.[24]

Executive functions are concerned with questions such as *when* and *how* will you complete a task, whereas cognitive functioning questions ask *what* will you do or *how much* do you know. [5] If cognition is affected by an injury, but executive functions are not, the person can continue to function independently even with significant cognitive decrements.[5] However, if executive functions are impaired a person's behavior will be greatly affected.[5] Occasionally impairments in executive functions can be obvious. The person can exhibit less self-control, heightened irritability, difficulty shifting attention and behavior, and so on.[5] Other times

impairments may be overlooked or the patient may be mistakenly classified as “lazy” or “spoiled”.[5]

There are many different neuropsychological tests for executive function, all of which require advanced processing of more than one stimulus.[16] Impaired executive function can in turn affect cognition, causing issues in planning abilities, motor performance, and cognitive abilities.[5] Impairments in cognition will typically be seen in certain domains, where as impairments in executive function will show up globally.[5] It is important to note that it can be very difficult to quantify executive function since there are many cognitive, social, and emotional changes that occur in the frontal lobes.[16]

The Gate Theory of Pain & The Neuromatrix

In 1965 Ronald Melzack and Patrick Wall revolutionized pain research by publishing the Gate Theory of Pain.[2] The Gate Theory of Pain proposes that there is a gate in the spinal cord (substantia gelatinosa) that is located in the dorsal horn of the spinal column.[25] The gate transmits sensory information and is controlled by the activity of the large and small afferent (sensory) fibers.[25] Large, myelinated A-beta fibers will close the gate, whereas small thinly myelinated A-delta and non-myelinated C-fibers will open the gate. Opening the gate will activate pathways that lead to experiencing pain and corresponding behaviors (Figure 2).[25]

Building on to this theory, in 2001 Melzak[3] added the concept of the neuromatrix and the neurosignature.[3] He proposed that people have their own specific network of neurons that have pathways to the thalamus, cortex, and limbic system.[3] A person’s neuromatrix is shaped by his or her genetics and later by personal experiences with sensory stimuli (Figure 3).[3] How the neuromatrix interprets the neural information that it is given turns into what is called a

neurosignature.[3] The brain then processes and analyzes this information, further etching a unique neurosignature for that person.[3] The neurosignature will then project neural impulses to other parts of the brain, causing activation of other pathways and eventually causing awareness and a pattern of movement.[3] The neuromatrix can be altered by psychological stress, which could alter the neurosignature and possibly lead to chronic pain.[3] More importantly, the neurosignature can even be triggered without a source of sensory input.[3]

Though many details of the original Gate Theory have now been proven to be inaccurate, Melzack and Wall's ideas transformed pain research forever. Emerging research has moved away from the original thought that pain was a simple cause and effect relationship and has adopted that pain is multifactorial. [3,23] There seems to be a genetic template for neural pathways, which can be triggered and altered by many factors without direct injury.[3] Pain states may influence which portion of the brain is active, indicating there is not just one specific "pain center" in the brain. [3,17] Current literature is still lacking how to accurately determine how pain is perceived.

Pain Processing

Acute pain can be defined as a typical anticipated physiological response to a chemical, thermal or mechanical stimulus that may be linked to surgery, trauma or illness.[11] According to the IASP, since pain is considered an "unpleasant experience," an emotional component is included as well. [10] Therefore, the individual personality and specific beliefs that the patient holds can strongly influence his or her pain experience. [11] Previous literature suggests that even an episode of acute pain can trigger a cascade of long term neural remodeling and psychological

distress, indicating, that although pain is typically classified into either acute or chronic, there are many links between them. [11]

Pain processing involves detection of impulses to the central nervous system (CNS) followed by interpretation of these signals. How pain is interpreted depends on many factors, including genetics, sociocultural influences, expectations, and one's cognitive experience. [17] Although there is an incomplete understanding of the brain in response to pain, research has indicated that there are four primary cortical regions of the brain that are consistently associated with pain. These cortical regions include the prefrontal cortex, the anterior cingulate cortex, the somatosensory cortex, and the insula (see figure 1). [1]

The prefrontal cortex (PFC) is associated with executive functions, which are responsible for complex mental tasks such as making plans and being able to voluntarily switch tasks. [1,16] The PFC is believed to encode acute and chronic pain, in addition to deciding how to interpret it and the best way to cope with it. [1] Research has indicated an inverse relationship between acute pain and prefrontal cortex activation. [1] This leads to the theory that the prefrontal cortex may provide inhibitory function, which in turn may reduce the experience of pain. [1]

The anterior cingulate cortex (ACC) is a part of the limbic system and forms a "collar" around the front portion of the corpus callosum. [1] It is thought to be related to emotional and motivational factors of pain. [1] Evidence shows this area is correlated to the concepts of pain suffering, motivation for pain coping, and behavior. [1] This area may also be responsible for the fear and memory of previous pain experiences.[1]

The somatosensory cortex can be broken down into the primary (S1) and secondary (S2) regions. [1] The S1 cortex is located posterior to the motor cortex, and the S2 cortex is located in the parietal lobe at the base of the S1 cortex.[1] These areas are responsible for encoding spatial

information in regards to injury (nociception).[1] Although the S2 neurons are the first to receive nociceptive input, the S1 neurons are more involved with encoding the severity and quality of the stimulus.[1] Seminowicz and Davis[24] looked at acute pain and cognition interaction and found that both the S2 and the insula are not just involved with pain, but also cognitive networks.[24] Both the right S2 and the posterior/mid insula became activated when pain was present, but when given a cognitive task in the absence of pain, these areas became inactive.[24] Their study concluded that task performance may not be altered by mild pain and that pain may be reduced with a cognitive task.[24]

The insula, similar to the ACC, is also part of the limbic system.[1] It is located near the sensory cortex, deep inside the Sylvian Fissure.[1] The insula is said to be the part of the brain that encodes how a person views his or her physical condition and becomes the most active when there is a threat to the body for survival.[1] In addition, the insula is somatopically organized, meaning that it is organized based on the type of tissue that is stimulated by pain.[26] Using functional magnetic resonance imaging (fMRI), Henderson et al.[26] found that muscle pain activated an area of the insula that was anterior to the area activated by cutaneous pain.[26] This organization may be essential in localizing pain and understanding the stimulus and type of tissue involved.[26]

Cortical responses will vary considerably based on a multitude of factors. Psychologically, patients who try to focus on thinking relaxing thoughts rather than catastrophizing the injury will show less activation in the prefrontal cortex and ACC.[1] Newer research shows that pain pathways within the brain may have condition specific cortical response patterns.[1] For example, in patients with back pain there is activity in the prefrontal cortex, but in

patients with knee osteoarthritis there is activity primarily in the insula.[1] Chronic pain has also been linked to changes in cortical volume and organization.[1]

Pain Assessment

Pain can be assessed using many different scales. [27] The Visual Analog Scale (VAS) and the Numeric Rating scale (NRS) are commonly used in many populations and are frequently cited in the literature. [27,28] The VAS and the NRS are both one-dimensional measures of pain intensity and are in public domain. [27] The VAS requires the patient to mark a line where he or she thinks his or her pain falls on a 0-100mm line. [27] At the 0mm mark, the scale reads "no pain" and at the 100mm mark the scale reads "worst imaginable pain." [27] A higher score represents higher pain intensity. [27] The validity of the VAS cannot be assessed since there is no gold standard for pain, however, it has been noted in the literature to have good test-retest reliability ($r = 0.94$, $P < 0.001$). [27] The VAS has previously been validated when looking at chronic pain, but Bijur and colleagues [29] reported the VAS to be a highly reliable tool for the assessment of acute pain as well. [29]

The NRS is a segmented version of the VAS that is administered verbally. [27] The patient is asked to rate their pain using a whole number on a scale from 0-10, with 0 representing "no pain" and 10 representing "the worst imaginable pain." [27] Like the VAS, a higher score indicates greater pain intensity, and test-retest reliability has been reported to be high. [27] Although these tools are commonly used in the clinical setting, they only provide a brief snap shot of the sensory experience of pain. [27] Other more detailed pain measures exist, such as the McGill Pain Questionnaire. The issue with the McGill Pain Questionnaire and some of the more detailed

assessments is that they are time consuming and contain vocabulary patients may not fully understand. [27]

Neuropsychological Testing

Neuropsychological testing is a way of evaluating the brain through a behavioral outcome. [5] Essentially, it is founded on the same assumptions and ideas as a psychological assessment, but focuses on brain function. [5] Many different neuropsychological tests exist to test cognitive functioning. A basic test battery will typically include tests that target the major dimensions of cognition. [5] These areas include but are not limited to attention, memory and learning, verbal functions, executive functions, and emotional status. [5] Broad testing measures may be used to measure complex functions; where as more specific tests may be used to measure the discrete functions of each cognitive subcategory. [5] It has been noted in the literature that the order of the testing measures within the battery does not significantly affect performance in most situations. [5]

The Digit Span Test is part of the Wechsler battery. [5] It is the most commonly used tool for measuring immediate verbal recall. [5] Each test involves the administrator reading aloud seven sets of random numbers at a rate of one number per second. [5] The test consists of two portions. There is a digit span forward and a digit span backward, which each test different areas of the brain, but both rely on short-term storage capacity. [5] Short-term storage capacity (short-term memory) specifically looks at attention and how much it can process at one time. Although these measures require the use of the subject's short-term memory, results of these tests are primarily evaluating attention and secondarily evaluating memory. [5]

The Rey Auditory Verbal Learning Test (RAVLT) measures auditory learning, verbal learning and memory. The test includes immediate recall, delayed recall and delayed recognition. It includes a list of 15 unrelated words with 5 trials. Between each trial the target list is read to the subject at a pace of one word per second. [30] After the fifth trial an interference list is read. [30] The interference list consists of 15 new words, and the subject is asked to recall them. [30] After the interference list is recalled, the subject is asked to recall the original words from the first five trials, and then again after 20 minutes. [30] Lastly, the RAVLT also contains a delayed recognition trial where the subject attempts to recognize as many words as possible from a word set that includes distractors. [30] It has been noted to have a moderate to low test-retest reliability, with the most reliable scores being the total score, delayed recall score, and the trial 5 score. [31] Literature indicates the RAVLT may be affected by age and formal education but not gender or intelligence. [32]

The Trail Making Test (TMT) measures complex attention. [5] More specifically, this test assesses visuomotor tracking, divided attention, and set shifting (executive function). [5,16] The TMT was originally developed by a U.S. Army psychologist and used in part of the Army Individual Test Battery (1944). [5] The TMT is given in two parts- Part A and Part B. In part A the subject is given a piece of paper and is asked to draw lines to connect consecutive numbers that are circled on the worksheet as fast as possible. Part B is the same concept, however, there are also letters requiring the subject to switch between two categories. The ability to change from one task to another "switch tasking" makes this portion of the test more taxing. This test is a measure of executive function because it requires more complex processing to switch between two different stimuli (letters and numbers). [16] The subject is instructed not to lift the pencil from

the paper during the test. Reliability coefficients for this test range from 0.6-0.9, with many reports of 0.8.[5] This test is easily administered, quickly completed, and accessible to the public.[5]

The National Adult Reading Test (NART) is a way of assessing premorbid intelligence.[5] The ability to word-read has been correlated to general intelligence.[5] The test consists of 50 phonetically irregular words that the patient is told to pronounce to the best of his or her ability.[5] Patients should attempt to pronounce all 50 words and are encouraged to guess on words they may not have seen before.[5] Scoring is done by using a mathematical equation, which can then be used to predict the Wechsler Adult Intelligence Scale (WAIS- Full Scale) IQ score.[5] NART IQ scores correlate significantly with education (r= .51) and social class (r=.36) based on a study performed in the United Kingdom.[5] Interrater reliability coefficients have been reported to be in the range of .96-98 with a test-retest reliability of .98.[5] A 61 word revised version of the NART was made specifically for North American and Canadian subjects called the North American Adult Reading Test (NAART, NART-R).[5] Words that were very unfamiliar from the NART were swapped for more familiar words in North America.[5] A 35-word version of the NAART also exists (NAART35) and has shown to be equally reliable and valid.[5]

Conclusion

Cognitive functions are responsible for input, storage, processing and output.[5] These functions can be assessed by using a multitude of neuropsychological testing measures. Typically these tests are administered in a neuropsychological battery that encompasses multiple cognitive domains. Previous literature suggests functions such as attentional capacity, processing speed, and psychomotor speed may be reduced when pain is present.[5] There is no specific "pain center" in the brain, though theories exist to try and explain how pain is modulated.[1,3,25] It is still

unclear how pain is processed and perceived. Factors such as emotions, attitudes, age, symptom experience, level of education, social support, anxiety, depression, resilience and other specific pain and lifestyle factors may contribute to developing chronic pain when triggers are present. [23] A large body of evidence indicates chronic pain affects neural pathways, but there is limited research on how acute pain affects cognition. Furthermore, when acute pain is present it is unclear what intensity is needed to cause cognitive impairment. [22]

Figure 1: Pain Processing Centers

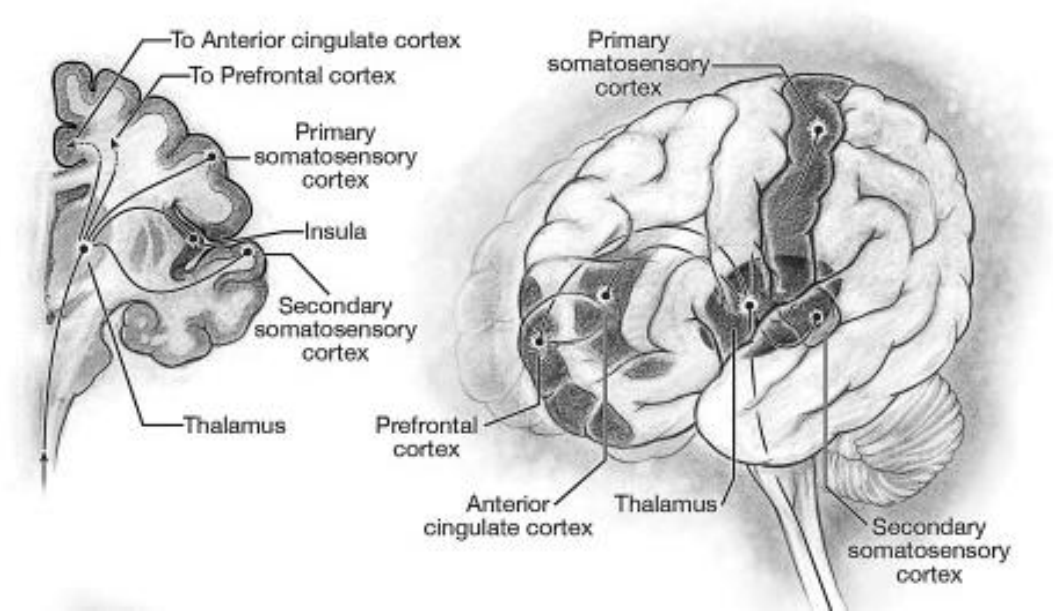

Figure 1: Primary Brain Structures in Pain Processing, adapted from Jensen 2010. [1] *The four primary cortical regions of the brain that are consistently associated with pain are shaded above and include the prefrontal cortex, the anterior cingulate cortex, the somatosensory cortex, and the insula.* [1]

Figure 2: The Gate Theory of Pain

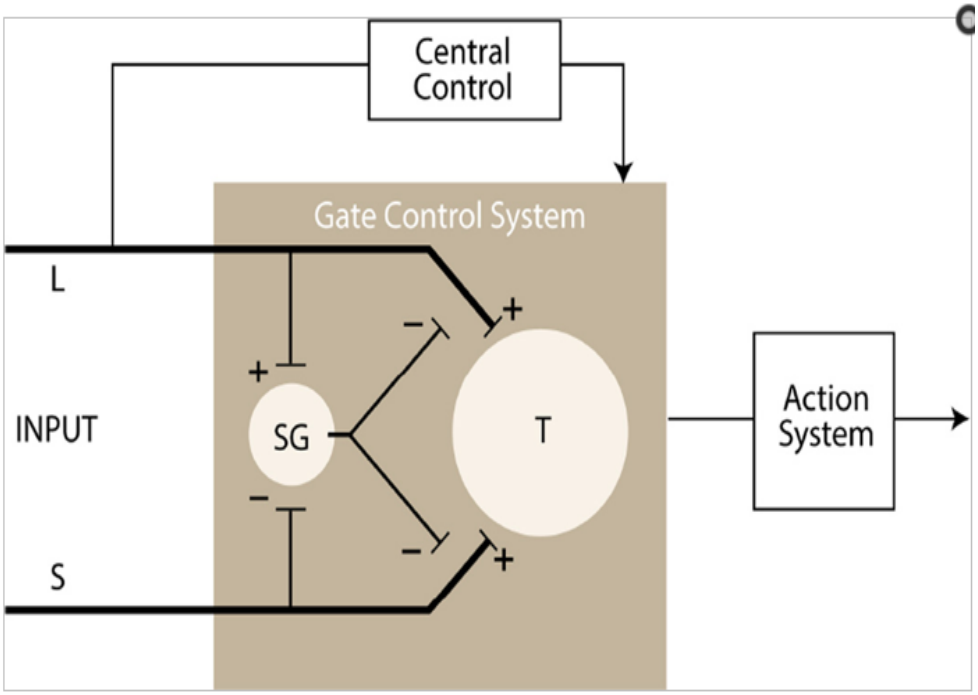

Figure 2: Melzack and Wall's Gate Theory of Pain, adapted from Mendell 2013. [2] *In the dorsal horn of the spinal cord the lagre (L) and small (S) sensory fibers excite the transmission (T) cells, which activates the Action System. Large unmyleinated A-beta fibers will close the gate located in the substantia gelatinosa (SG), whereas small thinly myleinated A-delta and non mylinated C-fibers will open the gate.* [2]

Figure 3: Melzack's Neuromatrix and Neurosignature

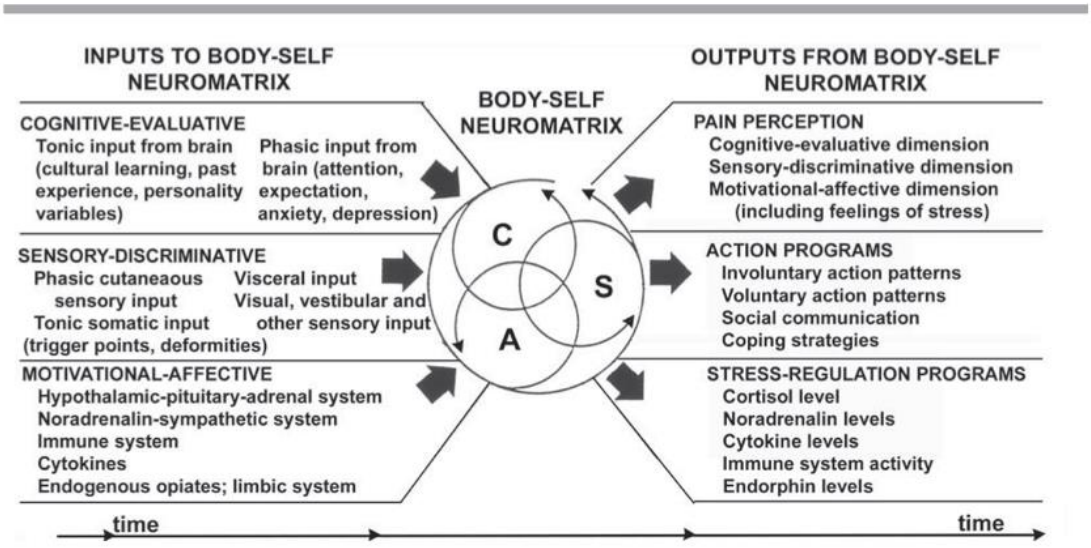

Figure 3: Factors influencing the Neurosignature, adapted from Melzack 2001.[3] *The neuromatrix is shaped by many factors derived from sensory, affective, and cognitive neuromodules.*[3] *The patterns from the neuromatirx will influence the neurosignature, shaping the individual's multidimensional pain experience and behavior.*

CHAPTER 3

METHODOLOGY

Research Setting

Participants were recreationally active (physically active for at least 20 minutes a day three times per week) individuals at a Division I university in the southeast United States. Those who were physically active for at least 20 minutes a day three times per week and those who presented in acute pain at the campus recreation center with a musculoskeletal injury were asked if they would be interested in participating in the study. If they were interested in participating, the nature of the studied was explained and informed consent was obtained. All individuals were deemed to have a musculoskeletal injury determined by a Certified Athletic Trainer (ATC). Neuropsychological testing took place in a quiet and private room inside the University's Recreation Activity Center (RAC).

Participants

If the participant met the inclusion criteria (see Table 2), he/she was taken to a private and quiet room in the campus recreation center to undergo neuropsychological testing. For this study, recreationally active was defined as being physically active for at least 20 minutes a day on at least three separate days of the week. [33] The primary investigator, university certified athletic trainers (ATCs) and athletic training students recruited participants for the study. Thirty-nine participants between the ages of 18 and 30 were recruited primarily from the recreation center.

Data were collected on all 39 participants, but only 24 participants (21.5±2.1 years) were included in the analyses. Participants who failed to show up for follow up testing were excluded

from the data set (*n*=4). The average estimated NART IQ was 110.08±4.49. Thirty-three percent of participants (*n*=8) were currently playing club sports, 54% were currently playing intramural sports (*n*=13), and 13% were currently playing in both club and intramural sports (*n*=3). Furthermore, educational data can be found in Table 1.

Information was recorded by pen and paper and stored in a locked cabinet in the athletic training room at the recreation center. All data was de-identified and put into an excel spreadsheet. Only the primary investigator had access to the excel data sheet.

Table 1
Descriptive Data
(n = 24)

	n	*%*
Master's	7	29%
Senior	5	21%
Junior	7	29%
Sophomore	3	13%
Freshman	2	8%

Table 2: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
18-30 years of age	Do not present in acute pain or present <4mm on the Visual Analog Scale (VAS)
Recreationally active (physically active for at least 20 minutes a day 3x week)	Existing chronic condition and/or a fracture
Present in acute pain on the Visual Analog Scale (VAS) > 4mm	Anyone taking any analgesic medication, non steroidal anti-inflammatory drugs (NSAIDs), or any pain mediator
Has an acute musculoskeletal injury within 0-72 hours	Previous history of a diagnosed mental illness (depression/anxiety) or diagnosed learning disability (ADD/ADHD)
	Those who have had any type of surgery in the last 6 months
	Those who have had a diagnosed concussion within the past year
	First language is not English

Study Design

Recreationally active participants were studied to examine how pain affects executive function and cognition using a prospective cohort design. Only participants who presented in acute pain were included in this study. After initial testing, participants were called five days from the initial injury. They were asked to return for follow up testing when they were no longer in acute pain, which was within two weeks from the initial testing session. Scores from both testing sessions were compared to see if pain affects cognition post musculoskeletal injury.

Procedures

All participants who presented in acute pain were first evaluated by an ATC and asked if they would like to participate in a research study. After the participant signed the consent form and completed the medical history questionnaire, acute pain was immediately assessed using the Visual Analog Scale (VAS) [27]. The patient was told to mark his or her current pain intensity on the scale. The VAS defines "no pain" as 0-4mm, "mild pain" as 5-44mm, "moderate pain" as 45-74mm, and "severe pain" as 75-100mm. Only those who presented above 4mm on the VAS were included in this study.

Those who met the inclusion criteria underwent a neuropsychological battery that included the following tests: the National Adult Reading Test (NART) [5], the Digit Span (DS) [5], the Rey Auditory Verbal Learning Test (RAVLT) [5] and Trail Making Test B (TMT-B) [5]. This battery took less than 45 minutes to complete.

Instrumentation

NART. The NART was only administered during the initial testing session to estimate general intelligence and consisted of 50 phonetically irregular words for the participant to pronounce. Participants attempted to pronounce all 50 words and were encouraged to guess on

unfamiliar words. The NART scoring was performed using a mathematical equation; that predicts the Wechsler Adult Intelligence Scale (WAIS- Full Scale) IQ score. To predict a WAIS-Full Scale IQ score from the NART, the equation is as follows: 128-0.83 x NART error score. Full scale IQ scores were classified as follows: very superior above 130, superior 120-129, high average 110-119, Average 90-109, low average 80-89, borderline 70-79, and intellectually deficient 69 and below. [34]

DS. The DS test was used to evaluate memory and attention and it was administered according to standard procedures. The test is broken into two parts: digits forward and backward, each with a total possible score of 12. In each trial of both parts the participant is asked to repeat a span of numbers forwards and in reverse order. The DS starts with only 2 digits with a forward and reverse trial, and progresses up to a span of 8 digits. Once the subject fails to recite the numbers correctly consecutively two times within the same string of numbers, or once the maximum digit span length is reached (8 forward, 7 backward), testing is terminated. Scoring is based on the number of trials correctly completed forward and backward, which produces an overall score. In this study the digits forward score and digits backward scores were analyzed separately to have a closer look at immediate recall (digits forward) versus working memory (digits backward).

RAVLT. The RAVLT measures auditory verbal learning and memory. It includes immediate recall, verbal learning, delayed recall, and delayed recognition. It includes five trials, each trial consisting of 15 unrelated words (List A). Between each trial the target list is read to the subject at a pace of one word per second. [30] After the fifth trial, an interference list is read. [30] The interference list (List B) consists of one trial of 15 new words, by which the participant must recite. [30] After the interference list is recalled, the subject is asked to recall the original words

from the first five trials (trial A6), and then again after 20 minutes (trial A7). [30] Lastly, the RAVLT also contains a recognition trial where the subject attempts to recognize as many words from List A as possible from a word set that includes distractors. [30] Scoring is based on the number of words recalled per trial. Immediate memory was derived from the total score from trial A1. Auditory and verbal learning were calculated by the sum of trials A1 to A5. This score is also noted to be a "total" score. Lastly, delayed recognition was measured using a numerical raw score for recognition list A. Overall, the RAVLT has been noted to have a moderate to low test-retest reliability, with the most reliable scores being the total score (sum A1 to A5), delayed recall score (A7), and the trial A5 score. [31] Literature indicates the RAVLT may be affected by age and formal education but not gender or intelligence. [32]

TMT-B. TMT-B will be used to measure complex attention, cognitive flexibility (executive function), and visual motor tracking. Typically, the TMT is given in two parts- Part A and Part B; however, for this study only part B was utilized since it is a more complex measure. For this test the subject was given a piece of paper and asked to draw lines to connect consecutive numbers and corresponding letters that are circled on the worksheet as quickly as possible. The subject is instructed not to lift the pencil from the paper during the test. This switch between letters and numbers during TMT-B makes the test taxing and a measure of executive function due to the complex processing involved with switching between stimuli. Scoring is based on the number of seconds required to complete a task, with a higher score indicating a greater deficiency.

Follow up testing was administered when the participant returned to the recreation center and was pain free (<4mm on the VAS) during the acute recovery time frame for a musculoskeletal injury (within 2 weeks of initial testing session). Follow up testing included a

second medical health questionnaire, DS, RAVLT (alternate form), and TMT-B. The primary investigator who has been trained to administer all previously listed neuropsychological assessments administered all testing. All participants were initially tested within 72 hours of injury and follow up tested within two weeks from their injury (8.88±2.5days).

Data Analyses

The DS was broken into two separate scores: digits forward and digits backward. The RAVLT was broken into four scores: A1 trial sum, sum of trials A1 through A5, trial A6, and list A recognition. Lastly, the TMT-B was analyzed using one score: the number of seconds it took to complete the test (Table 2).

Seven paired samples t-tests were conducted using Statistical Package for the Social Sciences (SPSS), SPSS v.23 (IBM) to compare scores in both conditions. A Bonferroni correction was made resulting in an adjusted alpha level of 0.007 used for the rejection of the null hypothesis. For this study, a minimum sample size of 26 was determined adequate by a power analysis using Cohen's *d*. Metrics and outcome variables (Table 3) were as follows:

- **Independent Variable**
  - Pain intensity (measured by VAS)
- **Dependent Variable**
  - Cognition (measured by Digit Span, RAVLT, TMT-B)
- **NART**
  - Estimated IQ: 1 numerical raw score
- **DIGIT SPAN**
  - Immediate recall: 1 numerical raw score
  - Working memory: 1 numerical raw score
- **RAVLT**
  - Trial A1 immediate memory: 1 numerical raw score
  - Sum A1 to A5 (auditory and verbal learning): 1 numerical raw score
  - Trial A6 (interference): 1 numerical raw score
  - Delayed Recognition List A: 1 numerical raw score
- **TMT-B**
  - Attention and set switching: 1 numerical raw score

Data was collected on 39 participants. Four of those participants did not show up for follow up testing and were therefore removed completely from the data set (*n*=35). After reviewing the data set for exclusion criteria using the medical health questionnaire, ten participants were removed from the data set (*n*=25). Two of these ten participants who were removed sustained another injury between testing points, six were currently taking pain medication on follow up testing, one was diagnosed with a mental illness, and one scored above 4mm on the VAS on follow up testing indicating pain was still present.

Lastly, one participant was removed from the entire data set due to consumption of 200mg of caffeine prior to testing. Previous studies looking at the effects of caffeine have typically seen enhancements in attention at 200-250mg. [35,36] However, the relationship between caffeine and cognition is affected by many factors including caffeine tolerance, time of consumption, task at hand, personality factors, etc. [35,36] Therefore, because the relationship between caffeine and cognition is not fully understood, those who ingested less than 200mg were included in the data set (*n*=24).

The sample of 24 participants was then screened for outliers, which were defined in this study as neuropsychological test scores that were two standard deviations from the sample mean. These outliers were removed from the individual tests within the battery. One score was dropped for RAVLT A6 due to an unexpected interruption during that trial, two scores were removed from RAVLT Rec-A due to outliers, and one participant was removed from TMT-B due to an error in administration. DS forwards, DS backward, RAVLT A1, and RAVLT Sum A1 to A5 had a total sample of 24 (*n*=24). RAVLT A6 had a sample of 23 (*n*=23), RAVLT Rec-A had a sample of 21 (*n*=21), and TMT-B had a sample of 22 (*n*=22).

Lastly, to ensure confidentiality, all data was stored in a locked cabinet located at the University's Recreation Activity Center. Data were de-identified and put into an excel spreadsheet. Only the primary investigator had access to the excel spreadsheet.

Table 3: Metrics and Outcome Variables

Metric	**Outcome Variable**	**Score**
VAS	Pain intensity	Measured in millimeters (100)
NART	Estimated IQ	128-0.83 x NART error score
Digit Span Forward Digit Span Backward	Immediate Recall Working Memory	Total correct trials (12) Total correct trials (12)
RAVLT A1 RAVLT Sum Trials A1 to A5 RAVLT A6 RAVLT Delayed Recognition	Auditory and Verbal Learning	Sum of recalled words trial A1 (15) Sum of words trials A1 to A5 (75) Sum of recalled words trial A6 (15) Sum of words from List A (15)
TMT-B	Executive function (attention, set shifting)	Seconds to complete

CHAPTER 4

RESULTS

Of the 24 participants, 67% (*n*=16) reported "mild" pain and 33% participants (*n*=8) reported "moderate" pain at the initial testing session (38.02±19.4mm). All participants reported as "no pain" on their second testing session (0.67±1.09mm).

Results of the paired samples t-test revealed that when the participants were pain free, their cognitive scores significantly improved in the DS forward ($t(1,23)=-3.943$; $p<0.001$) and TMT-B ($t(1,21)=4.488$; $p<0.001$). No significant difference was observed for the DS backward ($p=0.023$), RAVLT A1 ($p=.563$), RAVLT sum A1 to A5 ($p=0.953$, RAVLT A6 ($p=1.0$), RAVLT recognition list A ($p=0.009$).

Effect sizes were calculated using Cohen's *d*. DS forward had an effect size of 0.5 while DS backward had an effect size of 0.33. RAVLT A1 had an effect size of 0.20, RAVLT sum A1 to A5 0.01, RAVLT A6 0, RAVLT recognition list A 0.82. Lastly, TMT-B had an effect size of 0.79.

Table 4: Variations in cognitive performance during and after a musculoskeletal injury

Pair	Time	Mean	N	Std. Deviation	P	Cohen's *d*
DSF	1	8.7	24	1.8	0.001*	0.50
	2	9.6	24	1.8		
DSB	1	6.5	24	2.2	0.023	0.33
	2	7.3	24	2.3		
A1	1	6.4	24	1.7	0.563	0.20
	2	6.8	24	2.2		
SUM	1	53.8	24	7.7	0.953	0.01
	2	53.9	24	8.3		
A6	1	11.8	23	2.3	1	0
	2	11.8	23	2.4		
REC-A	1	14.6	21	.68	0.009	0.82
	2	13.8	21	1.2		
TMT-B	1	48.4	22	12.6	0.000*	0.79
	2	39.6	22	9.4		

Note: Table 4. DSF: Digit Span Forward, DSB: Digit Span Backward, A1: RAVLT A1, SUM: RAVLT Sum A1 to A5, A6: RAVLT A6, REC-A: RAVLT Delayed Recognition list A, TMT-B: Trails Making Test-B. Time point #1 (T1): pain state, and time point #2 (T2) non-pain state. **represents a significant difference between pre-post testing ($p<0.007$)*

CHAPTER 5

DISCUSSION

The purpose of this study was to determine if the recreationally active who presented in acute pain due to a musculoskeletal injury would have impairments in executive function as measured by the DS, RAVLT, and TMT-B. We hypothesized that acute pain would affect executive function, and that those in acute pain would have decreased neuropsychological scores compared to those who are pain free. These hypotheses were based on the findings of previous literature and the notion that the prefrontal cortex is responsible for both executive function and encoding pain. [37] Improved neuropsychological scores were seen in immediate recall and set switching when participants were pain free as measured by the DS forwards and TMT-B. No significance was found between conditions for working memory in the DS backward or auditory verbal learning measured by the RAVLT. A medium to large effect size was seen for TMT-B (0.79) and RAVLT recognition list A (0.82). The DS forwards had a medium effect size of 0.5, while a small effect size was seen for DS backward (0.33) and RAVLT A1 (0.20). The RAVLT sum A1 to A5 and RAVLT A6 had the smallest effect sizes of 0.01 and 0. Based on these results, our hypothesis was partially supported since there was a statistically significant difference in two of the seven measures. To our knowledge, this is the first study to examine the effect of acute pain due to a musculoskeletal injury on executive function in the recreationally active population.

Improved neuropsychological scores were seen for DS forward and TMT-B. These tests measure immediate recall, attention, and cognitive flexibility. Hutchison et al. [12] found that those who suffered from a musculoskeletal injury had lower neurocognitive scores compared to controls as measured by the Automated Neuropsychological Assessment Metrics (ANAM). The

ANAM subtests include Simple Reaction Time, Code Substitution Learning, Code Substitution Delayed, and Matching to Sample. The only subtest of the battery that reached significance in the study was the Matching to Sample subtest, which measures spatial and visuospatital working memory. [12] The mean and standard deviations for Matching to Sample were (1449±481.9ms) baseline, and (1553.6±382.3ms) post-musculoskeletal injury, with a lower score indicating better performance. [12] While our study did not directly measure visuospatial working memory, we did measure working memory using the DS backward, which is similar because both tests require the participant to extract information that is no longer in front of them. Contrary to the results of Matching to Sample, our results for working memory did not reach significance. This may be because visuospatial working memory focuses more on environmental orientation and working memory focuses on temporarily storing and manipulating information. Huchison's group [12] also measured visual searching, sustained attention, and encoding using the Code Substitution Learning subtest. This test is similar to TMT-B, which requires visual searching and complex attention to match the numbers and letters in the correct sequence. The means and standard deviations for Hutchison's group post musculoskeletal injury were (57.1±16.9) and (58.7±16.7) for the healthy controls.[12] Although these results were not statistically significant in Hutchison's study, they measured similar domains to our study, which we did find to be significant. In addition, although no other measures of cognition reached significance in Hutchison's study, those in the pain group did score lower than those in the non-pain group, which coincides with our findings.

Furthermore, Calandre et al. [38] assessed cerebral blood flow and neuropsychological scores in migraine patients with 60 control subjects and 30 healthy controls. The average DS forward score for healthy controls in this study was (6±1.2) compared to (9.6±1.8) in our study,

with a higher score indicating more digits recalled. Calandre et al. [38] studied 3 migraine groups, each with similar DS forward scores: < 3 attacks per month (6.48±1.3), 3-9 attacks per month (5.39±1.1), ≥10 attacks per month (6.05±1.2). Our acute pain score for DS forward was (8.7±1.8), which is higher than all migraine groups and the control group. This may be because our age ranged from 18-30 years, while theirs ranged from 18-68 years, and because musculoskeletal injuries and migraines offer different pain experiences. Unlike a musculoskeletal injury, a migraine is a central nervous system disease.[6] Those who suffer from migraines report acute painful attacks and have been noted to have altered brain structure and function leading to cognitive impairments similar to those who suffer from chronic pain conditions.[6]

Mathur et al. [6] found that there was altered brain neural activity related to pain-cognition interactions measured by functional magnetic resonance imaging (fMRI) when looking at those who suffer from acute pain due to migraines. The authors suggest that during a migraine cognitive resources may be primarily allotted to reducing pain rather than the task at hand.[6] Calandre et al.[38] stated brain perfusion abnormalities, specifically a lack of blood flow to the brain, were seen in 43% of migraine patients. Some patients exhibited brain hypoperfusion in multiple areas while others only had localized hypoperfusion. [38] Decreased blood flow during migraines may be due to decreased neuronal activity, suggesting a relationship between cerebral blood flow and cognitive impairments. [38] The link between hypoperfusion and neuropsychological impairments has been suggested in previous studies and is supported by this study with impairments seen on the RAVLT trial 5 and the Wechsler Memory Scale short-term visual reproduction test. [38] Although our study does not use fMRI or any other imaging

techniques to confirm our findings, patients in acute pain may exhibit abnormal cerebral blood flow similar to patients with chronic pain.

Improved TMT-B scores were seen when participants were not suffering from acute pain. This trend is consistent with chronic pain populations. The International Association of Pain (IASP) defines chronic pain as pain that "persists beyond the normal healing time." [10] Typically this is anywhere from 3-6 months, although 6 months or more is more commonly studied in the literature. [10] In a meta-analytical review that analyzed 22 articles on chronic pain and executive function, it was found that those who suffered from chronic pain had a small to moderate impairment in executive function compared to healthy controls. [39] When looking at set shifting within the meta-analysis, those with chronic pain were slower to complete Trails Making Test A and B. [39] In this study, those who were in acute pain were also slower to complete TMT-B (48.4±12.6seconds) compared to those who were not in pain (39.6±9.4seconds). Our TMT-B scores for those in acute pain were nearly the same as the normative data reported by Tombaugh[40] in ages 18-24 (48.97±12.7seconds). Tombaugh [40] also noted age and education accounted for 38% and 6% of variance, meaning TMT-B scores decreased with age and improved with years of education. In his group of normative data, the participants that were aged 18-24 were classified as having completed 0-12 years of school with a mean age of 20.17 years. Our TMT-B scores may be enhanced due to the fact that our mean age was 21.5 years and most participants were upperclassman in an undergraduate program (n=12) or pursuing master's degrees (n=7) at a young age.

More specifically, Weiner et al.[41] found that neuropsychological scores were dependent on pain severity and mediated the relationship between physical pain and performance in older

adults with chronic low back pain (CLBP) compared to pain free controls. Although we studied a younger recreationally active population, our findings overlap with Weiner et al. [41] who also found differences in immediate (p=.002) memory measured by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and mental flexibility measured by TMT-B (p=.019). The means and standard deviations for those with CLBP for immediate memory were (98.53±15.5) and (50.7±10.2) for TMT-B, which are similar to our TMT-B scores (48.4±12.6) of those in acute pain despite the fact that these participants ranged from 65-84 years old. [41] The age gap is reflected when looking at the pain free scores for both groups since our TMT-B score was (39.6±9.4) and their TMT-B score was (53.57±11.36). [41]

In 2005, Etherton et al.[42] published a study using the DS comparing three groups: a cold induced pain group, a simulated pain group, and a non-pain group. All participants were undergraduate student volunteers (*n*=60) in the southern United States who were all deemed healthy. The simulation group was read a script prior to testing that described in detail a scenario that they suffered an accident but needed to fake their memory impairment. The pain group was told to hold their hand and forearm in a bucket of ice water until they completed the DS. DS forward and backward were both completed in each group. Sixty-five percent of the simulation group scored 7 digits or lower, while the entire pain group reporting mild-severe pain scored 8 or higher (8.95±1.1) No differences were seen between the pain group and the control group, which partially coincides with our findings of DS backward not reaching significance in a predominantly mild pain population. Results of this study indicate the DS may be affected by a negative response bias rather than acute pain. Furthermore, in 2014 Etherton [43] published another study indicating cold induced pain does not impair working memory or processing speed measured by the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV). It is important to

note that in both studies the authors intentionally provoked acute pain in a healthy population, where as in our study participants were suffering from an acute pain due to an injury. Results of both studies suggest there are no differences between acute pain and healthy control groups in working memory, processing speed, and immediate recall.

No significance was seen for any trials of the RAVLT (A1, sum A1 to A5, A6, or Rec-A). Calandre et al. [38] also used the RAVLT to measure neuropsychological scores in those with migraines. The control group had a score of (5.83±1.8words) for trial A1 and a score of (50.2±9.5words) for the sum of trials A1 to A5. Our pain free group had a score of (6.8±2.2words) for trial A1 and a score of (53.9±8.3words) which is similar to their findings. In addition, our pain group had an A1 trial score of (6.4±1.7words) which is very similar to the migraine group with < 3 attacks per month (6.29±2.3words). Our A1 trial score was higher than the 3-9 attacks per month (5.0±1.8words) migraine group and the ≥10 attacks per month migraine group (4.95±1.4words). Our pain group had a score of (53.8±7.7words) for the sum of trials A1 to A5, which is also known as an RAVLT "total" score. The < 3 migraine group had a total score of (53.3±8.6words) which was the highest total score of all groups, including the control group. It seems our scores due to musculoskeletal pain are very comparable to those who suffer from migraine pain with < 3 attacks per month. Although a musculoskeletal injury is not classified as a central nervous system disease, there is an overlap in acute pain states since those who have migraines suffer from acute attacks. It makes the most sense that our scores would be most comparable to < 3 attacks per month instead of 3-9 attacks or ≥10 attacks per month since the latter categories may indicate more changes in brain structure and function. Additionally, 67% of our participants reported "mild" pain scores. Research indicates pain can alter neural networks and over time exacerbate the experience of pain, so those experiencing more migraines

per month may not only have cortical changes but also a pain experience that is more severe than "mild" pain. Those suffering from < 3 attacks per month may have pain that is more similar in the reported pain intensity in our study.

Research hypothesizes that those who suffer from chronic pain may have altered cortical regions that are not associated with pain, which may affect learning and memory. [39,44] In addition, chronic pain may alter neural network connectivity patterns, which can change overall brain activity. [39,45] In this study, learning and memory as measured by the RAVLT were not affected. Because acute pain is only within the 0-72 hour time frame, there may not be enough disruption to the brain to see significant changes in verbal memory and learning, or the RAVLT may not be sensitive enough to detect these changes.

Delimitations

When looking at cognitive function, many studies in the acute and chronic pain populations fail to account for psychiatric disorders, medication use, and the effect of sleep. In addition, many of these studies have a small sample size, which diminishes statistical power. This study aimed to control for psychiatric disorders, medication use, and sleep by using the health questionnaire (Appendix B). Participants were excluded if they had diagnosed anxiety, depression, ADD/ADHD, or any other disorder that they listed. Those who were currently taking any type of pain medication were also excluded in order to get a more truthful pain score and because pain medication may improve global cognition.[13] Effort was controlled for by excluding anyone who was unable to recite less than a total of 7 digits between the forward and backward trials (n=0), which has been reported in pain-related malingering. [46] Lastly, there was an open-

ended question for participants to utilize if they felt there was anything else that may affect the study.

Limitations

This study was a prospective cohort design that aimed to investigate if pain affects executive function and is not without limitations. During this study, participants completed follow up testing within two weeks of his or her initial testing session. Throughout this time some injuries may have healed faster than others. Therefore, the severity of injury and other factors that may trigger pain or re-injury in the two-week time frame cannot be accounted for. The sample population was specific to a convenience sample of those who were recreationally active at a Division I University in Southern Georgia and therefore may not be generalizable to other populations. There was also a small sample size of 24 participants. In regards to data collection methods, neuropsychological tests fail to account for other cognitive domains due to time constraints.

Implications and Future Research

Executive function embodies a large amount of cognitive tasks, and cannot be isolated. Results of this study suggest acute pain from a musculoskeletal injury may impair immediate recall and complex attention (visuomotor tracking and set switching).

Clinically this emphasizes the importance of pain management, especially when patients are playing sports. Sports involve precise visuomotor tracking and the ability to set shift very quickly from play to play, in addition to knowing which external cues to inhibit (crowd) and

which to attend to (coach). They also require immediate recall when being told specific instructions by the coach and calling plays, which then dictates performance. Clinicians should be aware that this ability may be diminished in those suffering from acute pain due to a musculoskeletal injury.

Future research should aim to study executive function while trying to control everyday confounding variables such as quality and quantity of sleep and the interaction of caffeine. Additionally, this study tested participants in a quiet room without distractions, which is not representative of sports or daily living. Replicating a sporting environment may give a more functional representation of how acute pain and executive function are related in the active population. A more detailed pain profile and accounting for mental and physical fatigue are also important factors to consider, especially in this population. Overall more research is needed on the interaction between executive function and acute pain across various populations and intensities.

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APPENDIX A

RESEARCH QUESTIONS AND HYPOTHESES

The research questions of this study were:

Question 1: Does acute pain affect executive function?

Hypothesis 1: Acute pain will affect cognition, which in turn will affect executive function.

Question 2: Do neuropsychological scores (Digit Span, RAVLT, TMT-B) decrease when in acute pain?

Hypothesis 2: Suffering from acute pain will lead to a decreased cognitive ability as measured by the Digit Span, RAVLT, and TMT-B.

ASSUMPTIONS

It was assumed that all participants were honest and gave 100% effort during their participation in the study. It was assumed that participants were honest if they did not meet inclusion or exclusion criteria, and that they were honest about their injury and level of pain. To try and control for effort and honesty, participants were told their results were confidential, stored in a lock cabinet, and that they could withdraw from the study at any time without any ramifications.

OPERATIONAL DEFINITIONS

For the purpose of this study, executive function was used as an umbrella term to refer to a subset of cognitive functions. Recreationally active was defined as being physically active for

at least 20 minutes a day three times per week. In addition, the follow up time frame of two weeks was deemed adequate by a consultation with a medical doctor (MD).

APPPENDIX B

CONSENT FORM

GEORGIA SOUTHERN UNIVERSITY INSTITUTIONAL REVIEW BOARD
INSTRUCTIONS FOR PREPARATION OF PROPOSAL NARRATIVE

GEORGIA SOUTHERN UNIVERSITY
COLLEGE OF HEALTH & HUMAN SCIENCES
POST OFFICE BOX 8076
STATESBORO, GEORGIA 30460-8076
TELEPHONE (912) 681-0200

CONSENT TO ACT AS A SUBJECT IN AN EXPERIMENTAL STUDY

Title of Project: The Influence of Acute Pain on Cognitive Functioning After Injury

Investigator's Name: Jenna Morogiello Phone: (912) 478-7230

Participant's Name:_____Participant's Phone: _____

Date:_____

Data Collection Location: The Recreation Activity Center (RAC), Georgia Southern University Campus

We are attempting to see if acute pain influences cognitive functioning post musculoskeletal injury. There will be about 50 participants in this study. The results of this study will help athletic trainers and other health care professionals in their evaluation, treatment, and rehabilitation skills with those who suffer from pain and musculoskeletal injuries.

You are being invited to participate in this study because you are in acute pain and meet the inclusion criteria for this study. You are currently not taking analgesics/NSAIDs/ or any pain mediator, have not had any type of musculoskeletal surgery within the last 6 months, you do not have a history of mental illness (anxiety/depression) or been diagnosed with ADD/ADHD or any learning disorder, and your first language is English.

If you agree to participate in this study you will be asked to rate your pain and then complete a neuropsychological testing session that will last about 45 minutes. You will be contacted for follow up testing 5 days after initial injury to see how you are feeling and to schedule follow up testing. Follow up testing must be completed within two weeks from the initial testing date when you are no longer in acute pain. During the neuropsychological testing session you will be asked to take 4 different verbal and handwritten tests in a privately located room. You will be asked to complete tasks such as repeating and temporarily memorizing numbers and words. We will record by hand your neuropsychological testing scores and your visual analog pain score. No testing will be video taped and no incentives will be provided.

The information we collect on your performance may be sent off campus for analysis, however any information sent will be devoid of identifying characteristics (no one will be able to tell it's you).

Your performance during these tasks will be compared to your performance during your follow up test.

GEORGIA SOUTHERN UNIVERSITY INSTITUTIONAL REVIEW BOARD
INSTRUCTIONS FOR PREPARATION OF PROPOSAL NARRATIVE

The risk assumed during the testing is no greater than you experience during your normal daily activities. There is minimal risk of physical injury or mental discomfort while performing this experiment. If discomfort does occur, testing can be stopped at any time. You understand that medical care is available in the event of injury resulting from research. Should medical care be required, you may contact your primary care physician, or if you are a student who has paid your Health Fee, you may schedule an appointment at Georgia Southern University via your Online Student Health Portal.

You will likely receive no direct benefit for participating in this study, however you will be provided your results, once calculated, if you so request. The results of this study may be used to better understand and treat individuals who have suffered from pain and musculoskeletal injuries.

You will participate in the initial pain and neuropsychological testing along with follow up testing. The follow up testing time frame will be dictated by the certified athletic trainer (ATC). Testing periods will take no longer than 45 minutes.

You understand that all data concerning yourself will be kept confidential and available only upon your written request to Jenna Morogiello, ATC. You understand that any information about your records will be handled in a confidential (private) manner consistent with medical records. A case number will indicate your identity on all records. You will not be specifically mentioned in any publication of research results. However, in unusual cases your research records may be inspected by appropriate government agencies or released to an order from a court of law. All information and research records will be kept for a period of 15 years after the termination of this investigation.

If you have any questions about this research project, you may email Jenna Morogiello at jm14781@georgiasouthern.edu (preferred method) or call at the athletic training room at (912) 478-7230. If you have any questions or concerns about your rights as a research participant in this study it should be directed to the IRB Coordinator at the Office of Research Services and Sponsored Programs at (912) 478-5465.

You will not receive compensation for your participation in this project. You will be responsible for no additional costs for your participation in this project.

You understand that you do not have to participate in this project and your decision to participate is purely voluntary. At any time you can choose to end your participation by telling the primary investigator, Jenna Morogiello.

You understand that you may terminate participation in this study at any time without prejudice to future care or any possible reimbursement of expenses, compensation, employment status, or course grade except provided herein, and that owing to the scientific nature of the study, the investigator may in his/her absolute discretion terminate the procedures and/or investigation at any time.

You understand there is no deception involved in this project.

GEORGIA SOUTHERN UNIVERSITY INSTITUTIONAL REVIEW BOARD
INSTRUCTIONS FOR PREPARATION OF PROPOSAL NARRATIVE

You certify you are 18 years of age or older and you have read the preceding information, or it has been read to you, and understand its contents. Any questions you have regarding the research have been, and will continue to be, answered by the investigators listed at the beginning of this consent form.

You have been provided a copy of this form to keep for your records. This project has been reviewed and approved by the GSU Institutional Review Board under tracking number H16448.

Title of Project: The Influence of Acute Pain on Cognitive Functioning After Injury

Principal Investigator	**Co-Investigators**
Jenna Morogiello, BS, ATC, CSCS	**Nicholas Murray, Ph.D**
Campus Recreation and Intramurals	**Tamerah Hunt, Ph.D**
Injury Prevention and Care	**Brandonn Harris, Ph.D**
Post Office Box 8078	**George Shaver, Psy.D**
Phone: (912) 478-7230	
Email: jm14781@georgiasouthern.edu	

_____ _____

Participant Signature **Date**

I, the undersigned, verify that the above informed consent procedure has been followed.

_____ _____

Investigator Signature **Date**

IRB NARRATIVE

Personnel. *Please list any individuals who will be conducting research on this study. Also please detail the experience, level of involvement in the process and the access to information that each may have.*

- Jenna Morogiello, B.S., ATC, CSCS Graduate Assistant Athletic Trainer and Graduate Athletic Training Student
- Nicholas Murray, Ph.D. Assistant Professor of Biomechanics, Director of Concussion Research, College of Health and Human Sciences
- Tamerah Hunt, Ph.D. Assistant Professor and Graduate Coordinator of Athletic Training
- Brandonn Harris, Ph.D. Associate Professor and Program Director of Sport and Exercise Psychology, Graduate Program Director of the School of Health and Kinesiology
- George Shaver, Psy.D. Director Academic, Regents Center for Learning Disorders
- Eric Roux, MS, ATC Injury Prevention and Care Coordinator

Jenna Morogiello is the primary investigator of this study and will contribute to research design, subject recruitment, data collection, and analysis. Dr. Murray is the faculty chair of this project and will also contribute to the research design, methods, and analysis of this study. All other members will contribute to research design, methods and analysis of this study. All individuals have completed CITI training. Certificates of completion are attached below.

Purpose. *1. Briefly describe in one or two sentences the purpose of your research. 2. What questions are you trying to answer in this experiment? Please include your hypothesis in this section. The jurisdiction of the IRB requires that we ensure the appropriateness of research. It is unethical to put participants at risk without the possibility of sound scientific result. For this reason, you should be very clear about how participants and others will benefit from knowledge gained in this project.*

Pain serves as one of the most basic mechanisms for survival. [1] Although pain plays a valuable role in the body, such as a protective mechanism or a promoter of rest, it can be very hard to treat and can cause a decrease in the quality of life of those who suffer from it. [1]Previous literature suggests that even an episode of acute pain can trigger a cascade of long term neural remodeling and psychological distress, which indicates that although pain is typically classified into either acute or chronic, there are many links between them. [2] Pain models date back to the 17th century and are undoubtedly a major public health concern. [3]

Even though the experience of pain is not fully understood, previous literature indicates that pain can affect cognition. [4] Cognition is mainly involved with information processing of behavior and typically receives the most attention in neuropsychology since cognitive symptoms are so prevalent. [4] One of the reasons it is thought that pain may affect cognition is the shared amount of neural resources in the brain. [5] It is unclear whether or not there is a certain pain intensity or cognitive load needed to see these effects,
and there is controversial evidence as to whether pain perception is reduced when cognitive distractions are present. [6] Many studies investigate the mystery of chronic pain, but few have looked at the cognitive response to acute pain. Knowing which cognitive
domains are impaired during acute pain (if any) could change clinical practice and further benefit the evaluation, treatment, and rehabilitation of patients. Therefore, the purpose of this study is to determine if acute pain affects cognition in the recreationally active athlete that sustains a musculoskeletal injury. Our first hypothesis is that acute pain will affect cognition. Our second hypothesis is that as pain intensity increases (as measured by the Visual Analog Scale), cognitive function will decrease based on our neuropsychological testing measures (Hopkins Verbal Learning Test Revised, Trail Making Test B, National Adult Reading Test, and the Digit Span).

Literature Review. *Provide a brief description of how this study fits into the current literature. Have the research procedures been used before? How were similar risks controlled for and documented in the literature?*

Have your instruments been validated with this audience? Include citations in the description. Do not include dissertation or thesis chapters.

Many people will experience pain at some point in their life. Casey and colleagues indicated 20% of the population experiences chronic pain. [7] Many pain phenomena that are commonly seen today include psychological symptoms and disabling pain
that cause restrictions to daily living. [7] The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with the actual or potential tissue damage." [8] Since pain is considered an unpleasant experience, it includes an emotional component as well. [8] Therefore, patients' beliefs and personalities can strongly affect their personal interpretation of pain. [2] Previous literature suggests that even an episode of acute pain can trigger a cascade of long term neural
remodeling and psychological distress, which indicates that although pain is typically classified into either acute or chronic, there are many links between them. [2] A study in 2011 by Hutchison compared 3 different groups: healthy controls (n=36), a concussed group (n=18), and a musculoskeletal group (n=18). [5] All three groups were tested within 72 hours of injury using the Automated Neuropsychological Assessment Metrics (ANAM) computerized test battery. [5] Both the concussed group and the musculoskeletal group had cognitive deficits compared to the healthy control group. [5] Findings of this study suggested that acute musculoskeletal injuries have the potential to disrupt cognitive function. [5]

Neuropsychological testing is a way of evaluating the brain through a behavioral outcome. [4] It is essentially based on the same assumptions and ideas as a psychological assessment, but focuses on the measurement of brain function. [4] Many different
neuropsychological tests exist to test cognitive functioning. A basic test battery will typically include tests that target the major dimensions of behavior. [4] These areas include but are not limited to attention, memory and learning, verbal functions, executive functions, and emotional status. [4] Broad testing measures may be used to measure complex functions; where as more specific tests may be used to measure the discrete functions of each cognitive subcategory. [4] It has been noted in the literature that the order of the testing measures within the battery does not significantly affect performance. [4]

The Trail Making Test (TMT) measures complex attention. [4] More specifically, this test looks at visuomotor tracking, divided attention, and cognitive flexibility (executive function). [4,9] The TMT is given in two parts- Part A and Part B. In part A the subject is given a piece of paper and is asked to draw lines to connect consecutive numbered circles on the worksheet as fast as possible. Part B is a similar task, however in addition to numbers there are also letters requiring the subject to switch between two categories. This switch is why the test is a measure of executive function- it requires more complex processing to switch between two different stimuli (letters and numbers) and this is why only part B will be used in this study. [9] The subject is instructed not to lift the pencil from the paper during the test. [4] Reliability coefficients for this test range from 0.6-0.9, with many reports of 0.8. [4] This test is easily administered, quickly completed, and accessible to the public. [4]

The Rey Auditory Verbal Learning Test (RAVLT) measures verbal learning and memory. The test includes immediate recall, recognition, and delayed recall. It includes a list of 15 unrelated words with 5 trials. Between each trial the target list is read to the subject at a pace of one word per second. [10] After the fifth trial the interference list is read. [10] The interference list consists of 15 new
words, and the subject is asked to recall them. [10] After the interference list is recalled, the subject is asked to recall the original words from the first trial, and then again after 20 minutes. [10] Lastly, the RAVLT also contains a recognition trial where the subject attempts to recognize and recall as many words as possible from a word set that includes distractors. [10] It has been noted to have a moderate to low test-retest reliability, with the most reliable scores being the total score, delayed recall score, and the trial 5 score. [11] Literature indicates the RAVLT may be affected by age and formal education but not gender or intelligence. [12]

The Digit Span Test is part of the Wechsler battery. [4] It is the most common tool for measuring immediate verbal recall. [4] Each test involves the administrator reading aloud seven pairs of random numbers at a rate of one number per second. [4] There is a digit span forward and a digit span backward, which each test different areas of the brain but both rely on short-term storage capacity.
[4]Short term storage capacity (short-term memory) specifically looks at attention and how much it can process at one time. [4] Although
these measures require the use of the subject's short-term memory, results of these tests are primarily evaluating attention and secondarily evaluating memory. [4]

The National Adult Reading Test (NART) is a way of assessing premorbid intelligence. [4] The ability to word-read has been correlated to general intelligence. [4] The test consists of 50 phonetically irregular words that

the patient is told to pronounce to the best of his or her ability. [4] Patients should attempt to pronounce all 50 words and are encouraged to guess on words they may not have seen before. [4] Scoring is done by using a mathematical equation, which can then predict the Wechsler Adult Intelligence Scale (WAIS- Full Scale) IQ score. [4] NART IQ scores correlate significantly with education (r= .51) and social class (r=.36) based on a study performed in the United Kingdom. [4] Interrater reliability coefficients have reported to be in the range of .96-98 with a test-retest reliability of .98. [4]

Pain can be assessed using many different scales. [13] The Visual Analog Scale (VAS) is commonly used in many populations and are frequently cited in the literature. [13,14] The VAS is a one-dimensional measure of pain intensity and is in public domain. [13] It requires the patient to mark a line where he or she thinks his or her pain falls on a 0-100mm line. [13] At the 0mm mark, the scale reads "no pain" and at the 100mm mark the scale reads "worst imaginable pain." [13] A higher score represents higher pain intensity. [13] The validity of the VAS cannot be assessed since there is no gold standard for pain, however, it has been noted in the literature to have good test-retest reliability ($r = 0.94$, $p < 0.001$). [13] The VAS has been previously validated when looking at chronic pain, but Bijur and colleagues reported the VAS to be a highly reliable tool for the assessment of acute pain as well. [14] In conclusion, each tool has been previously validated in the literature and was chosen to make a broad neuropsychological assessment battery that included the most relevant cognitive domains.

Outcome. *Please state what results you expect to achieve? Who will benefit from this study? How will the participants benefit (if at all). Remember that the participants do not necessarily have to benefit directly. The results of your study may have broadly stated outcomes for a large number of people or society in general.*

Based on previous research, we expect to see a decline in cognitive functioning when the participant is in acute pain. If this is the case, this could influence changes in clinical practice. Clinicians will benefit from this study in the treatment and the evaluation process if this study can identify that pain does affect cognition. If the brain is affected by pain, thinking processes can become delayed which can make a task that is normally easy to complete, more strenuous. It also may be harder for the patient to focus on the exercise if there are other distractions. If this is the case it may be harder for the patient to understand instructions or exercises, which may require modification or a different approach to teaching exercises Overall this means that rehabilitation exercises may be more taxing when the patient is in acute pain, which could change how the clinician communicates with the patient and how the exercise program is set up. Participants in this study will not directly benefit from this study, however the evaluation, treatment, and rehabilitation process of those who are in pain will.

Describe your subjects. *Give number of participants, and applicable inclusion or exclusion requirements (ages, gender requirements, etc.).*

We will recruit about 200 recreationally active subjects over the next three years. It is possible to receive 50-60 participants per year. Participants will be between the ages of 18 and 30 primarily from Georgia Southern University. Those who are not students but have a membership to the Recreation Center will also be included in the study. Recreationally active is defined as any form of physical activity for at least 20 minutes three times a week. This definition of recreationally active was adapted from Riemann et al 2003. [15] Inclusion criteria include those who are 18-30 years of age, recreationally active (at least 20 minutes 3 times per week), in acute pain with a musculoskeletal injury, who present with above 4mm on the Visual Analog Scale (VAS), who are not currently taking analgesics/NSAIDs/ or any pain mediator, who have not had musculoskeletal surgery within the past 6 months, who do not have a history of mental illness (anxiety/depression) or a diagnosed learning disability (ADD/ADHD), and whose first language is English. Those who are above the age of 30, not recreationally active (< 20 minutes 3 times per week) who are not in acute pain, who present less than 4mm on the VAS, do not have a musculoskeletal injury, currently taking analgesics/NSAIDs/ or any pain mediator, those who have had musculoskeletal surgery within the last 6 months, those who have a history of mental illness (anxiety/depression), those who have been diagnosed with ADD/ADHD or any learning disorder, or whose first language is not English will not be included in the study. To ensure participant confidentiality, all data will be de-identified and stored in a locked cabinet. No participants will be required to give their social security number nor their Eagle ID number. All names will be removed from the data and replaced with an ID number. Files will be stored in a locked cabinet inside the athletic training room located in the Recreation Activity Center (RAC). Only the primary investigator and the two Injury Prevention and Care Coordinators will have keys to the locked cabinet in the athletic training room

Recruitment and Incentives: *Describe how subjects will be recruited. (Attach a copy of recruitment emails, flyers or etc.) If provided, describe what incentives will be used and how they will be distributed.)*

The primary investigator, student and professional workers at the recreation center, and those in the athletic training department who are aware of the study will verbally recruit participants. Participants will mainly be recruited when they enter the campus athletic training room presenting in acute pain. Initially participants will be evaluated by a certified athletic trainer (ATC) to rule out fractures, life threatening injuries, or any non-musculoskeletal injuries. If the participants meet the inclusion and exclusion criteria, they will be asked if they want to participate in the study. Those who want to participate and meet the inclusion criteria will be given the informed consent documents and medical history sheet (see Appendix A) from the primary investigator. No one will be required nor pressured to participate in the study, nor will there be consequences for those who do not wish to participate. Incentives will not be provided at any time.

Research Procedures and Timeline: *Enumerate specifically what will you be doing in this study, what kind of experimental manipulations you will use, what kinds of questions or recording of behavior you will use. Focus on the interactions you will have with the human subjects. (Where applicable, attach a questionnaire, focus group outline, interview question set, etc.) Describe in detail any physical procedures you may be performing.*

A certified athletic trainer (ATC) will initially evaluate any participant that presents in acute pain at the campus recreation center. Acute pain will be assessed using the VAS (Appendix A, Figure 1), which defines no pain as 0-4mm, mild pain as 5-44mm, moderate pain as 45-74mm, and severe pain as 75-100mm. Only those who present above 4mm will be included in the study. If the patient would like to participate in the study, he or she will undergo the neuropsychological battery and will be informed that there will be no consequences for not participating and that testing can be stopped at any time.

The neuropsychological battery will include the Trail Making Test B (TMT-B) (Appendix A, Figure 2), the Digit Span Test (Appendix A, Figure 3), the Rey Auditory Verbal Learning Test (RAVLT)(Appendix A, Figure 4), and the National Adult Reading
Test (NART) (Appendix A, Figure 5). All tests have a standardized script that will be used for all testing. Trail Making Test B will be used to measure attention and visual motor tracking (executive function). The RAVLT will be used to measure verbal learning and memory. The RAVLT has alternate forms to control for a practice effect, which will be used for follow up testing. The Digit Span test (forward and backward) will be used to evaluate orientation and attention. Since the RAVLT has a delayed recall trial and can be affected by other verbal tests, the order of the neuropsychological assessments will be given as follows: NART, Digit Span, RAVLT, TMT-B. The delayed recall trial of the RAVLT will occur 20 minutes after the test is administered. During the 20 minute delay period participants will complete simple math sheets that will not be used in data collection. This is to ensure participants are not engaging in a verbal task during the waiting period since that may affect their performance on the RAVLT. All tests will take place in a private room in the recreation center. This battery will take no longer than 30 minutes.

Participants will be contacted by email and/or phone five days after initial injury to follow up and see how they are feeling and to schedule follow up testing. Follow up testing will be administered within two weeks from the initial injury to ensure adequate healing time and to ensure the participant is no longer in acute pain. The same neuropsychological assessments will be given in the same order to each participant and the VAS will be administered to make sure they are no longer in pain (less than 4mm). The primary investigator who has been trained to administer the previously listed neuropsychological assessments will administer all testing.

Data Analysis: Briefly describe how you will analyze and report the collected data. Include an explanation of how will the data be maintained after the study is complete and anticipated destruction date or method used to render it anonymous for future use.

A mixed model repeated measures analysis of variance (ANOVA) will be used to compare variable means (2 time points x 4 tests) using the computer software called Statistical Package for the Social Sciences (SPSS). Variables and outcome measures are as follows:

- Independent Variable: Pain intensity (measured by VAS)
- Dependent Variable: Cognition (measured by NART, TMT-B, Digit Span, RAVLT)
    - NART: Estimated IQ 1 raw score derived from correctly pronounced words)
    - DIGIT SPAN: Working memory (1 raw score based on total number of correct trials)
    - RAVLT: Auditory and Verbal Learning
        - Immediate memory: 1 raw score derived from Trial 1 total
        - Auditory Memory: 1 raw score derived from sum of words from trials 1-5
        - Auditory Memory Delayed: 1 raw score based on words recalled from trial 5- words recalled during trial 7
        - Interference Trial: 1 raw score derived from the difference between trial 6 and trial 5.
    - TMT-B: Attention (1 raw score derived from total time)

This will help answer the overall research question "*Does pain affect cognition?*" To ensure confidentiality, all data will be de-identified and stored in a locked room located at the University recreation center. The primary investigator along with the two Injury Prevention and Care Coordinators will have keys to the locked cabinet inside the athletic training room. Data files will be destroyed in 2031.

Special Conditions:

Risk. *Is there greater than minimal risk from physical, mental or social discomfort? Describe the risks and the steps taken to minimize them. Justify the risk undertaken by outlining any benefits that might result from the study, both on a participant and societal level. Even minor discomfort in answering questions on a survey may pose some risk to subjects. Carefully consider how the subjects will react and address ANY potential risks. Do not simply state that no risk exists. Carefully examine possible subject reactions. If risk is no greater than risk associated with daily life experiences state risk in these terms.*

There is minimal risk of any discomfort in this experiment. First the participant will be evaluated by a certified athletic trainer (ATC). Then the participant will be asked to rate his or her pain using the Visual Analog Scale (VAS). The (VAS) is a common scale that is used in the health care profession. Next, if the participant meets the inclusion criteria and is willing to participate, he/she will be taken to undergo neuropsychological testing. Testing will be held in a private room to minimize distractions and social discomfort. Testing will include the Trail Making Test B, Hopkins Verbal Learning Test, and the Digit Span, which will take no more than 30 minutes to complete. An ATC will be with the participant at all times to ensure safety and answer any questions. All metrics have been validated in the literature and to the best of the investigator's knowledge none report any adverse effects. If at any time the testing becomes uncomfortable or the participant does not want to participate anymore, the testing will be stopped with no consequence. Participants will be told their data will be filed in a locked cabinet to ensure confidentiality. Only the primary investigator and the full time athletic trainers at the recreation center (Eric Roux and Ryan Stuart) will have keys to the locked cabinet.

Research involving minors.

Minors will not be used in this study. If a person is under the age of 18, he/she will not be a participant in this study.

Deception.

Deception will not be used in this study.

Medical procedures.

There will be no medical procedures used in this study.

Literature Review Reference list (not counted in page limit):

1. Melzack R. Pain and the neuromatrix in the brain. *J Dent Educ*. 2001;65(12):1378.

2. Carr DB, Goudas LC. Acute pain. *The Lancet*. 1999;353(9169):2051-2058.

3. Smart KM, O'Connell NE, Doody C. Towards a mechanisms-based classification of pain in musculoskeletal physiotherapy? *Physical Therapy Reviews*. 2008;13(1):1-10.

4. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment.* Fourth ed. 198 Madison Avenue, New York, New York, 10016: Oxford University Press; 2004:1016.

5. Hutchison M, Comper P, Mainwaring L, Richards D. The influence of musculoskeletal injury on cognition: Implications for concussion research. *The American Journal of Sports Medicine*. 2011;39(11):2331-2337. doi:10.1177/0363546511413375.

6. Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. *J Neurophysiol*. 2007;97(5):3651-3659.

7. Casey G. Continuing professional development. pain -- the fifth vital sign. *KAI TIAKI NURS NZ*. 2011;17(5):24-29 6p.

8. Merskey H, Bogduk N. Classification of chronic pain.1994.

9. Gilbert SJ, Burgess PW. Executive function. *Current Biology*. 2008;18(3):R110-R114.

10. Sullivan K, Deffenti C, Keane B. Malingering on the RAVLT: Part II. detection strategies. *Archives of Clinical Neuropsychology*. 2002;17(3):223-233.

11. Strauss, E., Sherman, E.M.S., Spreen, O. *A compendium of neurospsychological tests: Administration, norms and commentary.*3rd ed. New York: Oxford University Press; 2006.

12. Messinis L, Tsakona I, Malefaki S, Papathanasopoulos P. Normative data and discriminant validity of rey's verbal learning test for the greek adult population. *Archives of Clinical Neuropsychology*. 2007;22(6):739-752.

13. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care & Research*. 2011;63(S11):S240-S252.

14. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med.* 2001;8(12):1153-1157.

15. Riemann BL, Tray NC, Lephart SM. Unilateral multiaxial coordination training and ankle kinesthesia, muscle strength, and postural control. *J Sport Rehabil.* 2003;12(1):13-30.

Cover page checklist. *Please provide additional information concerning risk elements checked on the cover page and not yet addressed in the narrative. If none, please state "none of the items listed on the cover page checklist apply." The cover page can be accessed from the IRB forms page. (Note – if a student, make sure your advisor has read your application and signed your cover page. (Your advisor is responsible for the research you undertake in the name of GSU.)*

None of the items listed on the cover page checklist apply.

Reminder: No research can be undertaken until your proposal has been approved by the IRB

FIGURE 1: THE VISUAL ANALOG SCALE (VAS)

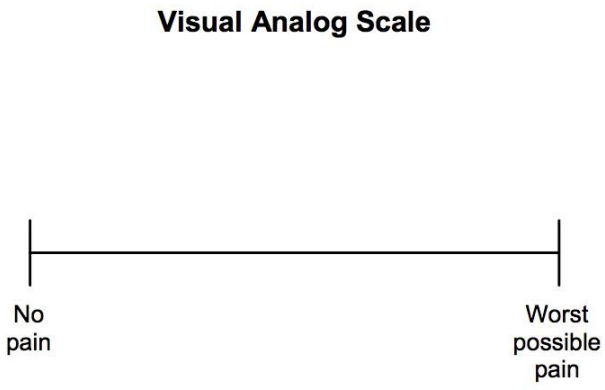


FIGURE 2: TRAIL MAKING TEST B (TMT-B) SAMPLE

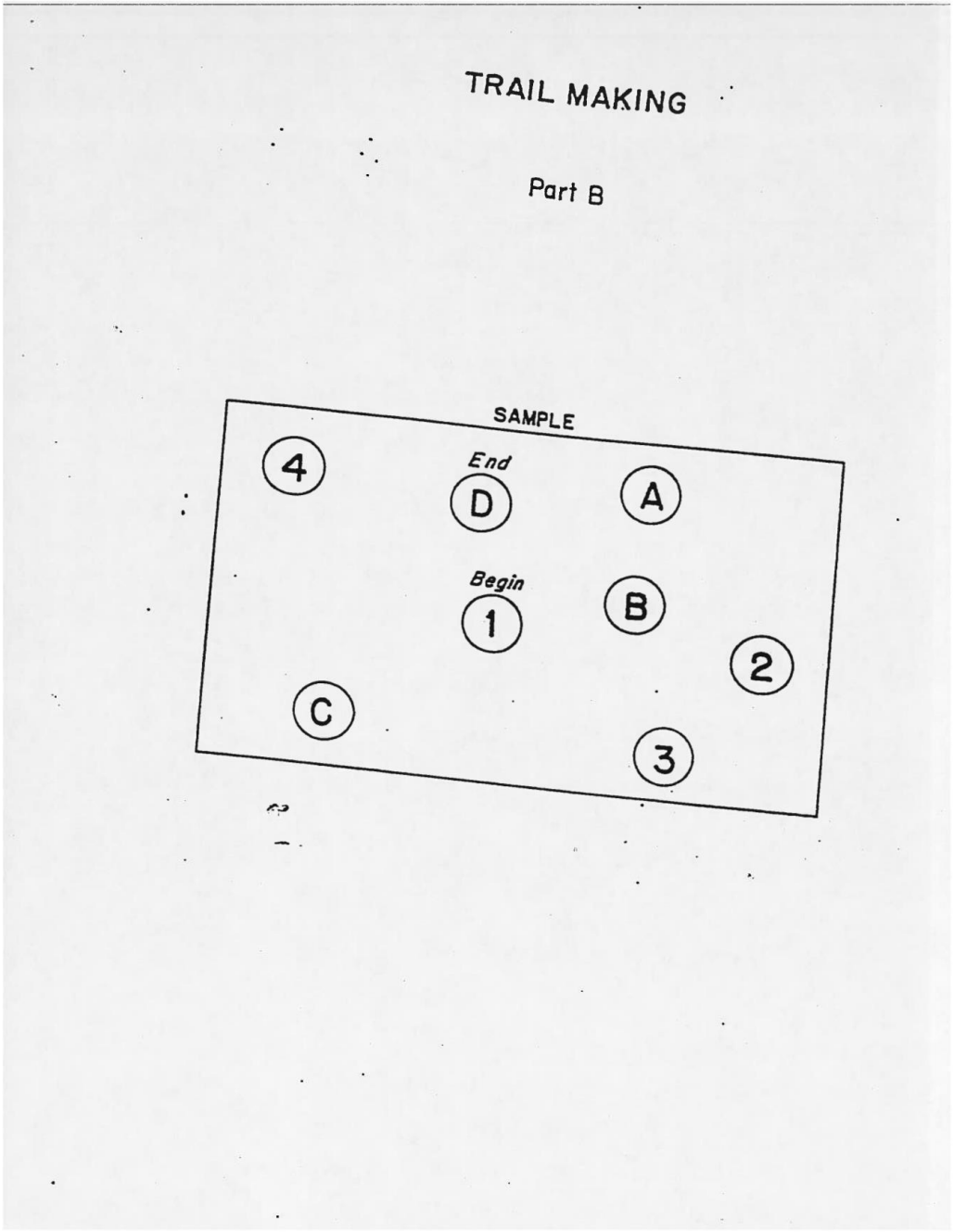


FIGURE 2: TRAIL MAKING TEST B (TMT-B)

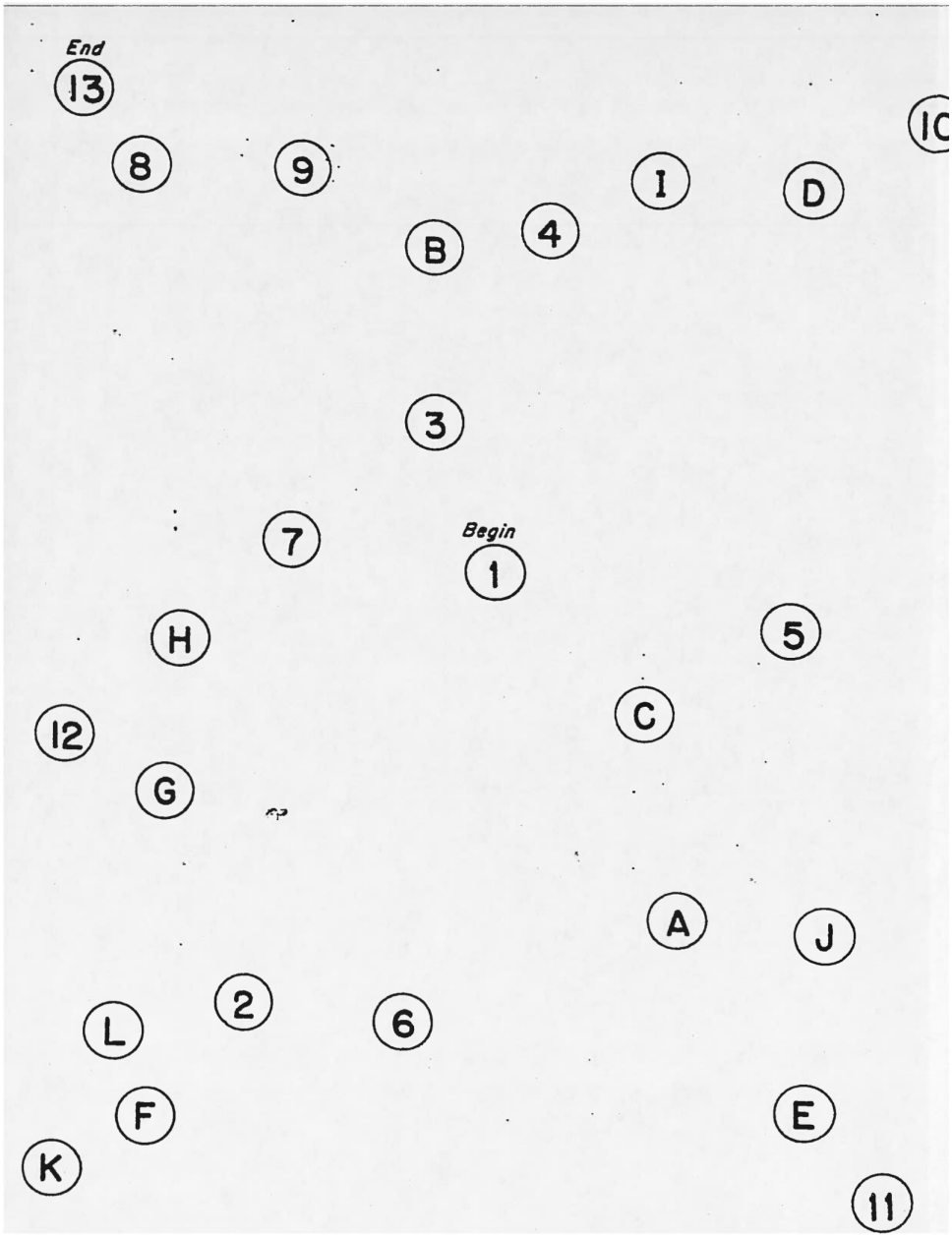
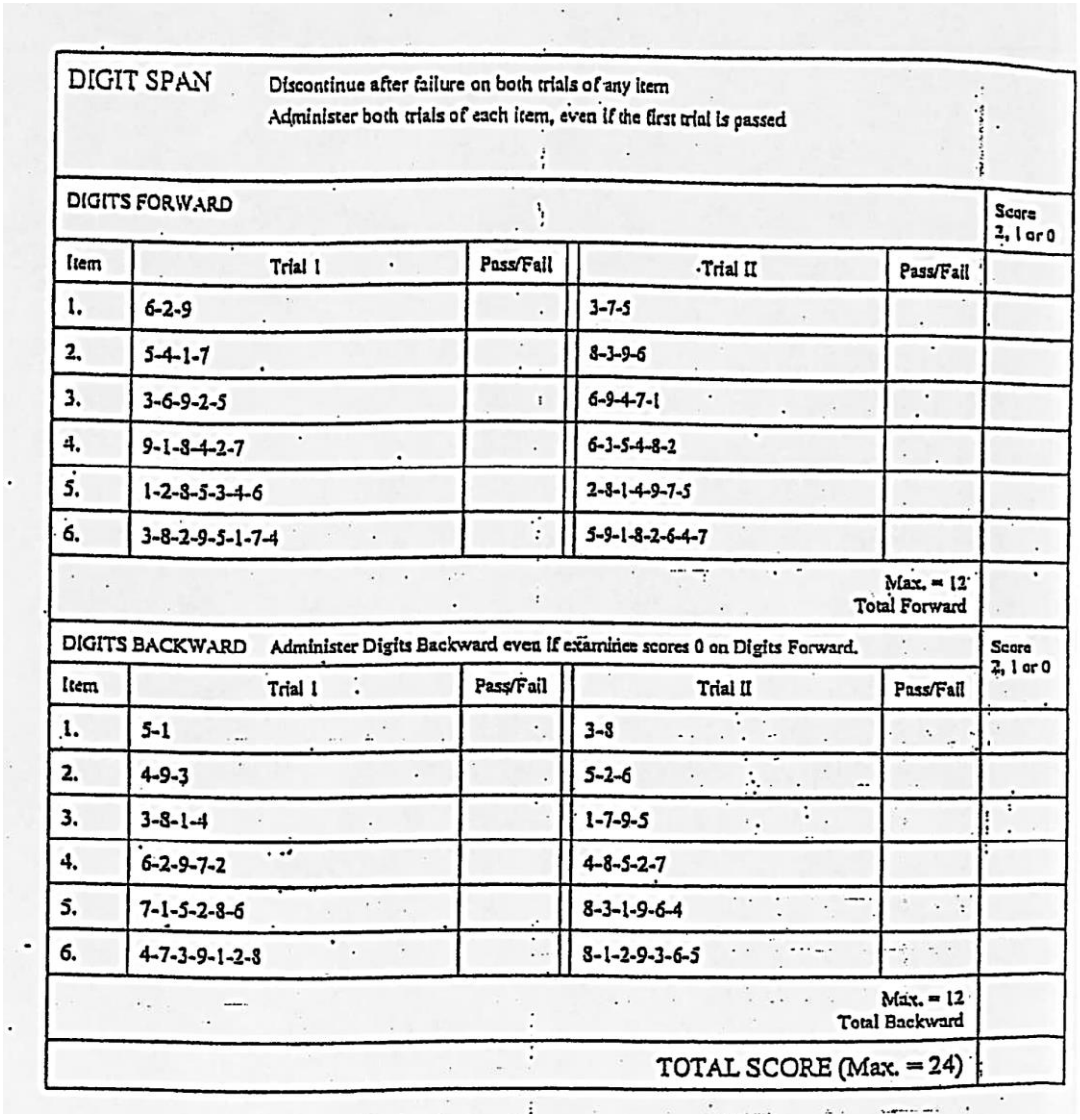


FIGURE 3: DIGIT SPAN TEST



DIGIT SPAN Discontinue after failure on both trials of any item
Administer both trials of each item, even if the first trial is passed

DIGITS FORWARD					Score 2, 1 or 0
Item	Trial I	Pass/Fail	Trial II	Pass/Fail	
1.	6-2-9		3-7-5		
2.	5-4-1-7		8-3-9-6		
3.	3-6-9-2-5		6-9-4-7-1		
4.	9-1-8-4-2-7		6-3-5-4-8-2		
5.	1-2-8-5-3-4-6		2-8-1-4-9-7-5		
6.	3-8-2-9-5-1-7-4		5-9-1-8-2-6-4-7		
				Max. = 12 Total Forward	

DIGITS BACKWARD Administer Digits Backward even if examinee scores 0 on Digits Forward.					Score 2, 1 or 0
Item	Trial I	Pass/Fail	Trial II	Pass/Fail	
1.	5-1		3-8		
2.	4-9-3		5-2-6		
3.	3-8-1-4		1-7-9-5		
4.	6-2-9-7-2		4-8-5-2-7		
5.	7-1-5-2-8-6		8-3-1-9-6-4		
6.	4-7-3-9-1-2-8		8-1-2-9-3-6-5		
				Max. = 12 Total Backward	
				TOTAL SCORE (Max. = 24)	

FIGURE 4: REY AUDITORY VERBAL LEARNING TEST (RAVLT)

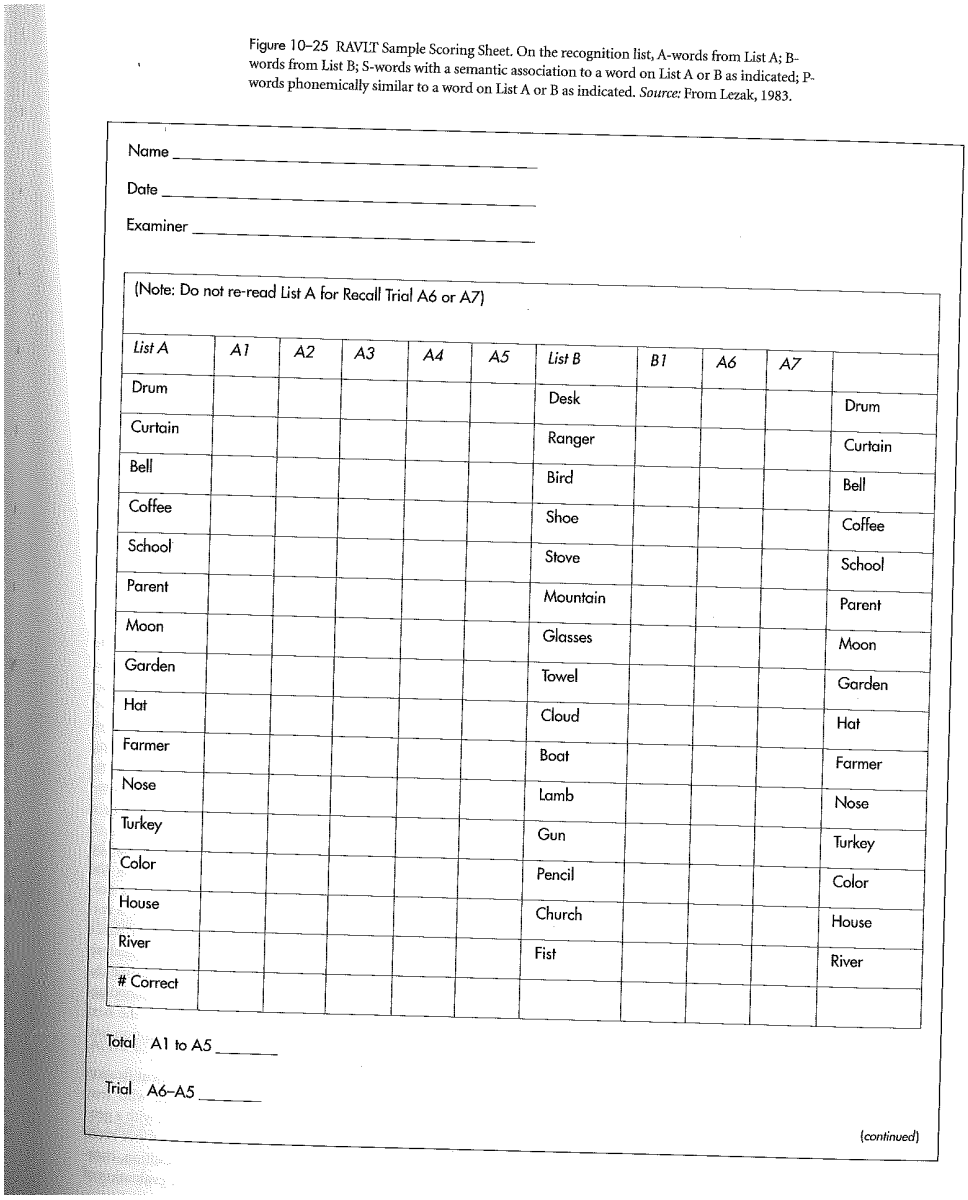


Figure 10–25 RAVLT Sample Scoring Sheet. On the recognition list, A-words from List A; B-words from List B; S-words with a semantic association to a word on List A or B as indicated; P-words phonemically similar to a word on List A or B as indicated. *Source:* From Lezak, 1983.

Name _____

Date _____

Examiner _____

(Note: Do not re-read List A for Recall Trial A6 or A7)

List A	*A1*	*A2*	*A3*	*A4*	*A5*	*List B*	*B1*	*A6*	*A7*	
Drum						Desk				Drum
Curtain						Ranger				Curtain
Bell						Bird				Bell
Coffee						Shoe				Coffee
School						Stove				School
Parent						Mountain				Parent
Moon						Glasses				Moon
Garden						Towel				Garden
Hat						Cloud				Hat
Farmer						Boat				Farmer
Nose						Lamb				Nose
Turkey						Gun				Turkey
Color						Pencil				Color
House						Church				House
River						Fist				River
# Correct										

Total A1 to A5 _____

Trial A6–A5 _____

(continued)

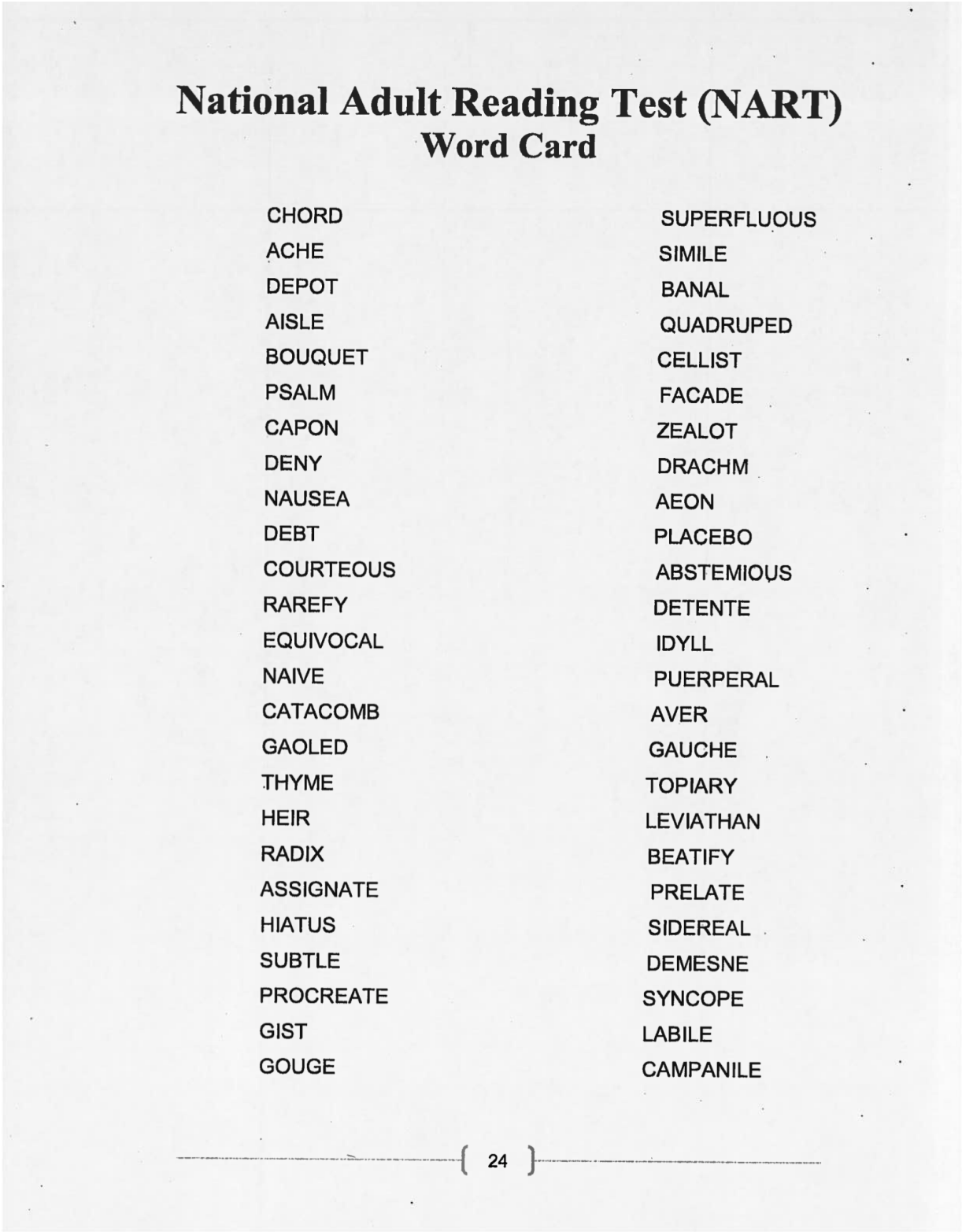
FIGURE 4: REY AUDITORY VERBAL LEARNING TEST (RAVLT), ALTERNATE FORM

Figure 10–26 Alternate form of the RAVLT by Geffen et al., 1994. Abbreviations for the recognition list are the same as in Figure 10–25. *Source:* Adapted from Geffen, et al. 1994.

List A	*Interference List B*			
Pipe	Bench			
Wall	Officer			
Alarm	Cage			
Sugar	Sock			
Student	Fridge			
Mother	Cliff			
Star	Bottle			
Painting	Soap			
Bag	Sky			
Wheat	Ship			
Mouth	Goat			
Chicken	Bullet			
Sound	Paper			
Door	Chapel			
Stream	Crab			

Recognition List				
Alarm (A)	Eye (SA)	Soap (B)	Ship (B)	Bottle (B)
Aunt (SA)	Crab (B)	Wall (A)	Car (PA)	Seat (SB)
Bag (A)	Star (A)	Clock (SA)	Mother (A)	Sock (B)
Creek (SA)	Rag (PA)	Sound (A)	Duck (SA)	Tone (SA)
Officer (B)	Bun (PA)	Bench (B)	Wheat (A)	Fridge (B)
Mouth (A)	Cage (B)	Bullet (B)	Floor (SPA)	Rock (SPB)
Arrow (SB)	Cliff (B)	Night (SA)	Sky (B)	Bread (SA)
Student (A)	Sugar (A)	Chapel (B)	Door (A)	Pipe (A)
Hail (PA)	Cream (PA)	Chicken (A)	Bridge (PB)	Ball (PA)
Paper (B)	Stream (A)	Coat (PB)	Painting (A)	Goat (B)

FIGURE 5: NATIONAL ADULT READING TEST (NART)



National Adult Reading Test (NART)
Word Card

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAIVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

24

FIGURE 5: NATIONAL ADULT READING TEST (NART) ANSWER SHEET

National Adult Reading Test (NART)
Answer Sheet

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAIVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

NART total errors:

	Obtained IQ	*NART Predicted IQ*	*predicted-obtained IQ*	*abnormality (%)*
Full Scale IQ				
Verbal IQ				
Performance IQ				

GEORGIA SOUTHERN UNIVERSITY
HEALTH QUESTIONNAIRE

Please answer the following as honestly as possible.
All answers will remain confidential.

Name: _____ Date: _____
Time:_____

DOB: _____ Current Age: _____ Cell Phone:
_____

Circle your current year in school

Freshman Sophomore Junior Senior Other_____

Master's Doctoral None (list the highest degree completed_____)

GPA_____

Is your primary language English? (Circle one) YES NO

Please check your ethnicity:
_____ White (not Hispanic origin)
_____ Black (not Hispanic origin)
_____ Hispanic
_____ Asian or Pacific Islander
_____American Indian or Alaskan
_____Other

Please circle the appropriate answer below:

1. Do you play club sports? YES NO
   a. If so what sport? _____
2. Do you play intramural sports? YES NO
   a. If so, what sport? _____
   b. If not, did you used to play? (if so state when and which sport)
      _____
3. If you currently participate in sports, did you have practice or have a game today?
   a. YES
   b. NO
   c. Not Applicable

4. How many hours a week are you physically active for? (Running, lifting, fitness classes, sports, swimming, etc.)

   _____ Hours

5. Are you physically tired from physical activities you participated in today?
   a. YES
   b. NO
   c. Not Sure

6. Have you ever been diagnosed with ADD or ADHD?
   a. YES
   b. NO
   c. Unknown

7. Have you ever been diagnosed with anxiety, depression, or any other mental illness?
   a. YES
   b. NO
   c. Unknown

8. Are you currently taking any pain medication including Advil/Tylenol?
   a. YES
   b. NO
   c. Unknown

9. Have you ever had a diagnosed concussion by a medical professional (doctor, athletic trainer, nurse, etc.)?
   a. YES (if yes, please list when each occurred _____)
   b. NO
   c. Unknown

10. Are you physically sick today? (cold, flu, allergies)
    a. YES
    b. NO
    c. Not sure

11. Have you had ANY SURGERIES in the last 6 months? If yes, please list all procedures and when they occurred.
    a. YES

_____

_____

    b. NO
    c. Unknown

12. Have you had any previous injuries?

a. YES (if yes, please list the injury & date of injury below)

_____

_____

_____

b. NO
c. Unknown

13. Which is your dominant hand?
    a. RIGHT
    b. LEFT

14. Have you had caffeine today? (coffee, soda, preworkout, etc.)
    a. YES (if yes, how much and what time? _____)
    b. NO
    c. Not sure

15. About how many hours of sleep did you get last night? _____

16. Have you ever been neuropsychologically tested and/or tested at the Student Disability Resource Center (SDRC)?
    a. YES (if yes, when and what did you do? _____)
    b. NO
    c. Not sure

17. Is there anything else you would like the researchers to know about that may affect this study? (if not, please leave this question blank)

_____

_____

_____

FOLLOW UP HEALTH QUESTIONNAIRE

Please answer the following as honestly as possible.
All answers will remain confidential.

Name: _____ Date: _____ Time:_____

Please circle the appropriate answer below:

1. Do you currently play club sports? YES NO
    a. If so what sport? _____
    b. If not, did you used to play? (if so state when and which sport)
    _____

2. Do you currently play intramural sports? YES NO
    a. If so, what sport? _____
    b. If not, did you used to play? (if so state when and which sport)
    _____

3. If you currently participate in sports, did you have practice or have a game today?
    a. YES
    b. NO
    c. Not Applicable

4. Are you physically tired from physical activities you participated in today?
    a. YES
    b. NO
    c. Not Sure

5. Are you currently taking any pain medication including Advil/Tylenol?
    a. YES
    b. NO
    c. Unknown

6. Are you physically sick today? (cold, flu, allergies)
    a. YES
    b. NO
    c. Not sure

7. Have you had injuries between your initial testing date and now?
    a. YES (if yes, please list the injury & date of injury below)

_____

    b. NO
    c. Unknown

8. Have you had caffeine today? (coffee, soda, preworkout, etc.)

a. YES (if yes, how much and what time? _____)
b. NO
c. Not sure

9. About how many hours of sleep did you get last night? _____

10. Is there anything else you would like the researchers to know about that may affect this study? (if not, please leave this question blank)

_____

_____

Georgia Southern University
Office of Research Services & Sponsored Programs

Institutional Review Board (IRB)

Phone: 912-478-5465
Fax: 912-478-0719
IRB@GeorgiaSouthern.edu
Veazey Hall 3000
PO Box 8005
Statesboro, GA 30460

To: Morgiello, Jenna
Murray, Nicholas; Hunt, Tamerah; Harris, Brandon; Shaver, George

From: Office of Research Services and Sponsored Programs
Administrative Support Office for Research Oversight Committees (IACUC/IBC/IRB)

Initial Approval Date: 7/25/2016

Expiration Date: 6/30/2017

Subject: Status of Application for Approval to Utilize Human Subjects in Research – **Expedited**

After a review of your proposed research project numbered **H16448** and titled **"The Influence of Acute Pain on Cognitive Functioning Post Injury"** it appears that (1) the research subjects are at minimal risk, (2) appropriate safeguards are planned, and (3) the research activities involve only procedures which are allowable. You are authorized to enroll up to a maximum of **200** subjects.

Therefore, as authorized in the Federal Policy for the Protection of Human Subjects, I am pleased to notify you that the Institutional Review Board has approved your proposed research. Description:

If at the end of this approval period there have been no changes to the research protocol; you may request an extension of the approval period. In the interim, please provide the IRB with any information concerning any significant adverse event, **whether or not it is believed to be related to the study**, within five working days of the event. In addition, if a change or modification of the approved methodology becomes necessary, you must notify the IRB Coordinator **prior** to initiating any such changes or modifications. At that time, an amended application for IRB approval may be submitted. Upon completion of your data collection, you are required to complete a *Research Study Termination* form to notify the IRB Coordinator, so your file may be closed.

Sincerely,

Eleanor Haynes
Compliance Officer

Georgia Southern University
Office of Research Services & Sponsored Programs

Institutional Review Board (IRB)

Phone: 912-478-5465
Fax: 912-478-0719
IRB@GeorgiaSouthern.edu
Veazey Hall 3000
PO Box 8005
Statesboro, GA 30460-8005

To: Morogiello, Jenna
Murray, Nicholas; Hunt, Tamerah; Harris, Brandon; Shaver, George

From: Office of Research Services and Sponsored Programs
Administrative Support Office for Research Oversight Committees (IACUC/IBC/IRB)

Date: 10/17/2016

Expiration Date: 6/30/2017

Subject: Status of Research Study Modification Request

After a review of your Research Study Modification Request on research project numbered **H16448** and titled **"The Influence of Acute Pain on Cognitive Functioning Post Injury,"** your request for modification appears that (1) the research subjects are at minimal risk, (2) appropriate safeguards are planned, and (3) the research activities involve only procedures which are allowable.

Therefore, as authorized in the Federal Policy for the Protection of Human Subjects, I am pleased to notify you that the Institutional Review Board has approved your modification request. **Description: This amendment adds question to the Medical Health Questionnaire as well as an additional follow-up questionnaire.**

The expiration date of your original application approval remains in effect. If additional time beyond your expiration date is required to complete your data collection and analysis and there have been no further changes to the research protocol; you may request an extension of the approval period. If your project will require approval beyond 36 months from the initial approval date, a new submission and review will be required. In the interim, please provide the IRB with any information concerning any significant adverse event, **whether or not it is believed to be related to the study**, within five working days of the event. In addition, another change or modification of the approved methodology becomes necessary; you must notify the IRB Coordinator **prior** to initiating any such changes or modifications. At that time, an amended application for IRB approval may be submitted. Upon completion of your data collection, you are required to complete a *Research Study Termination* form to provide the final information to allow your file to be closed.

Sincerely,

Eleanor Haynes
Compliance Officer