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Obtaining Normative Data on Capacity-Based Assessments of Cognitive Functioning

by

Luke J. Heckly

A thesis

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in the Department of Communication

Sciences and Disorders

Idaho State University

Summer 2014

Committee Approval

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Nicholas Altieri, PhD
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RE: Your application dated 9/18/2012 regarding study number 3801: Multisensory Integration

Dear Dr. Altieri:

I have reviewed your request for expedited approval of the new study listed above. This is to confirm that I have approved your application.

Notify the HSC of any adverse events. Serious, unexpected adverse events must be reported in writing within 10 business days.

Submit progress reports on your project in six months. You should report how many subjects have participated in the project and verify that you are following the methods and procedures outlined in your approved protocol. Then, report to the Human Subjects Committee when your project has been completed. Reporting forms are available on-line.

You may conduct your study as described in your application effective immediately. The study is subject to renewal on or before 9/25/2013, unless closed before that date.

Please note that any changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full board review. Contact Patricia Hunter (208-282-2179; fax 208-282-4529; email: humsubj@isu.edu) if you have any questions or require further information.

Sincerely,

Ralph Baergen, PhD, MPH, CIP
Human Subjects Chair

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Abstract

Dementia is becoming increasingly prevalent, and earlier identification is becoming more important for assisting physicians in addressing complications associated with the disease. One risk factor for dementia, mild cognitive impairment (MCI), has been described as being a major factor in the future development of dementia with over 40% of patients with MCI developing dementia later in life. Patients presenting with MCI have also been found to be sensitive to manipulations of workload. This report introduces a cued-picture recognition task utilizing a measure of capacity, and further discusses normative data gathered from a healthy adult population using this task.

Chapter 1: Introduction

"Dementia," broadly speaking, refers to classes of progressive and degenerative neurological disorders including, but not limited to Alzheimer's disease, vascular dementia, and Parkinson's disease. Patients with dementia experience a progressive decline in cognitive abilities that ranges from word finding difficulty and minor short-term memory disturbance in earlier stages, to long-term memory impairment, mutism, immobility and dysphagia in later stages. Ferri et al. (2005) described dementia as being "one of the most burdensome conditions of later life" (Ferri, et al., 2005, p. 1), due in large part to the cost of patient care, and end of life issues. This collection of disorders referred to as "dementia" has significant ramifications reaching beyond loss of cognitive abilities in the affected individual; these disorders also significantly impact the lives of caregivers and family members, making management and early intervention a significant priority for society at large.

Importantly, there are many early signs and preceding indicators of dementia that may be detectible with sensitive behavioral and imaging measures. This thesis focuses on the detection of one of the significant factors, a form of abnormal aging associated with memory loss known as "mild cognitive impairment (MCI)." Furthermore, MCI and dementia of the Alzheimer's type represents the most common and most costly subset of dementias (Monsonego, Nemirovsky, & Herpaz, 2013). This review will address questions related to how early stages of cognitive impairment that are predictive of dementia of the Alzheimer's type may be assessed optimally in order to facilitate early detection.

The risk for developing dementia after the age of 65 years is approximately 17 to 20% (Simmons, Hartmann, & DeJoseph, 2011) with the incidence of dementia rapidly growing worldwide as the proportion of elderly people relative to the population increases. Specifically, Ferri et al. (2005) estimated that approximately 24 million people were affected by dementia, and that the number was expected to double to 42 million by the year 2020. Additionally, Prince et al. (2013) carried out a meta-analysis that estimated the number of individuals affected by dementia. The authors estimated that by the year 2030, the prevalence of dementia would double every 20 years to 65.7 million, and by 2050, 115.4 million people would be affected (Prince, et al., 2013). Other forms of dementia that are also common include Dementia with Lewy Bodies, Vascular Dementia, and Fronto-temporal Dementia. These shall be briefly addressed and defined in the following subsection.

Classification of Dementias

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia and accounts for approximately 60%-80% of dementia cases. It is typically associated with a *sequela* of declining short-term and working memory capabilities, especially difficulties with acquiring new information (Alzheimer's Association, 2012). The progression of Alzheimer's disease has been broadly categorized into three discrete stages: early, middle, and late (Stefanakos & Crouch, 2001). According to Stefanakos and Crouch (2001), the early stage presents with degeneration in certain hippocampal subregions, leading to problems in forming new declarative memories, and encoding items into working short-term, and then into long-term memory. For example, patients in the early stages might become lost, or lose and misplace objects. A progressive deterioration of working, semantic, and lexical memory is also observed. Patients typically begin to exhibit difficulty with sustaining attention, retrieving words, understanding concepts. Changes in personality may occur in the early to middle stages as well in some patients; this is observed behaviorally as psychiatric and behavioral symptoms such as anxiety, depression, and even paranoia may become manifest. Some individuals may appear to become apathetic, disorganized, or otherwise impulsive (Stefanakos & Crouch, 2001).

The middle stage of AD presents with further decline of memory, difficulties with travel and finances, temporal and spatial orientation; a caregiver is often required to assist the patient in daily living. Finally, patients in the late stage of dementia become disoriented to self, time, and place, and lose most receptive and productive language function. They may also become incontinent, agitated, delusional, immobile, and commonly dysphagic. They will generally lose the ability to walk and recognize familiar people in the later stages. Language during later stages consists mostly of nonverbal communication due to the loss of ability to communicate verbally (Stefanakos & Crouch, 2001).

Vascular Dementia

Vascular Dementia (VaD) is resultant of disruption to the brain from cerebrovascular accidents (CVAs). CVAs result from long histories of untreated hypertension and symptoms present in a “stepwise” deterioration progression. Stefanakos and Crouch (2001) stated that the neurological signs are dependent on the site of lesion; therefore, the symptoms of vascular dementia may appear focal in the early stages of the disease. Damage to the perisylvian region, for instance, will typically result in aphasia or language disturbances such as word finding difficulties and dysfluency. Agnosias may be caused by damage to the left or right parietal regions, while memory impairments and attentional disorders may also be caused by diffuse damage. Subcortical damage can lead to motor impairments and other cognitive-linguistic abnormalities (Stefanakos & Crouch, 2001). Impairments in short-term memory early in the disorder may make dementia of the Alzheimer's type difficult to distinguish from vascular dementia.

Lewy Body Dementia

Dementia with Lewy bodies (DLB) is caused by the formation of protein deposits inside the nerve cells which are known as "Lewy bodies." Patients with DLB present with degeneration of the substantia nigra in the brainstem, decreased or ceased production of dopamine, cortical degeneration similar to AD, and shrinking of the temporal and parietal lobes and the cingulate gyrus (Stefanakos & Crouch, 2011). Patients may have similar symptoms to Parkinson's and AD, and AD can even coexist with DLB (Alzheimer's Association, 2012). Patients generally exhibit characteristics such as impaired recent and short-term memory, behavioral disturbances, word-retrieval problems, visuospatial difficulties, problems with attention, mental inflexibility, indecisiveness and lack of judgment, cognitive fluctuations early on, visual hallucinations, myoclonus, and immobility and profound dementia in the end stages. DLB is progressive, global, severe, and the course of the disease takes approximately seven years from the onset of symptoms to death (Stefanakos & Crouch, 2001).

Frontotemporal Dementias

Frontotemporal Dementia (FTD) is a dementia classification characterized by degeneration localized to the frontal and temporal lobes of the brain—at least in the early to middle stages of the disease. Consequently, Stefanakos and Crouch (2001) described how medical characteristics of FTD generally exhibit symptoms that differ from AD. Frontal degeneration may present with personality changes and loss of inhibition that may lead to inappropriate or rude behavior. These patients will present with mental inflexibility, failure to recognize faces, compulsive behavior, “childlike” behavior, obsessive food cravings, excessive alcohol use, oral obsessiveness, attentional deficits, sexual aggression, and incontinence. Temporal degeneration, on the other hand, is associated with deterioration of language production or comprehension capabilities. During earlier stages, the individual will typically retain temporal awareness and can recognize people and places. FTD characteristics may also include focal speech problems such as aphasia, echolalia, fluency disruption, and complete loss of communication (Stefanakos & Crouch, 2001). Table 1 provides a comparison between language and other characteristics that are often seen between various dementia types.

Major dementia subtypes and defining characteristics

Dementia Type	**Language Characteristics**	**Other Characteristics**
Alzheimer’s Disease	• Semantic and lexical systems deteriorate • Word finding problems • No verbal communication skills (Late stage)	• Attention difficulties • Difficulty understanding concepts • Depression • Changes in personality • Memory difficulties • Difficulty travelling • Temporal and spatial disorientation • Disorientation for self, time, and place • Incontinence • Agitation • Delusional • Dysphagia • Inability to walk • No longer recognizes familiar people

Vascular Dementia	• Symptoms dependent on site of lesion	• Symptoms dependent on site of lesion • Short-term memory impairment • CVA
Dementia with Lewy Bodies	• Word-finding problems	• Impaired recent memory • Behavioral disturbance with preserved memory • Visuospatial difficulties • Inattention • Mental inflexibility • Indecisiveness • Lack of judgment • Visual hallucinations • Clinical features of Parkinson's disease • Myoclonus • Eventual profound dementia • Immobility
Frontotemporal Dementia	• Echolalia • Muteness (middle to late stages) • Loss of speech fluency • Aphasia	• Personality changes • Loss of inhibition • Mental inflexibility • Failure to recognize faces • May use objects wrong • Compulsive behavior • Childlike behavior • Overeating • Excessive alcohol intake • Oral obsessiveness • Attentional deficits • Sexual aggression • Incontinence

Table 1: This table lists major dementia subtypes and defining characteristics (Stefanakos & Crouch, 2001)

Risk Factors Associated with Dementia

There are several risk factors for developing dementia used to assist diagnosis. While the greatest risk factor is age, others include family history, presence of the "apolipoprotein E4 genotype, cardiovascular comorbidities, chronic anticholinergenic use, and lower educational level" (Simmons, Hartmann, & DeJoseph, 2011, p. 895).

Additional risk factors include previous head injury and also gender – with females having a higher incidence (Santacruz & Swagerty, 2001, p. 703). A risk factor that this paper examines closely is mild cognitive impairment (MCI).

Longitudinal studies have also observed that pathological decline in cognitive capabilities, including processing speed, reaction times, memory, problem solving abilities, attention, orientation, and verbal memory, are observed at a higher rate in elderly people (DeCarli, 2003). Elderly adults have been observed to have poorer performance compared to younger adults on cognitive, memory, and IQ tasks. This suggests that a common result of normal aging includes memory impairment. Deficits that present in dementia are more pronounced and of a progressive nature, and affect cognitive capabilities to differing degrees.

Helm-Estabrooks and Albert (2004) stated that memory functions encompass numerous cognitive linguistic skills, including the ability to learn and retain new information for later retrieval (Helm-Estabrooks & Albert, 2004). Of course, "memory" does not refer to a homogenous construct, but rather the complex interaction of several logically distinct subsystems including *short term memory, working memory*, *long term memory,* and *procedural memory*, to name just a few of the most relevant to the topic at hand. *Short-term memory* refers to the individual's ability to retain information for a short period of time, which is subsequently converted into long-term knowledge upon rehearsal (Atkinson & Shiffrin, 1968). Without rehearsal strategies this information is eventually forgotten and is no longer retained (Cowan, 2008). *Working memory* has been described as an activated subset of short term memory that is consciously manipulated (Cowan, 2008). Therefore, working memory denotes the individual's ability to temporarily store and manipulate information. *Long term memory* refers to information that is stored permanently and does not decay (Atkinson & Shiffrin, 1968). Finally, *procedural memory* is related to the ability to learn and retain skilled performance (Willingham, Nissen, & Bullemer, 1989).

Declines in working memory due to “normal aging” impede a patient’s ability to memorize word lists, reason, utilize complex spoken and written language, process complex sentences, and identify unfamiliar words from context. Therefore, working and short-term memory are adversely affected in the early stages of dementia, and even to some degree, in normal and healthy older individuals. Because the ability to manipulate stored memory declines when working memory is impaired, processing speed is also negatively affected.

Related to the encoding and short term storage of information, Zelinski, Dalton, and Hindin (2011) described processing speed as “the rate at which rapid perception and execution of decisions occur” (Zelinski, Dalton, & Hindin, 2011, p. 13). Slowing processing speeds can make performing complex tasks, such as word retrieval or understanding rapid and complex speech, more difficult. Older adults and those with mild cognitive impairment (MCI) may incorrectly encode information and therefore “remember” events that did not happen and they have difficulties retrieving information that was previously learned.

Complaints of memory loss without accompanying impairment in social function among patients can be signs of mild cognitive impairment (MCI), which has been described as a precursor to dementia of the Alzheimer’s type (Kiral, Ozge, Sungur, & Tasdelen, 2013). Thus, some studies have suggested that MCI in the elderly may be a transitional stage between normal aging processes and AD, and is worthy of further study as a risk factor for developing AD (DeCarli, 2003; Wenger, Negash, Petersen, & Petersen, 2010; Pogessi et al., 2012; Campbell, Unverzagt, LaMantia, Babar, & Boustani, 2013). Critically, approximately 10% to 15% of patients with MCI develop AD per year after MCI is diagnosed. After a period of three or more years, this increases to over 40% (Kiral et al., 2013). Because MCI represents a significant risk for developing AD, this area is worth investigating further. Earlier diagnosis of MCI has the potential to assist physicians in earlier diagnosis of dementias, thus leading to more timely intervention. The purpose of this report is to provide normative data on a sensitive behavioral assessment of cognitive functioning recently tested in the mathematical psychology literature (Wenger, Negash, Petersen, & Petersen, 2010). Ideally, this measure may be useful for diagnosing early MCI or those at risk for dementia, versus normally aging individuals.

Chapter 2: Assessment of Dementia

McCarten (2013) pointed out that many individuals affected with dementia do not realize the extent of their cognitive decline, and may appear to be aging normally to others until later stages. Even if the patient recognizes symptoms they and their families may be in denial and discount the symptoms as part of the normal aging process. McCarten (2013) argued that screening for cognitive impairment is highly beneficial because living in ignorance of symptoms could be dangerous and that early detection and treatment could prevent injury, financial problems, etc. (McCarten, 2013). Earlier identification of Alzheimer's is useful for providing earlier treatment (Hänninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002) which preserves and maintains function, independence, and quality of life for as long as possible (Santacruz & Swagerty, 2001).

Incidentally, there are several signs, symptoms, and even familial risk factors that indicate the necessity for early dementia assessment. Santacruz and Swagerty (2001) stated that these signs may include changes in memory, cognition, and executive functioning. These changes in executive functioning can lead to difficulties in activities of daily living (ADLs) (McKinlay & Grace, 2011). The hallmark of dementias, and specifically AD, is impaired recent memory. Oftentimes, memory impairment may be the only clinical finding during early stages of the disease (Santacruz & Swagerty, 2001). Individuals with AD will also have difficulties with learning and remembering new information (McCarten, 2013). Santacruz and Swagerty (2001) stated that declines in memory may be difficult to detect during short office visits, especially when the patient converses well (Santacruz & Swagerty, 2001). First, this report shall focus on changes in memory, including some methods of how these changes have been assessed using traditional methods such as cognitive tests.

Standardized Assessments of Cognitive Function

In addition to informally observing signs and symptoms of cognitive impairment associated with dementia, clinicians and physicians also utilize standardized assessments of cognitive function. Standardized assessments are utilized to compare an individual's performance to a random sample of (usually) age matched controls. Paul and Norbury (2012) stated that standardized assessments are useful because they are typically well-constructed, generally have high reliability, and give the assessor a means of comparing the individual's performance to the norm of a group with a standard distribution. A good standardized assessment will outline specific methods of administering and scoring a test, minimalizing the extraneous variables during administration. However, there can also be disadvantages with using standardized assessments. While an assessment may detect memory deficits, it may not be able to separate deficits from normal aging or abnormal causes such as MCI or early AD, or other cognitive injury such as TBI. Standardized assessments also may not be effective if they are chosen improperly and not valid for the individual being assessed. This makes it difficult to find out a client's specific strengths and weaknesses (Paul & Norbury, 2012). For example, a study conducted by Iliffe, Manthorpe, and Eden (2003) found that many practitioners did not use common cognitive assessments due to the fact that administration was considered too long and, although indicated deficits, did not provide information to aid in making specific diagnoses (Iliffe, Manthorpe, & Eden, 2003).

There are a number of standardized assessments currently available. Many of these assessments vary in length and depth, making some assessments more appropriate for screenings, and others more appropriate for more complete evaluations. Some cognitive assessments that can be used as screening tools for AD or other forms of dementia include the *Mini-Mental State Examination* (*MMSE*) (Folstein, Folstein, & McHugh, 1975), the *Alzheimer's Quick Test* (*AQT*): *Assessment of Temporal-Parietal Function*, (Wiig, Nielsen, Minthon, & Warkentin, 2002) and the *Cognitive-Linguistic Quick Test* (*CLQT*) (Helm-Estabrooks, 2001). These aforementioned assessments generally do not require significant time commitments to administer. Other cognitive assessments that can give greater indication of deficits include the *Ross Information Processing Assessment – Geriatric* (*RIPA-G*) (PRO-ED, 1996), the *Woodcock – Johnson – III: Tests of Achievement* (*WJ-III*) (Woodcock, McGrew, & Mather, 2001), *Dementia Rating Scale* (Mattis, Jurica, & Leitten, 2001), *Arizona Battery for Communication Disorders of Dementia* (*ABCD*) (Bayles, 1993), *Communication Activities of Daily Living – 2* (*CADL-2*) (Holland, Frattali, & Fromm, 1999), and the *Severe Impairment Battery* (Saxton, McGonigle, & Swihart, 1993). However, these latter tests may require significant time to administer.

Assessments utilized in the diagnosis of dementia examine different areas of cognitive functioning such as attention and concentration, orientation, problem solving, memory, and comprehension. Attention and concentration can be assessed by giving the patient a task such as locating a "repeated pattern as quickly as possible," (*WJ-III*) as used in the *Woodcock – Johnson III*, or by having the patient count backwards by sevens from 100. Orientation can be assessed by the examiner asking the patient questions such as where they are currently, the current city they are in, and the capital of the United States (PRO-ED, 1996; Bayles, 1993). These questions obtain information about spatial orientation, while questions regarding the current time, date, and year give the examiner insight into the patient's temporal orientation (PRO-ED, 1996). Cognitive functions, such as problem solving and abstract reasoning, can be assessed by asking questions such as "why does a coffee cup have a handle" or "how can you cool food that is too hot" (*RIPA – G*).

Many assessments also evaluate both short-term and long-term memory abilities. Memory tasks can involve requiring the patient to repeat sequences of numbers and words (*RIPA-G*), remember previously learned objects (*MMSE*), or remember previously learned word lists (*ADAS*). Finally, questions requiring a 'yes' or 'no' responses can be asked to examine the patient's auditory comprehension, such as in the *RIPA – G* and the *ABCD*. 'Yes' or 'no' questions, however, can be problematic due to a 50% probability that the patient will correctly answer a question they do not know. In cases such as these, signal detection approaches are necessary. Signal detection approaches can be used in memory testing where the patient is presented a series of pictures and then shown more pictures and told to identify whether or not those words were seen previously. When using a signal detection approach, there are four possible outcomes for answers: hits (answers 'yes' when picture was seen before), misses (answers 'no' when picture was seen before), false alarms (answers 'yes' when picture was not seen before), and correct rejections (answers 'no' when the picture was not seen before). Two measures including *d'* (sensitivity), and bias measures (i.e., are the patients inherently biased toward 'yes' or 'no' responses) can be computed.

Imaging Techniques

Signs of dementia and neuro-degeneration may also be detected through neuroimaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). These methods of neuroimaging can be utilized both in structural and functional imaging settings – that is, facilities with the capabilities to accommodate the use of such equipment. Structural imaging techniques are useful for assessing changes in the brain such as diminishing size of the gyri and increasing size of the sulci of the brain. Tartaglia, Rosen, and Miller (2011) discussed how some of the earliest sites of cerebral deterioration in AD have been observed to be the hippocampus and entorhinal cortex. Consequently, many previous studies have used neuroimaging to show volume decreases compared to healthy adults in these two areas (Appel et al., 2009; Tartaglia, Rosen & Miller, 2011). In addition, other areas that are affected by deterioration have been identified as the lateral parietal regions, posterior superior temporal regions, and medial posterior portion of the cingulate gyrus, as well as atrophy in the frontal, temporal, and occipital lobes (Tartaglia, Rosen & Miller, 2011).

The structural changes in dementias vary, and Tartaglia, et al. (2011) pointed out that utilizing structural imaging can especially be useful when identifying more advanced cases that have more focal degeneration. For example, fronto-temporal dementia (FTD), which is characterized by degeneration in the anterior frontal, temporal, and insular cerebral regions shows focal signs of deterioration. On the other hand, Alzheimer's Dementia, and Dementia with Lewy bodies (DLB) exhibit more diffuse patterns of atrophy—often in the temporal-parietal junction.

Other methods of imaging include positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Both methods utilize chemical compounds to measure brain energy metabolism (PET) or to study the delivery of compounds in the cerebrum. PET scans of AD patients have shown a reduced metabolism of glucose in parietal and superior/posterior temporal regions. Metabolic deficits can be seen early in the development of AD and MCI in the medial portion of the parietal cortex, posterior cingulate, or retrosplenial region (Tartaglia et al., 2011), as well as frontal lobe hypoperfusion. PET can also be used to identify B-amyloid proteins that form plaques seen in AD. Temporoparietal hypoperfusion, hypometabolism, or posterior cingulate pathology can also be picked up by SPECT scans in AD patients (Tartaglia et al., 2011).

MRI has also been utilized to predict the likelihood of progression from MCI to AD by examining hippocampal and cortical volumes, and can detect vascular damage and biochemical changes. The brain's biochemistry can be examined by measuring levels of different metabolites such as N-acetylaspartate, choline, creatine, lactate, myoinositol, and glutamate (Tartaglia et al., 2011). Tartaglia et al. (2011) discussed functional magnetic resonance imaging (fMRI), which is an imaging technique that indirectly examines neuronal activation through changes in blood oxygenation levels (BOLD signal). Increases in cerebral blood flow alter the ratio of deoxyhemoglobin to oxyhemoglobin. Deoxyhemoglobin is paramagnetic. Consequently, changes in the ratio of blood oxygenation can be dynamically detected via fMRI. Increases in synaptic activity of the brain lead to increases in blood flow, consequently "mapping" patterns of neuronal activation. Previous studies found that patients with FTD exhibited decreased brain activity in the frontal lobes of the brain, and patients diagnosed with Dementia with Lewy Bodies exhibited increased activation in the temporal lobes than people diagnosed with AD (Tartaglia et al., 2011).

Tartaglia et al. (2011) discussed the use of fMRI in examining the resting-state of the brain. The term "resting-state" refers to the cerebral activity present when the brain is not using processing for cognitive activities. Being able to evaluate resting-state data is useful in assessing severely impaired patients. There are different brain networks, one of which is referred to as the default mode network. This network includes the posterior cingulate, inferior parietal, inferolateral temporal, ventral anterior cingulate, and hippocampal regions, and studies have found decreased activity in patients who exhibit AD and MCI (Tartaglia et al., 2011).

Imaging and Early Detection of AD

One fMRI study investigating early signs of dementia was carried out by Yassa, Guillermo, Cristinzio, and Bassett (2008). The authors examined activation in parietal regions of participants who had a familial-genetic risk for developing Alzheimer's disease. Two groups of participants were chosen. One group consisted of participants whose parents had been diagnosed with AD that had been confirmed at autopsy, while the other group consisted of age and education level matched controls. In a behavioral task, the participants were shown two three-dimensional images that were at a different orientation, and were instructed to identify whether or not one of the images could be rotated to look the same as the other. While the participants completed this task, their brain activation patterns were scanned using functional magnetic resonance imaging (fMRI). While both groups performed equally as well, in terms of accuracy, on the image rotation task, analysis of the images revealed that the at-risk group showed evidence for more extensive cortical activation. These findings indicated that individuals who have a familial history of AD have modifications in brain function for the purpose of compensating and bringing performance to typical levels (Yassa et al., 2008).

Capacity and RT-Based Techniques

While neuroimaging is very useful in detecting differences of structure and function of the brain, it comes at a high cost and is not always readily available at some facilities. Importantly however, findings from the mental rotational study (Yassa et al., 2008) indicated that while individuals may exhibit typical performance on tasks when compared to peers, there may still be underlying neural differences. Therefore, early stages of the pathology may not be detectable through traditional behavioral tests, but may manifest in other ways. For example, this change in neural function may indicate a less efficient use of processing resources and may not be detectable through the use of mean reaction times or accuracy on standardized measures. Significantly this may suggest that some older adults who score in age-normal ranges on standardized assessments could still be at risk for dementia—this may be especially true for adults who are at risk for dementia such as those in Yassa et al.'s (2008) study. While standardized assessments may fail to detect these subtle differences, changes in processing efficiency may be detectable through capacity measures that assess efficiency—that is, performance as a function of mental workload. Such "capacity measures" should yield better measures of neural function than mean reaction time or accuracy (Wenger & Gibson, 2004; Wenger, et al., 2010).

Wenger, Negash, Petersen, and Petersen (2010) examined methods of assessing MCI that involved implementing an RT based measure of capacity. Specifically, Wenger et al. (2010) discussed processing speed within the context of processing or workload capacity – where "workload" indicates the number of cues available in a cued recognition memory task. Processing speed refers to the rate at which a cognitive process, such as a memory task, can be performed. Building off of the concept of processing speech, *capacity* refers to "the amount of work the observer is capable of performing within some unit of time" (Wenger & Gibson, 2004, p. 708). Hence, capacity has been referred to as how a system is influenced when subjected to changes in workload (Townsend & Nozawa, 1995; Wenger et al., 2010), and not simply the overall speed in which a task is performed.

In the past, examining temporal and logical relationships between mental processes was used by using information relying on reaction times (RTs) (Townsend & Ashby, 1978; Townsend & Nozawa, 1995; Wenger et al., 2010). Investigating processing speeds in this way can give critical information about typical memory processing with aging and in "diseased states" (Wenger et al., 2010, p. 74). Wenger et al. (2010) investigated previous claims that processing speed could be "interpreted in terms of global differences in mental capacity" (Wenger et al., 2010, p. 74). A system with a capacity limitation will show degraded or no improvement in performance as workload increases. For example, a participant with a capacity limitation would have more difficulty identifying a full picture of a face presented to them because there is more information to process compared to when only half of the picture is shown. Conversely, a system that shows no change in performance when workload is increased is considered to have an unlimited capacity (Wenger et al., 2010).

Measuring Capacity

Previous studies assessing cognitive performance have typically only analyzed mean RT, but not efficiency as a function of workload (i.e., capacity). Wenger et al. (2010) stated that differences in processing speed may not necessarily be resultant of differences in capacity, meaning that someone with slow processing speed may have high capacity, or vice-versa. In other words, someone who is "slow" may still benefit from having more cues available and thus show evidence of high capacity. This implies that some people diagnosed based strictly on processing speed may be misdiagnosed.

Measuring capacity at the level of an individual participant involves using the hazard function to measure the RT distribution in its entirety.

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t} = \frac{f(t)}{S(t)}$$

In the equation above, the term h(t) denotes the hazard function, while f(t) denotes a probability density function, of say, the distribution of response times for a certain condition. The S(t) in the denominator is equivalent to 1-F(t) (where F(t) is a cumulative probability measure that sums to 1), indicating the probability that a process has not completed by a certain time. Together, a hazard function indicates the probability that recognition will occur in the next instant of time, given that it has not yet completed by time *t*. The hazard function used in the study is a measure used in previous works to characterize capacity. The hazard function can be rewritten using the notation below.

$$h(t) = \frac{f(t)}{1 - F(t)}$$

Estimating hazard functions has proven difficult. However, the Cox proportional hazard model can then be used to transform proportional hazard functions into linear regression, allowing for testing for ordering two or more hazard functions derived from different experimental conditions (e.g., Altieri et al., 2013; Wenger et al., 2010). The experimental conditions may correspond to the number of cues available in say, a cued memory task.

Wenger et al. (2010) pointed out that being able to characterize capacity using a hazard function "can allow for a principled distinction to be made between processing capacity and overall speed" (Wenger et al., 2010, p. 74). Furthermore, they stated that using capacity as a measure was a better choice than using mean RT, claiming "an inferential (statistical) advantage associated with having information from the entire RT distribution, rather than a point-estimate of central tendency" (Wenger et al., 2010, p. 76). Previous studies discovered that an "ordering on hazard functions always implies an ordering on means, whereas an ordering on means does not of necessity imply an ordering on hazard functions" (As cited by Wenger et al., 2010, p. 76). In addition, if one develops a hypothesis at the level of the hazard function regarding capacity, the Cox proportional hazards model can be used. The Cox proportional hazards model is useful because it removes assumptions about the baseline hazard function, making it possible to simplify the analysis of the independent variables.

To test the effectiveness of measures of capacity in distinguishing patients with MCI from normal aging or healthy elderly participants, Wenger et al. (2010) modified the *Free and Cued Selective Reminding Test* (*FCSRT*). The *FCSRT* was a test that was designed to assess memory deficits. Previous studies have determined the *FCSRT* to be accurate when diagnosing memory impairment. In this experiment, participants are required to verbally identify pictures of objects among sets of other pictures when they are given a category cue. Next, the participants recall as many items as possible during a certain period of time. Then the participants are given category cues to help them remember items they did not freely recall. Previous data regarding response times on cued trials had not been collected or reported by previous literature, so Wenger et al. (2010) manipulated the test by collecting RTs to the retrieval cues in the cued portion of the FCSRT. Five groups of participants were selected for the study. The first group consisted of 103 undergraduate students, the second consisted of 107 healthy subjects between 25-65 years old, and the third group consisted of 104 healthy subjects over 65 years old. Finally, the fourth and fifth groups consisted of 50 age-matched subjects, with one group having a diagnosis of MCI, and the other group being healthy older adults as a control. The participants were instructed to complete a naming-time task to differentiate the amount of time required in typical memory processing from time required in age-related slowing. The participants were presented with 24 line-drawings. The drawing was presented, then a word was presented, and the participant was required to verbally respond. Finally, the participants were required to locate an image among three other images when given a category cue and related instance cue. For the different trials, the participants were required to give manual responses, which were timed, via keyboard, or verbal responses.

The capacity data showed that participants who had MCI were more sensitive to manipulations of workload, and therefore, showed significant differences in capacity compared to the other groups. For example, they failed to benefit from additional cues to the same extent as healthy controls. A discriminant function analysis was utilized to evaluate the usefulness of RTs in diagnosing MCI, and the results indicated that when capacity and RT were both combined, the best measures were acquired. Finally, 34 MRI images were collected from the MCI and MCI control groups. Total hippocampal volume was estimated and was correlated with age and other variables that were looked at in the discriminant function analysis. The results showed that capacity measures had a reliable relationship to total hippocampal volume and were specific to individuals diagnosed with MCI. The findings were "consistent with the hypothesis drawn from the computational simulations that hippocampal atrophy is expressed most strongly in behavior in terms of processing capacity" (Wenger et al., 2010). The mental rotational study conducted by Yassa et al. (2008) found inefficient use of mental processes in adults with a family history of AD. In other words, this inefficient use due to hippocampal atrophy could be accurately detected by utilizing measures of processing capacity.

To test the capacity measure using a biologically plausible model of the hippocampus, the authors also developed a computational model of hippocampal circuitry, due to the fact that it is involved in the encoding of stimuli into memory. Specifically, the purpose of the computational model was to compare measures of processing capacity and measures of processing speed and accuracy to determine whether capacity was, in fact, a better predictor of hippocampal atrophy than the other variables. The model simulated the firing action potentials in a hippocampal circuit. The time required for a specific number of action potentials was measured, and then different processing loads were simulated by varying the specific number of action potentials. Brain atrophy was also simulated by reducing the number of cells in each region (Wenger et al., 2010). The outcomes of the simulations were plotted and analyzed and the data showed that changes in the hazard functions were greater than corresponding changes in the mean, which suggested that analyzing hazard functions may be better measures for memory performance and neural efficiency than mean RTs or mean accuracy.

Implications

Professionals assessing dementia utilize different methodologies to make the most accurate diagnoses possible. Often times, dementias are diagnosed through the use of standardized assessments, although after the problems present. These assessments, nonetheless, are often unable to detect differences in neural structure and processing, whereas neuroimaging can. However, the use of neuroimaging is not always practical or cost effective, necessitating a new practical and more cost effective approach to diagnosis. Previous studies have indicated that MCI is a strong risk factor for developing AD, suggesting that earlier identification of MCI may be of assistance in earlier identification of dementias. The task proposed in this study was to collect normative capacity data regarding manipulations of workload on persons without MCI to aid in future diagnosis of early MCI using a cued recognition task. These measures should be useful, especially in light of recent findings

Chapter 3: Materials and Methods

Participants

The participants in this study consisted of 81 healthy adults between the ages of 20 and 75 recruited from the Idaho State University Campus in Pocatello Idaho. Participants reported normal or corrected vision and no history of cognitive impairment. Participants were also administered hearing screenings in a sound attenuated chamber. The results from the hearing test are not reported in this study.

Procedure: Study Phase

The cued recognition task consists of two phases: a study phase and a test phase. During the study phase, the participant was presented an 8 x 6 inch black and white picture centered on a Dell computer monitor seated at approximately 24 inches from the monitor. The participant was exposed to 24 test pictures of items one at a time with exposure duration of 3,000 ms. Participants were instructed to attempt to remember each item they saw for the test phase.

Procedure: Test Phase

Participants were allotted a 1 minute break before the initiation of the cued-recognition test phase. In the test phase the participants were exposed to 24 of the pictures they viewed along with 24 new pictures in random order. Participants were provided 5,000 ms to respond before the next trial was initiated. The participant was instructed to press a keyboard key with their dominant hand indicating “yes,” the picture was seen before in the study phase; or “no,” the picture is a new one that was not seen previously in the study phase as quickly and as accurately as possible. Both RT and accuracy of the responses were measured.

A total of 48 trials were administered during the test phase (24 old, ‘yes’ pictures and 24 new ‘no’ pictures). The pictures are divided up into four sectors, one cue for each sector. Workload was manipulated by having the pictures completely visible, ¼ blocked out, or randomly ½ blocked out. Increasing the number of cues increases the workload because the participant is required to process a greater number of features of the picture. Of the 48 trials, 16 included pictures with four cues (8 old and 8 new), 16 included pictures with three cues (8 old and 8 new), and 16 included pictures with only two cues (8 old and 8 new). Figure 1 below illustrates examples of pictures with four cues, three cues, and 2 cues, respectively.

Figure 1: Example of Pictures and Workload Manipulation

4 Cues 3 Cues 2 Cues

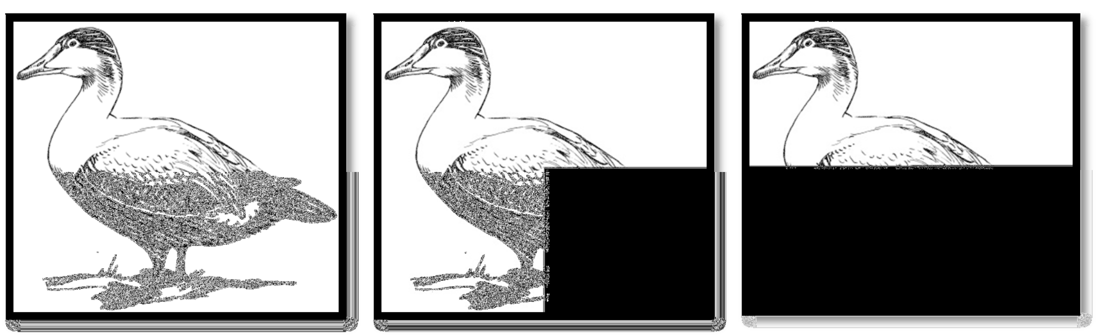

Figure 1: The above pictures are examples of pictures seen during the test phase of the cued recognition task. Workload is manipulated by reducing the available number of cues as illustrated here.

Chapter 4: Results

Data

Estimating the hazard function is difficult, so the Cox proportional hazard model was used to analyze the data. Proportional hazard model regression is used to test for an ordering of two or more hazard functions through a logarithmic transformation to linear regression. Each participant's independent variable, being the beta (β) value, or the predictor was included in one column in the matrix, and the RTs served as the "y" variable, which was included in the other column in the matrix. Analysis of the data is shown in Table 2.

Means and SDs of Data Measurements

	Beta (Z)	p-value	RT_4 cues	RT_3 cues	RT_2 cues	SE	Acc.
Mean	-.27 (-1.40)	.27	804	853	932	.19	.91
SD	.21 (1.01)	.29	114	131	152	.01	.06

Table 2: The means for the different scores are located in the top row and the standard deviations of the scores are located in the bottom row. The scores in this table represent the mean beta scores, p-values, reaction times in milliseconds (ms) (RT for four cues, three cues, and two cues, respectively), standard error, and accuracy across 81 participants.

The results revealed that the mean reaction time (see Figure 2) was 804 ms (SD = 114 ms) on pictures containing all four cues, 853 ms (SD = 131 ms) on pictures with three cues, and 932 ms (SD = 152 ms). Figure 2 shows a box plot of the results where the lines indicate the mean, 75th and 25th percentile, as well as 1.5 times the interquartile range. Outliers denoted by plus symbols (+) are also plotted. The results also reveal the overall accuracy of the 81 subjects was quite high at 91.2% accurate, with a standard deviation of 5.6% (see figure 3). Figure 3 also shows a box plot of the results where the lines indicate the mean, 75th and 25th percentile, as well as 1.5 times the interquartile range. Outliers are also denoted by plus symbols (+).

Beta (β) values denote the predictor of workload in the capacity measure, and represent the extent to which the number of cues served as a predictor for changes in processing speed. Next, the beta results (see Figure 4) show a mean beta value of -0.27 with a standard deviation of 0.21 across all 81 participants. Positive beta values signify a failure to benefit from an increased number of cues in the processing time domain. Conversely negative beta values indicate that observers responded more quickly as the number of cues in the picture increased. That is, these participants showed an increase in their proportional hazard function as the number of cues went from two to four. In other words, they were able to use these cues more efficiently.

Mean RT for Cueing Conditions

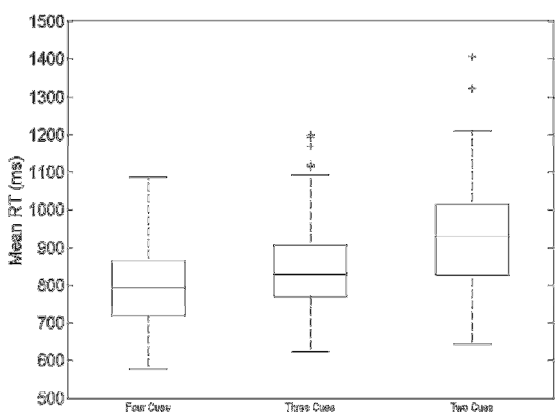

FIG. 2. Mean RT for Cueing Conditions. The lines in the middle of the boxes shows the mean reaction time values across all 81 participants for pictures consisting of four cues, three cues, and two cues, respectively. The 75th and 25th percentile are represented by the line above and below the middle line, respectively. The small bars on the top and bottom denote a value of 1.5 times the interquartile range.

Mean Accuracy Values

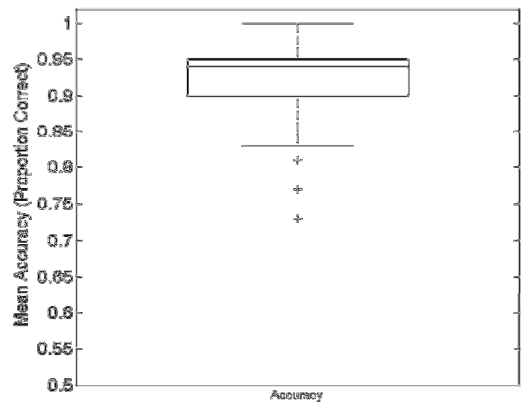

FIG. 3. Mean accuracy for all participants combined. The line in the middle of the box shows the mean accuracy of the scores across all 81 participants. The 75th and 25th percentile are represented by the line above and below the middle line, respectively. The small bars on the top and bottom denote a value of 1.5 times the interquartile range.

Mean Capacity Values

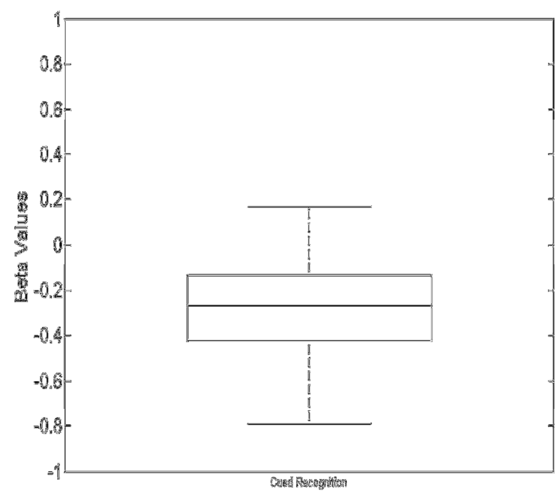

FIG. 4. Mean capacity values for all participants combined. The line in the middle of the box shows the beta values for capacity across all 81 participants. The 75th and 25th percentile are represented by the line above and below the middle line, respectively. The small bars on the top and bottom denote a value of 1.5 times the interquartile range.

Chapter 5: Discussion and Conclusion

The prevalence of dementia is growing considerably due, in large degree, to the relative increase in the aging and elderly population. Physicians and healthcare professionals have a variety of tools at their disposal to assist in identification and diagnosis of this disease. Among several different categories of dementia, Alzheimer's disease is the most prevalent, and initial signs and symptoms often present in the form of memory disturbance. Standardized assessments of cognitive functioning are commonly used to assess memory, but such tools may not detect deficits associated with cognitive decline until after the progression of the disease is well underway.

These assessments have also been described as being time consuming by select healthcare professionals (excluding therapy disciplines). Neuroimaging can be utilized to make more accurate diagnoses based on structural or functional imaging—particularly when the pathology has not progressed to the degree that behavioral deficits become manifest. fMRI has been used to identify excessive activation in patients with a family history of AD, suggesting less efficient use of mental processes. A downside to neuroimaging, however, is that it is costly and not readily available at all facilities. A more cost effective, timely, and available measure of cognitive function would be useful in early identification and treatment, therefore providing the best possible care to patients with dementia.

Wenger et al. (2010) used a capacity-based approach to examine memory processes in adults with MCI. Wenger was interested in MCI because it has been found to be a great risk factor for dementia and considered by some to be a transitional stage between normal cognitive functioning and dementia, with approximately more than 40%

of cases eventually developing dementia. Wenger found that using a capacity approach was a more sensitive measure of detecting MCI than the more common method of mean reaction time.

A cued-recognition measure was developed from the findings of Wenger et al.'s (2010) study. The experimental design used in this report was a somewhat simplified version of the cued memory task implemented by Wenger and colleagues, and this study was designed to provide proof of concept for such a test. Ideally, the version used in this paper can be readily implemented in a variety of settings within a quick period of time. This measure manipulates workload by varying the number of cues available to the participant, and accuracy and reaction times were measured on the participants' responses. This report gathered data on 81 healthy adult subjects between the ages of 20 and 75 years who participated in this cued-recognition measure of memory performance. The results found that the participants showed an increase in their proportional hazard functions as the number of cues increased, meaning they were able to use the cues efficiently when there were more cues to process.

Future studies will use this same cued-recognition task with adults diagnosed with MCI to examine differences between the data gathered from an MCI group and the data gathered from this study. Furthermore, capacity measures should be correlated with scores obtained from standardized measures, such as memory subtests of the ABCD. Statistically significant differences in group performance would indicate a use for identifying individuals with developing MCI who may have not yet developed memory impairments with a noticeable severity. This measure takes approximately five minutes to administer and can be administered to adults of any age, particularly adults with known risk factors for dementia. Utilization of this quick, simple measure would help identify individuals with MCI earlier, thus aiding in identification of individuals at great risk for dementia.

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