2021

Clinical utility of a novel digitized clock drawing task

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Dissertation

CLINICAL UTILITY OF A NOVEL DIGITIZED CLOCK DRAWING TASK

by

SABA AKHTAR CHOWDHRY

B.A., Case Western Reserve University, 2012
M.A., New York University, 2015

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

2021

Approved by

First Reader

Laura Grande, Ph.D.
Assistant Professor of Psychiatry

Second Reader

Elizabeth Leritz, Ph.D.
Assistant Professor of Psychiatry
Harvard Medical School

Third Reader

Maxine Krengel, Ph.D.
Assistant Professor of Neurology

CLINICAL UTILITY OF A NOVEL DIGITIZED CLOCK DRAWING TASK

SABA AKHTAR CHOWDHRY

Boston University School of Medicine, 2021

Major Professor: Laura Grande, Ph.D., Assistant Professor of Psychiatry

ABSTRACT

Objective: The goal of this research was to examine the clinical utility of the digital Clock in the Box (dCIB), a novel digitized cognitive screening test. This was accomplished by (1) creating cutoff scores for the dCIB, (2) evaluating performance on the dCIB relative to established cognitive screening and standardized neuropsychological measures, and (3) determining the efficacy of the dCIB to screen for subtle cognitive deficits associated with poor vascular health. Metabolic Syndrome (MetS; clinical syndrome of three or more cardiovascular risk factors) is a rising health epidemic associated with an increased risk for cerebrovascular disease and vascular dementia. Early detection of subtle deficits associated with MetS may assist in regulation of disease progression and prevention of future vascular dementia.

Methods: A community-based sample of adults with no self-reported history of cognitive impairment was recruited for a cross-sectional study in which they completed a metabolic assessment, blood draw, and a brief neuropsychological battery consisting of the dCIB, the Mini-Mental State Exam (MMSE), and measures of executive function, memory, and attention. For part of the analysis, participants were separated into MetS (n=21) and non-MetS (n=42) groups based on current diagnostic criteria for MetS.

Results: Participants (*N*=63) were older (62.49 ± 9.16 years), educated (16.46 ± 2.76 years), and diverse with 44.4% female (*n*=28) and 28.6% non-White (*n*=18). Receiver operating characteristic (ROC) analysis and Youden's *J* statistic determined the optimal cutoff value for the dCIB as 5.5 (dCIB score ≤ 6 indicating *suspected* impairment; dCIB score ≤ 5 indicating *probable* impairment). Performance on the dCIB (6.32 ± 2.32) was significantly correlated with the MMSE (28.19 ± 2.06); (Pearson's $r = 0.437$, $p = 0.000$). The dCIB had better sensitivity (72.7%) but poorer specificity (65.4%) compared to the MMSE (sensitivity 45.5%; specificity 94.2%). Using regression modeling, the dCIB significantly predicted performance on measures of executive function, memory, and attention. In a sample stratified by vascular risk, the dCIB successfully differentiated MetS (5.33 ± 2.75) and non-MetS (6.81 ± 1.93) groups, with lower dCIB scores in the MetS group relative to the non-MetS group ($F = 8.975$, $p = 0.004$).

Conclusion: The dCIB is a novel digitized clock drawing task designed to screen for cognitive impairment. Clinical utility for the dCIB was established by determining its test validity and demonstrating its sensitivity to detect subtle cognitive deficits in a sample with vascular risk. Because the dCIB is simple to administer and brief to complete, it may be an ideal option for routine cognitive screening in primary care settings.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

A1C.....Glycated hemoglobin

AD.....Alzheimer's Disease

ADL.....Activities of Daily Living

BMI.....Body Mass Index

CIB.....Clock in the Box

dCDT.....Digital Clock Drawing Test

dCIB.....Digital Clock in the Box

HDL.....High-density lipoprotein

IADL.....Instrumental Activities of Daily Living

LDL.....Low-density lipoprotein

MCI.....Mild Cognitive Impairment

MetS.....Metabolic Syndrome

MMSE.....Mini-Mental State Examination

MoCA.....Montreal Cognitive Assessment

NCEP.....National Cholesterol Education Program

P/O.....Planning/Organization

SLUMS.....Saint Louis University Mental Status Exam

VD.....Vascular Disease

WM.....Working Memory

CHAPTER ONE – INTRODUCTION

Significance

Dementia, which describes a decline in cognitive functioning that eventually leads to a loss of independent function, is a common and feared neurological syndrome among the geriatric population (Gale et al., 2018). An estimated 50 million individuals are currently living with dementia worldwide, with future projections of 152 million by 2050 (World Health Organization, 2020). More than 5 million U.S. adults over the age of 65 have dementia, and this number is expected to triple by 2050 (Alzheimer's Association, 2020). Dementia is a major source of disability and reflects one of the most expensive challenges facing healthcare. The total lifetime cost of care for someone with dementia is estimated at $357,297 (Alzheimer's Association, 2020), with worldwide annual costs estimated at $818 billion (World Health Organization, 2020). In addition to the financial cost, there is tremendous burden on dementia caregivers, the majority of whom are family members of the patient, with evidence of an association between caregiver stress and elevated levels of depression and anxiety (Cheng, 2017).

Dementia is not itself a disease, but the clinical presentation of an underlying disease (Centers for Disease Control, 2019; Gale et al., 2018). The two most common etiologies of dementia are Alzheimer's Disease (AD) and vascular disease (VD) (Centers for Disease Control, 2019), leading to AD dementia and vascular dementia, respectively. AD is a progressive neurodegenerative disease typically characterized by initial problems with learning new information and forming episodic memories (Amirrad et al., 2017). As

the disease spreads across the brain from the medial temporal lobes to the association cortices of the frontal, temporal, and parietal lobes, AD typically changes from a memory disorder to a global brain disorder and eventually leads to deficits in a number of other cognitive domains including language, abstract reasoning, executive function, and visuospatial ability (Alzheimer's Association, 2020; Amirrad et al., 2017; Bondi et al., 2017). Vascular dementia is characterized by significant cognitive decline in a fluctuating or stepwise pattern which reflects the course of neuroanatomical changes that result from a variety of vascular events (e.g., small vessel disease, stroke) that may be caused by uncontrolled or poorly controlled metabolic risk factors (e.g., hypertension, obesity) (Dichgans & Leys, 2017; Smith, 2017). These neuroanatomical changes have been shown to impact a series of parallel pathways that interconnect various regions of the frontal lobe to subcortical structures, leading to deficits in cognitive domains dependent upon the integrity of these frontal-subcortical circuits including frontally mediated executive functions and attention (Sudo et al., 2017; Pugh & Lipsitz, 2002). Diagnosis for dementia is met if there is substantial impairment in one or more cognitive domains and the impairment is sufficient enough to interfere with independence in everyday activities (American Psychiatric Association, 2013). If the etiology is suspected AD, cognitive decline usually begins in the domain of memory and eventually progresses to affect all cognitive domains (e.g., executive function, language, visuospatial ability); if the etiology is vascular, cognitive decline is usually in the domains of executive function and attention while eventually progressing to affect all other domains (American

Psychiatric Association, 2013). It is well documented that executive functioning, in particular, is the strongest cognitive predictor of everyday "real world" functioning (i.e., planning, decision making) (Mansbach & Mace, 2019; McDougall et al., 2019; Farias et al., 2009), and therefore executive dysfunction may negatively impact functional independence. Cognitive deterioration associated with progressive dementias eventually leads to a loss of functional independence including difficulties performing basic activities of daily living (ADL; e.g., bathing, dressing) and complex instrumental activities of daily living (IADL; e.g., shopping, managing finances) (Slachevsky et al., 2019).

Timely diagnosis of dementia may have a significant impact on the care, treatment, and quality of life for patients. An early diagnosis may provide options and opportunities for patients and their families including planning for the future (e.g., finances, power of attorney, preparation of a last will and testament), taking advantage of patient support and other appropriate services, and accessing interventions and therapies (e.g., clinical trials, medication) (Dhedhi et al., 2014; Morley et al., 2015; Phillips et al., 2011; Phillips et al., 2012). However, current estimates indicate almost half of individuals living with dementia are undiagnosed or diagnosed later into the disease progression (Jammeh et al., 2018; Connolly et al., 2011). Recent estimates of cognitive impairment among patients are as high as 30%, of which 30% to 75% go unrecognized by attending physicians (Palsetia et al., 2018). There are a number of healthcare barriers that may explain this low diagnostic rate, including lack of physician familiarity with

cognitive assessment and time constraints related to the short duration of primary care visits (Sabbagh et al., 2020; Aminzadeh et al., 2012; Bradford et al., 2009). Training programs for primary care physicians provide limited exposure to cognitive assessment and, as a result, many physicians report feeling poorly equipped, inexperienced, or uncomfortable monitoring cognitive functioning (Lee et al., 2018). A recent survey found that 22% of primary care physicians had no residency training in dementia diagnosis and/or care – and among the 78% who had training, 65% reported that the training was "very little" (Alzheimer's Association, 2020). Furthermore, primary care visits are often less than 20 minutes (Linzer et al., 2015) which limits the time and depth of cognitive assessment available to patients (Bradford et al., 2009; Chen et al., 2009). The short duration of the average clinic visit reflects a key obstacle to the practice of cognitive evaluation in primary care and highlights the need for brief tests in this setting. Despite these barriers, it is important for physicians to monitor cognitive status in their patients. Some physicians are uncertain that a dementia diagnosis, particularly in the early stages, provides a clear benefit to the patient given that there is currently no effective treatment for dementia (Sabbagh et al., 2020; Bradford et al., 2009). However, encouraging results from clinical trials and other recent advances in dementia research offer hope that one or more disease-modifying treatments are on the horizon (Sibley et al., 2019; Liu et al., 2017). Given the potential for a therapy, there is need for routine cognitive screening to ensure that patients in early stages of dementia are identified in a timely manner (Liu et al., 2017). Furthermore, routine screening is critical in identifying

treatable or reversible etiologies of dementia (e.g., metabolic abnormalities; vitamin deficiencies) (Sibley et al., 2019) as well as identifying cognitive changes in at-risk populations (Roebuck-Spencer et al., 2017) for which there is evidence that primary care screening contributes to higher rates of detection compared to informal observation alone (Cordell et al., 2013).

Detecting dementia may be challenging due to the nature of the syndrome itself and the complexity of dementia diagnosis. Not only are there many etiologies of dementia (e.g., Alzheimer's Disease, vascular disease), clinical symptoms are often non-specific and may overlap with other medical conditions such as mood disorders (i.e., depression) (Rubin, 2018). Furthermore, preclinical or early stages of dementia present with mild symptoms at onset, making it difficult to attribute symptoms to dementia. Later stages of dementia may go undetected due to the incorrect belief that significant cognitive impairment is a normal part of aging or the bias that diagnostics are unnecessary for conditions without treatment (Phillips et al., 2011; Bradford et al., 2009). Differentiating symptoms of dementia from cognitive changes that reflect normal aging (e.g., declines in speed of information processing, problems remembering names) often serves as a challenge in healthcare settings (Phillips et al., 2011), thereby reflecting the need for reliable tools to aid in dementia screening. Neuropsychological assessment is a performance-based method of measuring cognitive functioning through the administration of standardized, norm-based psychological tests. Using a comprehensive battery of tests, cognition can be assessed across multiple domains (i.e., executive

functioning, memory, attention, language, visuospatial abilities) and overall performance can indicate severity of impairment and aid in diagnosis and/or treatment planning (Roebuck-Spencer et al., 2017). As the gold standard for cognitive evaluation, neuropsychological assessment may be helpful in identifying subtle cognitive deficits associated with early stages of dementia. However, testing batteries are often lengthy (i.e., 2 to 5 hours to administer) and require specialized training to administer (i.e., by a licensed clinical neuropsychologist) (Muller et al., 2017), making their use unfeasible in primary care settings (Sudo et al., 2017). Instead, "brief and widely accessible tests would be more suitable for clinical use than extensive sophisticated neuropsychological batteries" (Sudo et al., 2017, p. 372). Cognitive screening tests are usually brief and narrow in scope and can be used as part of a routine clinical visit to identify the presence of cognitive impairment (Roebuck-Spencer et al., 2017). Although cognitive screeners are not in and of themselves diagnostic, they may indicate the likelihood of cognitive impairment and help identify patients who require more extensive, comprehensive, and diagnostic neuropsychological assessment (Roebuck-Spencer et al., 2017). Key differences between cognitive screening tests and comprehensive neuropsychological evaluations are summarized in Table 1 (Roebuck-Spencer et al., 2017, p. 495).

Table 1.

Summary of Key Differences between Cognitive Screening Tests and Comprehensive Neuropsychological Batteries

	Cognitive Screening Tests	**Comprehensive Neuropsychological Batteries**
Potential Uses	• Early identification of individuals at potential risk for condition or disorder • May indicate need for further evaluation or intervention • May be used to monitor progression of symptoms or response to intervention • Does not provide definitive diagnosis	• Determination of presence and magnitude of impairment • Determination of diagnoses • Determination of functional status, abilities, and capacities • Assistance with medical treatment planning
Administration	• Generally brief (<30 min) • May be administered as part of routine clinical visit • Requires minimal training for administrator or can be self-administered	• Varies but typically several hours • Typically occurs as a separate encounter or appointment • Requires specialized training in administration and interpretation
Domains Assessed	• Narrow in scope	• Multidimensional • Provides information about functioning across multiple domains

Note. Reprinted with permission from "Cognitive Screening Tests versus Comprehensive Neuropsychological Test Batteries: A National Academy of Neuropsychology Education Paper" by T. M. Roebuck-Spencer, T. Glen, A. E. Puente, R. L. Denney, R. M. Ruff, G. Hostetter, and K. J. Bianchini, 2017, *Archives of Clinical Neuropsychology, 32*(4), p. 495 (https://doi.org/10.1093/arclin/acx021). Copyright 2020 by Oxford University Press.

Cognitive Screening

As the elderly population continues to grow, early detection of cognitive changes and of possible underlying dementia becomes increasingly important (Segal-Gidan, 2013). Cognitive screening tools are an attractive option for detecting compromised cognitive functioning because they are rapid, non-invasive, and inexpensive. It is important to note that screeners are not intended to be stand-alone tests, nor are they meant to take the place of a more comprehensive neuropsychological evaluation. Rather, they are intended to provide healthcare providers with quick feedback regarding cognitive status that can help inform medical recommendations. When used properly, cognitive screeners are designed to flag cognitive changes so that patients may be referred to a specialist (e.g., clinical neuropsychologist, neurologist, occupational therapist) who can provide further evaluation and assist in cognitive assessment and symptom management. An ideal cognitive screening tool has high sensitivity (i.e., true positive rate; individuals with impairment correctly classified as cognitively impaired) as well as high specificity (i.e., true negative rate; individuals who are unimpaired correctly identified as not having cognitive problems) (Segal-Gidan, 2013). Values for sensitivity and specificity range between 0% and 100% and "well-designed tests usually try to maximize both criteria, allowing trade-offs to reflect the consequences of making an incorrect decision" (Hebben & Milberg, 2009, p. 45).

A great number of cognitive screening instruments have been developed, with a recent review describing the details and characteristics for 50 different screeners

including both paper-and-pencil and computerized tasks (de Roeck et al., 2019). Among the screeners frequently used in clinical practice today are the Mini-Mental State Exam (MMSE-2; Folstein et al., 2010), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and the Saint Louis University Mental Status (SLUMS; Tariq et al., 2006). The MMSE is an 11-item test that assesses five domains: registration, orientation, attention and calculation, verbal recall, and language [possible score range of 0-30; cutoff score of ≤25 for suspected impairment]. The MMSE is the most commonly used cognitive screener for dementia (de Roeck et al., 2019; Tsoi et al., 2015) and has become the reference against which other measures are judged. Designed to detect milder forms of cognitive impairment, the MoCA is the second most commonly used screener and includes items assessing visuospatial ability, executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation [possible score range of 0-30; cutoff scores of ≤25 for suspected MCI and ≤ 20 for suspected dementia]. The MoCA has been administered to a wide range of populations and disorders including mild cognitive impairment [MCI] (Abd Razak et al., 2019; Ciesielska et al., 2016), Alzheimer's Disease [AD] (de Roeck et al., 2019; Pinto et al., 2019; Davis et al., 2015), Parkinson's Disease [PD] (Dalrymple-Alford et al., 2010; Hoops et al., 2009), vascular dementia (Ghafar et al., 2019; Freitas et al., 2012), traumatic brain injury [TBI] (Frenette et al., 2019; de Guise et al., 2014), Huntington's Disease [HD] (Bezdicek et al., 2013; Gluhm et al., 2013; Videnovic et al., 2010), and multiple sclerosis [MS] (Freitas et al., 2018; Dagenais et al., 2013), and there is strong psychometric data (i.e., high specificity)

supporting its use (de Roeck et al., 2019; Siqueira et al., 2019). However, despite its one-page format, the MoCA requires the longest administration time among the three tests (Slavych, 2019) which may make it difficult to use in a busy clinic setting. The SLUMS is similar to the MMSE in format (i.e., 11 items) but it offers enhanced tasks of attention and calculation, immediate and delayed recall, and figure recognition, along with novel tasks of animal naming, digit span, clock drawing, and story/narrative memory [possible score range of 0-30; score of 21 to 26 for suspected MCI and ≤ 20 for suspected dementia]. The most notable disadvantage of the SLUMS is its lack of use with different clinical populations and the dearth of research regarding its psychometric properties (Slavych, 2019). Because the MMSE demands little time to administer and has been used with various patient populations (e.g., MCI/dementia, stroke, Parkinson's Disease, depression) with substantial literature regarding its psychometric properties (Carnero-Pardo, 2014), it is often the preferred cognitive screener over the MoCA and SLUMS.

The MMSE is user-friendly and its ease and brevity are among the reasons for its popularity with healthcare providers (Palsetia et al., 2018). The MMSE is utilized in most medical institutions making its administration and interpretation universally understood, which has facilitated its placement as the benchmark cognitive screener (Carnero-Pardo, 2014). Furthermore, there are vast amounts of available data using the MMSE, which makes it easy to find standards for comparison in a variety of different settings (Carnero-Pardo, 2014). However, the MMSE has a number of notable drawbacks. Among patients with dementia, completion times can take up to fifteen

minutes, making this test relatively time consuming among individuals with serious cognitive impairment (Rakusa et al., 2018). Among individuals with mild cognitive impairment (MCI), the MMSE has been criticized for its insensitivity in detecting early cognitive changes, and thereby its limited ability to differentiate between MCI and healthy controls (de Roeck et al., 2019; Mitchell, 2009). This finding initiated the creation of more sensitive screeners, such as the MoCA and SLUMS, to detect subtle deficits that may otherwise go undetected by the MMSE (Nasreddine et al., 2005; Tariq et al., 2006). A meta-analysis determined MMSE test sensitivity to range from 71% to 85% and MMSE test specificity to range from 81% to 96% when screening for dementia and mild cognitive impairment (MCI) (Mitchell, 2009). In primary care, sensitivity values as low as 64% have been reported for the MMSE (Larner, 2018). Furthermore, false positives on the MMSE have been linked to older age, limited education, foreign culture, depression, and sensory impairment (Palsetia et al., 2018). Widespread use of the MMSE may result in practice effects or patients learning appropriate responses (Palsetia et al., 2018). Perhaps the greatest limitation that has been identified in the literature is that the MMSE excludes an assessment of executive functioning, which may make this screener unsuitable for identifying executive deficits (Palsetia et al., 2018; Rakusa et al., 2018). This is supported by research showing that the MMSE is less sensitive to frontal and subcortical changes (i.e., regions implicated in vascular disease leading to vascular dementia) (Palsetia et al., 2018). Because of these limitations, the

MMSE may not meet the current needs for dementia screening, and perhaps another test would be more suitable.

Neuropsychological Approach to Clock Drawing

In recent years, clock drawing has become a popular cognitive screening tool because of its brief and simple administration, acceptability among patients, low cost, good psychometric properties, sensitivity to subtle cognitive impairment, and evidence of significant correlations with other established and validated cognitive tests (i.e., MMSE) (Hazan et al., 2018; Ismail et al., 2010; Nyborn et al., 2013; Rabin et al., 2005; Shulman, 2000; Shulman et al., 2006). Clock drawing taps into an array of cognitive abilities that span across a number of domains – verbal comprehension (i.e., comprehending instructions); verbal working memory (i.e., recalling and holding instructions in mind); visual memory (i.e., retrieving a mental representation of a clock); executive function (i.e., developing an organized multi-step plan of action; detecting and correcting errors); visuospatial ability (i.e., mentally constructing the clock; judging line length and orientation for the hour and minute hands); symbolic knowledge (i.e., demonstrating intact symbolic representation of the twelve numbers and hour and minute hands set to represent time); sustained attention (i.e., concentrating to complete the task); and fine motor skills (i.e., constructing an accurate and organized layout of a clock) (Young, 2018; Freedman, 1994; Amodeo et al., 2015) – and errors in one or many of these areas may help inform cognitive processes and functional outcome.

Support for the use of clock drawing as a cognitive screener comes from studies demonstrating its strong psychometric properties (Shulman, 2000) including high levels of diagnostic accuracy (Carnero-Pardo et al., 2019; Duro et al., 2019; Nair et al., 2010; Park et al., 2018; Vyhnalek et al., 2017), inter-rater reliability (Fuzikawa et al., 2003; Nair et al., 2010), and test-retest reliability (Hubbard et al., 2008; Mendez et al., 1992; Strauss et al., 2006). There are a number of existing versions of clock drawing, with three major differences between the versions: the clock circle (i.e., whether the circle should be pre-drawn or drawn by the examinee); the time the clock is set (i.e., "ten after eleven"); and the scoring system (see *Palsetia et al., 2018* for a review) (Rakusa et al., 2018). Depending on the version used, test sensitivity ranges from 67% to 98% and test specificity from 69% to 95% when screening for possible dementia (Smedslund et al., 2015). Recent data suggests sensitivity as high as 84% to 90% and specificity 76% to 78% in diagnosing patients with Alzheimer's Disease (Duro et al., 2019). Furthermore, clock drawing has been shown to have significant correlations with other established cognitive tests including verbal fluency, verbal learning and recall, Block Design, Digit Symbol, Trail Making Test, Rey-Osterrith Complex Figure, Mini-Mental State Examination, Hooper Visual Organization Test, and Raven's Colored Progressive Matrices (Grande et al., 2013; Shulman, 2000).

Clock drawing has a rich history in neuropsychological testing (Frankenburg, 2019; Hazan et al., 2018). The first documented clinical case of clock drawing dates back to 1915 when British neurologist Sir Henry Head (1926) used clock drawing as part

of his medical evaluations of individuals with difficulties speaking, reading, writing, and understanding language (i.e., aphasia) (Frankenburg, 2019; Hazan et al., 2018). Head asked patients to set a clock based on written commands and verbal commands, to state the time, and to write down the time (Head, 1926). In his book *Aphasia and Kindred Disorders of Speech*, Head (1926) reviewed findings from several clinical cases, making note of interesting patterns of behavior including slow completion time and inconsistencies in verbal and written time telling.

In addition to capturing language deficits in aphasia, clock drawing was also used to assess constructional apraxia in World War II soldiers who suffered head injuries to the occipital and parietal lobes (Spenciere et al., 2017). Trauma to these brain regions was associated with the inability to spontaneously draw objects and copy figures (i.e., constructional apraxia), which could be successfully evaluated by asking injured soldiers to draw a clock (Spenciere et al., 2017).

As the field of neuropsychology burgeoned in the 1970s, clock drawing became more prevalent in the literature. In a seminal book entitled *The Assessment of Aphasia and Related Disorders*, Edith Kaplan and Harold Goodglass (1972) outlined tests of clock drawing, clock copying, and clock setting. In the clock drawing condition, patients were asked to "draw the face of a clock showing the numbers and the two hands, set to ten after eleven" (Goodglass et al., 1983). In the copy condition, patients were asked to copy an already drawn clock. Scoring for clock drawing and clock copying was based on three possible points for outline of the clock face, symmetry of number placement, and

accuracy of numbers (Goodglass et al., 1983). In the clock setting condition, patients were presented with four clock faces and asked to set the times to 1:00, 3:00, 7:30, and 9:15 (Goodglass et al., 1983). Scoring for clock setting was out of a possible three points on appropriate length of hour and minute hands, correct hour hand placement, and correct minute hand placement (Goodglass et al., 1983). Although all three tests rely on overlapping cognitive domains (i.e., language, memory, executive function), each test highlights specific cognitive processes. Clock drawing measures comprehension of verbal instructions (i.e., language), recall of the semantic representation of a clock (i.e., memory), recall of the instructions for time setting (i.e., working memory), and planning clock size and orientation (i.e., executive function) (Freedman et al., 1994). Tests of clock drawing are sensitive to temporal lobe dysfunction exhibited by language deficits (in the language-dominant, usually left, hemisphere) and/or memory deficits (both hemispheres) as well as frontal lobe dysfunction resulting in executive deficits (Freedman et al., 1994). Clock copying is an assessment of perceptual functioning, making it a sensitive test for parietal lobe dysfunction (Freedman et al., 1994). Clock setting has been linked to bilateral hemi-attentional processing and executive functions (Freedman et al., 1994). Kaplan's choice of "ten after eleven" for clock drawing required patients to draw the minute hand and the hour hand on each side of the clock (i.e., bilateral hemi-attentional processing) and to process information semantically, instead of perceptually, thereby requiring patients to re-code "ten" in order to set the minute hand to the correct place at the number two (i.e., executive function) (Freedman et al., 1994). Kaplan was

especially interested in the types of errors patients made on the clock drawing test, as error type could help inform lesion localization (Grande et al., 2013). The types of errors common in patients with frontal lobe dysfunction (e.g., vascular dementia) include planning errors (e.g., misjudging size of the clock, improper spacing of numbers) and stimulus-bound errors (e.g., inability to re-code "ten" to the number two), which reflect underlying deficits in executive function and inhibition (Lee et al., 2009; Salmon & Filoteo, 2007). Errors made by patients with temporal lobe dysfunction (e.g., Alzheimer's dementia) may be conceptual errors (e.g., misrepresenting the clock by drawing a face, writing the time in the clock face) which reflect deficits in accessing knowledge of the features and meaning of a clock (i.e., loss of semantic memory, impairment in semantic knowledge) (Lee et al., 2009; Salmon & Filoteo, 2007). Kaplan and Goodglass administered their set of clock tests to aphasic patients and used that data to create the first database on clock drawing (Goodglass et al., 1983).

Scoring guidelines were created by Shulman and colleagues (1986) to flag cognitive impairment in a sample of 75 older individuals with and without neurocognitive disorders. The results from this study identified significant correlations between clock drawing and existing short measures of global cognition (e.g., Mini-Mental State Exam [MMSE; Folstein et al., 1975]) (Shulman et al., 1986). Based on these findings, Shulman was among the first to suggest the use of clock drawing as a clinical screener for cognitive impairment in the elderly—a suggestion Shulman himself followed when completing patient assessments in his geriatric-focused psychiatric clinical practice

(Shulman et al., 1986). Shulman's work reflected a shift away from using clock drawing as a measure of domain-specific impairment and instead, an introduction of clock drawing as a screening instrument.

Over the past decade, there has been an increasing trend towards the utilization and incorporation of digital technologies to modernize current approaches to neuropsychological assessment, including clock drawing (Parsons & Duffield, 2019). This trend reflects the increased accessibility of technological devices in the digital era (i.e., desktop computers, laptop computers, smartphones, tablets) and how data from these devices may provide behavioral measurement with a level of precision and standardization that is difficult or otherwise impossible to achieve with traditional paper-and-pencil neuropsychological assessment (Germine et al., 2019). The potential benefits of digitized testing over paper-and-pencil testing are numerous: "the capacity to test a large number of individuals quickly; ready availability of assessment services without advance notice; the ability to measure performance on time-sensitive tasks, such as reaction time, more precisely; potentially reduced assessment times through the use of adaptive testing protocols; reduced costs related to test administration and scoring; ease of administering measures in different languages; automated data exporting for research purposes; increased accessibility to patients in areas or settings in which professional neuropsychological services are scarce; and the ability to integrate and automate interpretive algorithms such as decision rules for determining impairment or statistically reliable change" (Bauer et al., 2012, p. 362).

One cognitive test that has incorporated digital technologies is clock drawing. For example, The Digital Clock Drawing Test [dCDT] (Davis et al., 2010; Penney, Davis, et al., 2010; Penney, Libon, et al., 2010) utilizes digital pen technology with software developed by Lahey Clinic and the Massachusetts Institute of Technology (MIT). The instructions used to administer the dCDT are consistent with traditional clock drawing administration (i.e., draw the face of a clock, put in all the numbers, set the hands for 10 after 11) (Davis et al., 2014). The off-the-shelf digital pen (from Anoto Inc.) can be used on regular paper and functions like an ordinary ballpoint while simultaneously measuring its position on the paper every 12ms with an accuracy of ± 0.002 (Davis et al., 2014). Data collected with the dCDT is time-stamped, allowing the pen to digitally capture the final drawing (i.e., clock) as well as the behaviors that produced it (e.g., pauses, hesitations, drawing time, thinking time [time spent simply holding the pen and presumably thinking]) (Davis et al., 2014). Furthermore, time-stamped data also means the program can play back a recording of how the clock was drawn (e.g., stroke sequence, pen speed, perseverations, errors) which allows for later review (Davis et al., 2014). This level of sensitivity to graphomotor characteristics and decision-making latencies may provide more precise and accurate data than what can otherwise be gathered through traditional assessment (Diaz-Orueta et al., 2020; Germine et al., 2019). The Lahey Clinic/ MIT software classifies each pen stroke as a clock feature (i.e., clock face, clock numbers, clock hands) with up to 84% accuracy in healthy controls (Penney, Libon, et al., 2010). This software can label and calculate latencies for the length and

number of strokes associated with individual clock features; the dimensions and orientation of the clock face, clock numbers, and clock hands; the time elapsed during and between drawing individual clock features; and deviations of clock features from ideal placement (Davis et al., 2014; Binaco et al., 2020).

The dCDT has been used with both healthy controls and patient populations to explore individual differences in graphomotor organization and decision-making. Among patients with multiple sclerosis (MS), Libon et al. (2014) demonstrated slowed latencies and longer completion time on the dCDT, which supports the presence of bradyphrenia (i.e., reduced processing speed) often observed in this population. In a sample of patients diagnosed with major depression, Cohen et al. (2014) found that younger patients spent a smaller proportion of time actually drawing (i.e., *"ink" time*; total time the pen is in contact with the paper) relative to not drawing (i.e., *"think" time*; total time the pen is not in contact with the paper) compared to older patients. Despite similar overall performance on the dCDT, nuanced differences in *"ink" time* and *"think" time* differentiated aspects of psychomotor slowing between older and younger depressed groups (Cohen et al., 2014). Lamar et al. (2016) found that individuals who use anchor numbers on clock drawing (i.e., 3, 6, 9, 12) required fewer strokes to complete the dCDT and demonstrated overall better performance on tasks of executive function and learning/memory/recognition compared to individuals who do not use anchor numbers. In a large sample of older adults, Piers et al. (2017) demonstrated an effect of age on total time to completion, pen strokes, and latencies. Most recently, Dion et al. (2020)

demonstrated dCDT performance differences between older adults with and without mild cognitive impairment (MCI), such that slower total completion time, larger clock faces, and longer *"think" time* were observed in the group with MCI compared to the group without MCI.

When screening for cognitive impairment, the need for quick feedback regarding cognitive status has motivated the use of machine learning (Bratic et al., 2018; Yim et al., 2020). Machine learning is an algorithm that can learn patterns from complex neuropsychological data in order to classify patients using either a binary classification (i.e., demented; not demented) or ternary classification (i.e., healthy; cognitively impaired; demented) (Bratic et al., 2018). Using a classification system provides an immediate and automated diagnosis, which optimizes time and efficiency in healthcare settings (i.e., primary care) as manual scoring of data is not only time consuming, but scores may be subject to error (i.e., not objective or consistent) by busy clinic staff (Bratic et al., 2018). Furthermore, an automated diagnosis makes the use of cognitive screeners more feasible in healthcare settings as specialized clinicians (i.e., licensed clinical neuropsychologists) are not required for immediate score interpretation (Bratic et al., 2018).

Machine learning algorithms have been proposed to help establish the relationship between features of dCDT performance and level of cognitive decline (Binaco et al., 2018; Davis et al., 2014; Souillard-Mandar et al., 2016). Using machine learning, Davis et al. (2014) demonstrated that the dCDT can successfully differentiate healthy controls

from patients with Alzheimer's Disease (AD) and other dementias. Souillard-Mandar et al. (2016) reported classification rates on dCDT data from healthy controls, patients with mild cognitive impairment (MCI), and patients with several other dementias using a variety of machine learning methods. Lastly, Binaco et al. (2018) demonstrated the ability of a machine learning algorithm with hundreds of features from dCDT drawings to classify mild cognitive impairment (MCI) subtypes and AD with 70-80% accuracy. Altogether, these studies suggest that machine learning may help improve diagnostics of cognitive impairment on tasks of clock drawing.

The use of a digital pen is not the only technological advancement that has been applied to clock drawing. In the last year, researchers have begun to develop clock drawing tests that utilize a digital interface (i.e., computer, tablet), including a digital clock drawing test administered on a Windows Surface Pro 4 tablet with a handheld stylus pen (Muller et al., 2019; Zhao et al., 2019). Similar to traditional clock drawing instructions, participants are asked to draw the face of a clock with all the numbers and to set the hands to 10 after 11 (Muller et al., 2019; Zhao et al., 2019). Zhao and colleagues administered this test to a sample of older adults with cerebral small vessel disease and observed an effect of disease severity on test performance, such that patients with severe small vessel disease performed worse on digitized clock drawing compared to patients with little/no small vessel disease (Zhao et al., 2019). Muller and colleagues have also used this test to demonstrate the diagnostic value of digitized clock drawing in differentiating patients with amnestic MCI, patients with mild AD, and healthy controls.

In one study, Muller et al. (2017) found that the time to transition the stylus from one stroke to the next (i.e., *time-in-air*; similar to *"think" time*) on the digitized test yielded higher diagnostic accuracy when discriminating between MCI patients and healthy controls than the use of the traditional paper-and-pencil test. In a later study, Muller et al. (2019) demonstrated how digitized clock drawing holds comparable diagnostic values to other screening tests (i.e., CERAD) when discriminating between patients with MCI and/or AD and healthy controls. Although digitized clock drawing is relatively new in the literature, these early findings are encouraging and provide preliminary support for the use of digitized clock drawing as a screening instrument.

Introduction of the Clock in the Box

One modified version of the classic clock drawing test is the Clock in the Box (CIB) (Grande et al., 2005; Grande et al., 2011a). This modification was reportedly included to increase working memory demands with the goal of increasing sensitivity of the task (L. J. Grande, personal communication, October 25, 2019). Participants are provided written instructions before completing the task, requiring them to hold the instructions in mind (i.e., WM; working memory) with specific directions to draw in a predetermined location on the response sheet (i.e., P/O; planning/organization). The inclusion of these executive elements was designed to make the CIB a more comprehensive screener for cognitive impairment compared to alternative screeners on the market (i.e., MMSE).

During administration of the CIB, participants are given a sheet of paper with a set of four instructions: (1) In the blue box on the next page, (2) Draw a picture of a clock, (3) Put in all the numbers, and (4) Set the hands to ten after eleven. The instructions are taken away and participants are free to draw on the response sheet that shows four colored boxes (yellow, red, green, blue) each in a quadrant. A sample CIB is illustrated in Appendix A.

Performance on the CIB is based on specific scoring criteria (see Appendix B). Each CIB is scored using an 8 point total scale (1 point each, range of 0 to 8, with lower scores indicating poorer performance) consisting of a 4 point Working Memory (WM) subscale and a 4 point Planning/Organization (P/O) subscale. Overall scoring criteria include location in the blue box, resemblance to a clock, number inclusion, number order, number spacing, correct time, appropriate size, and hand length and origin. The working memory component scores details specific to the set of written instructions, while the planning/organization component scores organizational and abstract features of the clock.

To date, the CIB has been used for cognitive screening in a handful of populations. In a sample of older hospitalized veterans, poorer performance on the CIB predicted discharge to a location other than home following hospitalization (e.g., subacute rehabilitation facilities, nursing facilities) (Jackson et al., 2016). Among cardiac surgery patients, better pre-operative cognitive status, as measured by the CIB, was significantly associated with discharge to home following surgery (Harrington et al., 2011). More recently, the CIB was used to quantify executive dysfunction and predict

prognosis in a sample of older patients with hematologic cancers (Hshieh et al., 2018). Performance on the CIB has been shown to be predictive of glycemic control among elderly Type 1 diabetic patients (Munshi et al., 2006). CIB performance has also been shown to predict performance on other standardized measures of executive function in an elderly community sample (Chester et al., 2011), as well as older patients with cardiovascular risk (Grande et al., 2011b).

The CIB was recently converted from a paper-and-pencil format to a digitized format. This modification was made to assist in making the CIB more attractive to healthcare providers and to provide a standardized administration. The digital Clock in the Box [dCIB] is a novel digitized clock drawing task administered on an iPad tablet with a stylus pen.

The dCIB shares many features with existing digitized clock drawing tests (i.e., dCDT and Windows Surface Pro 4, as discussed above). All three tests require examinees to draw the clock face (i.e., no pre-drawn circle), to set the clock to the same time (i.e., ten after eleven), and to use a handheld pen to complete the drawing (i.e., digital pen for the dCDT; stylus pen for the dCIB and Windows Surface Pro 4). In addition to similar administration, these tests all record drawing performance which can be used to evaluate important qualitative details of how the clock was drawn (i.e., time to completion, order of clock details, self-corrections) and inform behavioral and cognitive processes.

The dCIB offers a number of advantages over existing digitized clock drawing tests. One advantage is its inclusion of executive elements, which we postulate makes the dCIB more sensitive to executive dysfunction and thereby furthers its utility beyond other clock drawing tests. Another advantage is that the dCIB program is designed to score performance and compare it to normative data in real time. This feature offers healthcare providers immediate feedback (i.e., score indicating performance outside normal limits) that can be used to inform on-the-spot medical recommendations. This is in contrast to the dCDT which utilizes a sophisticated digital pen to record clock drawings that are later downloaded and scored by Lahey Clinic/MIT software, as well as data from the clock drawing test administered on the Windows Surface Pro 4 tablet which is scored by hand. Although administration and collection of clock drawings on the Windows Surface Pro 4 is similar to that of the iPad, its functionality is limited as data cannot be immediately scored and interpreted.

The goal of this research is to examine the clinical utility of the dCIB. Evidence that the dCIB can detect early changes to cognition among those who have not yet been identified as cognitively impaired (i.e., have not been referred for a neuropsychological assessment or evaluation of cognition) would help establish its utility as a successful cognitive screener. Individuals with vascular risk, who may exhibit subtle cognitive deficits that can go unnoticed by the patient and his or her friends and family (Ng et al., 2016), are a logical population choice test out the dCIB.

Vascular Risk

Because subtle cognitive impairment precedes dementia (Farias et al., 2017), early detection of these changes may help identify those at greater risk for developing dementia in the future. Poor vascular health, marked by the presence of three or more cardiovascular risk factors, has been identified as a major cause of cognitive impairment and dementia in the growing aging population (Anand et al., 2020; Atti et al., 2019; Lai et al., 2020; Lee et al., 2020; Saklayen, 2018; Song et al., 2020; Zheng et al., 2020). Individuals with vascular risk often show only subtle deficits, yet they are at risk for developing vascular dementia in the future if the underlying risk factors remain uncontrolled (Ates et al., 2020; Azarpazhooh et al., 2019; Hughes et al., 2020; Ng et al., 2016; Pal et al., 2018). Cardiovascular risk factors include hypertension, obesity, diabetes, dyslipidemia (i.e., high levels of low-density lipoprotein cholesterol [LDL], low levels of high-density lipoprotein cholesterol [HDL], high levels of triglycerides) and hyperglycemia (i.e., high fasting blood glucose) (Grundy, 2005; Triposkiadis et al., 2019). Vascular risk factors often do not present with symptoms that are easily detected or experienced by the individuals (i.e., patients may not feel 'sick') (Bennett, 2017), so individuals may be unaware that their vitals are abnormal and that their cardiovascular health is outside of the normal range. However, these risk factors have been shown to impair cognitive functioning. Chronic hypertension is a leading cause of age-related cognitive impairment in executive function, processing speed, and, less frequently, memory (Hay et al., 2020; Hoffmann et al., 2020; Hughes & Sink, 2016; Iadecola et al.,

2016; Mehra et al., 2020; Moraes et al., 2019; Ou et al., 2020; Zhou et al., 2019). Diabetes mellitus has been associated with impaired attention, processing speed, executive function, and verbal memory (Cakir et al., 2020; Karvani et al., 2019; Kim, 2019; Lyu et al., 2020; Moheet et al., 2015; Sinclair et al., 2020; Valenza et al., 2020; Zhao et al., 2020; Zilliox et al., 2016). Negative associations between obesity and executive function have been reported in the literature (Bischof & Park, 2015; Dye et al., 2017; Favieri et al., 2019; Ganguli et al., 2020; Yang et al., 2018). Elevated risk factors below current threshold for clinical diagnosis have also been associated with poorer cognitive performance, highlighting the potential impact of subclinical risk (Kresge et al., 2018; Sacre et al., 2018; Wendell et al., 2009). Untreated vascular risk factors can lead to more serious conditions such as cardiovascular disease (i.e., conditions of the heart blood vessels), cerebrovascular disease (i.e., conditions of the brain blood vessels), and vascular dementia (see *Pal et al., 2018* for a review). Given these associations, individuals with poor vascular health may be at greater risk for cognitive impairment.

Vascular risk factors rarely occur in isolation but often present together in a clinical constellation. First described as 'Syndrome X' (Reaven, 1988) and 'Insulin Resistance Syndrome', the name 'Metabolic Syndrome' was introduced by the World Health Organization in 1998 to describe this specific co-occurrence of vascular risk factors (Oda, 2018). Over the past few decades, the incidence of Metabolic Syndrome (MetS) has risen in tandem with rising numbers of its component vascular risk factors (Saklayen, 2018). An estimated 23% (Beltran-Sanchez et al., 2013) to 35% (Aguilar et

al., 2015; Hirode & Wong, 2020) of U.S. adults are considered to have MetS, with age continually cited as a major risk factor (Lai et al., 2020; Zheng et al., 2020). The most recent data analyzes MetS trends, with more than one third of adults of all socioeconomic groups in the U.S. meeting diagnostic criteria (Hirode & Wong, 2020; Moore et al., 2017). Given these climbing numbers, MetS has been considered a rising health epidemic.

MetS has been associated with age-related cognitive changes (Assuncao et al., 2018; Bae et al., 2017; Bezrukov et al., 2018; Lai et al., 2020), accelerated cognitive aging (Kulshreshtha et al., 2019; Tsentidou et al., 2019), and an increased risk for vascular dementia (Atti et al., 2019; Lee et al., 2020; Moon et al., 2019; Ng et al., 2016; Pal et al., 2018). Component risk factors of MetS (e.g., dyslipidemia) lead to fatty buildup in the blood vessels (i.e., atherosclerosis) which, over time, causes the vessels to narrow and restricts the flow of oxygen-rich blood (Blumenfeld, 2018; Sudo et al., 2017). Atherosclerotic vessel narrowing is especially dangerous to small blood vessels as it may lead to occlusion of the vessel with serious consequences such as infarct or hemorrhage (Blumenfeld, 2018; Sudo et al., 2017). Over time, this chronic damage (i.e., small vessel disease) results in subcortical lesions, including lacunar infarcts and cerebral microbleeds, that interrupt interconnections among different brain regions and cause disturbances to complex cognitive functions (Sudo et al., 2017). Many small vessels sit within frontal-subcortical circuits, highlighting that cognitive abilities dependent upon the integrity of these frontal-subcortical circuits, especially frontally mediated executive

functions, may be particularly vulnerable to vascular risk (Pugh & Lipsitz, 2002). The literature supports this assertion, linking vascular risk factors with deficits in executive functioning (e.g., planning, organizing, multi-tasking) (Moraes et al., 2019; Yang et al., 2018). Across the literature, executive dysfunction is the predominant cognitive deficit associated with MetS (Alcorn et al., 2019; Falkowski et al., 2014; Lai et al., 2020; Ogawa et al., 2020; Reijmer et al., 2011; Rouch et al., 2014; Schuur et al., 2010; Strong et al., 2020; Viscogliosi et al., 2015; Yates et al., 2012). MetS has also been linked to deficits in memory (Komulainen et al., 2007, Ogawa et al., 2020; Rouch et al., 2014; Strong et al., 2020), verbal memory (Bezrukov et al., 2018; Dik et al., 2007), visual working memory (Raffaitin et al., 2011), attention (Bezrukov et al., 2018), sustained attention (Wooten et al., 2019), fluid intelligence (Dik et al., 2007; Ghisletta et al., 2019), information processing speed (Dik et al., 2007; Przybycien-Gaweda et al., 2020), and general cognition (Dik et al., 2007; Lai et al., 2020; Przybycien-Gaweda et al., 2020; Raffaitin et al., 2011; Viscogliosi et al., 2012). These cognitive deficits may be linked to underlying structural brain abnormalities associated with MetS, including reduced cortical thickness in frontal, parietal, and occipital regions (Schwarz et al., 2018), decreased gray matter volume in predominantly frontal and temporal areas (Kotkowski et al., 2019), microstructural damage to gray and white matter (Sala et al., 2014), as well as silent lacunar infarcts, periventricular white matter hyperintensities, and subcortical white matter lesions (Yates et al., 2012) (see *Alfaro et al., 2018* for a review). Underlying

pathophysiological mechanisms (e.g., metabolic, inflammatory) may contribute to both neuroanatomical changes and cognitive decline (Wang et al., 2016).

MetS can begin as early as middle age with poor cardiovascular health in midlife as a significant predictor of later life executive dysfunction (Debette et al., 2011; Knopman et al., 2018). Many individuals with MetS often show only subtle cognitive deficits, yet they are at risk for developing vascular dementia in the future, especially if the underlying risk factors remain uncontrolled (Ates et al., 2020; Azarpazhooh et al., 2019; Ng et al., 2016). Longitudinal studies have demonstrated the negative impact of midlife MetS on later life cognitive functioning (Bangen et al., 2019), as well as the association of later life MetS with accelerated cognitive and functional decline (i.e., inability to perform basic activities of daily living [ADLs; e.g., bathing, dressing] and complex instrumental activities of daily living [IADLs; e.g., shopping, managing finances]) (Viscogliosi et al., 2017). Recent studies have demonstrated the link between good cardiovascular health during midlife and better outcomes in later life including better physical functioning and lower risk for dementia (Sabia et al., 2019; Urtamo et al., 2020; von Bonsdorff et al., 2019). Because deficits associated with vascular risk factors may progress over time, with subtle cognitive impairment preceding full-blown dementia (Farias et al., 2017), early identification of subtle cognitive deficits may help identify those at risk for developing vascular dementia in the future and engender lifestyle changes (e.g., behavioral modification, medication use) (Reamy et al., 2018) that may help regulate disease progression. With its strengthened executive elements, the dCIB

may be an excellent screening tool for individuals with MetS. If the dCIB can detect early changes to cognition, particularly executive deficits expected in individuals with poor vascular health (i.e., MetS), this may help establish its utility as a successful cognitive screener.

Study Overview

In this research, we administered the dCIB to a community-based sample of adults who have not been identified as cognitively impaired but may exhibit subtle cognitive deficits associated with poor vascular health. We addressed four aims that may help showcase the clinical utility of the dCIB. The dCIB is a novel digitized test and this research is the first of its kind to examine its utility.

Aim 1

Our first aim was to create cutoff scores for the dCIB. Cutoff scores indicating cognitive impairment offer healthcare providers immediate feedback (i.e., score indicating performance outside normal limits) that can be used to inform medical recommendations (i.e., referral for comprehensive neuropsychological evaluation). Not only are cutoff scores easy and practical to use, they are also highly feasible in a busy clinic setting (i.e., primary care) where staff are under considerable time constraints.

Hypotheses Because the same scoring criteria is used for both the paper-and-pencil CIB and the dCIB, we expected similar cutoff scores between the two tests. Grande and colleagues (2011b) determined clinical cutoff scores for the CIB such that *suspected* impairment reflects a score of 6 or below and *probable* impairment reflects a score of 5 or below.

Aim 2

Our second aim was to examine correlations between the dCIB and MMSE to determine concurrent validity and compare how the dCIB performs alongside a widely used

cognitive screener. Additionally, we calculated the sensitivity and specificity probabilities for the dCIB to determine whether it can correctly identify those with impairment (i.e., sensitivity) and correctly identify those without impairment (i.e., specificity). We also calculated sensitivity and specificity for the MMSE and compared psychometric data between the two screeners. Because the MMSE has been criticized for its low sensitivity and limited ability to detect subtle cognitive deficits, findings from this aim may help demonstrate the dCIB as a superior screener if it is better able to flag subtle impairment.

Hypotheses Consistent with previous literature demonstrating significant correlations between clock drawing and existing cognitive screeners, we expected significant positive correlations between the dCIB and the MMSE. Additionally, we expected higher sensitivity values for the dCIB compared to the MMSE. Not only has the MMSE been criticized for its low sensitivity, clock drawing tasks consistently demonstrate good psychometric properties.

Aim 3

Our third aim was to determine the predictive validity of the dCIB on cognitive functioning. Neuropsychological tests were used as a performance reference because, although lengthy, they are comprehensive assessments of cognitive domains with high sensitivity and specificity. In the interest of reducing the number of variables in our analysis, we created domain-specific composite scores which serve as a single representative score for a cognitive domain. If the dCIB was able to predict cognitive

performance on these composite scores, this would help establish construct validity insofar that the dCIB is measuring what it was designed to measure. Moreover, if associations between the dCIB and neuropsychological outcomes were found, this finding would be consistent with other studies using clock drawing tasks and would therefore provide face validity that the dCIB is capturing cognitive performance.

Hypotheses Because clock drawing relies on cognitive abilities that span across executive function, memory, and attention domains, we expected that the dCIB would predict performance on neuropsychological tests that assess these domains. Using domain-specific composite scores, we hypothesize that the dCIB will predict performance on Composite Scores of Executive Function, Memory, and Attention.

Aim 4

Our fourth aim was to determine the efficacy of the dCIB as a cognitive screening instrument. Individuals in our sample were separated into groups (MetS versus non-MetS) using current diagnostic criteria for MetS (see *Methods*). If the dCIB was able to correctly differentiate groups based on cognitive performance, this may establish its ability to identify subtle cognitive impairment in this population. Because of the executive elements embedded within the test, the dCIB may be especially useful for populations and disorders with executive dysfunction. This highlights a potential advantage of the dCIB over existing screeners – particularly the MMSE, which is

currently the most widely used cognitive screener despite its omission of items assessing executive functioning.

Hypotheses Executive dysfunction has been shown to be the predominant cognitive deficit associated with MetS; therefore, we expected a lower Executive Function Composite Score in the MetS group relative to the non-MetS group. Although MetS has been linked to deficits in memory and attention, these findings are far less robust than the association between MetS and executive dysfunction and, therefore, we did not expect significant group differences on Composite Scores of Memory or Attention. Moreover, we expected lower dCIB scores in the MetS group relative to the non-MetS group. With its inclusion of executive elements, we expected the dCIB to be sensitive to executive dysfunction in individuals with higher vascular risk.

CHAPTER TWO – METHODS

Study Design

This research was designed to be cross-sectional with data from veterans and civilians aged between 45 and 90 years. Participants were recruited through multiple sources including targeted newspaper advertisements, flyers on the VA Boston Healthcare System and Harvard Medical School campuses, posters on the MBTA transit system, word of mouth, and direct recruitment from clinics within the VA Boston Healthcare System (Preventative Cardiology, Geriatric Research, Education, and Clinical Center [GRECC], Neuropsychology, Neurology, Optometry, Diabetes). Preliminary inclusionary and exclusionary criteria were determined by phone screen (see *Sample* for details). If determined eligible, participants were scheduled for a future visit and mailed details about the study, instructions to prepare, and directions to the lab located at the VA Boston Healthcare System campus in Jamaica Plain, Massachusetts.

Beginning the evening before the scheduled study visit, participants were instructed to complete a 10 to 12 hour fast (water allowed) to prepare for the blood draw. Upon arrival to the lab, participants reviewed a detailed consent form during which they were free to choose whether or not to partake in the research study. Background and health information was collected by study staff in the form of questionnaires and interviews. Questions focused broadly on educational level, work history, history with smoking and alcohol consumption, past surgeries, other major accidents or illnesses, functional status, and psychiatric history. A list of current medications was also

collected, as certain medications are known to have an effect on brain structure and cognitive function.

Participants completed a blood draw as well as a brief health evaluation (see *Sample* for details). All measures were collected by a phlebotomist. Blood samples of approximately 26ml were aliquoted and sent for processing to Quest Diagnostics for chemistry and cholesterol analysis.

Our study used a sample of participants collected as part of a larger research project designed to examine the impact of vascular risk factors on brain structure and function. Because untreated vascular risk factors have been shown to impair cognitive functioning, participants were administered a comprehensive neuropsychological battery consisting of paper-and-pencil tests and computerized tasks to assess cognitive status. In the interest of reducing variables, we created composite scores of three general cognitive domains: executive function, memory, and attention. We were interested in these particular domains because of their association with vascular risk in the literature (Alcorn et al., 2019; Bezrukov et al., 2018; Dik et al., 2007; Falkowski et al., 2014; Komulainen et al., 2007; Reijmer et al., 2011; Rouch et al., 2014; Schuur et al., 2010; Viscogliosi et al., 2015; Yates et al., 2012). The presence of vascular risk factors has been repeatedly linked to deficits in executive functioning (Gatlin & Insel, 2015; Moraes et al., 2019; Yang et al., 2018), and therefore we chose to include measures of executive function as part of the neuropsychological assessment. Associations between vascular risk and memory are far less consistent in the literature. Some studies report poorer performance

on memory tests in individuals with vascular risk compared to controls, while other studies report little/no association between vascular risk and memory performance (see *Alcorn et al., 2019* for a review). Attentional deficits are also inconsistent in the vascular literature, with some studies reporting worse attention in individuals with vascular risk compared to controls (Wooten et al., 2019) and other studies reporting little/no association between vascular risk and attention (see *Alcorn et al., 2019* for a review). Therefore, we chose to include measures of both memory and attention in our assessment in order to determine whether vascular risk impacts these cognitive domains in our sample.

This study was supported by grants from the National Institute of Neurological Disorders and Stroke (NINDS) and Consortia for Improving Medicine with Innovation and Technology (CIMIT). Protocol approval was granted by the Institutional Review Board (IRB) of the VA Boston Healthcare System.

Sample

Inclusionary criteria included English-speaking adults between the ages of 45 and 90 years with or without symptoms of MetS. Willingness to complete a 10 to 12 hour fast and subsequent blood draw was required for inclusion. Willingness and ability to undergo an MRI scan was also required for inclusion.

Exclusionary criteria included a history of any of the following medical conditions: stroke; heart attack, cardiac arrest, or congestive heart failure; dementia; Parkinson's Disease; Huntington's Disease; brain infection (encephalitis, meningitis);

multiple sclerosis; head injury with a loss of consciousness for more than 30 minutes; HIV; hepatitis C; severe liver functioning issues (hepatic encephalopathy); emphysema; moderate to severe chronic obstructive pulmonary disease; seizure disorder; severe anemia; severe hypothyroidism or hyperthyroidism; severe visual or hearing impairment; and cancer in which the individual received chemotherapy or radiation treatment within the last 12 months. Individuals with a history of neurosurgery, cardiac surgery, or other major surgery were excluded. Further exclusionary criteria included a history of any of the following psychiatric or substance abuse conditions: schizophrenia; psychotic disorder; current major depressive disorder; bipolar disorder; severe obsessive-compulsive disorder; agoraphobia; severe anxiety disorder; drug addiction for cocaine, heroin, or any other drugs besides alcohol or marijuana; and hospitalization (greater than a week) for severe psychiatric issues. Participants were also excluded if taking medications known to negatively affect performance on cognitive tests or central nervous system functioning.

Participants underwent physiological and metabolic assessment including vital sign and body measurements (height in inches, weight in pounds, waist-to-hip ratio), as well as a blood draw to collect fasting glucose and a full cholesterol panel with the following outcome variables: low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, total cholesterol, fasting glucose, insulin, and glycated hemoglobin (A1C). For part of our analysis, we characterized our sample into MetS and non-MetS groups using diagnostic criteria established in 2001 by the National Cholesterol

Education Program (NCEP) Adult Treatment Panel III: (1) abdominal obesity, defined by elevated waist circumference greater than or equal to 40 inches (males) or 36 inches (females); (2) dyslipidemia, defined by elevated triglycerides greater than 150 mg/dL or (3) reduced HDL less than or equal to 40 mg/dL (males) or 59 mg/dL (females); (4) hypertension, defined by elevated blood pressure greater than or equal to 130/85 mmHG; and (5) elevated fasting plasma glucose greater than 100 mg/dL ("Executive Summary", 2001; Grundy, 2005). Triglycerides, HDL levels, and blood pressure were counted as abnormal if these symptoms were being controlled through medication or other drug treatments ("Executive Summary", 2001; Grundy, 2005). If three or more NCEP-III criteria were met, participants were classified into a MetS group; if fewer than three NCEP-III criteria were met, participants were classified in a non-MetS group. Statistical analyses were performed on demographic information (t-tests for age and education; chi square tests for gender and ethnicity/race) to determine whether significant differences exist between these groups, and any variable determined to be significantly different was controlled for as a covariate.

Measures

Neuropsychological testing was administered to provide an assessment of executive function, memory, and attention. Multiple tests within each domain were administered to create a more complete understanding of individual cognitive functioning.

Executive functioning has been shown to be the strongest cognitive predictor of everyday "real world" functioning (Mansbach & Mace, 2019; McDougall et al., 2019; Farias et al., 2009), with recent literature exploring the specific subdomains of executive functioning (e.g., inhibition, shifting attention) most involved in functional abilities (McAlister & Schmitter-Edgecombe, 2016). Longitudinal studies have reported that poor executive functioning at baseline is a significant predictor of future functional decline in community-dwelling older adults (Kraybill et al., 2013) as well as individuals with vascular dementia (Jefferson et al., 2006). Given that many everyday tasks rely on underlying executive functions, age-related and/or vascular-related declines in executive functioning may lead to functional deficits that could negatively impact functional independence (e.g., IADLs; shopping, managing finances).

Changes in memory are one of the most common cognitive complaints among older adults (Howieson et al., 2015; Park et al., 2019), and tests of memory can be used to differentiate normal age-related memory changes (e.g., declines in speed of information processing, problems remembering names) from abnormal functioning (e.g., dementia) in older adults. Additionally, memory is the most commonly reported cognitive difficulty in

returning veterans and is therefore appropriate to assess in a sample that includes veterans.

Attention is a building block upon which other cognitive abilities rely and, therefore, must be included in any assessment to ensure observed deficits are due to underperformance in a particular domain (e.g., executive function, memory) and not from underlying inattention and distractibility.

"Typical approaches to the characterization and classification of cognitive performance in clinical neuropsychology refer to domains of cognitive performance. Within each domain there are typically subdomains, which refer to component ability processes within the larger constructs. Individual neuropsychological tests are characterized under these subdomains, with these tests measuring one or more discrete abilities" (Harvey, 2019, p. 227). Utilizing this approach, we grouped the following list of measures by domain, subdomain, and the individual tests administered to our sample, including outcome variable(s) of interest.

Executive Function

Word Generation

This executive test is intended to measure the spontaneous production of words under restricted search conditions (Strauss et al., 2006). Word generation includes tests of both phonemic and category fluency. Phonemic fluency tasks require participants to orally produce as many words as possible that begin with a specified letter (i.e., F, A, S) within one minute. Category fluency tasks require participants to orally produce as many words as possible that belong to a designated semantic category (i.e., animals) within one minute. For this study, word generation was evaluated with the Letter Fluency + Category Fluency conditions of the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test (Delis et al., 2001). Test performance was based on the total number of words generated across F, A, and S (*Letter Fluency*) and the total number of words generated for the Animals category (*Category Fluency*). Performance was compared to published normative data (Delis et al., 2001).

Shifting Attention

This executive test is intended to measure attention, cognitive flexibility, and processing speed using specific skills of visual scanning and number-letter switching (Strauss et al., 2006). Tests of shifting attention require participants to change their focus of attention from one stimulus or stimulus domain to another. The most commonly administered clinical measure of shifting attention involves

connecting encircled numbers and letters in alternating and ascending order (1, A, 2, B, 3, C…) as quickly as possible. For this study, shifting attention was evaluated with the Number-Letter Switching condition of the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (Delis et al., 2001). Test performance was based on time to completion (*Number-Letter Switching*). Performance was compared to published normative data (Delis et al., 2001).

Color-Word Inhibition

This executive test is intended to measure cognitive flexibility and inhibition of a familiar or dominant response (Strauss et al., 2006). Tests of color-word inhibition require participants to name the color of printed words and inhibit or ignore reading the word (the dominant response). Stimulus words (color names) are printed in colored ink. For this study, color-word inhibition was evaluated with the Inhibition condition of the Delis-Kaplan Executive Function System (D-KEFS) Color Word Interference Test (Delis et al., 2001). Test performance was based on time to completion (*Inhibition*). Performance was compared to published normative data (Delis et al., 2001).

Memory

Word List Learning and Memory

This memory test is intended to measure verbal learning and memory using multiple-trial supra-span list learning tasks (Strauss et al., 2006). Tests are administered to assess both immediate (learning) and delayed (memory)

conditions. For this study, word list learning and memory were evaluated with the California Verbal Learning Test II (CVLT-II; Delis, 2000). Participants were read aloud 16 words from a list and asked to recall the words over the course of five learning trials. After a 20 minute delay, participants were again asked to spontaneously recall words from the list. Test performance was based on total correct responses from trial learning (*Trials 1-5 Free Recall* [possible range of 0-80]) and total correct responses from delayed recall (*Long Delay Free Recall* [possible range of 0-16]). We chose to exclude *Cued Recall* conditions on the CVLT-II because cueing provides the participant a way to organize words by category, thereby removing self-generated organizational strategies. We also chose to exclude *Recognition* given that this condition facilitates retrieval beyond the active, complex search process required in *Free Recall* conditions. Performance was compared to published normative data (Benedict et al., 1998; Delis, 2000).

Story/Narrative Memory

This memory test is intended to measure verbal learning and memory using a story format (Strauss et al., 2006). This test includes both immediate learning and delayed memory. We chose to include a story memory test as it closely resembles everyday memory demands and provides information as to how context and meaning contribute to learning and recall (Lezak et al., 2004). For this study, story memory was evaluated using the Logical Memory subtest from the

Wechsler Memory Scale IV (WMS-IV; Wechsler, 2009). Participants were read aloud two short stories and asked to immediately retell each story in full detail. Repeated presentation of one of the stories was offered for individuals over the age of 65 years. Following a 20 to 30 minute delay, participants were again asked to retell the stories in full detail. Test performance was based on spontaneous recollection of story details immediately following story presentation (*Immediate Recall* [possible range of 0-25]) and spontaneous recollection of story details following a delay after presentation (*Delayed Recall* [possible range of 0-25]). We chose to exclude the *Recognition* condition given that it places less demands on memory retrieval compared to *Free Recall* conditions. Performance was compared to published normative data (Wechsler, 2009).

Nonverbal Learning and Memory

This memory test is intended to measure visual learning and memory (Strauss et al., 2006). Tests are administered to assess both immediate (learning) and delayed (memory) conditions. Nonverbal memory tests often use abstract geometric designs or nonsense figures as an attempt to minimize verbal encoding (e.g., 'this looks like a house'). For this study, nonverbal learning and memory were evaluated with the Brief Visuospatial Memory Test Revised (BVMT-R; Benedict, 1997). Participants were shown a visual display of six figures arranged in a 2 x 3 matrix over three consecutive 10 second learning trials and asked to draw the figures from memory after each learning trial. After a 20 to 25 minute

delay, participants were asked to draw the figures from memory. Scoring is based on a 2 point scale for both figure accuracy (1 point) and figure placement (1 point) for each detail of the drawing [range of 0-2 for each figure, 6 figures]. Test performance was based on the number of correct figure details recalled immediately following the learning trials (*Total Recall* [possible range of 0-36]) and following a delay (*Delayed Recall* [possible range of 0-12]). We chose to exclude *Recognition* given that this condition facilitates retrieval beyond the active search process required in *Free Recall* conditions. Performance was compared to published normative data (Benedict, 1997).

Attention

Auditory Attention

This attention test is intended to measure simple attention using auditory stimuli. For this study, auditory attention was evaluated using Digit Span Forward on the Digit Span subtest of the Wechsler Adult Intelligence Scale IV (WAIS-IV; Wechsler, 2008). Participants listened to a sequence of numbers and repeated the numbers out loud in the same order. Test performance was based on total correct responses (*Digit Span Forward* [possible range of 0-16]). Performance was compared to published normative data (Wechsler, 2008).

Visual Attention

This attention test is intended to measure focused attention and processing speed, using specific skills of visual scanning and number sequencing (Strauss et al.,

2006). For this study, visual attention was evaluated using the Number Sequencing condition of the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (Delis et al., 2001). Participants were asked to draw lines to connect numbers randomly arranged on a page into ascending order (1, 2, 3, 4, 5…) as quickly as possible. Test performance was based on time to completion (*Number Sequencing*). Performance was compared to published normative data (Delis et al., 2001).

Comparison Measure

Digital Clock in the Box (dCIB)

The Digital Clock in the Box (dCIB) is a digitized version of the CIB that is administered on an iPad tablet. In consultation with Dr. Laura Grande, the dCIB was programmed for the purposes of this study by John Stricker, Ph.D., who was familiar with the paper version of the CIB. To administer the dCIB, participants were handed an iPad Air (screen size of 9.7 inches) and a stylus pen. A practice trial was administered to familiarize participants with how to use the tablet and stylus. For the practice trial, four dots forming the corners of a 3" square were centered on the screen and participants were asked to use the stylus to connect the dots. If needed, the practice trial was repeated up to four times. If unable to complete the practice trial after the fourth attempt, test administration for the dCIB was discontinued. Following the practice trial, the dCIB was administered. The initial screen stated the following directions: "Please read and do the

following carefully" (in Times font and 16 font size, bold and italicized) and a list of four instructions (in Times font and 20 font size): (1) "In the blue box on the next page", (2) "Draw a picture of a clock", (3) "Put in all the numbers", and (4) "Set the hands to ten after eleven". Once participants read through the instructions, they selected the "Next" button, which removed the instructions and prompted the response screen. The response screen showed four boxes (approximately 2.25" x 3.5") with colored outlines (yellow, red, green, blue) each in a quadrant, with the blue box positioned in the lower right quadrant. When a response location was selected, the selected box increased in size (approximately 4" x 5") while the other boxes became disabled. Participants then used the stylus to complete the task in the selected box. Scoring for the dCIB is completed using an 8 point total scale (1 point each, range of 0-8, with lower scores indicating poorer performance), consisting of a 4 point Working Memory Subscore and a 4 point Planning/Organization Subscore. The Working Memory (WM) Subscore focuses on four details specific to the set of written instructions including: (1) whether the drawing is completed in the correct (blue) square (credit is given if the drawing is in the blue square or if the blue box itself is used as the clock's outline; no credit is awarded if the clock is drawn in multiple boxes or across multiple boxes); (2) whether the drawing resembles a clock (any type of clock is acceptable [e.g., grandfather clock]); (3) whether the drawing includes all numbers (credit is given for inclusion of 1-12 in any order and in any location

[e.g., written in a line] as well as numbers written in Roman numerals; no credit is awarded if any number(s) other than 1-12 are present); and (4) whether the correct time is indicated (credit is given if time is written [e.g., "ten past eleven"] or if the 11 and 2 are circled or otherwise highlighted). The Planning/Organization (P/O) Subscore focuses on four organizational and abstract features of the clock including: (1) whether the drawing is an appropriate size (credit is given if the drawing is small enough to fit in the blue square, does not intersect other squares, and is large enough to accommodate numbers 1-12; no credit is awarded if the blue box itself is used as the clock's outline); (2) whether the numbers are in correct order (numbers may be written in any format [e.g., in a line]); (3) whether the numbers are evenly spaced and drawn within the clock's outline (credit is given if the opposing anchor numbers of 3 & 9 and 12 & 6 are relatively well-aligned and the other numbers are relatively well placed; no credit is given if numbers intersect the perimeter of the clock or if two or more quadrants have poor number spacing); and (4) whether the clock hands originate at the center of the drawing and are drawn of different lengths (the hour hand must be 80% or less the length of the minute hand, and the origin of hands must be drawn within 50% of the clock center). Test performance was based on the dCIB *Total Score*, which is calculated by adding the *WM Subscore* and the *P/O Subscore*. Complete scoring criteria for the dCIB is described in Appendix B.

Neuropsychological Composite Scores

As described above, a number of cognitive measures were included to assess the domains of interest, and a number of specific scores were utilized to assess these behaviors. To reduce the number of variables in our analysis, composite scores were created from the means of standardized scores for the outcome variables of the neuropsychological tests administered to our sample. The use of domain-specific cognitive composite scores, which serve as a single representative score for a cognitive domain, has grown in popularity as a preferred method in neuropsychological assessment data analysis (Jonaitis et al., 2019; Crane et al., 2012; Gibbons et al., 2012). We used a theory-driven approach in which established neuropsychological theories are used to combine scores within a particular cognitive domain (Jonaitis et al., 2019; Riordan, 2017). The choice of individual tests used to create composite scores closely matches the study designs for populations of aging (Halliday et al., 2019; Palta et al., 2018), mild cognitive impairment (MCI) (Ganguli et al., 2019), Alzheimer's Disease (AD) (Bejanin et al., 2017; Malek-Ahmadi et al., 2018), and vascular risk (Boss et al., 2017; Lal et al., 2017).

Raw test scores were converted into standardized z-scores based on age adjusted published norms, and these individual test z-scores were then averaged into z-score composites. We created composite scores for three general cognitive domains: executive function, memory, and attention. The Executive Function Composite Score was created from tests of (1) word generation, (2) shifting attention, and (3) color-word inhibition.

The Memory Composite Score was created from tests of (1) word list learning and memory, (2) story/narrative memory, and (3) nonverbal learning and memory. Lastly, the Attention Composite Score was created from tests of (1) auditory attention, and (2) visual attention. Participants without at least one test from each of these domains were excluded from analysis. A complete list of tests administered to our sample is provided in Appendix C.

CHAPTER THREE – AIMS, HYPOTHESES, & STATISTICAL ANALYSES

AIM 1: DETERMINE CLINICAL CUTOFF SCORES FOR THE DCIB

Hypotheses

- Clinical cutoff scores have been established for the paper-and-pencil CIB (Grande et al., 2011b) such that *suspected* impairment reflects a score of 6 or below and *probable* impairment reflects a score of 5 or below; because the same scoring criteria is used for both the dCIB and CIB, we hypothesized similar cutoff scores between the dCIB and CIB.

Statistical Analysis (using IBM SPSS statistical software version 27)

- To determine optimal cutoff values for the dCIB, we used a receiver operating characteristic (ROC) curve to plot the true positive rate (i.e., sensitivity; proportion of impaired individuals for which the dCIB correctly identifies as impaired) against the false positive rate (i.e., 1 – specificity; proportion of unimpaired individuals for which the dCIB incorrectly identifies as impaired) in our sample for all possible cutoff scores. Participants were dichotomized based on cognitive impairment. Based on the typical criteria for cognitive impairment among MCI populations (see *Petersen & Morris, 2005*), evidence of impairment in our sample was determined by neuropsychological scores falling more than 1.5 *SD* below appropriate norms from at least two tests within any cognitive domain (Jak et al., 2009). If neuropsychological scores fell more than 1.5 *SD* below appropriate norms on one test (or no test), individuals were classified as

unimpaired. We ran an ROC curve analysis (test variable = dCIB Total Score; state variable = cognitive impairment) which offered a graphical illustration of the true positive rate (i.e., sensitivity) and false positive rate (i.e., 1 – specificity) for all possible cutoff scores, with each point on the plot corresponding to a cutoff score. For our ROC curve analysis, we reported each cutoff score and its corresponding true positive and false positive rates. In the literature, a commonly used approach for cutoff selection is based on the Youden index (*J*), which describes the summation of true positive and false positive rates for each score (*J* = sensitivity + [specificity – 1]) (Habibzadeh et al., 2016). On the graph, the Youden index represents the point on the ROC curve with the highest vertical distance from the 45° diagonal reference line (this line represents the output of a test with no diagnostic value) (Habibzadeh et al., 2016). In our analysis, the dCIB score that corresponded with the maximum Youden index was determined to be the optimal cutoff score.

AIM 2: INVESTIGATE HOW THE DCIB COMPARES TO THE MMSE

- Correlations between the dCIB and MMSE to determine concurrent validity and compare performance between these tests
- Sensitivity and specificity probabilities to compare psychometric properties between the dCIB and MMSE

Hypotheses

- Prior research shows significant correlations between clock drawing and existing cognitive screeners like the MMSE (Palsetia et al., 2018); therefore, we hypothesized significant positive correlations between the dCIB and the MMSE.
- Because clock drawing tasks consistently demonstrate good psychometric properties (Shulman, 2000) and the MMSE has been criticized for its low sensitivity (de Roeck et al., 2019; Mitchell, 2009), we hypothesized higher sensitivity values for the dCIB compared to the MMSE in the detection of cognitive impairment.

Statistical Analysis (using IBM SPSS statistical software version 27)

- To compare the dCIB and the MMSE, a bivariate Pearson's *r* correlation was calculated (variables = dCIB Total Score, MMSE Total Score). Pearson's *r* correlational coefficient ranges from 1 (i.e., perfect positive correlation; as one variable increases, the other variable increases) to -1 (i.e., perfect negative correlation; as one variable increases, the other variable decreases), and 0 indicating no association between the two variables. In our analysis, a correlation

was determined to be statistically significant if the *p*-value was ≤ 0.05. For this correlation, we reported the Pearson's *r* value as well as the *p*-value.

- To create sensitivity and specificity probabilities, participants were dichotomized based on cognitive impairment criteria described in *Aim 1* (i.e., impairment if neuropsychological scores fall more than 1.5 *SD* below appropriate norms from at least two tests within any cognitive domain; no impairment if neuropsychological scores fall more than 1.5 *SD* below appropriate norms on 0-1 tests from within any domain). Cutoff scores from *Aim 1* were entered into a 2x2 cross-tabulation (row = dCIB impairment; column = cognitive impairment) to determine sensitivity and specificity for the dCIB. This same methodology was repeated for the MMSE. MMSE scores were dichotomized using a cutoff score of 25, with impairment classified by an MMSE score of ≤ 25 while MMSE scores > 26 were classified as unimpaired. These variables were entered into a 2x2 cross-tabulation (row = MMSE impairment; column = cognitive impairment) to determine sensitivity and specificity for the MMSE. For each cross-tabulation in our analyses, we reported the sensitivity and specificity probabilities.

AIM 3: DETERMINE PREDICTIVE VALIDITY OF THE DCIB ON COGNITIVE FUNCTIONING

Hypotheses

- Clock drawing relies on cognitive abilities that span across executive function, memory, and attention domains (Young, 2018; Freedman, 1994); using regression modeling, we hypothesized that the dCIB would predict performance on tests that assess executive functioning, memory, and attention. Using domain-specific composite scores, we hypothesized that the dCIB would predict performance on Composite Scores of Executive Function, Memory, and Attention.

Statistical Analysis (using IBM SPSS statistical software version 27)

- A set of linear regressions were conducted where the dCIB was entered into a linear regression model predicting each of the three Composite Scores: (IV = dCIB Total Score; DVs = Composite Score [Executive Function Composite Score, Memory Composite Score, Attention Composite Score]). A useful property of a linear regression is that it can be used to predict the value of one variable (i.e., Composite Score) based on the value of another variable (i.e., dCIB score). Output from a linear regression provides the correlation (*R* value), as well as how much of the total variance in the outcome is explained by the predictor (R^2 value). For our predictor, we reported the unstandardized beta coefficient (*B*), standard error for the unstandardized beta coefficient (*SE*

B), t-test statistic (*t*), and p-value (*p*). The *B* coefficient tells us the nature of the relationship between the outcome variable (i.e., Composite Score) and the predictor variable (i.e., dCIB score), with the ± sign indicating the direction of the relationship. For every 1 unit increase in the predictor variable, the outcome variable either increases (+ sign) or decreases (- sign) by the *B* coefficient. In our analysis, a predictor variable was determined to be statistically significant if the *p*-value was ≤ 0.05.

AIM 4: APPLICATION OF THE DCIB IN A SAMPLE STRATIFIED BY VASCULAR RISK

- Neuropsychological differences between MetS and non-MetS groups using generated Composite Scores of Executive Function, Memory, and Attention
- dCIB performance differences between MetS and non-MetS groups

Hypotheses

- Executive dysfunction has been shown to be the predominant cognitive deficit associated with MetS (Alcorn et al., 2019); therefore, we hypothesized a lower Executive Function Composite Score in the MetS group relative to the non-MetS group. Although MetS has been linked to deficits in memory and attention (Alcorn et al., 2019), these findings are far less robust than the association between MetS and executive dysfunction; therefore, we did not expect significant group differences on Composite Scores of Memory or Attention.
- With its inclusion of executive elements, we expected the dCIB to be sensitive to executive dysfunction in individuals with vascular risk; therefore, we hypothesized lower dCIB scores in the MetS group relative to the non-MetS group.

Statistical Analysis (using IBM SPSS statistical software version 27)

- Statistical analyses were performed on demographic information (t-tests for age and education; chi square tests for gender and ethnicity/race) to determine

whether significant differences exist between MetS and non-MetS groups. In the case that a demographic variable is determined to be significantly different between groups, an ANCOVA is used in place of an ANOVA for the remainder of the statistical analyses to accommodate for the covariate(s).

- Multivariate ANOVA was used to determine whether MetS and non-MetS groups differ on neuropsychological performance using generated Composite Scores of Executive Function, Memory, and Attention (IV = group [MetS, non-MetS]; DVs = Executive Function Composite Score, Memory Composite Score, Attention Composite Score). In order to better understand what individual tests were driving our findings, we broke down the significant Composite Scores to their individual test z scores and compared performance across groups. Significance was determined by a p-value of ≤ 0.05. For each of the three Composite Scores, we reported the F-value and the p-value generated by the ANOVA.
- Multivariate ANOVA was used to determine whether MetS and non-MetS groups differ on dCIB performance (IV = group [MetS, non-MetS]; DVs = dCIB Total Score, WM Subscore, P/O Subscore). Significance was determined by a p-value of ≤ 0.05. For the dCIB and its subscores, we reported the F-value and the p-value generated by the ANOVA.

CHAPTER FOUR – RESULTS

Detailed characteristics for our sample (*N*=63) are listed in Table 2. In this community-based sample of adults, the average age was 62.49 ± 9.16 years [range of 46 to 80]. Participants were mostly college-educated with a mean of 16.46 ± 2.76 years of education [range of 10 to 20], male (55.6%), and reflected the demographic composition of the greater Boston area (U.S. Census Bureau, 2019) [self-identified White (69.9%); self-identified non-White (28.6%)]. Eleven participants (17.5% of total sample) met criteria for cognitive impairment. Evidence of cognitive impairment was determined by neuropsychological scores falling more than 1.5 *SD* below appropriate norms from at least two tests within any cognitive domain.

Age, in years	M (*SD*)	62.49 (*9.16*)
Education, in years	M (*SD*)	16.46 (*2.76*)
Gender		
Male	*n* (% total)	35 (55.6%)
Female	*n* (% total)	28 (44.4%)
Ethnicity		
White	*n* (% total)	44 (69.9%)
Non-White	*n* (% total)	18 (28.6%)
Black or African American	*n*	11
Hispanic or Latino	*n*	2
Asian	*n*	5
Missing/ Prefer not to respond	*n* (% total)	1 (1.5%)
Cognitive Impairment		
Impaired	*n* (% total)	11 (17.5%)
Unimpaired	*n* (% total)	52 (82.5%)

Table 2. Sample Characteristics

Table 3 provides descriptive statistics across all neuropsychological measures administered to our sample. Table 4 shows a frequency table of scores for dCIB Total Score and WM and P/O Subscores.

	M *(SD)*	Range
Cognitive Screeners		
MMSE	28.19 (*2.06*)	22–30
dCIB *Total Score*	6.32 (*2.32*)	0–8
WM Subscore	3.29 (*1.13*)	0–4
P/O Subscore	3.03 (*1.29*)	0–4
Executive Function		
D-KEFS VF *Letter Fluency*	45.57 (*14.70*)	14–85
D-KEFS VF *Category Fluency*	43.92 (*11.59*)	22–80
D-KEFS TMT *Number-Letter Switching* +	101.41 (*42.41*)	43–250
D-KEFS CWI *Inhibition* +	62.95 (*17.50*)	32–107
Memory		
CVLT-II *Trials 1-5 Free Recall*	48.95 (*12.10*)	26–75
CVLT-II *Long Delay Free Recall*	10.43 (*3.53*)	2–16
WMS-IV LM *Immediate Recall*	15.90 (*4.67*)	3–25
WMS-IV LM *Delayed Recall*	14.35 (*4.60*)	4–23
BVMT-R *Total Recall*	19.89 (*7.37*)	4–34
BVMT-R *Delayed Recall*	8.29 (*3.09*)	0–12
Attention		
Digit Span *Forward*	10.57 (*2.39*)	6–16
D-KEFS TMT *Number Sequencing* +	39.92 (*15.54*)	20–111
Composite Scores		
Executive Function Composite Score	0.00 (*0.74*)	-2.09 – 2.13
Memory Composite Score	0.00 (*0.82*)	-1.78 – 1.56
Attention Composite Score	0.00 (*0.71*)	-1.99 – 0.71

+ Denotes a timed test, such that a lower value indicates better performance

Table 3. Descriptive Data for Neuropsychological Outcomes for Total Sample

	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
dCIB *Total Score*	5	0	0	2	2	7	10	7	30
WM Subscore	5	0	3	19	36	--	--	--	--
P/O Subscore	5	4	9	11	34	--	--	--	--

Table 4. Frequency Table for dCIB Total Score, WM Subscore, and P/O Subscore

AIM 1: DETERMINE CLINICAL CUTOFF SCORES FOR THE DCIB

A receiver operating characteristic (ROC) curve was run to determine optimal cutoff scores for the dCIB (test variable = dCIB Total Score; state variable = cognitive impairment). Cognitive impairment was determined by neuropsychological scores falling more than 1.5 *SD* below appropriate norms from at least two tests within any cognitive domain (Jak et al., 2009). Our analysis generated various cutoff scores and their corresponding true positive and false positive rates [see Table 5]. Figure 1 illustrates the graphical ROC curve produced by plotting the true positive rate (i.e., sensitivity) and false positive rate (i.e., 1 – specificity) for each possible cutoff score, with each point on the plot corresponding to a cutoff score. The area under the ROC curve (AUC) was a value of 0.767. Our results reveal that the cutoff value corresponding with the maximum Youden index ($J = 0.463$) was a score of 5.5. Because the dCIB was scored using whole numbers (i.e., 0, 1, 2) we posit that a score ≤ 6 indicates *suspected* impairment and a score ≤ 5 indicates *probable* impairment.

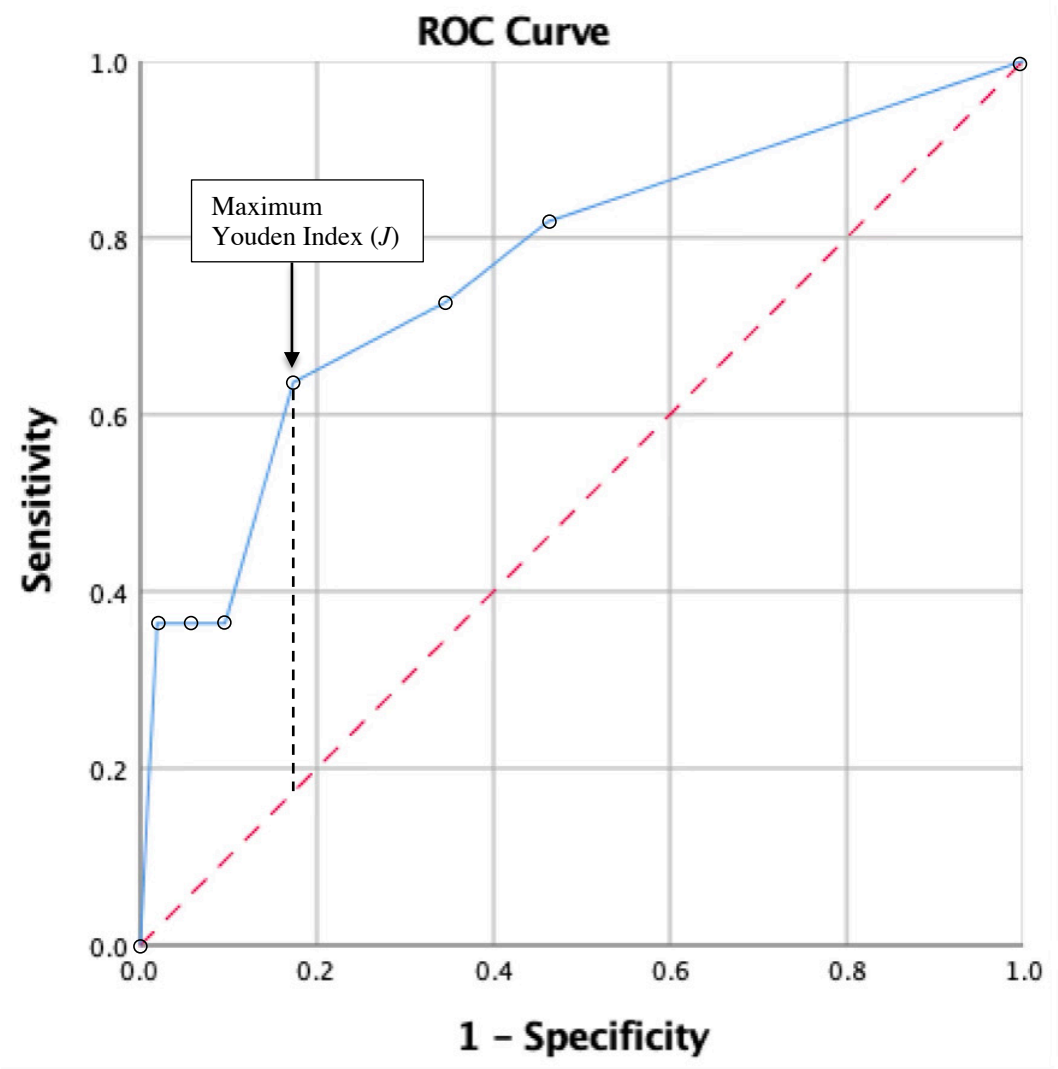

Figure 1. Graph of ROC Curve for All Possible dCIB Cutoff Scores

Cutoff Score	True Positives (Sensitivity)	False Positives (1 – Specificity)	Youden Index (*J*)
-1.00	0.000	0.000	--
1.50	0.364	0.019	0.345
3.50	0.364	0.058	0.306
4.50	0.364	0.096	0.268
5.50*	0.636	0.173	0.463
6.50	0.727	0.346	0.381
7.50	0.818	0.462	0.356
9.00	1.000	1.000	--

* Cutoff score with the maximum Youden Index

Table 5. Youden Index for All Possible dCIB Cutoff Scores

AIM 2: INVESTIGATE HOW THE DCIB COMPARES TO THE MMSE

Correlations between the dCIB and MMSE

All participants completed the dCIB and MMSE measures. A bivariate Pearson's *r* correlation was calculated to assess the relationship between the dCIB and MMSE (variables = dCIB Total Score, MMSE Total Score) [see Table 6]. Results revealed significant positive correlations between the MMSE and dCIB, such that a lower score on the dCIB correlates with a lower score on the MMSE, $r(61) = 0.437$, $p = 0.000$. Figure 2 illustrates the positive correlation between the dCIB and MMSE using a scatterplot.

	MMSE Total Score	
	Pearson's *r*	Sig. (2 tailed)
dCIB *Total Score***	**0.437**	**0.000**

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 6. Correlations between the MMSE and dCIB

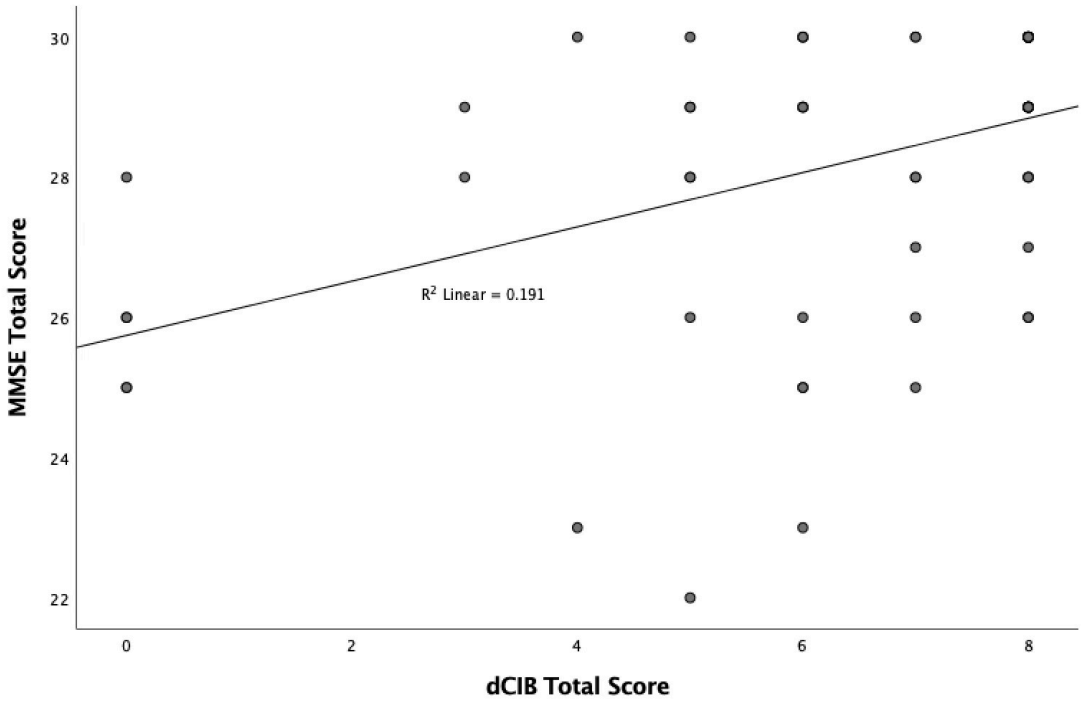

Figure 2. Scatterplot of the Correlation between the MMSE and dCIB

Sensitivity and specificity probabilities for the dCIB and MMSE

dCIB cutoff scores from *Aim 1* were entered into a 2x2 cross-tabulation (row = dCIB impairment; column = cognitive impairment) to determine sensitivity and specificity for the dCIB [see Table 7]. Results differed based on a dCIB cutoff score of 6 (sensitivity 72.7%; specificity 65.4%) or a dCIB cutoff score of 5 (sensitivity 63.6%; specificity 82.7%) [see Table 8]. MMSE scores (impairment classified by an MMSE score of ≤ 25) were also were entered into a 2x2 cross-tabulation (row = MMSE impairment; column = cognitive impairment) [see Table 7]. Results revealed a sensitivity of 45.5% and a specificity of 94.2% on the MMSE [see Table 8]. These results indicate better sensitivity and poorer specificity on the dCIB compared to the MMSE.

		Cognitively Impaired		**Cognitively Unimpaired**	
		n	%	*n*	%
Total		**11**	**100%**	**52**	**100%**
dCIB	≤ 6	8	72.7%	18	34.6%
	> 6	3	27.3%	34	65.4%
	≤ 5	7	63.6%	9	17.3%
	> 5	4	36.4%	43	82.7%
MMSE	≤ 25	5	45.5%	3	5.8%
	> 25	6	54.5%	49	94.2%

Table 7. Cross-tabulations between Cognitive Impairment and Impairment on the dCIB and MMSE

	Sensitivity	Specificity
dCIB *suspected* impairment (≤ 6)	72.7%	65.4%
dCIB *probable* impairment (≤ 5)	63.6%	82.7%
MMSE	45.5%	94.2%

Table 8. Sensitivity and Specificity Probabilities for the dCIB and MMSE

AIM 3: DETERMINE PREDICTIVE VALIDITY OF THE DCIB ON COGNITIVE FUNCTIONING

Executive Function Composite Score

A linear regression was calculated to determine the predictive validity of the dCIB on executive functioning (IV = dCIB Total Score; DV = Executive Function Composite Score) [see Table 9]. The B coefficient suggests that a higher dCIB score is associated with a higher Executive Function Composite Score. Our model moderately predicted performance on standardized measures of executive functioning ($R = 0.302$), with 9.1% of variance in the outcome explained by the predictor. Results from this regression reveal that dCIB score ($t = 2.477$, $p = 0.016$) is a significant predictor of the Executive Function Composite Score, thereby providing preliminary support for associations between the dCIB and executive functioning. Figure 3 visually illustrates the regression of the Executive Function Composite Score using a scatterplot.

	B	**SE B**	**t**	**p**	**95% CI for B**	
					Lower	Upper
dCIB *Total Score***	0.096	0.039	2.477	0.016	0.019	0.174

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 9. Linear Regression for Executive Function Composite Score

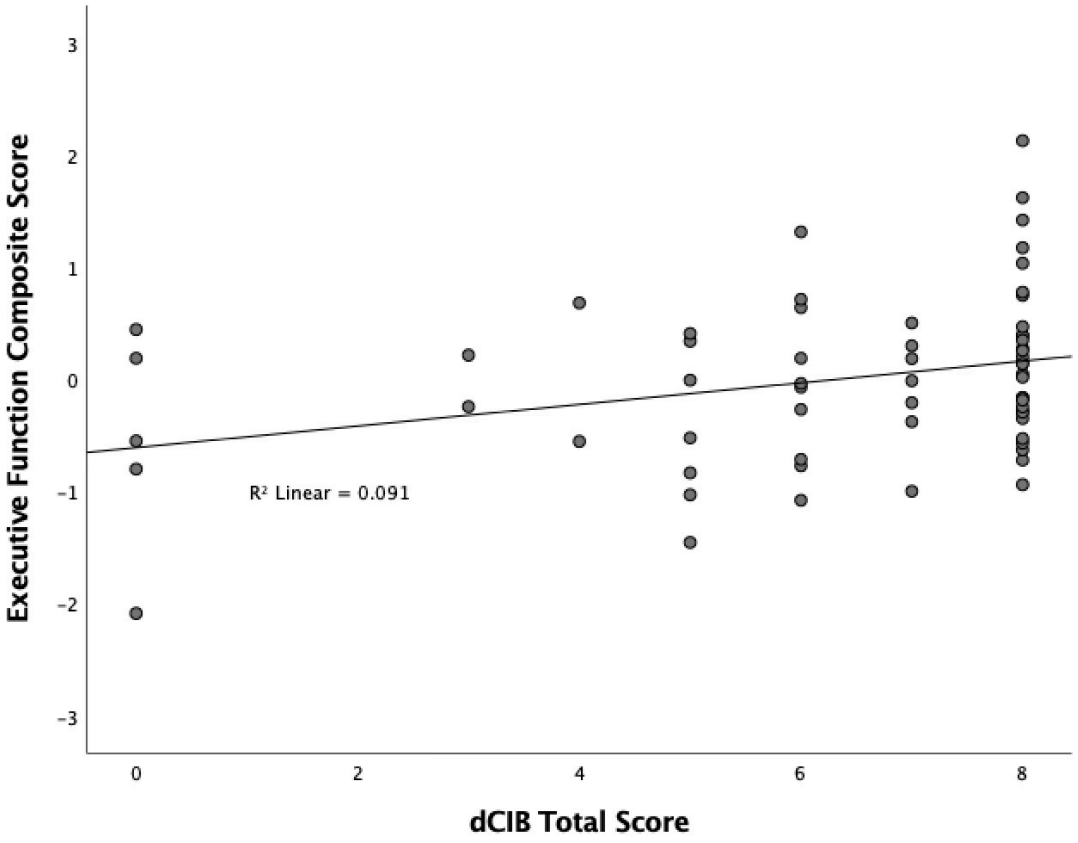

Figure 3. Scatterplot of the Linear Regression for Executive Function Composite Score

Memory Composite Score

A linear regression was calculated to determine the predictive validity of the dCIB on memory (IV = dCIB Total Score; DV = Memory Composite Score) [see Table 10]. The B coefficient suggests that a higher dCIB score is associated with a higher Memory Composite Score. Our model moderately predicted performance on standardized measures of memory ($R = 0.383$), with 14.7% of variance in the outcome explained by the predictor. Results from this regression reveal that dCIB score ($t = 3.242$, $p = 0.002$) is a significant predictor of the Memory Composite Score, thereby providing preliminary support for associations between the dCIB and memory. Figure 4 visually illustrates the regression of the Memory Composite Score using a scatterplot.

	B	**SE B**	**t**	**p**	**95% CI for B**	
					Lower	Upper
dCIB *Total Score***	0.136	0.042	3.242	0.002	0.052	0.220

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 10. Linear Regression for Memory Composite Score

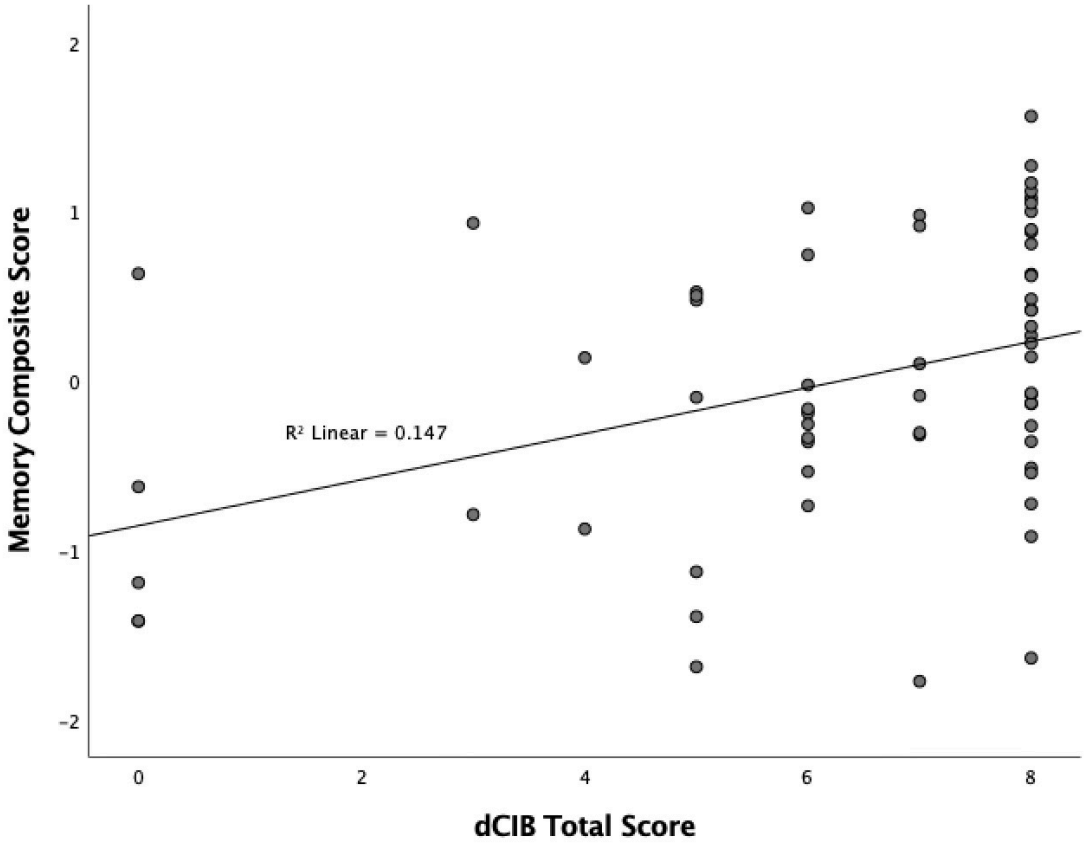

Figure 4. Scatterplot of the Linear Regression for Memory Composite Score

Attention Composite Score

A linear regression was calculated to determine the predictive validity of the dCIB on attention (IV = dCIB Total Score; DV = Attention Composite Score) [see Table 11]. The B coefficient suggests that a higher dCIB score is associated with a higher Attention Composite Score. Our model moderately predicted performance on standardized measures of attention ($R = 0.367$), with 13.5% of variance in the outcome explained by the predictor. Results from this regression reveal that dCIB score ($t = 3.082$; $p = 0.003$) is a significant predictor of the Attention Composite Score, thereby providing preliminary support for associations between the dCIB and attention. Figure 5 visually illustrates the regression of the Attention Composite Score using a scatterplot.

	B	**SE B**	**t**	**p**	**95% CI for B**	
					Lower	Upper
dCIB *Total Score***	0.113	0.037	3.082	0.003	0.040	0.186

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 11. Linear Regressions for Attention Composite Score

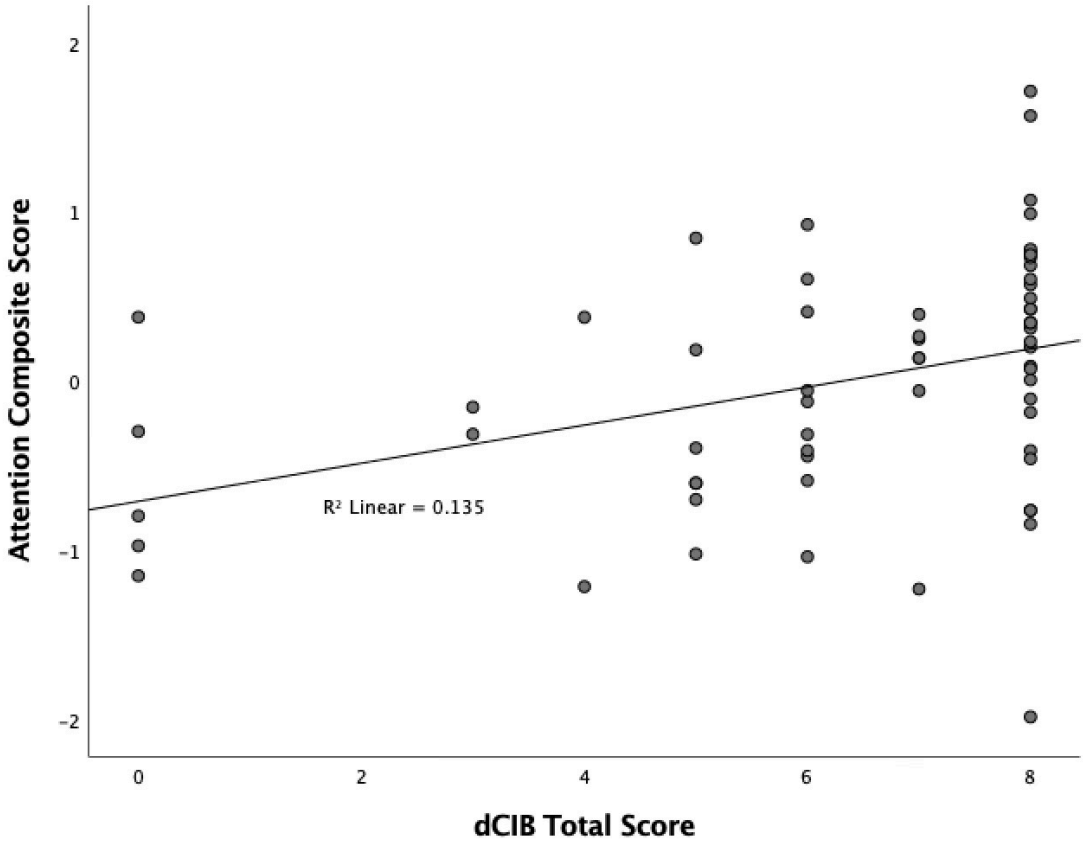

Figure 5. Scatterplot of the Linear Regression for Attention Composite Score

AIM 4: APPLICATION OF THE DCIB IN A SAMPLE STRATIFIED BY VASCULAR RISK

The sample used in the present study consisted of 63 participants characterized into MetS (*n*=21) or non-MetS (*n*=42) groups using NCEP-III criteria. In order to determine whether significant differences in demographic variables exist between our groups, t-tests were performed on age and education and chi square tests were performed on gender and ethnicity/race [see Table 12]. No significant group differences were found on education between the MetS group (M = 16.29 years, SD = 2.952) and the non-MetS group (M = 16.55 years, SD = 2.698); $t(61) = 0.352$, $p = 0.726$. There were also no significant group differences on gender between the MetS group (male [*n*=13, 61.9%]; female [*n*=8, 38.1%]) and the non-MetS group [male [*n*=22, 52.4%]; female [*n*=20, 47.6%]); $x^2(1, N = 63) = 0.514$, $p = 0.473$. Additionally, there were no significant group differences found on ethnicity/race between the MetS group (White [*n*=16, 76.2%]; non-White [*n*=5, 23.8%]) and the non-MetS group (White [*n*=27, 64.2%]; non-White [*n*=13, 31.0%]); $x^2(4, N = 63) = 2.127$, $p = 0.712$. However, there was a significant difference in age between the MetS group (M = 67.10 years, SD = 7.81) and the non-MetS group (M = 60.19 years, SD = 8.98); $t(61) = -2.997$, $p = 0.004$. To account for this difference, the following statistical analyses adjusted for this difference by including age as a covariate.

		MetS (*n*=21)	**Non-MetS** (*n*=42)
Age, in years*	M (*SD*)	67.10 (*7.81*)	60.19 (*8.98*)
Education, in years	M (*SD*)	16.29 (*2.95*)	16.55 (*2.69*)
Gender			
Male	*n* (% total)	13 (61.9%)	22 (52.4%)
Female	*n* (% total)	8 (38.1%)	20 (47.6%)
Ethnicity			
White	*n* (% total)	16 (76.2%)	28 (66.6%)
Non-White	*n* (% total)	5 (23.8%)	13 (31.0%)
Black or African American	*n*	4	7
Hispanic or Latino	*n*	0	2
Asian	*n*	1	4
Missing/ Prefer not to respond	*n* (% total)	0 (0%)	1 (2.4%)
Cognitive Impairment			
Impaired	*n* (% total)	4 (19.1%)	7 (16.6%)
Unimpaired	*n* (% total)	17 (80.9%)	35 (83.3%)

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 12. Demographic Information for MetS and non-MetS Groups

	MetS (*n*=21)		**Non-MetS** (*n*=42)	
	M (*SD*)	Range	M (*SD*)	Range
Cognitive Screeners				
MMSE	27.76 (*1.61*)	25–30	28.40 (*2.23*)	22–30
dCIB *Total Score*	5.33 (*2.75*)	0–8	6.81 (*1.93*)	0–8
WM Subscore	2.76 (*1.34*)	0–4	3.55 (*0.92*)	0–4
P/O Subscore	2.57 (*1.54*)	0–4	3.26 (*1.11*)	0–4
Executive Function				
D-KEFS VF *Letter Fluency*	41.71 (*14.32*)	14–71	47.50 (*14.67*)	27–85
D-KEFS VF *Category Fluency*	40.67 (*8.95*)	25–57	45.55 (*12.49*)	22–80
D-KEFS TMT *Number-Letter Switching* +	110.29 (*50.32*)	54–250	96.98 (*37.73*)	43–206
D-KEFS CWI *Inhibition* +	66.90 (*15.44*)	45–107	60.98 (*18.29*)	32–106
Memory				
CVLT-II *Trials 1-5 Free Recall*	45.25 (*11.75*)	27–63	50.76 (*12.00*)	26–75
CVLT-II *Long Delay Free Recall*	9.50 (*3.15*)	4–15	10.88 (*3.66*)	2–16
WMS-IV LM *Immediate Recall*	15.52 (*5.08*)	3–22	16.10 (*4.49*)	4–25
WMS-IV LM *Delayed Recall*	13.67 (*4.78*)	6–20	14.69 (*4.53*)	4–23
BVMT-R *Total Recall*	17.00 (*6.87*)	4–29	21.33 (*7.26*)	7–34
BVMT-R *Delayed Recall*	7.10 (*3.09*)	2–12	8.88 (*2.94*)	0–12
Attention				
Digit Span *Forward*	9.95 (*1.99*)	7–13	10.88 (*2.53*)	6–16
D-KEFS TMT *Number Sequencing* +	44.43 (*17.76*)	27–111	37.67 (*13.99*)	20–94
Composite Scores				
Executive Function Composite Score	-0.2445 (*0.66*)	-2.09 – 0.71	0.1223 (*0.75*)	-1.45 – 2.13
Memory Composite Score	-0.2638 (*0.68*)	-1.69 – 0.93	0.1371 (*0.86*)	-1.78 – 1.56
Attention Composite Score	-0.2746 (*0.66*)	-1.99 – 0.92	0.1373 (*0.71*)	-1.23 – 1.71

+ Denotes a timed test, such that a lower value indicates better performance

Table 13. Descriptive Data for Group Neuropsychological Outcomes

Neuropsychological differences between MetS and non-MetS groups

Two participants did not complete the CVLT-II due to time limitations. All participants completed the D-KEFS Verbal Fluency, D-KEFS Trail Making Test, D-KEFS Color-Word Inhibition, WMS-IV Logical Memory, BVMT-R, Digit Span, and dCIB measures. Because there was a significant difference in age between the MetS and non-MetS groups, age adjusted ANCOVA analyses were used in place of ANOVA tests for the following statistical analyses.

A set of univariate ANCOVA tests, controlling for age, was completed to compare performance between MetS and non-MetS groups on cognitive functioning (IV = group [MetS, non-MetS]; DV = Composite Score [Executive Function Composite Score, Memory Composite Score, Attention Composite Score]; covariate = age) [see Table 14]. We found significant group differences on the Executive Function Composite Score, such that the MetS group [M = -0.2445, SD = 0.66] performed worse on executive functioning measures relative to the non-MetS group [M = 0.1223, SD = 0.75]; $F(1,62)$ = 4.122, p = 0.047. Performance differences between our groups approached significance on the Memory Composite Score (MetS group [M = -0.2638, SD = 0.68]; non-MetS group [M = 0.1371, SD = 0.86]; $F(1,62)$ = 3.551, p = 0.065). We also found significant group differences on the Attention Composite Score, such that the MetS group [M = -0.2746, SD = 0.66] performed worse on attention measures relative to the non-MetS group [M = 0.1373, SD = 0.71]; $F(1,62)$ = 4.284, p = 0.043.

To better understand which tests were driving our findings, we broke down the Composite Scores to their individual test z scores and compared performance across groups. Univariate ANCOVA tests, adjusting for age, were completed to compare performance between MetS and non-MetS groups on individual tests used to generate our Composite Scores (IV = group [MetS, non-MetS]; DV = neuropsychological measure [D-KEFS Verbal Fluency, D-KEFS Trail Making Test, D-KEFS Color-Word Inhibition, CVLT-II, WMS-IV Logical Memory, BVMT-R, Digit Span]; covariate = age) [see Table 14]. We found significant group differences, such that the MetS group performed worse than the non-MetS group, on the following measures: D-KEFS Verbal Fluency *Letter Fluency* (MetS group [M = -0.2624, SD = 0.97]; non-MetS group [M = 0.1312, SD = 0.99]; $F(1,62) = 4.118$, $p = 0.047$); BVMT-R *Total Recall* (MetS group [M = -0.3921, SD = 0.93]; non-MetS group [M = 0.1960; SD = 0.98]; $F(1,62) = 4.315$, $p = 0.042$); BVMT-R *Delayed Recall* [MetS group [M = -0.3856, SD = 1.00]; non-MetS group [M = 0.1928, SD = 0.95]; $F(1,62) = 4.689$, $p = 0.034$), and Digit Span *Forward* (MetS group [M = -0.2593, SD = 0.83]; non-MetS group [M = 0.1296, SD = 1.06]; $F(1,62) = 4.282$; $p = 0.043$).

	MetS (*n*=21)	**Non-MetS** (*n*=42)		
	M (*SD*)	M (*SD*)	F	Sig.
Executive Function Composite Score*	-0.2445 (*0.66*)	0.1223 (*0.75*)	4.122	0.047
D-KEFS VF *Letter Fluency**	-0.2624 (*0.97*)	0.1312 (*0.99*)	4.118	0.047
D-KEFS VF *Category Fluency*	-0.2806 (*0.77*)	0.1403 (*1.08*)	2.043	0.158
D-KEFS TMT *Number-Letter Switch*	-0.2092 (*1.19*)	0.1046 (*0.89*)	2.206	0.143
D-KEFS CWI *Inhibition*	-0.2258 (*0.88*)	0.1129 (*1.05*)	1.046	0.311
Memory Composite Score	-0.2638 (*0.68*)	0.1371 (*0.86*)	3.551	0.065
CVLT-II *Trials 1-5 Free Recall*	-0.3057 (*0.97*)	0.1491 (*0.99*)	2.792	0.100
CVLT-II *Long Delay Free Recall*	-0.2622 (*0.89*)	0.1279 (*1.03*)	1.916	0.172
WMS-IV LM *Immediate Recall*	-0.0816 (*1.09*)	0.0408 (*0.96*)	0.797	0.376
WMS-IV LM *Delayed Recall*	-0.1482 (*1.04*)	0.0741 (*0.98*)	1.214	0.275
BVMT-R *Total Recall**	-0.3921 (*0.93*)	0.1960 (*0.98*)	4.315	0.042
BVMT-R *Delayed Recall**	-0.3856 (*1.00*)	0.1928 (*0.95*)	4.689	0.034
Attention Composite Score*	-0.2746 (*0.66*)	0.1373 (*0.71*)	4.284	0.043
Digit Span *Forward**	-0.2593 (*0.83*)	0.1296 (*1.06*)	4.282	0.043
D-KEFS TMT *Number Sequencing*	-0.2900 (*1.14*)	0.1450 (*0.90*)	0.816	0.370

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 14. Summary Statistics and ANCOVA on Composite Scores

dCIB performance differences between MetS and non-MetS groups

A set of univariate ANCOVA tests, controlling for age, was completed to compare performance between MetS and non-MetS groups on the dCIB (IV = group [MetS, non-MetS]; DVs = dCIB Total Score, WM Subscore, P/O Subscore; covariate = age) [see Table 15]. We found a significant group difference on dCIB Total Score between MetS (M = 5.33, SD = 2.75) and non-MetS groups (M = 6.81, SD = 1.93); $F(1,61) = 8.975$, p = 0.004, such that the MetS group performed worse on the dCIB relative to the non-MetS group. Figure 6 illustrates mean group differences on dCIB Total Score. Results also revealed a significant difference between MetS and non-MetS groups on both the WM and P/O Subscores of the dCIB. We found significant group differences on the WM Subscore such that the MetS group had lower overall WM Subscores relative to the non-MetS group (MetS group [M = 2.76, SD = 1.34]; non-MetS group [M = 3.55, SD = 0.92]; $F(1,61) = 11.547$, p = 0.001), as well as significant group differences on the P/O Subscore such that the MetS group had lower overall P/O Subscores relative to the non-MetS group (MetS group [M = 2.57, SD = 1.54]; non-MetS group [M = 3.26, SD = 1.11]; $F(1,61) = 5.787$, p = 0.019). Figure 7 illustrates mean group differences on the WM and P/O Subscores of the dCIB. Sample dCIB drawings are provided in Figure 8.

	MetS (*n*=21)	**Non-MetS** (*n*=42)		
	M (*SD*)	M (*SD*)	F	Sig.
dCIB *Total Score***	5.33 (*2.75*)	6.81 (*1.93*)	8.975	0.004
WM Subscore**	2.76 (*1.34*)	3.55 (*0.92*)	11.547	0.001
P/O Subscore*	2.57 (*1.54*)	3.26 (*1.11*)	5.787	0.019

* Outcome is significant at the 0.05 level
** Outcome is significant at the 0.01 level

Table 15. Summary Table for Group Performance Differences on the dCIB

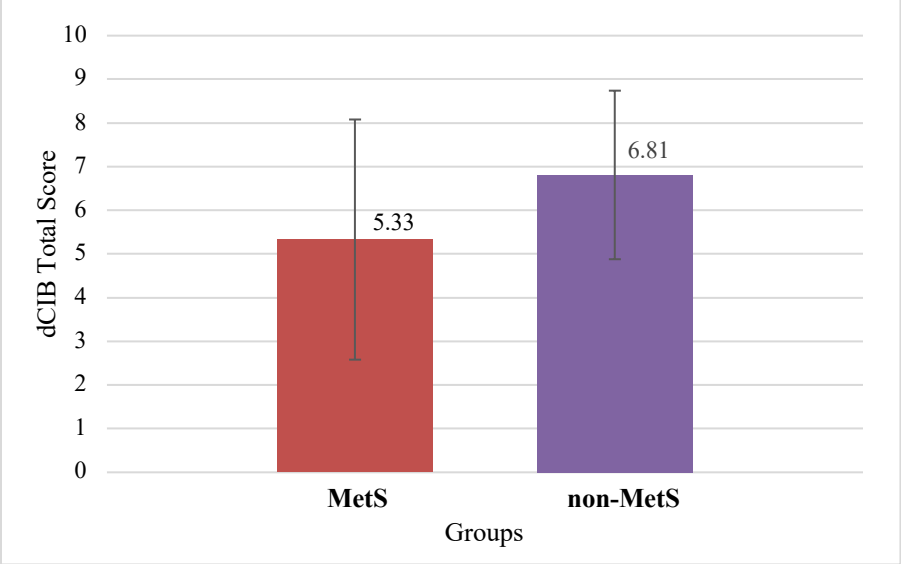

Figure 6. Bar Graph of Mean Group Performance Differences on dCIB Total Score. Line Indicates Standard Error.

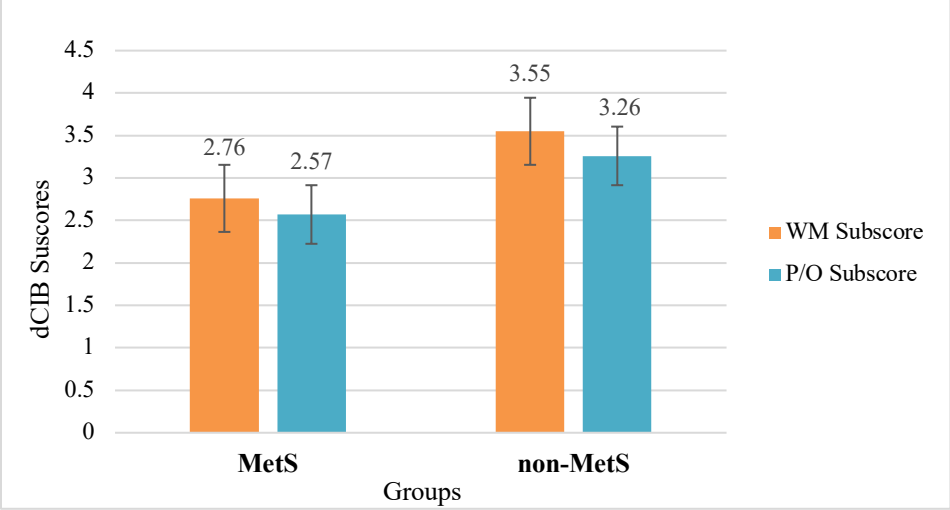

Figure 7. Bar Graph of Mean Group Performance Differences on dCIB WM Subscore and P/O Subscore. Line Indicates Standard Error.

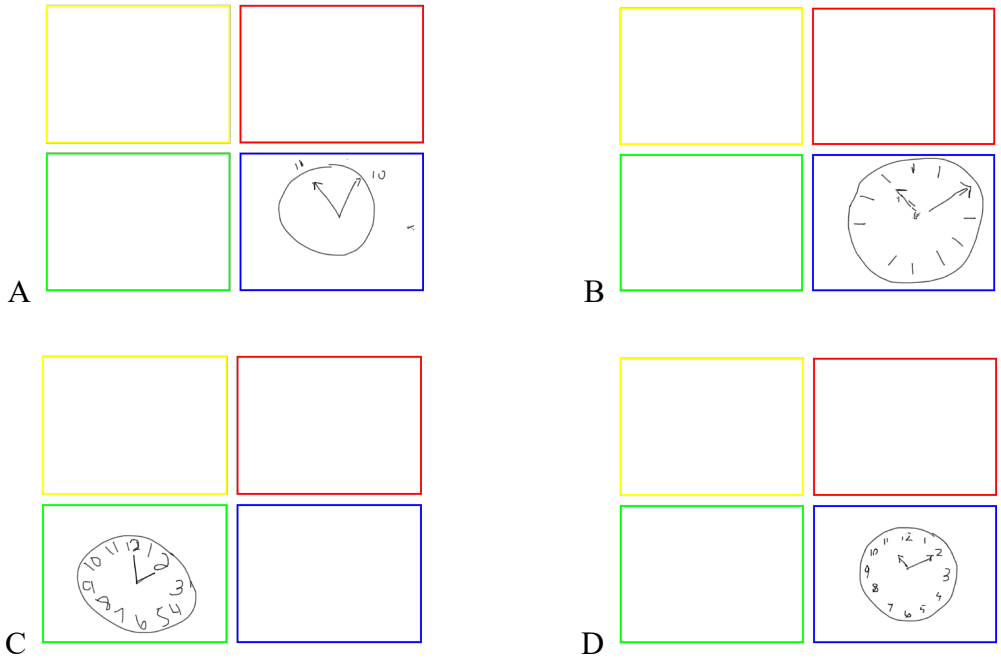

Figure 8. **Sample dCIB drawings.** dCIB **A** represents a score of 3 because the drawing is an appropriate size, resembles a clock, and is drawn in the correct box. Points were deducted for number inclusion, number order, number spacing, time, and hand length and origin. dCIB **B** represents a score of 5 because the drawing is an appropriate size, resembles a clock, is drawn in the correct box, and shows the correct time with hands of appropriate length and origin. Points were not given for number inclusion, number order, and number spacing. dCIB **C** represents a score of 6, with 2 points deducted because the drawing shows the incorrect time and is drawn in the incorrect box. dCIB **D** represents a score of 8 because the drawing is an appropriate size, resembles a clock, is drawn in the correct box, includes all numbers in the correct order with appropriate spacing, and shows the correct time with hands of appropriate length and origin.

CHAPTER FIVE – DISCUSSION

Overview

In recent years, clock drawing has become a popular cognitive screening test because of its brief and simple administration, acceptability among patients, low cost, good psychometric properties, sensitivity to subtle cognitive impairment, and evidence of significant correlations with other established and validated cognitive tests (Hazan et al., 2018; Ismail et al., 2010; Nyborn et al., 2013; Rabin et al., 2005; Shulman, 2000; Shulman et al., 2006). In this research, we introduce the digital Clock in the Box [dCIB], a novel digitized clock drawing task with strengthened executive elements. Over the course of four aims, we illustrate its clinical utility as a cognitive screener.

For our first aim, we created cutoff scores for the dCIB. Cognitive screening instruments are designed to optimize time and efficiency in healthcare settings (i.e., primary care) by providing quick feedback regarding cognitive status. Cutoff scores that help classify patients as "impaired" (i.e., score indicating performance outside normal limits) or "unimpaired" (i.e., score indicating performance within normal limits) are both practical and feasible in a busy clinic setting where staff are under considerable time constraints. Although these scores are not in and of themselves diagnostic, they may indicate the likelihood of cognitive impairment so that patients may be referred to a specialist (e.g., clinical neuropsychologist) who can provide more extensive, comprehensive, and diagnostic neuropsychological assessment. Our results revealed that a dCIB score of 5.5 corresponded to the maximum Youden index (*J*) (Habibzadeh et al.,

2016) and was therefore determined to be the optimal cutoff score, with a dCIB score ≤ 6 indicating *suspected* impairment and a dCIB score ≤ 5 indicating *probable* impairment. These values are consistent with cutoff scores created for the paper-and-pencil CIB (Grande et al., 2011b). Despite differing formats for administration (digital versus paper-and-pencil), we expected similar cutoff scores between the dCIB and CIB given that both tests utilize the same scoring criteria [see Appendix B]. Similar cutoffs between the two tests provide a type of concurrent validity – although, ideally, subsequent studies should directly compare performance on the dCIB and CIB to provide stronger evidentiary support of concurrent validity.

For our second aim, we compared the dCIB to the MMSE. Because the MMSE is the most commonly used cognitive screener for dementia (de Roeck et al., 2019; Tsoi et al., 2015), it is often used for comparison against other measures. The dCIB and the MMSE were found to be significantly correlated, which supports our hypothesis and is consistent with existing literature reporting significant correlations between clock drawing and the MMSE (Palsetia et al., 2018). By demonstrating that our novel test correlates well with a previously validated test (i.e., MMSE), we provide evidence of concurrent validity. A significant relationship between scores from the dCIB and scores from the MMSE suggests that the two screeners measure the same construct (i.e., cognitive functioning) and differentiate individuals in the same way (i.e., impaired or unimpaired). Because the MMSE is a well-validated screener for cognitive impairment

(Carnero-Pardo, 2014), associations between the MMSE and the dCIB suggest that the dCIB might also be successfully used to screen for cognitive impairment.

We also compared psychometric data between the dCIB and the MMSE. We calculated the sensitivity and specificity probabilities for both the dCIB and the MMSE to determine how well each test could correctly identify those with impairment (i.e., sensitivity) and those without impairment (i.e., specificity). Results revealed better sensitivity and poorer specificity on the dCIB compared to the MMSE. We expected higher sensitivity values for the dCIB not only because clock drawing has good psychometric properties (Shulman, 2000) but because the MMSE has been criticized for its low sensitivity (de Roeck et al., 2019; Mitchell, 2009). Better sensitivity on the dCIB means that it may identify a greater number of true positive results (cognitively impaired individuals correctly identified as impaired) compared to the MMSE, which suggests a better ability to screen for cognitive impairment. However, poorer specificity suggests that the dCIB may also identify a greater number of false positive results (cognitively unimpaired individuals incorrectly identified as impaired) for which there are potential costs to both the patient (e.g., emotional and psychosocial consequences; unnecessary follow-up neuropsychological evaluation and/or treatment) and the healthcare system (e.g., economic costs; misallocated time and energy of healthcare providers). Intraindividual variability is characteristic of healthy adults and, therefore, abnormal performance on some proportion of neuropsychological tests in a battery is psychometrically normal (Binder et al., 2009; Tanner-Eggen et al., 2015; Schretlen et al.,

2003). Reduced specificity for the dCIB may be explained by patient factors that affect test performance. Greater age and lower education have been reported to influence performance on neuropsychological tests (Hebben & Milberg, 2009; Lam et al., 2013; Shanhu et al., 2019; Bento-Torres et al., 2017; Tripathi et al., 2014); therefore, the broad range of ages [46 and 80 years] and levels of education [10 to 20 years] in our sample might contribute to low specificity. Numerous non-neurological factors may also negatively impact performance on the dCIB including medication effects, sleep deprivation, or fatigue from lengthy neuropsychological testing (Hebben & Milberg, 2009; Adhikari et al., 2020; Roy et al., 2020; Ma et al., 2020; Kusztor et al., 2019; Aasvik et al., 2018; Strober & DeLuca, 2013). Other possible sources for false positive errors (i.e., psychiatric status, depression) were excluded for in the original design of the study; however, it is possible that participants were not formally diagnosed with a condition and therefore did not indicate presence of an exclusionary criteria. Although the goal is to maximize both sensitivity and specificity, the two are often inversely related so increased sensitivity usually comes at the expense of reduced specificity. The creation of two cutoff scores for the dCIB offers an advantage because, if higher specificity is desired, a cutoff value of ≤ 5 (sensitivity of 63.6%; specificity of 82.7%) may be used over a cutoff value ≤ 6 (sensitivity of 72.7%; specificity of 65.4%). The optimal balance between sensitivity and specificity may depend on the purpose for which the test is used (Hebben & Milberg, 2009). Ideally, screening tests should be highly sensitive in order to detect as many individuals as possible with cognitive impairment, whereas follow-up confirmatory

tests (i.e., comprehensive neuropsychological evaluation) should be highly specific to ensure that individuals flagged for impairment are truly impaired (Hebben & Milberg, 2009).

Sensitivity and specificity values for both *suspected* impairment (dCIB score ≤ 6) and *probable* impairment (dCIB score ≤ 5) are generally consistent with literature on psychometric values for clock drawing (Smedslund et al., 2015). Values for the MMSE are also consistent with previous literature reporting low sensitivity (Mitchell, 2009). The MMSE is predominantly used on populations with significant cognitive dysfunction (i.e., dementia), which does not describe our sample (i.e., adults with no self-reported history of cognitive impairment). Therefore, a possible explanation for low MMSE sensitivity in our study is based on the characteristics of our sample. It is likely that any presence of cognitive impairment in our sample is not significant enough to be captured by the MMSE. Furthermore, the MMSE includes fewer items associated with executive functioning which may make it unsuitable as a screener for subtle executive deficits expected in individuals with vascular risk. The dCIB, on the other hand, includes executive elements designed to increase working memory demands with the goal of increasing task sensitivity. Of the 11 participants in our sample who were identified as cognitively impaired from neuropsychological assessment, over half (6 individuals; 54.5%) were not detected by the MMSE; however, the dCIB (using criteria for *probable* impairment; dCIB score ≤ 5) captured 4 of the 6 individuals who were missed by the MMSE. All 4 participants had compromised executive functioning, as evidenced by low

Executive Function Composite Scores (3 participants with scores greater than 1.5 *SD* below the mean), which went undetected by the MMSE. This illustrates how the executive elements embedded within the dCIB increases overall sensitivity to cognitive impairment and offers an advantage over the MMSE, which is currently the most commonly used cognitive screener despite its poor sensitivity and limited items assessing executive functioning.

For our third aim, we examined the predictive validity of the dCIB on cognitive functioning. Clock drawing relies on cognitive abilities that span across domains of executive function (i.e., developing an organized multi-step plan of action; detecting and correcting errors); memory (i.e., retrieving a mental representation of a clock); and attention (i.e., concentrating to complete the task) (Young, 2018; Freedman, 1994; Amodeo et al., 2015). Neuropsychological tests assessing these domains are used as a performance reference because they are comprehensive assessments of cognitive domains and have high sensitivity and specificity, as well as good diagnostic accuracy and predictive value. We created Composite Scores of Executive Function, Memory, and Attention from the outcome variables of the neuropsychological tests administered to our sample and used these domain-specific composite scores for our analyses. The dCIB significantly predicted performance on all three composite scores, suggesting that dCIB score may be a significant predictor of overall executive functioning, memory, and attention. This finding is consistent with literature associating clock drawing with these specific domains. However, clock drawing also taps into cognitive abilities that extend

beyond the domains of executive function, memory, and attention and therefore performance on the dCIB may serve as a broader representative score for general cognitive functioning.

For our fourth aim, we explored whether the dCIB can detect the presence of subtle cognitive deficits among individuals with vascular risk. Evidence that the dCIB can detect early changes to cognition, particularly subtle executive deficits associated with poor vascular health, may help establish its utility as a cognitive screener. We separated our sample into groups (MetS versus non-MetS) using current diagnostic criteria for MetS (i.e., presence of three or more cardiovascular risk factors; see *Methods* for details). Interestingly, 21 of 63 participants (33.3% of our sample) met criteria for MetS which reflects current estimates of MetS levels in the U.S. adult population (1 in every 3 adults) (Hirode & Wong, 2020; Moore et al., 2017). The MetS group scored lower on the Executive Function Composite Score compared to the non-MetS group. We expected a lower Executive Function Composite Score in the MetS group given that executive dysfunction has been shown to be the predominant cognitive deficit associated with MetS (Alcorn et al., 2019). Poor executive functioning observed in our MetS group is consistent with existing literature linking vascular risk factors with deficits in executive functioning (Moraes et al., 2019; Yang et al., 2018). Uncontrolled or poorly controlled component risk factors of MetS lead to atherosclerotic vessel narrowing which may cause a variety of vascular events (e.g., small vessel disease, stroke) (Blumenfeld, 2018; Dichgans & Leys, 2017; Smith, 2017), and chronic damage from these vascular events

may result in neuroanatomical changes (i.e., lacunar infarcts, cerebral microbleeds) (Sudo et al., 2017; Pugh & Lipsitz, 2002). These neuroanatomical changes have been shown to impact a series of parallel pathways that interconnect various regions of the frontal lobe to subcortical structures, leading to deficits in cognitive domains dependent upon the integrity of these frontal-subcortical circuits including frontally mediated executive functions (Sudo et al., 2017; Pugh & Lipsitz, 2002).

We also found significant group differences on the Attention Composite Score, with lower scores in the MetS group compared to the non-MetS group. Furthermore, the MetS group scored lower on the Memory Composite Score relative to the non-MetS group, but the difference failed to reach significance. Both findings do not reflect the general literature on the cognitive effects of MetS. Associations between vascular risk and memory are inconsistent, with some studies reporting poorer performance on memory tests in individuals with vascular risk compared to controls and other studies reporting little/no association between vascular risk and memory performance (see *Alcorn et al., 2019* for a review). Attentional deficits are also inconsistent in the vascular literature, with some studies reporting worse attention in individuals with vascular risk compared to controls (Wooten et al., 2019) and other studies reporting little/no association between vascular risk and attention (see *Alcorn et al., 2019* for a review). To better understand what might be driving our results, we broke down the Memory and Attention Composite Scores to their individual test components and compared performance between groups.

Although the overall Memory Composite Score (comprising of outcome variables from both verbal [i.e., CVLT-II, WMS-IV] and non-verbal tests [i.e., BVMT-R]) was not significant, our results revealed significant group differences on non-verbal memory. Recent literature has suggested that visual memory may be especially sensitive to emergent cognitive decline (De Anna et al., 2014; Didic et al., 2013; Oltra-Cucarella et al., 2018; Okonkwo et al., 2014). For example, Ye and colleagues (2015) found that, among a group of MCI patients with verbal deficits and a group of MCI patients with visual deficits, the latter group was at greater risk for progression to dementia. More recently, Wasserman and colleagues (2019) found within-group differences among MCI patients, such that individuals with dysexecutive MCI performed worse on the BVMT-R (total and delayed free recall) compared to individuals with amnestic MCI. As noted by the authors, a possible reason to explain this finding is that visual memory tasks recruit a wide set of cognitive domains, including memory (i.e., encoding figures and their locations), attention (i.e., visual scanning), executive abilities (i.e., mental planning), and motor skills (i.e., drawing a response) and that "the diversity of neurocognitive skills necessary in these visual episodic memory tests is far greater than verbal episodic memory tests where patients are most often asked to encode and subsequently remember a list of words" (Wasserman et al., 2019, p. 3). Therefore, it is possible that executive deficits, like those we see in the MetS group, negatively impact performance on visual memory tests to a greater extent than verbal memory tests. Based on this literature, it is possible that lower scores on the BVMT-R in our MetS group may be a predictor of

emergent decline. Longitudinal studies support the assertion that poor visual memory may be predictive of future decline. Several studies have reported that changes in visual memory may precede a formal diagnosis of dementia by several years (Kawas et al., 2003; Zonderman et al., 1995). Summers & Saunders (2012) found that MCI patients with baseline deficits on a visual memory task progressed to dementia after 20 months. In a recent study examining temporal changes of visual memory in patients diagnosed with MCI, Campos-Magdaleno and colleagues (2020) found that low baseline scores predicted changes in cognitive status at 18-month follow up, suggesting that "this [visual memory] decline may be a cognitive indicator of the progression in the continuum ranging from the stage characterized by the presence of cognitive complaints without objective cognitive impairment to dementia, through the different levels of severity of MCI" (p. 9).

Significant group differences were also found on Digit Span Forward. Digit Span Forward assesses components of working memory (i.e., the ability to temporarily store and manipulate information). In the literature, a widely accepted model of working memory (Baddeley & Hitch, 1974) consists of three components: a verbal storage system called the *phonological loop*, a visual storage system called the *visuospatial sketchpad*, and a *central executive*. Digit Span Forward involves momentary storage and rehearsal of serial verbal information and is therefore considered a measure of attention span and *phonological loop* capacity. According to Baddeley and Hitch's framework (Baddeley & Hitch, 1974), over the course of a forward digit span task, longer digit strings would

eventually exhaust *phonological loop* capacity and additional processing resources would be recruited from the *central executive* – thus, Digit Span Forward may be influenced by both *phonological loop* and *central executive* functioning. It is possible that, when completing Digit Span Forward, participants in our study began to rely more heavily on executive functions as the digit strings became longer and the task became more challenging; therefore, poor performance on Digit Span Forward in the MetS group may actually reflect impaired executive functioning. This theory is supported by studies suggesting that the *central executive* component of working memory is recruited for both forward and backward span tasks (Hester et al., 2004; Gregoire & Van der Linden, 1997; Miyake et al., 2001). Although Digit Span Forward is traditionally considered a measure of simple attention, Digit Span Backward (i.e., participants listen to a sequence of numbers and repeat the numbers out loud in the reverse order) is thought to increase executive demands by requiring the simultaneous storage and manipulation of serial verbal information. In a community sample of normally aging adults, Hester and colleagues (2004) reported no evidence of a differential rate of decline between forward and backward digit span, suggesting that the *central executive* may contribute to both tasks and that age-related declines in executive functioning may impact both tasks equivalently. McCabe and colleagues (2010) used a factor analysis approach to examine the relationship between working memory and executive function and found that the two constructs were strongly correlated and shared a large proportion of common variance. This finding led the authors to conclude that tests of working memory capacity and

executive function may share a common underlying executive-attention component (McCabe et al., 2010). The concept of an executive-attention component to working memory was first proposed by Kane and Engle (2002) to describe the active maintenance of information in the presence of mental and environmental distractors. The authors posited that the ability to prevent a loss of attentional focus in the presence of interference (i.e., inhibitory control) is a critical executive element of working memory and the primary mechanism linking the two constructs.

Given this literature, compromised executive functioning in the MetS group may be driving performance on BVMT-R and Digit Span Forward. If this is true, MetS may not be associated with deficits in memory and attention. Future studies should utilize a more extensive assessment battery, including memory and attention tests less reliant on executive abilities, to better clarify preserved and compromised areas of functioning among individuals with MetS.

In addition to comparing performance on neuropsychological measures, we also compared group performance on the dCIB. We found that the dCIB successfully differentiated MetS and non-MetS groups, with lower dCIB scores in the MetS group relative to the non-MetS group. This finding illustrates the sensitivity of the dCIB in detecting subtle cognitive deficits among individuals with vascular risk. We also found significant group differences on WM and P/O Subscores of the dCIB, with worse performance in the MetS group relative to the non-MetS group. On the dCIB, working memory (WM) demands are increased by requiring participants to hold in mind a set of

instructions provided before the start of the task, while planning/organization (P/O) demands are increased by requiring participants to draw in a predetermined location on the response screen (i.e., blue box). These modifications were designed to increase overall task sensitivity and, as a result, improve the detection of cognitive impairment beyond traditional clock drawing. By increasing sensitivity to executive dysfunction, the dCIB may be especially useful for populations and disorders with impaired executive functioning.

Altogether, we believe these four aims provide preliminary evidentiary support for the clinical utility of the dCIB. Creating cutoff values for the dCIB that immediately classify patients as "impaired" or "unimpaired" facilitates score interpretation for primary care physicians and other clinic staff with limited exposure to cognitive assessment. Not only are cutoff scores easy and practical to use, they optimize time and efficiency in primary care where the average clinic visit is often less than 20 minutes (Linzer et al., 2015). In addition to discussing its potential application in healthcare settings, clinical utility for the dCIB was also evaluated by determining test validity. First, we compared how the dCIB performs alongside a commonly used cognitive screener. We found significant correlations between the dCIB and the well-validated MMSE, which establishes concurrent validity. Second, we used neuropsychological tests as a performance reference against the dCIB because, although lengthy, they are comprehensive assessments of cognitive domains with high sensitivity and specificity. The dCIB successfully predicted cognitive performance on these tests, which establishes

construct validity insofar that the dCIB is measuring what it was designed to measure. Furthermore, associations between the dCIB and neuropsychological outcomes are consistent with other studies using clock drawing tasks and therefore provide face validity that the dCIB is capturing cognitive performance. Lastly, we demonstrated the efficacy of the dCIB as a cognitive screening instrument in a community-based sample of adults who have not been identified as cognitively impaired. The dCIB successfully detected the presence of subtle cognitive impairment in our sample, particularly subtle executive deficits likely associated with poor vascular health, thereby substantiating its utility as a successful cognitive screener.

Study Considerations and Future Directions

At the heart of preventative medicine, primary care provides patients with routine screenings to monitor overall health status; unfortunately, screenings do not typically include an evaluation of cognitive status. It is worthwhile to note that, among our sample of adults who had not been identified as cognitively impaired, 11 of 63 participants (17.5%) demonstrated compromised performance on neuropsychological testing – thereby reinforcing the need for better cognitive screening. Of the 11 participants who were identified as cognitively impaired from neuropsychological assessment, the dCIB flagged 8 with *suspected* impairment (72.7%; dCIB score ≤ 6). In this study, we explored the utility of a novel digitized screener that is brief, simple, and can be used for routine cognitive screening in healthcare settings.

There are several strengths to this research. (1) Using a diverse sample that is representative of the demographic composition of the greater Boston area (U.S. Census Bureau, 2019) improves the external validity and generalizability of our findings. (2) Comparing the dCIB to other cognitive screeners (MMSE) and neuropsychological tests increases face validity that the dCIB is accurately capturing cognitive status. (3) Because the dCIB was able to predict cognitive performance, this helps establish construct validity insofar that the dCIB is measuring what it was designed to measure. (4) Despite the surge of technological devices in the digital era, it is possible that some individuals may not be comfortable or may not know how to use an iPad tablet. Therefore, a practice trial was incorporated into test administration to familiarize participants with how to use the tablet

and stylus. This was included to ensure that a low score on the dCIB was due to poor performance and not due to unfamiliarity with the technology. (5) As a digitized measure, the dCIB can gather supplementary data (i.e., time to completion, self-corrections, order of clock details) with a level of precision and standardization that is difficult or otherwise impossible to achieve with traditional paper-and-pencil neuropsychological assessment. Evaluating these empirically derived qualitative features (as opposed to unempirical qualitative observation) encompasses the spirit of the Boston Process Approach (Ashendorf et al., 2013) and has the potential to help elucidate and differentiate patient populations. As the first study utilizing the dCIB, we chose to exclude qualitative data in our analysis and instead focus on overall performance; however, future studies may choose to analyze qualitative details and use their findings to help refine the dCIB and further expand its clinical utility.

This research also has important limitations. (1) Although our sample is diverse and reflects the local demographics, it is also small (N=63) and therefore may not be representative of the larger population. However, even with a small sample, we were able to see significant effects within our analyses and thus we expect that future studies with larger samples would continue to hold similar associations. (2) Using current diagnostic criteria for MetS ("Executive Summary", 2001; Grundy, 2005), individuals in our sample were separated into groups that were of unequal sizes. The variability of scores observed in the smaller MetS group (n=21; M=5.33; SD=2.75), compared to the non-MetS group (n=42; M=6.81; SD=1.93), may be explained by unequal sizes across these groups. (3)

Our neuropsychological battery did not include the paper-and-pencil CIB, and therefore we could not directly compare performance between the dCIB and CIB. Subsequent studies will need to administer both the dCIB and CIB to provide evidentiary support of concurrent validity. (4) Like all cognitive screening instruments, the dCIB may be challenged by floor and ceiling effects. A floor effect (i.e., participant scores cluster towards the lowest possible value; dCIB score of 0) is likely minimized by our sample of adults with no history of cognitive impairment. However, there is evidence of a ceiling effect (i.e., participant scores cluster towards the highest possible value; dCIB score of 8) in our study – 30 of 63 participants received a maximum score of 8 – which can be explained by the fact that our sample was generally cognitively intact. Future studies should include participants with more cognitive impairment so as to improve understanding of the cognitive effects associated with low dCIB scores. (5) Because the dCIB is digitally administered and does not require direct examiner observation, clinically useful information may be missed during testing such as important behavioral indicators of emotion (i.e., displays of frustration), motivation, and mental status. Other factors potentially impacting test performance (i.e., premorbid reading level, medication effects, psychiatric status) may also not be considered. (6) The dCIB may be unsuitable for those with visual or physical handicaps. Drawing a clock may be challenging or impossible for individuals who have compromised fine motor movement. Individuals with color blindness may struggle to perceive the colored outlines of the four boxes (yellow, red, green, blue) on the response screen [see Appendix A]. A possible solution

may be to change the parameters from color to texture, such that the boxes are outlined by single line, double line, dashed line, etc. (7) Our study did not include longitudinal data on cognitive performance. Although we do not know how practice effects might disrupt retesting, future studies on dCIB reliability are needed to determine whether participants who are flagged for cognitive impairment by the dCIB remain impaired or continue to decline over time. Longitudinal assessments will also help determine how dCIB performance is affected by cognitive changes associated with normal aging.

Perhaps the most valuable next step is to create a normative database for the dCIB. Normative data is used to determine how an individual's performance compares to others of the same age and education; therefore, to meaningfully interpret an individual's dCIB score, we must have norms against which we can compare. Although tempting to borrow norms from the paper-and-pencil CIB, it is important to note that programming a test for digital administration (i.e., dCIB) creates a new and different test (Bauer et al., 2012). "It cannot be assumed that the normative data obtained for an examiner-administered test apply equally to a computerized version of the same test, due to changes in the method used to conduct the administration and variations in computer familiarity according to patient demographics" (Bauer et al., 2012, p. 368). Therefore, norms specific to the dCIB must be created. Future studies will need to create dCIB norms for healthy controls and, to further clinical utility, dCIB norms should also be created for different clinical populations to show the range and patterns of performance among those with cognitive impairment.

Another important next step is to develop software for the iPad that can automatically score the dCIB and compare performance to normative data in real time. This feature would offer healthcare providers immediate feedback that can be used to inform on-the-spot medical recommendations, thereby furthering the clinical utility of the dCIB.

Conclusion

In this research, we introduced the digital Clock in the Box [dCIB], a novel digitized clock drawing task designed to screen for cognitive impairment. The dCIB is quickly and easily administered on an iPad tablet which makes it an ideal option for routine cognitive screening in busy primary care settings. Associations between the dCIB and established cognitive screening and standardized neuropsychological measures provide support for the validity of the dCIB. In a sample stratified by vascular risk, the dCIB successfully detected subtle deficits associated with poor vascular health and differentiated groups based on cognitive impairment, thereby demonstrating its utility and success as a screening instrument. For these reasons, the dCIB shows promise as an effective cognitive screener, though additional studies are needed to further expand its clinical utility and explore its use with different populations and disorders.

APPENDIX A

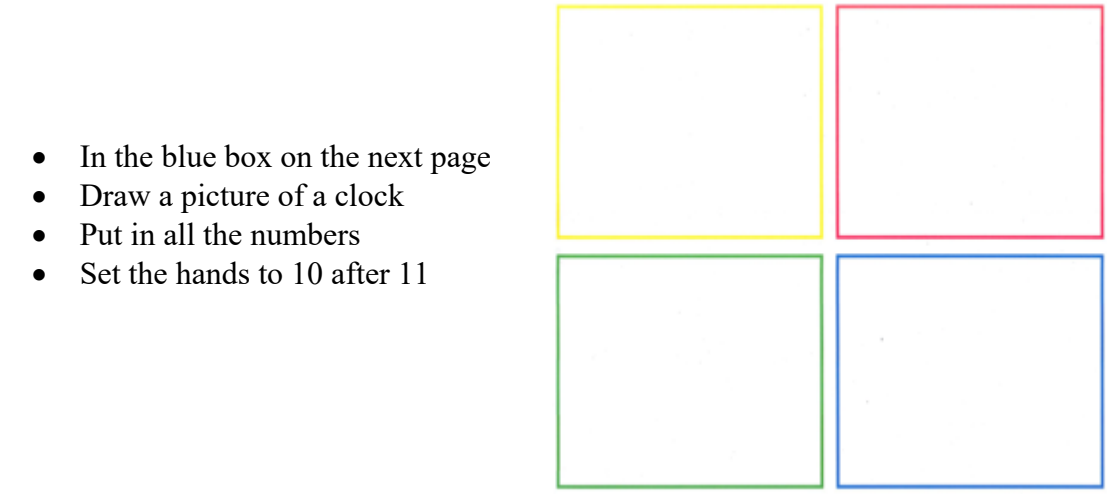

Figure 9. Sample CIB. During administration of the CIB, participants were given a sheet of paper with a set of four instructions: (1) In the blue box on the next page, (2) Draw a picture of a clock, (3) Put in all the numbers, and (4) Set the hands to 10 after 11. The instructions were taken away and participants were free to draw on the response sheet that shows four colored boxes (yellow, red, green, blue) each in a quadrant. For the dCIB, the presentation remains the same, but is administered on an iPad tablet. Instead of switching to a separate paper response sheet, participants swiped to the next screen. *Note*: Reprinted from Clock in the Box by Grande et al., 2011a. Retrieved from http://www.heartbrain.com/cib/clockinstructions.htm

APPENDIX B

Working Memory (WM) Subscore (4 possible points)

Location

Drawing is completed in the correct (blue) square

- Only in the blue square
- If drawn in multiple boxes (e.g. clock drawn in both blue & yellow boxes), no credit is given
- If drawn across multiple boxes (e.g. large clock covers more than one box), no credit is given
- If blue box itself it used as the clock's outline, credit is given

Object

Drawing resembles a clock

- Any type of clock is acceptable (e.g. grandfather clock)

Numbers

Drawing includes all numbers

- 1-12 in any order is given credit
- Numbers any location (e.g. written in a line) is given credit
- Roman numerals are given credit
- If numbers other than 1-12 are present, no credit is given

Time

Correct time is indicated in any manner

- Credit is given if time is written (e.g. "ten past eleven")
- Credit is given if the 11 and 2 are circled (or otherwise highlighted)
- If the participant did not receive credit for the Numbers feature above due to the addition of extra numbers, but the time is correctly indicated, credit is given

Planning/Organization (P/O) Subscore (4 possible points)

Size Drawing of clock is appropriate size • Small enough to fit in the blue square • Should not intersect other squares • Large enough to accommodate numbers 1-12 • If blue box itself it used as the clock's outline, no credit is given
Number Order Numbers are in correct order • Numbers may be written in any format (e.g. in a line)
Number Spacing Numbers are evenly spaced and drawn within clock's outline • If clock is scored as appropriate size, no credit is given if numbers intersect perimeter of clock • Opposing anchor numbers of 3 & 9 and 12 & 6 should be relatively well-aligned • If anchor numbers are well-aligned, the remaining numbers should be relatively well placed. If two or more quadrants have poor spacing, no credit is given.
Hand Length & Origin Hands should originate at center of clock and hands should be of different length • Hour hand must be 80% or less the length of the minute hand • Origin of hands must be within 50% of center

WM Subscore + P/O Subscore = dCIB Total Score

Table 16. Detailed Scoring Criteria for the CIB

Note: Reprinted from Clock in the Box by Grande et al., 2011a. Retrieved from

http://www.heartbrain.com/cib/clockinstructions.htm

APPENDIX C

Cognitive Screeners

- Digital Clock in the Box (dCIB)
- Mini-Mental State Exam 2 (MMSE-2)

Executive Function

- Delis-Kaplan Executive Function System (D-KEFS) – Trail Making Test
- Delis-Kaplan Executive Function System (D-KEFS) – Verbal Fluency
- Delis-Kaplan Executive Function System (D-FEKS) – Color Word Interference

Memory

- California Verbal Learning Test II (CVLT-II)
- Wechsler Memory Scale IV (WMS-IV) – Logical Memory
- Brief Visuospatial Memory Test Revised (BVMT-R)

Attention

- Wechsler Adult Intelligence Scale IV (WAIS-IV) – Digit Span
- Delis-Kaplan Executive Function System (D-KEFS) – Trail Making Test

BIBLIOGRAPHY

Aasvik, J., Stiles, T. C., Woodhouse, A., Borchgrevink, P. & Landro, N. I. (2018). The Effect of Insomnia on Neuropsychological Functioning in Patients with Comorbid Symptoms of Pain, Fatigue, and Mood Disorders. *Archives of Clinical Neuropsychology, 33*(1), 14-23.

Abd Ghafar, M. Z. A., Miptah, H. N. & O'Caoimh, R. (2019). Cognitive Screening Instruments to Identify Vascular Cognitive Impairment: A Systematic Review. *International Journal of Geriatric Psychiatry, 34*(8), 1114-1127.

Abd Razak, M. A., Ahmad, N. A., Chan, Y. Y., Kasim, N. M., Yusof, M., Abdul Ghani, M. K. A., Omar, M., Abd Aziz, F. A. & Jamaluddin, R. (2019). Validity of Screening Tools for Dementia and Mild Cognitive Impairment Among the Elderly in Primary Health Care: A Systematic Review. *Public Health, 169*, 84-92.

Adhikari, A., Tripathy, S., Chuzi, S., Peterson, J. & Stone, N. J. (2020). Association between Statin Use and Cognitive Function: A Systematic Review of Randomized Clinical Trials and Observational Studies. *Journal of Clinical Lipidology*. Advance online publication: https://doi.org/10.1016/j.jacl.2020.10.007

Aguilar, M., Bhuket, T., Torres, S., Liu, B. & Wong, R. J. (2015). Prevalence of the Metabolic Syndrome in the United States, 2003-2012. *JAMA, 313*(19), 1973-1974.

Alcorn, T., Hart, E., Smith, A. E., Feuerriegel, D., Stephan, B. C. M., Siervo, M. & Keage, H. A. (2019). Cross-sectional Associations between Metabolic Syndrome and Performance Across Cognitive Domains: A Systematic Review. *Applied Neuropsychology: Adult, 26*(2), 186-199.

Alfaro, F. J., Gavrieli, A., Saade-Lemus, P., Lioutas, V., Upadhyay, J. & Novak, V. (2018). White Matter Microstructure and Cognitive Decline in Metabolic Syndrome: A Review of Diffusion Tensor Imaging. *Metabolism, 78*, 52-68.

Alfaro, F. J., Lioutas, V. A., Pimentel, D. A., Chung, C. C., Bedoya, F., Yoo, W. K. & Novak, V. (2016). Cognitive Decline in Metabolic Syndrome is Linked to Microstructural White Matter Abnormalities. *Journal of Neurology, 263*(12), 2505-2514.

Alzheimer's Association. (2020). 2020 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia, 16*(3), 391-460.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Washington, DC: American Psychiatric Publishing.

Aminzadeh, F., Molnar, F. J., Dalziel, W. B. & Ayotte, D. (2012). A Review of Barriers and Enablers to Diagnosis and Management of Persons with Dementia in Primary Care. *The Canadian Geriatrics Journal, 15*(3), 85-94.

Amirrad, F., Bousoik, E., Shamloo, K., Al-Shiyab, H., Nguyen, V. V. & Aliabadi, H. M. (2017). Alzheimer's Disease: Dawn of a New Era? *Journal of Pharmacy & Pharmaceutical Sciences, 20*, 184-225.

Amodeo, S., Mainland, B. J., Herrmann, N. & Shulman, K. I. (2015). The Times They Are a-Changin': Clock Drawing and Prediction of Dementia. *Journal of Geriatric Psychiatry, 28*(2), 145-155.

Anand, S. S., Friedrich, M. G., Desai, D., Schulze, K. M., Awadalla, P., Busseuil, D., Dummer, T. J. B., Jacquemont, S., Dick, A., Kelton, D., Kirpalani, A., Lear, S. A., Leipsic, J., Noseworthy, M. D., Parker, L., Parraga, G., Poirier, P., Robson, P., Tardif, J., Teo, K., Vena, J., Yusuf, S., Moody, A. R., Black, S. E., Smith, E. E. & Canadian Alliance for Healthy Hearts and Minds Cohort. (2020). Reduced Cognitive Assessment Scores Among Individuals with Magnetic Resonance Imaging-Detected Vascular Brain Injury. *Stroke, 51*(4), 1158-1165.

Ashendorf, L., Swenson, R. & Libon, D. (Eds.) (2013). *The Boston Process Approach to Neuropsychological Assessment: A Practitioner's Guide*. Oxford University Press.

Assuncao, N., Sudo, F. K., Drummond, C., de Felice, F. G. & Mattos, P. (2018). Metabolic Syndrome and Cognitive Decline in the Elderly: A systematic review. *PLoS One, 13*(3), e0194990.

Ates, M. P. & Can, F. Y. (2020). Which Factors Can We Control the Transition from Mild Cognitive Impairment to Dementia? *Journal of Clinical Neuroscience, 73*, 108-110.

Atti, A. R., Valente, S., Iodice, A., Caramella, I., Ferrari, B., Albert, U., Mandelli, L. & De Ronchi, D. (2019). Metabolic Syndrome, Mild Cognitive Impairment, and Dementia: A Meta-Analysis of Longitudinal Studies. *The American Journal of Geriatric Psychiatry, 27*(6), 625-637.

Azarpazhooh, M. R. & Hachinski, V. (2019). Vascular Cognitive Impairment: A Preventable Component of Dementia. *Handbook of Clinical Neurology, 167*,

377-391.

Baddeley, A. D. & Hitch, G. (1974). Working Memory. In G. H. Bower (Ed.), *Recent Advances in Learning and Motivation* (Vol. 8, pp. 47-89). New York, NY: Academic Press.

Bae, S., Shimada, H., Lee, S., Makizako, H., Lee, S., Harada, K., Doi, T., Tsutsumimoto, K., Hotta, R., Nakakubo, S., Park, H. & Suzuki, T. (2017). The Relationships between Components of Metabolic Syndrome and Mild Cognitive Impairment Subtypes: A Cross-Sectional Study of Japanese Older Adults. *Journal of Alzheimer's Disease, 60*(3), 913-921.

Bangen, K. L., Armstrong, N. M., Au, R. & Gross, A. L. (2019). Metabolic Syndrome and Cognitive Trajectories in the Framingham Offspring Study. *Journal of Alzheimer's Disease, 71*(3), 931-943.

Bauer, R. M., Iverson, G. L., Cernich, A. N., Binder, L. M., Ruff, R. M. & Naugle, R. I. (2012). Computerized Neuropsychological Assessment Devices: Joint Position Paper of the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology. *Archives of Clinical Neuropsychology, 27*(3), 362-373.

Beck, A. T., Steer, R. A. & Brown, G. K. (1996). *Manual for Beck Depression Inventory II*. San Antonio, TX: The Psychological Corporation.

Bejanin, A., Schonhaut, D. R., Joie, R. L., Kramer, J. H., Baker, S. L., Sosa, N., Ayakta, N., Cantwell, A., Janabi, M., Lauriola, M., O'Neil, J. P., Gorno-Tempini, M. L., Miller, Z. A., Rosen, H. J., Miller, B. L., Jagust, W. J. & Rabinovici, G. D. (2017). Tau Pathology and Neurodegeneration Contribute to Cognitive Impairment in Alzheimer's Disease. *Brain, 140*(12), 3286-3300.

Beltran-Sanchez, H., Harhay, M. O., Marhay, M. M. & McElligott, S. (2013). Prevalence and Trends of Metabolic Syndrome in the Adult U.S. Population, 1999-2010. *Journal of the American College of Cardiology, 62*(8), 697-703.

Benedict, R. H. B. (1997). *Brief Visuospatial Memory Test – Revised*. Odessa, FL: Psychological Assessment Resources.

Benedict, R. H. B., Schretlen, D., Groninger, L. & Brandt, J. (1998). The Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Interform and Test-retest Reliability. *The Clinical Neuropsychologist, 12*, 43-55.

Bennett, V. (2017). Combating the 'silent killer' that is hypertension. *Nursing Standard, 31*(25), 28.

Bento-Torres, N. V. O., Bento-Torres, J., Tomas, A. M., Costa, V. O., Correa, P. G. R., Costa, C. N. M., Jardim, N. Y. V. & Picanco-Diniz, C. W. (2017). Influence of Schooling and Age on Cognitive Performance in Healthy Older Adults. *Brazilian Journal of Medical and Biological Research, 50*(4), 1-9.

Bezdicek, O., Majerova, V., Novak, M., Nikolai, T., Ruzicka, E. & Roth, J. (2013). Validity of the Montreal Cognitive Assessment in the Detection of Cognitive Dysfunction in Huntington's Disease. *Applied Neuropsychology: Adult, 20*(1), 33-40.

Bezrukov, V. V., Bachinskaya, N. Y., Kopchak, O. O., Kholin, V. O. & Pulyk, O. R. (2018). Age Related Characteristics of Cognitive Changes in Patients with Metabolic Syndrome. *Wiad Lek, 71*(8), 1515-1523.

Binaco, R., Calzaretto, N., Epifano, J., McGuire, S., Umer, M., Emrani, S., Wasserman, V., Libon, D. J. & Polikar, R. (2020). Machine Learning Analysis of Digital Clock Drawing Test Performance for Differential Classification of Mild Cognitive Impairment Subtypes versus Alzheimer's Disease. *Journal of the International Neuropsychological Society, 26*(7), 690-700.

Bischof, G. N. & Park, D. C. (2015). Obesity and Aging: Consequences for Cognition, Brain Structure, and Brain Function. *Psychosomatic Medicine, 77*(6), 697-709.

Blaum, C. S., West, N. A. & Haan, M. N. (2007). Is the Metabolic Syndrome, With or Without Diabetes, Associated with Progressive Disability in Older Mexican Adults? *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 62*(7), 766-773.

Blumenfeld, H. (2018). Cerebral Hemispheres and Vascular Supply. In *Neuroanatomy Through Clinical Cases* (2nd ed.). Sunderland, MA: Sinauer Associates, Inc.

Bondi, M. W., Edmonds, E. C. & Salmon, D. P. (2017). Alzheimer's Disease: Past, Present, and Future. *Journal of the International Neuropsychological Society, 23*(9-10), 818-831.

Boss, H. M., Van Schaik, S. M., Witkamp, T. D., Geerlings, M. I., Weinstein, H. C. & Van den Berg-Vos, R. M. (2017). Cardiorespiratory Fitness, Cognition, and Brain Structure after TIA or Minor Ischemic Stroke. *International Journal of Stroke, 12*(7), 724-731.

Bradford, A., Kunik, M. E., Schulz, P., Williams, S. P. & Singh, H. (2009). Missed and Delayed Diagnosis of Dementia in Primary Care: Prevalence and Contributing Factors. *Alzheimer Disease & Associated Disorders, 23*(4), 306-314.

Brady, C. B., Spiro III, A., McGlinchey-Berroth, R., Milberg, W. & Gaziano, J. M. (2001). Stroke Risk Predicts Verbal Fluency Decline in Healthy Older Men: Evidence from the Normative Aging Study. *Journal of Gerontology: Psychological Sciences, 56B*(6), P340-P346.

Bratic, B., Kurbalija, V., Ivanovic, M., Oder, I. & Bosnic, Z. (2018). Machine Learning for Predicting Cognitive Diseases: Methods, Data Sources, and Risk Factors. *Journal of Medical Systems, 42*(243), 1-15.

Cakir, E., Harmankaya, N. O., Cengiz, H. & Varim, C. (2020). Evaluation of Cognitive Functions in Diabetic Patients. *International Journal of Research in Medical Sciences, 8*(6), 2039-2043.

Campos-Magdaleno, M., Leiva, D., Pereiro, A. X., Lojo-Seoane, C., Mallo, S. C., Facal, D. & Juncos-Rabadan, O. (2020). Changes in Visual Memory in Mild Cognitive Impairment: A Longitudinal Study with CANTAB. *Psychological Medicine*. Advance online publication. https://doi.org/10.1017/s0033291720001142

Carnero-Pardo, C. (2014). Should the Mini-Mental State Examination be Retired? *Neurologia, 29*(8), 473-481.

Carnero-Pardo, C., Rego-Garcia, I., Mene Llorente, M., Alonso Rodenas, M. &. Vilchez Carrillo, R. (2019). Diagnostic Performance of Brief Cognitive Tests in Cognitive Impairment Screening. *Neurologia*. Advance online publication. https://doi.org/10.1016/j.nrl.2019.05.007

Carriere, I., Peres, K., Ancelin, M. L., Gourlet, V., Berr, C., Barberger-Gateau, P., Bouillon, K., Kivimaki, M., Ritchie, K. & Akbaraly, T. (2014). Metabolic Syndrome and Disability: Findings from the Prospective Three-City Study. *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 69*(1), 79-86.

Centers for Disease Control and Prevention. (2019, April 5). Alzheimer's Disease and Healthy Aging: What is Dementia? Retrieved from https://www.cdc.gov/aging/dementia/index.html

Chen, L. M., Farwell, W. R. & Jha, A. K. (2009). Primary Care Visit Duration and Quality: Does Good Care Take Longer? *Archives of Internal Medicine, 169*(20),

1866-1872.

Cheng, S. T. (2017). Dementia Caregiver Burden: A Research Update and Critical Analysis. *Current Psychiatry Reports, 19*(9), 64.

Chester, J. G., Grande, L. J., Milberg, W. P., McGlinchey, R. E., Lipsitz, L. A. & Rudolph, J. L. (2011). Cognitive Screening in Community-dwelling Elders: Performance on the Clock-in-the-Box. *The American Journal of Medicine, 124*(7), 662-229.

Ciesielska, N., Sokolowski, R., Mazur, E., Podhorecka, M., Polak-Szabela, A. & Kedziora-Kornatowska, K. (2016). Is the Montreal Cognitive Assessment (MoCA) Test Better Suited than the Mini-Mental State Examination (MMSE) in Mild Cognitive Impairment (MCI) Detection Among People Aged Over 60? Meta-analysis. *Psychiatria Polska, 50*(5), 1039-1052.

Cohen, J., Penney, D. L., Davis, R., Libon, D. J., Swenson, R. A., Ajilore, O., Kumar, A. & Lamar, M. (2014). Digital Clock Drawing: Differentiating 'thinking' versus 'doing' in Younger and Older Adults with Depression. *Journal of the International Neuropsychological Society, 20*(9), 920-928.

Connolly, A., Gaehl, E., Martin, H., Morris, J. & Purandare, N. (2011). Underdiagnosis of Dementia in Primary Care: Variations in the Observed Prevalence and Comparisons to the Expected Prevalence. *Aging & Mental Health, 15*(8), 978-984.

Cordell, C. B., Borson, S., Boustani, M., Chodosh, J., Reuben, D., Verghese, J., Thies, W., Fried, L. B. & Medicare Detection of Cognitive Impairment Workshop. (2013). Alzheimer's Association Recommendations for Operationalizing the Detection of Cognitive Impairment during the Medicare Annual Wellness Visit in a Primary Care Setting. *Alzheimer's & Dementia, 9*(2), 141-150.

Cornelis, E., Gorus, E., Schelvergem, N. V. & Vriendt, P. D. (2019). The Relationship between Basic, Instrumental, and Advanced Activities of Daily Living and Executive Functioning in Geriatric Patients with Neurocognitive Disorders. *International Journal of Geriatric Psychiatry, 34*(6), 889-899.

Crane, P. K., Carle, A., Gibbons, L. E., Insel, P., Mackin, R. S., Gross, A., Jones, R. N., Mukherjee, S., Curtis, S. M. & Harvey, D. (2012). Development and Assessment of a Composite Score for Memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging and Behavior, 6*(4), 502-516.

Dagenais, E., Rouleau, I., Demers, M., Jobin, C., Roger, E., Chamelian, L. & Duquette, P. (2013). Value of the MoCA test as a Screening Instrument in Multiple Sclerosis. *Canadian Journal of Neurological Sciences, 40*(3), 410-415.

Dalrymple-Alford, J. C., MacAskill, M. R., Nakas, C. T., Livingston, L., Graham, C., Crucian, G. P., Melzer, T. R., Kirwan, J., Keenan, R., Wells, S., Porter, R. J., Watts, R. & Anderson, T. J. (2010). The MoCA: Well-Suited Screen for Cognitive Impairment in Parkinson's Disease. *Neurology, 75*(19), 1717-1725.

Davis, D. H. J., Creavin, S. T., Yip, J. L. Y., Noel-Storr, A. H., Brayne, C. & Cullum, S. (2015). Montreal Cognitive Assessment for the Diagnosis of Alzheimer's Disease and Other Dementias. *Cochrane Database of Systematic Reviews, 10*(CD010775), 1-44.

Davis, R., Libon, D., Au, R., Pitman, D. & Penney, D. L. (2014). *THink: Inferring Cognitive Status from Subtle Behaviors*. Proceedings of the AAAI Conference on Artificial Intelligence, Quebec, Canada, 2898-2905.

Davis, R., Penney, D. L., Pittman, D., Libon, D. J., Swenson, R. & Kaplan, E. *The Digital Clock Drawing Test (dCDT) I: Development of a New Computerized Quantitative System*. Presented at The International Neuropsychological Society Conference, Montreal, Canada, 2010.

de Anna, F., Felician, O., Barbeau, E., Mancini, J., Didic, M. & Ceccaldi, M. (2014). Cognitive Changes in Mild Cognitive Impairment Patients with Impaired Visual Recognition Memory. *Neuropsychology, 28*(1), 98-105.

de Guise, E., Alturki, A. Y., LeBlanc, J., Champoux, M., Couturier, C., Lamoureux, J., Desjardins, M., Marcoux, J., Maleki, M. & Feyz, M. (2014). The Montreal Cognitive Assessment in Persons with Traumatic Brain Injury. *Applied Neuropsychology: Adult, 21*(2), 128-135.

de Roeck, E. E., De Deyn, P. P., Dierckx, E. & Engelborghs, S. (2019). Brief Cognitive Screening Instruments for Early Detection of Alzheimer's Disease: A Systematic Review. *Alzheimer's Research & Therapy, 11*(21).

Debette, S., Seshadri, S., Beiser, A., Au, R., Himali, J. J., Palumbo, C., Wolf, P. A. & DeCarli, C. (2011). Midlife Vascular Risk Factor Exposure Accelerates Structural Brain Aging and Cognitive Decline. *Neurology, 77*(5), 461-468.

Delis, D. C., Kaplan, E. & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E. & Ober, B. A. (2000). *California Verbal Learning Test – Second Edition, Adult Version.* (2nd ed.) San Antonio, TX: The Psychological Corporation.

Dhedhi, S. A., Swinglehurst, D. & Russell, J. (2014). 'Timely' diagnosis of dementia: What does it mean? A narrative analysis of GP's accounts. *British Journal of General Practice Open, 4*(3), 1-9.

Didic, M., Felician, O., Barbeau, E. J., Mancini, J., Latger-Florence, C., Tramoni, E. & Ceccaldi, M. (2013). Impaired Visual Recognition Memory Predicts Alzheimer's Disease in Amnestic Mild Cognitive Impairment. *Dementia and Geriatric Cognitive Disorders, 35*(5-6), 291-299.

Diaz-Orueta, U., Blanco-Campal, A., Lamar, M., Libon, D. J. & Burke, T. (2020). Marrying Past and Present Neuropsychology: Is the Future of the Process-Based Approach Technology-Based? *Frontiers in Psychology, 11*(361), 1-15.

Dichgans, M. & Leys, D. (2017). Vascular Cognitive Impairment. *Circulation Research, 120*(3), 573-591.

Dik, M. G., Jonker, C., Comijs, H. C., Deeg, D. J., Kok, A., Yaffe, K. & Penninx, B. W. (2007). Contribution of Metabolic Syndrome Components to Cognition in Older Individuals. *Diabetes Care, 30*(10), 2655-2660.

Dion, C., Arias, F., Amini, S., Davis, R., Penney, D., Libon, D. J. & Price, C. C. (2020). Cognitive Correlates of Digital Clock Drawing Metrics in Older Adults with and without Mild Cognitive Impairment. *Journal of Alzheimer's Disease, 75*(1), 73-83.

Duro, D., Freitas, S., Tabuas-Pereira, M., Santiago, B., Botelho, M. A. & Santana, I. (2019). Discriminative Capacity and Construct Validity of the Clock Drawing Test in Mild Cognitive Impairment and Alzheimer's Disease. *The Clinical Neuropsychologist, 33*(7), 1159-1174.

Dye, L., Boyle, N. B., Champ, C. & Lawton, C. (2017). The Relationship between Obesity and Cognitive Health and Decline. Pr*oceedings of the Nutrition Society, 76*(4), 443-454.

Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2001). *JAMA, 285*(19), 2486-2497.

Falkowski, J., Atchison, T., Debutte-Smith, M., Weiner, M. F. & O'Bryant, S. (2014). Executive Functioning and the Metabolic Syndrome: A project FRONTIER study. *Archives of Clinical Neuropsychology, 29*(1), 47-53.

Farias, S. T., Cahn-Weiner, D. A., Harvey, D. J., Reed, B. R., Mungas, D., Kramer, J. H. & Chui, H. (2009). Longitudinal Changes in Memory and Executive Functioning are Associated with Longitudinal Change in Instrumental Activities of Daily Living in Older Adults. *The Clinical Neuropsychologist, 23*(3), 446-461.

Farias, S. T., Lau, K., Harvey, D., Denny, K. G., Barba, C. & Mefford, A. N. (2017). Early Functional Limitations in Cognitively Normal Older Adults Predict Diagnostic Conversion to Mild Cognitive Impairment. *Journal of the American Geriatrics Society, 65*(6), 1152-1158.

Favieri, F., Forte, G. & Casagrande, M. (2019). The Executive Functions in Overweight and Obesity: A Systematic Review of Neuropsychological Cross-Sectional and Longitudinal Studies. *Frontiers in Psychology, 10*(2126), 1-27.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (1975). "Mini Mental State". A Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Folstein, M. F., Folstein, S. E., White, T. & Messer, M. A. (2010). *Mini Mental State Examination 2*. Lutz, FL: Psychological Assessment Resources.

Frankenburg, F. R. (2019, Summer). The Clock Drawing Test: A useful screening and teaching tool. *The Pharos*, 49-53. Retrieved from http://alphaomegaalpha.org/pharos/2019/Summer/19_Summer_Frankenburg.pdf

Freedman, M., Leach, L., Kaplan, E., Winocur, G., Shulman, K. I. & Delis, D. C. (1994). *Clock Drawing: A Neuropsychological Analysis*. New York: Oxford University Press.

Freitas, S., Batista, S., Afonso, A. C., Simoes, M. R., de Sousa, L., Cunha, L. & Santana, I. (2018). The Montreal Cognitive Assessment (MoCA) as a Screening Test for Cognitive Dysfunction in Multiple Sclerosis. *Applied Neuropsychology: Adult, 25*(1), 57-70.

Freitas, S., Simoes, M. R., Alves, L., Vicente, M. & Santana, I. (2012). Montreal Cognitive Assessment (MoCA): Validation Study for Vascular Dementia. *Journal of the International Neuropsychological Society, 18*(6), 1031-1040.

Frenette, L. C., Tinawi, S., Correa, J. A., Alturki, A. Y., LeBlanc, J., Feyz, M. & de Guise, E. (2019). Early Detection of Cognitive Impairments with the Montreal Cognitive Assessment in Patients with Uncomplicated and Complicated Mild Traumatic Brain Injury. *Brain Injury, 33*(2), 189-197.

Fuzikawa, C., Lima-Costa, M. F., Uchoa, E., Barreto, S. M., Shulman, K. & Bambui Health and Ageing Study (2003). A Population based Study on the Intra and Inter-rater Reliability of the Clock Drawing Test in Brazil: The Bambui Health and Ageing Study. *International Journal of Geriatric Psychiatry, 18*(5), 450-456.

Gale, S. A., Acar, D. & Daffner, K. R. (2018). Dementia. *The American Journal of Medicine, 131*(10), 1161-1169.

Ganguli, M., Beer, J. C., Zmuda, J. M., Ryan, C. M., Sullivan, K. J., Chang, C. H. & Rao, R. H. (2020). Aging, Diabetes, Obesity, and Cognitive Decline: A Population-Based Study. *Journal of the American Geriatrics Society, 68*(5), 991-998.

Ganguli, M., Jia, Y., Hughes, T. F., Snitz, B. E., Chang, C. H., Berman, S. B., Sullivan, K. J. & Kamboh, M. I. (2019). Mild Cognitive Impairment that Does Not Progress to Dementia: A Population-based Study. *Journal of the American Geriatrics Society, 67*(2), 232-238.

Gatlin, P. K. & Insel, K. C. (2015). Severity of Type 2 Diabetes, Cognitive Function, and Self-Care. *Biological Research for Nursing, 17*(5), 540-548.

Germine, L., Reinecke, K. & Chaytor, N. S. (2019). Digital Neuropsychology: Challenges and Opportunities at the Intersection of Science and Software. *The Clinical Neuropsychologist, 33*(2), 271-286.

Ghisletta, P., Mason, F., Dahle, C. L. & Raz, N. (2019). Metabolic Risk Affects Fluid Intelligence Changes in Healthy Adults. *Psychology and Aging, 34*(7), 912-920.

Gibbons, L. E., Carle, A. C., Mackin, R. S., Harvey, D., Mukherjee, S., Insel, P., Curtis, S. M., Mungas, D. & Crane, P. K. (2012). A Composite Score for Executive Functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging and Behavior, 6*(4), 517-527.

Gluhm, S., Goldstein, J., Brown, D., van Liew, C., Gilbert, P. E. & Corey-Bloom, J. (2013). Usefulness of the Montreal Cognitive Assessment (MoCA) in Huntington's Disease. *Movement Disorders, 28*(12), 1744-1747.

Golden, C. J. (1978). *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Chicago, IL: Stoelting Co.

Goodglass, H. & Kaplan, E. (1972). *The Assessment of Aphasia and Related Disorders*. Philadelphia, PA: Lea and Febiger.

Goodglass, H., Kaplan, E. & Barresi, B. (1983). *Boston Diagnostic Aphasia Examination (BDAE)*. Philadelphia, PA: Lea and Febiger.

Grande, L. J., McGlinchey, R. & Milberg, W. (2011a). Clock in the Box. Retrieved from http://www.heartbrain.com/cib/clockinstructions.htm

Grande, L. J., Milberg, W. P. & Rudolph, J. L. (2005). A Timely Screening for Executive Functions and Memory. *Journal of the International Neuropsychological Society, 11*(s1), 9-10.

Grande, L. J., Rudolph, J. L., Davis, R., Penney, D. L., Price, C. C., Swenson, R., Libon, D. J. & Milberg, W. (2013). Clock drawing: Standing the Test of Time. *The Boston Process Approach to Neuropsychological Assessment: A Practitioner's Guide*. New York: Oxford University Press.

Grande, L. J., Rudolph, J. L., Milberg, W. P., Barber, C. E. & McGlinchey R. E. (2011b). Detecting Cognitive Impairment in Individuals at Risk for Cardiovascular Disease: The "Clock-in-the-Box" Screening Test. *International Journal of Geriatric Psychiatry, 26*(9), 969-975.

Green, E., Fairchild, J. K., Kinoshita, L. M., Noda, A. & Yesavage, J. (2016). Effects of Posttraumatic Stress Disorder and Metabolic Syndrome on Cognitive Aging in Veterans. *Gerontologist, 56*(1), 72-81.

Gregoire, J. & Van der Linden, M. (1997). Effect of Age on Forward and Backward Digit Spans. *Aging, Neuropsychology, and Cognition, 4*(2), 140-149.

Grundy, S. M. (2005). Metabolic Syndrome Scientific Statement by the American Heart Association and the National Heart, Lung, and Blood Institute. *Arteriosclerosis, Thrombosis, and Vascular Biology, 25*(11), 2243-2244.

Habibzadeh, F., Habibzadeh, P. & Yadollahie, M. (2016). On Determining the Most Appropriate Test Cut-off Value: The Case of Tests with Continuous Results. *Biochemia Medica, 26*(3), 297-307.

Halliday, D. W. R., Gawryluk, J. R., Garcia-Barrera, M. A., MacDonald, S. W. S. & The

Alzheimer's Disease Neuroimaging Initiative. (2019). White Matter Integrity is Associated with Intraindividual Variability in Neuropsychological Test Performance in Healthy Older Adults. *Frontiers in Human Neuroscience, 13*(352), 1-10.

Harrington, M. B., Kraft, M. Grande, L. J. & Rudolph, J. L. (2011). Independent Association between Preoperative Cognitive Status and Discharge Location after Cardiac Surgery. *American Journal of Critical Care, 20*(2), 129-138.

Harvey, P. D. (2019). Domains of Cognition and their Assessment. *Dialogues in Clinical Neuroscience, 21*(3), 227-237.

Hassenstab, J. J., Sweat, V., Bruehl, H. & Convit, A. (2010). Metabolic Syndrome is Associated with Learning and Recall Impairment in Middle Age. *Dementia & Geriatric Cognitive Disorders, 29*(4), 356-362.

Hay, M., Barnes, C., Huentelman, M., Brinton, R. & Ryan, L. (2020). Hypertension and Age-Related Cognitive Impairment: Common Risk Factors and a Role of Precision Aging. *Current Hypertension Reports, 22*(10), 80.

Hazan, E., Frankenburg, F., Brenkel, M. & Shulman, K. (2018). The Test of Time: A history of clock drawing. *International Journal of Geriatric Psychiatry, 33*(1), e22-e30.

Head, H. (1926). *Aphasia and Kindred Disorders of Speech*. Cambridge, UK: Cambridge University Press.

Hebben, N. & Milberg, W. (2009). *Essentials of Neuropsychological Assessment* (2nd ed.) (A. S. Kaufman & N. L. Kaufman, Eds.). Hoboken, NJ: John Wiley & Sons, Inc.

Hester, R. L., Kinsella, G. J. & Ong, B. (2004). Effect of Age on Forward and Backward Span Tasks. *Journal of the International Neuropsychological Society, 10*(4), 475-481.

Hirode, G. & Wong, R. J. (2020). Trends in the Prevalence of Metabolic Syndrome in the United States, 2011-2016. *JAMA, 323*(24), 2526-2528.

Hoffman, S. S., Winkler, A., Weimar, C., Muller-Gerards, D., Abramowski, J., Moebus, S., Jockel, K., Erbel, R. & Jokisch, M. (2020). Blood Pressure and Cognitive Decline – The Impact of Hypertension Over One Decade. *Neuropsychology, Development, and Cognition: Section B, Aging, Neuropsychology, and Cognition*.

Advance online publication. https://doi.org/10.1080/13825585.2020.1792403

Hoops, S., Nazem, S., Siderowf, A. D., Duda, J. E., Xie, S. X., Stern M. B. & Weintraub, D. (2009). Validity of the MoCA and MMSE in the Detection of MCI and Dementia in Parkinson's Disease. *Neurology, 73*(21), 1738-1745.

Howieson, D. B., Mattek, N., Dodge, H. H., Erten-Lyons, D., Zitzelberger, T. & Kaye, J. A. (2015). Memory Complaints in Older Adults: Prognostic Value and Stability in Reporting Over Time. *SAGE Open Medicine, Jan-Dec*(3), 1-7.

Hshieh, T. T., Jung, W. F., Grande, L. J., Chen, J., Stone, R. M., Soiffer, R. J., Driver, J. A. & Abel, G. A. (2018). Prevalence of Cognitive Impairment and Association with Survival Among Older Patients with Hematologic Cancers. *JAMA Oncology, 4*(5), 686-693.

Hubbard, E. J., Santini, V., Blankevoort, C. G., Volkers, K. M., Barrup, M. S., Byerly, L., Chaisson, C., Jefferson, A. L., Kaplan, E., Green, R. C. & Stern, R. A. (2008). Clock Drawing Performance in Cognitively Normal Elderly. *Archives of Clinical Neuropsychology, 23*(3), 295-327.

Hughes, D., Judge, C., Murphy, R., Loughlin, E., Costello, M., Whiteley, W., Bosch, J., O'Donnell, M. J. & Canavan, M. (2020). Association of Blood Pressure Lowering with Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-Analysis. *JAMA, 323*(19), 1934-1944.

Hughes, T. M. & Sink, K. M. (2016). Hypertension and its Role in Cognitive Function: Current Evidence and Challenges for the Future. *American Journal of Hypertension, 29*(2), 149-157.

Iadecola, C., Yaffe, K., Biller, J., Bratzke, L. C., Faraci, F. M., Gorelick, P. B., Gulati, M., Kamel, H., Knopman, D. S., Launer, L. J., Saczynski, J. S., Seshadri, S. & Al-Hazzouri, A. Z. (2016). Impact of Hypertension on Cognitive Function: A Scientific Statement from the American Heart Association. *Hypertension, 68*(6), e67-e94.

Ismail, Z., Rajji, T. K. & Shulman, K. I. (2010). Brief Cognitive Screening Instruments: An update. *International Journal of Geriatric Psychiatry, 25*(2), 111-120.

Jackson C. E., Grande, L. J., Doherty, K., Archambault, E., Kelly, B., Driver, J. A., Milberg, W. P., McGlinchey, R. & Rudolph, J. L. (2016). The Clock-in-the-Box, a brief cognitive screen, is associated with failure to return home in an elderly hospitalized sample. *Clinical Interventions in Aging, 11*, 1715-1721.

Jak, A. J., Bondi, M. W., Delano-Wood, L., Wierenga, C., Corey-Bloom, J., Salmon, D. P. & Delis, D. C. (2009). Quantification of Five Neuropsychological Approaches to Defining Mild Cognitive Impairment. *The American Journal of Geriatric Psychiatry, 17*(5), 368-375.

Jammeh, E. A., Carroll, C. B., Pearson, S. W., Escudero, J., Anastasiou, A., Zhao, P., Chenore, T., Zajicek, J. & Ifeachor, E. (2018). Machine-learning Based Identification of Undiagnosed Dementia in Primary Care: A Feasibility Study. *British Journal of General Practice Open, 2*(2), 1-13.

Jefferson, A. L., Cahn-Weiner, D., Boyle, P., Paul, R. H., Moser, D. J., Gordon, N. & Cohen, R. A. (2006). Cognitive Predictors of Functional Decline in Vascular Dementia. *International Journal of Geriatric Psychiatry, 21*(8), 752-754.

Jonaitis, E. M., Koscik, R. L., Clark, L. R., Ma, Y., Betthauser, T. J., Berman, S. E., Allison, S. L., Mueller, K. D., Hermann, B. P., Van Hulle, C. A., Christian, B. T., Bendlin, B. B., Blennow, K., Zetterberg, H., Carlsson, C. M., Asthana, S. & Johnson, S. C. (2019). Measuring longitudinal cognition: Individual tests versus composites. *Alzheimer's & Dementia, 11*, 74-84.

Jones, S., Laukka, E. J. & Backman, L. (2006). Differential Verbal Fluency Deficits in the Preclinical Stages of Alzheimer's Disease and Vascular Dementia. *Cortex, 42*(3), 347-355.

Kane, M. J. & Engle, R. W. (2002). The Role of Prefrontal Cortex in Working-Memory Capacity, Executive Attention, and General Fluid Intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review, 9*(4), 637-671.

Karvani, M., Simos, P., Stavrakaki, S. & Kapoukranidou, D. (2019). Neurocognitive Impairment in Type 2 Diabetes Mellitus. *Hormones, 18*(4), 523-534.

Kawas, C. H., Corrada, M. M., Brookmeyer, R., Morrison, A., Resnick, S. M., Zonderman, A. B. & Arenberg, D. (2003). Visual Memory Predicts Alzheimer's Disease More than a Decade Before Diagnosis. *Neurology, 60*(7), 1089-1093.

Kim, H. (2019). Cognitive Dysfunctions in Individuals with Diabetes Mellitus. *Yeungnam University Journal of Medicine, 36*(3), 183-191.

Kim, M. S., Boone, K. B., Victor, T., Marion, S. D., Amano, S., Cottingham, M. E., Ziegler, E. A. & Zeller, M. A. (2010). The Warrington Recognition Memory Test for Words as a Measure of Response Bias: Total Score and Response Time Cutoffs Developed on "Real World" Credible and Noncredible Subjects.

Archives of Clinical Neuropsychology, 25(1), 60-70.

Kim, S., Jahng, S., Yu, K. H., Lee, B. C. & Kang, Y. (2018). Usefulness of the Clock Drawing Test as a Cognitive Screening Instrument for Mild Cognitive Impairment and Mild Dementia: An Evaluation Using Three Scoring Systems. *Dementia and Neurocognitive Disorders, 17*(3), 100-109.

Knopman, D. S., Gottesman, R. F., Sharrett, A. R., Tapia, A. L., Thomas, S. D., Windham, B. G., Coker, L., Schneider, A. L. C., Alonso, A., Coresh, J., Albert, M. S. & Mosley, T. H. (2018). Midlife Vascular Risk Factors and Midlife Cognitive Status in Relation to Prevalence of Mild Cognitive Impairment and Dementia in Later Life: The Atherosclerosis Risk in Communities Study. *Alzheimer's & Dementia, 14*(11), 1406-1415.

Komulainen, P., Lakka, T. A., Kivipelto, M., Hassinen, M., Helkala, E. L., Haapala, I., Nissinen, A. & Rauramaa, R. (2007). Metabolic Syndrome and Cognitive Function: A population-based follow-up study in elderly women. *Dementia and Geriatric Cognitive Disorders, 23*(1), 29-34.

Kotkowski, E., Price, L. R., Franklin, C., Salazar, M., Woolsey, M., DeFronzo, R. A., Blangero, J. & Glahn, D. C. (2019). A Neural Signature of Metabolic Syndrome. *Human Brain Mapping, 40*(12), 3575-3588.

Kraybill, M. L., Thorgusen, S. R. & Suchy, Y. (2013). The Push-Turn-Taptap Task Outperforms Measures of Executive Functioning in Predicting Declines in Functionality: Evidence-based Approach to Test Validation. *The Clinical Neuropsychologist, 27*(2), 238-255.

Kresge, H. A., Khan, O. A., Wagener, M. A., Liu, D., Terry, J. G., Nair, S., Cambronero, F. E., Gifford, K. A. Osborn, K. E., Hohman, T. J., Pechman, K. R., Bell, S. P., Wang, T. J., Carr, J. J. & Jefferson, A. L. (2018). Subclinical Compromise in Cardiac Strain Relates to Lower Cognitive Performance in Older Adults. *Journal of the American Heart Association, 7*(4).

Kulshreshtha, A., Goetz, M., Alonso, A., Shah, A. J., Bremner, J. D. & Vaccarino, V. (2019). Association between Cardiovascular Health and Cognitive Performance: A Twins Study. *Journal of Alzheimer's Disease, 71*(3), 957-968.

Kusztor, A., Raud, L., Juel, B. E., Nilsen, A. S., Storm, J. F. & Huster, R. J. (2019). Sleep Deprivation Differentially Affects Subcomponents of Cognitive Control. Sleep, 42(4), 1-11.

Lahav, O. & Katz, N. (2020). Independent Older Adult's IADL and Executive Function According to Cognitive Performance. *OTJR: Occupation, Participation, and Health, 40*(3), 183-189.

Lai, M. M. Y., Ames, D. J., Cox, K. L., Ellis, K. A., Sharman, M. J. R., Hepworth, G., Desmond, P., Cyarto, E. V., Szoeke, C., Martins, R., Masters, C. L. & Lautenschlager, N. T. (2020). Association between Cognitive Function and Clustered Cardiovascular Risk of Metabolic Syndrome in Older Adults at Risk of Cognitive Decline. *The Journal of Nutrition, Health, and Aging, 24*(3), 300-304.

Lal, B. K., Dux, M. C., Sikdar, S., Goldstein, C., Khan, A. A., Yokemick, J. & Zhao, L. (2017). Asymptomatic Carotid Stenosis is Associated with Cognitive Impairment. *Journal of Vascular Surgery, 66*(4), 1083-1092.

Lam, M., Eng, G. K., Rapisarda, A., Subramaniam, M., Kraus, M., Keefe, R. S. E. & Collinson, S. L. (2013). Formulation of the Age-education Index: Measuring Age and Education Effects in Neuropsychological Performance. *Psychological Assessment, 25*(1), 61-70.

Lamar, M., Ajilore, O., Leow, A., Charlton, R., Cohen, J., GadElkarim, J., Yang, S., Zhang, A., Davis, R., Penney, D., Libon, D. L. & Kumar, A. (2016). Cognitive and Connectome Properties Detectable through Individual Differences in Graphomotor Organization. *Neuropsychologia, 85*, 301-309.

Larner, A. J. (2018). Mini-Mental State Examination: Diagnostic Test Accuracy Study in Primary Care Referrals. *Neurodegenerative Disease Management, 8*(5), 301-305.

Lau, K. M., Parikh, M., Harvey, D. J., Huang, C. J., & Farias, S. T. (2015). Early Cognitively based Functional Limitations Predict Loss of Independence in Instrumental Activities of Daily Living in Older Adults. *Journal of the International Neuropsychological Society*, *21*, 688-698.

Laudisio, A., Bandinelli, S., Gemma, A., Ferrucci, L. & Incalzi, R. A. (2014). Metabolic Syndrome and Functional Ability in Older Age: The InCHIANTI Study. *Clinical Nutrition, 33*(4), 626-633.

Lawton, M. P. & Brody, E. M. (1969). Assessment of Older People: Self-maintaining and Instrumental Activities of Daily Living. *The Gerontologist, 9*(3), 179-186.

Lee, A. Y., Kim, J. S., Choi, B. H. & Sohn, E. H. (2009). Characteristics of Clock Drawing Test (CDT) Errors by the Dementia Type: Quantitative and Qualitative Analyses. *Archives of Gerontology and Geriatrics, 48*(1), 58-60.

Lee, J. E., Shin, D. W., Han, K., Kim, D., Yoo, J. E., Lee, J., Kim, S., Son, K. Y., Cho, B. & Kim, M. J. (2020). Changes in Metabolic Syndrome Status and Risk of Dementia. *Journal of Clinical Medicine, 9*(1), 1-17.

Lee, L., Weston, W. W. & Hillier, L. M. (2018). Education to Improve Dementia Care: Impact of a Structured Clinical Reasoning Approach. *Family Medicine, 50*(3), 195-203.

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannah, H. J. & Fischer, J. S. (2004). *Neuropsychological Assessment* (4th ed.). New York, NY: Oxford University Press.

Liaw, F., Kao, T., Wu, L., Wang, C., Yang, H., Peng, T., Sun, Y., Chang, Y. & Chen, W. (2016). Components of Metabolic Syndrome and the Risk of Disability among the Elderly Population. *Scientific Reports, 6*, 1-9.

Libon, D. J., Penney, D. L., Davis, R., Tabby, D. S., Eppig, J., Nieves, C., Bloch, A., Donohue, J. B., Brennan, L., Rife, K. L., Wicas, G., Lamar, M., Price, C. C., Au, R., Swenson, R. & Garrett, K. D., on behalf of the Clock Sketch Consortium. (2013). Deficits in Processing Speed and Decision Making in Relapsing-Remitting Multiple Sclerosis: The Digit Clock Drawing Test (dCDT). *Journal of Multiple Sclerosis, 1*(2), 1-8.

Linzer, M., Bitton, A., Tu, S., Plews-Ogan, M., Horowitz, K. R., Schwartz, M. D. & Association of Chiefs and Leaders in General Internal Medicine (ACLGIM) Writing Group. (2015). The End of the 15-20 Minute Primary Care Visit. *Journal of General Internal Medicine, 30*(11), 1584-1586.

Liu, J. L., Hlavka, J. P., Hillestad, R. & Mattke, S. (2017). *Assessing the Preparedness of the U.S. Health Care System Infrastructure for an Alzheimer's Treatment*. Santa Monica, CA: RAND Corporation.

Lugtenburg, A., Voshaar, R. C. O., Zelst, W. V., Schoevers, R. A., Enriquez-Geppert, S. & Zuidersma, M. (2017). The Relationship between Depression and Executive Function and the Impact of Vascular Disease Burden in Younger and Older Adults. *Age and Ageing, 46*(4), 697-701.

Lyu, F., Wu, D., Wei, C. & Wu, A. (2020). Vascular Cognitive Impairment and Dementia in Type 2 Diabetes Mellitus: An Overview. *Life Sciences, 254*, 1-6.

Ma, Y., Liang, L., Zheng, F., Shi, L., Zhong, B. & Xie, W. (2020). Association between Sleep Duration and Cognitive Decline. *JAMA Network Open, 3*(9), 1-14.

Malek-Ahmadi, M., Chen, K., Perez, S. E., He, A. & Mufson, E. J. (2018). Cognitive Composite Score Association with Alzheimer's Disease Plaque and Tangle Pathology. *Alzheimer's Research & Therapy, 10*(90), 1-12.

Mansbach, W. E. & Mace, R. A. (2019). Predicting Functional Dependence in Mild Cognitive Impairment: Differential Contributions of Memory and Executive Functions. *Gerontologist, 59*(5), 925-935.

Martin, P. K., Schroeder, R. W., Olsen, D. H., Maloy, H., Boettcher, A., Ernst, N. & Okut, H. (2020). A Systematic Review and Meta-analysis of the Test of Memory Malingering in Adults: Two Decades of Deception Detection. *Archives of Clinical Neuropsychology, 34*(1), 88-119.

McAlister, C. & Schmitter-Edgecombe. (2016). Executive Function Subcomponents and their Relations to Everyday Functioning in Healthy Older Adults. *Journal of Clinical and Experimental Neuropsychology, 38*(8), 925-940.

McCabe, D. P., Roediger III, H. L., McDaniel, M. A., Balota, D. A. & Hambrick, D. Z. (2010). The Relationship between Working Memory Capacity and Executive Functioning: Evidence for a Common Executive Attention Construct. *Neuropsychology, 24*(2), 222-243.

McDougall, G. J., Han, A., Staggs, V. S., Johnson, D. K. & McDowd, J. M. (2019). Predictors of Instrumental Activities of Daily Living in Community-Dwelling Older Adults. *Archives of Psychiatric Nursing, 33*(5), 43-50.

Mehra, A., Suri, V., Kumari, S., Avasthi, A. & Grover, S. (2020). Association of Mild Cognitive Impairment and Metabolic Syndrome in Patients with Hypertension. *Asian Journal of Psychiatry, 53*, 1-7.

Mendez, M. F., Ala, T. & Underwood, K. L. (1992). Development of Scoring Criteria. for the Clock Drawing Task in Alzheimer's Disease. *Journal of the American Geriatrics Society, 40*(11), 1095-1099.

Mitchell, A. J. (2009). A Meta-analysis of the Accuracy of the Mini-Mental State Examination in the Detection of Dementia and Mild Cognitive Impairment. *Journal of Psychiatric Research, 43*(4), 411-431.

Miyake, A., Friedman, N. P., Rettinger, D. A., Shah, P. & Hegarty, M. (2001). How are Visuospatial Working Memory, Executive Functioning, and Spatial Abilities Related? A Latent-variable Analysis. *Journal of Experimental Psychology: General, 130*(4), 621-640.

Moheet, A., Mangia, S. & Seaquist, E. R. (2015). Impact of Diabetes on Cognitive Function and Brain Structure. *Annals of the New York Academy of Sciences, 1353*, 60-71.

Moon, S. H., Seo, H. J., Lee, D. Y., Kim S. M. & Park, J. M. (2019). Associations Among Health Insurance Type, Cardiovascular Risk Factors, and the Risk of Dementia: A Prospective Cohort Study in Korea. *International Journal of Environmental Research and Public Health, 16*(14), 1-9.

Moore, J. X., Chaudhary, N. & Akinyemiju, T. (2017). Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Preventing Chronic Disease, 14*, 1-16.

Moraes, N. C., Aprahamian, I. & Yassuda, M. S. (2019). Executive Function in Systemic Arterial Hypertension: A Systematic Review. *Dementia & Neuropsychologia, 13*(3), 284-292.

Morley, J. E., Morris, J. C., Berg-Weger, M., Borson, S., Carpenter, B. D., del Campo, N., Dubois, B., Fargo, K., Fitten, L. J., Flaherty, J. H., Ganguli, M., Grossberg, G. T., Malmstrom, T. K., Petersen, R. D., Rodriguez, C., Saykin, A. J., Scheltens, P., Tangalos, E. G., Verghese, J., Wilcock, G., Winblad, B., Woo, J. & Vellas, B. (2015). Brain Health: The Importance of Recognizing Cognitive Impairment: An IAGG Consensus Conference. *Journal of the American Medical Directors Association, 16*(9), 731-739.

Muller, S., Herde, L., Preische, O., Zeller, A., Heymann, P., Robens, S., Elbing, U. & Laske, C. (2019). Diagnostic Value of Digital Clock Drawing Test in Comparison with CERAD Neuropsychological Battery Total Score for Discrimination of Patients in the Early Course of Alzheimer's Disease from Healthy Individuals. *Scientific Reports, 9*(3543), 1-10.

Muller, S., Preische, O., Heymann, P., Elbing, U. & Laske, C. (2017). Increased Diagnostic Accuracy of Digital vs. Conventional Clock Drawing Test for Discrimination of Patients in the Early Course of Alzheimer's Disease from Cognitively Healthy Individuals. *Frontiers in Aging Neuroscience, 9*(101), 1-10.

Munshi, M., Grande, L., Hayes, M., Ayres, D., Suhl, E., Capelson, R., Milberg, W. & Weinger, K. (2006). Cognitive Dysfunction is Associated with Poor Diabetes Control in Older Adults. *Diabetes Care, 29*(8), 1794-1799.

Nair, A. K., Gavett, B. E., Damman, M., Dekker, W., Green, R. C., Mandel, A., Auerbach, S., Steinberg, E., Hubbard, E. J., Jefferson, A. & Stern R. A. (2010).

Clock Drawing Test Ratings by Dementia Specialists: Interrater Reliability and Diagnostic Accuracy. *The Journal of Neuropsychiatry and Clinical Neurosciences, 22*(1), 85-92.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L. & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699.

Ng, T. P., Feng, L., Nyunt, M. S., Feng, L., Gao, Q., Lim, M. L., Collinson, S. L., Chong, M. S., Lim, W. S., Lee, T. S., Yap, P. & Yap, K. B. (2016). Metabolic Syndrome and the Risk of Mild Cognitive Impairment and Progression to Dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort. *JAMA Neurology, 73*(4), 456-463.

Oda, E. (2018). Historical Perspectives of the Metabolic Syndrome. *Clinics in Dermatology, 36*(1), 3-8.

Ogawa, E. F., Leritz, E., McGlinchey, R., Milberg, W. & Bean, J. F. (2021). Metabolic Syndrome and Physical Performance: The Moderating Role of Cognition among Middle-to-Older-Aged Adults. *Journal of the International Neuropsychological Society, 27*(2), 172-180.

Oh, H. M., Kim, S. H., Kang, S. G., Park, S. J. & Song, S. W. (2011). The Relationship between Metabolic Syndrome and Cognitive Function. *Korean Journal of Family Medicine, 32*(6), 358-366.

Okonkwo, O. C., Oh, J. M., Koscik, R., Jonaitis, E., Cleary, C. A., Dowling, N. M., Bendlin, B. B., LaRue, A., Hermann, B. P., Barnhart, T. E., Murali, D., Rowley, H. A., Carlsson, C. M., Gallagher, C. L., Asthana, S., Sager, M. A., Christian, B. T. & Johnson, S. C. (2014). Amyloid Burden, Neuronal Function, and Cognitive Decline in Middle-aged Adults at Risk for Alzheimer's Disease. *Journal of the International Neuropsychological Society, 20*(4), 422-433.

Oltra-Cucarella, J., Sanchez-SanSegundo, M., Lipnicki, D. M., Crawford, J. D., Lipton, R. B., Katz, M. J., Zammit, A. R., Scarmeas, N., Dardiotis, E., Kosmidis, M. H., Guaita, A., Vaccaro, R., Kim, K. W., Han, J. W., Kochan, N. A., Brodaty, H., Perez-Vicente, J. A., Cabello-Rodriguez, L., Sachdev, P. S., Ferrer-Cascales, R. & Cohort Studies of Memory in an International Consortium (COSMIC). (2018). Visual Memory Tests Enhance the Identification of Amnestic MCI Cases at Greater Risk of Alzheimer's Disease. *International Psychogeriatrics, 31*(7), 997-1006.

Osterrieth, P. A. (1944). Le test de copie d'une figure complex: Contribution a l'etude de la perception et de la memoire. *Archives de Psychologie, 30*, 286-356.

Ou, Y., Tan, C., Shen, X., Xu, W., Hou, X., Dong, Q., Tan, L. & Yu, J. (2020). Blood Pressure and Risks of Cognitive Impairment and Dementia. *Hypertension, 76*(1), 217-225.

Pal, K., Mukadam, N., Petersen, I. & Cooper C. (2018). Mild Cognitive Impairment and Progression to Dementia in People with Diabetes, Prediabetes, and Metabolic Syndrome: A Systematic Review and Meta-analysis. *Social Psychiatry and Psychiatric Epidemiology, 53*(11), 1149-1160.

Palsetia, D., Rao, G. P., Tiwari, S. C., Lodha, P. & Sousa, A. D. (2018). The Clock Drawing Test versus Mini-mental Status Examination as a Screening Tool for Dementia: A Clinical Comparison. *Indian Journal of Psychological Medicine, 40*(1), 1-10.

Palta, P., Carlson, M. C., Crum, R. M., Colantuoni, E., Sharrett, A. R., Yasar, S., Nahin, R. L., DeKosky, S. T., Snitz, B., Lopez, O., Williamson, J. D., Furberg, C. D., Rapp, S. R. & Golden, S. H. (2018). Diabetes and Cognitive Decline in Older Adults: The Ginkgo Evaluation of Memory Study. *Journals of Gerontology: Medical Sciences, 73*(1), 123-130.

Pantsiou, K., Sfakianaki, O., Papaliagkas, V., Savvoulidou, D., Costa, V., Papantoniou, G. & Moraitou, D. (2018). Inhibitory Control, Task/Rule Switching, and Cognitive Planning in Vascular Dementia: Are There Any Differences from Vascular Aging? *Frontiers in Aging Neuroscience, 10*(330), 1-17.

Park, J., Jeong, E. & Seomun, G. (2018). The Clock Drawing Test: A Systematic Review and Meta-analysis of Diagnostic Accuracy. *Journal of Advanced Nursing, 74*(12), 2742-2754.

Park, S., Lee, J., Lee, J., Cho, Y., Park, H. G., Yoo, Y., Youn, J., Ryu, S., Hwang, J. Y., Kim, J. & Lee, J. (2019). Interactions between Subjective Memory Complaint and Objective Cognitive Deficit on Memory Performances. *BMC Geriatrics, 19*(294), 1-8.

Parsey, C. M. & Schmitter-Edgecombe, M. (2013). Applications of Technology in Neuropsychological Assessment. *The Clinical Neuropsychologist, 27*(8), 1-30.

Parsons, T. D. & Duffield, T. (2019). National Institutes of Health Initiatives for Advancing Scientific Developments in Clinical Neuropsychology. *The Clinical*

Neuropsychologist, 33(2), 246-270.

Penney, D. L., Davis, R., Libon, D. J., Lamar, M., Price, C. C., Swenson, R., Garrett, K. D., Freedland, A., Weninger, C., Scala, S., Giovannetti, T. & Kaplan, E. (2010). *The Digital Clock Drawing Test (dCDT) II: A New Computerized Quantitative System.* Presented at The International Neuropsychological Society, Montreal, Canada, 2010.

Penney, D. L., Libon, D. J., Lamar, M., Swenson, R., Price, C. C., Weninger, C., Freedland, A., Garrett, K. D., Scala, S., Davis, R. (2010). *The Digital Clock Drawing Test (dCDT) III: Clinician Reliability for a New Quantitative System.* Presented at The International Neuropsychological Society, Montreal, Canada, 2010.

Petersen, R. C. & Morris, J. C. (2005). Mild Cognitive Impairment as a Clinical Entity and Treatment Target. *JAMA Neurology Archives, 62*(7), 1160-1163.

Phillips, J., Pond, C. D. & Goode, S. M. (2011). A Report for Alzheimer's Australia: *Timely Diagnosis of Dementia: Can we do better?* Australia.

Phillips, J., Pond, C. D. & Paterson, N. E. (2012). Difficulties in Disclosing the Diagnosis of Dementia: A Qualitative Study in General Practice. *British Journal of General Practice, 62*(601), e546-e553.

Piers, R. J., Devlin, K. N., Ning, B., Liu, Y., Wasserman, B., Massaro, J. M., Lamar, M., Price, C. C., Swenson, R., Davis, R., Penney, D. L., Au, R. & Libon, D. J. (2017). Age and Graphomotor Decision Making Assessed with the Digital Clock Drawing Test: The Framingham Heart Study. *Journal of Alzheimer's Disease, 60*(4), 1611-1620.

Pinto, T. C C., Machado, L., Bulgacov, T. M., Rodrigues-Junior, A. L., Costa, M. L. G., Ximenes, R. C. C. & Sougey, E. B. (2019). Is the Montreal Cognitive Assessment (MoCA) Screening Superior to the Mini-Mental State Examination (MMSE) in the Detection of Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) in the Elderly? *International Psychogeriatrics, 31*(4), 491-504.

Przybycien-Gaweda, P. M., Gwee, X., Gao, Q., Chua, D. Q. L., Fam, J. & Ng, T. P. (2020). Metabolic Syndrome and Cognition: Follow up Study of Chinese Over-55-Year-Olds. *Dementia and Geriatric Cognitive Disorders, 7*, 1-9.

Pugh, K. G. & Lipsitz, L. A. (2002). The Microvascular Frontal-subcortical Syndrome of Aging. *Neurobiology of Aging, 23*(3), 421-431.

Rabin, L. A., Barr, W. B. & Burton, L. A. (2005). Assessment Practices of Clinical Neuropsychologists in the United States and Canada: A Survey of INS, NAN, and APA Division 40 Members. *Archives of Clinical Neuropsychology, 20*(1), 33-65.

Raffaitin, C., Feart, C., Le Goff, M., Amieva, H., Helmer, C., Akbaraly, T. N., Tzourio, C., Gin, H. & Barberger-Gateau, P. (2011). Metabolic Syndrome and Cognitive Decline in French Elders: The Three-City Study. *Neurology, 76*(6), 518-525.

Rakusa, M., Jensterle, J. & Mlakar, J. (2018). Clock Drawing Test: A Simple Scoring System for the Accurate Screening of Cognitive Impairment in Patients with Mild Cognitive Impairment and Dementia. *Dementia and Geriatric Cognitive Disorders, 45*(5-6), 326-334.

Reamy, B. V., Williams, P. M. & Kuckel, D. P. (2018). Prevention of Cardiovascular Disease. *Primary Care: Clinics in Office Practice, 45*(1), 25-44.

Reaven, G. M. (1988). Role of Insulin Resistance in Human Disease. *Diabetes, 37*, 1595-1607.

Reijmer, Y. D., van den Berg, E., Dekker, J. M., Nijpels, G., Stehouwer, C. D., Kappelle, L. J. & Biessels, G. J. (2011). The Metabolic Syndrome, Atherosclerosis, and Cognitive Functioning in a Non-demented Population: The Hoorn Study. *Atherosclerosis, 219*(2), 839-845.

Reitan, R. M. & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery*. Tuscon, AZ: Neuropsychology Press.

Repousi, N., Masana, M. F., Sanchez-Niubo, A., Haro, J. M. & Tyrovolas, S. (2018). Depression and Metabolic Syndrome in the Older Population: A Review of Evidence. *Journal of Affective Disorders, 237*, 56-64.

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie, 28*, 286-340.

Riordan, H. J. (2017). Constructing Composites to Optimize Cognitive Outcomes. *Journal for Clinical Studies, 9*(2), 40-45.

Roebuck-Spencer, T. M., Glen, T., Puente, A. E., Denney, R. L., Ruff, R. M., Hostetter, G. & Bianchini, K. J. (2017). Cognitive Screening Tests versus Comprehensive Neuropsychological Test Batteries: A National Academy of Neuropsychology Education Paper. *Archives of Clinical Neuropsychology, 32*(4), 491-498.

Roriz-Cruz, M., Rosset, I., Wada, T., Sakagami, T., Ishine, M., Roriz-Filho, J. S., Cruz, T. R. S., Rodrigues, R. P., Resmini, I., Sudoh, S., Wakatsuki, Y., Nakagawa, M., Souza, A. C., Kita, T. & Matsubayashi, K. (2007). Stroke-Independent Association between Metabolic Syndrome and Functional Dependence, Depression, and Low Quality of Life in Elderly Community-Dwelling Brazilian People. *Journal of the American Geriatrics Society, 55*(3), 374-382.

Rouch, I., Trombert, B., Kossowsky, M. P., Laurent, B., Celle, S., Ntougou Assoumou, G., Rouche, F. & Barthelemy, J. C. (2014). Metabolic Syndrome is Associated with Poor Memory and Executive Performance in Elderly Community Residents: The PROOF Study. *The American Journal of Geriatric Psychiatry, 22*(11), 1096-1104.

Roy, S., Hyman, D., Ayyala, S., Bakhshi, A., Kim, S. H., Anoruo, N., Weinstock, J., Balogun, A., D'Souza, M., Filatova, N., Penabad, J., Shah, P., Perez, C., Mehta, A. & Hunter, K. (2020). Cognitive Function Assessment in Patients on Moderate or High Intensity Statin Therapy. *Journal of Clinical Medicine Research, 12*(4), 255-265.

Rubin, R. (2018). Exploring the Relationship between Depression and Dementia. *JAMA, 320*(10), 961-962.

Sabbagh, M. N., Boada, M., Borson, S., Chilukuri, M., Dubois, B., Ingram, J., Iwata, A., Porsteinsson, K. L., Possin, G. D., Rabinovici, G. D., Vellas, B., Chao, S., Vergallo, A. & Hampel, H. (2020). Early Detection of Mild Cognitive Impairment (MCI) in Primary Care. *The Journal of Prevention of Alzheimer's Disease, 7*(3), 165-170.

Sabia, S., Fayosse, A., Dumurgier, J., Schnitzler, A., Empana, J. P., Ebmeier, K. P., Dugravot, A., Kivimaki, M. & Singh-Manoux, A. (2019). Association of Ideal Cardiovascular Health at Age 50 with Incidence of Dementia: 25 year follow-up of Whitehall II cohort study. *The British Medical Journal, 366*, 1-10.

Sacre, J. W., Ball, J., Wong, C., Chan, Y., Stewart, S., Kingwell, B. A. & Carrington, M. J. (2018). Mild Cognitive Impairment is Associated with Subclinical Diastolic Dysfunction in Patients with Chronic Heart Disease. *European Heart Journal: Cardiovascular Imaging, 19*(3), 285-292.

Sala, M., de Roos, A., van den Berg, A., Altmann-Schneider, I., Slagboom, P. E., Westendorp, R. G., van Buchem, M. A., de Craen, A. J. M. & van der Grond, J. (2014). Microstructural Brain Tissue Damage in Metabolic Syndrome. *Diabetes Care, 37*(2), 493-500.

Salmon, D. P. & Filoteo, J. V. (2007). Neuropsychology of Cortical versus Subcortical Dementia Syndromes. *Seminars in Neurology, 27*(1), 7-21.

Saklayen, M. G. (2018). The Global Epidemic of the Metabolic Syndrome. *Current Hypertension Reports, 20*(12), 1-8.

Schretlen, D. J., Munro, C. A., Anthony, J. C. & Pearlson, G. D. (2003). Examining the Range of Normal Intraindividual Variability in Neuropsychological Test Performance. *Journal of the International Neuropsychological Society, 9*(6), 864-870.

Schuur, M., Henneman, P., van Swieten, J. C., Zillikens, M. C., de Koning, I., Janssens, A. C., Witteman, J. C., Aulchenko, Y. S., Frants, R. R., Oostra, B. A., van Dijk, K. W. & van Duijn, C. M. (2010). Insulin-resistance and Metabolic Syndrome are Related to Executive Function in Women in a Large Family-based Study. *European Journal of Epidemiology, 25*(8), 561-568.

Schwartz, E. S., Erdodi, L., Rodriguez, N., Ghosh, J. J., Curtain, J. R., Flashman, L. A. & Roth, R. M. (2016). CVLT-II Forced Choice Recognition Trial as an Embedded Validity Indicator: A Systematic Review of the Evidence. *Journal of the International Neuropsychological Society, 22*(8), 851-858.

Schwarz, N. F., Nordstrom, L. K., Pagen, L. H. G., Palombo, D. J., Salat, D. H., Milberg, W. P., McGlinchey, R. E. & Leritz, E. C. (2018). Differential Associations of Metabolic Risk Factors on Cortical Thickness in Metabolic Syndrome. *NeuroImage: Clinical, 17*, 98-108.

Segal-Gidan, F. (2013). Cognitive Screening Tools. *Clinician Reviews, 23*(1), 12-18.

Segura, B., Jurado, M. A., Freixenet, N., Albuin, C., Muniesa, J. & Junque, C. (2009). Mental Slowness and Executive Dysfunctions in Patients with Metabolic Syndrome. *Neuroscience Letters, 462*(1), 49-53.

Shanhu, X., Linhui, C., Xiaoqing, J., Jing, Y., Saizhu, X., Ying, X., Caixia, L. & Yu, J. (2019). Effects of Age and Education on Clock-drawing Performance by Elderly Adults in China. *The Clinical Neuropsychologist, 33*, 96-105.

Sharma, B. & Jain, R. (2014). Right Choice of a Method for Determination of Cut-off Values: A Statistical Tool for Diagnostic Test. *Asian Journal of Medical Sciences, 5*(3), 30-34.

Sheehan, B. (2012). Assessment Scales in Dementia. *Therapeutic Advances in*

Neurological Disorders, 5(6), 349-358.

Shulman, K. I. (2000). Clock-drawing: Is it the ideal cognitive screening test? *International Journal of Geriatric Psychiatry, 15*(6), 548-561.

Shulman, K. I., Herrmann, N., Brodaty, H., Chiu, H., Lawlor, B., Ritchie, K. & Scanlan, J. M. (2006). IPA Survey of Brief Cognitive Screening Instruments. *International Psychogeriatrics, 18*(2), 281-294.

Shulman, K. I., Shedletsky, R. & Silver, I. L. (1986). The Challenge of Time: Clock-drawing and Cognitive Function in the Elderly. *International Journal of Geriatric Psychiatry, 1*, 135-140.

Sibley, S. R., Strout, K. & Poirier, P. (2019, September 20). *Screening for Cognitive Decline in Primary Care.* Clinical Advisor. https://www.clinicaladvisor.com/home/topics/neurology-information-center/screening-for-cognitive-decline-in-primary-care/2/

Sinclair, A. & Abdelhafiz, A. (2020). Cognitive Dysfunction in Older Adults with Type 2 Diabetes: Links, Risks, and Clinical Implications. *Clinics in Geriatric Medicine, 36*(3), 407-417.

Siquiera, G. S. A., Hagemann, P. M. S., Coelho, D. S., Santos, F. H. D. & Bertolucci, P. H. F. (2019). Can MoCA and MMSE be Interchangeable Cognitive Screening Tools? A Systematic Review. *Gerontologist, 59*(6), 743-763.

Slachevsky, A., Forno, G., Barraza, P., Mioshi, E., Delgado, C., Lillo, P., Henriquez, F., Bravo, E., Farias, M., Munoz-Neira, C., Ibanez, A., Parra, M. A. & Hornberger, M. (2019). Mapping the Neuroanatomy of Functional Decline in Alzheimer's Disease from Basic to Advanced Activities of Daily Living. *Journal of Neurology, 266*(6), 1310-1322.

Slavych, B. (2019, May 30). *Pros and Cons of Various Screening Tools for Dementia*. ASHAWire. https://leader.pubs.asha.org/do/10.1044/pros-and-cons-of-screening-tools-for-assessing-dementia/full/

Smedslund, G., Siqveland, J., Leiknes, K. A. (2015). *Psychometric Assessment of the Clock Drawing Test [Internet]*. (NOKC Publication No. 16-2015). Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH).

Smith, E. E. (2017). Clinical Presentations and Epidemiology of Vascular Dementia.

Clinical Science: London, 131(11), 1059-1068.

Snyder, H. R. (2013). Major Depressive Disorder is Associated with Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. *Psychological Bulletin, 139*(1), 81-132.

Song, R., Xu, H., Dintica, C. S., Pan, K., Qi, X., Buchman, A. S., Bennett, D. A. & Xu, W. (2020). Associations between Cardiovascular Risk, Structural Brain Changes, and Cognitive Decline. *Journal of the American College of Cardiology, 75*(20), 2525-2534.

Souillard-Mandar, W., Davis, R., Rudin, C., Au, R., Libon, D. J., Swenson, R., Price, C. C., Lamar, M. & Penney, D. L. (2016). Learning Classification Models of Cognitive Conditions from Subtle Behaviors in the Digital Clock Drawing Test. *Machine Learning, 102*(3), 393-441.

Spenciere, B., Alves, H. & Charchat-Fichman, H. (2017). Scoring Systems for the Clock Drawing Test: A historical review. *Dementia & Neuropsychologia, 11*(1), 6-14.

Spreen, O. & Benton, A. L. (1977). *Neurosensory Center Comprehensive Examination for Aphasia*. Victoria, Canada: University of Victoria.

Strauss, E., Sherman, E. S. & Spreen, O. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary* (3rd ed.). New York, NY: Oxford University Press.

Strober, L. B. & DeLuca, J. (2013). Fatigue: Its influence on cognition and assessment. In P. A. Arnett (Ed.), *Secondary Influences on Neuropsychological Test Performance: Research Findings and Practical Applications*. (pp. 117-141). New York, NY: Oxford University Press.

Strong, J., Fonda, J. R., Grande, L., Milberg, W., McGlinchey, R. & Leritz, E. (2020). The Role of Cognitive Reserve in the Relationship between Metabolic Syndrome and Cognitive Functioning. *Neuropsychology, Development, and Cognition: Section B, Aging, Neuropsychology, and Cognition*. Advance online publication. https://doi.org/10.1080/13825585.2020.1817304

Sudo, F. K., Amado, P., Alves, G. S., Laks, J. & Engelhardt, E. (2017). A Continuum of Executive Function Deficits in Early Subcortical Vascular Cognitive Impairment: A Systematic Review and Meta-Analysis. *Dementia & Neuropsychologia, 11*(4), 371-380.

Summers, M. J. & Saunders, N. L. J. (2012). Neuropsychological Measures Predict Decline to Alzheimer's Dementia from Mild Cognitive Impairment. *Neuropsychology, 26*(4), 498-508.

Tanner-Eggen, C., Balzer, C., Perrig, W. J. & Gutbrod, K. (2015). The Neuropsychological Assessment of Cognitive Deficits Considering Measures of Performance Variability. *Archives of Clinical Neuropsychology, 30*(3), 217-227.

Tariq, S. H., Tumosa, N., Chibnall, J. T., Perry, M. H. III & Morley, J. E. (2006). Comparison of the Saint Louis University Mental Status Examination and the Mini-Mental State Examination for Detecting Dementia and Mild Neurocognitive Disorder – A Pilot Study. *The American Journal of Geriatric Psychiatry, 14*(11), 900-910.

Tombaugh, T. N. (1996). *Test of Memory Malingering (TOMM)*. Toronto, Canada: Multi-Health Systems, Inc.

Tripathi, R., Kumar, K., Bharath, S., Marimuthu, P. & Varghese, M. (2014). Age, Education and Gender Effects on Neuropsychological Functions in Healthy Indian Older Adults. *Dementia & Neuropsychologia, 8*(2), 148-154.

Triposkiadis, F., Xanthopoulos, A. & Butler, J. (2019). Cardiovascular Aging and Heart Failure: JACC Review Topic of the Week. *Journal of the American College of Cardiology, 74*(6), 804-813.

Tsentidou, G., Moraitou, D. & Tsolaki, M. (2019). Cognition in Vascular Aging and Mild Cognitive Impairment. *Journal of Alzheimer's Disease, 72*(1), 55-70.

Tsoi, K. K. F., Chan, J. Y. C., Hirai, H. W., Wong, S. Y. S. & Kwok, T. C. Y. (2015). Cognitive Tests to Detect Dementia: A systematic review and meta-analysis. *JAMA Internal Medicine, 175*(9), 1450-1458.

United States Census Bureau. (2019). *QuickFacts: Boston, Massachusetts.* https://www.census.gov/quickfacts/bostoncitymassachusetts

Urtamo, A., Jyvakorpi, S. K., Kautiainen, H., Pitkala, K. H. & Strandberg, T. E. (2020). Major Cardiovascular Disease (CVD) Risk Factors in Midlife and Extreme Longevity. *Aging Clinical and Experimental Research, 32*(2), 299-304.

Valenza, S., Paciaroni, L., Paolini, S., Bonfigli, A. R., Rosa, M. D., Rabini, R. A., Tortato, E., Pelliccioni, P. & Pelliccioni, G. (2020). Mild Cognitive Impairment Subtypes and Type 2 Diabetes in Elderly Subjects. *Journal of Clinical Medicine,*

9(7), 1-12.

Vaughan, L. & Giovanello, K. (2010). Executive Function in Daily Life: Age-Related Influences of Executive Processes on Instrumental Activities of Daily Living. *Psychology and Aging, 25*(2), 343-355.

Videnovic, A., Bernard, B., Fan, W., Jaglin, J., Leurgans, S. & Shannon, K. M. (2010). The Montreal Cognitive Assessment as a Screening Tool for Cognitive Dysfunction in Huntington's Disease. *Movement Disorders, 25*(3), 401-404.

Viscogliosi, G., Andreozzi, P., Chiriac, I. M., Cipriana, E., Servello, A., Ettorre, E. & Marigliano, V. (2012). Screening Cognition in the Elderly in Metabolic Syndrome. *Metabolic Syndrome and Related Disorders, 10*(5), 358-362.

Viscogliosi, G., Chiriac, I. M., Andreozzi, P. & Ettore, E. (2015). Executive dysfunction assessed by Clock-Drawing Test in older non-demented subjects with metabolic syndrome is not mediated by white matter lesions. *Psychiatry and Clinical Neurosciences, 69*, 620-629.

Viscogliosi, G., Donfrancesco, C., Palmieri, L. & Giampaoli, S. (2017). The Metabolic Syndrome and 10 year Cognitive and Functional Decline in Very Old Men. A population-based study. *Archives of Gerontology and Geriatrics, 70*, 62-66.

von Bonsdorff, M. B., Haapanen, M. J., Tormakangas, T., Pitkala, K. H., Stenholm, S. & Strandberg, T. E. (2019). Midlife Cardiovascular Status and Old Age Physical Functioning Trajectories in Older Businessmen. *Journal of the American Geriatrics Society, 67*(12), 2490-2496.

Vyhnalek, M., Rubinova, E. Markova, H., Nikolai, T., Laczo, J., Andel, R. & Hort, J. (2017). Clock Drawing Test in Screening for Alzheimer's Dementia and Mild Cognitive Impairment in Clinical Practice. *International Journal of Geriatric Psychiatry, 32*, 933-939.

Wasserman, V., Emrani, S., Matusz, E. F., Miller, D., Garrett, K. D., Gifford, K. A., Hohman, T. J., Jefferson, A. L., Au, R., Swenson, R., Libon, D. J. & the Consortium for Clinical and Epidemiological Neuropsychological Data Analysis (CENDA). (2019). Visual and Verbal Serial List Learning in Patients with Statistically-Determined Mild Cognitive Impairment. *Innovation in Aging, 3*(2), 1-12.

Wang, Z. & Dong, B. (2018). Screening for Cognitive Impairment in Geriatrics. *Clinics in Geriatric Medicine, 34*(4), 515-536.

Wang, M., Norman, J. E., Srinivasan, V. J. & Rutledge, J. C. (2016). Metabolic, inflammatory, and microvascular determinants of white matter disease and cognitive decline. *American Journal of Neurodegenerative Disease, 5*(5), 171-177.

Warrington, E. K. (1984). *Recognition Memory Test: Manual*. Berkshire, UK: NFER-Nelson.

Wechsler, D. (1997). *Wechsler Memory Scale – Third Edition* (3rd ed.). San Antonio: TX: The Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale* (4th ed.). San Antonio, TX: Pearson Assessment.

Wechsler, D. (2009). *Wechsler Memory Scale* (4th ed.). San Antonio, TX: Pearson Assessment.

Wendell, C. R., Zonderman, A. B., Metter, E. J., Najjar, S. S. & Waldstein, S. R. (2009). Carotid Intimal Medial Thickness Predicts Cognitive Decline among Adults without Clinical Vascular Disease. *Stroke, 40*(10), 3180-3185.

World Health Organization. (2020, September 21). Dementia. Retrieved from https://www.who.int/news-room/fact-sheets/detail/dementia

Wooten, T., Ferland, T., Poole, V., Milberg, W., McGlinchey, R., DeGutis, J., Esterman, M. & Leritz, E. (2019). Metabolic Risk in Older Adults is Associated with Impaired Sustained Attention. *Neuropsychology, 33*(7), 947-955.

Yang, Y., Shields, G. S., Guo, C. & Liu, Y. (2018). Executive Function Performance in Obesity and Overweight Individuals: A Meta-analysis and Review. *Neuroscience & Biobehavioral Reviews, 84*, 225-244.

Yates, K. F., Sweat, V., Yau, P. L., Turchiano, M. M. & Convit, A. (2012). Impact of Metabolic Syndrome on Cognition and Brain: A Selected Review of the Literature. *Arteriosclerosis, Thrombosis, and Vascular Biology, 32*(9), 2060-67.

Ye, B. S., Chin, J., Kim, S. Y., Lee, J., Kim, E., Lee, Y., Hong, C. H., Choi, S. H., Park, K. W., Ku, B. D., Moon, S. Y., Kim, S., Han, S., Lee, J., Cheong, H., Park, S. A., Jeong, J. H., Na, D. L. & Seo, S. W. (2015). The Heterogeneity and Natural History of Mild Cognitive Impairment of Visual Memory Predominant Type. *Journal of Alzheimer's Disease, 43*(1), 143-152.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M. & Leirer, V. O. (1983). Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. *Journal of Psychiatric Research, 17*(1), 37-49.

Yim, D., Yeo, T. Y. & Park, M. H. (2020). Mild Cognitive Impairment, Dementia, and Cognitive Dysfunction Screening Using Machine Learning. *Journal of International Medical Research, 48*(7), 1-10.

Young, L. A. (2018, November 5). 3 Versions of the Clock Drawing Test for Cognition. *Eat Speak & Think*. https://eatspeakthink.com/3-versions-clock-drawing-test/

Zhao, H., Wei, W., Do, E. Y. & Huang, Y. (2019). Assessing Performance on Digital Clock Drawing Test in Aged Patients with Cerebral Small Vessel Disease. *Frontiers in Neurology, 10*(1259), 1-6.

Zhao, Q., Zhang, Y., Liao, X. & Wang, W. (2020). Executive Function and Diabetes: A Clinical Neuropsychology Perspective. *Frontiers in Psychology, 11*(2112), 1-9.

Zheng, L., Matthews, F. E. & Anstey, K. J. (2021). Cognitive Health Expectancies of Cardiovascular Risk Factors for Cognitive Decline and Dementia. *Age and Ageing, 50*(1), 169-175.

Zhou, T. L., Kroon, A. A., van Sloten, T. T., van Boxtel, M. P. J., Verhey, F. R. J., Schram, M. T., Kohler, S., Stehouwer, C. D. A. & Henry, R. M. A. (2019). Greater Blood Pressure Variability is Associated with Lower Cognitive Performance. *Hypertension, 73*(4), 803-811.

Zilliox, L. A., Chadrasekaran, K., Kwan, J. Y. & Russell, J. W. (2016). Diabetes and Cognitive Impairment. *Current Diabetes Reports, 16*(9), 87.

Zonderman, A. B., Giambra, L. M., Arenberg, D., Resnick, S. M., Costa Jr, P. T. & Kawas, C. H. (1995). Changes in Immediate Visual Memory Predict Cognitive Impairment. *Archives of Clinical Neuropsychology, 10*(2), 111-123.

CURRICULUM VITAE